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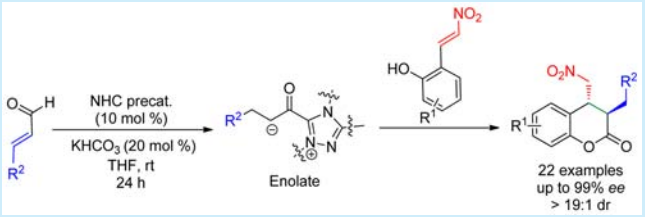
Chemoselective N-Heterocyclic Carbene-Catalyzed Cascade of Enals with Nitroalkenes

Zijun Wu, Xu Wang, Fangyi Li, Jicheng Wu, and Jian Wang*

Department of Pharmacology and Pharmaceutical Science, School of Medicine, Tsinghua University, Beijing 117543, China

Supporting Information

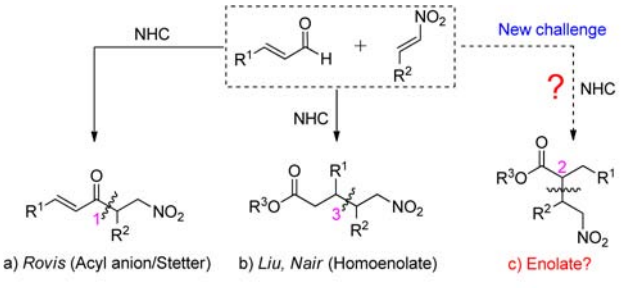
ABSTRACT: An unprecedented N-heterocyclic carbene catalyzed chemoselective and enantioselective cascade reaction of enals with nitroalkenes has been developed. A wide range of enantioenriched dihydrocoumarins has been prepared, and the reaction goes through an enolate intermediate generated under a catalytic process.

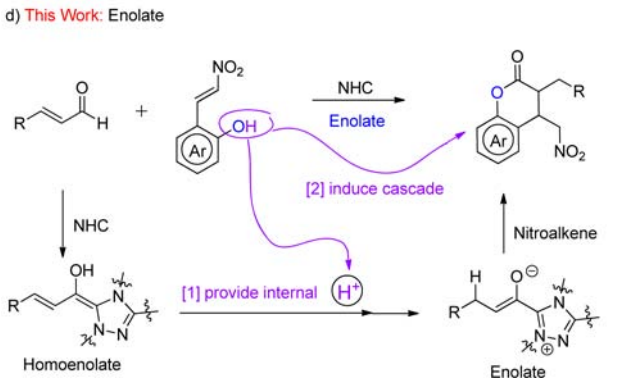


Over the past decade, N-heterocyclic carbene (NHC) catalysis has provided numerous opportunities for the development of new transformations that are based on polarity reversal or Umpolung reactivity.[1] The exploration of these unconventional reactivity patterns with new electrophilic coupling partners facilitates a broad construction of natural products and drug-like scaffolds.[2] In this context, NHCs are traditionally used as acyl anion equivalents to react with a variety of Michael acceptors. In 2004, Bode[3] and Glorius[4] group independently reported the NHC generated homoenolate in annulations between enals and aldehydes to construct γ-lactones. This breakthrough stimulates a variety of transformations to synthesize lactones, lactams, and carbocycles.[5] Beyond acyl anion and homoenolates,[5c,d,6] in 2004, Bode[7a] and Rovis[8a] et al. also disclosed a NHC-mediated formation of enolate intermediates and developed this concept into an impressive range of unique reactions.[7,8] Despite these advances, two challenging issues remain for the reaction of enals with nitroalkenes: (i) the difficulty of chemo-control, regio-control, and stereoinduction; (ii) the differentiation among of acyl anion, homoenolate, and enolate equivalents.

Among electrophiles, the nitroalkene is probably one of the most useful acceptors because transformation of the unique nitro group in the resulting product can facilitate further structural elaboration.[9] In this context, the Scheidt group utilized the nucleophilic acylation reaction of a protected thiazolium carbinol with a nitroalkene promoted by a thiourea/fluoride anion combination.[10] Later, the Rovis group reported the elegant intermolecular enantioselective Stetter reaction of aldehydes or enals with nitroalkenes catalyzed by a special chiral triazolium based fluorine contained N-heterocyclic carbene catalyst (Scheme 1a).[11] In 2009, the Nair group reported an NHC-catalyzed reaction between enals and nitroalkenes via homoenolate pathway. With the use of an achiral imidazolium precatalyst, aromatic enals and nitrostyrene derivatives were coupled in good yield and good *anti*-selectivity (Scheme 1b).[12] Next, Liu and co-workers rendered an NHC-catalyzed enantioselective version of various enals reacting with aromatic nitrodienes, nitroenynes, and nitrostryenes in excellent *ee* and good *anti*-diastereoselectivity (Scheme 1b).[13]

