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Controlling Stereoselectivity in the Aminocatalytic Enantioselective Mannich Reaction of Aldehydes with In Situ Generated N-Carbamoyl Imines

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Abstract: A simple and convenient method for the direct, aminocatalytic, and highly enantioselective Mannich reactions of aldehydes with in situ generated N-carbamoyl imines has been developed. Both α-imino esters and aromatic imines serve as suitable electrophilic components. Moreover, the judicious selection of commercially available secondary amine catalysts allows selective access to the desired stereoisomer of the *N*-*tert*-butoxycarbonyl (Boc) or *N*-carbobenzyloxy (Cbz) Mannich adducts, with high control over the *syn* or *anti* relative configuration and almost perfect enantioselectivity. Besides the possibility to fully control the stereochemistry of the Mannich reaction, the main advantage of this method lies in the operational simplicity; the highly reactive N-carbamate-protected imines are generated in situ from stable and easily handled α-amido sulfones.

Keywords: asymmetric catalysis · imines · Mannich reaction · organocatalysis · sulfones

Introduction

Asymmetric aminocatalysis is nowadays recognized as a fundamental and reliable synthetic strategy for the stereoselective construction of chiral molecules.[1] The rapid affirmation of organocatalysis over the last decade has been warranted by its efficiency, cost-effectiveness, low environmental impact, and operational simplicity. All of these features have generated a remarkable scientific competition, which has guided asymmetric aminocatalysis towards excellent levels of development and opened new synthetic opportunities that were considered inaccessible only a few years ago.[2] The extraordinary pace of innovation and progress has been mainly dictated by the discovery of generic catalytic-activation modes of carbonyl compounds that have enabled previously unknown transformations. To the same extent, the design of novel structural classes of organic catalysts has also ignited the field and enabled the activation of more challenging carbonyl substrates. Within this context, venerable chemical transformations that lead to the preparation of useful chiral building blocks have been generally chosen as benchmarks for developing novel, more effective aminocatalysts. Among them, the catalytic asymmetric Mannich reaction has been considered a point of reference for measuring the progress of aminocatalysis.[3] The discovery that chiral secondary amines, such as proline and its derivatives, are able to catalyze the direct addition of unmodified carbonyl compounds to N-PMP imines (PMP = *p*-methoxyphenyl) with very high stereoselectivity[4] has greatly contributed to the development of new atom-economy-based Mannich strategies.[5] While proline-catalyzed addition of aldehydes to N-PMP imines affords *syn*-β-amino aldehydes with high diastereo- and enantiocontrol,[4,5] the development of an effective *anti*-Mannich protocol has represented a challenging synthetic problem for a long time. Only by the rational design of specific, novel, chiral amine catalysts, which often required several synthetic steps for their preparation, was it possible to partially address this synthetic challenge.[6] Recently, an important advance was introduced by List and coworkers,[7] who identified suitable reaction conditions that involve the use of a preformed aromatic N-Boc imine (Boc = *tert*-butoxycarbonyl) in proline-catalyzed *syn*-Man-

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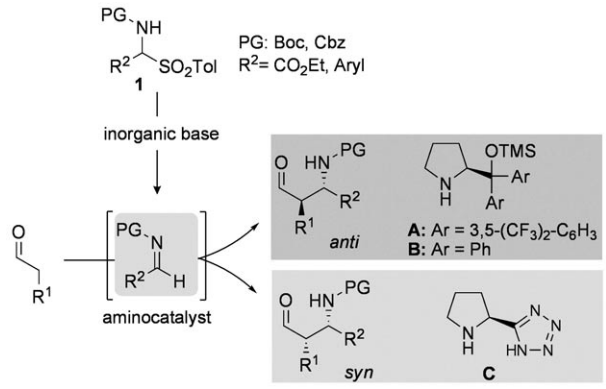
nich reactions of aldehydes. This study provided important synthetic benefits due to the easy removal of the N-protecting group to directly deliver unfunctionalized chiral amines.

