Organocatalysis

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# Synthesis of Highly Functionalized Chiral Cyclopentanes by Catalytic Enantio- and Diastereoselective Double Michael Addition Reactions**

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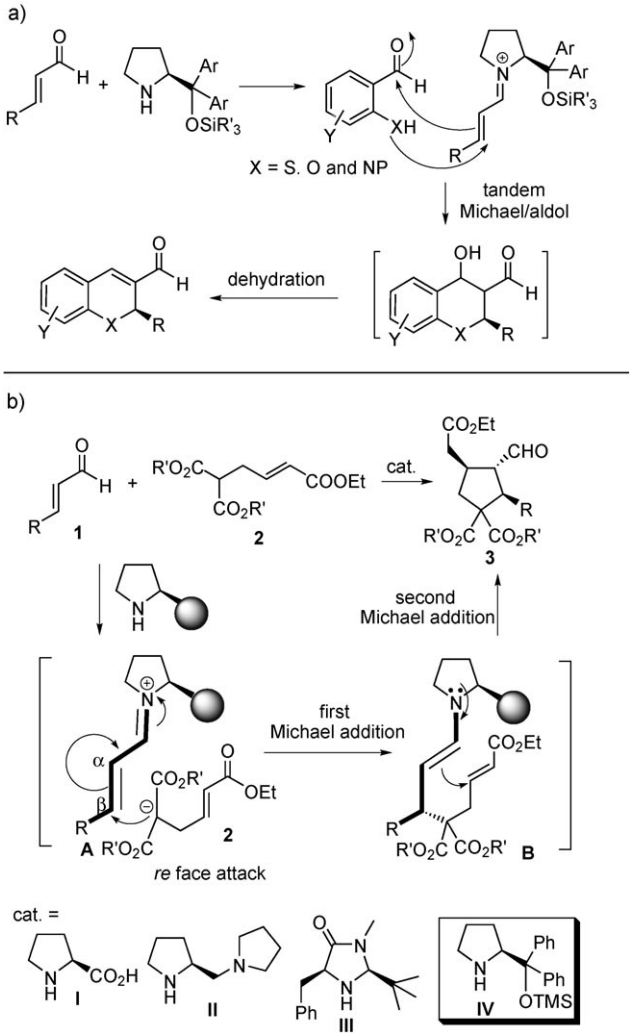
Reactions that involve the formation of C–C bonds are considered the most important processes in organic synthesis. Cascade reactions that involve the production of multiple C–C bonds and multiple stereogenic centers in a single manipulation are a particularly appealing strategy in the rapid construction of complex molecular architectures because of their operational simplicity, atom economy, low use of energy, and minimization of chemical waste.[1] While significant progress has been made in the use of chiral precursors for stereocontrol, the development of catalytic enantio- and diastereoselective cascade reactions has proven to be a challenging task.[1] Notably the recent development of organocatalytic asymmetric domino reactions based on chiral small molecules has been hotly pursued.[2–5]

Recently, we and the research group of Córdova simultaneously described enantioselective cascade sulfa-, oxa-, and aza-Michael/aldol/dehydration reactions promoted by chiral secondary amines (Scheme 1a).[6,7] We envisioned that the employment of a nucleophilic carbon atom instead of heteroatoms S, O, and N for the initial Michael addition could enable the generation of two new C–C bonds. Furthermore, change of the aldehyde group to an α,β-unsaturated ester **2** as the electrophile, which allows for a second conjugate addition reaction, would produce a new cascade double conjugate addition process (Scheme 1b).[8,9] To the best of our knowledge, such a process has not been described to date.[10] Significantly, the cascade process would afford a product with the formation of three stereogenic centers rather than one, which was observed in the Michael/aldol/dehydration sequence (Scheme 1a). Herein we wish to report the results of an investigation that has led to a novel organocatalytic diastereo- and enantioselective cascade double Michael reaction, in which two C–C bonds and three contiguous stereogenic centers are efficiently created in a one-pot transformation with a high control of relative and absolute stereochemistry. This new catalytic methodology serves as a facile approach to synthetically useful, highly functionalized chiral cyclopentanes.[11]




***Scheme 1.*** Organocatalytic, enantioselective Michael initiated cascade reactions: a) the cascade Michael/aldol/dehydration reaction, and b) the cascade double Michael reaction. X = S, O, or NPG, PG = protecting group, TMS = trimethylsilyl, sphere = chiral side chain.