Scheme 1. Strategies for NHC-Catalyzed Reactions of Enals with Nitroalkenes





Recently, Rovis et al. reported a unique homoenolate example of NHC-catalyzed addition of enals to nitroalkenes with excellent *syn*-diastereoselectivity.[14a] Herein we report our own concurrent study on the reaction of enals and nitroalkenes[14b] that delivers complementary chemoselectivity for the assembly of structurally different products, such as enantioenriched coumarins. It is

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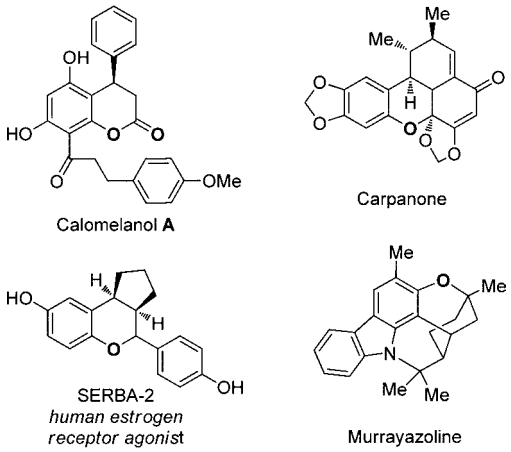
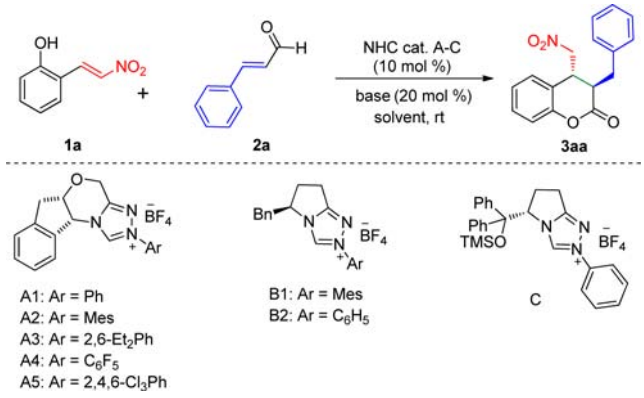


Figure 1. Selected bioactive coumarin analogues.

Table 1. Optimization of the Reaction Conditions[a]



entry	NHC cat.	base	solvent	yield (%)[b]	dr[c]	*ee* (%)[d]
1	A1	$KHCO_3$	THF	trace		
2	A2	$KHCO_3$	THF	85	>19:1	99
3	A3	$KHCO_3$	THF	90	>19:1	99
4	A4	$KHCO_3$	THF	0		
5	A5	$KHCO_3$	THF	0		
6	B1	$KHCO_3$	THF	n.r.[e]		
7	B2	$KHCO_3$	THF	n.r.[e]		
8	C	$KHCO_3$	THF	n.r.[e]		
9	A3	NaOAc	THF	30	>19:1	97
10	A3	K_2CO_3	THF	72	>19:1	95
11	A3	TEA	THF	40	>19:1	99
12	A3	$KHCO_3$	toluene	90	>19:1	99
13	A3	$KHCO_3$	CH_3CN	20		
14	A3	$KHCO_3$	CH_2Cl_2	<5		

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), chiral NHC catalyst A–C (10 mol %), $KHCO_3$ (20 mol %), THF (0.17 M in **1a**), 24 h. [b]Isolated yield after column chromatography. [c]Diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy. [d]The *ee* values were determined by chiral HPLC. [e]No reaction.

important to note that stereoselective reactions of various Michael acceptors with enolates, deriving from the *in situ* formation of enals and NHC precatalysts, have been intensively studied.[15] To our surprise, such an expected reaction of NHC generated enolates with nitroalkenes has remained elusive (Scheme 1c). In 2013, Enders group reported a [2 + 3] annulation of nitrovinylindoles with an enolate intermediate, but generated from α-chloroaldehydes and NHC catalyst.[16] Regarding biological importance of privileged structure coumarin, several important examples are selected and highlighted in Figure 1.[17,18]

