# Highly enantio- and diastereoselective organocatalytic cascade aza-Michael–Michael reactions: a direct method for the synthesis of trisubstituted chiral pyrrolidines†

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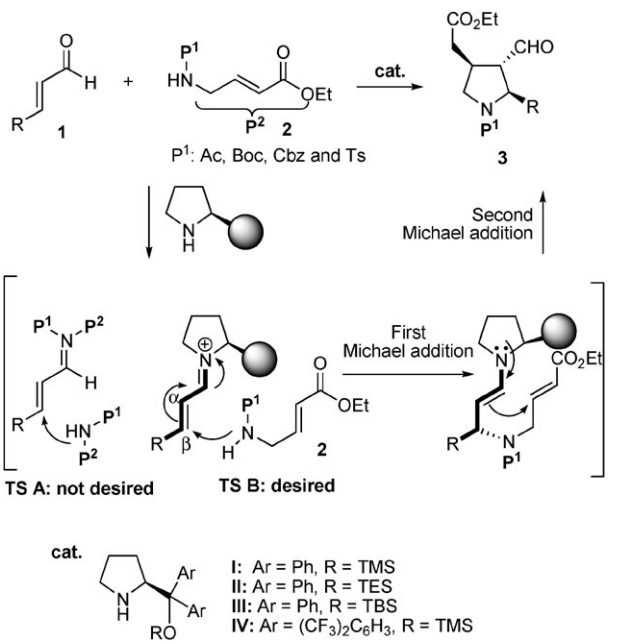
**An unprecedented highly enantio- and diastereoselective cascade aza-Michael–Michael reaction of α,β-unsaturated aldehydes with *trans*-γ-Ts protected amino α,β-unsaturated ester has been developed; the simple and practical process, efficiently catalyzed by chiral diphenylprolinol TMS ether, serves as a powerful access to highly functionalized trisubstituted chiral pyrrolidines.**

Substituted chiral pyrrolidines are ubiquitous structural components of numeous naturally occurring alkaloids and biologically active synthetic substances.[1] For example, trisubstituted pyrrolidines are represented in natural products neuroexcitatory amino acids (−)-kainic acid and (+)-α-allokainic acid,[2] promising a new anti-cancer agent ABT-627,[3] and influenza drug A-192558.[4] In addition, the "privileged" structures are an important synthetic target in diversity oriented synthesis.[5] Despite their broad applications, synthetic methods for the efficient preparation of chiral pyrrolidines are highly limited. The state of the art in chiral pyrrolidine synthesis prevalently relies on chiral auxiliary controlled asymmetric synthesis and transition-metal-catalyzed asymmetric dipolar addition reactions.[6] In contrast, organocatalyzed asymmetric processes are largely undeveloped. Only three related examples of employing organocatalyzed enantioselective [3+2] cycloaddition strategy were disclosed recently by Vicario, Córdova and Gong, respectively.[7] Furthermore, the asymmetric catalytic synthesis of trisubstituted densely functionalized chiral pyrrolidines remains elusive and the discovery of catalytic asymmetric reactions that yield such a framework is an important challenge.

In this communication, we wish to report a new organocatalytic cascade aza-Michael–Michael process that directly converts simple achiral substrates to highly fuctionalized trisubstituted chiral pyrrolidines with high levels of enantio- and diastereoselectivity.[8–10] The reactions are accomplished with remarkable efficiency by a simple chiral diphenylprolinol silyl ether as promoter. This one-pot transformation produces a complex molecular architecture formed with high stereocontrol of three new stereogenic centers and an array of exploitable orthogonal functionality for further synthetic elaboration.

Central to the implementation of new proposed cascade aza-Michael–Michael reaction was the recognition of several reactivity and selectivity issues that must be addressed (Scheme 1). First, although "N"-centered nucleophile has been employed for conjugate addition reactions, the more active specific species was required as a result of its weak nucleophilicity.[11] Second, the amine in **2** should not function as catalyst for the formation of iminium (TS **A**), and must serve as nucleophile for conjugate addition to the catalyst activated iminium (*e.g.* TS **B**). Third, the substrate amine ester **2** should be stable during the reaction without undergoing intramolecular lactamization. Consequently, in considering these parameters, we designed a *trans* 4-amino protected α,β-unsaturated ester **2**. The protected amino group (*e.g.* amides, carbamates or sulfonamides) inhibited forming an iminium with enal **1**, while the enhanced acidity rendered it to be readily deprotonated under basic conditions to produce a more nucleophilic nitrogen anion for the first Michael addition reaction. Moreover, the *trans*-geometry could significantly




