Highly diastereo- and enantioselective Mannich reaction of lactones with *N*-Boc-aldimines catalyzed by bifunctional rosin-derived amine thiourea catalysts†‡

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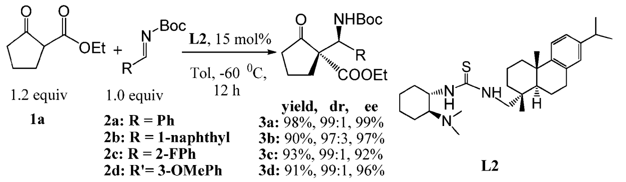
A highly efficient diastereo- and enantioselective Mannich reaction of lactones with a variety of *N*-Boc-aldimines by using bifunctional rosin-derived amine thiourea catalysts was investigated for the first time, in general, affording the adducts bearing quaternary stereogenic centers with high levels of enantio- and diastereoselectivity (up to 99% ee, and > 20 : 1 dr).

The asymmetric construction of chiral quaternary stereocenters on highly functionalized organic molecules represents a considerable challenge in modern organic synthesis.[1] The direct asymmetric Mannich-type reaction[2] of *N*-protected-aldimines, to date, has become one of the most important and versatile reactions for the construction of chiral amine-containing synthons bearing quaternary carbon centers,[3] and the development of asymmetric catalytic protocols in this field of research remains a highly desirable goal. In recent years, considerable effort has been devoted to the development of efficient chiral catalysts for enantioselective Mannich reactions and catalytic asymmetric Mannich reactions of aldehydes, ketones,[4] enolates and enolizable β-dicarbonyl compounds[5] have been presented by several groups. We recently reported a new class of thiourea bifunctional catalysts[6] based on rosin, which have successfully been applied to the construction of contiguous stereogenic centers containing an asymmetric quaternary carbon by the Michael reaction of α-substituted β-ketoesters to nitroalkenes.[7] Encouraged by these elegant advances, we found that this rosin-derived bifunctional thiourea was also revealed to be highly efficient for the construction of contiguous stereogenic centers containing an asymmetric quaternary carbon under the Mannich-type reaction system, and the excellent enantio- and diastereoselectivities were still observed when the electrophiles were further extended to *N*-Boc-aldimines (Scheme 1). In the context of our interest in the construction of quaternary carbon stereocenters,[7,8] and during our recent efforts for expanding the synthetic utility of this kind of rosin-derived amine thiourea,[9] we wished that the substrate scope could be extended to heterocyclic donors such as lactones considering their potential versatility as chiral building blocks.[10] To the best of our knowledge, despite only a few cases in the reported literature[3g,11] when the Mannich reaction of α-acetyl-γ-butyrolactone to one or two aldimines was achieved, a poor selectivity was observed without exception. Furthermore, the use of lactones as nucleophiles in catalytic asymmetric Mannich reaction have not yet been investigated systematically, and we believe this represents a major challenge.

We postulated that the chiral tertiary amine-thiourea would act in a bifunctional fashion (Scheme 2). The asymmetric Mannich reaction of lactone **4a** to *N*-Boc-aldimines might be initiated, in the presence of a chiral tertiary amine, by activating both *N*-Boc-aldimines and nucleophiles simultaneously to generate ternary complex **A**, affording stereoselective products by controlling the approach of nucleophiles to *N*-Boc-aldimines. Herein, the catalytic asymmetric Mannich reaction of several representative and useful lactones to a variety of *N*-Boc-aldimines by using rosin-derived tertiary amine-thiourea was investigated firstly, affording the products bearing quaternary stereogenic centers with up to 99% ee, and > 20 : 1 dr. We present our preliminary results in this field.

During the initial elaboration of solvent and reaction temperature, our investigation began by screening tertiary amine-thiourea catalysts **L1–L6** (Fig. 1) to evaluate their ability to promote the Mannich reaction of α-acetyl-γ-butyrolactone (**4a**) to *N*-Boc-aldimines (**2a**) in the presence of 15 mol% of ligand loading at −60 °C in toluene (Table 1). These results indicated that a dramatic ligand effect on yield and stereoselectivity was observed. Although thiourea **L1** provided high overall yield and excellent diastereoselectivity, poor enantioselectivity was obtained for the major diastereomer of **5a** (Table 1, entry 1). Tertiary amine-thiourea **L2**, which provided the best results in terms of yield and stereochemical outcome, was found to be the most promising catalyst for the



Scheme 1 Catalytic asymmetric Mannich-type reaction of ethyl cyclopentanone 2-carboxylate with *N*-Boc-aldimines.