In the frame of our studies on aminocatalysis,[8] we were interested in expanding the synthetic potential and the scope of the asymmetric aminocatalytic Mannich reaction. Specifically, we focused on the development of highly stereoselective enamine-catalyzed additions of unmodified aldehydes to N-carbamoyl imines to promote the formation of versatile N-Boc- or N-Cbz-protected (Cbz = carbobenzyloxy) adducts. To be broadly applicable and useful to the synthetic community, such a methodology should also be simple and reliable. The main drawback associated with the use of N-carbamoyl imines is their inherent high reactivity, which introduces practical complications. They are rather sensitive to moisture and air, as a result their preparation and storage can be quite disadvantageous, and the catalytic reaction requires strictly controlled conditions. To greatly simplify the procedure, we sought to introduce the use of stable α-amido sulfones **1** as imine precursors for the design of a more efficient asymmetric Mannich methodology. Recently, the benefit of using stable α-amido sulfones **1** as imine surrogates[9] has been exploited in phase-transfer-catalyzed Mannich-type reactions[9b,c] and later extended to chiral-base catalysis,[9d] with important procedural simplification. Inspired by these studies and convinced of the compatibility between a chiral secondary amine (able to activate the aldehydic component by induction of enamine formation) and an inorganic base (necessary for the in situ generation of N-carbamoyl imines from **1**), we developed a simple protocol for the first *anti*-selective addition of aldehydes to N-Cbz and N-Boc-protected α-imino esters, catalyzed by the commercially available TMS-diaryl prolinol-derived catalysts **A** and **B** (TMS = trimethylsilyl).[10,11] Herein, we describe our contribution to the progress of the aminocatalytic Mannich transformation by reporting the application of our approach to the hitherto difficult *anti*- and highly enantioselective Mannich reactions of N-carbamoyl aromatic imines (Scheme 1).



Scheme 1. Strategy for the aminocatalytic *anti*- and *syn*-Mannich reactions of aldehydes with in situ generated N-carbamoyl imines.

Moreover, we recognized the development of a *syn*-Mannich version as a crucial target, because it would allow selective access to all four stereoisomers of the valuable β-amino aldehydes by simply selecting the appropriate organocatalyst for use in a very simple protocol. We found that the commercially available proline-derived tetrazole catalyst **C** is able to promote the enantioselective *syn*-Mannich addition[12] to aromatic N-carbamoyl imines generated in situ from stable α-amido sulfones **1** (Scheme 1). We believe that the described approach provides an easy and convenient protocol, which significantly expands the synthetic potential of the asymmetric aminocatalytic Mannich reaction of aldehydes.

Results and Discussion

Aminocatalytic *anti*-selective Mannich reaction of in situ generated *N*-carbamoyl α-imino ethyl glyoxylate:[10] The catalytic asymmetric Mannich reaction constitutes one of the most powerful synthetic routes for the construction of chiral nitrogen-containing molecules. Therefore, much effort has been devoted toward the development of new and effective catalytic and asymmetric methodologies.[3] Within this context, the proline-catalyzed, direct, highly enantioselective addition of unmodified carbonyl compounds to N-PMP imines[4,5] has represented a cornerstone reaction. Successively, the identification of more efficient aminocatalytic tactics has been mainly focused on the ability to selectively access *syn*- or *anti*-β-amino aldehydes with high levels of absolute and relative stereocontrol, as well as the possibility to use easily removable N-protecting groups. Accordingly, some *anti*-selective asymmetric Mannich reactions with N-PMP-protected imines, catalyzed by carefully engineered catalysts, have recently been reported.[6,10,11] The power of proline to catalyze the direct addition of aldehydes to preformed N-Boc-protected imines, leading to *syn*-β-amino aldehydes, has been recently established.[7] Very recently, we focused our attention upon the, at that time,[10,11] unprecedented *anti*-selective direct addition of aldehydes to N-Cbz- and N-Boc-protected imines, a method that would allow easy access to unfunctionalized chiral amines due to the easy removal of the N-protecting group. However, because of their inherent high reactivity, the preparation and use of N-carbamoyl imines requires particular operational conditions. To us, a useful synthetic method should be reproducible and easily executed. Toward this aim, we sought to develop a simple protocol for the aminocatalytic *anti*-Mannich reaction of aldehydes using stable α-amido sulfones **1** as imine precursors. This approach would introduce important synthetic advantages by avoiding the requirement to prepare and isolate the unstable imines.

