Michael Addition

DOI: 10.1002/anie.200701079

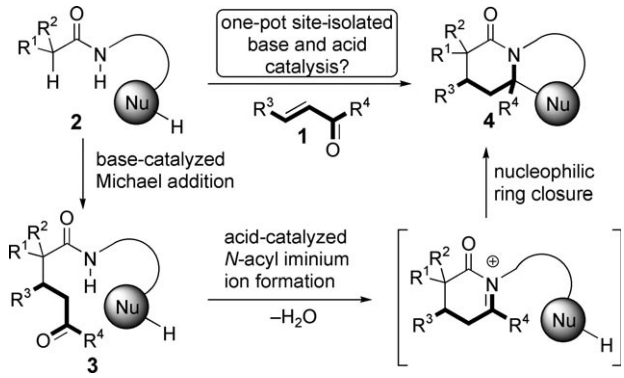
Site-Isolated Base- and Acid-Mediated Michael-Initiated Cyclization Cascades**

*Adam W. Pilling, Jutta Boehmer, and Darren J. Dixon**

Cascade reactions are attractive in modern synthetic strategies as they enable several bond-forming events to occur in the same reaction vessel without the necessary drain of resources associated with one-reaction, one-pot approaches.[1] This allows rapid and efficient syntheses of complex molecules from relatively simple starting materials whilst minimizing cost and waste, and thus, the impact of the chemistry on the environment. Many examples involving cascade sequences catalyzed by a single chemical entity have been reported.[1] However, those involving more than one mutually compatible catalyst are much less common.[2] Furthermore, the use of site-isolated catalysts that would otherwise be mutually destructive and thus ineffective in solution phase to facilitate reaction cascades is in its infancy.[3]

Although pioneered around 30 years ago by Cohen et al.,[4] recent papers reporting new ways of preventing mutual deactivation of reagents have brought site isolation to the forefront again.[5,6] Reported sequences have included acid- and base-catalyzed condensation of carbonyl compounds with active methylene compounds to form electron-deficient alkenes, which are subsequently attacked by a nucleophilic reagent or reduced by using hydrogen over a palladium catalyst. However, to date the concept has not been exploited to generate complex molecular structures and accordingly, we believed the true synthetic power of cascades catalyzed by both basic and acidic reagents in one pot was still to be realized.

By combining a base-catalyzed intermolecular Michael addition reaction of an α,β-unsaturated carbonyl compound **1** and a suitable amide pronucleophile **2** with an acid-catalyzed intramolecular *N*-acyl iminium ion cyclization[7] of the resulting adduct **3**, we believed site isolated base and acid (SIBA) catalysis could be exploited to form structurally complex multiring heterocyclic molecules **4** in one pot and under mild conditions (Scheme 1). With five points of diversity present in the reaction products, this procedure could be a powerful tool for both library generation and target synthesis. Herein we present our findings.



Scheme 1. Concept of combining a base-catalyzed Michael addition with an acid-catalyzed *N*-acyl iminium ion cyclization for a one-pot complex heterocycle synthesis.

Proof-of-principle studies were required to determine the necessity and feasibility of the SIBA catalysis cascade. β-Keto amide **5** containing an acidic methine group and pendant nucleophilic pyrrole substituent was chosen as a test substrate. When a dichloromethane solution of **5** and methyl vinyl ketone **6** (1.1 equiv) at room temperature was treated with PS-BEMP[8] (10%), Michael adduct **7** was formed as the sole reaction product in an excellent yield.[9] When the reaction was repeated by using Amberlyst A15 (200%) in the presence or absence of liquid BEMP (10%), the only observed reaction product was substituted pyrrole **8** in 68% yield; **7** was not present in the reaction mixture. However, when the reaction was repeated by using a combination of PS-BEMP (10%) and Amberlyst A15 (200%), the sole reaction product was the desired tetracyclic product **9** produced in 83% yield as a 1:1 mixture of diastereoisomers (Scheme 2). By using substoichiometric quantities of PS-BEMP (10%) and Amberlyst A15 (50%), an 85% conversion to tetracyclic product **9** after 5 days was produced. These results demonstrate that: a) base catalysis is required for the β-keto amide Michael addition; b) under acidic conditions, a Michael addition of the pyrrole ring occurs but at a significantly lower rate; c) BEMP is effectively quenched by Amberlyst A15; d) Michael adduct **7** will, through an *N*-acyl iminium ion intermediate, cyclize to tetracycle **9** under acidic conditions but not basic conditions; e) PS-BEMP and Amberlyst A15 can operate as mutually compatible strongly basic and strongly acidic reagents, respectively, in the same vessel to facilitate the Michael-initiated *N*-acyl iminium ion cyclization cascade.

