

## Organocatalytic and Enantioselective Mannich Reaction of Dicyanoolefins with $\alpha$ -Amido Sulfones

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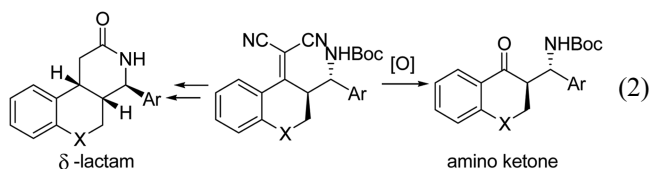
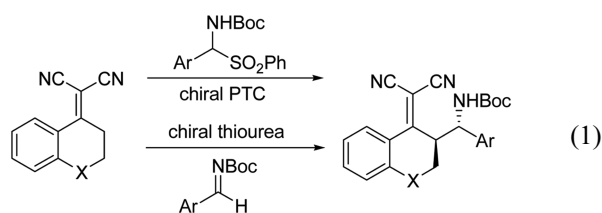
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Catalytic enantioselective Mannich reaction is one of the most versatile and attractive protocols for the synthesis of optically active chiral amine compounds, and great strides have been made which are catalyzed by chiral metal complexes or small organic molecules over the last several years.<sup>1</sup> Recently, the direct enantioselective vinylogous Mannich reaction of N-Boc aldimine with  $\alpha,\alpha$ -dicyanoolefins catalyzed by chiral bifunctional thioureas has been developed, the desired products could be obtained in excellent yields and enantioselectivities (Eq. 1).<sup>2</sup> As precursors to carbamate protected chiral alkyl amines, carbamate-protected alkyl imines constitute a particularly important class of imine substrates. However, their instability renders it extremely challenging for their employment in organic reactions. So the reactions with *in situ* generation of carbamate-protected aryl and alkyl imines from stable  $\alpha$ -amido sulfones have received more and more attention.<sup>3</sup> Among which, it was reported that the chiral vinylogous Mannich adducts could be obtained smoothly in the reaction of  $\alpha,\alpha$ -dicyanoolefins and  $\alpha$ -amido sulfones in the presence of chiral phase-transfer catalyst. The multi-functional products of vinylogous Mannich reaction of N-Boc aldimine with  $\alpha,\alpha$ -dicyanoolefins are versatile intermediates that can be converted to a wide variety of synthetically useful compounds, such as  $\delta$ -lactam and amino ketone (Eq. 2). There is still scope to develop a simple and practical method for the asymmetric vinylogous Mannich reaction under mild reaction conditions, although the remarkable levels of selectivity have been reported.<sup>4</sup>



In connection to our interest in the asymmetric reactions, we present here the asymmetric vinylogous Mannich reaction with broad substrate scope based on the use of  $\alpha$ -amido sulfones and commercially available chiral phase-transfer catalysts (PTC).

Initially, we focused on chiral salts derived from cinchona alkaloids and were pleased to find that the reaction proceeded smoothly at room temperature, affording the vinylogous Mannich product as a single regioisomer.

The feasibility of our organocatalytic asymmetric approach was first tested by mixing  $\alpha$ -amido sulfone and  $\alpha,\alpha$ -dicyanoolefin in toluene with a series of cinchona alkaloid derivatives. The results of the investigation revealed that the reaction could proceed smoothly to yield the desired products. However, the enantioselectivities varied greatly depending on the cinchona alkaloid derived salts and bases used. The catalytic system of chiral quaternary ammonium salt derived from cinchonidine (20 mol %) and  $K_2CO_3$  exhibited the most promising results in terms of ee (76%) and yield (98%) at 20 °C (Table 1, entry 2).

Next, we investigated the effect of reaction medium, reaction temperature and chiral PTC loadings. It was found that the reaction proceeded smoothly in non-polar solvents, but no product was obtained with polar protic solvent. By lowering the temperature to 0 °C, the desired product could be furnished in poor yield and enantioselectivity. No further improvements could be obtained when the process were carried out under other reaction conditions, such as the change of solvents, bases and chiral PTC loadings.