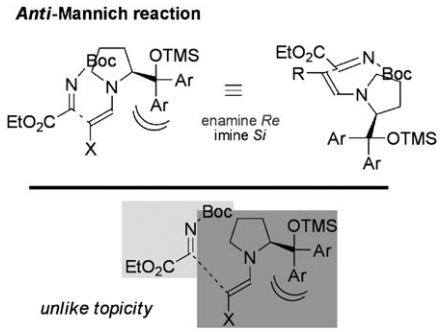
For the exploratory studies, we selected the reaction between hydrocinnamaldehyde (**2a**) and the bench-stable α-amido sulfone **1a**, catalyzed by the commercially available TMS-diaryl prolinol-derived catalysts **A** and **B** (Table 1).[13] The choice of the chiral amines was triggered by their

Table 1. Optimization studies.[a]

Entry	Catalyst	Base ([equiv])	Solvent	t [h]	Yield [%][b]	d.r.[c]	ee [%][d]
1	**A**	K_3PO_4 (1)	toluene	36	32	13:1	92
2	**A**	K_2CO_3 (1)	toluene	36	53	13:1	92
3	**B**	K_2CO_3 (1)	toluene	24	65	5.3:1	85
4	**A**	K_2CO_3 (aq)[e] (1)	toluene	36	24	8:1	91
5	**A**	KF (3)	toluene	36	31	19:1	95
6	**A**	KF (3)	$CHCl_3$	24	95	16:1	96
7[f]	**A**	KF (3)	$CHCl_3$	24	65	16:1	95
8[f]	**A**	KF (5)	$CHCl_3$	24	87	16:1	96

[a] Reactions carried out on a 0.1 mmol scale using 2 equiv of **2a**. [b] Isolated yield after chromatography. [c] Diastereomeric ratio (d.r.), determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess (*ee*) determined by HPLC analysis on chiral stationary phases. [e] 0.1 M solution of K_2CO_3. [f] Reaction carried out with 10 mol% of catalyst.

known ability to impart high *anti*-selectivity in the direct addition of aldehydes to preformed N-PMP imines[6b] by exploitation of a "steric-control approach".[13] As shown in Scheme 2, the efficient shielding of the bulky chiral fragment of the catalyst determines the selective engagement of the imine *Si* face with the *Re* face of the enamine intermediate (*Re* when X is of highest priority), an unlike topicity that forges an *anti* relative configuration in the β-aminoaldehyde product.



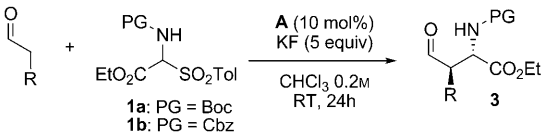
Scheme 2. Origin of the stereoselectivity in the *anti*-Mannich reaction, catalyzed by TMS-diaryl prolinol-derived catalysts **A** and **B**; X is the group of highest priority.

The α-amido sulfone **1a** was selected as the precursor of N-Boc-protected α-imino ethyl glyoxylate, a highly challenging substrate due to its synthetic importance and the intrinsic instability that has greatly hampered its use in the Mannich reaction. Despite the fact that N-carbamate-protected α-imino esters would directly lead to synthetically useful amino acid derivatives, they are known to be unstable, and their use in organic synthesis has been rather limited because they must be used immediately after preparation.[14] The in situ preparation method seems a suitable route to overcome such a limitation.

Optimization studies highlighted the ability of a range of bases, either solid or as an aqueous solution (Table 1, entries 1–5), to generate the N-Boc imino ester in situ. Notably, catalyst **A** imparted very high stereocontrol, even at room temperature, albeit the *anti*-adduct **3a** was isolated with moderate yield. The use of α,α-diphenyl prolinol silyl ether **B** afforded slightly lower selectivity, although with improved reactivity (Table 1, entry 3). This evidence prompted us to select **A** as the catalyst of choice and further optimization of the standard reaction parameters was carried out. The nature and the amount of inorganic base and solvent[15] was crucial to achieve high reaction efficiency. By using 5 equiv of KF in chloroform, the catalyst loading could be reduced to 10 mol% and afforded **3a** with high diastereo- and enantiocontrol, in high yield (Table 1, entry 8). These catalytic conditions were selected for further explorations aimed at expanding the scope of this transformation.

