Organocatalysis

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Organocatalytic Enantioselective Cascade Michael–Aldol Condensation Reactions: Efficient Assembly of Densely Functionalized Chiral Cyclopentenes**

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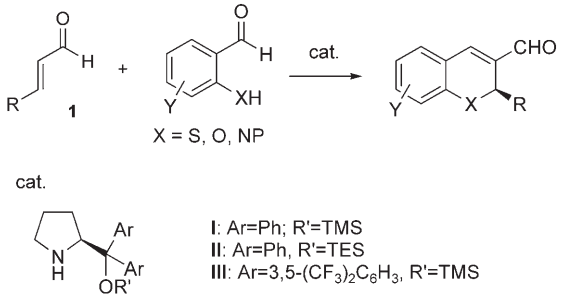
The development of asymmetric methods for the preparation of functionalized cyclopentenes has been of long-standing interest to organic chemists. As a result of their broad applications in organic synthesis they are widely distributed in a vast array of bioactive molecules.[1,2] In the past, significant advances have been made in this area by using transition-metal-mediated [3+2] and [4+1] cycloaddition reactions.[1] Furthermore, stereospecific ring opening of chiral cyclopropanes,[3] ring-closing metathesis of chiral dienes,[4] and organometallic-catalyzed Nazarov cyclizations[5] have also been described. Herein, we report a novel strategy for the preparation of chiral cyclopentenes through an organocatalytic, highly enantioselective cascade Michael–aldol condensation reaction. Significantly, the cascade sequence enables quick construction of heavily functionalized cyclopentenes with the generation of two new C–C bonds with high enantioselectively (91–97% *ee*) from readily available starting materials under mild reaction conditions.

C–C bond-forming reactions are considered the most important processes in organic synthesis. Developing novel cascade reactions that achieve the formation of multiple C–C bonds in one operation is a particularly attractive strategy for the efficient construction of complex molecular architectures. The formation of more than one bond adds an environmentally friendly aspect owing to the elimination of time-consuming and costly purification procedures and protection/deprotection steps.[6–8] Having established the capacity of chiral diarylprolinol silyl ethers to catalyze asymmetric cascade Michael–aldol condensation processes by using heteroatoms S, O, or N as nucleophiles for the formation of new C–X and C–C bonds (Scheme 1),[9–12] we sought to extend the concept for the construction of multiple C–C bonds in a one-pot transformation. The development of such processes has been a challenging task, and only few examples have been recently described.[9c,d,10f,j,k]



Scheme 1. Cascade organocatalytic enantioselective conjugate addition–aldol condensation reactions involving the formation of sequential C–X and C–C bonds. NP = nitrogen-protected form, TMS = trimethylsilyl, TES = triethylsilyl.

Motivation for this study was influenced by the lack of catalytic asymmetric approaches to the Michael–aldol condensation process involving the production of multiple new C–C bonds. Development of such a catalytic cascade process requires a stable and electron-rich carbon species as nucleophile for the initial Michael addition to an α,β-unsaturated aldehyde **1** (Scheme 2). On the other hand, the carbon nucleophilic species should be compatible with an electrophilic aldehyde functionality in one chemical entity **2**, which serves as a latent electrophile for the subsequent aldol reaction.

An even more challenging issue is that the two aldehyde groups in the respective α,β-unsaturated aldehyde **1** and nucleophilic aldehyde **2** could compete with the catalyst chiral diarylprolinol silyl ethers **I**–**III** (Scheme 3). Undesired reaction of **2** with the catalyst to produce an iminium **C** or enamine **D** could significantly complicate the cascade process. Potentially the iminium **C** could undergo reversible intramolecular cyclopropanation and thus slow down the desired cascade process. Moreover, the enamine **D** could participate in the Michael reaction with iminium **A**. We envisioned that these problems could be minimized by the use of bulky and readily enolizable malonates and the sterically hindered

