

# Enantioselective Assembly of Substituted Dihydropyrones via Organocatalytic Reaction in Water Media

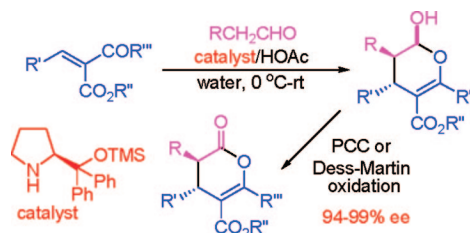
Jing Wang,<sup>†</sup> Fang Yu,<sup>‡</sup> Xiaojing Zhang,<sup>‡</sup> and Dawei Ma<sup>\*†</sup>

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China, and Shenyang Pharmaceutical University, 103 Wenhua Lu, Shenyang 110016, China

madw@mail.sioc.ac.cn

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## ABSTRACT



The diarylprolinol ether/HOAc-catalyzed cascade Michael addition and cyclization of aldehydes and  $\alpha$ -keto- $\alpha,\beta$ -unsaturated esters proceeds smoothly in water to afford cyclic hemiacetals, which are oxidized to furnish highly functionalized 3,4,5,6-tetrasubstituted dihydropyrones with excellent enantioselectivities.

In recent years more and more examples have demonstrated the broad applicability and great efficiency of diarylprolinol ethers **1** as amine-based catalysts for reactions involving aldehydes. They normally give rise to an excellent asymmetric induction via enamine or iminium ion intermediates by a steric control approach.<sup>1</sup> The scope of reactions includes Michael addition of aldehydes to electron-deficient olefins,<sup>2</sup>  $\alpha$ -functionalization of aldehydes,<sup>3</sup> epoxidation of  $\alpha,\beta$ -

unsaturated aldehydes,<sup>4</sup> and conjugate addition of nucleophiles to  $\alpha,\beta$ -unsaturated aldehydes.<sup>5</sup> Recently, we found that the combination of diarylprolinol ether/Brønsted acid as a catalyst and water as solvent is a highly efficient system for

<sup>†</sup> Chinese Academy of Sciences.

<sup>‡</sup> Shenyang Pharmaceutical University.

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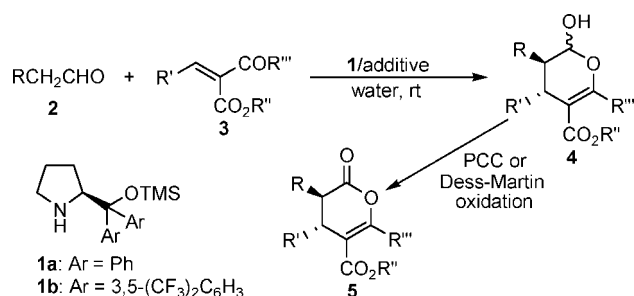
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promoting Michael addition of aldehydes to nitroalkenes.<sup>2g</sup> When this system was used in Michael addition of aldehydes **2** and  $\alpha$ -keto- $\alpha,\beta$ -unsaturated esters **3**,<sup>6</sup> cyclic hemiacetals **4** were isolated, which were oxidized with PCC or Dess–Martin periodinane to afford highly functionalized 3,4,5,6-tetrasubstituted dihydropyrones **5**<sup>7</sup> with excellent

Scheme 1



enantioselectivities (Scheme 1). Herein we wish to detail our results.

