Asymmetric Organocatalysis (1)

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Aminocatalytic Enantioselective *anti*-Mannich Reaction of Aldehydes with In Situ Generated *N*-Cbz and *N*-Boc Imines**

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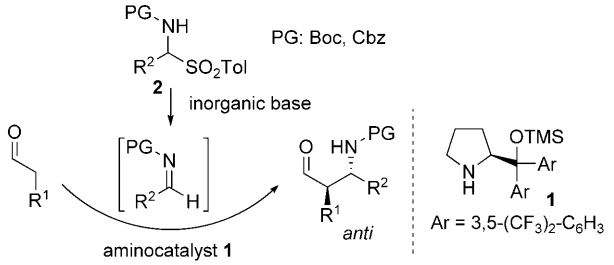
The catalytic asymmetric Mannich reaction constitutes one of the most powerful routes for accessing chiral β-amino carbonyl compounds, and much effort has been devoted toward the development of new and effective methodologies.[1] In this context, the discovery that chiral secondary amines, such as proline and its derivatives, are able to catalyze the direct, highly enantioselective addition of unmodified carbonyl compounds to *N*-PMP (*p*-methoxyphenyl) imines[2] has represented an important achievement from an atom-economy standpoint. Accordingly, an impressive scientific competition toward the identification of more efficient aminocatalytic tactics started, and the Mannich reaction has represented a benchmark for measuring the progress of asymmetric aminocatalysis.[3] Although proline-catalyzed addition of aldehydes to *N*-PMP imines affords *syn*-β-amino aldehydes with high diastereo- and enantiocontrol,[2] the development of an effective *anti*-Mannich protocol has represented a challenging synthetic problem that was solved by the rational design of new chiral amine catalysts.[4] Recently, an important breakthrough was advanced by List and co-workers,[5] who identified suitable reaction conditions that account for the use of preformed aromatic *N*-Boc imine (Boc = *tert*-butyloxycarbonyl) in proline-catalyzed *syn*-Mannich reactions of aldehydes. This study introduced important synthetic advances owing to the easy removal of the N-protecting group, which allows access to unfunctionalized chiral amines.

Herein, we describe our contribution to the progress of the aminocatalytic Mannich reaction and report the first *anti*-selective addition of aldehydes to N-Cbz- and N-Boc-protected imines (Cbz = benzyloxycarbonyl) catalyzed by the commercially available chiral secondary amine **1**. Besides the high stereocontrol achieved, the main feature of this research lies in the identification of a suitable procedure that allows the in situ generation of carbamate-protected imines from stable α-amido sulfones **2** (Scheme 1). We felt that our approach provides a simple and convenient protocol that significantly expands the synthetic potential and the scope of the asymmetric aminocatalytic Mannich reaction of aldehydes.



Scheme 1. In situ generation of *N*-carbamoyl imines. TMS = trimethylsilyl.

Because of their inherent high reactivity, the *N*-carbamoyl imines are rather sensitive to moisture, and their employment introduces practical complications. Recently, the benefit of using stable α-amido sulfones **2** as an imine surrogate[6] has been exploited in phase-transfer-catalyzed Mannich-type reactions[7a,b] and, later, extended to chiral base catalysis,[7c] with important procedural simplification. Inspired by these studies, and convinced of the compatibility between a chiral secondary amine such as **1** and an inorganic base, necessary for the in situ generation of *N*-carbamoyl imines from **2**, we sought to develop a simple protocol for the aminocatalytic *anti*-Mannich reaction of aldehydes. For the exploratory studies, we selected the reaction between hydrocinnamaldehyde and the bench-stable α-amido sulfone **2a** catalyzed by **1** (Table 1). The choice of the chiral amine **1** was triggered by its known ability to impart high *anti* selectivity in the direct addition of aldehydes to preformed *N*-PMP imines,[4b,f]

Table 1: Optimization studies.[a]

