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Cite this: *RSC Adv.*, 2017, **7**, 24547

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

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Received 15th March 2017
Accepted 27th April 2017

DOI: 10.1039/c7ra03069j

rsc.li/rsc-advances

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).

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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.

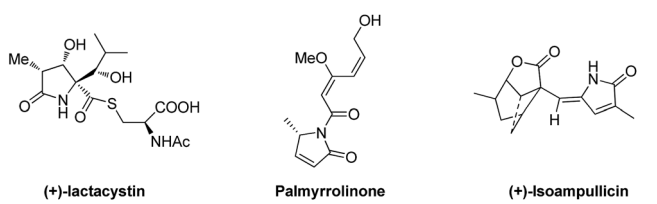

Fig. 1 Representative compounds containing pyrrolone scaffold.

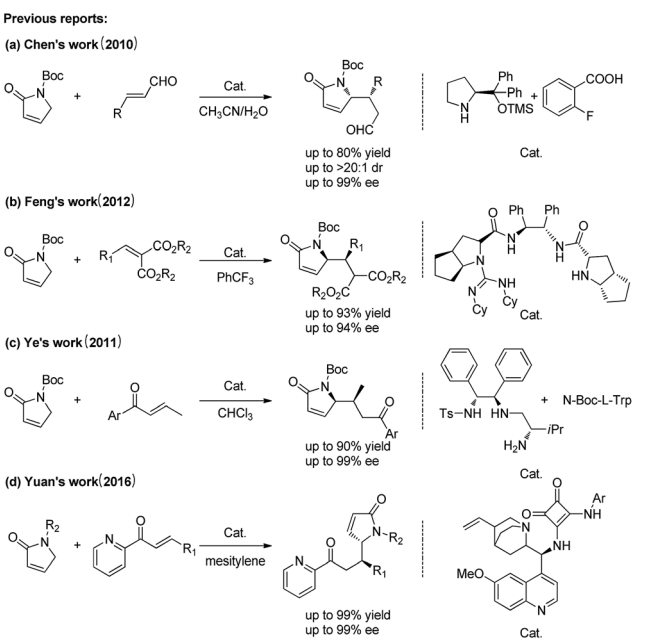

Fig. 2 Asymmetric Michael addition reactions of pyrrolones reported previously.

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

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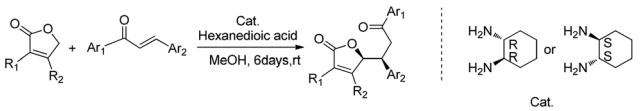
In our previous report, we have successfully realized the asymmetric Michael addition reactions of furanones with chalcones using simple chiral primary-diamine salts (Scheme 1).[15] As an extension of our work, herein, we wish to disclose an efficient asymmetric Michael addition reaction of pyrrolones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

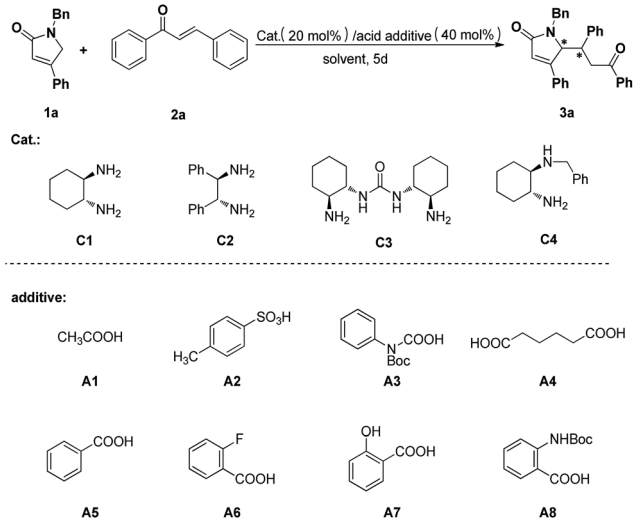
Our initial investigation began with the reaction of 4-phenyl *N*-benzyl pyrrolone (**1a**) and chalcone (**2a**) using chiral (1R, 2R)-cyclohexane-1,2-diamine (**C1**, 20 mol%) as catalyst and acetic acid (**A1**, 40 mol%) as additive in methanol at room temperature, and the desired product **3a** was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

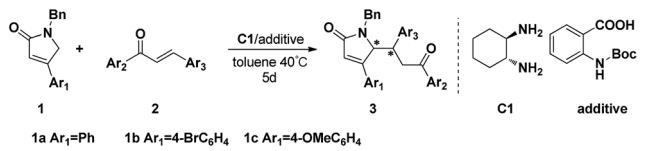
Table 1 Optimization of reaction conditions[a]



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.

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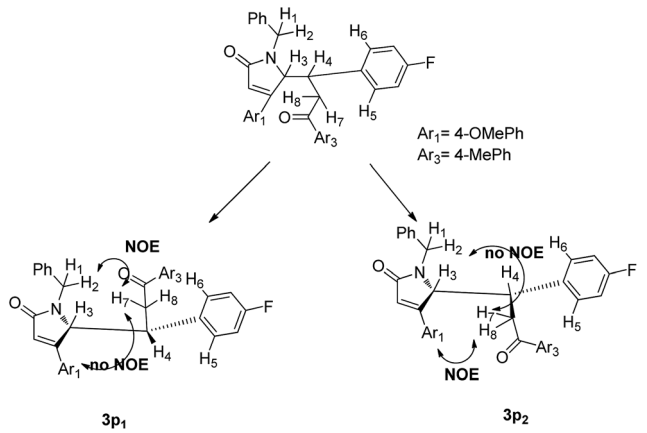

Fig. 3 NOESY analysis of product **3p**.

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.

Acknowledgements

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

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