**Table 1.** The Effect of Additive on the Addition Reaction of *n*-Pentanal to Ethyl 2-Acyl-2-heptenoate Catalyzed by Amines **1**<sup>a</sup>

entry	catalyst	acid/mol %	time (h)	yield (%) <sup>b</sup>	ee [%] <sup>c</sup>
1	<b>1a</b>	PhCO <sub>2</sub> H/50	36	73	>99
2	<b>1a</b>	AcOH/50	24	83	>99
3	<b>1a</b>	AcONa	72	33	>99
4	<b>1a</b>	none	48	44	>99
5	<b>1b</b>	AcOH/50	72	<5	
6	<b>1a</b>	AcOH/100	24	86	98 <sup>d</sup>

<sup>a</sup> Reaction conditions for first step: **1** (0.025 mmol), *n*-pentanal (0.5 mmol), **3a** (0.25 mmol), additive, water (0.25 mL), 0 °C for 1 h, then rt for the indicated time. <sup>b</sup> Isolated yield for addition step. <sup>c</sup> Determined by HPLC analysis of **5a** on a chiral stationary phase. <sup>d</sup> 1 mmol of *n*-pentanal was used.

As indicated in Table 1, we conducted our initial experiment by stirring a mixture of *n*-pentanal (0.5 mmol), ethyl 2-acyl-2-heptenoate **3a** (0.25 mmol), **1a** (0.025 mmol), and benzoic acid (0.125 mmol) in water. Upon the complete

consumption of **3a**, cyclic hemiacetal **4a** was isolated in 73% yield as a 1:1 diastereomeric mixture, which was treated with PCC to afford **5a** with greater than 99% ee (entry 1). Switching the additive to acetic acid gave an improved yield (entry 2), while NaOAc or no additive gave poor yields (entries 3 and 4). The use of catalyst **1b** gave rise to poor yields (entry 5), which probably resulted from the additional steric hindrance caused by two bulkier aromatic groups. Additionally, increasing the aldehyde and additive loadings could further improve the yield (entry 6). Searching for practical usage, we gave up these conditions in late investigation.

The optimized **1a**/HOAc combination was then applied to a variety of aldehydes and olefins. In general, the desired *trans*-dihydropyrones were obtained in good yields and with excellent enantioselectivities. In either case the corresponding *cis*-isomers were isolated in 3–4% yield, illustrating a diastereomeric ratio of around 94:6. Two functionalized aldehydes were compatible with this process (Table 2, entries 1 and 2), thereby providing an access to more complex dihydropyrones. When 3-methylbutanal was utilized, the cycloaddition turned out to be sluggish and the catalyst loading had to be increased to ensure good conversion (Table 2, entry 3), which demonstrates that the steric bulk of the aldehydes greatly affects the cycloaddition step. Switching from ethyl esters to *tert*-butyl esters had only little influence on this process (compare entries 1 and 4, 2 and 5, Table 2). This advantage provides an opportunity for the acid-induced cleavage of the ester moiety in the examined dihydropyrones.

Variation of the 4-position of **5** is possible, as evident from the fact that *tert*-butyl 2-acyl-6-benzoxylhexenoate furnished the corresponding dihydropyrones **5g–i** in good yields (Table 2, entries 6–8). The slight drop in ee value for **5i** illustrates that the steric hindrance of the aldehydes might impair asymmetric induction. Interestingly, better results were obtained when diethyl 2-acetylfumarate was employed (Table 2, entries 9 and 10). In these cases the first step turned out to be significantly faster, and only 10 mol % of catalyst **1** was required even for sterically hindered 3-methylbutanal (compare entries 3 and 10, Table 2). This result demonstrates that the additional ester group, which renders the  $\alpha,\beta$ -unsaturated ketone more electron deficient, greatly facilitates the addition reaction.

In our studies the required  $\alpha$ -keto- $\alpha,\beta$ -unsaturated esters **3** were synthesized via TiCl<sub>4</sub>-catalyzed Knoevenagel condensation of aldehydes and  $\beta$ -keto esters.<sup>8</sup> In the case of aliphatic aldehydes, only *Z*-olefins were isolated in good yields. However, a chromatographically separable mixture of *E*- and *Z*-olefins (2:1 ratio) was obtained when aromatic aldehydes were used, which provided an opportunity to examine the influence of the double bond geometry of the  $\alpha$ -keto- $\alpha,\beta$ -unsaturated esters on the cycloaddition. Much to our surprise, both **6a** and its *Z*-isomer **3e** gave rise to **5m** as the major product (entries 1 and 2, Table 3). Careful

