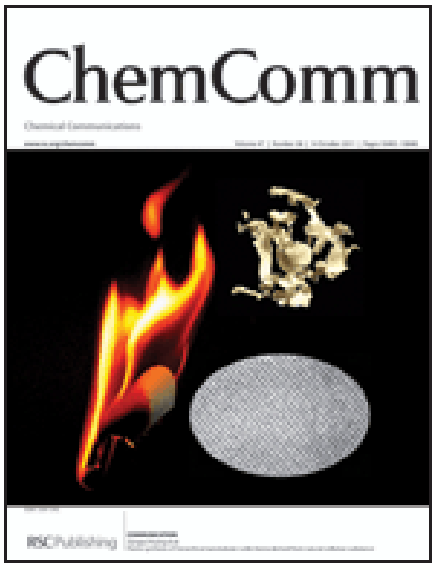

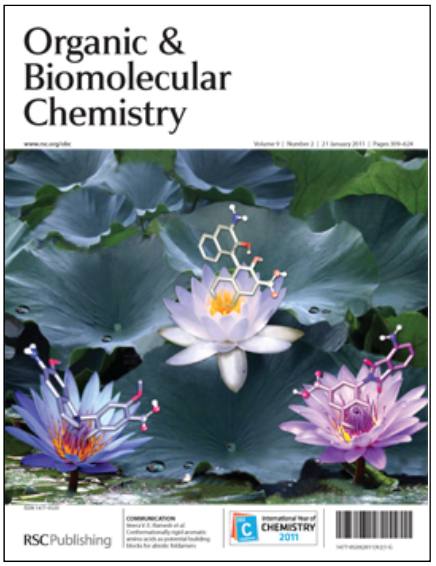

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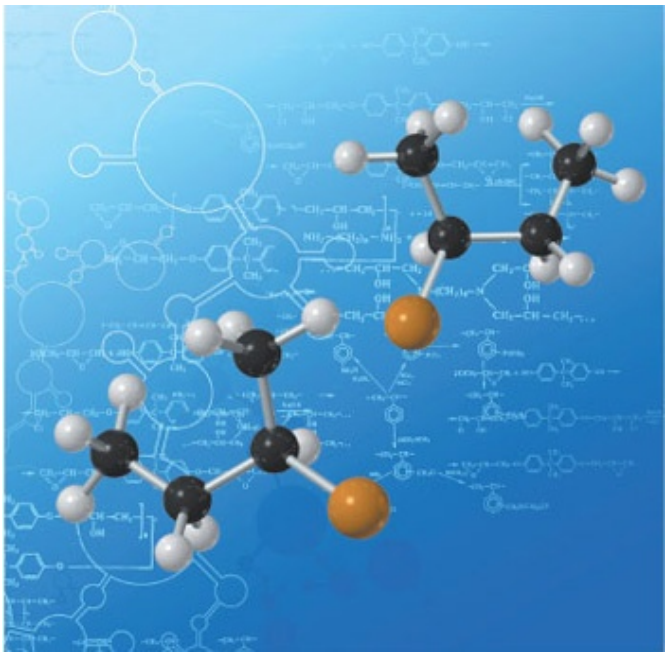

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PAPER

Highly efficient asymmetric *anti*-Mannich reactions of carbonyl compounds with *N*-carbamoyl imines catalyzed by amino-thiourea organocatalysts†§‡

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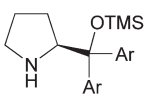
A series of pyrrolidine-based organocatalysts which bear three synergistic features, *i.e.* secondary amino group, various H-bond donor groups at the 4-position and a stereocontrol silyl ether group at the α-position of the pyrrolidine nitrogen atom, were developed. They were screened in *anti*-Mannich reactions of carbonyl compounds with preformed or *in situ* generated *N*-protected α-imino ethylglyoxylate and aldehydes with preformed or *in situ* generated *N*-carbamoyl imines. The influence of H-bond donor ability at the 4-position was also investigated. Among all the catalysts, **2a** was identified as a general efficient organocatalyst suitable for various types of *anti*-Mannich reactions and broad substrate scope. Excellent results (up to 98% yield, >99% ee and >99 : 1 dr) were achieved with 5 mol% catalyst load. Sulfones with *ortho* substituents or very strong withdrawing groups on the aromatic ring, which have been regarded as challenging substrates in the direct *anti*-Mannich reactions of aldehydes with *in situ* generated *N*-carbamoyl imines, also worked well. The optimization of our catalytic system also offered alternative and easily operational protocols to access *anti*-Mannich products with orthogonal *N*-Boc or *N*-Cbz protecting groups.

Introduction

The catalytic asymmetric Mannich reaction has emerged as one of the most powerful tools for the synthesis of enantiomerically pure amino carbonyl compounds that constitute an important structural framework of biologically active molecules.[1] Accordingly, the asymmetric organocatalytic Mannich-type reaction has recently been the subject of intense research. Great success has been achieved in the development of 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. Methodologies have been well established for the *syn*-selective[4] Mannich reactions while only a limited number of reports were documented for *anti*-selective variants[5] when aldimines (preformed or made *in situ*) were used as electrophile substrates.

Mannich reactions involving preformed aldimines are disadvantageous in terms of operational considerations. Aldimines are sensitive to moisture and air, and their preparation and storage can be quite troublesome. To circumvent such a drawback, Melchiorre's group developed the first protocol for aminocatalytic (**1a** and **1b**)[5a,b] *anti*-Mannich reaction of aldehydes with *in situ* generated *N*-carbamoyl α-imino ethyl glyoxylate and aldimines derived from aromatic aldehydes. Hayashi's group expanded the "*in situ* strategy" to the *anti*-Mannich reaction of aldehydes with aldimines derived from alkyl aldehydes catalyzed by **1a**.[5c] Although direct asymmetric *anti*-Mannich reactions with *in situ* generated *N*-carbamoyl imines are advantageous over that with preformed aldimines, until now there have only been three reports and only catalyst **1**, in which stereoselectivity was controlled primarily by steric interactions, was proved to be applicable as far as we know (Fig. 1).[5a–c]

The major limitation of the catalytic system developed by Melchiorre's group is decreased reactivity towards either sterically hindered substrates or aldimines with strong electron withdrawing substituents on the aromatic ring. When the only



1a: Ar = 3,5-$(CF_3)_2$-C_6H_3
1b: Ar = Ph

Fig. 1 Literature reported catalysts.

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§These two authors contributed equally to this work.

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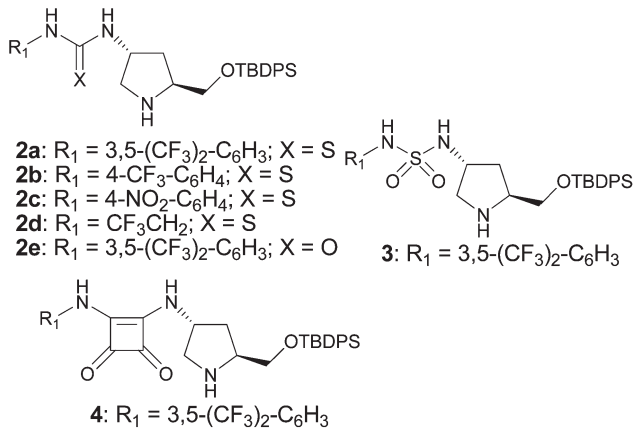
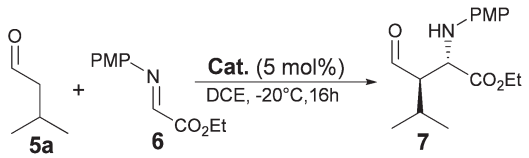


Fig. 2 Designed and synthesized pyrrolidine-based catalysts.

slightly more-encumbered isovaleraldehyde was used as the nucleophile donor, a long reaction time was needed. When $-NO_2$ was the substituent on the aromatic ring of the aldimine, only 27% yield was achieved.[5b] Such limitations have lowered the synthetic utility of this catalytic system. Thus, there is still an urgent need to explore structurally and electronically novel catalysts to expand the scope of direct asymmetric *anti*-Mannich reactions with *in situ* generated *N*-carbamoyl aldimines (Fig. 2).

