Site isolated base and acid catalyzed azaspirocyclization cascades†

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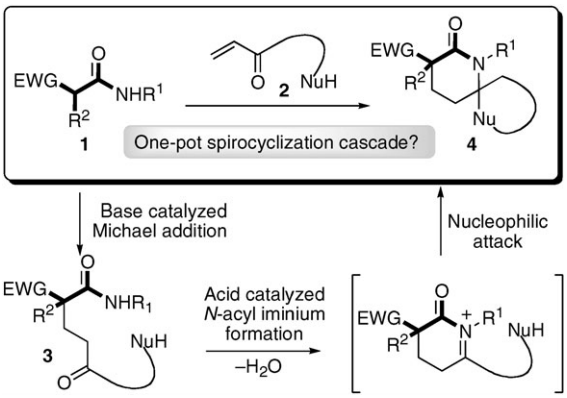
A one-pot, site isolated base (PS-BEMP) and acid (Si-TsOH) catalyzed cyclization cascade to azaspirocyclic molecules is reported; the reaction is simple to perform, atom efficient (water is the only byproduct) and broad in its scope to a diverse range of azaspirocyclic products.

The desire for practically simple and synthetically efficient organic transformations has led to the development of many new innovative strategies and concepts. Cascade reaction strategies allow rapid and efficient synthesis of complex molecules from relatively simple starting materials by enabling several bond-forming events to occur in the same reaction vessel. This also negates the necessary drain of resources associated with one-reaction, one-pot approaches. A myriad of elegant cascade sequences catalyzed by single chemical entities has been reported[1] but those involving more than one mutually compatible catalyst are much less common.[2] Furthermore, the concept of anchoring mutually destructive reagents onto solid supports (known commonly as *site isolation*) to allow their simultaneous use in one-pot cascade sequences has still to be fully exploited.[3] Despite some recent advances concerning the types of materials that provide the solid support required to permit such reaction cascades,[4] the organic transformations achieved by the cascades themselves have been largely limited to deprotections and condensations.

Realizing the potential of site-isolated reagents for facilitating multistep reaction sequences, we recently reported a new cyclization cascade mediated by strongly basic and strongly acidic reagents for the one-pot construction of complex polyheterocyclic molecules.[5] In an advancement of this work, here we present the use of two site isolated catalysts for the efficient one-pot formation of complex azaspirocyclic compounds. The concept of the cascade is shown in Scheme 1. In a base catalyzed process, a carboxamide pro-nucleophile **1** should undergo a Michael addition reaction with an enone Michael acceptor **2** bearing a tethered π-nucleophilic trapping group. The Michael adduct **3** is then poised to undergo an acid catalyzed *N*-acyl iminium ion formation/trap sequence.[6] Combining these two powerful reactions through the site isolation concept should allow direct access to the azaspirocycle motif **4**,

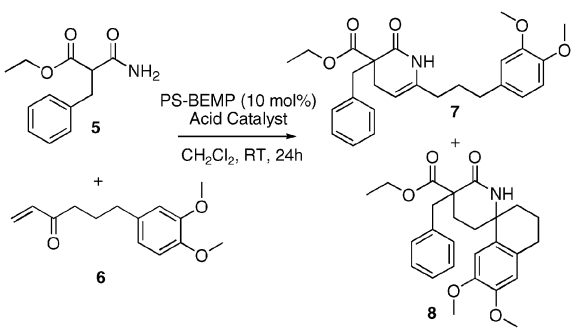


Scheme 1 Site isolation catalysis: combining a base catalyzed Michael addition with an acid catalyzed *N*-acyl iminium ion cyclization.

the core structure of numerous natural product targets,[7] in one pot.

