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Asymmetric Synthesis

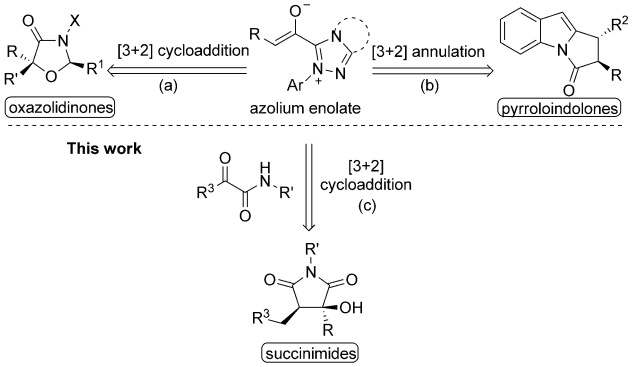
NHC-Catalyzed Asymmetric Synthesis of Functionalized Succinimides from Enals and α-Ketoamides

Lei Wang, Qijian Ni, Marcus Blümel, Tao Shu, Gerhard Raabe, and Dieter Enders*[a]

Abstract: The efficient asymmetric synthesis of highly substituted succinimides from α,β-unsaturated aldehydes and α-ketoamides via NHC-catalyzed [3+2] cycloaddition has been developed. The new scalable protocol significantly expands the utility of NHC catalysis for the synthesis of heterocycles and provides easy access to assemble a wide range of succinimides from simple starting materials.

Privileged heterocyclic systems are important objectives in chemical synthesis and pharmaceutical sciences, due to their wide existence in numerous biologically active molecules.[1] Recently, *N*-heterocyclic carbene (NHC) catalysis has emerged as a powerful tool for synthesis.[2] Owing to the unique properties of NHC catalysts, huge advances have been made.[3–7] Among these advances several different types of cycloaddition reactions for the construction of lactams and lactones are involved.[4a,b,e,8] In the recorded cycloaddition research of NHC catalysis, [3+2] cycloaddition reactions are emphasized here. However, most NHC-catalyzed [3+2] cycloaddition reactions for the synthesis of lactams and lactones involve a homoenolate intermediate;[3a,c,9] [3+2] cycloaddition via azolium enolates are rare.

Ye and co-workers were the first to describe a direct approach for the construction of oxazolidin-4-ones from oxaziridines with ketenes by NHC catalysis via the azolium enolate pathway (Scheme 1 a).[10] Later, Wang et al. reported the NHC-catalyzed reaction of indole-2-carbaldehydes with α-cyclopropyl-aldehydes forming pyrroloindolones.[11] Then, this azolium enolate chemistry was extended by our group, by reacting 2-nitrovinylindoles with α-chloroaldehydes to yield pyrroloindolones (Scheme 1 b).[12] To date no other research group has focused on applying the azolium enolate strategy in order to synthesize useful heterocycles by [3+2] cycloaddition reactions. For example, succinimide derivatives, belonging to one type of cyclic imides, are of particular interest due to the prevalence of the succinimide moiety in Nature.[13] Therefore, a concise strategy to synthesize succinimides by NHC catalysis is eminently noteworthy. Herein, we describe that simple cinnamaldehydes serve as azolium enolate precursors for the highly enantioselective synthesis of succinimides through a [3+2] cycloaddition with α-ketoamides as a new strategy (Scheme 1 c).[14]



Scheme 1. NHC-catalyzed [3+2] cycloaddition reactions via NHC-derived azolium enolates.

The succinimide moiety is present in a large number of compounds with a broad spectrum of pharmacological activities (Figure 1). Ranirestat, an aldose reductase inhibitor, has been developed for the treatment of diabetic neuropathy.[15] Ethosuximide is a succinimide anticonvulsant, mainly used in absence seizures.[16] Besides the succinimide motif in various pharmaceuticals, it is also part of different types of natural products. Haterumaimide A, due to its potential inhibition of protein synthesis, has been screened for antitumor activity.[17] Among the metabolites isolated from *Aspergillus japonicus* JV-23, asperparaline A has the ability of paralyzing silkworm larvae.[18] Recently, hirsutellone A, isolated from the insect pathogenic fungus *Hirsutella nivea* BCC 2594, has been shown to have good activity against *Mycobacterium tuberculosis* H37Ra.[19]

Owing to the importance of the succinimide moiety and our interest in NHC chemistry, we envisioned that a novel method for the asymmetric synthesis of succinimides might be developed by NHC-catalyzed cycloaddition of easily available enals and α-ketoamides via an azolium enolate pathway.

