ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 3260–3262

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A facile direct *anti*-selective catalytic asymmetric Mannich reaction of aldehydes with preformed *N*-Boc and *N*-Cbz imines†

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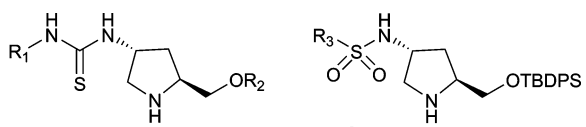
Received 29th November 2010, Accepted 12th January 2011
DOI: 10.1039/c0cc05249c

***Anti*-selective Mannich reactions of *N*-Boc and *N*-Cbz protected imines with unmodified aldehydes proceeded smoothly under the catalysis of a secondary amine–thiourea catalyst, which led to high yields (70%–95%) and excellent enantioselectivity (up to 96 : 4 dr and > 99% ee) under conventional organic synthetic operations.**

Tremendous efforts have been devoted to the development of new and effective methodologies of direct diastereo- and enantioselective organocatalytic Mannich reactions in the last decade.[1] So far, great success has been achieved for both *syn*-[2] and *anti*-[3]selective variants of direct Mannich reactions of ketones and aldehydes with preformed (or made *in situ*) *N*-PMP-protected α-imino esters. Good results have also been obtained for the *syn*-selective[4] and a limited number of reports were documented for *anti*-selective variants[5] of Mannich reactions when aldimines (preformed or made *in situ*) were used as electrophile substrates.

Protective groups on the amine of the amino carbonyl compounds are crucial to the further synthetic utility of the Mannich products. Although *p*-methoxyphenyl group is the most commonly used protective group in the aldimine formation, the removal of such a protective group in the resulting Mannich products often requires drastic oxidative conditions, and thus have limited the synthetic potential and the scope of the direct asymmetric catalytic Mannich reaction. Benzyloxycarbonyl (Cbz-) and *tert*-butoxycarbonyl (Boc-) have often been used as an orthogonal *N*-protecting group in organic synthesis due to the property of easy removability under mild conditions. Accordingly, the use of *N*-Boc or *N*-Cbz protected imine as an electrophile in the direct Mannich reaction has spurred particular interest. Enders *et al.* has first introduced *N*-Boc imine into the *syn*-Mannich reaction[4a,b] and an important advance was achieved by List *et al.* who used preformed aromatic *N*-Boc imines in proline-catalyzed Mannich reactions of aldehydes.[4c–e] Such a reaction protocol was also established by other groups.[4f–h] However, the work was mainly focused on *syn*-fashion reactions, progress in the *anti*-Mannich reactions of *N*-Boc or *N*-Cbz protected imines is very limited. To the best of our knowledge, only two groups have reported in this area. Maruoka's group have identified an axially chiral bifunctional amino sulfonamide as an effective catalyst for the direct *anti*-Mannich reaction of aldehyde to *N*-Boc imine. However, the reaction required controlled addition of the *N*-Boc imine with the assistance of a syringe pump to prevent from deactivation of the catalyst by higher concentration of the *N*-Boc imine;[5a,b] Melchiorre's group have found that diaryl prolinol silyl ether was also effective for the catalysis of *anti*-Mannich reaction of aldehydes with *in situ* generated *N*-Boc and *N*-Cbz imines. But, the reactivity is rather sensitive to the steric hindrance of the aldehyde. When only slightly more-encumbered isovaleraldehyde was used as the nucleophile substrate, reaction time up to 65 h was needed. Thus the sensitivity to steric hindrance has lowered the synthetic utility of this catalytic system.[5c,d] Therefore, from the synthetic standpoint of practical application of *anti*-selective Mannich reactions of *N*-Boc and *N*-Cbz imines, development of highly effective catalytic systems, in particular, those that are compatible with diverse substrates, and that are free from deactivation of catalysts is still in demand.

