

## PAPER

 View Article Online  
 View Journal | View Issue
Cite this: *RSC Adv.*, 2017, 7, 24547

Received 15th March 2017

Accepted 27th April 2017

DOI: 10.1039/c7ra03069j

rsc.li/rsc-advances

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

Xiaolei Du,‡ Dawei Yin,‡ Zemei Ge, Xin Wang\* and Runtao Li 

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.

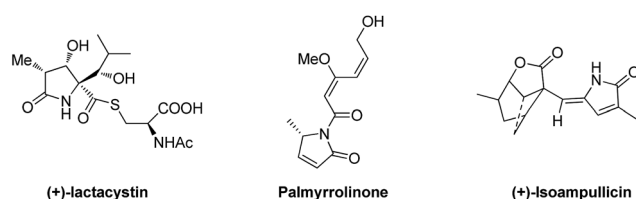


Fig. 1 Representative compounds containing pyrrolone scaffold.

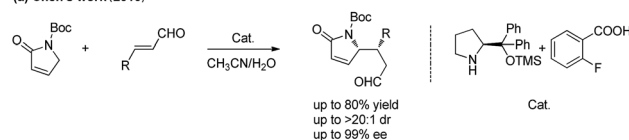
State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Science, Peking University, Beijing 100191, China. E-mail: ximwang@bjmu.edu.cn; lirt@bjmu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra03069j

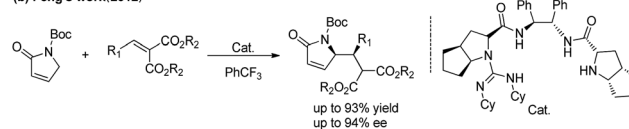
‡ These authors contributed equally to the work.

## Previous reports:

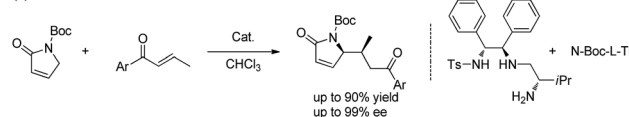
## (a) Chen's work (2010)



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



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



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

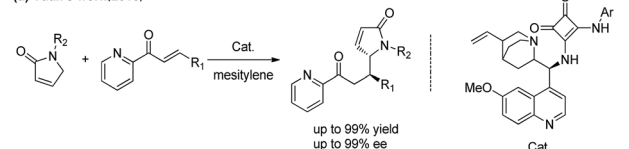
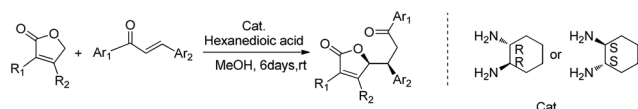


Fig. 2 Asymmetric Michael addition reactions of pyrrolones reported previously.



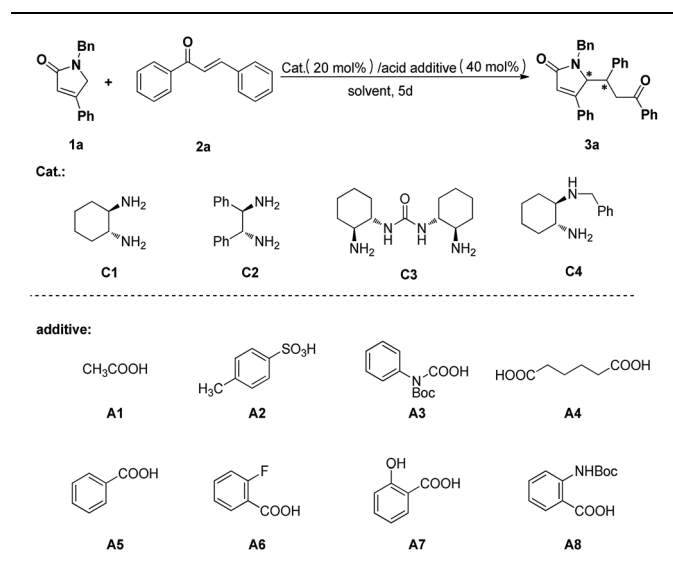
In our previous report, we have successfully realized the asymmetric Michael addition reactions of furanones with chalcones using simple chiral primary-diamine salts (Scheme 1).<sup>15</sup> As an extension of our work, herein, we wish to disclose an efficient asymmetric Michael addition reaction of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