**Scheme 1** Proposed mechanism for the asymmetric aza-Michael–Michael process promoted by an organocatalyst.

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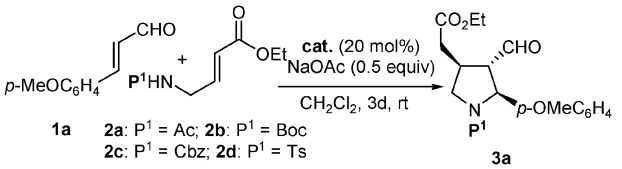
**Table 1** Optimization of organocatalytic enantioselective aza-Michael–Michael addition reactions[a]

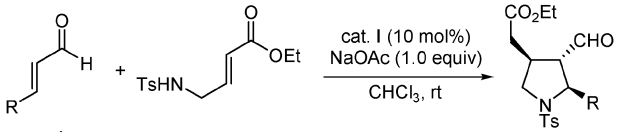



1a 2a: $P^1$ = Ac; 2b: $P^1$ = Boc; 2c: $P^1$ = Cbz; 2d: $P^1$ = Ts → 3a

| Entry | Cat | $P^1$ | Yield (%)[b] | ee (%)[c] | dr[d] |
|---|---|---|---|---|---|
| 1 | **I** | Ac | 0 | ND[e] | ND[e] |
| 2 | **I** | Boc | 0 | ND[e] | ND[e] |
| 3 | **I** | Cbz | 0 | ND[e] | ND[e] |
| 4 | **I** | Ts | 83 | 93 | 15 : 1 |
| 5 | **II** | Ts | 78 | 91 | 13 : 1 |
| 6 | **III** | Ts | 75 | 87 | 14 : 1 |
| 7 | **IV** | Ts | <5 | ND[e] | ND[e] |

[a] Unless otherwise specified, to a solution of *trans*-4-methoxycinnamaldehyde **1a** (32 mg, 0.2 mmol) in the presence of catalyst (20 mol%) and NaOAc (8.2 mg, 0.1 mmol) in $CH_2Cl_2$ (0.5 mL) was added **2** (0.1 mmol) and the resulting solution was stirred for 3 d at rt. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Chiralcel OD-H). [d] Determined by $^1$H NMR. [e] Not determined.

**Table 2** Catalyst **I** promoted cascade aza-Michael–Michael reactions for one-pot synthesis of chiral pyrrolidines[a]




1 2d → 3

| Entry | R | 3 | *t*/d | Yield (%)[b] | ee (%)[c] | dr[d] |
|---|---|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4$ | **3a** | 4 | 92 | >99[e] | >30 : 1 |
| 2 | 3-$MeOC_6H_4$ | **3b** | 3 | 91 | >99[e] | 30 : 1 |
| 3 | 2-$MeOC_6H_4$ | **3c** | 4 | 90 | 96 | 7.5 : 1 |
| 4 | Ph | **3d** | 3 | 94 | >99 | 21 : 1 |
| 5 | 3-MeO-4-$AcC_6H_3$ | **3e** | 4 | 88 | 96[e] | 27 : 1 |
| 6 | 4-$CF_3C_6H_4$ | **3f** | 4 | 92 | >99 | 12 : 1 |
| 7 | 4-$NO_2C_6H_4$ | **3g** | 4 | 85 | >99 | 10 : 1 |
| 8 | 3-$NO_2C_6H_4$ | **3h** | 3 | 80 | >99 | 7 : 1 |
| 9 | 4-$CNC_6H_4$ | **3i** | 3 | 89 | >99 | >30 : 1 |
| 10 | 4-$FC_6H_4$ | **3j** | 4 | 85 | >99[e] | 14 : 1 |
| 11 | 4-$BrC_6H_4$ | **3k** | 4 | 90 | >99 | 18 : 1 |

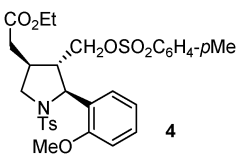
[a] Reaction conditions: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H, AD, OJ-H, or Chiralcel OD-H). [d] Determined by $^1$H NMR. [e] Converted to enone *via* reacting product aldehyde with $Ph_3P$=CHCOPh for chiral HPLC analysis.

reduce intramolecular lactamization. With respect to the catalysts, we reasoned that sterically bulky catalysts such as chiral diarylprolinol ethers **I–IV** would be of choice due to their established capacity to effectively participate in iminium activation with enals and create high stereo-control.[12]