With the goal of developing efficient and general useful chiral organocatalysts for asymmetric synthesis, we have established a series of organocatalysts based on the pyrrolidine scaffold, which bear three synergistic elements, *i.e.* a secondary amino group to activate the carbonyl substrate as nucleophile *via* enamine formation, 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. These catalysts have been successfully used in several asymmetric transformations, such as the asymmetric Michael addition of ketones and aldehydes to nitroolefins,[6a,b] the *anti*-selective Mannich reaction of carbonyl compounds with preformed *N*-PMP iminoglyoxylates[3j] and aldehydes with preformed aldimines.[5l] In those reactions, we have identified that the catalytic performance is closely linked to H-bond donating ability of the catalyst at the 4-position. Recently, Cheng's group has systematically studied the structure–activity–enantioselectivity relationship in three types of asymmetric Michael additions catalyzed by chiral thiourea organocatalysts. They found that excellent linear free energy relationships (LFERs) exist among catalyst acidity, reactive activity and stereoselectivity, suggesting a general trend, that more acidic catalysts render faster reactions and better enantioselectivities.[7] We postulated that replacement or partial replacement of stereocontrol to H-bond control might solve the reactivity problems brought by either steric hindrance or aldimines with strong electron withdrawing substituted aromatic groups. In this aspect, we further modified and expanded our catalytic system in two aspects, *i.e.* changing the H-bond donating ability by adjusting the steric and electronic nature of the substituent at the 4-position, and shifting the types of H-bond donating functional groups. Thus more extensive catalysts, **2a–2e**, **3** and **4**, were developed and evaluated in the *anti*-selective Mannich reaction of carbonyl compounds with preformed *N*-PMP iminoglyoxylates and aldehydes with preformed aldimines, and more importantly, we expect to explore the optimal catalyst in the direct asymmetric *anti*-Mannich reactions of aldehydes with *in situ* generated *N*-carbamoyl α-imino ethyl glyoxylate and aldimines. Herein, we hope to report the results in this paper.

Table 1 Screening the catalysts in the *anti*-Mannich reaction of aldehyde with *N*-PMP α-imino ethylglyoxylate[a]



Entry	Cat.	Yield (%)[b]	Dr (*anti* : *syn*)[c]	Ee (%) *anti*[c]
1	**2a**	96	98 : 2	>99
2	**2b**	84	98 : 2	>99
3	**2c**	83	98 : 2	>99
4	**2d**	81	98 : 2	>99
5	**2e**	86	99 : 1	>99
6	**3**	64	93 : 7	92
7	**4**	93	96 : 4	>99

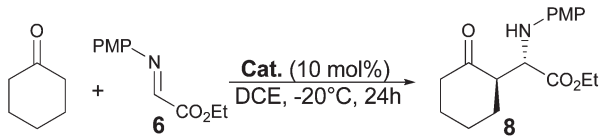
[a] Reaction procedure: **5a** (1 mmol, 5 equiv.) was added to a mixture of **6** (0.2 mmol, 1 equiv.) and catalyst (0.01 mmol, 5 mol%) in 1 mL DCE at −20 °C and stirred further for 16 h. [b] Isolated yield. [c] Determined by chiral HPLC.

Results and discussion

anti-Mannich reaction of aldehydes or ketones with *N*-PMP protected α-imino ethylglyoxylate

We selected the Mannich-type reaction of isovaleraldehyde (**5a**) and cyclohexanone with *N*-*p*-methoxyphenyl (PMP)-protected α-iminoglyoxylate (**6**) to evaluate the catalytic efficiency of the catalysts, **2b–2e**, **3** and **4**, in comparison with that of **2a**. When isovaleraldehyde was used as the nucleophile substrate (Table 1), as expected, catalysts **2a–2e** and **4** showed good reactivities (81%–96% yield) and excellent stereoselectivities (>99% ee; >96 : 4 dr) (Table 1, entries 1–5 and 7). **2d** is an alkyl-substituted thiourea catalyst. In the case of chiral thiourea–tertiary amine conjugate catalysts based on a cyclohexanediamine skeleton, trifluoroethyl aliphatic thiourea exhibited superior performance to the well-recognized 3,5-bis(trifluoromethyl)phenyl aromatic counterparts in the Michael addition of 3-substituted oxindole to nitrostyrene owing to the steric effect.[7] Interestingly, in the pyrrolidine-based catalytic system, the aromatic thiourea **2a** was more reactive than aliphatic thiourea **2d**, while they showed the same diastereoselectivity and enantioselectivity in the selected *anti*-Mannich model reaction (Table 1, entries 1 and 4). The chiral urea catalyst **2e** also worked well and resulted in good yield (86%) and excellent stereoselectivities (>99% ee and 99 : 1 dr). Comparatively, the sulfonamide catalyst **3** showed lower reactivity and stereoselectivity with only 64% yield, 92% ee and 93 : 7 dr (Table 1, entry 6). **2a** was slightly better than the squaramide catalyst **4** in both the reactivities (96% yield *vs.* 93% yield) and diastereoselectivities (98 : 2 dr *vs.* 96 : 4 dr). They behaved similarly in the aspect of enantioselectivity (>99% ee)

Table 2 Screening the catalysts in the *anti*-Mannich reaction of cyclohexanone with *N*-PMP α-imino ethylglyoxylate[a]



Entry	Cat.	Yield (%)[b]	Dr (*anti* : *syn*)[c]	Ee (%) *anti*[c]
1	**2a**	85	>99 : 1	>99
2	**2b**	55	>99 : 1	93
3	**2c**	83	>99 : 1	93
4	**2d**	38	>99 : 1	93
5	**2e**	78	90 : 10	96
6	**3**	Trace	nd	nd
7	**4**	91	>99 : 1	80

[a] Reaction procedure: cyclohexanone (2 mmol, 10 equiv.) was added to a mixture of **6** (0.2 mmol, 1 equiv.) and catalyst (0.02 mmol, 10 mol%) in 1 mL DCE at −20 °C and stirred further for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC.

(Table 1, entries 1 and 7). So, it can be concluded that **2a** is the best catalyst among the screened catalysts **2a–2e**, **3** and **4**, in the *anti*-Mannich reaction of isovaleraldehyde with *N*-PMP protected α-iminoglyoxylate.

When cyclohexanone was used as nucleophile substrate (Table 2), the catalysts differed greatly in performance. Good reactivities were achieved with **2a**, **2c** and **4**. **2a** is superior to **2c** and **4** in enantioselectivity. They were similar in diastereoselectivity (Table 2, entries 1, 3 and 7). Only moderate yields were obtained with **2b** and **2d** (Table 2, entries 2 and 4). Interestingly, the sulfonamide catalyst **3** showed no reactivity to catalyze this reaction (Table 2, entry 6). In summary, **2a** gave the best performance in the catalytic *anti*-selective Mannich reaction of cyclohexanone with *N*-PMP α-iminoglyoxylate.