Interested in developing efficiently and broadly useful chiral organocatalysts for asymmetric synthesis, we have designed and synthesized a pool of catalysts **1a–2c** based on the pyrrolidine scaffold. Those catalysts bear various H-bond donor groups at the 4-position to activate electrophiles and a cooperative stereocontrol silyl ether group at the α-position of the pyrrolidine nitrogen atom (Scheme 1). The catalysts **1a–1c**, **2a** and **2b** have been shown excellent performance in the *anti*-selective Mannich reaction of aldehydes and ketones to *N*-PMP iminoglyoxylates[3j] and the asymmetric Michael



1a: R_1=4-MeOC$_6$H$_4$; R_2=TBDPS
1b: R_1=Ph; R_2=TBDPS
1c: R_1=3,5-(CF$_3$)$_2$C$_6$H$_3$; R_2=TBDPS
1d: R_1=3,5-(CF$_3$)$_2$C$_6$H$_3$; R_2=TES
1e: R_1=3,5-(CF$_3$)$_2$C$_6$H$_3$; R_2=TBS
1f: R_1=3,5-(CF$_3$)$_2$C$_6$H$_3$; R_2=TPS

2a: R_3=4-MeC$_6$H$_4$
2b: R_3=CF$_3$
2c: R_3= 3,5-(CF$_3$)$_2$C$_6$H$_3$

Scheme 1 Designed and synthesized pyrrolidine-based catalysts.

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† Electronic supplementary information (ESI) available: Catalysts synthesis, spectroscopic data, enantioselectivities measurement, and absolute configuration determinations for **5c**. See DOI: 10.1039/c0cc05249c

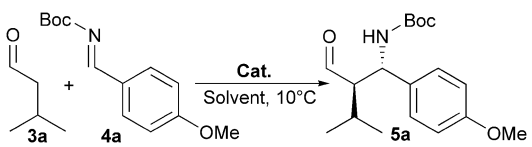
addition reactions of ketones and aldehydes to nitroolefins.[6] Inspired by these results, we further evaluated our organocatalyst pool in the direct Mannich reactions of unmodified aldehydes to *N*-Boc and *N*-Cbz imines. Herein we report the results.

The reaction of isovaleraldehyde **3a** with anisaldehyde *N*-Boc imine **4a** was selected as the model to evaluate the efficiency of the catalysts **1a–2c**. As shown in Table 1, the reaction proceeded smoothly, giving moderate to excellent yields and diastereoselectivities. However, all the reactions gave excellent enantioselectivities (Table 1, entries 1–9). Both H-bond donating ability of the group at the 4-position and the steric hindrance of the α-substituent of the pyrrolidine have great influence on the reactivities and diastereoselectivities. The H-bond donating ability is closely related to acidity of the thiourea or sulfonamide group, and is governed by the electronic nature of the R_1 and R_3 substituents. Comparison of the results obtained from the thiourea catalysis of **1a–1c**, which contains the same α-substituent (–CH_2OTBDPS), we can see that the catalytic performance of **1c** is superior to that of **1a** and **1b** (Table 1, entries 1–3). This maybe ascribed to the two strong electron-withdrawing-CF_3 groups on the phenyl ring in **1c**, which led to stronger acidity and thus H-bond donating ability than that of **1a** and **1b**. In **1a**, the electron-donating –OMe group has made the resulting catalyst the weakest H-bond donating ability among **1a** to **1c**, thus gave the poorest results. When the α-substituent was changed from –CH_2OTBDPS into –CH_2OTES (**1d**), –CH_2OTBS (**1e**) and –CH_2OTPS (**1f**), the reactivities and diastereoselectivities decreased to different extents, however, enantioselectivities remained almost unchanged (Table 1, entries 4–6). When the thiourea group at the 4-position was replaced by sulfonamides (**2a–2c**), high reactivities were observed, but both the diastereoselectivities and enantioselectivities decreased (Table 1, entries 7–9). All of the results indicated that the catalytic performance of **1c** was the best.

Among the examined solvents (Table 1, entries 3, 10–17), CH_2Cl_2 and $CHCl_3$ exhibit slightly better reactivity and diastereoselectivity, giving 96% yield and 92 : 8 dr, and 94% yield and 92 : 8 dr, respectively. In both cases, >99% ee was achieved (Table 1, entries 3 and 10). When catalyst load was 5 mol% and the reaction temperature was 0 °C, the diastereoselectivity in $CHCl_3$ is slightly better than that in CH_2Cl_2. Thus $CHCl_3$ was the preferred solvent. The reaction went smoothly with the catalyst load of equal to or higher than 5 mol% (Table 1, entries 10 and 17). When the catalyst load was lower than 5 mol%, a decrease in diastereoselectivity was observed such as in the case of **1c** (Table 1, entry 18), in which 85 : 15 dr was obtained with 3 mol% catalyst.

