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## Asymmetric Michael addition reactions of pyrrolones with chalcones catalyzed by vicinal primary-diamine salts†

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The efficient asymmetric Michael addition reactions of pyrrolones with chalcones catalyzed by a simple and commercially available chiral 1,2-diaminocyclohexane-2-(*N*-Boc-amino)benzoic acid have been developed to provide the corresponding Michael adducts in good yields (up to 90%) and high enantioselectivities (up to 95% ee).

Pyrrolones are privileged heterocyclic scaffolds found in a number of natural and synthetic molecules (Fig. 1),<sup>1</sup> which are reported to possess important pharmacological activities, especially antibacterial and antifungal,<sup>2</sup> anti-tubercular,<sup>3</sup> anti-convulsant activity,<sup>4</sup> immunosuppressive activity,<sup>5</sup> anticancer activity,<sup>6</sup> analgesic and anti-inflammatory activity.<sup>7</sup> Additionally, optical pyrrolones can act as synthetic precursors of some natural products.<sup>8</sup> In particular, chiral 5-substituted pyrrolones and their derivatives display marvelous biological properties,<sup>9</sup> which undoubtedly increase their importance both in chemical synthesis and synthetic methodologies. Therefore, the exploration of asymmetric reactions from readily available starting material pyrrolones to their 5-substituted derivatives has recently appeared extremely attractive.

In general, these asymmetric reactions include asymmetric Michael addition reaction, asymmetric Aldol condensation reaction and asymmetric Mannich reaction.<sup>10</sup> Recently, some secondary and tertiary amines, such as proline and its derivatives, thioureas, quinines and cinchona alkaloids were reported to catalyze above asymmetric reactions.<sup>11</sup> Great improvement

has been made in asymmetric Michael addition reaction (Fig. 2). For example, Chen and co-workers achieved satisfied results in the enantio- and diastereoselective Michael reaction of *N*-Boc pyrrolone with  $\alpha,\beta$ -unsaturated aldehydes catalyzed by proline,<sup>12</sup> Feng's group developed a novel guanidine combining with secondary amine as bifunctional catalysts for the asymmetric Michael reaction of *N*-Boc pyrrolone with malonates.<sup>13</sup> However, to the best of our knowledge, chiral primary amine has rarely been used to the 5-deprotonation of pyrrolone pathway,<sup>14</sup> and the poor reactive chalcones have never been reported to proceed asymmetric Michael reaction with pyrrolones. So it still represents a challenging task regarding the reactivity and stereo-selectivity of the two relatively inert reactants.

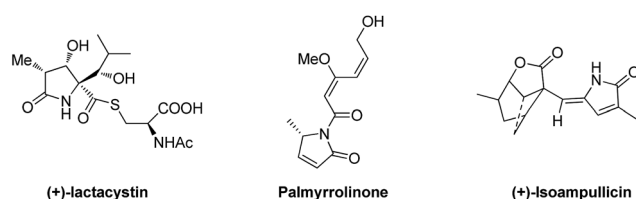


Fig. 1 Representative compounds containing pyrrolone scaffold.

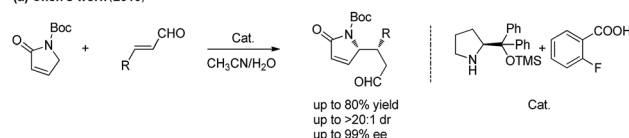
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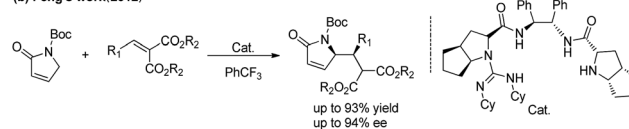
‡ These authors contributed equally to the work.

## Previous reports:

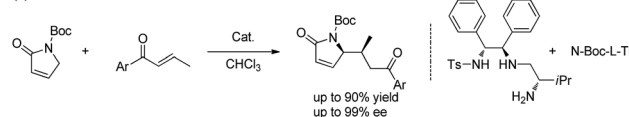
## (a) Chen's work (2010)



## (b) Feng's work (2012)



## (c) Ye's work (2011)



## (d) Yuan's work (2016)

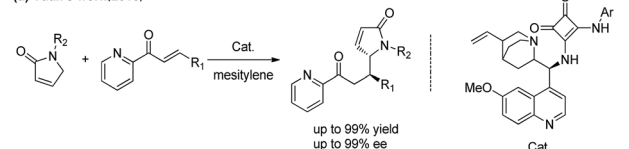
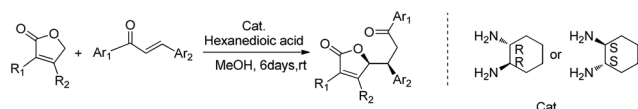


Fig. 2 Asymmetric Michael addition reactions of pyrrolones reported previously.