As shown in Table 2, different aliphatic aldehydes were suitable substrates for the Mannich reaction. Products of type **3** were isolated in high yields and with very high optical purity and *anti* diastereoselectivity. The catalyst **A** also proved active with the more encumbered reagent isovaleraldehyde and furnished **3c** in good yield, without affecting the efficiency of the system (Table 2, entry 4). By using the same conditions, the method was extended to the N-Cbz-protected α-amido sulfone **1b**, to afford the expected *anti*-β-amino aldehydes **3d–g** in good yields and with high stereocontrol. The extension of the *anti*-Mannich strategy to different carbamates represents an important feature from a synthetic standpoint, providing a choice of easily removable N-protecting groups.[16] As expected, it is possible to access both of the enantiomers of the *anti* products **3** simply by se-

Table 2. *Anti*-Mannich reaction with in situ generated aromatic N-carbamoyl α-imino ethyl glyoxylate.[a]

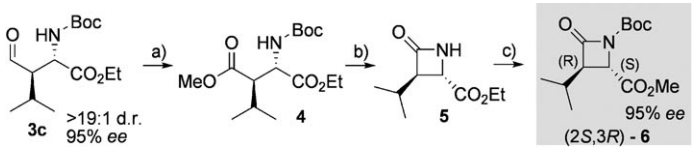


Entry	R	PG	**3**	Yield [%][b]	d.r.[c]	ee [%][d]
1	Bn	Boc	**a**	87	16:1	96
2	Bn	Boc	**a**	82	13:1	−96[e]
3	Me	Boc	**b**	92	10:1	94[f]
4[g]	*i*Pr	Boc	**c**	65	>19:1	95
5	Et	Cbz	**d**	95	13:1	96
6	Bn	Cbz	**e**	95	10:1	92
7	*n*Bu	Cbz	**f**	96	11.5:1	98
8	*i*Pr	Cbz	**g**	85	13:1	95
9	*i*Pr	Cbz	**g**	87	13:1	−95[e]

[a] Reactions carried out on a 0.2 mmol scale using 2 equiv of aldehyde. [b] Isolated yield after chromatography. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] Reaction carried out using the D-enantiomer of the catalyst **A**, leading to the opposite antipode of *anti* products **3**. [f] *ee* determined by HPLC analysis of the corresponding oxime prepared with *O*-benzylhydroxylamine. [g] Reaction on a 1.2 mmol scale.

lecting the appropriate catalyst enantiomer, and still maintain a very high level of selectivity (Table 2, entries 2 and 9).

The Mannich adducts **3** represent versatile intermediates for accessing valuable chiral building blocks. In Scheme 3, a concise preparation of *trans*-β-lactam **6** is reported, based on



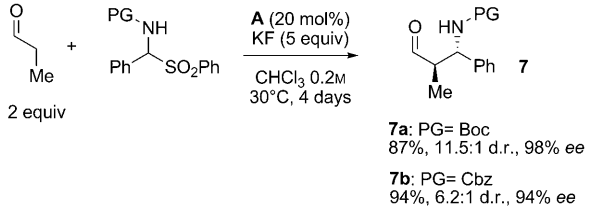
Scheme 3. Assignment of the absolute configuration of *anti*-**3c**: Conditions: a) i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O; ii) $TMSCHN_2$; b) i) trifluoroacetic acid (TFA); ii) Et_3N, TMSCl; iii) *t*BuMgCl; c) i) NaOH; ii) $TMSCHN_2$; iii) Boc_2O, 4-dimethylaminopyridine (DMAP), Et_3N.

a simple oxidation–esterification step to afford the aspartic acid derivative **4** and subsequent cyclization. Thus, treatment of *anti*-**3c** with $NaClO_2$, followed by the addition of $TMSCHN_2$ led to the formation of the corresponding methyl ester **4** (83% yield over two steps). Subsequent Boc deprotection and cyclization, based on a known procedure,[17] gave β-lactam **5**. Finally, a saponification-methylation-protection sequence afforded the N-Boc-protected lactam **6**. HPLC analysis on a chiral stationary phase confirmed that the whole synthetic sequence did not affect the enantiopurity of compound **6**. The absolute configuration was determined to be (2*S*,3*R*) by comparison of the specific optical rotation with the value reported in the literature,[18] the *trans* configuration was confirmed by the observed ^1H NMR coupling constant (J(H2,H3) = 3.2 Hz).

Therefore, catalyst **A** promotes the asymmetric formation of (2*S*,3*R*)-amino acid derivatives **3**. The stereochemical outcome of the Mannich reaction can be rationalized on the basis of the proposed transition state depicted in Scheme 2. The efficient coverage of the *Si* face of the chiral enamine intermediate leaves the *Re* face available for the imine approach. The steric hindrance of the catalyst also determines the enantiofacial selectivity of the electrophile and enforces an unlike topicity for the Mannich reaction.

