NHC Organocatalysis

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N-Heterocyclic Carbene Catalyzed Activation of Esters: A New Option for Asymmetric Domino Reactions**

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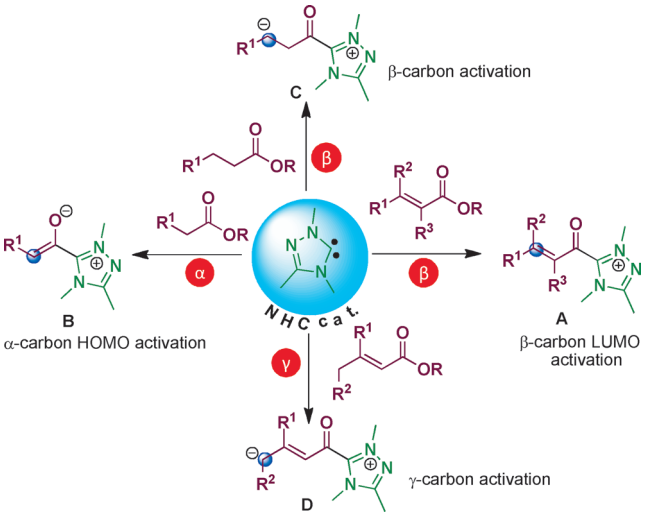
asymmetric synthesis · domino reactions · esters · N-heterocyclic carbenes · organocatalysis

In recent years we have witnessed tremendous progress in the field of asymmetric organocatalytic domino reactions due to the inherent advantages associated with these cascade sequences as well as many applications in the asymmetric synthesis of precious multifunctionalized chiral molecules including natural products and drugs.[1] Over the last five years, N-heterocyclic carbenes (NHCs) have caught up in importance with other organocatalyts in the development of new asymmetric domino transformations.[2] In particular, the organocatalytic functionalization of important carbonyl compounds such as aldehydes and ketones as well as their α,β-unsaturated variants plays a central role in the design of new asymmetric domino reactions through Lewis base catalysis employing amines or NHCs.

Esters represent a basic class of important organic carbonyl compounds that play a central role in biological and synthetic organic transformations. Whereas the organocatalytic activation of esters via iminium/enamine intermediates is not possible, NHC-mediated activation of esters for transesterification reactions were well established in the first decade of this century.[3] Only recently it has been realized that the α-, β- and γ-functionalization of esters could be achieved by using an NHC as catalyst. NHCs being Lewis basic in nature, easily add to the esters bearing a good leaving group (OR) to give more reactive species. Upon reaction with an NHC catalyst the α,β-unsaturated esters are converted to the unsaturated acyl azolium intermediates **A** (Scheme 1).[4,5] An ester bearing α-hydrogens reacts with an NHC to form, after deprotonation, the reactive enolates **B**.[6–9] It is also possible to activate the β-carbon of a saturated ester by the addition of an NHC to the ester carbonyl group, which makes it possible to use a nucleophilic species **C** for an electrophilic attack.[10] Similarly, unsaturated esters bearing a hydrogen atom at the γ-carbon are also activated by NHCs by deprotonation to form vinylogous enolates **D**.[11] The reactive intermediates **A**–**D** can then eventually be used in stereoselective domino addition/cyclization reactions with suitable substrates to form biologically interesting compounds such as lactones and lactams. Esters are therefore unique substrates for NHC-mediated transformations and exhibit several advantages like high stability and easy availability; in addition, ester substrates do not entail the use of relatively expensive oxidants in contrast to previously used substrates such as ketenes, aldehydes, enals, haloenals, ynals, and acid halides.



Scheme 1. Activation of esters by NHC catalysis. HOMO = highest occupied molecular orbital, LUMO = lowest unoccupied molecular orbital.

The use of esters as substrates in NHC-catalyzed domino reactions was reported by Lupton and co-workers in 2009, who developed the domino addition/acylation sequence between enolates and α,β-unsaturated acyl azolium intermediates, both generated from an NHC and α,β-unsaturated esters.[4] The asymmetric version of this transformation employing ester **1** as the substrate and **I** as the precatalyst provided the dihydropyranone **2** in 50% *ee* (Scheme 2). This report is regarded as a significant breakthrough, because it represents the first conjugate addition to the α,β-unsaturated acyl azolium intermediates generated from esters. The proposed mechanism involves the conjugate addition of the enolate **3** formed in parallel to **4** to generate the enolate **5**, which after proton transfer via **6** and intramolecular acylation provides the desired dihydropyranone **2**.