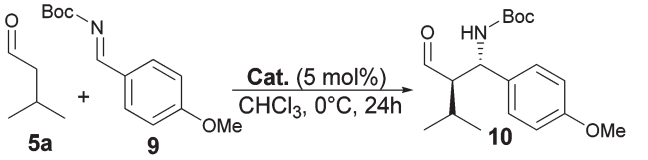
anti-Selective catalytic asymmetric Mannich reaction of aldehyde with preformed *N*-Boc aldimine

We have identified **2a** as an efficient catalytic system for the direct *anti*-Mannich reaction of unmodified aldehydes with preformed *N*-Boc aldimine.[5l] Here we further compared the performance of catalyst **2a** with **2b–2e**, **3** and **4** in the same reaction conditions, and the results are shown in Table 3. The catalysts **2a–2e** and **4** showed efficient catalytic performance and resulted in good yields (74%–90%) and excellent stereoselectivities (89% ee–99% ee, 88 : 12 dr–97 : 3 dr). When sulfonamide catalyst **3** was used to catalyze the same reaction, only 18% yield was obtained. None of the screened catalysts, **2b–2e**, **3** and **4**, is superior to that of **2a** in catalytic performance.

anti-Selective Mannich reaction of aldehydes with *in situ* generated *N*-Cbz α-imino ethylglyoxylate

We selected *N*-Cbz-protected α-imino ethyl glyoxylate, a substrate of great synthetic importance but of limited use in the Mannich reaction due to its intrinsic instability. The *in situ* generated *N*-Cbz α-imino ethyl glyoxylate approach would circumvent the limitation by avoiding the requirement to prepare

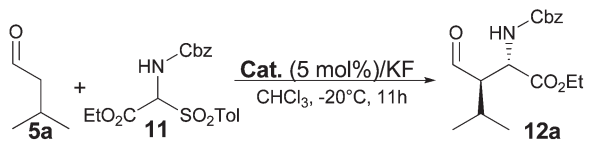
Table 3 Screening the catalysts in the *anti*-Mannich reaction of aldehyde with preformed *N*-Boc aldimine[a]



Entry	Cat.	Yield (%)[b]	Dr (*anti* : *syn*)[c]	Ee (%) *anti*[c]
1	**2a**	90	96 : 4	>99
2	**2b**	84	97 : 3	98
3	**2c**	74	91 : 9	89
4	**2d**	82	88 : 12	98
5	**2e**	78	95 : 5	97
6	**3**	18	87 : 13	92
7	**4**	85	95 : 5	>99

[a] Reaction procedure: **5a** (1 mmol, 5 equiv.) was added to a mixture of **9** (0.2 mmol, 1 equiv.) and catalyst (0.01 mmol, 5 mol%) in 1 mL $CHCl_3$ at 0 °C and stirred further for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC.

Table 4 Screening the catalysts in the *anti*-Mannich reaction of aldehyde with *in situ* generated *N*-Cbz α-imino ethylglyoxylate[a]



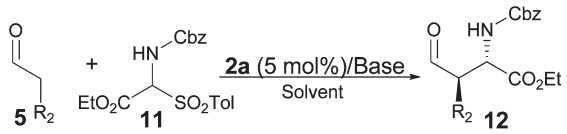
Entry	Cat.	Yield (%)[b]	Dr (*anti* : *syn*)[c]	Ee (%) *anti*[c]
1	**2a**	90	>99 : 1	>99
2	**2b**	89	90 : 10	>99
3	**2c**	98	95 : 5	>99
4	**2d**	92	95 : 5	96
5	**2e**	89	>99 : 1	92
6	**3**	61	98 : 2	>99
7	**4**	80	96 : 4	93

[a] Reaction procedure: **11** (0.2 mmol, 1 equiv.) and KF (1 mmol, 5 equiv.) were added to a mixture of **5a** (1 mmol, 5 equiv.) and catalyst (0.01 mmol, 5 mol%) in 1 mL $CHCl_3$ at −20 °C and stirred further for 11 h. [b] Isolated yield. [c] Determined by chiral HPLC.

and isolate the unstable imines. We tried to use the catalysts **2a–2e**, **3** and **4** to promote the reaction of isovaleraldehyde **5a** with α-amido sulfone **11** in the presence of inorganic base KF. The results are shown in Table 4. Good results were obtained when the reaction was catalyzed by **2a–2e** and **4**. The yields ranged from 80%–98%, with enantioselectivities of over 92% ee and diastereoselectivities of over 90 : 10 dr (Table 4, entries 1–5, and 7). Catalyst **3** gave lower yields (61%) but good stereoselectivities (>99% ee, 98 : 2 dr) (Table 4, entry 6). Although **2c** gave higher yield (98%) than **2a** (90% yield) with the same enantioselectivity (>99%), the latter is superior in diastereoselectivity (**2a**: >99 : 1 dr, **2c**: 95 : 5 dr) (Table 4, entries 1 and 3). Once again, **2a** is demonstrated to be the most efficient catalyst.

Optimization of the reaction conditions with **2a** as catalyst was carried out (Table 5). The nature and the amount of inorganic base and solvent were found to be crucial to achieve high

Table 5 Optimization the conditions and the scope of the *anti*-Mannich reaction of aldehydes with *in situ* generated *N*-Cbz α-imino ethylglyoxylate[a]



Entry	R_2	Solvent	Base	T (°C)	t (h)	Yield (%)[b]	Dr[c] (*anti* : *syn*)	Ee (%) *anti*[c]
1	^{i}Pr	THF	KF (5 eq.)	−20	11	69	>99 : 1	96
2	^{i}Pr	CH_2Cl_2	KF (5 eq.)	−20	11	84	>99 : 1	90
3	^{i}Pr	DCE	KF (5 eq.)	−20	11	70	94 : 6	>99
4	^{i}Pr	Tol	KF (5 eq.)	−20	11	44	95 : 5	95
5	^{i}Pr	$CHCl_3$	KF (5 eq.)	−20	11	90	>99 : 1	>99
6	^{i}Pr	$CHCl_3$	KF (3 eq.)	−20	25	78	>99 : 1	92
7	^{i}Pr	$CHCl_3$	KF (1 eq.)	−20	48	12	97 : 3	>99
8	^{i}Pr	$CHCl_3$	$K_3PO_4{\cdot}3H_2O$ (5 eq.)	−20	17	82	89 : 11	>99
9	^{i}Pr	$CHCl_3$	K_2CO_3 (5 eq.)	−20	17	85	90 : 10	98
10	^{i}Pr	$CHCl_3$	CH_3CO_2K	−20	17	94	95 : 5	99
11	^{i}Pr	$CHCl_3$	$NaHCO_3$	−20	17	Trace	nd	Nd
12[d]	^{i}Pr	$CHCl_3$	KF (5 eq.)	−20	24	74	96 : 4	>99
13[e]	^{i}Pr	$CHCl_3$	KF (5 eq.)	−20	24	52	>99 : 1	90
14	^{i}Pr	$CHCl_3$	KF (5 eq.)	0	5	83	>99 : 1	93
15	^{i}Pr	$CHCl_3$	KF (5 eq.)	rt	3	78	90 : 10	80
16	Et	$CHCl_3$	KF (5 eq.)	−20	16	85	80 : 20	97
17	Pr	$CHCl_3$	KF (5 eq.)	−20	18	83	85 : 15	98
18	Bu	$CHCl_3$	KF (5 eq.)	−20	25	76	89 : 11	>99
19	Amyl	$CHCl_3$	KF (5 eq.)	−20	36	67	83 : 17	97

[a] Reaction procedure: **11** (0.2 mmol, 1 equiv.) and base were added to a mixture of **5** (1 mmol, 5 equiv.) and catalyst **2a** (0.01 mmol, 5 mol%) in 1 mL solvent at the reaction temperature and stirred further for the designated time. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 3 equiv. of 5 was used. [e] 1.5 equiv. of 5 was used.