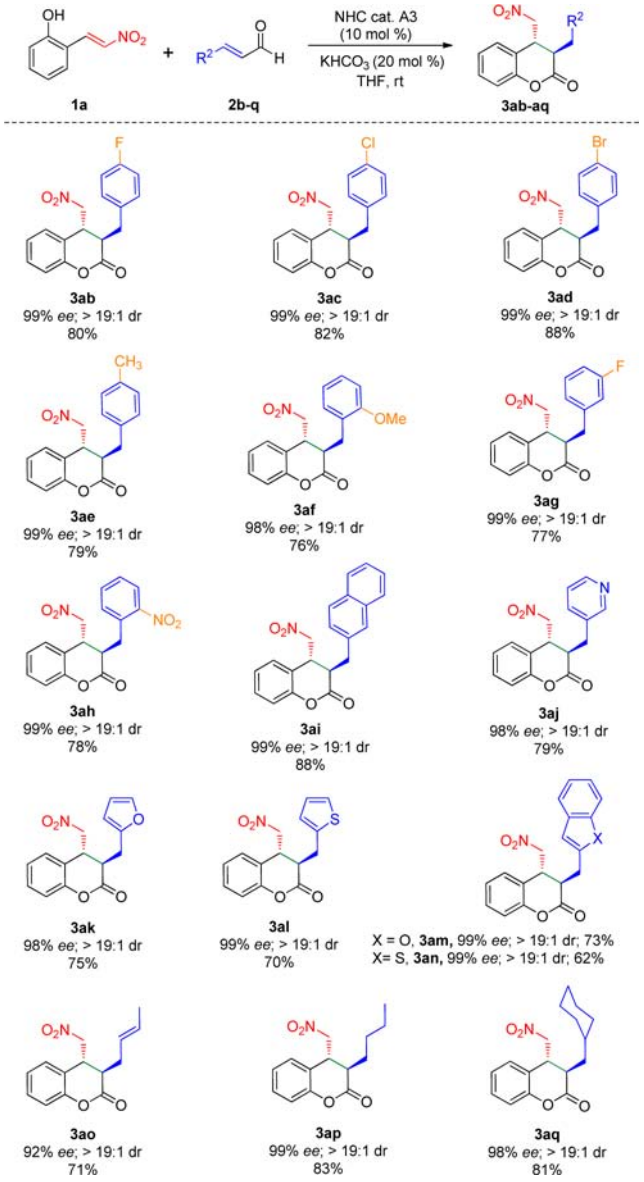


Figure 2. Scope of enals. Conditions are as indicated in Table 1.

Key results of condition optimization are summarized in Table 1. The reaction of nitroalkene **1a** (0.1 mmol) and enal **2a** (0.2 mmol) was chosen as a model. $KHCO_3$ and THF were used as base and medium, respectively. Studies on chiral NHC catalysts displayed that when indanol-derived catalyst **A2** and **A3** with a *N*-2,4,6-trimethyl- or *N*-2,6-diethylphenyl substituent were used, the expected cycloaddition product **3aa** was efficiently formed, albeit with an excellent enantioselectivity and diastereoselectivity (Table 1, entries 2 and 3, 99% *ee*, dr > 19:1). Surprisingly, all other chiral catalysts gave no products or afforded only a trace amount of **3aa** (entry 1, 4–8). The results of solvent screening indicated that the reaction process is very sensitive to medium. Toluene was the only other one that offered similar benefits in enantioselective control and reliable chemical yield (entry 12, 99% *ee*, 90% yield). A switch of base from $KHCO_3$ to NaOAc or TEA led to a dramatic decrease in chemical yield (entries 9 and 11, 30% and 40%, respectively).

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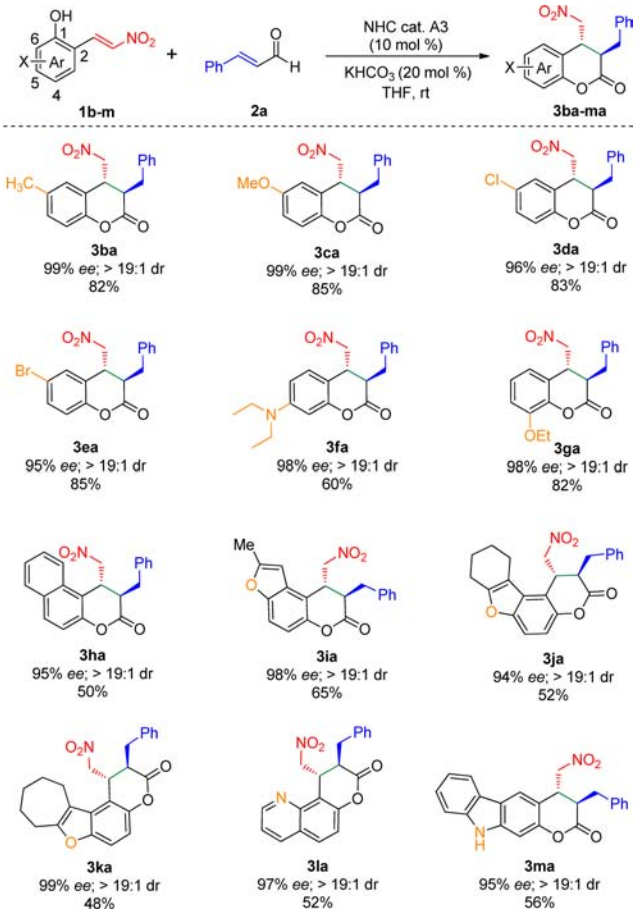
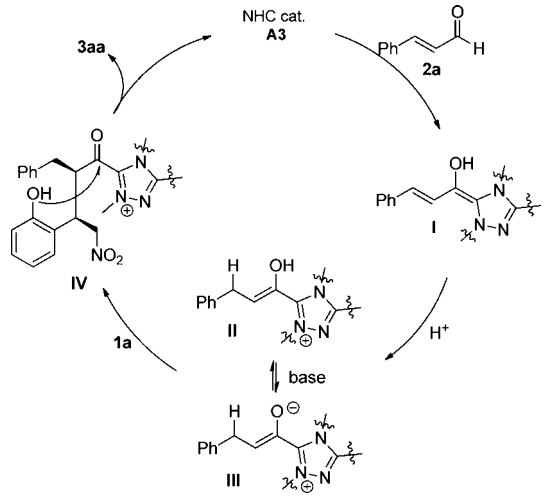


