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Construction of chiral α -*tert*-amine scaffolds via amine-catalyzed asymmetric Mannich reactions of alkyl-substituted ketimines†

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Stereoselective Mannich reactions of aldehydes with ketimines provide chiral β -amino aldehydes that bear an α -*tert*-amine moiety. However, the structural variation of the ketimines is limited due to the formation of inseparable *E/Z* isomers, low reactivity, and other synthetic difficulties. In this study, a highly diastereodivergent synthesis of hitherto difficult-to-access β -amino aldehydes that bear a chiral α -*tert*-amine moiety was achieved using the amine-catalyzed Mannich reactions of aldehydes with less-activated *Z*-ketimines that bear both alkyl and alkynyl groups.

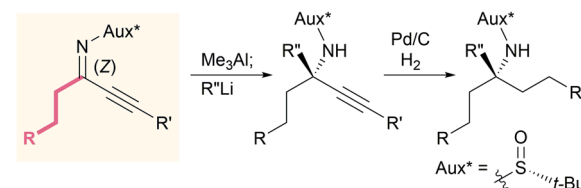
Introduction

The asymmetric Mannich reaction is one of the most basic and useful methods for the synthesis of chiral β -amino carbonyl compounds,¹ which are fundamental and frequent motifs in bioactive compounds, as well as versatile building blocks for the synthesis of structurally complex molecules.² In particular, the use of ketimines provides an efficient access to β -amino carbonyl compounds that bear an α -*tert*-amine moiety, and a wide variety of Mannich reactions with ketimines have been developed to date.^{3–8} During the face-selective nucleophilic addition to ketimines, the geometry of the *N*-substituent of the ketimine significantly affects the enantioselectivity because the chiral catalyst interacts with the *N*-substituent or the lone pair of the imine nitrogen atom. Therefore, dialkyl-substituted ketimines, which exist as an inseparable mixture of nearly equal amounts of the *E*- and *Z*-ketimine,⁹ are rarely used in asymmetric synthesis compared to ketimines that exist as single geometric isomers.^{3–7}

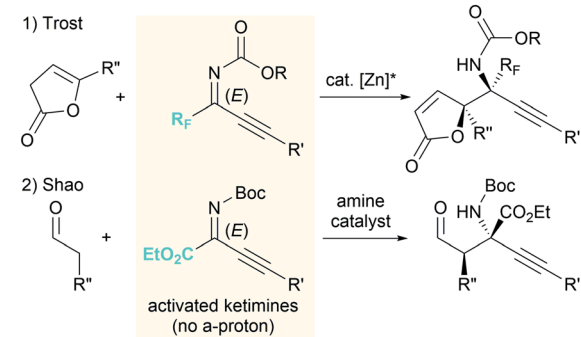
Recently, we found that the *Z* isomer of ketimines can be obtained selectively by replacing one alkyl substituent with a less sterically hindered alkynyl group.¹⁰ This type of ketimine can be considered a synthetic equivalent of the dialkyl-substituted ketimine, since the alkynyl group can be converted to an alkyl group by simple hydrogenation. *Via* the introduction of a chiral auxiliary to the alkynyl-substituted

ketimines, the asymmetric synthesis of α -*tert*-amine derivatives has been realized (Scheme 1a).¹¹ However, stoichiometric quantities of the chiral auxiliary are required, as well as highly reactive reagents to achieve the nucleophilic addition to the less-reactive ketimines. We thus became interested in

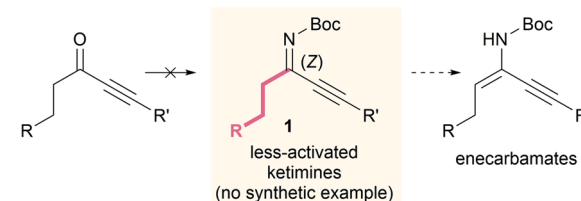
a) Asymmetric synthesis of dialkyl-substituted α -*tert*-amines



b) Asymmetric Mannich reactions of alkynyl-substituted ketimines



c) Problems of *N*-Boc-protected alkyl-substituted ketimines



Scheme 1 Alkynyl-substituted ketimines for asymmetric reactions.

