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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 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.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 stereo-selectivity of the two relatively inert reactants.

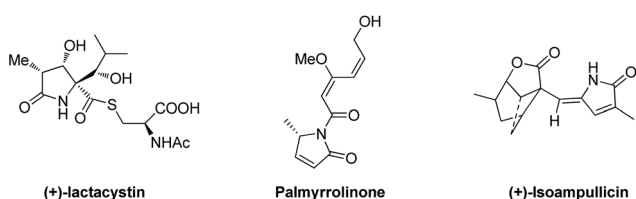


Fig. 1 Representative compounds containing pyrrolone scaffold.

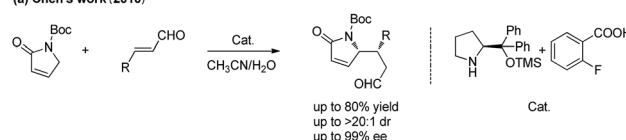
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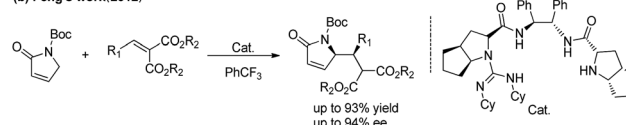
‡ These authors contributed equally to the work.

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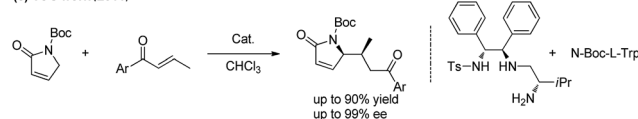
(a) Chen's work (2010)



(b) Feng's work (2012)



(c) Ye's work (2011)



(d) Yuan's work (2016)

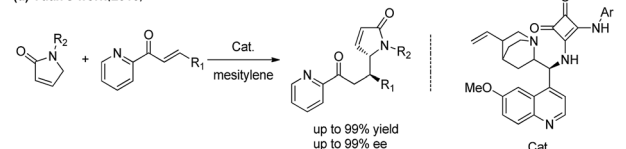
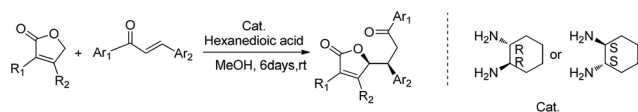


Fig. 2 Asymmetric Michael addition reactions of pyrrolones reported previously.



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).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 (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^a

additive:

A1: CH₃COOH
A2: H₃C-C₆H₄-SO₃H
A3: C₆H₅-N(Boc)-COOH
A4: HOOC(CH₂)₄COOH
A5: C₆H₅-COOH
A6: C₆H₄(F)-COOH
A7: C₆H₄(OH)-COOH
A8: C₆H₄(NHBoc)-COOH

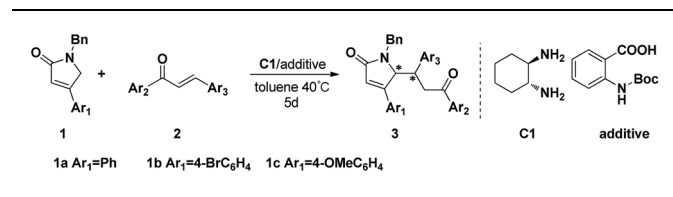
Entry	Cat.	Solvent	Additive	T (°C)	Yield ^b (%)	dr ^c	ee ^d (%)
1	C1	MeOH	A1	r.t.	25	8 : 1	89
2	C2	MeOH	A1	r.t.	Trace	—	—
3	C3	MeOH	A1	r.t.	0	—	—
4	C4	MeOH	A1	r.t.	Trace	—	—
5	C1	MeOH	A2	r.t.	0	—	—
6	C1	MeOH	A3	r.t.	20	12 : 1	93
7	C1	MeOH	A4	r.t.	25	18 : 1	91
8	C1	MeOH	A5	r.t.	27	10 : 1	94
9	C1	MeOH	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.

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). 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

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 ₆ H ₄	3d /70	4 : 3	90
5	1a	Ph	4-ClC ₆ H ₄	3e /62	2 : 1	81
6	1a	Ph	3-NO ₂ C ₆ H ₄	3f /75	2 : 1	92
7	1c	Ph	3-MeOC ₆ H ₄	3g /64	3 : 1	93
8	1c	Ph	3-MeC ₆ H ₄	3h /55	5 : 3	85
9	1c	Ph	4-MeC ₆ H ₄	3i /60	2.5 : 1	85
10	1c	Ph	3-ClC ₆ H ₄	3j /82	2 : 1	83
11	1c	Ph	4-ClC ₆ H ₄	3k /64	2 : 1	87
12	1c	Ph	4-FC ₆ H ₄	3l /55	2 : 1	85
13	1c	4-MeC ₆ H ₄	Ph	3m /69	5 : 4	84
14	1c	4-MeC ₆ H ₄	3-MeC ₆ H ₄	3n /66	1 : 1	85
15	1c	4-MeC ₆ H ₄	3-BrC ₆ H ₄	3o /64	2.5 : 1	86
16	1c	4-MeC ₆ H ₄	4-FC ₆ H 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.



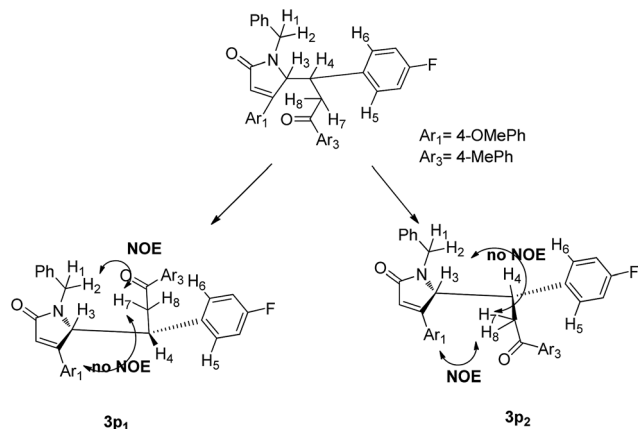


Fig. 3 NOESY analysis of product **3p**.

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 **3p**₁, and no correlations between the hydrogens on Ar_1 and hydrogen 7. As for **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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