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**Table 2.** Synthesis of 3,4,5,6-Tetrasubstituted Dihydropyrones **5**<sup>a</sup>

entry	product	time (h) <sup>b</sup>	yield (%) <sup>c</sup> (addition/ oxidation)	ee (%) <sup>d</sup>
1		36	79/73	>99
2		36	72/75	98
3		36	69/79	98 <sup>e</sup>
4		36	78/75	98
5		36	72/75	98
6		36	78/81	99
7		36	72/74	99
8		24	81/67	94
9		24	88/75	>99
10		24	81/84	>99

<sup>a</sup> Reaction conditions for cycloaddition: **1a** (0.025 mmol), aldehyde **2** (0.5 mmol), olefin **3** (0.25 mmol), HOAc (0.125 mmol), water (0.25 mL), 0 °C for 1 h, then rt for the indicated time. <sup>b</sup> For the addition step. <sup>c</sup> Isolated yield. <sup>d</sup> Determined by chiral-phase HPLC analysis. <sup>e</sup> 0.05 mmol **1a** and 0.25 mmol HOAc were used.

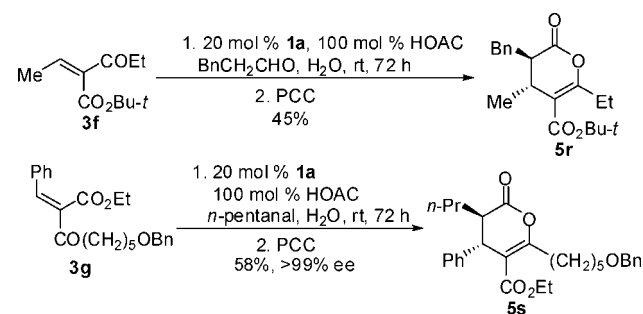
monitoring of the reaction process by TLC revealed that isomerization of **6a** to **3e** occurred first, and the latter was the actual reactant in the cycloaddition. Similar results were observed when functionalized  $\beta$ -aryl enones were utilized (Table 3, entries 3–6).

**Table 3.** Synthesis of 6-Methyl Dihydropyrones **5m–q** ( $R''' = \text{Me}$ ) from  $\beta$ -Aryl Enones **6** and **3e**<sup>a</sup>

entry	aldehyde	enone	product/yield (%) <sup>b</sup>	ee [%] <sup>c</sup>
1	<i>n</i> -pentanal	<b>6a</b>	<b>5m</b> /64 (3)	>99
2	<i>n</i> -pentanal	<b>3e</b>	<b>5m</b> /62 (3)	>99
3	2-methylbutanal	<b>6a</b>	<b>5n</b> /56 (2) <sup>d</sup>	>99
4	<i>n</i> -pentanal	<b>6b</b>	<b>5o</b> /45 (6)	>99
5	<i>n</i> -pentanal	<b>6c</b>	<b>5p</b> /44 (10)	98
6	<i>n</i> -pentanal	<b>6d</b>	<b>5q</b> /51 (4)	>99

<sup>a</sup> Reaction conditions for cycloaddition: **1a** (0.025 mmol), aldehyde (1.0 mmol), enone (0.25 mmol), HOAc (0.25 mmol), water (0.25 mL), 0 °C for 1 h, then rt for 48 h. <sup>b</sup> Isolated yields for two steps, the yield for the corresponding cis-isomer is indicated in parentheses. <sup>c</sup> Determined by HPLC on a chiral stationary phase. <sup>d</sup> 0.05 mmol **1a** and 0.25 mmol HOAc were used.