With proof of concept established and the desired product isolated in high yield, the scope of the reaction cascade was

[*] A. W. Pilling, Dr. D. J. Dixon
School of Chemistry
The University of Manchester
Oxford Road, Manchester M13 9PL (UK)
Fax: (+44) 161-275-4939
E-mail: Darren.Dixon@man.ac.uk
Dr. J. Boehmer
Syngenta
Jealott's Hill International Research Centre
Bracknell, Berkshire RG42 6EY (UK)

[**] We thank EPSRC and Syngenta for a studentship (to A.W.P.).
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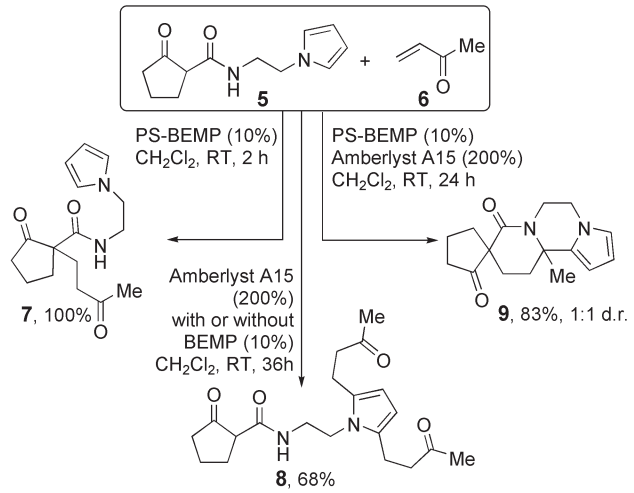
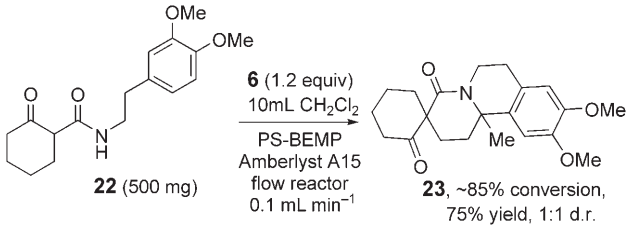


Scheme 2. Feasibility study on SIBA-mediated Michael-initiated *N*-acyl iminium ion cyclization cascades.

surveyed by probing changes to the amide pronucleophile, the α,β-unsaturated carbonyl, and the *N*-acyl iminium ion trap. The results of the reactions facilitated by PS-BEMP (10%) and Amberlyst A15 (200%) in CH_2Cl_2 at room temperature are presented in Scheme 3. The amide pronucleophile could be: a cyclic β-keto amide with ring size ranging from 5–7 (no other ring sizes were tested); an acyclic β-keto amide; or a malonamide. Methyl vinyl ketone, ethyl vinyl ketone, acrolein, and crotonaldehyde all participated in the sequence and typically gave their respective products in high yields. The *N*-acyl iminium ion nucleophilic trap could be an electron-rich aromatic ring, an electron-rich heterocycle (indole, pyrrole), an alkene, and even a *tert*-butoxycarbonyl (Boc)-protected amine. In all cases, the reactions were complete within 24 h and the products were isolated in good to excellent yields.