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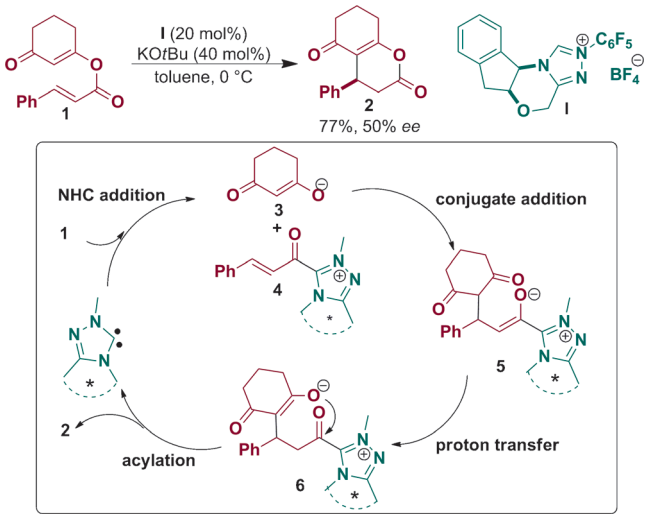
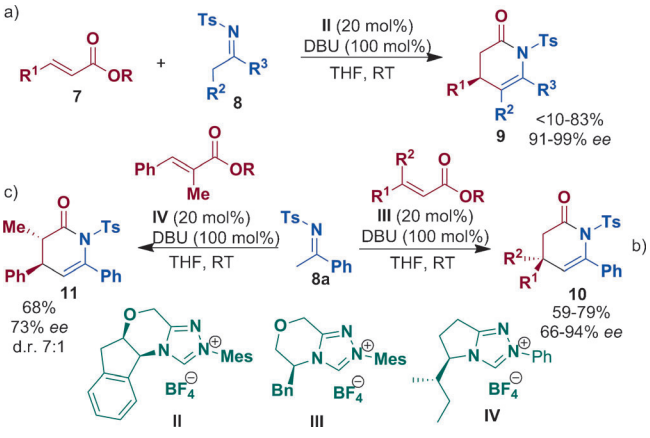


Scheme 2. NHC-catalyzed conjugate addition/acylation domino reaction to form dihydropyranones.

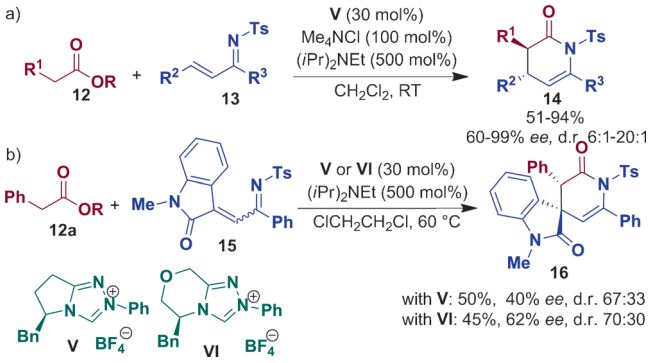
Recently, Chi's group described a similar LUMO activation of α,β-unsaturated esters **7** with NHCs by utilizing the corresponding acyl azoliums to develop a domino Michael/lactamization reaction with *N*-tosylimines **8** to give lactams **9**–**11** with high stereoselectivity (Scheme 3).[5] Various unsaturated esters **7** were converted under NHC catalysis with **II** (Scheme 3a); however, NHCs **III** and **IV** provided better



Scheme 3. Domino addition/lactamization via α,β-unsaturated acyl azolium intermediates. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, Mes = mesityl, Ts = tosyl.

results in terms of the yields and stereoselectivities of lactams **10** and **11** obtained from β-disubstituted and α-substituted esters, respectively (Scheme 3b,c). The postulated reaction pathway for these transformations involves the 1,4-addition of an enamide (formed from imine **8** under basic conditions) to the α,β-unsaturated acyl azolium intermediate **A** (Scheme 1), followed by an aza-Claisen rearrangement and a subsequent lactamization to yield the desired product. Alternatively Michael addition of **8** to **A** should be considered.