reaction efficiency. We first investigated the influence of solvent on the reaction (Table 5, entries 1–5). Among THF, CH_2Cl_2, DCE, Tol and $CHCl_3$, DCE and $CHCl_3$ (Table 5, entries 3 and 5) gave better overall results. In $CHCl_3$, higher yield (90%) was obtained than in DCE (70% yield) with the same stereoselectivities (>99% ee, >99 : 1 dr) (Table 5, entries 3 and 5), and so the best solvent was $CHCl_3$. The influence of the additive inorganic base on the reactivity was also investigated (Table 5, entries 5 and 8–11). Additives such as KF, $K_3PO_4{\cdot}3H_2O$, K_2CO_3 and CH_3CO_2K gave good reactivities (82%–94% yields). CH_3CO_2K gave a slightly higher yield than KF, while the latter led to better diastereoselectivity (>99 : 1 dr *vs.* 95 : 5 dr). Excellent enantioselectivity was achieved in both cases (Table 5, entries 5 and 10). When $NaHCO_3$ was used as an additive, no product was observed (Table 5, entry 11). So, the most suitable additive was KF. We also evaluated the influence of KF amount on the reaction (Table 5, entries 5–7), and found that 5 equivalents of KF were necessary for obtaining good results. When the amount was reduced to 3 equivalents, the yield and enantioselectivity decreased from 90% to 78% and from 99% ee to 92% ee, respectively (Table 5, entries 5 and 6). The amount of isovaleraldehyde also influenced the efficiency of the reaction (Table 5, entries 5, 12 and 13). When the amount of isovaleraldehyde was reduced from 5 equivalents to 3 equivalents, the reaction time was extended from 11 h to 24 h, leading to decrease of both yield (90% to 74%) and diastereoselectivity (99 : 1 dr to 96 : 4 dr, respectively) (Table 5, entries 5 and 12). When the reaction temperature was elevated from −20 °C to 0 °C, the reaction time was shortened from 11 h to 5 h, resulting in decrease of both yield and enantioselectivity (90% to 83%, >99% ee to 93% ee, respectively) while diastereoselectivity remained the same (Table 5, entries 5 and 14). At room temperature, yield and enantioselectivity decreased further and diastereoselectivity started to decrease (Table 5, entries 14 and 15).

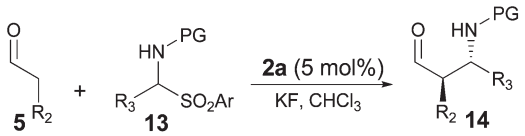
With the optimal conditions in hand, the scope of the reaction was examined. When linear aldehydes were used as the nucleophiles, good yields (67%–85%) and diastereoselectivities (80 : 20 dr–89 : 11 dr) were achieved with excellent enantioselectivities (97% ee–99% ee) (Table 5, entries 16–19).

anti-Selective Mannich reaction of aldehydes with *in situ* generated *N*-carbamoyl aromatic imines

The utility of a methodology is measured by both the efficiency and general applicability. Convinced of the synthetic utility of our catalytic system and encouraged by the results of *anti*-selective Mannich reaction of aldehydes with *in situ* generated *N*-Cbz α-imino ethyl glyoxylate, we sought to expand the synthetic utility of our catalytic system to the *anti*-selective Mannich reaction of aldehydes with *in situ* generated *N*-carbamoyl aromatic imines with the optimal reaction conditions (Table 6).

Under catalysis by **2a** and at −20 °C, isovaleraldehyde **5a** reacted with α-amido sulfone **13** smoothly, leading to **14a** (>99% ee and 95 : 5 dr) at 97% yield (Table 6, entry 1). To our delight, at 0 °C, the reaction time was shortened to 8 h without detriment to the yield or enantioselectivity (Table 6, entries 1 and 2). So at 0 °C or −20 °C, good yields (70%–98%), diastereoselectivities (85 : 15 dr–>99 : 1 dr) and excellent enantioselectivities (≥92% ee) were achieved. The results are compared

Table 6 Scope of the *anti*-Mannich reaction of aldehydes with *in situ* generated *N*-carbamoyl aromatic imines[a]



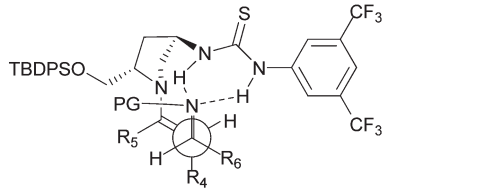
Entry	Product	*T* (°C)	*t* (h)	Yield (%)[b]	Dr[c] (*anti* : *syn*)	Ee (%) *anti*[c]
1	**14a**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 4-MeOC$_6$H$_4$	−20	24	97	95 : 5	>99
2	**14a**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 4-MeOC$_6$H$_4$	0	8	97	97 : 3	>99
3	**14b**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 2-MeOC$_6$H$_4$	0	12	87	95 : 5	98
4	**14c**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 4-MeC$_6$H$_4$	0	11	95	96 : 4	>99
5	**14d**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 2-MeC$_6$H$_4$	0	11	90	>99 : 1	>99
6	**14e**: R_2 = ^{i}Pr, PG = Cbz, R_3 = Ph	0	12	97	95 : 5	>99
7	**14f**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 4-ClC6H4	0	11	98	91 : 9	>99
8	**14g**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 4-BrC$_6$H$_4$	0	11	98	>99 : 1	>99
9	**14h**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 3-BrC$_6$H$_4$	0	11	89	97 : 3	>99
10	**14i**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 2-BrC$_6$H$_4$	0	15	85	>99 : 1	>99
11	**14j**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 2-naphthyl	0	13	96	96 : 4	>99
12	**14k**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 2-thienyl	0	12	95	95 : 5	>99
13	**14l**: R_2 = ^{i}Pr, PG = Cbz, R_3 = 2-furyl	0	12	95	97 : 3	>99
14	**14m**: R_2 = Me, PG = Cbz, R_3 = 4-MeOC$_6$H$_4$	−20	66	93	87 : 13	98
15	**14n**: R_2 = Et, PG = Cbz, R_3 = 4-MeOC$_6$H$_4$	−20	37	86	91 : 9	>99
16	**14o**: R_2 = Bu, PG = Cbz, R_3 = 4-MeOC6H4	−20	46	90	91 : 9	>99
17	**14p**: R_2 = ^{i}Pr, PG = Boc, R_3 = 4-MeC$_6$H$_4$	0	11	84	88 : 12	98
18	**14q**: R_2 = ^{i}Pr, PG = Boc, R_3 = 2-MeOC$_6$H$_4$	0	12	87	88 : 12	>99
19	**14r**: R_2 = ^{i}Pr, PG = Boc, R_3 = Ph	0	24	86	89 : 11	>99
20	**14s**: R_2 = ^{i}Pr, PG = Boc, R_3 = 2-naphthyl	0	12	85	85 : 15	>99
21	**14t**: R_2 = ^{i}Pr, PG = Boc, R_3 = 4-ClC$_6$H$_4$	0	12	83	98 : 2	98
22	**14u**: R_2 = ^{i}Pr, PG = Boc, R_3 = 2-CF$_3$C$_6$H$_4$	0	12	70	>99 : 1	>99
23	**14v**: R_2 = ^{i}Pr, PG = Boc, R_3 = 4-NO$_2$C$_6$H$_4$	0	13	75	96 : 4	>92
24	**14w**: R_2 = Me, PG = Boc, R_3 = Ph	−20	35	93	85 : 15	99
25	**14x**: R_2 = Bu, PG = Boc, R_3 = Ph	−20	46	95	85 : 15	>99
26	**10**: R_2 = ^{i}Pr, PG = Boc, R_3 = 4-MeOC$_6$H$_4$	0	11	90	92 : 8	99

[a] Reaction procedure: **13** (0.2 mmol, 1 equiv.) and KF (1 mmol, 5 equiv.) were added to a mixture of **5** (1 mmol, 5 equiv.) and catalyst **2a** (0.01 mmol, 5 mol%) in 1 mL $CHCl_3$ at the reaction temperature and stirred further for the designated time. [b] Isolated yield. [c] Determined by chiral HPLC.

favourably with those of direct *anti*-selective Mannich reactions using preformed aldimines catalyzed by **2a**.[5l] The results also hinted that the presence of inorganic base KF interfered with neither the enamine formation between the secondary amino group of the catalyst and the carbonyl substrate, nor the hydrogen-bonding interactions between thiourea protons of the catalyst and the imine nitrogen. Under the Mannich reaction conditions, we also monitored whether the silyl group of the catalysts was removed by KF, and to our delight, we did not find any products resulting from silyl group removal from the catalysts in the reaction procedure.