The scope of the *anti*-selective Mannich reaction was investigated (Table 2). *N*-Boc and *N*-Cbz imines gave the

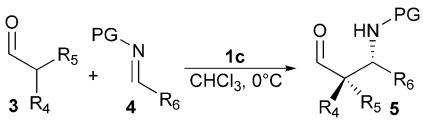
Table 1 Screening the catalysts and optimizing the reaction conditions[a]



Entry	Cat.	Solvent	*t*/h	Yield[b] (%)	dr[c] *anti* : *syn*	ee[c] (%)
1	**1a**	CH_2Cl_2	8	71	73 : 27	>97/10
2	**1b**	CH_2Cl_2	8	85	84 : 16	>98/26
3	**1c**	CH_2Cl_2	6	96	92 : 8	>99
4	**1d**	CH_2Cl_2	8	40	56 : 44	>99/76
5	**1e**	CH_2Cl_2	8	85	80 : 20	98
6	**1f**	CH_2Cl_2	8	95	88 : 12	99
7	**2a**	CH_2Cl_2	4.5	81	82 : 18	96
8	**2b**	CH_2Cl_2	1	84	89 : 11	96
9	**2c**	CH_2Cl_2	8	80	83 : 17	98
10	**1c**	$CHCl_3$	7	94	92 : 8	>99
11	**1c**	DCE	8	88	90 : 10	>99
12	**1c**	CCl_4	8	96	84 : 16	99
13	**1c**	Toluene	8	95	90 : 10	>99
14	**1c**	THF	8	87	83 : 17	>99
15	**1c**	TBME	8	96	84 : 16	99
16[d]	**1c**	CH_2Cl_2	5.5	96	93 : 7	>99
17[d]	**1c**	$CHCl_3$	**5.5**	**94**	**95 : 5**	**>99**
18[e]	**1c**	$CHCl_3$	7	93	85 : 15	>99/24

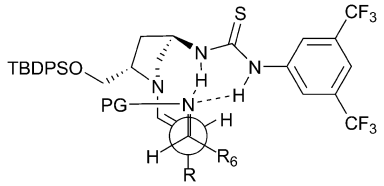
[a] Reaction conditions: **3a** (0.2 mmol, 1 equiv.), **4a** (1 mmol, 5 eqiuv.), 10 mol% catalyst (0.02 mmol) in 1 mL DCM at 10 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] With **1c** (0.01 mmol, 5 mol%) at 0 °C. [e] With **1c** (0.006 mmol, 3 mol%) at 0 °C.

Table 2 Generality and scope of the *anti*-selective Mannich reaction[a]