Chi and co-workers disclosed the formation of triazolium enolates **B** (Scheme 1) derived from arylacetic esters **12** under



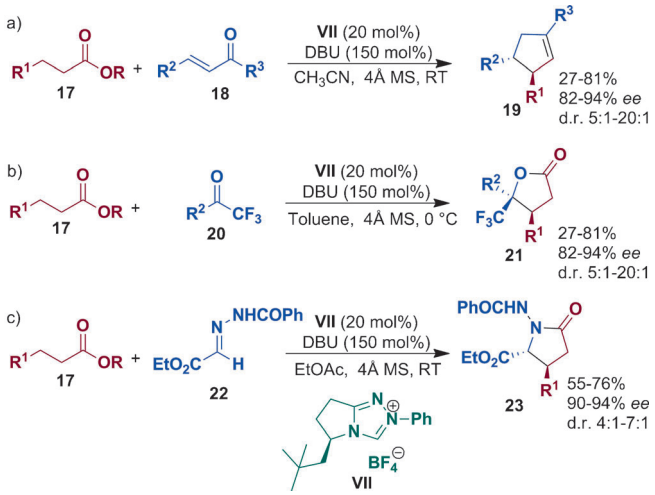
Scheme 4. Domino Michael addition/lactamization via enolates.

NHC catalysis, and their application in enantioselective domino Michael/lactamization reactions with α,β-unsaturated imines (Scheme 4).[6] With a catalytic amount of **V** the aryl esters bearing α-hydrogens reacted with various α,β-unsaturated aryl and heteroaryl imines **13** to give direct access to the corresponding δ-lactams **14** in moderate to very good yields, enantioselectivities, and diastereomeric ratios (Scheme 4a). The direct catalytic activation of aliphatic *p*-nitrophenyl esters by means of NHC organocatalysts is also possible in the same manner.[7] In addition, NHCs derived from **V** and **VI** catalyzed the domino reaction of ester **12a** with the α,β-unsaturated imine **15** obtained from isatin, providing spirooxindole **16** in moderate yield and stereoselectivity (Scheme 4b).[8] NHCs derived from **II** and **III** were used to generate acetic ester derived triazolium enolates which were applied in related Michael addition/cyclization sequences.[9]

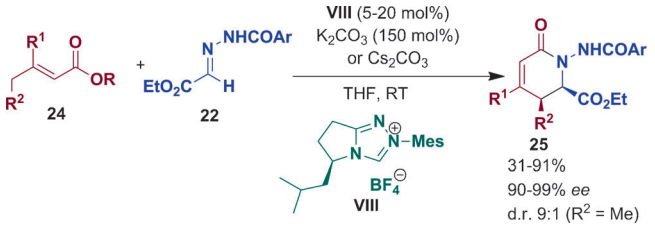
Chi and co-workers further envisaged that the activation of the β-sp^3 carbon of saturated esters as nucleophiles could be achieved through NHC organocatalysis.[10] The NHC- and DBU-generated nucleophilic β-carbons undergo enantioselective domino reactions with electrophiles such as enones, ketones, and hydrazones (Scheme 5). Domino reactions of saturated esters **17** with enones **18** catalyzed by NHC **VII** proceeded by a Michael/aldol/lactonization sequence followed by decarboxylation to afford the corresponding cyclopentenes **19** in acceptable to very good yields and high stereoselectivities (Scheme 5a). The β-ester activation strategy was further extended to develop domino 1,2-addition/lactonization or lactamization sequences with trifluoromethyl ketones **20** and hydrazones **22** to give the corresponding lactones **21** and lactams **23** with moderate to good stereocontrol (Scheme 5b,c).

Very recently, the direct γ-carbon functionalization of α,β-unsaturated esters **24** through NHC catalysis has been reported.[11] The NHC precatalyst **VIII** generated the vinylogous triazolium enolate **D** (Scheme 1) and underwent an asymmetric 1,2-addition/lactamization sequence with the hydrazones **22** to provide the δ-lactams **25** with excellent stereoselectivities (Scheme 6). The δ-lactams **25** served as precursors for a four-step synthesis of the corresponding pipecolic acid derivatives.

These recently reported organocatalytic one-pot sequences summarized in this Highlight impressively demonstrate the great synthetic potential of the rapidly growing field of



Scheme 5. Domino reactions via β-activated esters.



Scheme 6. Domino reactions via γ-activated esters.

asymmetric NHC organocatalysis. The selective and flexible α-, β-, and γ-activation of simple and easily available esters as substrates constitutes an important improvement and will pave the way for new asymmetric domino reactions.

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