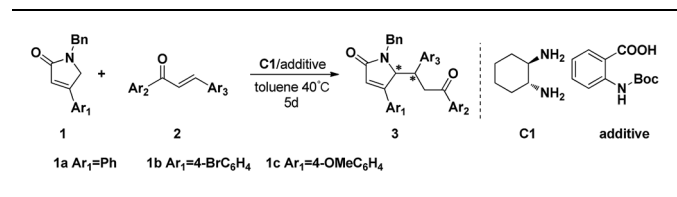
Entry	Cat.	Solvent	Additive	T (°C)	Yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>d</sup> (%)
1	C1	MeOH	A1	r.t.	25	8 : 1	89
2	C2	MeOH	A1	r.t.	Trace	—	—
3	C3	MeOH	A1	r.t.	0	—	—
4	C4	MeOH	A1	r.t.	Trace	—	—
5	C1	MeOH	A2	r.t.	0	—	—
6	C1	MeOH	A3	r.t.	20	12 : 1	93
7	C1	MeOH	A4	r.t.	25	18 : 1	91
8	C1	MeOH	A5	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 **2a**<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.



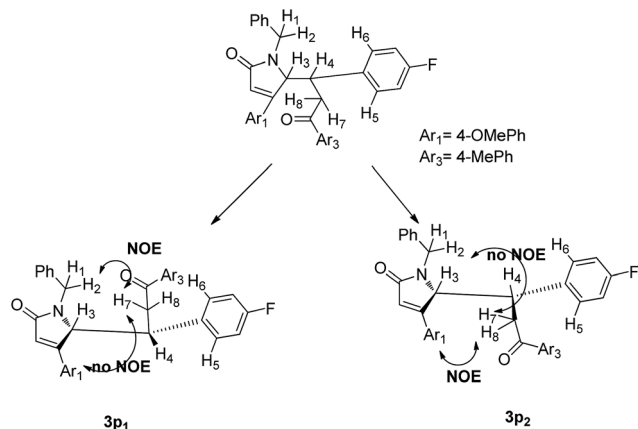


Fig. 3 NOESY analysis of product **3p**.

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  $\text{Ar}_2$  or  $\text{Ar}_3$  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  $\text{Ar}_1$  and hydrogen 7. As for **3p**<sub>2</sub>, on the contrary, there were strong correlations between the hydrogens on  $\text{Ar}_1$ , 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.

## Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (no. 81673287).

## Notes and references

- (a) K. C. Nicolaou, S. M. Dalby and U. Majumder, *J. Am. Chem. Soc.*, 2008, **130**, 14942–14943; (b) P. Magnus, T. Katoh, I. R. Matthews and J. C. Huffman, *J. Am. Chem.*