Our orienting experiments were performed with *trans*-cinnamaldehyde **1a** with *trans* γ-*N*-protected α,β-unsaturated esters **2** in the presence of diphenylprolinol silyl ether catalyst **I** and NaOAc as base (Table 1). The preliminary studies revealed that the reaction efficiency highly depended on the protection form of the nitrogen nucleophile (entries 1–4). No reaction occurred with Ac, Boc and Cbz whereas a promising result was obtained when Ts was used. This indicated that the nucleophilicity of the nitrogen was critical for the cascade process. The strong electron-withdrawing capacity of Ts group rendered the NH more acidic and thus readily generating more nucleophilic nitrogen anion under basic conditions. Furthermore, notably we did not observe the lactamization reaction in **2**. The subsequent survey of different chiral organocatalysts disclosed that similar results were achieved with catalysts **II** and **III** (entries 5–6). However, the process proceeded very poorly with **IV** (entry 7).

In further optimization of reaction conditions, we focused on varying reaction parameters including base, solvent and catalyst loading (see ESI† for detail). In these experiments, the optimal results with respect to reaction time, yields, enantio- and diastereoselectivity of the aza-Michael–Michael reaction were obtained when the reaction cascade was performed with 10 mol% **I** in $CHCl_3$ using 1.0 equiv. of NaOAc.

As revealed in Table 2, the cascade process serves as a general approach to the preparation of highly functionalized trisubstituted chiral pyrrolidines. Significantly, three new stereogenic centers are created in a one-pot transformation in high yields (80–94%) and with excellent levels of enantioselectivities (96–>99% ee) and high diastereoselectivities (7 : 1 to >30 : 1 dr). Significant structural variation of α,β-unsaturated aldehydes can be tolerated. The electronic nature of the aryl rings of α,β-unsaturated aldehydes **1** has apparently limited influence on the stereochemical outcome. The reaction system is inert to the electronic effect, as evidenced that in all cases, extremely high enantioselectivity (96–>99% ee) and high diastereoselectvity (up to >30 : 1) are observed regardless of electron-donating (entries 1–3), neutral (entry 4), combination of electron-donating and withdrawing (entry 5) and withdrawing (entries 6–11) substituents tested. Probing the steric effect on the enantio- and diasteroselectivity of the cascade processes indicates that such impact is also minimal (96% ee, 7.5 : 1 dr, entry 3). The relative and absolute configuration of product **3c** is determined by the X-ray crystal structural analysis based on its derivative **4** (Fig. 1).[13]




**4**

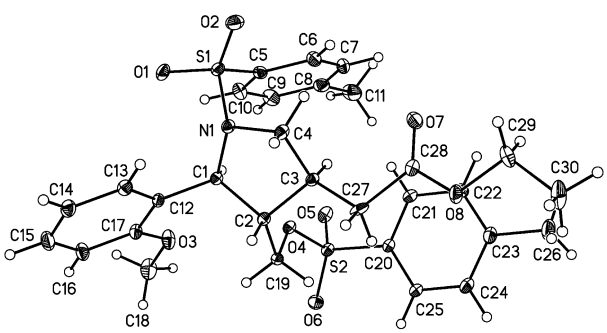



**Fig. 1** X-Ray crystallographic structure **4**.

In conclusion, driven by the lack of an efficient method for the preparation of synthetically significant trisubstituted chiral pyrrolidines, we have uncovered an unprecedented organocatalytic, highly enantioselective cascade aza-Michael–Michael reaction. The process is efficiently catalyzed by readily available (*S*) diphenylprolinol TMS ether to give trisubstituted synthetically useful, highly functionalized chiral pyrrolidines.[14] The scaffold serves as an efficient starting point for further synthetic manipulation in total synthesis of natural products, biologically significant therapeutics and the diversity oriented library synthesis. Moreover, in principle, the cascade strategy can be exploited for the synthesis of synthetically and medicinally important chiral piperidines. These represent our future endeavour aimed at demonstrating the synthetic utility and expanding the scope of the powerful domino processes.

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13 CCDC-693305 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk and supporting information†.

14 We carried out a 1 g scale of reaction of **1a** with **2d** in the presence of **I** (10 mol%) and NaOAc (1.0 equiv.) in $CHCl_3$ for 4 d to afford **3a** in 93% yield, >99% ee and >30 : 1 dr.

 