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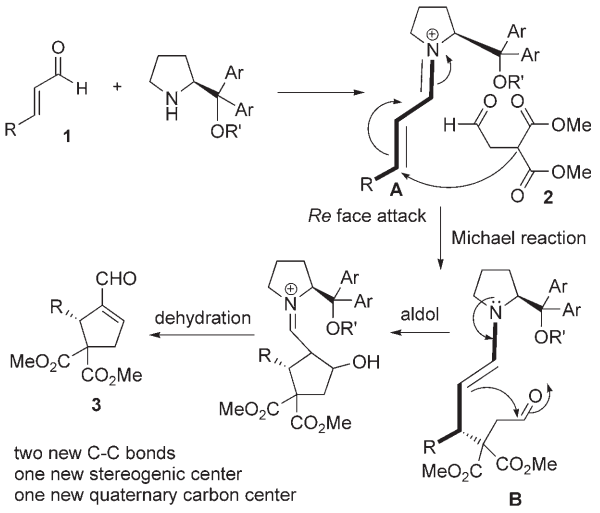
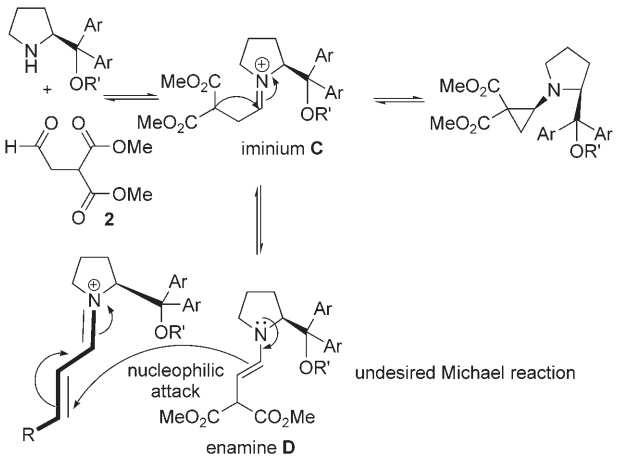


Scheme 2. Cascade organocatalytic enantioselective conjugate addition–aldol condensation reactions involving the formation of two new C–C bonds.

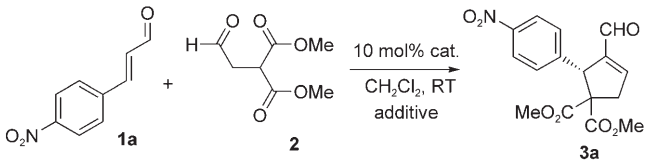


Scheme 3. Possible undesired reactions of catalysts **I**–**III** with malonate aldehydes **2**.

organocatalysts **I**–**III**. Accordingly, compound **2** with a nucleophilic malonate and an electrophilic aldehyde was designed for the cascade Michael–aldol condensation process (Schemes 2 and 3).

Validation of the proposed cascade Michael–aldol condensation process started by evaluating a model reaction between *trans*-4-nitro cinnamaldehyde (**1a**) with dimethyl 2-oxoethylmalonate (**2**) in the presence of 10 mol% **I** in CH_2Cl_2 (Table 1). The cascade Michael–aldol condensation process proceeded smoothly to afford desired product **3a** in 74% yield and 89% *ee* (Table 1, entry 1). No side products were detected. Encouraged by this, we surveyed pyrrolinol ethers **II** and **III** for the reaction under the same reaction conditions. While **II** afforded comparable results with a slightly higher *ee* value (Table 1, entry 2), no reaction occurred for the more sterically bulky catalyst **III** (Table 1, entry 8). Screening additives including acid (Table 1, entry 3) and bases (Table 1, entries 4–7) revealed that they had an effect on the process, and the use of 0.5 equiv NaOAc gave the best

Table 1: Organocatalytic enantioselective cascade Michael–aldol condensation reaction of **1a** with **2**.[a]



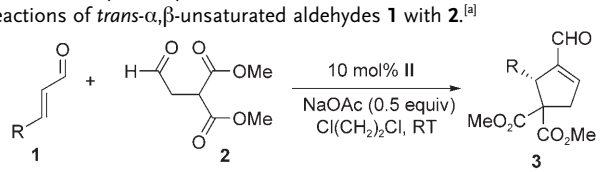
Entry	Cat.	Additive	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**I**	none	18	74	89
2	**II**	none	18	73	91
3	**II**	$PhCO_2H$ (0.1 equiv)	36	54	88
4	**II**	TEA (0.1 equiv)	48	33	69
5	**II**	NaOAc (0.1 equiv)	18	78	91
6	**II**	NaOAc (0.5 equiv)	12	78	90
7[d]	**II**	NaOAc (0.5 equiv)	12	88	92
8	**III**	none	48	<5	n.d.[e]

[a] Unless specified, see the Experimental Section for reaction conditions. [b] Yields of isolated products. [c] Determined by HPLC on a chiral stationary phase (Chiralpak AS-H). [d] In $Cl(CH_2)_2Cl$. [e] Not determined.

result (Table 1, entry 6). To further determine the scope of the cascade process, examination of the reaction medium led to the selection of $Cl(CH_2)_2Cl$ (Table 1, entry 7). The increased reaction yield with $Cl(CH_2)_2Cl$ is probably due to the increased solubility of the base, which thereby favorably facilitates the enolization of the malonate moiety in **2**.