Aminocatalytic *anti*-selective Mannich reaction of in situ generated N-carbamoyl aromatic imines: The proline-catalyzed asymmetric Mannich reaction is arguably one of the most useful ways to synthesize chiral β-amino carbonyl compounds. The recent discovery that this simple amino acid can also enforce incredible levels of enantioselectivity and *syn*-diastereoselectivity in the addition of aldehydes to N-Boc-protected aromatic imines has broadly expanded the applicability of this asymmetric system.[7] The facile and efficient removal of the N-protecting group to yield the unfunctionalized amine avoids drastic oxidative conditions involving harmful reagents, generally required for the removal of the commonly used PMP group from nitrogen and thus, represents a crucial achievement to render the aminocatalytic Mannich reaction more attractive as a synthetic tool. However, a general and highly efficient version for obtaining *anti*-β-amino-β-aryl aldehydes still represents a difficult target. Few and limited examples have been reported that address the catalytic asymmetric *anti*-Mannich reactions with N-Boc-protected aromatic imines. Very recently, during our investigations, Maruoka and co-workers reported an amino sulfonamide catalyzed *anti*-Mannich reaction of aldehydes and preformed aromatic N-Boc imines, a procedure that afforded a wide range of adducts with high levels of stereocontrol.[11]

Convinced of the synthetic utility of our approach, which avoids the need to prepare and isolate unstable imines, we turned our attention to the addition of aldehydes to N-carbamoyl aromatic imines generated in situ from stable α-amido sulfones. Specifically, we investigated the reaction between propanal and aromatic sulfones, by using the same catalytic conditions developed for the *anti*-Mannich reaction of in situ generated N-Carbamoyl α-imino ethyl glyoxylate. As reported in Scheme 4, catalyst **A** promotes the addition

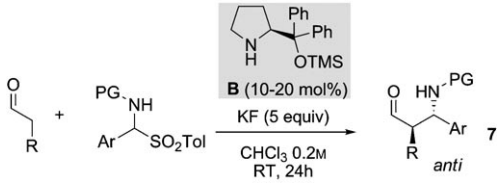


Scheme 4. *Anti*-Mannich addition of propanal to in situ generated N-Cbz and N-Boc-protected phenyl imines, catalyzed by TMS-diaryl prolinol-derived catalyst **A**.

of propanal to in situ generated N-Cbz- and N-Boc-phenyl imines with high levels of efficiency; the *anti*-adducts **7** were obtained in good yield and with high stereoselectivity. However, the lower reactivity of aromatic imines relative to imino glyoxylate derivatives requires longer and impractical reaction times and thus, lowers the synthetic utility of the method.

We considered these results quite encouraging for the development of the catalytic system because they clearly demonstrate that the N-carbamoyl aromatic imines can also be formed in situ in the presence of KF, an inorganic base that seems not to interfere with the catalytic efficiency of chiral secondary amines. For this reason, we wondered whether the less-encumbered catalyst **B**, which bears a simple phenyl ring on the crucial bulky chiral fragment of the pyrrolidine ring, may be useful to speed up the Mannich reaction of aromatic imines, but still maintain high levels of *anti* diastereoselectivity and good enantiocontrol. It is known that catalyst **A** generally enforces a higher geometry control and better facial discrimination relative to **B**, albeit at the expense of reactivity. To our delight, however, we found that the use of 10 mol% of the less-encumbered catalyst **B** promoted the addition of propanal to in situ generated N-Boc phenyl imine in excellent yield and with useful levels of enantioselectivity and *anti* diastereoselectivity (Table 3, entry 1).

Table 3. Scope of the *anti*-Mannich reaction with in situ generated N-carbamoyl aromatic imines.[a]



Entry	R	Ar	PG	7	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me	Ph	Boc	**a**	95	5.2:1	94
2	Bu	Ph	Boc	**c**	90	5:1	96
3	Bn	Ph	Boc	**d**	70	5.2:1	76
4[e]	*i*Pr	Ph	Boc	**e**	94	9.2:1	98
5[f]	H	Ph	Boc	**f**	64	–	64[g]
6[f,h]	H	Ph	Boc	**f**	31	–	77[g]
7[e]	*i*Pr	4-MeC_6H_4	Boc	**g**	74	6:1	84[g]
8[e]	*i*Pr	4-MeOC_6H_4	Boc	**h**	95	7:1	91
9[e]	*i*Pr	4-ClC_6H_4	Boc	**i**	73	10:1	94
10[e]	*i*Pr	4-$NO_2C_6H_4$	Boc	**j**	27	>19:1	99
11[e]	*i*Pr	2-thienyl	Boc	**k**	73	8:1	96
12[e]	*i*Pr	2-pyridyl	Boc	**l**	60	9:1	87[g]
13[e]	*i*Pr	4-MeC_6H_4	Cbz	**m**	74	8:1	93[g]
14[e]	*i*Pr	4-MeOC_6H_4	Cbz	**n**	82	9:1	99

