

An Unexpected Organocatalytic Asymmetric Tandem Michael/Morita–Baylis–Hillman Reaction**

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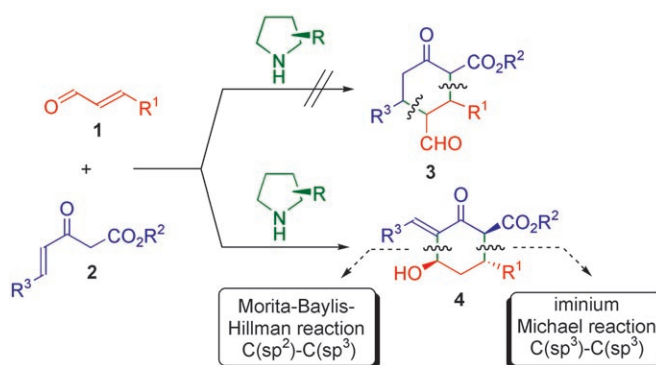
A new direction in organocatalysis^[1] is the development of cascade or tandem reactions.^[2] These allow the rapid construction of structurally complex molecules from simple starting materials in only one operation, thereby minimizing the cost, waste, and manual efforts.^[3] One of the most successful class of organocatalysts used for this purpose are secondary amines. These catalysts allow the sequential functionalization of aldehydes to give enamine^[4] and iminium ion^[5] intermediates, that in combination with electrophiles or nucleophiles, respectively, enables the stereoselective syntheses of highly functionalized molecules by consecutive amine-catalyzed reactions.

A number of fascinating organocatalytic cascade reactions have been reported during the last two years.^[6] Some of the most attractive reactions are exemplified by the triple cascade reaction of aldehydes, α,β -unsaturated aldehydes, and nitroalkenes described by Enders et al., who employed a sequential enamine–iminium–enamine activation;^[7] the iminium–iminium–enamine triple activation of α,β -unsaturated aldehydes and activated methylene compounds developed by our research group;^[6c] and the tandem Michael–Henry reaction of pentane-1,5-dial and nitroalkenes reported recently by Hayashi et al.^[6f]

The Morita–Baylis–Hillman reaction is a powerful tool for the atom-economic construction of optically active α -methylene- β -hydroxycarbonyl derivatives using a chiral tertiary amine or phosphine catalyst.^[8] A few examples of the use of chiral secondary amines—mainly proline—for this reaction have been reported, and in all the cases the addition of a tertiary amine as co-catalyst was found to be essential for activation of the double bond.^[9]

We report herein the diastereo- and enantioselective Michael/Morita–Baylis–Hillman tandem reaction of α,β -unsaturated aldehydes **1** with Nazarov reagent **2**, with both steps being catalyzed by a chiral secondary amine.

During the development of a new cascade reaction, we started to investigate the reaction of α,β -unsaturated aldehydes **1** with the Nazarov reagent **2** using proline derivatives as organocatalysts (Scheme 1). Surprisingly, the expected



Scheme 1. Asymmetric organocatalytic tandem reaction.

compound **3**, which should be formed by addition of Nazarov reagent **2**^[10] to the α,β -unsaturated aldehyde **1** followed by ring closure by enamine addition to the double bond, was not observed. On the contrary, cyclohexenone **4** was obtained as the main product through an intramolecular Morita–Baylis–Hillman pathway. This observation led us to investigate the reaction of cinnamaldehyde (**1a**) and Nazarov reagent **2a** under various catalyst and solvent conditions (Table 1). The screening of the catalysts (Table 1, entries 1–5) was carried out using 20 mol % of catalyst and benzoic acid as an additive in toluene at room temperature. Under these conditions, all the chiral secondary amines tested, except proline **5a**, catalyzed the tandem reaction to afford **4a**, in its enolic form, in good yields after 18 hours.