The design of a catalytic cascade double Michael addition reaction required the consideration of several factors. The reactivity of the α,β-unsaturated system in **2** that participates in the second conjugate addition reaction must be high enough to allow for the intramolecular Michael reaction, but

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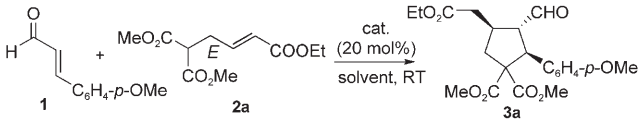
lower than that of the α,β-unsaturated iminium **A**, which was derived from an α,β-unsaturated aldehyde **1** (Scheme 1b). Recognition of this reactivity profile should allow the design of systems capable of undergoing efficient double Michael addition sequences. Generally, an α,β-unsaturated ester **2** undergoes a conjugate addition at a lower rate than an α,β-unsaturated aldehyde **1** and will not interfere with the secondary amine catalyst. Furthermore, a carbon nucleophile should be active enough to only engage in the first Michael addition reaction. To address this concern, we used an enolizable malonic ester in the α,β-unsaturated ester **2** (Scheme 1).

Initial efforts focused on the establishment of the optimal conditions for the catalytic asymmetric double Michael addition process. Gratifyingly, upon an initial screen of a set of chiral secondary amine organocatalysts **I**–**IV**, (*S*)-diphenylprolinyl TMS ether (**IV**) was found to be the best promoter (Table 1, entry 4).[12,13] A survey of solvents

***Table 1:*** Optimization of the organocatalytic enantioselective double Michael addition reaction.[a]



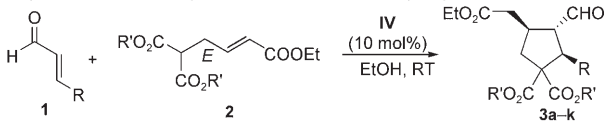

| Entry | Cat. | Solvent | *t* [h] | Yield [%][b] | *ee* [%][c] | d.r.[d] |
|---|---|---|---|---|---|---|
| 1 | **I** | EtOH | 12 | 90 | 11 | 10:1 |
| 2 | **II** | EtOH | 10 | 96 | 24 | 4:1 |
| 3 | **III** | EtOH | 24 | 0 | nd[e] | nd[e] |
| 4 | **IV** | EtOH | 12 | 95 | 99 | 10:1 |
| 5[f] | **IV** | EtOH | 18 | 92 | 99 | 10:1 |
| 6 | **IV** | $CH_2Cl_2$ | 15 | 32 | 99 | 5:2 |
| 7 | **IV** | toluene | 15 | 30 | 93 | 14:1 |
| 8 | **IV** | THF | 15 | 17 | nd[e] | 10:1 |
| 9 | **IV** | DMSO | 15 | 12 | nd[e] | 10:1 |

[a] For reaction conditions unless specified, see the Experimental Section. DMSO = dimethylsulfoxide. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H). [d] Determined by $^1$H NMR spectroscopy; major isomer: *trans*. [e] Not determined. [f] 10 mol% catalyst was used.

revealed that EtOH was optimal for the cascade process; in this case, the reaction proceeded efficiently to give the adduct **3a** in an excellent yield (95%) and with an excellent *ee* value (99%) and a good d.r. value (10:1). Similar results were obtained when the catalyst loading was lowered to 10 mol% (Table 1, entry 5).