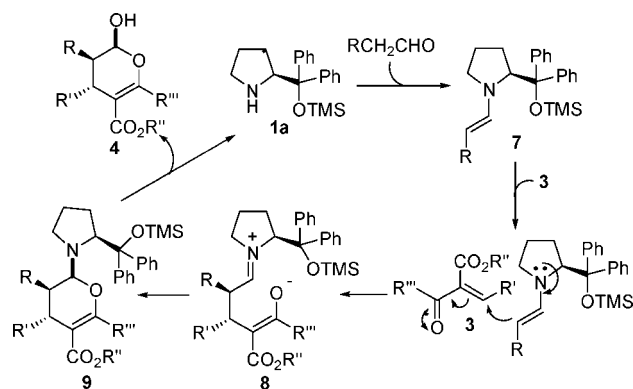
To explore the variability of the 6-position of the dihydropyrones **5**, enones **3f** and **3g** were synthesized from the corresponding  $\beta$ -keto esters. We were pleased that these two substrates gave the desired products **5r** and **5s**, although an increased catalyst loading was required to obtain complete conversion in the cycloaddition (Scheme 2). Importantly,

**Scheme 2**

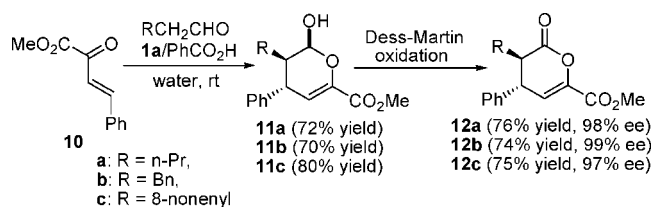
compound **5r** had been synthesized by Evans and co-workers,<sup>7a</sup> and by comparing the analytical data we could establish the stereochemistry of our reaction products as **3*R*,4*R***.

The present cyclic hemiacetal formation might proceed via a stepwise Michael addition/cyclization process as depicted in Scheme 3. After the initial attack of enamines **7** that formed from amine **1a** and aldehydes on  $\alpha$ -keto- $\alpha,\beta$ -unsaturated esters from its *Re* face to afford *syn*-adducts **8**, intramolecular attack of enol anion on iminium ion might occur to provide cyclization products **9**, which might undergo hydrolysis to afford cyclic hemiacetals **4**. This mechanism could be used for rationalizing the established stereochemistry of the dihydropyrones **5**. However, it is also possible

Scheme 3



Scheme 4



to rationalize all the experimental phenomena by a hetero-Diels–Alder reaction mechanism as reported by Juhl and Jørgensen for the reaction of aldehydes and  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters.<sup>9,10</sup> Additional experiments are required to solve this problem.

Considering that in Jørgensen's studies the enantioselectivities (80–94% ee) are not excellent for many substrates, we tried our conditions for the reaction of  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoester **10** with some aldehydes. Gratifyingly, when 10 mol % **1a** and 50 mol % benzoic acid were used as the catalytic system, this reaction worked well in water, to provide 3,4,6-trisubstituted dihydropyrones **12** with greater than 97% ee (Scheme 4).

In conclusion, we have developed a convenient and highly enantioselective method for the assembly of highly functionalized 3,4,5,6-tetrasubstituted dihydropyrones, which relies on a Michael addition/cyclization process. Considering the fact that the C=C double bond in dihydropyrones can

be hydrogenated to afford saturated lactones, and ring-opening of these compounds followed by decarboxylation would give highly functionalized  $\delta$ -keto esters (from **5a** to **5s**) and 1,2-diester (from **5j** to **5l**), this method should find various applications in organic synthesis. Additionally, the discovery that our conditions are superior to those reported by Jørgensen with regard to enantioselectivity in the reaction of aldehydes and  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoesters is remarkable. These results set another impressive example to illustrate the efficiency of the diarylprolinol ether/Brønsted acid/water system<sup>11</sup> for reactions involving aldehydes, which may prompt the further exploration of the applicability of this system in organocatalytic reactions.

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**Supporting Information Available:** Experimental procedures and copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for all new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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