Our investigation started with the NHC-catalyzed cycloaddition of cinnamaldehyde (**1 a**) with α-ketoamide (**2 a**) using azo-

[a] *Dr. L. Wang, Q. Ni, M. Blümel, T. Shu, Prof. Dr. G. Raabe, Prof. Dr. D. Enders*
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: enders@rwth-aachen.de

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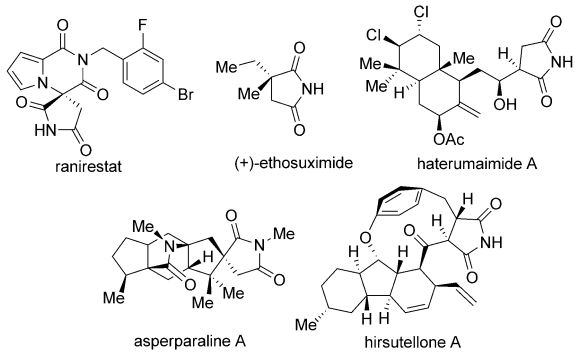


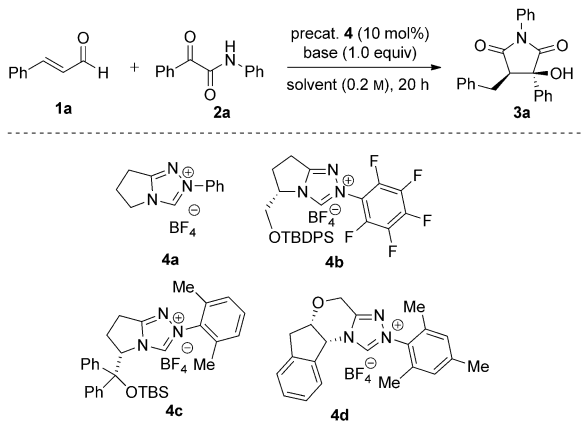
Figure 1. Typical examples of pharmaceuticals and natural products containing a succinimide moiety.

lium salt **4a** as the NHC precatalyst and K_3PO_4 as the base in CH_2Cl_2 at room temperature (Table 1, entry 1). Gratifyingly, the reaction proceeded smoothly and afforded the desired product **3a** in 34% yield. Encouraged by this result, we carried out a screening with different NHC precatalysts, which displayed remarkable effects on the outcome of the reaction (entries 2–4). To our delight, the desired succinimide **3a** could be formed in 53% yield with 99% *ee* and excellent diastereoselectivity when the precatalyst **4d** was employed (entry 4). Then we continued the optimization of the reaction conditions with base and solvent screenings (Table 1, entries 5–17). The application of organic bases such as DIPEA, DABCO, DMAP and TMEDA resulted in excellent diastereoselectivities and enantioselectivities of the desired product (Table 1, entries 6–9). Similar results were achieved with inorganic bases such as K_2CO_3. The use of other bases, such as DBU, KO*t*Bu and NaOAc, resulted in traces or no formation of the desired product (entries 5, 10 and 12). Varying the solvents led to no improvement in the reaction performance and CH_2Cl_2 was proven to be the best solvent for this transformation (entries 7 and 13–17).

With the optimal reaction conditions in hand, we started to investigate the generality of the procedure in terms of different substrates. As shown in Scheme 2, the cycloaddition of α-ketoamide (**2a**) with different α,β-unsaturated aldehydes **1**, including those bearing electron-withdrawing and electron-releasing substituents, was investigated under the optimized reaction conditions. Excellent enantioselectivities ranging from 98 to 99% *ee* and moderate to very good diastereoselectivities were obtained for all tested aldehydes (Scheme 2, **3a**–**3i**). The α-naphthyl-substituted enal also underwent the cycloaddition with excellent diastereo- and enantioselectivity (**3j**). Gratifyingly, the extension of the optimized conditions to a variety of heterocycle- or alkyl-substituted enals (**3k**–**3m**) was also successful and provided the succinimide adducts in high enantioselectivities.