Aromatic sulfones with electron-releasing and -withdrawing groups on the aromatic ring were tolerated and led to the desired products (Table 6, entries 2–10). The substitution pattern only affected reactivity to a certain extent. Diastereoselectivity and enantioselectivity were almost unaffected. For example, when the bromination position of the aromatic sulfone was changed from *para* to *meta* and *ortho*, the reactivity was decreased. The yields were 98%, 89% and 85%, respectively. In the case of *ortho* substitution, a lengthened reaction time was required for the completion of the reaction. However, in all cases, both the enantioselectivities and diastereoselectivities remained excellent (>99% ee, 97 : 3 dr–>99 : 1 dr) (Table 6, entries 8–10). Notably, those sulfones (or preformed aldimines) possessing *ortho* substituents on the aromatic ring reacted smoothly to give the desired products with good yields and stereoselectivities in this catalytic system (Table 6, entries 3, 5, 10, 18 and 22). To the best of our knowledge, there has been no report on successful reactions of those substrates with aldehydes in the direct Mannich reactions. This may be partially due to the unfavorable steric effect. Naphthalene ring and heteroaromatic substituents also tested and were again proved to be suitable for the Mannich reaction (Table 6, entries 11–13). Besides isovaleraldehyde, other linear aldehydes were also examined as the nucleophilic components in the *anti*-Mannich protocol. The reactions gave the desired products with 98% ee to >99% ee and 87 : 13 dr to 91 : 9 dr in 86%–93% yield (Table 6, entries 14–16). Furthermore, good results were achieved with *in situ* generated *N*-Boc-protected aromatic imines resulting in the Mannich products with orthogonal *N*-protecting groups (Table 6, entries 17–26). Finally, aromatic sulfones with very strong electron withdrawing groups (–CF_3 and NO_2) were investigated and found to work well. Up to 75% yield, 96 : 4 dr and >92% ee were achieved within 13 h (Table 6, entries 22–23). In comparison with the results obtained with catalyst **1**, *e.g.* 27% yield after 65 h in the case NO_2 substituted substrate,[5b] it can be concluded that our developed amino–thiourea catalysts were more efficient than **1a** and **1b** in the catalysis of *anti*-Mannich reaction with aromatic sulfones with strong electron withdrawing groups.

The stereochemical outcome of the *anti*-Mannich reaction of carbonyl compounds with *in situ* generated *N*-carbamoyl imines was in agreement with that observed in the corresponding



a: R_5 = H; R_4 = -Alkyl; R_6 = -CO_2Et; PG = PMP
b: R_5 R_4 = -(C_4H_8)-; R_6 = -CO_2Et; PG = PMP
c: R_5 = H; R_4 = -Alkyl; R_6 = -CO_2Et; PG = Cbz
d: R_5 = H; R_4 = -Alkyl; R_6 = -Ar; PG = Cbz or Boc

Scheme 1 The transition state models of **2a**-catalyzed the *anti*-Mannich reactions.

reaction with preformed imines. The absolute configuration of *N*-Boc-protected **14r** was determined to be (1*S*,2*R*) by comparison of the HPLC retention times with the data reported in the literature.[5d] To account for the observed outcome, the transition state models are proposed and depicted in Scheme 1 (a–d). The bulky group (–CH_2OTBDPS) should effectively shield the *Re*-face of an enamine double bond, and the nucleophile attack from the *Si*-face to give the observed major enantiomer. Both thiourea protons in the catalyst are believed to form hydrogen-bonding interactions with imine (generated *in situ*) nitrogen simultaneously, which may serve to activate the imine substrate effectively.

Conclusion

We have designed and developed a series of highly efficient organocatalysts based on the pyrrolidine scaffold, which bear three features, namely secondary amino group, various H-bond donor groups at the 4-position and a stereocontrol silyl ether group at the α-position of the pyrrolidine nitrogen atom. **2a** was identified as the best catalyst, which could be broadly applied in direct enantioselective *anti*-Mannich reactions of aldehydes and ketones with preformed *N*-PMP protected α-imino ethylglyoxylate, aldehydes with preformed *N*-carbamoyl imines, aldehydes with *in situ* generated *N*-Cbz α-imino ethylglyoxylate and *N*-carbamoyl imines. Excellent results (up to 98% yield, ≥92% ee and >99 : 1 dr) were achieved with 5 mol% catalyst load. The aromatic sulfones with *ortho* substituents or very strong withdrawing groups, which have been regarded as challenging substrates in the direct *anti*-Mannich reactions of aldehydes with *in situ* generated *N*-carbamoyl imines, also worked well. Not only did our catalytic systems provide alternative protocols to access *anti*-Mannich products with orthogonal *N*-Boc or *N*-Cbz protecting groups, but more importantly they demonstrated superb catalytic ability and thus expand the utility of the *anti*-Mannich reaction.

Experimental section

General procedure for the *anti*-Mannich reaction of aldehydes with *in situ* generated *N*-Cbz α-imino ethylglyoxylate or *N*-Cbz and *N*-Boc imines

To a mixture of aldehyde **5** (1 mmol, 5 equiv.) and catalyst **2a** (0.01 mmol, 5 mol%) in 1 mL $CHCl_3$, α-amido sulfone **11** or **13** (0.2 mmol, 1 equiv.) and KF (1 mmol, 5 equiv.) were added successively at the given temperature and stirred further until the disappearance of the α-amido sulfone in the reaction mixture monitored by TLC. The mixture was quenched with aqueous saturated ammonium chloride solution and extracted with CH_2Cl_2 (three times). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified by flash column chromatography (AcOEt–PE) to afford the corresponding Mannich addition products. The ee and dr of all products were determined by chiral-phase HPLC analysis.

For details of the synthesis of the catalysts **2a–2e**, **3**, **4** see the ESI.†

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((3*R*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidin-3-yl)thiourea (2a). Mp 119–121 °C, $[\alpha]_D^{25}$ = ¬14.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 2H), 7.62 (d, *J* = 7.3 Hz, 5H), 7.41 (dd, *J* = 13.2, 8.6 Hz, 6H), 7.26 (s, 1H), 3.49 (dd, *J* = 28.4, 8.5 Hz, 3H), 3.07 (s, 2H), 1.99 (s, 2H), 1.84 (d, *J* = 5.5 Hz, 1H), 1.06 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.25, 135.41, 132.68, 131.78, 130.06, 128.41, 127.92, 124.80, 123.29, 121.18, 118.27, 64.20, 57.90, 54.87, 33.33, 26.82, 23.89, 19.14 ppm. IR (neat) : 3243, 3069, 2933, 2858, 1542, 1470, 1387, 1278, 1178, 1128, 703, 505 cm^{-1}. HRMS (FT-ESI) calcd for $C_{30}H_{34}F_6N_3OSSi$ $[M + H]^+$ 626.2096; found 626.2079.