In terms of selectivity, the protected diaryl prolinol derivatives **5d** and **5e**^[11] (Table 1, entries 4 and 5) showed both high diastereo- and enantioselectivity (92 % and 94 % *ee*, respectively), while nearly racemic product **4a** was obtained when the unprotected catalyst **5c** was used (Table 1, entry 3). The substitution on the aromatic ring of the catalyst was found to have a remarkable effect on the reactivity, and an incomplete reaction was obtained after 40 hours using the trifluoromethyl-substituted catalyst **5d**. The best results were achieved with (*S*)-2-(diphenyltrimethylsilyloxymethyl)pyrrolidine **5e** as the catalyst.

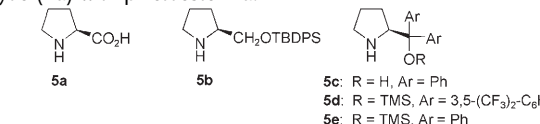
Other solvents, such as CH_2Cl_2 , Et_2O , or CH_3CN , and neat conditions were also studied (Table 1, entries 7–10); however, in all cases lower selectivity was obtained, relative to the use of toluene. Full conversion was also obtained when the

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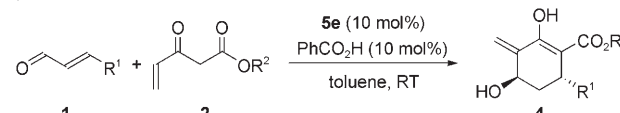
Table 1: Representative screening results for the reaction of cinnamaldehyde (**1a**) with β -ketoester **2a**.^[a]



Entry	Cat.	Solvent	Conversion [%]	d.r. ^[b]	Yield [%] ^[c]	ee [%] ^[d]
1	5a	toluene	n.r. ^[e]	—	—	—
2	5b	toluene	> 98	9:1	52	49
3	5c	toluene	> 98	12:1	57	2
4	5d	toluene	80 ^[f]	16:1	51	92
5	5e	toluene	> 98	14:1	74	94
6	5e	toluene	> 98	7:1	55	94 ^[g]
7	5e	CH ₂ Cl ₂	> 98	9:1	63	94
8	5e	Et ₂ O	> 98	3:1	71	92
9	5e	CH ₃ CN	> 98	3:1	75	91
10	5e	neat	> 98	4:1	55	90

[a] All reactions were performed on a 0.2-mmol scale with PhCO₂H (20 mol%) as additive in 0.2 mL of solvent and stopped after 18 h. [b] The diastereoisomeric ratio was determined by ¹H NMR analysis of the crude mixture, which consisted of epimers at the alcohol position. [c] Yield of the diastereoisomeric mixture after flash chromatography. [d] Determined by HPLC on a chiral stationary phase (see the Supporting Information). [e] No reaction. [f] The reaction was stopped after 40 h. [g] 10 mol% of catalyst **5e** and PhCO₂H were used. TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

Table 2: Reaction of α,β -unsaturated aldehydes **1a–i** with β -ketoesters **2**.^[a]