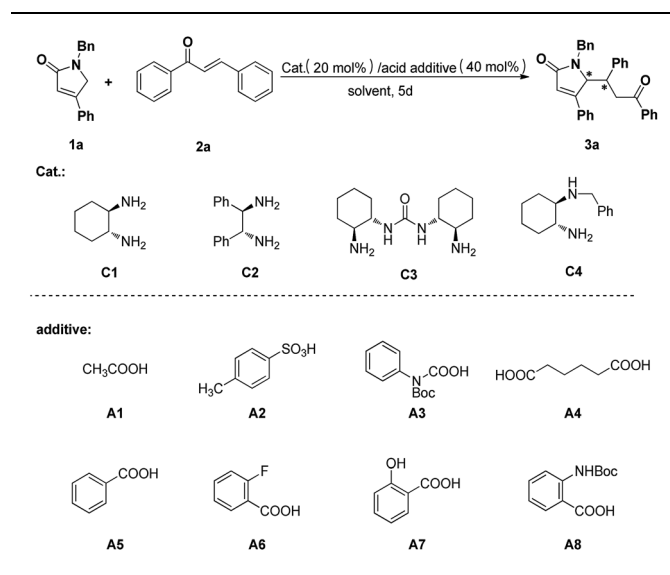
In our previous report, we have successfully realized the asymmetric Michael addition reactions of furanones with chalcones using simple chiral primary-diamine salts (Scheme 1).<sup>15</sup> As an extension of our work, herein, we wish to disclose an efficient asymmetric Michael addition reaction of pyrrolones with chalcones catalyzed by chiral primary-diamine salts (Table 1).

Our initial investigation began with the reaction of 4-phenyl *N*-benzyl pyrrolone (**1a**) and chalcone (**2a**) using chiral (1*R*, 2*R*)-cyclohexane-1,2-diamine (**C1**, 20 mol%) as catalyst and acetic



Scheme 1 Organocatalyzed direct Michael addition reactions of furanones to chalcones.

Table 1 Optimization of reaction conditions<sup>a</sup>



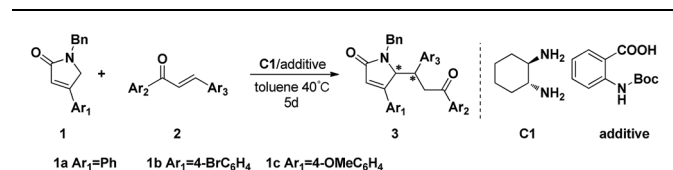
| Entry | Cat. | Solvent | Additive | T (°C) | Yield <sup>b</sup> (%) | dr <sup>c</sup> | ee <sup>d</sup> (%) |
|-------|------|---------|----------|--------|------------------------|-----------------|---------------------|
| 1     | C1   | MeOH    | A1       | r.t.   | 25                     | 8 : 1           | 89                  |
| 2     | C2   | MeOH    | A1       | r.t.   | Trace                  | —               | —                   |
| 3     | C3   | MeOH    | A1       | r.t.   | 0                      | —               | —                   |
| 4     | C4   | MeOH    | A1       | r.t.   | Trace                  | —               | —                   |
| 5     | C1   | MeOH    | A2       | r.t.   | 0                      | —               | —                   |
| 6     | C1   | MeOH    | A3       | r.t.   | 20                     | 12 : 1          | 93                  |
| 7     | C1   | MeOH    | A4       | r.t.   | 25                     | 18 : 1          | 91                  |
| 8     | C1   | MeOH    | A5       | r.t.   | 27                     | 10 : 1          | 94                  |
| 9     | C1   | MeOH    | A5       | 40     | 45                     | 1 : 1           | 55                  |
| 11    | C1   | EtOH    | A5       | 40     | 30                     | 2 : 1           | 85                  |
| 12    | C1   | PhMe    | A5       | 40     | 48                     | 1 : 1           | 90                  |
| 13    | C1   | PhMe    | A6       | 40     | 50                     | 3 : 1           | 91                  |
| 14    | C1   | PhMe    | A7       | 40     | 80                     | 1 : 1           | 80                  |
| 15    | C1   | PhMe    | A8       | 40     | 65                     | 3 : 2           | 95                  |