The evaluation of the scope of the α-ketoamides **2** was carried out using the α,β-unsaturated aldehyde **1a** as the reaction partner under the optimized conditions (Scheme 3). A variety of α-ketoamides gave the succinimides **3n**–**3q** in good yields with excellent *ee* and high d.r. values. Notably, the introduction of different substituents at the amide nitrogen was tolerated

Table 1. Optimization of the reaction conditions.[a]



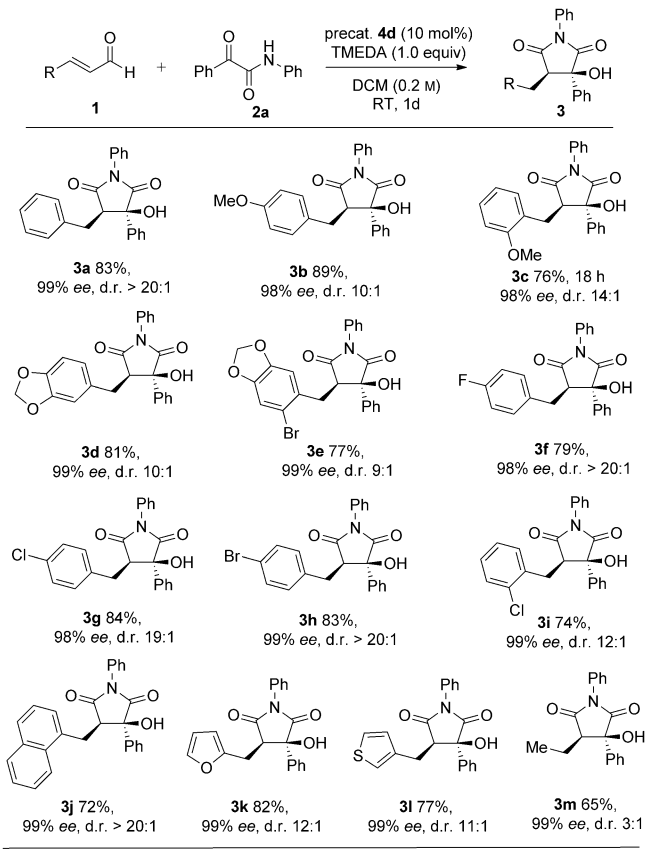
Entry	4	Solvent	Base	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4a**	CH_2Cl_2	K_3PO_4	34	15:1	–
2	**4b**	CH_2Cl_2	K_3PO_4	17	>20:1	15
3	**4c**	CH_2Cl_2	K_3PO_4	<10	n.d.	–
4	**4d**	CH_2Cl_2	K_3PO_4	53	>20:1	99
5	**4d**	CH_2Cl_2	DBU	n.r.	–	–
6	**4d**	CH_2Cl_2	DIPEA	54	>20:1	98
7	**4d**	**CH_2Cl_2**	**TMEDA**	**83**	**>20:1**	**99**
8	**4d**	CH_2Cl_2	DABCO	34	>20:1	99
9	**4d**	CH_2Cl_2	DMAP	79	>20:1	99
10	**4d**	CH_2Cl_2	KO*t*Bu	n.r.	–	–
11	**4d**	CH_2Cl_2	K_2CO_3	20	>20:1	98
12	**4d**	CH_2Cl_2	NaOAc	<10	n.d.	–
13	**4d**	MeCN	TMEDA	63	>20:1	97
14	**4d**	THF	TMEDA	55	>20:1	98
15	**4d**	dioxane	TMEDA	50	>20:1	98
16	**4d**	DCE	TMEDA	80	>20:1	99
17	**4d**	toluene	TMEDA	65	>20:1	99

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), **4** (10 mol%), base (1.0 equiv), solvent (1 mL), at RT for 20 h. [b] The yield of the isolated product **3a** after column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* value was determined by HPLC on a chiral stationary phase. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCE = 1,2-dichloroethane, DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, TMEDA = tetramethylethylenediamine, DABCO = 1,4-diazabicyclo[2.2.2]octane, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, n.r. = no reaction, n.d. = not determined.