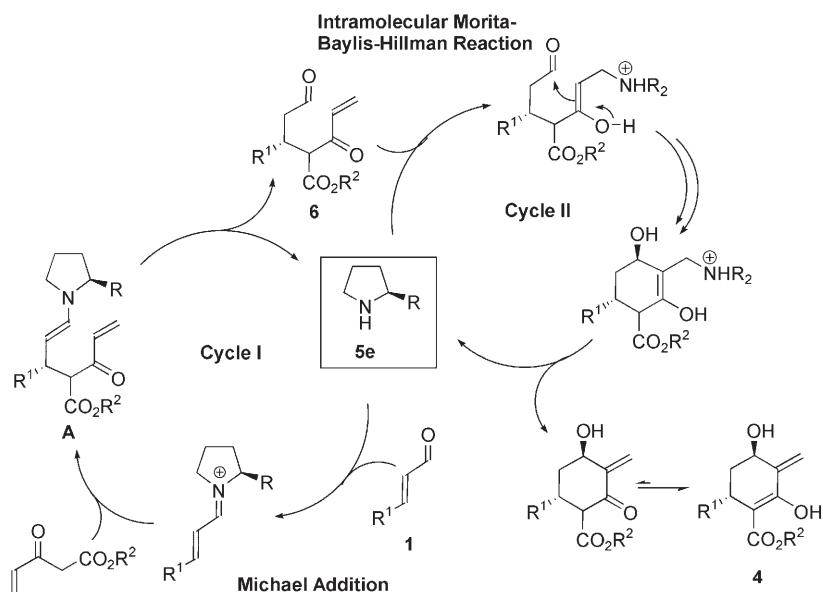
Entry	R ¹	R ²	d.r. ^[b]	Prod.	Yield [%] ^[c]	ee [%] ^[d]
1	Ph (1a)	Et (2a)	7:1	4a	55	94
2	Ph (1a)	Et (2a)	11:1	4a	53	—95 ^[e,f]
3	Ph (1a)	<i>t</i> Bu (2b)	5:1	4b	68	94
4	Ph (1a)	allyl (2c)	6:1	4c	45	94
5	<i>p</i> -ClC ₆ H ₄ (1b)	Et (2a)	7:1	4d	49 (76) ^[f]	93 (95) ^[f]
6	<i>p</i> -MeOC ₆ H ₄ (1c)	Et (2a)	9:1	4e	69	93
7	<i>p</i> -NO ₂ C ₆ H ₄ (1d)	Et (2a)	4:1	4f	58	96
8	<i>p</i> -NO ₂ C ₆ H ₄ (1d)	<i>t</i> Bu (2b)	4:1	4g	51	95
9	2-thienyl (1e)	Et (2a)	6:1	4h	57	95
10	2-furyl (1f)	Et (2a)	4:1	4i	66	92
11	CO ₂ Et (1g)	Et (2a)	5:1	4j	51	98 ^[f]
12	Et (1h)	Et (2a)	6:1	4k	64	86 ^[f,g]
13	(<i>Z</i>)-hex-3-enyl (1i)	Et (2a)	3:2	4l	51	92 ^[f,g]

[a] All reactions were performed on a 0.2-mmol scale with PhCO₂H (10 mol%) as additive in 0.2 mL of toluene. [b] The diastereoisomeric ratio was determined by ¹H NMR spectroscopic analysis of the crude mixture, which consisted of epimers at the alcohol. [c] Yield of the diastereoisomeric mixture after flash chromatography. [d] Determined by HPLC on a chiral stationary phase (see the Supporting Information). [e] The *R* enantiomer of the catalyst **5e** was used. [f] 20 mol% of catalyst **5e** and PhCO₂H were used. [g] The *ee* value was determined after derivatization (see the Supporting Information).

catalyst loading was decreased to 10 mol% (Table 1, entry 6), without any variation in the enantioselectivity, although a slight drop in the diastereoselectivity was observed. The reaction can also be performed on a 2-mmol scale with 20 mol% of the catalyst to give **4a** in 72% yield and 94% *ee*.

The scope of the Michael–Morita–Baylis–Hillman reaction was studied for different α,β -unsaturated aldehydes and β -ketoesters in the presence of 10 mol% of catalyst **5e** and benzoic acid in toluene (Table 2). The tandem reaction is a general reaction for β -ketoesters **2** with different ester groups, and similar yields as well as diastereo- and enantioselectivities were obtained in all cases (Table 2, entries 1, 3, 4, 8). A broad range of groups—aromatic, heteroaromatic, ester, and aliphatic—at the β -position of the aldehyde could be tolerated, and afforded the corresponding products **4** in high enantioselectivities (86–98% *ee*) and good yields (49–76%). The opposite enantiomer of product **4a** could also be easily obtained by carrying out the reaction with the *R* enantiomer of catalyst **5e** (Table 2, entry 2).

We propose a two amine-catalyzed cycle mechanism for the formation of the products **4** (Scheme 2). First, catalyst **5e** activates the α,β -unsaturated aldehyde **1**, thereby forming an iminium intermediate which undergoes a Michael addition



Scheme 2. Proposed mechanism for the Michael/Morita–Baylis–Hillman tandem reaction.

with Nazarov reagent **2a** (Cycle I). Then, hydrolysis of the intermediate **A** leads to intermediate **6** and recovery of the catalyst. In the second cycle (Cycle II), we suggest that **5e**—now acting as a nucleophilic catalyst for the activation of the double bond—is involved in the intramolecular Morita–Baylis–Hillman reaction of **6**. However, according to our

knowledge, no reports of enantioselective Morita–Baylis–Hillman reactions catalyzed by a secondary amine have been described.