<sup>a</sup> All reactions were carried out using 1.0 equiv. of **1a** (0.15 mmol), 1.5 equiv. of **2a** (0.225 mmol), and 20 mol% of catalyst (0.03 mmol), 40 mol% of additive (0.06 mmol). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by NMR. <sup>d</sup> Determined by chiral HPLC analysis.

acid (**A1**, 40 mol%) as additive in methanol at room temperature, and the desired product **3a** was obtained in 25% yield with 8 : 1 dr and 89% ee (Table 1, entry 1). Encouraged by this result, we began the further optimization as follows. Firstly, different chiral primary amine catalysts were screened (Table 1, entries 1–4) and **C1** still was the best one. Then, the effect of the additive on the reaction was tested (Table 1, entries 5–8). It can be seen that all selected additives except **A2** worked well and **A5** is better by comparison (Table 1, entry 8). By raising the reaction temperature from r.t. to 40 °C, the yield of **3a** was improved to 45%, unfortunately, its stereoselectivity was significantly decreased (Table 1, entry 9). Further, solvent screening revealed that compound **3a** could be obtained in 48% yield with 90% ee in toluene at 40 °C (Table 1, entry 12). In order to further optimize the yield and stereoselectivity, the derivatives of benzoic acid (**A6–A8**) were examined (Table 1, entries 13–15). The results revealed that, using **C1** as catalyst and **A8** as additive, the reaction between substrates **1a** and **2a** in toluene at 40 °C gave the desired product **3a** in 65% yield, 3 : 2 dr and 95% ee (Table 2, entry 15).

With the optimized conditions in hand, the application scope of the catalytic system was then explored. As shown in Table 2, different 4-aromatic ring substituted *N*-benzyl pyrrolones react well with variety of chalcones giving the corresponding products **3** in moderate to good yields and high enantioselectivities. For *N*-benzyl pyrrolones (Table 2, entries 1–3), the electron nature of the substituents on the aromatic ring at the 4-position of *N*-benzyl pyrrolones (**1**) did not have an

Table 2 Substrate scope for the Michael addition reaction of **1** and **2**<sup>a</sup>



| Entry | 1         | Ar <sub>2</sub>                   | Ar <sub>3</sub>                                 | 3/yield <sup>b</sup> (%) | dr syn : anti <sup>c</sup> | ee (%) (syn) <sup>d</sup> |
|-------|-----------|-----------------------------------|---|--------------------------|----------------------------|---------------------------|
| 1     | <b>1a</b> | Ph                                | Ph  | <b>3a</b> /65            | 3 : 2                      | 95                        |
| 2     | <b>1b</b> | Ph                                | Ph  | <b>3b</b> /40            | 2.5 : 1                    | 90                        |
| 3     | <b>1c</b> | Ph                                | Ph  | <b>3c</b> /60            | 2 : 1                      | 90                        |
| 4     | <b>1a</b> | Ph                                | 3-MeOC <sub>6</sub> H <sub>4</sub>              | <b>3d</b> /70            | 4 : 3                      | 90                        |
| 5     | <b>1a</b> | Ph                                | 4-ClC <sub>6</sub> H <sub>4</sub>               | <b>3e</b> /62            | 2 : 1                      | 81                        |
| 6     | <b>1a</b> | Ph                                | 3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | <b>3f</b> /75            | 2 : 1                      | 92                        |
| 7     | <b>1c</b> | Ph                                | 3-MeOC <sub>6</sub> H <sub>4</sub>              | <b>3g</b> /64            | 3 : 1                      | 93                        |
| 8     | <b>1c</b> | Ph                                | 3-MeC <sub>6</sub> H <sub>4</sub>               | <b>3h</b> /55            | 5 : 3                      | 85                        |
| 9     | <b>1c</b> | Ph                                | 4-MeC <sub>6</sub> H <sub>4</sub>               | <b>3i</b> /60            | 2.5 : 1                    | 85                        |
| 10    | <b>1c</b> | Ph                                | 3-ClC <sub>6</sub> H <sub>4</sub>               | <b>3j</b> /82            | 2 : 1                      | 83                        |
| 11    | <b>1c</b> | Ph                                | 4-ClC <sub>6</sub> H <sub>4</sub>               | <b>3k</b> /64            | 2 : 1                      | 87                        |
| 12    | <b>1c</b> | Ph                                | 4-FC <sub>6</sub> H <sub>4</sub>                | <b>3l</b> /55            | 2 : 1                      | 85                        |
| 13    | <b>1c</b> | 4-MeC <sub>6</sub> H <sub>4</sub> | Ph  | <b>3m</b> /69            | 5 : 4                      | 84                        |
| 14    | <b>1c</b> | 4-MeC <sub>6</sub> H <sub>4</sub> | 3-MeC <sub>6</sub> H <sub>4</sub>               | <b>3n</b> /66            | 1 : 1                      | 85                        |
| 15    | <b>1c</b> | 4-MeC <sub>6</sub> H <sub>4</sub> | 3-BrC <sub>6</sub> H <sub>4</sub>               | <b>3o</b> /64            | 2.5 : 1                    | 86                        |
| 16    | <b>1c</b> | 4-MeC <sub>6</sub> H <sub>4</sub> | 4-FC <sub>6</sub> H <sub>4</sub>                | <b>3p</b> /90            | 1 : 1                      | 87                        |