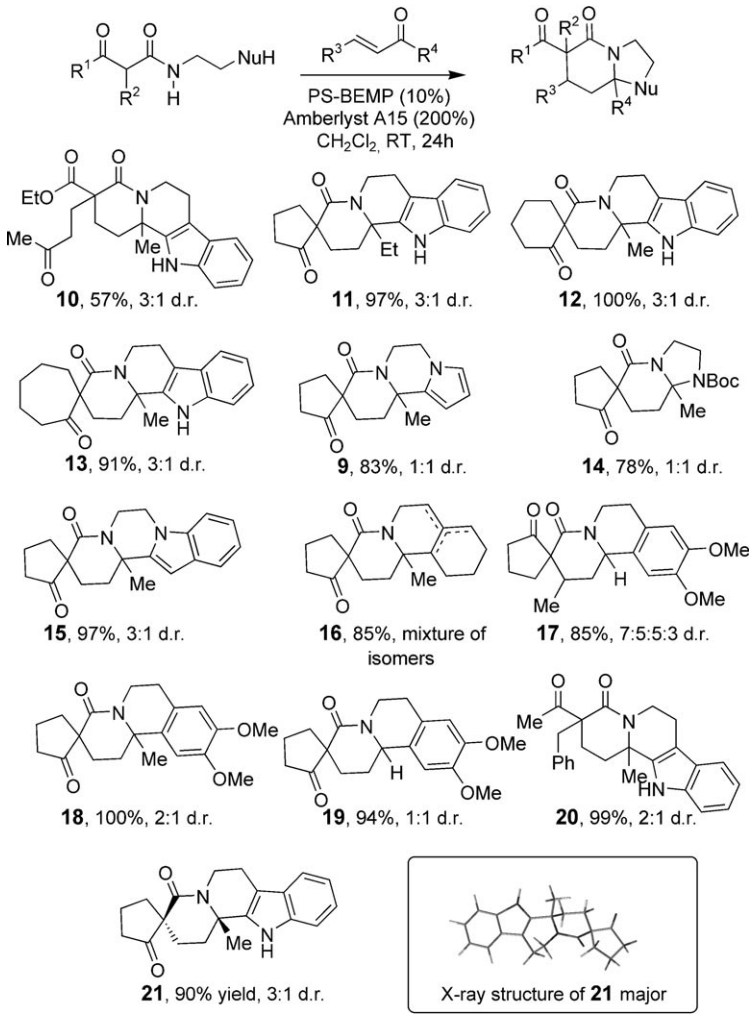
Notably, the reactions resulted in products in which a new 6,6-bicyclic ring system containing at least two new stereogenic centres was created. Both stereogenic centres may be fully substituted and when an indole was used as the nucleophilic trap, stereoselectivities up to 3:1 were observed. In **21**, the stereochemistry of the major diastereomer (unambiguously determined by single-crystal X-ray diffraction) suggested that where diastereocontrol was witnessed, the major product results from attack of the π-nucleophile from the opposite face of the *N*-acyl iminium ion to the carbonyl group of the ketone.

The benefits of having site-isolated acidic and basic reagents can be exploited further in a flow reactor apparatus,[10] which is ideal for scaling up reactions and for recovery of catalysts. One column containing solely PS-BEMP and another containing solely Amberlyst A15 were connected in series and a dichloromethane solution of ketoamide **22** and methyl vinyl ketone **6** was passed through at 0.1 mL min^{-1}. The reaction product was isolated in 75% yield on a 500-mg scale after a single pass (Scheme 4).



Scheme 4. Michael-initiated *N*-acyl iminium ion cyclization cascade by using a flow-reactor apparatus.

In conclusion, SIBA catalysis has been exploited in one-pot base-catalyzed Michael addition, acid-mediated *N*-acyl iminium ion cyclization cascades with amide pro-nucleophiles, and α,β-unsaturated carbonyl compounds. The reaction has broad scope, is atom efficient (water is the only by-product), and can be scaled by way of a flow reactor to



Scheme 3. Scope of the SIBA-mediated Michael-initiated *N*-acyl iminium ion cyclization cascade.

produce significant quantities of multiring heterocyclic products.

Further, one-pot reaction-cascade sequences catalyzed by site-isolated chemical entities, which would otherwise be mutually destructive in solution, are under investigation and the results will be reported in due course.

Experimental Section

General Method for cascade reactions: Starting material (0.20 mmol), PS-BEMP (9.0 mg, 0.02 mmol), and Amberlyst A-15 (85.0 mg, 0.40 mmol) were stirred in dichloromethane (2 mL) at room temperature. Michael acceptor (0.22 mmol) was added through a syringe and the mixture was stirred at room temperature until all starting material had been consumed as indicated by thin-layer chromatography. The polymers were removed through filtration and the filtrate was passed through a 2-cm plug of silica and concentrated to dryness to give an essentially pure mixture of diastereomers. Further chromatography allowed isolation of a small amount of the major diastereomer for characterization where possible.

Received: March 12, 2007
Published online: June 11, 2007

Keywords: cascade reactions · cyclization · iminium ions · Michael addition

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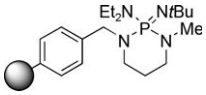

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