Figure 3. Scope of nitroalkenes. Conditions are as indicated in Table1.

Scheme 2. Postulated Mechanism



With optimized reaction conditions in hand, the substrate scope of enals was evaluated. A variety of 3,4-dihydrocoumarins were obtained in excellent enantioselectivities and diastereoselectivities (Figure 2). Both electron-deficient and -rich aryl enals provided the corresponding products in good to high yields (**3ab**–**ah**). Replacing the β-phenyl substituent with a naphthyl (**2i**) or heteroaryl (**2j**–**2n**) unit did not significantly change chemical yield, enantio- and diastereo-control (**3ai**–**an**, 62–88% yield, all 98–99% *ee*, >19:1 dr). When the β-aryl group of the enal was changed to a vinyl substituent (**2o**), 92% *ee* and >19:1 dr were observed (**3ao**). When replacing the β-phenyl group in enal **1a** with either a linear or bulkyl carbon unit (**2p** and **2q**), high yield and excellent enantio- and diastereo-control were still clearly observed (**3ap** and **3aq**).

The generality of nitroalkenes were then examined. Electron-deficient and -rich aryl alkenes all gave corresponding cycloadducts in excellent stereoselectivity, albeit with high yields (Figure 3, **3ba**–**3ga**). Additionally, tolerated products of functional groups (e.g., halogen (**3da**–**ea**), ether (**3ca** and **3ga**), and amine (**3fa**)) are highly valuable intermediates for further structure modification and structure–activity relationship (SAR) study. Naphthyl ring fused δ-lactone (**3ha**) was well constructed with 95% *ee* and >19:1 dr (Figure 3). However, a decreased yield (50%) was obtained due to the side intermolecular redox esterification of −OH group (**1**) and carbonyl group (**2**). It is noteworthy that this new chemistry could also be applied to construct a few drug-like heterocyclic structures. For examples, various substituted benzofuran fused δ-lactones (**3ia**–**ka**) were obtained in excellent stereoselectivities and with moderate chemical yields. Aza-heterocyclic structures, such as quinoline and carbazole, were successfully incorporated to give the corresponding products in excellent enantioselectivities (**3la** and **3ma**). The absolute configuration of **3ea** was determined by X-ray single crystallography, and the other products were assigned by analogy.[19]

A postulated reaction pathway of this reaction is illustrated in Scheme 2. The reaction starts with the formation of Breslow intermediate **I** by the addition of catalyst **A3** to enal **2a** in the presence of a base. Protonation of the enal β-carbon of **I** results in an NHC-bounded enolate ester intermediate **III** that readily undergoes a cycloaddition reaction with nitroalkene **1a** to eventually give the product **3aa** with a regeneration of the NHC catalyst **A3**.

In summary, the study of chemoselective NHC-catalyzed cascade reactions of enals and nitroalkenes to prepare enantioenriched 3,4-dihydrocoumarins through enolate activation is presented. With the proper choice of an appropriate combination of a NHC precatalyst and a base, the formation of 3,4-dihydrocoumarin scaffold occurs efficiently and proceeds in good to high yield with excellent enantioselectivity and stereoselectivity. Further study of the new reactivities of modified nitroalkenes in the presence of NHC catalysts is in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data for all new compounds, and CIF of compound **3ea**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01692.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangjian2012@tsinghua.edu.cn.

Notes

The authors declare no competing financial interest.

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(19) CCDC 1018588 (**3ea**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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