After the optimal conditions had been established, the generality of the cascade Michael–aldol condensation processes was explored. The organocatalytic enantioselective cascade reactions serve as an efficient route for the preparation of highly functionalized cyclopentenes (Table 2). Significantly, the new stereogenic center is created in high enantioselectivity (91–97% *ee*) in the one-pot procedure. Moreover, the process affords the formation of a new quaternary carbon

Table 2: Catalyst **II** promoted cascade Michael–aldol condensation reactions of *trans*-α,β-unsaturated aldehydes **1** with **2**.[a]



Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	$4\text{-}NO_2C_6H_4$	**3a**	12	88	92
2	$4\text{-}FC_6H_4$	**3b**	24	73	93[d]
3	$4\text{-}CF_3C_6H_4$	**3c**	18	75	93
4	$4\text{-}CNC_6H_4$	**3d**	36	63	94
5	$2\text{-}NO_2C_6H_4$	**3e**	14	85	94
6	$2\text{-}ClC_6H_4$	**3f**	24	82	95
7	$2\text{-}MeOC_6H_4$	**3g**	48	78	97
8	$4\text{-}MeOC_6H_4$	**3h**	48	80	96
9	$3\text{-}MeO\text{-}4\text{-}AcOC_6H_3$	**3i**	48	78	95
10	Ph	**3j**	24	81	93
11	2-furanyl	**3k**	36	89	91

[a] Unless specified, see the Experimental Section for reaction conditions. [b] Yields of isolated products. [c] Determined by HPLC on a chiral stationary phase (Chiralpak AS-H, or Chiralcel OD-H or OJ-H). [d] Determined after conversion into the corresponding enone with $Ph_3P{=}COPh$.

center, and significant structural variation of α,β-unsaturated aldehydes can be tolerated. The electronic nature of the aromatic rings of α,β-unsaturated aldehydes **1** has limited influence on the stereochemical outcome. It demonstrates that the electron-withdrawing (Table 2, entries 1–6), electron-donating (Table 2, entries 7 and 8), combined electron-withdrawing and -donating (Table 2, entry 9), neutral (Table 2, entry 10), and heteroaromatic (Table 2, entry 11) systems can participate in the reactions. Probing the steric effect on the enantioselectivity of the cascade processes indicates that such impact is also minimal (Table 2, entries 5–7). Finally, less reactive aliphatic enals were used, and almost no reaction occurs. The absolute configuration of product **3 f** was determined by X-ray crystal structural analysis (Figure 1).[13]

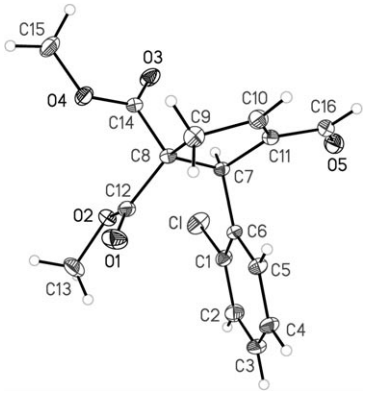


Figure 1. X-ray crystal structure of **3 f**. Thermal ellipsoids are drawn at the 20% probability level.

In conclusion, we have described a novel organocatalytic, enantioselective cascade Michael–aldol condensation reaction. The process is efficiently catalyzed by readily available (*S*)-diphenylprolinol triethylsilyl ether to give synthetically useful, highly functionalized chiral cyclopentenes. The significance of the methodology is highlighted by its correlation to the protocols for the preparation of cyclohexenes, developed by the Enders[10f] and Hayashi groups.[10j] In principle, the strategy described can also be extended to the preparation of six-membered ring systems. This approach constitutes our future direction aimed at expanding the scope of the powerful cascade processes.

Experimental Section

General procedure (Table 2, entry 1): A mixture of **1 a** (21 mg, 0.12 mmol), **2** (17 mg, 0.1 mmol), NaOAc (5 mg, 0.05 mmol), and the catalyst **II** (3.4 mg, 0.01 mmol) in $Cl(CH_2)_2Cl$ (0.5 mL) was stirred at room temperature for 12 h. The mixture was purified by silica gel column chromatography, eluted by hexane/EtOAc (20:1 to 2:1) to give the desired product in 88% yield, 92% *ee* as determined by HPLC on a chiral stationary phase (Chiralpak AS-H column, 70:30 hexanes/*i*PrOH at 0.5 mL min^{-1}, $\lambda = 254$ nm); $t_{minor} = 37.5$ min, $t_{major} = 52.9$ min; $[\alpha]_D^{23}$ (major) $= -194.4$ deg cm^3 g^{-1} dm^{-1} ($c = 1.3$ g cm^{-3}, $CHCl_3$).

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[13] The structure of the compound derived from molecule **3f** was determined by X-ray crystal analysis. CCDC-652571 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

