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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),[1] which are reported to possess important pharmacological activities, especially antibacterial and antifungal,[2] anti-tubercular,[3] anti-convulsant activity,[4] immunosuppressive activity,[5] anticancer activity,[6] analgesic and anti-inflammatory activity.[7] Additionally, optical pyrrolones can act as synthetic precursors of some natural products.[8] In particular, chiral 5-substituted pyrrolones and their derivatives display marvelous biological properties,[9] which undoubtably 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.[10] Recently, some secondary and tertiary amines, such as proline and its derivatives, thioureas, quinines and cinchona alkaloids were reported to catalyze above asymmetric reactions.[11] 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 α,β-unsaturated aldehydes catalyzed by proline,[12] 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.[13] However, to the best of our knowledge, chiral primary amine has rarely been used to the 5-deprotonation of pyrrolone pathway,[14] 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 stereoselectivity of the two relatively inert reactants.

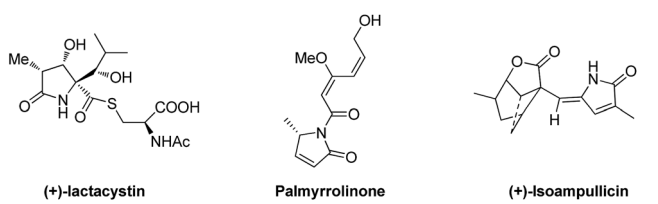


Fig. 1 Representative compounds containing pyrrolone scaffold.

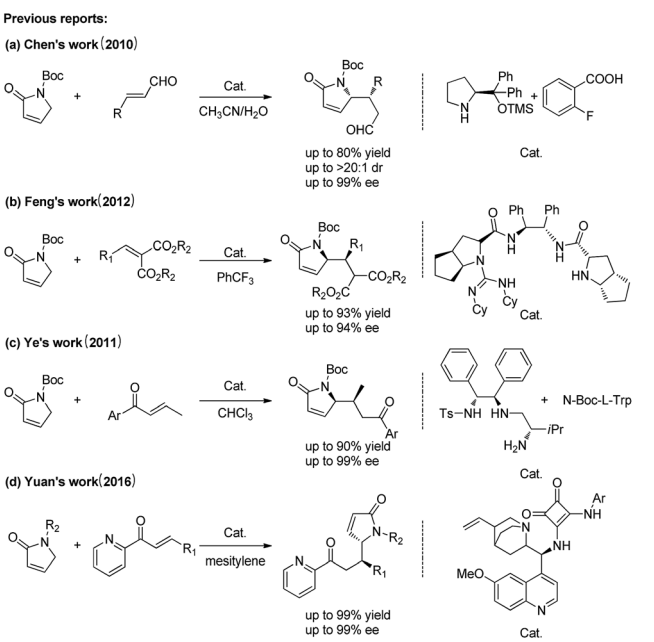


Fig. 2 Asymmetric Michael addition reactions of pyrrolones reported previously.

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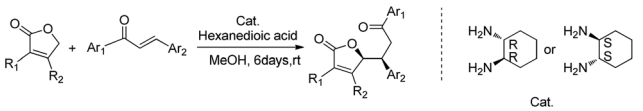
In our previous report, we have successfully realized the asymmetric Michael addition reactions of furanones with chalcones using simple chiral primary-diamine salts (Scheme 1).[15] As an extension of our work, herein, we wish to disclose an efficient asymmetric Michael addition reaction of pyrrolones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

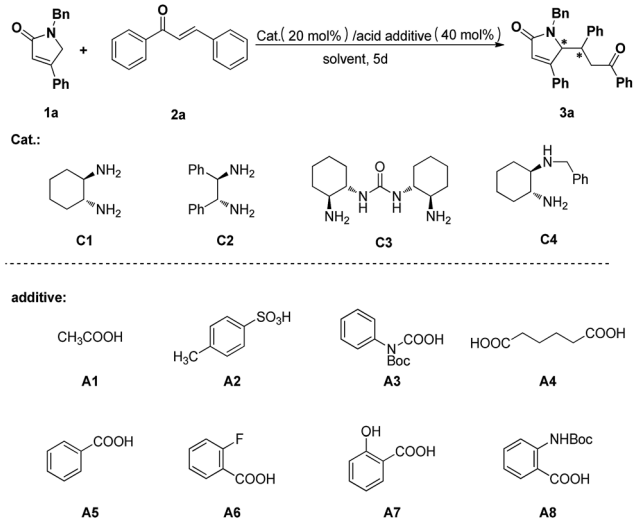
Our initial investigation began with the reaction of 4-phenyl *N*-benzyl pyrrolone (**1a**) and chalcone (**2a**) using chiral (1R, 2R)-cyclohexane-1,2-diamine (**C1**, 20 mol%) as catalyst and acetic acid (**A1**, 40 mol%) as additive in methanol at room temperature, and the desired product **3a** was 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 been 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). Furtherly, 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