1-((3*R*,5*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)pyrrolidin-3-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (2b). Mp 109–110 °C, $[\alpha]_D^{20}$ = +20 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.56 (ddd, *J* = 19.3, 10.5, 5.4 Hz, 8H), 7.50–7.35 (m, 6H), 4.87 (s, 1H), 4.21 (s, 2H), 3.72 (dt, *J* = 17.7, 12.4 Hz, 2H), 3.54 (dd, *J* = 10.7, 4.3 Hz, 1H), 3.24–3.09 (m, 2H), 2.03 (t, *J* = 12.7 Hz, 2H), 1.05 (d, *J* = 13.3 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.52, 141.51, 135.50, 132.38, 132.22, 130.32, 130.29, 128.10, 126.22, 126.18, 122.88, 63.17, 58.86, 54.94, 33.27, 29.75, 26.97, 19.22 ppm. IR (KBr): 3421, 3072, 2956, 2928, 1631, 1594, 1384, 1348, 1113, 1066, 823, 741, 703, 505 cm^{-1}. HRMS (FT-ESI) calcd for $C_{29}H_{34}F_3N_3OSSi$ $[M + H]^+$ 558.2222; found 558.2244.

1-((3*R*,5*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)pyrrolidin-3-yl)-3-(4-nitrophenyl)thiourea (2c). Mp 100–102 °C, $[\alpha]_D^{20}$ = +15.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.9 Hz, 2H), 7.61–7.27 (m, 10H), 6.69 (s, 1H), 4.83 (s, 1H), 3.77 (d, *J* = 7.8 Hz, 2H), 3.49 (d, *J* = 7.8 Hz, 1H), 3.27 (d, *J* = 11.6 Hz, 1H), 3.17–3.03 (m, 1H), 2.01 (s, 2H), 1.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.17, 145.17, 143.19, 135.45, 132.07, 131.78, 130.50, 130.48, 128.24, 128.18, 62.23, 59.26, 54.66, 51.55, 32.89, 26.97, 19.26 ppm. IR (KBr): 3421, 3070, 2956, 2930, 2856, 1631, 1596, 1384, 1344, 1255, 1177, 822, 780, 741, 504 cm^{-1}. HRMS (FT-ESI) calcd for $C_{28}H_{34}N_4O_3SSi$ $[M + H]^+$ 535.2199; found 535.2214.

1-((3*R*,5*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)pyrrolidin-3-yl)-3-(2,2,2-trifluoroethyl)thiourea (2d). Mp 59–61 °C, $[\alpha]_D^{20}$ = −3.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.58–7.47 (m, 4H), 7.42–7.24 (m, 6H), 4.51–3.95 (m, 4H), 3.63–3.29 (m, 3H), 2.91 (d, *J* = 15.5 Hz, 2H), 1.85 (dd,

J = 21.3, 14.3 Hz, 2H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.25, 135.49, 132.62, 130.19, 128.03, 126.27, 63.80, 58.01, 54.76, 49.57, 45.48, 33.05, 26.96, 19.21 ppm. IR (KBr): 3308, 3072, 2957, 2932, 2858, 1631, 1559, 1427, 1368, 1255, 1161, 1133, 1111, 853, 741, 704, 608, 505 cm^{-1}. HRMS (FT-ESI) calcd for $C_{24}H_{32}F_3N_3OSSi$ $[M + H]^+$ 496.2066; found 496.2081.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((3*R*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidin-3-yl)urea (2e). Mp 147–149 °C, $[\alpha]_D^{20}$ = +26 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.64–7.51 (m, 4H), 7.42 (dq, J = 14.1, 7.0 Hz, 7H), 7.26 (s, 1H), 6.69 (s, 1H), 4.34 (s, 1H), 3.63 (dt, J = 26.3, 10.2 Hz, 3H), 3.00 (s, 2H), 1.92 (s, 2H), 1.07 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.89, 140.94, 135.45, 132.12, 130.38, 128.09, 125.03, 121.42, 117.92, 115.36, 63.79, 58.27, 51.72, 50.80, 33.77, 26.94, 19.20 ppm. IR (KBr): 3347, 3074, 2960, 2934, 2860, 1671, 1575, 1474, 1389, 1279, 1180, 1132, 881, 741, 703, 610, 505 cm^{-1}. HRMS (FT-ESI) calcd for $C_{30}H_{33}F_6N_3O_2Si$ $[M + H]^+$ 610.2324; found 610.2341.

***N*-(3,5-Bis(trifluoromethyl)phenyl)-*N'*-3-((3*R*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidine)sulfamide (3).** Mp 79–81 °C, $[\alpha]_D^{20}$ = −10 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.57 (dd, J = 12.9, 6.4 Hz, 5H), 7.41–7.27 (m, 6H), 7.22 (d, J = 7.7 Hz, 1H), 4.33 (s, 1H), 4.18 (s, 1H), 4.01 (d, J = 9.1 Hz, 2H), 3.72–3.52 (m, 3H), 2.16–2.00 (m, 2H), 1.24 (d, J = 8.8 Hz, 1H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.33, 135.64, 132.29, 130.43, 128.03, 124.97, 121.12, 119.11, 117.26, 62.10, 59.76, 53.07, 52.07, 33.01, 29.67, 19.05 ppm. IR (KBr): 3421, 3075, 2959, 2931, 2860, 1630, 1593, 1470, 1379, 1280, 1136, 1112, 1001, 741, 703, 611, 505 cm^{-1}. HRMS (FT-ESI) calcd for $C_{29}H_{33}F_6N_3O_3SSi$ $[M + H]^+$ 646.1994; found 646.2019.

3-(3,5-Bis(trifluoromethyl)phenylamino)-4-((3*R*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidin-3-ylamino)cyclobut-3-ene-1,2-dione (4). Mp 106–106.5 °C, $[\alpha]_D^{20}$ = 20.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 55.1 Hz, 2H), 7.76–7.10 (m, 11H), 4.89 (s, 1H), 3.96 (s, 1H), 3.44 (dt, J = 68.3, 30.5 Hz, 4H), 3.00 (d, J = 11.3 Hz, 1H), 2.00 (s, 1H), 1.77 (s, 1H), 1.18–0.82 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.29, 140.48, 135.43, 132.81, 130.27, 127.95, 125.17, 121.17, 118.50, 117.50, 115.96, 111.47, 64.71, 58.49, 52.43, 35.99, 29.78, 26.92, 19.31 ppm. IR (KBr): 3422, 3074, 2959, 2933, 2859, 1794, 1683, 1630, 1602, 1473, 1430, 1380, 1278, 1182, 1133, 1112, 740, 702, 505 cm^{-1}. HRMS (FT-ESI) calcd for $C_{33}H_{33}F_6N_3O_3Si$ $[M + H]^+$ 662.2274; found 662.2310.

(2*S*,3*R*)-Ethyl 3-formyl-2-(4-methoxyphenylamino)-4-methylpentanoate (7). The title compound was prepared according to the general procedure, as described above in 96% yield. HPLC condition: ChiralPak AS-H, hexane–iPrOH = 90 : 10, 254 nm, 0.5 mL min^{-1}, t_{major} = 15.40 min, t_{minor} = 25.90 min, *anti*: ee > 99%, dr = 98/2; $[\alpha]_D^{25}$ = −35.6 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.74 (d, J = 3.4 Hz, 1H), 6.75 (d, J = 8.9 Hz, 2H), 6.65 (d, J = 8.9 Hz, 2H), 4.35 (d, J = 7.7 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.00 (brs, 1H), 3.73 (s, 3H), 2.57–2.61 (m, 1H), 2.04–2.11 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.22, 172.80, 153.19, 140.40, 115.81, 114.71, 61.30, 59.54, 57.15, 55.56, 27.50, 21.21, 19.09, 14.09 ppm.