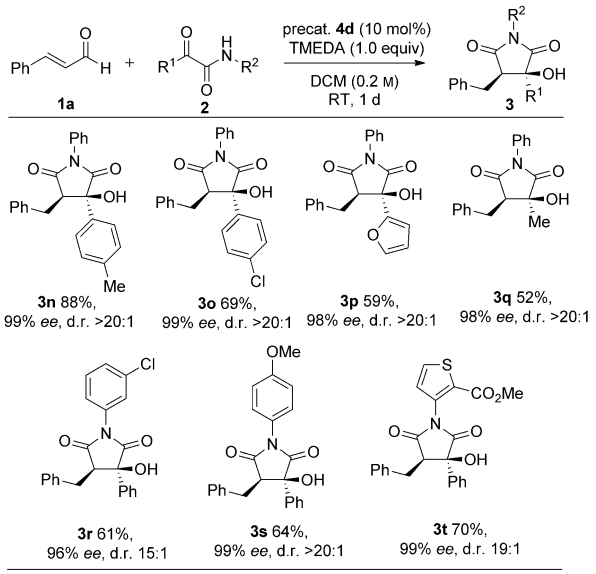
well and resulted in excellent levels of stereoselectivity (**3r**, **3s**). Furthermore, the thiophene-substituted amide also worked well for the reaction, affording the desired succinimide **3t** in good yield with excellent enantioselectivity and a high diastereoselectivity value.

An X-ray crystallographic analysis on compound **3h** was performed in order to determine the relative and absolute configuration of the succinimide products (Figure 2).[20]

Interestingly, simple changing of the NHC catalyst from **4d** to **4a** resulted in the formation of the isomeric highly substituted γ-lactones ***rac*-5**. In this transformation, the homoenolate formation was considered as the crucial step (Scheme 4). The reaction of cinnamaldehydes (**1a**, **1b**) with various α-ketoamides **2** gave the γ-lactones in moderate to good yields. However, the diastereoselectivities were poor (***rac*-5a**, ***rac*-5d**).



Scheme 2. Scope of the enals **1**. All reactions were performed on a 0.4 mmol scale. The yields of the isolated products are after column chromatography. The diastereomeric ratios were determined by ^{1}H NMR spectroscopy. The *ee* values were determined by HPLC analysis on a chiral stationary phase.



Scheme 3. Scope of the α-ketoamides. All reactions were performed on a 0.4 mmol scale. The yields of the isolated products are after column chromatography. The diastereomeric ratios were determined by ^{1}H NMR spectroscopy. The *ee* values were determined by HPLC analysis on a chiral stationary phase.

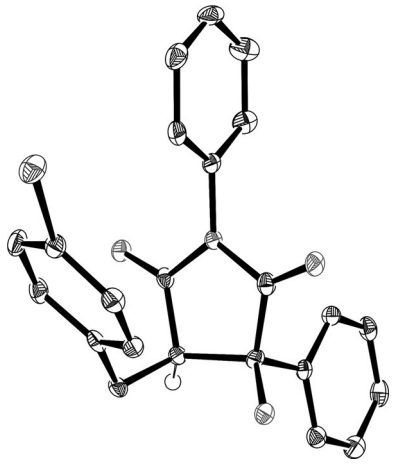
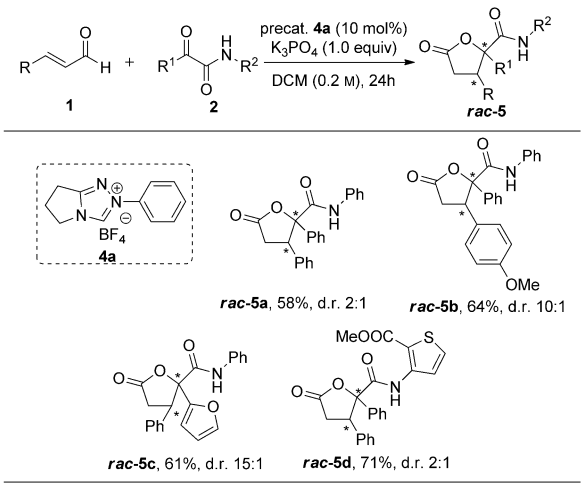


Figure 2. Crystal structure of **3h** determined by X-ray analysis.

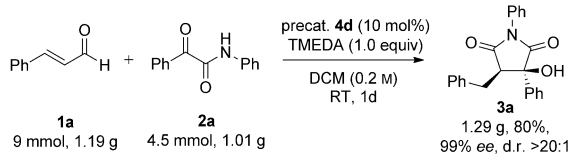


Scheme 4. Scope of the γ-lactones. All reactions were performed on a 0.4 mmol scale. The yields of isolated lactones are after column chromatography. The diastereomeric ratios were determined by ^{1}H NMR spectroscopy.