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

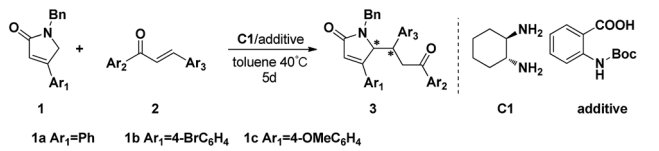
Table 1 Optimization of reaction conditions[a]




| Entry | Cat. | Solvent | Additive | T (°C) | Yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|---|---|
| 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 |

[a] 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). [b] Isolated yield. [c] Determined by NMR. [d] Determined by chiral HPLC analysis.

Table 2 Substrate scope for the Michael addition reaction of **1** and **2**[a]




| Entry | **1** | $Ar_2$ | $Ar_3$ | **3**/yield[b] (%) | dr *syn* : *anti*[c] | ee (%) (*syn*)[d] |
|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | Ph | **3a**/65 | 3 : 2 | 95 |
| 2 | **1b** | Ph | Ph | **3b**/40 | 2.5 : 1 | 90 |
| 3 | **1c** | Ph | Ph | **3c**/60 | 2 : 1 | 90 |
| 4 | **1a** | Ph | 3-$MeOC_6H_4$ | **3d**/70 | 4 : 3 | 90 |
| 5 | **1a** | Ph | 4-$ClC_6H_4$ | **3e**/62 | 2 : 1 | 81 |
| 6 | **1a** | Ph | 3-$NO_2C_6H_4$ | **3f**/75 | 2 : 1 | 92 |
| 7 | **1c** | Ph | 3-$MeOC_6H_4$ | **3g**/64 | 3 : 1 | 93 |
| 8 | **1c** | Ph | 3-$MeC_6H_4$ | **3h**/55 | 5 : 3 | 85 |
| 9 | **1c** | Ph | 4-$MeC_6H_4$ | **3i**/60 | 2.5 : 1 | 85 |
| 10 | **1c** | Ph | 3-$ClC_6H_4$ | **3j**/82 | 2 : 1 | 83 |
| 11 | **1c** | Ph | 4-$ClC_6H_4$ | **3k**/64 | 2 : 1 | 87 |
| 12 | **1c** | Ph | 4-$FC_6H_4$ | **3l**/55 | 2 : 1 | 85 |
| 13 | **1c** | 4-$MeC_6H_4$ | Ph | **3m**/69 | 5 : 4 | 84 |
| 14 | **1c** | 4-$MeC_6H_4$ | 3-$MeC_6H_4$ | **3n**/66 | 1 : 1 | 85 |
| 15 | **1c** | 4-$MeC_6H_4$ | 3-$BrC_6H_4$ | **3o**/64 | 2.5 : 1 | 86 |
| 16 | **1c** | 4-$MeC_6H_4$ | 4-$FC_6H_4$ | **3p**/90 | 1 : 1 | 87 |

[a] 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). [b] Isolated yield. [c] Determined by NMR. [d] Determined by chiral HPLC analysis.

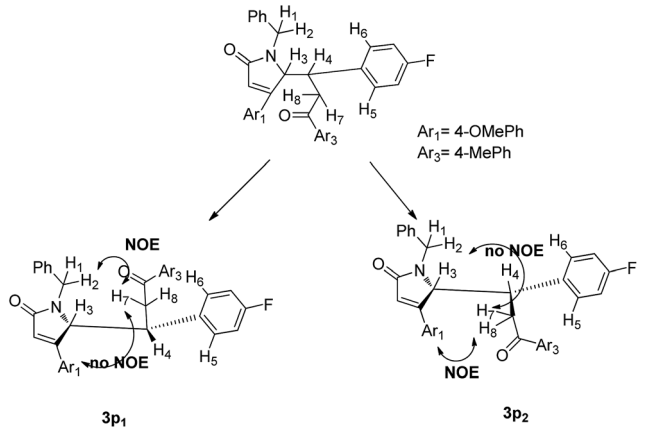



Fig. 3 NOESY analysis of product **3p**.

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**,[16] revealed strong correlations between hydrogen 2 and 5, 6, 7, 8 on $\mathbf{3p_1}$, and no correlations between the hydrogens on $Ar_1$ and hydrogen 7. As for $\mathbf{3p_2}$, 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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