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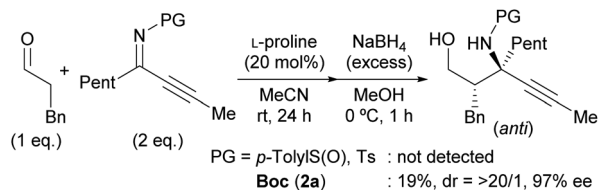


developing a catalytic asymmetric Mannich reaction using both alkyl and alkynyl-substituted ketimines under mild conditions.

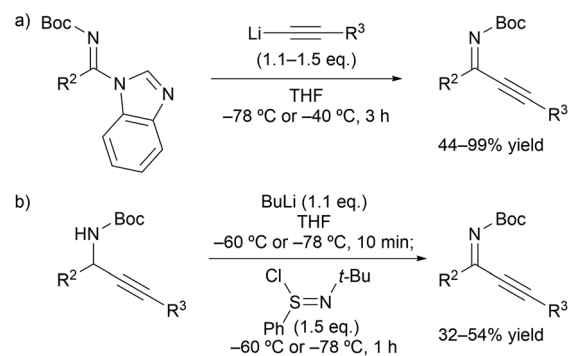
Some alkynyl-substituted ketimines have been used for asymmetric reactions¹² including Mannich reactions, although the applicable ketimines are limited to those activated by an electron-withdrawing perfluoroalkyl or ester group (Scheme 1b).⁸ To the best of our knowledge, examples of catalytic asymmetric reactions of alkynyl-substituted ketimines that bear an electron-donating alkyl group on the imine carbon have not yet been reported. This can be attributed in part to the limited number of available alkyl- and alkynyl-substituted ketimines^{11,13} and difficulties associated with their synthesis. For example, *N*-Boc-protected ketimines **1** cannot be synthesized from the corresponding ketones (Scheme 1c, left). Furthermore, unlike ketimines that bear a perfluoroalkyl or ester group, alkyl-substituted ketimines **1** can isomerize to the corresponding enecarbamates due to the presence of the ketimine α -protons (Scheme 1c, right). Herein, we report amine-catalyzed asymmetric Mannich reactions of less-activated alkyl- and alkynyl-substituted ketimines.¹⁴ The use of newly synthesized *N*-Boc-protected ketimines **1** and appropriate amine catalysts provides an effective solution to the aforementioned problems.

Results and discussion

Our initial investigation focused on the installation of a protecting group on the alkyl- and alkynyl-substituted ketimines to facilitate their amine-catalyzed Mannich reaction with an aldehyde (Scheme 2). The resulting product was treated *in situ* with sodium borohydride and converted into the corresponding alcohol to facilitate its isolation and avoid product decomposition. First, the Mannich reaction of an *N*-sulfinyl-protected ketimine, which was prepared following a known procedure,¹¹ with 3-phenylpropanal in the presence of *L*-proline was examined; however, the desired Mannich adduct was not obtained probably due to the low reactivity of the ketimine. Next, an *N*-Ts-protected ketimine, which was synthesized by the oxidation of the *N*-sulfinyl-ketimine (for details, see the ESI†), was used in the Mannich reaction. Although this ketimine is considered to be more reactive than the *N*-sulfinyl-ketimine, the desired product was not observed, probably due to the deactivation of the catalyst through its addition to the ketimine. We then decided to use a ketimine activated by a Boc protecting group. However, the *N*-Boc-protected ketimine was unfortunately not accessible *via* common approaches, such as dehydrative condensation^{11,13d} or an aza-Wittig reaction with the corresponding



Scheme 2 Amine-catalyzed asymmetric Mannich reaction of *Z*-ketimines.