<sup>a</sup> All reactions were carried out using 1.0 equiv. of **1a** (0.15 mmol), 1.5 equiv. of **2a** (0.225 mmol), and 20 mol% of catalyst (0.03 mmol), 40 mol% of additive (0.06 mmol). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by NMR. <sup>d</sup> Determined by chiral HPLC analysis.



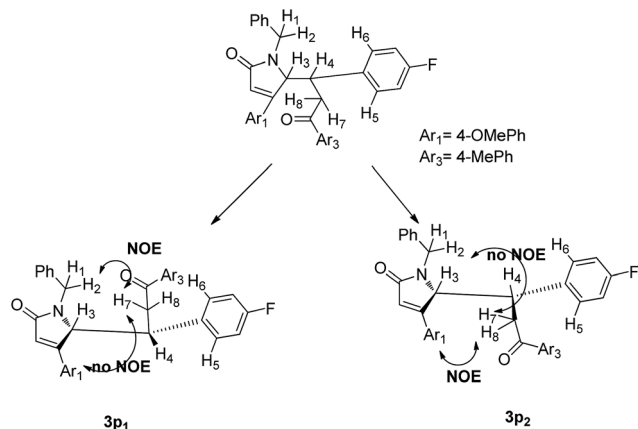


Fig. 3 NOESY analysis of product **3p**.

obvious effect on either diastereoselectivity or enantioselectivity when ignoring the fact that 4-bromo substituent decreased the yield (Table 2, entry 2). As regards chalcones, whatever their aromatic rings  $Ar_2$  or  $Ar_3$  contained electron-rich or electron-deficient substituents, the reaction remained stable yields and high enantioselectivities.

NOESY experiments performed on compound **3p**,<sup>16</sup> revealed strong correlations between hydrogen 2 and 5, 6, 7, 8 on **3p**<sub>1</sub>, and no correlations between the hydrogens on  $Ar_1$  and hydrogen 7. As for **3p**<sub>2</sub>, on the contrary, there were strong correlations between the hydrogens on  $Ar_1$ , hydrogen 7, but no correlations between hydrogen 2 and 7, 8. Thus, the NOESY experiments allowed us to confirm the relative configuration of product **3p** (Fig. 3). (see ESI†). Unfortunately, we were unable to grow quality crystals to determine compound **3p**'s absolute configuration.

## Conclusions

In conclusion, we have developed an efficient asymmetric Michael addition reaction of 4-aromatic ring substituted *N*-benzyl pyrrolones with chalcones utilizing the simple and commercially available chiral 1,2-diaminocyclohexane-2-(*N*-Boc-amino)benzoic acid as the cooperative catalysts. The corresponding Michael addition products were obtained in moderate to good yields (up to 90%) and excellent enantioselectivity (up to 95% ee). Further studies and applications of vicinal primary diamine as catalyst in asymmetric reactions are currently underway in our laboratory.

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