Entry	Product	*t*/h	Yield[b] (%)	dr[c] *anti* : *syn*	ee[c] (%)
1	**5a**: R_4 = ^{i}Pr, R_5 = H; PG = Boc, R_6 = 4-$CH_3OC_6H_4$	5.5	94	95 : 5	>99
2	**5b**: R_4 = ^{i}Pr, R_5 = H; PG = Boc, R_6 = 4-$CH_3C_6H_4$	6	93	90 : 10	>99
3	**5c**: R_4 = ^{i}Pr, R_5 = H; PG = Boc, R_6 = Ph	23	91	90 : 10	>99
4	**5d**: R_4 = ^{i}Pr, R_5 = H; PG = Boc, R_6 = 4-FC_6H_4	24	92	90 : 10	98
5	**5e**: R_4 = ^{i}Pr, R_5 = H; PG = Boc, R_6 = 4-ClC_6H_4	28	84	95 : 5	98
6	**5f**: R_4 = ^{i}Pr, R_5 = H; PG = Boc, R_6 = 2-naphthyl	7	81	92 : 8	>99
7	**5g**: R_4 = ^{i}Pr, R_5 = H; PG = Boc, R_6 = 2-furyl	8.5	89	91 : 9	>99
8[d]	**5h**: R_4 = Me, R_5 = H; PG = Boc, R_6 = 4-$CH_3OC_6H_4$	2	88	91 : 9	>99
9[d]	**5i**: R_4 = Et, R_5 = H; PG = Boc, R_6 = 4-$CH_3OC_6H_4$	3	94	90 : 10	>99
10[d]	**5j**: R_4 = Bu, R_5 = H; PG = Boc, R_6 = 4-$CH_3OC_6H_4$	5	84	89 : 11	>99
11	**5k**: R_4 = R_5 = Me; PG = Boc, R_6 = 4-$CH_3OC_6H_4$	24	70	—	92
12	**5l**: R_4 = ^{i}Pr, R_5 = H; PG = Cbz, R_6 = 4-$CH_3OC_6H_4$	10	86	95 : 5	>99
13	**5m**: R_4 = ^{i}Pr, R_5 = H; PG = Cbz, R_6 = 4-$CH_3C_6H_4$	10.5	84	93 : 7	>99
14	**5n**: R_4 = ^{i}Pr, R_5 = H; PG = Cbz, R_6 = Ph	22	88	95 : 5	>99
15	**5o**: R_4 = ^{i}Pr, R_5 = H; PG = Cbz, R_6 = 4-ClC_6H_4	24	90	94 : 6	>99
16	**5p**: R_4 = ^{i}Pr, R_5 = H; PG = Cbz, R_6 = 4-BrC_6H_4	24	82	96 : 4	>99
17	**5q**: R_4 = ^{i}Pr, R_5 = H; PG = COOEt, R_6 = Ph	24	95	95 : 5	>99

[a] Reaction conditions: **3** (0.2 mmol, 1 equiv.), **4** (1 mmol, 5 eqiuv.), **1c** (0.01 mmol, 5 mol%) in 1 mL $CHCl_3$ at 0 °C. [b] Isolated yield. [c] Detemined by chiral HPLC. [d] Reaction proceeded at −20 °C.



Scheme 2 Proposed transition state model of **1c**-catalyzed *anti*-Mannich reaction.

anti-Mannich products with high yields (81–95%), good diastereoselectivity (90 : 10–96 : 4 dr), and excellent enantioselectivity (98%–>99% ee) at 0 °C under conventional organic synthetic operations (Table 2, entries 1–7, 12–16). Linear aldehydes gave high yields and excellent ee (Table 2, entries 8–10). Even hindered 3-methylbutanal reacted smoothly to afford aminoaldehyde **5k** with good enantioselectivity (Table 2, entry 11). Interestingly, *N*-CO_2Et imine also gave excellent results (95% yield, 95 : 5 dr, and >99% ee) (Table 2, entry 17). Regrettably, **1c** could not catalyze the reaction between isovaleraldehyde and cyclohexanecarboxaldehyde *N*-Cbz imine, or that between acetone and anisaldehyde *N*-Boc imine.

The absolute configuration of *N*-Boc-protected **5c** was determined to be (1*S*, 2*R*) by comparison of the HPLC retention times with the data reported in the literature.[5a,b] To account for the stereochemical outcome, a transition state model is proposed and shown in Scheme 2. The bulky group (–CH_2OTBDPS) should effectively shield the *re*-face of an enamine double bond, and make the *si*-face available for attack to give the observed major enantiomer. Both thiourea protons in the catalyst are believed to bind to the imine nitrogen through hydrogen bonding interactions and may serve to activate the imine substrate effectively.

In conclusion, we have identified an efficient catalytic system for the direct *anti*-Mannich reaction of unmodified aldehydes with preformed *N*-Boc and *N*-Cbz imines. Only 5 mol% catalyst loading was enough to give the corresponding products in excellent yields (up to 95%), diastereoselectivities (up to 96 : 4 dr) and enantioselectivities (up to >99% ee). Further applications of the present catalysts in other asymmetric transformations are ongoing in our laboratory.

This work was supported by the Natural Science Foundation of China (NSFC 20872120) and the Municipal Science Foundation of Chongqing City (CSTC, 2009BB5110).

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