(*S*)-Ethyl 2-(4-methoxyphenylamino)-2-((*R*)-2-oxocyclohexyl) acetate (8). The title compound was prepared according to the general procedure, as described above in 85% yield. HPLC condition: ChiralPak AS-H, hexane–iPrOH = 90 : 10, 254 nm, 0.5 mL min^{-1}, t_{major} = 24.25 min, t_{minor} = 30.23 min, *anti*: ee > 99%, dr = 98/2; $[\alpha]_D^{25}$ = +28.6 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73–6.78 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 8.7 Hz, 2H), 4.13 (m, 2H), 3.98 (d, J = 3.8 Hz, 1H), 3.74 (s, 3H), 3.08–3.13 (m, 1H), 2.29–2.48 (m, 2H), 2.04–2.08 (m, 2H), 1.86–1.98 (m, 2H), 1.64–1.76 (m, 2H), 1.19–1.25 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.03, 173.05, 152.74, 142.09, 115.61, 114.72, 61.18, 59.07, 55.67, 53.55, 41.80, 30.51, 26.83, 24.52, 14.09 ppm.

(2*S*,3*R*)-Ethyl 2-(benzyloxycarbonylamino)-3-formyl-4-methylpentanoate (12a). The title compound was isolated as a colorless oil in 90% yield. HPLC analysis on a Daicel ChiralPak AD-H column: 90 : 10 hexane–iPrOH, flow rate 0.7 mL min^{-1}, λ = 214 nm, 254 nm, t_{major} = 18.61 min, t_{minor} = 27.35 min, *anti*: ee > 99%, dr > 99/1; $[\alpha]_D^{20}$ = +62.1 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.50–7.15 (m, 5H), 5.67 (d, J = 10.1 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 5.10 (d, J = 12.3 Hz, 1H), 4.68 (dd, J = 10.1, 3.6 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.98 (dd, J = 8.2, 3.6 Hz, 1H), 2.09 (tt, J = 9.9, 4.9 Hz, 1H), 1.24 (d, J = 7.1 Hz, 2H), 1.22–1.15 (m, 4H), 1.10 (d, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.75, 171.45, 156.61, 136.27, 128.33, 127.94, 67.14, 61.86, 59.03, 52.31, 27.47, 21.44, 20.50, 14.03 ppm.

Benzyl (1*S*,2*R*)-2-formyl-1-(2-methoxyphenyl)-3-methylbutylcarbamate (14b). The title compound was isolated as a colorless oil in 87% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 76 : 24 hexane–iPrOH, flow rate 0.5 mL min^{-1}, λ = 220 nm, t_{major} = 14.16 min, t_{minor} = 11.99 min, *anti*: ee = 98%, dr = 95/5; $[\alpha]_D^{20}$ = +16.0 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, J = 4.0 Hz, 1H), 7.39–7.13 (m, 6H), 6.99–6.80 (m, 2H), 6.01 (d, J = 9.9 Hz, 1H), 5.39 (dd, J = 19.1, 9.9 Hz, 1H), 5.15–4.95 (m, 2H), 3.82 (s, 3H), 2.86–2.72 (m, 1H), 1.86–1.67 (m, 1H), 1.10–0.86 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.24, 156.71, 156.15, 136.70, 129.09, 129.02, 128.51, 128.16, 127.70, 127.38, 120.68, 110.80, 66.85, 60.70, 54.93, 51.65, 28.36, 21.40, 18.25 ppm. IR (neat): 3429, 3333, 3033, 3006, 2961, 2874, 2838, 2739, 1716, 1602, 1494, 1461, 1345, 1283, 1244, 1115, 1050, 1026, 993, 755, 698, 598 cm^{-1}. HRMS (ESI): calcd For $C_{21}H_{25}NO_4$ $[M + Na]^+$ 378.1681; found 378.1694.

Benzyl (1*S*,2*R*)-2-formyl-1-(2-methylphenyl)-3-methylbutylcarbamate (14d). The title compound was isolated as colorless oil in 90% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 94 : 6 hexane–iPrOH, flow rate 0.5 mL min^{-1}, λ = 220 nm, t_{major} = 26.99 min, t_{minor} = 21.92 min, *anti*: ee > 99%, dr > 99/1; $[\alpha]_D^{20}$ = +27.4 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85–9.67 (m, 1H), 7.39–7.22 (m, 4H), 7.15 (s, 5H), 5.84 (d, J = 9.2 Hz, 1H), 5.52–5.38 (m, 1H), 5.12–4.95 (m, 2H), 2.64 (d, J = 3.0 Hz, 1H), 2.44 (d, J = 19.6 Hz, 3H), 2.06–1.86

(m, 1H), 1.11–0.96 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.52, 155.69, 138.82, 136.31, 135.18, 130.97, 128.50, 128.12, 127.53, 126.52, 125.96, 66.95, 61.39, 49.92, 28.49, 21.30, 19.43 ppm. IR (neat): 3320, 3064, 3032, 2962, 2874, 2740, 1698, 1520, 1458, 1390, 1337, 1286, 1253, 1030, 993, 754, 731, 698, 633, 598 cm^{-1}. HRMS (ESI): calcd For $C_{21}H_{25}NO_3$ $[M + Na]^+$ 362.1732; found 362.1734.

Benzyl (1*S*,2*R*)-1-(3-bromophenyl)-2-formyl-3-methylbutylcarbamate (14h). The title compound was isolated as colorless oil in 89% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 94 : 6 hexane–iPrOH, flow rate 0.5 mL min^{-1}, λ = 220 nm: t_{major} = 34.93 min, t_{minor} = 33.78 min, *anti*: ee > 99%, dr = 97/3; $[\alpha]_D^{20}$ = +23.6 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, J = 2.7 Hz, 1H), 7.57–6.97 (m, 8H), 6.00 (d, J = 9.2 Hz, 1H), 5.12 (d, J = 8.1 Hz, 1H), 5.06 (d, J = 2.2 Hz, 2H), 2.62 (d, J = 29.8 Hz, 1H), 2.02–1.79 (m, 1H), 1.12–0.95 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.88, 155.60, 143.03, 136.04, 130.75, 130.33, 129.71, 128.54, 128.19, 128.04, 125.27, 122.90, 67.11, 62.23, 53.15, 28.39, 21.14, 19.30 ppm. IR (neat): 3338, 3064, 3034, 2962, 2874, 2738, 1683, 1539, 1473, 1338, 1260, 1133, 1073, 1030, 997, 779, 738, 698, 597 cm^{-1}. HRMS (ESI): calcd For $C_{20}H_{22}BrNO_3$ $[M + Na]^+$ 426.0681; found 426.0663.

Benzyl (1*S*,2*R*)-2-formyl-3-methyl-1-(naphthalen-2-yl)butylcarbamate (14j). The title compound was isolated as colorless oil in 96% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 94 : 6 hexane–iPrOH, flow rate 0.5 mL min^{-1}, λ = 220 nm, t_{major} = 41.95 min, t_{minor} = not found, *anti*: ee > 99%, dr = 96/4; $[\alpha]_D^{20}$ = +14.2 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (d, J = 3.1 Hz, 1H), 7.78 (t, J = 14.5 Hz, 4H), 7.59–6.91 (m, 7H), 5.89 (d, J = 8.9 Hz, 1H), 5.35 (t, J = 7.2 Hz, 1H), 5.17–4.92 (m, 2H), 2.81 (t, J = 12.1 Hz, 1H), 1.92 (dp, J = 13.4, 6.7 Hz, 1H), 1.05 (dt, J = 25.1, 12.5 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.11, 155.73, 137.84, 136.25, 133.28, 132.83, 128.81, 128.52, 128.06, 127.66, 126.45, 126.17, 125.72, 124.27, 67.05, 62.43, 53.80, 28.42, 21.48, 19.08 ppm. IR (KBr): 3404, 3057, 3038, 3019, 2976, 2838, 2734, 1721, 1700, 1632, 1599, 1519, 1461, 1390, 1317, 1257, 1214, 980. 837, 750, 697, 552, 484 cm^{-1}. HRMS (ESI): calcd For $C_{24}H_{25}NO_3$ $[M + Na]^+$ 398.1732; found 398.1744.