We reasoned that isolation of the intermediate **6** and the determination of the role of the catalyst in the intramolecular Morita–Baylis–Hillman reaction of the later (Cycle II) would be important for providing support for the proposed mechanism.

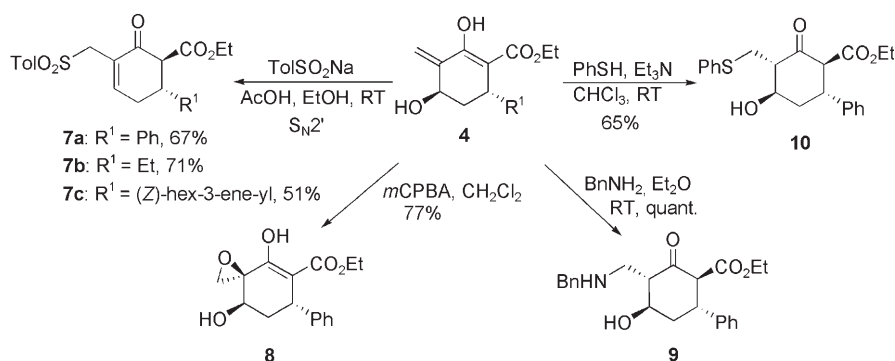
It was found that an incomplete reaction takes place on cooling the reaction temperature to 4 °C, and that **6** could be isolated as an inseparable mixture of diastereoisomers (d.r. 1:1).^[12] Then, we studied the cyclization of **6** to **4a** by adding different catalysts to a solution of **6** in toluene. No reaction took place in the absence of catalyst or by addition of water or benzoic acid (Table 3, entries 1–3). However, the use of 20 mol % of catalyst (*S*)-**5e** afforded the Morita–Baylis–Hillman product **4a** as a 5:1 mixture of diastereoisomers, with the major diastereomer having 89 % *ee* (Table 3, entry 4), while the enantiomer ((*R*)-**5e**) afforded the same diastereoselectivity and with the major diastereomer in 94 % *ee* (Table 3, entry 5). Another secondary amine, pyrrolidine, and typical Morita–Baylis–Hillman catalysts, such as DABCO or PPh₃, also catalyzed the cyclization of **6** to **4a** (Table 3, entries 6–8). It should also be noted that similar enantioselectivities and the same approach for the addition of this reaction step (pro-*R* face with respect to the aldehyde) was achieved with all the nonchiral catalysts, thus showing that the selectivity of this step is controlled by the stereocenter at the β-position of the aldehyde formed in the first cycle (Scheme 2).

The tandem reaction between **1a** and the Nazarov reagent substituted with a methyl group at the γ- or δ-positions of the alkene did not take place, and only a sluggish Michael

addition was observed, as a result of the steric hindrance associated with the Morita–Baylis–Hillman reaction.

All these mechanistic tests seem to support the active role of catalyst **5e** in the intramolecular Morita–Baylis–Hillman reaction (Cycle II, Scheme 2).

The stereoselective synthesis of complex structures in a short pathway is the main aim of synthetic chemists.^[13] The high level of functionalization presented in the tandem products **4** indicated to us that simple transformations could give a wide range of interesting products. In fact, we developed a diastereo- and enantioselective synthesis of cyclohexanones and cyclohexenones with up to four stereocenters in a two-step synthesis (starting from the α,β-unsaturated aldehyde; Scheme 3). For example, following an S_N2' mechanism, the addition of the tosyl sodium salt to a



Scheme 3. Stereoselective synthesis of diverse products. Tol = tolyl, mCPBA = *meta*-chloroperoxybenzoic acid, Bn = benzyl.

solution of the corresponding cyclohexenone **4** in EtOH afforded **7** in good yields (51–71 %). The spiro compound **8** was obtained in 77 % yield by a diastereoselective epoxidation of the double bond in **4a** using mCPBA. Furthermore, conjugate addition of the corresponding amine or thiol to **4a** leads to the amino alcohol **9** and the thio alcohol **10**, respectively.