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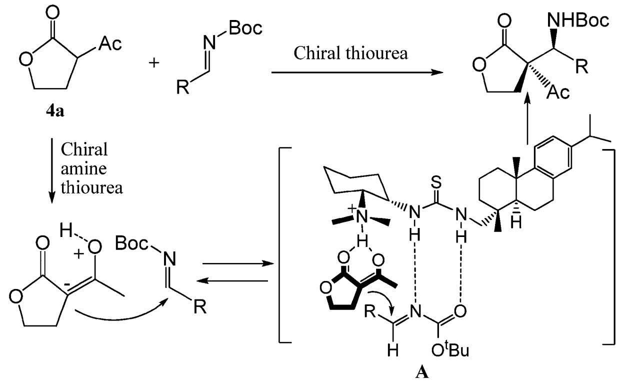


Scheme 2 Proposed mechanism for the asymmetric Mannich reaction of lactones with *N*-Boc-aldimines catalyzed by a rosin-derived amine thiourea catalyst.

reaction (Table 1, entry 2). With the purpose of obtaining a higher stereoselectivity, the reaction temperature was further lowered. Notably, no enhancement in the enantioselectivity was achieved with a significantly decrease in yield when the reaction was carried out at −78 °C (Table 1, entry 7).

Next, we explored the scope of the asymmetric Mannich reaction with respect to the lactones by using rosin-derived tertiary amine-thiourea **L2**. As can be seen by the results summarized in Table 2, the corresponding products **5a–8a** could be obtained with excellent diastereoselectivities. These results indicated that the enantioselectivity was found to depend significantly on the substituent $\mathbf{R^1}$ and the size of the cycle of the starting lactone. The reactions of five cyclic lactones bearing acetyl and propionyl groups as nucleophiles furnished the desired product in high yields (86% and 82%, respectively) with excellent enantioselectivities (91% and 90%, respectively, entries 1 and 4). In contrast, the benzoyl-substituted lactones gave low enantioselectivities (Table 2, entries 2 and 3).

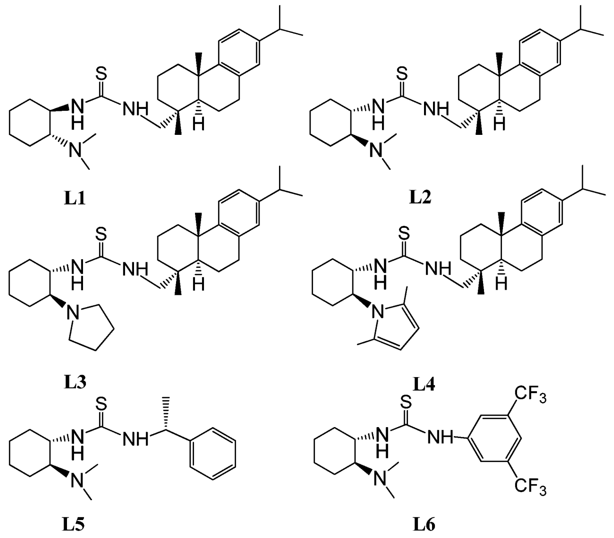
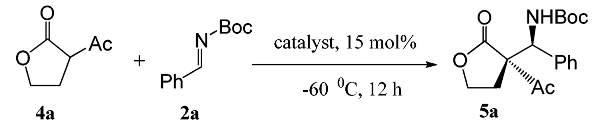


Fig. 1 Structure of thiourea catalysts.

Table 1 Screening of tertiary amine-thiourea catalysts[a]

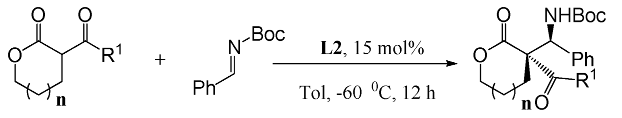


4a 1.2 equiv
2a 1.0 equiv
5a

Entry	Catalyst	Yield (%)[b]	dr[c]	ee (%)[d]
1	**L1**	88	> 20 : 1	46
2	**L2**	86	> 20 : 1	91
3	**L3**	65	> 20 : 1	73
4	**L4**	Trace	n.d.	n.d.
5	**L5**	55	3 : 1	22
6	**L6**	72	4 : 1	65
7[e]	**L2**	58	> 20 : 1	90

[a] The reaction was conducted with α-acetyl-γ-butyrolactone **4a** (0.12 mmol) and *N*-Boc-aldimines **2a** (0.1 mmol) in toluene (1.0 mL) at −60 °C for 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR and HPLC. [d] The ee values were determined by HPLC, and the relative and absolute configurations were determined by X-ray crystal data of **5g**. [e] The reaction was stirred at −78 °C.