Benzyl (1*S*,2*R*)-2-formyl-3-methyl-1-(thiophen-2-yl)butylcarbamate (14k). The title compound was isolated as a brown oil in 95% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 92 : 8 hexane–iPrOH, flow rate 0.5 mL min^{-1}, λ = 220 nm: t_{major} = 34.37 min, t_{minor} = not found, *anti*: ee > 99%, dr = 95/5; $[\alpha]_D^{20}$ = +10.6 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (t, J = 4.1 Hz, 1H), 7.39–7.24 (m, 4H), 7.18 (dd, J = 4.5, 1.7 Hz, 1H), 6.97–6.86 (m, 2H), 5.87 (d, J = 9.2 Hz, 1H), 5.52–5.40 (m, 1H), 5.07 (d, J = 12.3 Hz, 2H), 2.76 (td, J = 6.3, 3.0 Hz, 1H), 2.06–1.93 (m, 1H), 1.06 (t, J = 7.5 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.57, 155.53, 144.58, 136.19, 128.51, 128.16, 128.08, 126.99, 124.80, 124.61, 67.07, 62.74), 49.74, 28.57, 21.32, 19.14 ppm. IR (neat): 3379, 3272, 3092, 3063, 2873, 2826, 1631, 1591, 1540, 1457, 1436, 1375, 1317, 1305, 1262, 1239, 1180, 1078, 1021, 984, 849, 758, 702, 506 cm^{-1}. HRMS (ESI): calcd For $C_{18}H_{21}NO_3S$ $[M + Na]^+$ 354.1140; found 354.1145.

Benzyl (1*S*,2*R*)-1-(4-methoxyphenyl)-2-methyl-3-oxopropylcarbamate (14m). The title compound was isolated as a white solid in 93% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 90 : 10 hexane–iPrOH, flow rate 0.5 mL min^{-1}, λ = 220 nm: t_{major} = 65.78 min, t_{minor} = 52.93 min, *anti*: ee = 98%, dr = 87/13; $[\alpha]_D^{20}$ = −11.6 (c = 1, $CHCl_3$); mp 56–59.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (d, J = 2.9 Hz, 1H), 7.28 (d, J = 16.5 Hz, 5H), 7.17 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.48 (dd, J = 21.3, 8.8 Hz, 1H), 5.06 (dd, J = 6.0, 3.4 Hz, 2H), 4.88 (t, J = 8.0 Hz, 1H), 3.79 (s, 3H), 2.87 (d, J = 31.8 Hz, 1H), 1.02 (d, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.28, 159.22, 155.80, 135.95, 131.52, 128.53, 128.17, 128.08, 128.00, 114.07, 67.02, 55.30, 51.91, 11.95 ppm. IR (KBr): 3334, 3064, 3035, 2962, 2938, 2837, 2717, 1720, 1684, 1613, 1514, 1456, 1293, 1250, 1181, 1143, 1096, 1027, 921, 831, 753, 730, 697, 662, 570 cm^{-1}. HRMS (ESI): calcd For $C_{19}H_{21}NO_4$ $[M + Na]^+$ 350.1368; found 350.1374.

Benzyl (1*S*,2*R*)-2-formyl-1-(4-methoxyphenyl)hexylcarbamate (14o). The title compound was isolated as a white solid in 90% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 92 : 8 hexane–iPrOH, flow rate 0.5 mL min^{-1}, λ = 220 nm: t_{major} = 45.54 min, t_{minor} = not found, *anti*: ee > 99%, dr = 91/9; $[\alpha]_D^{20}$ = +11.3 (c = 1, $CHCl_3$); mp 56–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (d, J = 3.6 Hz, 1H), 7.41–7.05 (m, 6H), 6.84 (t, J = 7.1 Hz, 2H), 5.61 (t, J = 14.9 Hz, 1H), 5.09–4.97 (m, 2H), 4.92 (t, J = 8.3 Hz, 1H), 3.77 (d, J = 3.1 Hz, 3H), 2.70 (s, 1H), 1.72–1.45 (m, 1H), 1.38–1.12 (m, 5H), 0.86 (dt, J = 22.0, 6.7 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.92, 159.08, 155.66, 136.25, 132.13, 128.48, 128.10, 128.02, 127.99, 114.06, 67.00, 57.51, 55.25, 29.18, 26.80, 22.44, 13.69 ppm. IR (KBr): 3345, 3067, 3036, 3009, 2959, 2934, 2858, 2839, 2719, 1723, 1688, 1631, 1612, 1516, 1457, 1295, 1249, 1029, 834, 754, 698, 592 cm^{-1}. HRMS (ESI): calcd For $C_{22}H_{27}NO_4$ $[M + Na]^+$ 392.1838; found 392.1838.

***tert*-Butyl (1*S*,2*R*)-2-formyl-3-methyl-1-(2-(trifluoromethyl) phenyl)butylcarbamate (14u).** The title compound was isolated as a colorless oil in 70% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 96 : 4 hexane–iPrOH, flow rate 0.5 mL min^{-1}, λ = 220 nm, t_{major} = 13.98 min, t_{minor} = 10.25 min, *anti*: ee > 99%, dr >99 : 1; $[\alpha]_D^{20}$ = +32.6 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, J = 1.9 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.55–7.41 (m, 2H), 7.36 (t, J = 7.5 Hz, 1H), 5.89 (s, 1H), 5.52 (s, 1H), 2.84 (s, 1H), 2.11 (s, 1H), 1.58 (s, 1H), 1.43 (s, 9H), 1.07 (dd, J = 15.1, 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.41, 154.64, 140.39, 131.99, 129.72, 128.46, 127.51, 126.49, 122.38, 79.64, 61.40, 49.57, 29.04, 28.27, 20.89, 20.03 ppm. IR (neat): 3422, 3359, 3270, 3142, 3075, 2967, 2935, 2875, 2743, 1727, 1609, 1584, 1500, 1369, 1312, 1282, 1249, 1164, 1121, 1038, 1018, 959, 875, 770, 661, 600, 560 cm^{-1}. HRMS (ESI): calcd For $C_{18}H_{24}F_3NO_3$ $[M + Na]^+$ 382.1606; found 382.1610.

***tert*-Butyl (1*S*,2*R*)-2-formyl-3-methyl-1-(4-nitrophenyl)butylcarbamate (14v).** The title compound was isolated as a colorless oil in 75% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 96 : 4 hexane–iPrOH, flow rate 0.5 mL min^{-1}, λ = 220 nm, t_{major} = 26.55 min, t_{minor} = 28.97 min, *anti*: ee > 99%, dr = 96/4; $[\alpha]_D^{20}$ = +28.4 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 9.70 (d, J = 1.1 Hz, 1H), 8.17–8.20 (d, J = 7.9 Hz, 2H), 7.45–7.48 (m, 2H), 5.78–5.80 (d, J = 6, Hz, 1H), 5.17 (s, 1H), 2.73 (s, 1H), 2.00–2.03 (m, 1H), 1.41 (s, 9H), 1.09–1.14 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.39, 155.05, 148.90, 147.20, 127.46, 123.88, 80.32, 62.10, 52.48, 28.53, 28.27, 21.21, 19.64 ppm. IR (neat): 3335, 3114, 3080, 2970, 2934, 2876, 2740, 1717, 1605, 1523, 1349, 1252, 1167, 1108, 1046, 961, 858, 782, 753, 633 cm^{-1}. HRMS (ESI): calcd For $C_{17}H_{24}N_2O_5$ $[M + Na]^+$ 359.1583; found 359.1593.

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