In our previous studies, super-stoichiometric amounts of Amberlyst® 15 resin (2 equiv.) were required for satisfactory reaction rates in the acid mediated cyclization step. Therefore our primary objective was to find conditions that would allow the proposed azaspirocyclization cascade to proceed using catalytic quantities of both solid-supported base and solid-supported acid. Commercially available PS-BEMP[8,9] had

Table 1 Proof of principle and acid screen of Michael addition/*N*-acyl iminium ion cyclization cascade



Acid	Loading	Product(s) (yield)
Amberlyst® 15	10 mol%	**7** (74%)
MP-TsOH II	10 mol%	**7** (71%)
K10 montmorillonite	100 mass%[a]	**7** (6%), **8** (61%)
KSF montmorillonite	100 mass%[a]	**7** (9%), **8** (70%)
Si-TsOH	10 mol%	**8** (85%)

[a] 100 mass% refers to 1 mg of montmorillonite per 1 mg of **5**.

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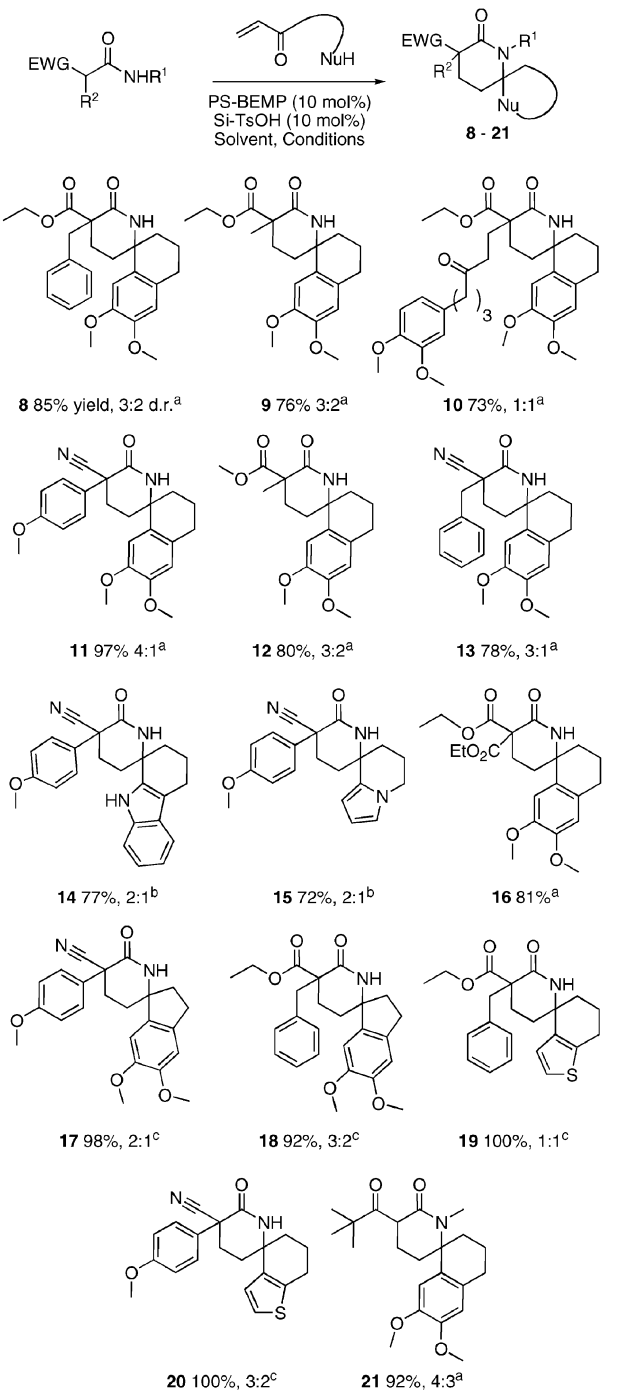
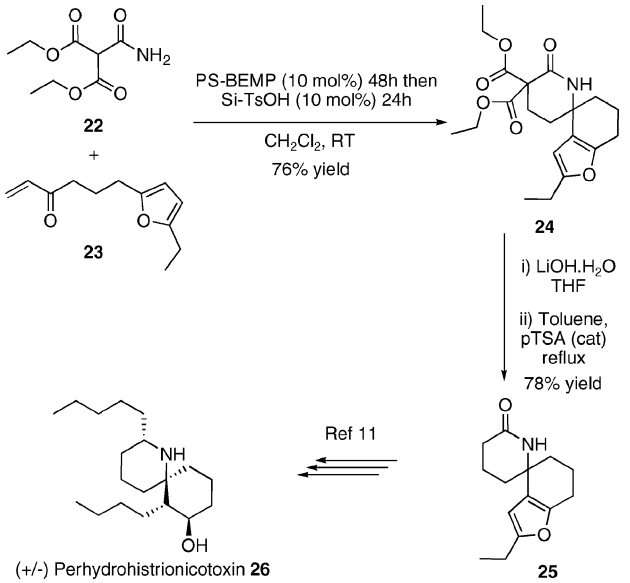
† Electronic supplementary information (ESI) available: Experimental procedures, and spectral data for compounds **7–21**, **24** and **25**. See DOI: 10.1039/b716568d