Having optimized the reaction conditions for the asymmetric Mannich reaction of  $\alpha,\alpha$ -dicyanoolefin with  $\alpha$ -amido sulfone in toluene, it was extended to other substrates under the optimizing catalytic system. A variety of  $\alpha,\alpha$ -vinyl malononitriles and  $\alpha$ -amido sulfones were evaluated under the optimized reaction conditions, and the results are summarized in Table 1. As shown in Table 1, various  $\alpha$ -amido sulfone with both electron-donating and electron-withdrawing substituents could react with  $\alpha,\alpha$ -dicyanoolefins to furnish the desired products in good yields and moderate to good enantioselectivities smoothly, and only the *anti*-products were observed in the reactions (Figure 1). When the acyclic and cyclic aliphatic  $\alpha,\alpha$ -dicyanoolefins were tested,

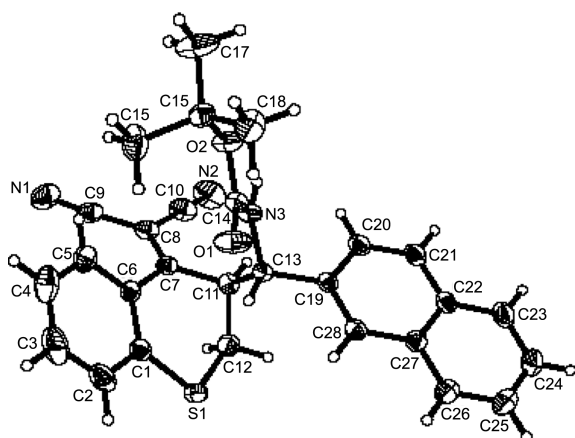


Figure 1. X-ray crystallographic structure of *rac*-3i.

Table 1. Asymmetric vinylogous Mannich reaction of  $\alpha,\alpha$ -dicyano-olefins and  $\alpha$ -amido sulfone<sup>a</sup>

Entry	Ar	X	Product	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	C <sub>6</sub> H <sub>5</sub>	S	<b>3a</b>	91	78
2	C <sub>6</sub> H <sub>5</sub>	O	<b>3b</b>	98	76
3	C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub>	<b>3c</b>	90	68
4	4-FC <sub>6</sub> H <sub>4</sub>	S	<b>3d</b>	92	75
5	4-MeOC <sub>6</sub> H <sub>4</sub>	S	<b>3e</b>	90	74
6	2-ClC <sub>6</sub> H <sub>4</sub>	S	<b>3f</b>	80	72
7	3-ClC <sub>6</sub> H <sub>4</sub>	S	<b>3g</b>	88	90
8	2-Thienyl	S	<b>3h</b>	90	54
9	2-Naphthyl	S	<b>3i</b>	85	65
10	3-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub>	<b>3j</b>	88	70

<sup>a</sup>The reaction was carried out on 0.5 mmol scale in toluene at 20 °C.

<sup>b</sup>Isolated yields after chromatographic purification. <sup>c</sup>Determined by chiral HPLC analysis; the relative and absolute configuration of products was assigned by comparison with optical rotation and/or retention time on chiral HPLC in ref. 2(e).

the products were obtained in low ee.

This method offers several advantages such as moderate to good enantioselectivity, high conversions, cleaner reaction profiles, simple experimental and work-up procedures.

In conclusion, this simple and easy reproducible procedure catalyzed by chiral quaternary ammonium salt derived from

cinchonidine could afford multifunctional products with two vicinal chiral tertiary carbon centers simultaneously. Further studies are under way to expand the synthetic utility of this new reaction, as well as the application of this catalytic system in other asymmetric transformations.

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- Crystallographic data for the structure *rac*-3i have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 700241. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- Typical Experimental Procedure.** A mixture of **1a** (0.55 mmol), **2a** (0.5 mmol), chiral PTC (0.1 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.2 mmol) in toluene (5.0 mL) was stirred for 8 h at rt. Then the reaction was quenched by adding 5 mL 1 M HCl. The mixture was extracted with EtOAc, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the desired product **3a** in 91% yield.  $[\alpha]_D^{25} = -203.7$  ( $c = 0.98$ , EtOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.89 (d,  $J = 7.9$  Hz, 1H), 7.45–7.33 (m, 6H), 7.26 (d,  $J = 8.0$  Hz, 1H), 7.22 (d,  $J = 7.4$  Hz, 1H), 4.92–4.85 (m, 2H), 3.80–3.78 (m, 1H), 3.20 (d,  $J = 13.6$  Hz, 1H), 2.52 (dd,  $J = 3.5$ , 13.9 Hz, 1H), 1.36 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  177.2, 154.3, 138.3, 137.7, 133.7, 129.4, 128.9, 126.9, 125.2, 118.1, 113.5, 113.1, 85.1, 80.5, 55.6, 47.2, 28.2, 25.6; MS: C<sub>24</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>S<sup>+</sup>Na 440.24; The enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min),  $t_{\text{minor}} = 7.031$  min,  $t_{\text{major}} = 9.529$  min.