Table 2 Variation of the lactones[a]



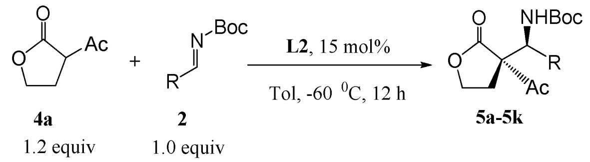
4a, n = 0, R^1 = Me
4b, n = 0, R^1 = Ph
4c, n = 1, R^1 = Ph
4d, n = 0, R^1 = Et
2a
5a-8a

Entry	4	Yield (%)[b]	dr[c]	ee (%)[d]
1	**4a**	(**5a**) 86	> 20 : 1	**91**
2[e]	**4b**	(**6a**) 72	> 20 : 1	**57**
3[f]	**4c**	(**7a**) 70	> 20 : 1	**30**
4	**4d**	(**8a**) 82	> 20 : 1	**90**

[a] The reaction was conducted with lactones (0.12 mmol) and *N*-Boc-aldimines **2a** (0.1 mmol) in toluene (1.0 mL) at −60 °C for 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR and HPLC, the other diastereomer was not observed by ^{1}HNMR and HPLC. [d] The ee values were determined by HPLC, and the relative and absolute configurations were determined by X-ray crystal data of **5g**. [e] The reaction was stirred at 0 °C. [f] The reaction was stirred at −15 °C.

We then investigated the generality of the protocol with respect to *N*-Boc-protected aldimines under the optimized reaction conditions. A range of substituted aromatic and heterocyclic *N*-Boc-aldimines was first examined in the catalytic Mannich-type reaction with lactone **4a** (Table 3). It is seen that a variety of aromatic *N*-Boc-aldimines bearing various types of substituents underwent the reaction to afford the desired products containing an asymmetric quaternary carbon in excellent diastereoselectivities (> 20 : 1) and high to excellent yields (81%–92%, entries 1–9). Although a comparatively low enantioselectivity was observed in *para*-Cl-substituted aromatic aldimines (75% ee, entry 9), in general, the reactions afforded high to excellent enantioselectivities (81%–99%). As expected, the reactions of heterocyclic *N*-Boc-aldimines also proceeded in > 20 : 1 dr, high to excellent enantioselectivities (93% and 87%, respectively) and high yields (80% and 81%, respectively, entries 10 and 11). The relative and absolute configurations of the products were determined by X-ray crystal structure analysis of **5g** (see the Supporting Information‡).

Table 3 Asymmetric Mannich reaction of lactone **4a** with a variety of *N*-Boc-aldimines[a]



Entry	R	Yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	(**5a**) 86	> 20 : 1	91
2	4-MePh	(**5b**) 82	> 20 : 1	99
3	2-MePh	(**5c**) 83	> 20 : 1	93
4	2-MeOPh	(**5d**) 89	> 20 : 1	88
5	3-MeOPh	(**5e**) 83	> 20 : 1	99
6	3-MePh	(**5f**) 92	> 20 : 1	82
7	2-BrPh	(**5g**) 85	> 20 : 1	98
8	2-FPh	(**5h**) 85	> 20 : 1	81
9	4-ClPh	(**5i**) 81	> 20 : 1	75
10	2-Thienyl	(**5j**) 80	> 20 : 1	93
11	3-Furyl	(**5k**) 81	> 20 : 1	87

[a] The reaction was conducted with lactone **4a** (0.12 mmol) and *N*-Boc-aldimines (0.1 mmol) in toluene (1.0 mL) at −60 °C for 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR and HPLC, the other diastereomer was not observed by ^{1}HNMR and HPLC. [d] The ee values were determined by HPLC, and the relative and absolute configurations were determined by X-ray crystal data of **5g**.

In summary, we have disclosed a highly efficient diastereo- and enantioselective Mannich reaction of lactones with a variety of *N*-Boc-aldimines catalyzed by bifunctional rosin-derived amine thiourea catalysts, affording the adducts bearing quaternary stereogenic centers with high levels of enantio- and diastereoselectivity (up to 99% ee, and > 20 : 1 dr). These organocatalysts based on rosin have been proved to be very effective promoters for this kind of catalytic asymmetric process. Further investigation and synthetic utility of the products are ongoing in our laboratories.

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