Using these optimized reaction conditions, the scope of the asymmetric double Michael addition reactions catalyzed by **IV** was investigated next. The new methodology provided a facile approach to a range of tetrasubstituted, highly functionalized chiral cyclopentanes **3** with the generation of 3 new stereogenic centers in high enantiomeric excess (84 to 99% *ee*) and high diastereoselectivity (9:1 to >20:1 d.r.; Table 2). It appears that the size of the R′ group of the malonate ester moiety in **2** has a limited effect on the processes (Table 2, entries 1–4). Moreover, it seems that large substituents (Table 2, entries 5, 10, and 11) can also be tolerated. Finally, we used an unsaturated aldehyde substituted with a β-alkyl group (for example, R = $nC_3H_7$; Table 2, entry 12) and a similar good result was also obtained (84% yield, 94% *ee*, and 9:1 d.r.). The absolute configuration of the products **3** from the double Michael addition process was determined by comparison with a derivative from compound **3j** (Table 2,entry 10, and see the Supporting Information for details).[14]

***Table 2:*** Cascade double Michael addition reactions promoted by catalyst **IV** for the one-pot formation of chiral cyclopentanes.[a]




| Entry | R | R′ | *t* [h] | Yield [%][b] | *ee* [%][c] | d.r.[d] |
|---|---|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4$ | Me | 18 | 92 | 99 | 10:1 |
| 2 | 4-$MeOC_6H_4$ | Et | 18 | 92 | 99 | 11:1 |
| 3 | 4-$MeOC_6H_4$ | *i*Pr | 24 | 87 | 99 | 11:1 |
| 4 | 4-$MeOC_6H_4$ | Bn | 18 | 90 | 99 | >20:1 |
| 5 | 2-$MeOC_6H_4$ | Me | 18 | 91 | 99 | 19:1 |
| 6 | Ph | Me | 16 | 92 | 84 | 16:1 |
| 7 | 4-$NO_2C_6H_4$ | Me | 12 | 90 | 98 | 17:1 |
| 8 | 4-$CNC_6H_4$ | Me | 15 | 87 | 99 | 9:1 |
| 9 | 4-$FC_6H_4$ | Me | 12 | 95 | 97 | 15:1 |
| 10 | 2-$ClC_6H_4$ | Me | 16 | 93 | 99 | >20:1 |
| 11 | 2-naphthyl | Me | 24 | 86 | 98 | >20:1 |
| 12 | $n$-$C_3H_7$ | Bn | 20 | 85 | 94 | 9:1 |

[a] For reaction conditions unless specified, see the Experimental Section. Bn = benzyl. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralpak AS-H, or Chiralcel OD-H). [d] Determined by $^1$H NMR spectroscopy; major isomer: *trans*.

Motivated by the paucity of catalytic asymmetric methods for the powerful double Michael addition reactions, we have developed an unprecedented organocatalytic asymmetric version of the cascade process. This transformation, which results in the formation of two C–C bonds and three contiguous stereogenic centers, enables the facile assembly of tetrasubstituted, highly functionalized cyclopentanes from simple achiral molecules with high levels of enantio- and diastereocontrol in a single operation. Through variation of both the nucleophiles and the electrophiles, it is our anticipation that this general organocatalytic methodology will stimulate further contributions to the rapidly growing family of catalytic cascade reactions with a significantly expanded scope.

## Experimental Section

General Procedure (Table 2, entry 1): A mixture of **1a** (0.12 mmol), **2a** (0.1 mmol), and the catalyst **IV** (0.01 mmol) in EtOH (0.2 mL) was stirred at room temperature for 18 h. The mixture was purified by column chromatography on silica gel, eluted by hexane/EtOAc (10:1 to 3:1) to give the desired product in 92% yield, 99% *ee* (HPLC on a Chiralcel OD-H column, hexane/EtOH 4:1 at 0.5 mL min$^{-1}$, $\lambda$ = 254 nm); $t_{minor}$ = not observed, $t_{major}$ = 23.38 min; 10:1 d.r. (determined by $^1$H NMR); $[\alpha]_D^{23}$(major) = −19.4 ($c$ = 1.0, $CHCl_3$).

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