Scheme 3 Synthesis of *N*-Boc-protected *Z*-ketimines.

ketone.⁸ This may be due to the instability of *N*-Boc-ketimines at high reaction temperatures.¹⁵ In seeking to develop new methods for the synthesis of such ketimines, we found that the nucleophilic substitution of amidines that bear a benzimidazole moiety with organolithium reagents could provide the desired ketimines at low temperature (Scheme 3a). We also found that these *Z*-ketimines could be prepared by the oxidation of *N*-Boc-protected amines (Scheme 3b).¹⁶ The Mannich reaction of the thus obtained ketimine furnished the desired adduct **2a** with high diastereo- and enantioselectivity, albeit in low yield due to undesired side reactions such as homoaldol condensation, hydrolysis of the ketimine and isomerization to the enecarbamate.

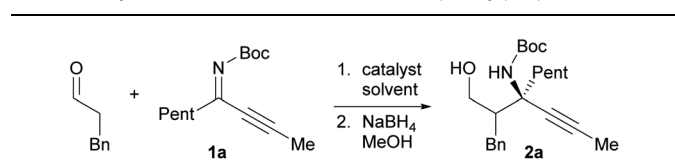
Encouraged by this promising result, the reaction conditions were optimized to suppress these side reactions (Table 1). Solvent screening revealed that the Mannich reaction in chloroform proceeded to give **2a** in moderate yield with high *anti*- and enantioselectivity (entry 3). When diphenylprolinol (*S*)-**3** was used as the catalyst instead of proline, the reaction did not proceed (entry 4). This result indicates that the present Mannich reaction requires the activation of the ketimine by a catalyst with an acidic functionality, such as a carboxylic acid. Catalyst (*S*)-**4** with a tetrazole moiety, which is a bioisostere of carboxylic acid, gave the Mannich adduct in 45% yield with lower *anti*-selectivity (entry 5). When the TBS-protected hydroxyproline (*S,R*)-**5** was used to improve the solubility of the catalyst, *anti*-**2a** was obtained in low yield (entry 6).

We have previously developed the axially chiral amino sulfonamide catalyst (*S*)-**6**¹⁷ and the chiral phenylcyclopropane-based amine catalyst (*S,R*)-**7**.¹⁸ In the Mannich reaction with aldimines, (*S*)-**6** and (*S,R*)-**7** show a diastereoselectivity opposite to proline and related catalysts. Fortunately, the binaphthyl-based amine catalyst (*S*)-**6** promoted the reaction of 3-phenylpropanal with **1a** to preferentially afford *syn*-**2a**, albeit with low *syn*-selectivity (entry 7). Use of the recently developed catalyst (*S,R*)-**7** improved the *syn*-selectivity, although the yield remained low due to the isomerization and hydrolysis of **1a** (entry 8). Further investigations revealed that **2a** was obtained in good yield with high *syn*- and enantioselectivity when the reaction was performed at 5 °C (entry 9).

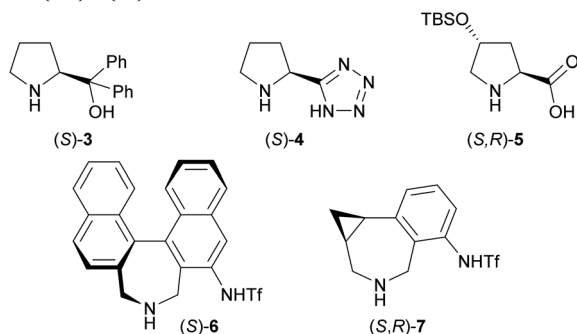
Using the optimal reaction conditions, the *anti*-selective Mannich reaction of several aldehydes with *Z*-ketimines was



Table 1 Asymmetric Mannich reaction of 3-phenylpropanal with **1a**^a



Entry	Catalyst (mol%)	Solvent	Yield ^b (%)	<i>anti/syn</i> ^c	ee ^d (%)
1	L-Proline (20)	MeCN	19	>20/1	97
2	L-Proline (20)	DMSO	37	>20/1	95
3	L-Proline (20)	CHCl ₃	67	>20/1	97
4	(S)-3 (20)	CHCl ₃	n.d.	—	—
5	(S)-4 (20)	CHCl ₃	45	10/1	99
6	(S,R)-5 (20)	CHCl ₃	9	>20/1	99
7 ^e	(S)-6 (10)	MeCN	31	1/4	99
8 ^e	(S,R)-7 (10)	MeCN	33	1/6	98
9 ^{e,f}	(S,R)-7 (10)	MeCN	84	1/13	99