Entry	Base (equiv)	Solvent	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	K_3PO_4 (1)	toluene	36	32	93:7	92
2	K_2CO_3 (1)	toluene	36	53	93:7	92
3	$K_2CO_{3(aq)}$ (1)[e]	toluene	36	24	89:11	91
4	KF (3)	toluene	36	31	95:5	95
5	KF (3)	$CHCl_3$	24	95	94:6	96
6[f]	KF (3)	$CHCl_3$	24	65	94:6	95
7[f]	KF (5)	$CHCl_3$	24	87	94:6	96

[a] Reactions carried out on a 0.1 mmol scale using 2 equiv of aldehydes. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy of the crude mixture. [d] Determined by chiral HPLC analysis. [e] 0.1 M solution of K_2CO_3. [f] Reaction carried out with 10 mol% of the catalyst **1**.

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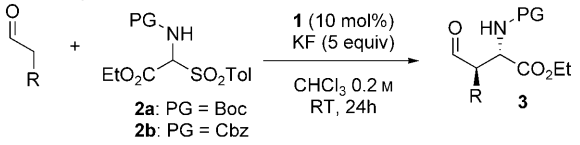
whereas **2a** might be the precursor of N-Boc-protected α-imino ethyl glyoxylate, a highly challenging substrate owing to its synthetic importance and the intrinsic instability that has greatly hampered its use in the Mannich reaction.[8]

Initial results highlighted the ability of a range of bases, either as a solid or as an aqueous solution (Table 1, entries 1–4), to generate in situ the *N*-Boc imino ester. Under these conditions, catalyst **1** imparted very high stereocontrol even at room temperature, although the *anti* adduct **3a** was isolated with only moderate yield.[9] Further optimization of the standard reaction parameters revealed that the nature of the inorganic base and the solvent were crucial to obtain high reaction efficiency. By using 5 equivalents of KF in chloroform, the catalyst loading could be reduced to 10 mol% while affording **3a** with high diastereo- and enantiocontrol and in high yield (Table 1, entry 7). These catalytic conditions were selected for further exploration aimed at expanding the scope of this transformation.

As highlighted in Table 2, the method proved to be successful for a wide range of aliphatic aldehyde substituents. More importantly, the N-Cbz-protected α-amido sulfones **2b** can also be employed, leading to the formation of the expected β-formyl-functionalized amino acids **3d–g** (Table 2, entries 4–7) in good yield and high stereocontrol.[10] The extension of the *anti*-Mannich strategy to different carbamates represents an important feature from a synthetic standpoint, as it provide orthogonal sets of easily removable N-protecting groups.

Interestingly, under the reported reaction conditions, acetaldehyde proved to be a suitable nucleophilic partner (Table 2, entry 8), and its addition to the in situ generated *N*-Cbz imino ester provides easy access to the Mannich adduct **3h**. Although the stereocontrol achieved was unsatisfactory, our approach allows the direct synthesis of aspartate derivatives, which are valuable chiral compounds that can not be prepared by the recently reported proline-catalyzed asymmetric addition of acetaldehyde to aromatic and aliphatic *N*-Boc imines.[11]

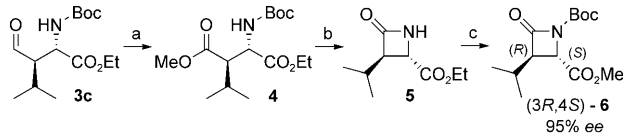
Table 2: Scope of the *anti*-Mannich reaction.[a]



Entry	R	PG	3	[%] yield[b]	d.r.[c]	[%] *ee*[d]
1	Bn	Boc	**a**	87	94:6	96
2	Me	Boc	**b**	92	91:9	94[e]
3[f]	*i*Pr	Boc	**c**	65	98:2	95
4	Et	Cbz	**d**	95	93:7	96
5	Bn	Cbz	**e**	95	91:9	92
6	*n*Bu	Cbz	**f**	96	92:8	98
7	*i*Pr	Cbz	**g**	85	92:8	95
8	H	Cbz	**h**	39	–	15[g]