- Soc.*, 1989, **111**, 6707–6711; (c) S. E. Denmark, Y. C. Moon and C. B. W. Senanayake, *J. Am. Chem. Soc.*, 1990, **112**, 311–315.
- A. Husain, M. S. Y. Khan, S. M. Hasan and M. M. Alam, *Eur. J. Med. Chem.*, 2005, **40**, 1394–1404.
- (a) A. Husain, S. M. Hasan, S. Lal and M. M. Alam, *Indian J. Pharm. Sci.*, 2006, **68**, 536–538; (b) A. Ahmad, A. Husain, S. A. Khan, M. Mujeeb and A. Bhandari, *J. Saudi Chem. Soc.*, 2015, **19**, 340–346.
- C. Grunwald, C. Rundfeldt, H. J. Lankau, T. Arnold, N. Hofgen, R. Dost, U. Egerland, H. J. Hofmann and K. Unverferth, *J. Med. Chem.*, 2006, **49**, 1855–1866.
- R. D. Alessio, A. Bargiotti, O. Carlini, F. Colotta, M. Ferrari, P. Gnocchi, A. Isetta, N. Mongelli, P. Motta, A. Rossi, M. Rossi, M. Tibolla and E. Vanotti, *J. Med. Chem.*, 2000, **43**, 2557–2565.
- M. M. Alam, A. Husain, S. M. Hasan and T. Anwer, *Eur. J. Med. Chem.*, 2009, **44**, 2636–2642.
- S. Olla, F. Manetti, E. Crespan, G. Maga, A. Angelucci, S. Schenone, M. Bologna and M. Botta, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1512–1516.
- (a) G. R. Pettit, S. Freeman, M. J. Simpson, M. A. Thompson, M. R. Boyd, M. D. Williams, G. R. Pettit and D. L. Doubek, *Anti-Cancer Drug Des.*, 1995, **10**, 243–249; (b) K. Sakata, K. Aoki, C. F. Chang, A. Sakurai, S. Tamura and S. Murakoshi, *Agric. Biol. Chem.*, 1978, **42**, 457–459; (c) M. Tereda, M. Sano, A. I. Ishii, H. Kino, S. Fukushima and T. J. Noro, *J. Pharm. Soc. Jpn.*, 1982, **79**, 93–98; (d) H. Shinozaki and M. Ishida, *Brain Res.*, 1985, **334**, 33–40; (e) D. Li, Y. J. Wang, L. Q. Wang, J. Wang, P. X. Wang, K. Z. Wang, L. Liu, D. S. Liu, X. X. Jiang and D. X. Yang, *Chem. Commun.*, 2016, **52**, 9640–9643.
- (a) L. Lin, J. Zhang, X. Ma, X. Fu and R. Wang, *Org. Lett.*, 2011, **13**, 6410–6413; (b) J. Zhang, X. Liu, X. Ma and R. Wang, *Chem. Commun.*, 2013, **49**, 9329–9331; (c) C. Curti, B. Ranieri, L. Battistini, G. Rassu, V. Zambrano, G. Pelosi, G. Casiraghi and F. Zanardi, *Adv. Synth. Catal.*, 2010, **352**, 2011–2022; (d) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 3666–3667.
- (a) A. R. Choudhury and S. Mukherjee, *Org. Biomol. Chem.*, 2012, **10**, 7313–7320; (b) Y. Chen, U. Das, M. Liu and W. Lin, *J. Org. Chem.*, 2015, **80**, 1985–1992; (c) J. L. Zhang, X. H. Liu, X. J. Ma and R. Wang, *Chem. Commun.*, 2013, **49**, 3300–3302; (d) J. L. Zhang, X. H. Liu, X. J. Ma and R. Wang, *Chem. Commun.*, 2013, **49**, 9329–9331; (e) Y. Zhang, Y. L. Shao, H. S. Xu and W. Wang, *J. Org. Chem.*, 2011, **76**, 1472–1474; (f) T. Y. Liu, H. L. Cui, J. Long, B. J. Li, Y. Wu, L. S. Ding and Y. C. Chen, *J. Am. Chem. Soc.*, 2007, **129**, 1878–1879; (g) N. E. Shepherd, H. Tanabe, Y. J. Xu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 3666–3667; (h) J. T. Li, S. Qiu, X. Y. Ye, B. Zhu, H. J. Liu and Z. Y. Jiang, *J. Org. Chem.*, 2016, **81**, 11916–11923; (i) H. Tanabe, Y. J. Xu, B. Sun, S. Matsunaga and M. Shibasaki, *Heterocycles*, 2012, **86**, 611–622; (j) S. G. Zlotin and S. V. Kochetkov, *Russ. Chem. Rev.*, 2015, **84**, 1077–1099; (k) J. C. Kizirian, *Chem. Rev.*, 2008, **108**,



- 140–205; (l) Y. H. Lam, M. N. Grayson, M. C. Holland, A. Simon and K. N. Houk, *Acc. Chem. Res.*, 2016, **49**, 750–762.
- 11 (a) W. Wu, X. Li, H. C. Huang, X. Q. Yuan, J. Z. Lu, K. L. Zhu and J. X. Ye, *Angew. Chem., Int. Ed.*, 2013, **52**, 1743–1747; (b) J. W. Xie, L. Yue, D. Xue, X. L. Ma, Y. C. Chen, Y. Wu, J. Zhu and J. G. Deng, *Chem. Commun.*, 2006, **48**, 1563–1565; (c) T. B. Poulsen, C. Alemparte and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 11614–11615; (d) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726–3748; (e) J. L. Zhang, X. H. Liu, X. J. Ma and R. Wang, *Chem. Commun.*, 2013, **49**, 3300–3302.
- 12 X. Feng, H. Cui, S. Xu, L. Wu and Y. Chen, *Chem.–Eur. J.*, 2010, **16**, 10309–10312.
- 13 Y. Yang, S. Dong, X. Liu, L. Lin and X. Feng, *Chem. Commun.*, 2012, **48**, 5040–5042.
- 14 H. Huang, Z. Jin, K. Zhu, X. Liang and J. Ye, *Angew. Chem., Int. Ed.*, 2011, **50**, 3232–3235.
- 15 J. F. Wang, C. Qi, Z. M. Ge, T. M. Cheng and R. T. Li, *Chem. Commun.*, 2010, **46**, 2124–2126.
- 16 G. Chaubet, T. Coursindel, X. Morelli, S. Betzi, P. Roche, Y. Guari, A. Lebrun, L. Toupet, Y. Collette, I. Parrot and J. Martinez, *Org. Biomol. Chem.*, 2013, **11**, 4719–4726.