[a] Reactions carried out at room temperature on a 0.2 mmol scale using 2 equiv of aldehyde and 10 mol% of catalyst **B**. [b] Isolated yield after chromatography. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] Reaction carried out with 20 mol% of catalyst **B** over 65 h. [f] Reaction carried out using 5 equiv of acetaldehyde and 20 mol% of catalyst; the absolute configuration of **7f** was determined to be (*S*) by comparison of the specific optical rotation with the value reported in the literature, see ref. [11a]. [g] Determined by HPLC analysis after reduction of the isolated aldehydic product. [h] Reaction carried out in the presence of 20 mol% of catalyst **A**.

More importantly, the reaction reaches completion after 24 h, hence the aim of identifying a simple, yet practical, *anti*-Mannich protocol has been addressed.

As portrayed in Table 3, the catalytic system allows a wide scope in terms of the nucleophilic component. Aldehydes with a long alkyl chain, a benzylic moiety, and a more-encumbered chain all worked well in the *anti*-Mannich protocol and gave products **7c–e** in high yields, with good to very high stereocontrol (Table 3, entries 2–4). Interestingly, under the reported reaction conditions, acetaldehyde (the simplest among the aldehydic donors, only recently introduced in the aminocatalytic scenario)[19] proved to be a suitable nucleophilic partner. Reaction under the *anti*-Mannich conditions delivered highly important synthetic intermediate **7f**[19a] in good yield, although with moderate enantioselectivity (Table 3, entry 5). The use of the catalyst **A** enforced higher enantioselectivity in this transformation (77% *ee*, Table 3, entry 6), but with poor chemical yield.

We performed a series of experiments to determine the scope of the imine component in this aminocatalytic *anti*-Mannich protocol.[20] Given the higher level of stereoinduction achieved when using isovaleraldehyde (R = *i*Pr, Table 3, entry 4), we further investigated its employment as a Mannich donor with several in situ generated aromatic imines in the presence of catalyst **B** (20 mol%). Significant variation in the steric and electronic demand of the aromatic ring substituent can be accommodated without loss of stereochemical control. Both electron-releasing and -withdrawing groups were tolerated and led to the formation of variously substituted aromatic N-Boc-protected *anti*-β-amino aldehydes **7g–j** (Table 3, entries 7–10). Heteroaromatic substituents also proved to be suitable substrates for the Mannich reaction, products **7k** and **7l** were afforded with good stereocontrol (Table 3, entries 11 and 12). The corresponding in situ generated N-Cbz-protected aromatic imines were also tested. The high reactivity and stereoselectivity observed further highlight the generality of our approach; Mannich products with orthogonal N-protecting groups can be easily accessed (Table 3, entries 13 and 14).

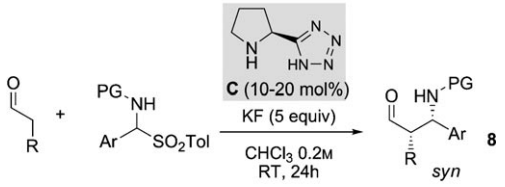
The stereochemical outcome of the *anti*-Mannich reaction of aromatic imines is in agreement with that observed in the *anti*-selective reaction of in situ generated *N*-carbamoyl α-imino ethyl glyoxylate, further support for the plausible transition state reported in Scheme 2.

Aminocatalytic *syn*-selective Mannich reaction of in situ generated N-carbamoyl aromatic imines: Achieving the full matrix of all possible stereoisomeric products in the preparation of molecules with multiple stereocenters is a challenging synthetic target. This is particularly important for compounds intended for biomedical applications because incomplete collections of stereoisomers impair efforts to extract powerful stereochemistry-based structure–activity relationships (SARs) from primary screening data.[21] Due to the usefulness of the Mannich adducts as versatile building blocks to access medicinally relevant chemical structures, the development of highly efficient catalytic methodologies that allow full control of the stereochemistry of the Mannich reaction is exceedingly important. Prompted by these considerations, we sought to apply our simple protocol to the asymmetric, aminocatalytic *syn*-selective Mannich reaction. The main issue lies in the identification of a suitable amine catalyst that may coexist with the reaction conditions necessary to generate the reactive imines in situ, but still impart high *syn*-diastereo- and enantioselectivity to the Mannich process.