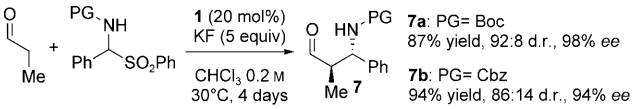
[a] Reactions carried out on a 0.2 mmol scale, using 2 equiv of aldehydes. Bn = $PhCH_2$. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy of the crude mixture. [d] Determined by chiral HPLC analysis. [e] Determined by HPLC analysis of the corresponding oxime prepared with *O*-benzylhydroxylamine. [f] Reaction on a 1.2 mmol scale. [g] The absolute configuration of **3h** was determined to be *S* by comparison of the specific optical rotation with the value reported in the literature; *ee* value determined after oxidation to *N*-Cbz aspartic acid; see the Supporting Information for details.

The Mannich adducts **3** represent versatile intermediates for accessing valuable chiral building blocks. Scheme 2 shows a concise preparation of *trans*-β-lactam **6** based on a simple oxidation–esterification step to afford the aspartic acid derivative **4** and subsequent cyclization. The absolute configuration of N-Boc-protected **6** was determined to be 3*R*,4*S* by comparison of the specific optical rotation with the value reported in the literature (see the Supporting Information for details).



Scheme 2. Preparation of *trans*-β-lactam **6**. Conditions: a) 1) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O; 2) $TMSCHN_2$; b) 1) trifluoroacetic acid; 2) Et_3N, TMSCl; 3) *t*BuMgCl; c) 1) NaOH; 2) $TMSCHN_2$; 3) Boc_2O, 4-dimethylaminopyridine, Et_3N.

The utility of a methodology is measured by its efficiency as well as its applicability. As a proof-of-concept for demonstrating the scope of the presented asymmetric, catalytic Mannich approach, the addition of propanal to in situ generated *N*-Cbz and *N*-Boc phenyl imines is reported in Scheme 3. The *anti* adducts **7** are obtained in good yield and high stereoselectivity.



Scheme 3.

In summary, we have developed the first aminocatalyzed *anti*-selective Mannich reaction of aldehydes with N-Cbz- and N-Boc-protected imines generated in situ from stable α-amido sulfones **2**. Besides the high level of efficiency and stereocontrol achieved, this approach introduces important synthetic advantages, by avoiding the requirement to preform the *N*-carbamoyl imines. The potential extension of this method to the extremely challenging aliphatic imines would further improve the utility of the aminocatalytic Mannich reaction. Studies toward this aim are ongoing.[12]

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[8] N-carbamate-protected α-imino esters are known to be unstable, and their use in organic synthesis has been rather limited. Generally, they must be used immediately after their preparation; see, for example: a) Y. Nakamura, R. Matsubara, H. Kiyohara, S. Kobayashi, *Org. Lett.* **2003**, *5*, 2481. For an asymmetric organocatalytic Mannich reaction of Boc-imino ester, generated in situ by following the procedure developed by Kobayashi, see: b) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 2956; *Angew. Chem. Int. Ed.* **2005**, *44*, 2896.

[9] The use of a different α,α-diaryl prolinols silyl ether, with a phenyl group as the aromatic moiety, in the aminocatalytic Mannich reaction afforded lower selectivity, albeit with slightly improved reactivity (toluene, 1 equiv of K_2CO_3, 24 h, 65% yield, 84:16 d.r. and 85% *ee*; compare with entry 2 in Table 1).

[10] Aminocatalytic Mannich strategies are limited to N-Boc-protected imines; see Ref. [5]. Extension of our method to Fmoc-protected aminosulfone (Fmoc = 9-fluorenylmethyloxycarbonyl) failed under the reported reaction conditions.

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[12] Under the reported conditions, in situ generated cyclohexyl imine reacts very slowly, albeit with high stereocontrol (1 week, 12% conversion, 95:5 d.r., 98% *ee*). Studies are focusing on the identification of a more active catalytic system.