Scheme 2 Library of azaspirocyclic compounds generated *via* the catalytic cascade.

already proven to be a very efficient basic catalyst for Michael additions and thus was employed here.

Accordingly, proof of principle studies were combined with an acid screen in the reaction of malonamate **5** with enone **6** in the presence of PS-BEMP (10%) and acid catalyst in dichloromethane at room temperature for 24 h. The results are summarized in Table 1.‡ Amberlyst® 15 and MP-TsOH II proved to be ineffective, giving only the enamide intermediate **7**, whilst K10 and KSF montmorillonite clays gave unsatisfactory yields. Pleasingly, the use of Si-TsOH[10] (10 mol%) gave smooth conversion to the desired azaspirocycle **8** in 85% yield.



Scheme 3 Formal total synthesis of (±)-perhydrohistrionicotoxin.

With proof of concept established and the desired product isolated in good yield, the scope of the reaction cascade was probed. Four points of diversity (the electron withdrawing group, C-2 substituent and *N*-substitution of the Michael donor, and the *N*-acyl iminium ion trap) were identified and systematically varied to establish the breadth of the sequence. The results are presented in Scheme 2.‡ The Michael donor can be a malonamate, β-keto amide or cyanoacetamide; the C-2 substituent can be methyl, benzyl, *p*-methoxy phenyl or ester; *N*-methyl and primary amides can be used and dimethoxy phenyl, indole, pyrrole and thiophene traps can be employed to generate 6,6 or 6,5 azaspirocyclic frameworks.

The utility of this reaction was further demonstrated in the formal total synthesis of (±)-perhydrohistrionicotoxin **26** (Scheme 3). When diester **22** was treated with enone **23** in the presence of PS-BEMP then Si-TsOH in the same reaction vessel, smooth conversion to adduct **24** was observed.‡ Subsequent double ester hydrolysis and decarboxylation furnished known spirocyclic lactam **25**,[11] the formation of which constitutes a formal total synthesis of (±)-perhydrohistrionicotoxin.

In conclusion, the concept of site isolation has been exploited in one-pot base catalyzed Michael addition–acid catalyzed *N*-acyl iminium ion spirocyclization cascades to generate a series of complex azaspirocycles. The reaction has broad scope, is atom efficient (water is the only byproduct) and its utility has been demonstrated in a formal total synthesis of (±)-perhydrohistrionicotoxin.

Further developments of these reaction sequences requiring both acid and base catalysts are ongoing and will be reported in due course.

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Notes and references

‡ Michael donors represented by **1** were synthesised by alkylation of commercially available malonamates and cyanoacetamides following

the relevant procedure in ref. 12. Michael acceptors represented by **2** were synthesised from the corresponding commercially available carboxylic acids *via* transformation to the Weinreb amide (ref. 13) and subsequent addition of vinyl magnesium bromide (ref. 14). **22** was synthesised from ethyl malonamate and ethyl chloroformate following the relevant procedure in ref. 15 and **23** was synthesised in three steps from 2-ethylfuran (ref. 16).

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