The absolute configuration of the tandem products **4** and **8–10** were assigned by a single-crystal X-ray analysis of **7a**^[14] as well as by NMR spectroscopic studies.^[15]

In conclusion, we have developed a new organocatalytic tandem reaction of α,β-unsaturated aldehydes and Nazarov reagent catalyzed by a diarylprolinol ether following a Michael/Morita–Baylis–Hillman mechanism. The reaction proceeds in high enantio- and diastereoselectivity for a wide range of α,β-unsaturated aldehydes and different β-ketoesters. Mechanistic studies indicate that the TMS-protected prolinol also acts as the catalyst in the Morita–Baylis–Hillman reaction, and is the first chiral secondary amine catalyst reported for this reaction. Furthermore, a number of stereoselective transformations have been presented that lead to various types of optically active cyclohexenone and cyclohexanone derivatives with up to four stereocenters.

Experimental Section

General procedure for the Michael/Morita–Baylis–Hillman reaction: The corresponding β-ketoester **2a** (0.2 mmol) was added to a stirred

Table 3: Catalyst investigations for the Morita–Baylis–Hillman step.^[a]

$1a + 2a \xrightarrow[\text{toluene, 12 h, 4 } ^\circ\text{C}]{\text{5e (10 mol\%), PhCO}_2\text{H (10 mol\%)}} \text{6 (d.r. 1:1)} \xrightarrow{\text{catalyst}} \text{4a}$				
Entry	Catalyst	mol %	d.r. ^[b]	<i>ee</i> [%] ^[c]
1	–	–	n.r.	–
2	H ₂ O	100	n.r.	–
3	PhCO ₂ H	20	n.r.	–
4	(<i>S</i>)- 5e	20	5:1	89
5	(<i>R</i>)- 5e	20	5:1	94
6	pyrrolidine	20	6:1	92
7	DABCO	50	11:1	93
8	PPh ₃	20	> 20:1	94

[a] All reactions were performed in toluene with the diastereoisomeric mixture of intermediate **6** and the corresponding catalyst. [b] Diastereoisomeric ratio determined by ¹H NMR spectroscopic analysis of the crude mixture. n.r.: no reaction. [c] Determined by HPLC (see the Supporting Information). DABCO = 1,4-diazabicyclo[2.2.2]octane.

solution of catalyst **5e** (0.02 mmol), benzoic acid (0.02 mmol), and the corresponding aldehyde **1a-i** (0.6 mmol) in toluene (0.2 mL) in an ordinary vial. After complete consumption of the β -ketoester, usually within 14–18 h (as monitored by ^1H NMR spectroscopy), the crude product was directly charged on to silica gel and subjected to flash chromatography. For example, (+)-**4a** was obtained after flash chromatography (eluent 4:1, hexanes/Et₂O) as a colorless oil (55% yield). The *ee* value was determined by HPLC using a Chiralpak OD column (hexane/*i*PrOH 90:10); flow rate 1.0 mL min⁻¹; $\tau_{\text{minor}} = 18.3$ min, $\tau_{\text{major}} = 44.6$ min (94% *ee*). $[\alpha]_{\text{D}}^{20} = +4.0$ ($c = 0.3$ g cm⁻³, CH₂Cl₂). ^1H NMR (400 MHz, CDCl₃): $\delta = 12.27$ (s, 1H), 7.26–7.13 (m, 5H), 6.07 (s, 1H), 5.67 (s, 1H), 4.39 (ddd, $J = 10.4, 4.0, 2.0$ Hz, 1H), 4.04–3.94 (m, 1H), 3.92–3.85 (m, 2H), 2.38–2.32 (m, 1H), 2.06–2.02 (brs, 1H), 1.76–1.68 (m, 1H), 0.78 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃): $\delta = 172.3, 163.4, 146.6, 142.1, 128.3$ (2C), 126.7 (2C), 125.9, 115.4, 102.3, 68.6, 60.4, 41.7, 39.1, 13.5 ppm; MS (TOF ES⁺): $[M+\text{Na}]^+$ calcd for C₁₆H₁₈NaO₄: 297.1103; found: 297.1102.

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