We focused on the use of the commercially available proline-derived tetrazole catalyst **C**. This catalyst had been originally designed and synthesized with the intention of overcoming some of the drawbacks associated with the use of proline, such as the solubility in conventional organic solvents, yet preserving the dual-activation ability of the catalyst.[12] Due to the similarity in pK_a between the proline carboxylic acid and the tetrazole moiety, catalyst **C** can effectively mimic the bifunctional activation mode of proline catalysis.[22] Ley and co-workers have demonstrated the ability of the tetrazole catalyst **C** to impart high *syn* diastereoselectivity in the Mannich reaction between ketones and preformed N-PMP-protected α-imino ethyl glyoxylate.[12] On this basis, we decided to investigate the potential of **C** to catalyze the *syn*-selective addition of aldehydes to in situ generated imines. Using the same reaction protocol devel-

oped for the *anti*-version, we found that the tetrazole catalyst preserves its efficiency in the presence of KF and catalyzes the highly stereoselective Mannich reaction to lead directly to highly enantioenriched *syn*-β-aminoaldehydes (Table 4).

Table 4. Scope of the *syn*-Mannich reaction with in situ generated N-carbamoyl imines.[a]



Entry	R	Ar	PG	8	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me	Ph	Boc	**a**	77	16:1	99
2	Bu	Ph	Boc	**b**	70	10:1	99
3	Bn	Ph	Boc	**c**	89	10:1	>99
4[e]	*i*Pr	Ph	Boc	**d**	80	11.2:1	>99
5[e,f]	H	Ph	Boc	**7f**	43	–	84[g]
6[e]	*i*Pr	4-MeC_6H_4	Boc	**e**	76	11:1	>99[g]
7[e]	*i*Pr	4-MeOC_6H_4	Boc	**f**	85	7:1	99
8[e]	*i*Pr	4-ClC_6H_4	Boc	**g**	73	3:1	>99
9[e]	*i*Pr	4-$NO_2C_6H_4$	Boc	**h**	16	2.5:1	94
10[e]	*i*Pr	2-thienyl	Boc	**i**	86	9:1	99
11[e]	*i*Pr	2-pyridyl	Boc	**j**	50	2.5:1	90[g]
12[e]	*i*Pr	4-MeC_6H_4	Cbz	**k**	70	3.2:1	98[g]
13[e]	*i*Pr	4-MeOC_6H_4	Cbz	**l**	70	5:1	>99

[a] Reactions carried out at room temperature on a 0.2 mmol scale using 2 equiv of aldehyde and 10 mol% of catalyst **C**. [b] Isolated yield after chromatography. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] Reaction carried out with 20 mol% of catalyst **C** over 65 h. [f] Reaction carried out with 5 equiv of acetaldehyde for 36 h; the absolute configuration of **7f** was determined to be (*S*) by comparison of the specific optical rotation with the value reported in the literature, see ref. [11a]. [g] Determined by HPLC analysis after reduction of the isolated aldehydic product.

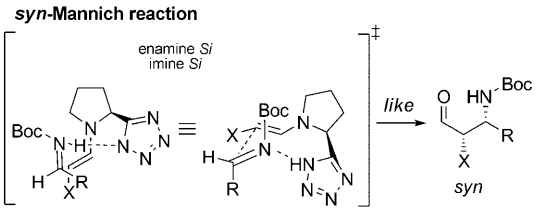
The *syn*-stereochemical outcome of the reaction can be rationalized on the basis of a transition state that resembles the classical catalysis model of proline,[23] in which a specific hydrogen-bonding interaction determines the stereoselectivity of the process by directing the electrophile approach from the upper face of the enamine (hydrogen-bonding-directed catalysis, Scheme 5).[24]

As shown in Table 4, tetrazole catalyst **C** proved to be highly effective in the *syn*-Mannich addition of aldehydes to in situ formed N-carbamoyl imines and furnished excellent results in terms of stereocontrol. The method proved to be successful for a wide range of aliphatic aldehyde substituents and led to β-amino aldehydes **8a–d** in high yields, with high diastereocontrol, and almost perfect enantioselectivity. Interestingly, the *syn*-Mannich products **8** can be easily isolated in good yields by simple trituration of the crude mixture with cool hexane, thus avoiding time-consuming and costly column chromatography. To prove that the remarkably high stereoselectivity achieved did not arise from enantioenrichment during the purification process and is only ascribable to the catalyst efficiency, the enantiomeric purity of product **8b** (Table 4, entry 2) has been measured after isolation by column chromatography on silica gel (99% *ee*).