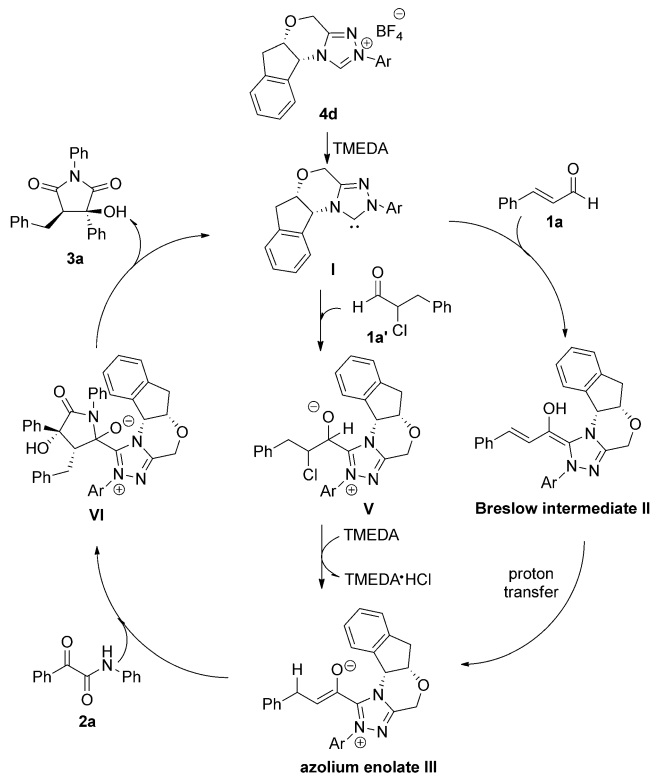
To prove the synthetic practicability of the novel asymmetric synthesis succinimides, we performed the reaction on gram-scale (4.5 mmol). Under the standard reaction conditions, the formal [3+2] reaction proceeded successfully and gave the succinimide **3a** in 80% yield (1.29 g), 99% *ee* and >20:1 d.r. (Scheme 5).

A control experiment was also carried out to advance the understanding of this [3+2] cycloaddition. Under the optimized conditions, in the absence of enal, 2-chloro-3-phenylpropanal (**1a′**) was applied to prove the enolate concept of this annulation chemistry. The annulation reaction proceeded smoothly and provided succinimide **3a** in 38% yield with excellent d.r. (>20:1) and 99% *ee*.

In agreement with the control experiment, the proposed catalytic cycle is illustrated in Scheme 6. First, the free carbene **I** is generated by deprotonation of the triazolium salt **4d**. The nucleophilic addition of the NHC organocatalyst **I** to enal **1a** results in the formation of the NHC Breslow intermediate **II**,



Scheme 5. Gram-scale reaction.



Scheme 6. Plausible catalytic cycles.

which undergoes a proton transfer to form the enolate azolium **III**. Alternatively, this intermediate can also be obtained from the NHC attack on the **1a**′ to produce adduct **V**, followed by HCl elimination. The intermediate **III** then undergoes a [3+2] cycloaddition with the α-ketoamide **2a** to form the zwitterionic azolium enolate intermediate **VI**, from which the carbene catalyst is released to form the desired succinimide **3a**.

In conclusion, we have developed an asymmetric, NHC-catalyzed formal [3+2] cycloaddition of α,β-unsaturated aldehydes with α-ketoamides. The desired succinimides are obtained in moderate to good yields with excellent enantioselectivities and moderate to excellent d.r. values. This strategy also represents a novel approach to access pharmaceutically important succinimide derivatives bearing a tetra-substituted stereogenic center. The new scalable protocol can be switched depending on the NHC catalyst used to form either the title compound or the isomer γ-lactones.

Experimental Section

A dried and argon-filled Schlenk tube was charged with α-ketoamide **2** (0.4 mmol, 1.0 equiv) and triazolium salt **4d** (0.04 mmol, 10 mol%) in 2 mL anhydrous DCM. Subsequently, the α,β-unsaturated aldehyde **1** (0.8 mmol, 2.0 equiv) and TMEDA (0.4 mmol, 1.0 equiv) were added. The mixture was stirred at room temperature until the consumption of the starting material as monitored by TLC. After purification by column chromatography on silica gel (pentane/ether 20:1 to 10:1) the desired succinimide **3** was obtained.

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[20] CCDC 1039519 (**3h**) 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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