Notably, the employment of acetaldehyde in the presence of **C** gave rise to the highly important synthetic intermediate **7f** with interesting enantioselectivity (84% *ee*, Table 4, entry 5). Notably, both the TMS-diaryl prolinol and tetrazole catalysts catalyzed the Mannich reaction of acetaldehyde enforcing the same stereoinduction; the related β-amino aldehyde **7f** was formed with the *S* absolute configuration.[11,19a,b] This observation is in line with the proposed transition states for the Mannich reactions shown in Schemes 2 and 5, in which the electrophile facial selectivity is common to both transformations. In fact, the opposite *syn* or *anti* relative stereochemistry observed when using linear aldehydes that lead to α,β-branched β-amino aldehydes arises from an opposite enamine facial selectivity imparted by the two catalyst types.

We examined the generality of the reaction by using isovaleraldehyde (R = *i*Pr) as a nucleophilic donor and various aromatic N-Boc- and N-Cbz-sulfones as imine precursors.[20] Catalyst **C** afforded products **8e–l**, which contain a range of different aromatic substituents, with high levels of diastereocontrol and with almost total enantiopurity (Table 4, entries 6–13).

The absolute configuration of the *syn*-Mannich product **8a** was determined to be (1*S*,2*S*) by comparison of the specific optical rotation with the value reported in the literature.[7b] This supports a bifunctional mode of catalysis with **C**, as depicted in Scheme 5, which is able to activate both the reaction partners and leads to a well-organized transition state, which mimics the accepted mechanism of the proline-catalyzed Mannich reaction.[23]



Scheme 5. Origin of the *syn*-stereoselectivity in the Mannich reaction, catalyzed by **C**; X is the group of highest priority.

Conclusion

We have developed a highly efficient system for the asymmetric aminocatalytic Mannich reaction of unmodified aldehydes with in situ generated N-carbamoyl imines. The main feature of this method lies in the operational simplicity: the highly reactive N-carbamate-protected imines are generated in situ from stable, easily handled α-amido sulfones. The judicious selection of commercially available chiral amine catalysts **A–C** allows full control of the stereochemistry of the Mannich process; either the *syn*- or *anti*-β-amino aldehydes

are accessible with very high stereocontrol. From a synthetic standpoint, the presented method is a rare example of a highly *anti*-selective Mannich reaction with N-carbamoyl aromatic imines. We believe that our approach provides a simple and convenient protocol that may be useful to the synthetic community.

Experimental Section

General procedure for the *anti*-Mannich reaction of aldehydes with in situ generated N-Cbz and N-Boc imines: The reactions were carried out with no precautions to exclude air or moisture and by using the appropriate TMS-diaryl prolinol-derived catalysts **A** or **B** for α-imino esters and aromatic imines, respectively. Aldehyde (0.4 mmol, 2 equiv) was added to a solution of catalyst (0.02 mmol, 0.1 equiv) in $CHCl_3$ (1.0 mL) at room temperature. After stirring for 5 min, α-amido sulfone **2** (0.2 mmol, 1 equiv) and KF (58.1 mg, 1.0 mmol, 5 equiv) were added successively. Stirring was continued for 24 h, then the crude reaction mixture was diluted with CH_2Cl_2 (2 mL) and flushed through a short plug of silica (1:1 CH_2Cl_2/Et_2O). The solvent was removed in vacuo and the residue was purified by flash column chromatography with mixtures of ethyl acetate/hexane as the eluent. Since the Mannich products are prone to epimerization during silica gel chromatography, which could affect the diastereomeric ratio of the isolated compounds **3** and **7**, flash chromatography was performed quickly.

General procedure for the *syn*-Mannich reaction of aldehydes with in situ generated N-carbamoyl aromatic imines: The reactions were carried out by using 10–20 mol% of the proline-derived tetrazole catalyst **C**, by following the same experimental procedure described above. The only difference concerns the isolation of the *syn*-adducts **8**, which were obtained in good yields after simple trituration of the crude mixture with cool hexane.

Full compound characterization, further experimental details, and NMR spectroscopy and HPLC traces can be found in the Supporting Information.

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