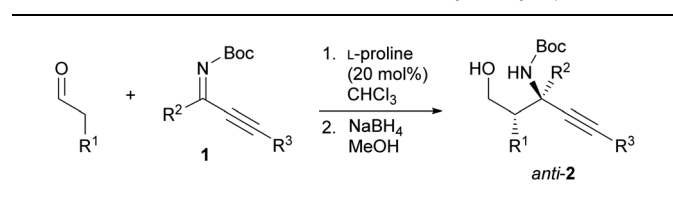
^a Performed using 3-phenylpropanal (0.1 mmol) and **1a** (0.2 mmol) in the specified solvent (100 μ L) for 24 h at room temperature. ^b Isolated yield. ^c Determined by ¹H NMR spectroscopy. ^d The ee of the major diastereomer was determined *via* HPLC using a chiral column. ^e Performed for 48 h using 3-phenylpropanal (0.2 mmol) and **1a** (0.1 mmol). ^f Performed at 5 $^{\circ}$ C. n.d. = not detected.

examined in the presence of L-proline as the catalyst (Table 2). Both aliphatic aldehydes and functionalized aldehydes bearing a protected hydroxy or amino group were tolerated under the applied reaction conditions (entries 1–6). However, when propanal was used as the nucleophile, the reaction furnished the desired adduct with slightly lower *anti*-selectivity (entry 2). Other alkyl-substituted ketimines (R^2 = methyl or isobutyl) were also applicable to this reaction (entries 7 and 8). Replacing the R^3 (Me) group on *Z*-ketimine **1a** with a butyl, phenyl, or TIPS group, did not affect the *anti*- and enantioselectivity (entries 9–11).

Next, we examined the *syn*-selective Mannich reaction catalyzed by (S,R)-7 (Table 3). The reactions between various aldehydes and *Z*-ketimines furnished Mannich products with high *syn*- and enantioselectivity. While the use of aldehydes that bear a protected amino group, an isobutyl-substituted ketimine, or a phenylethynyl-substituted ketimine resulted in poor *syn*-selectivity (*syn/anti* < 10/1), lowering the reaction temperature increased the *syn*-selectivity (entries 6, 8, and 10).

A structural analysis of *syn*-2k using X-ray crystallography provided clear proof that the Mannich reaction catalyzed by (S,R)-7 gave *syn*-products with a 2*R*,3*R* configuration (Fig. 1). The absolute configuration of *anti*-2a, which was obtained from the

Table 2 *anti*-Selective Mannich reaction catalyzed by L-proline^a



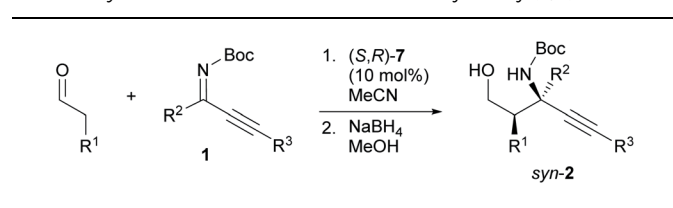
Entry	R ¹	R ²	R ³	Yield ^b (%)	<i>anti/syn</i> ^c	ee ^d (%)	
1	Bn	Pent	Me	2a	67	>20/1	97
2 ^e	Me	Pent	Me	2b	49	8/1	99
3 ^e	Bu	Pent	Me	2c	73	>20/1	98
4 ^e	Allyl	Pent	Me	2d	45	>20/1	99
5	(CH ₂) ₂ OBn	Pent	Me	2e	45	>20/1	96
6 ^e	(CH ₂) ₂	Pent	Me	2f	61	17/1	99
			NHCOCF ₃				
7	Bn	Me	Me	2g	61	13/1	98
8	Bn	i-Bu	Me	2h	64	>20/1	96
9	Bn	Pent	Bu	2i	62	>20/1	97
10	Bn	Pent	Ph	2j	77	>20/1	99
11	Bn	Pent	TIPS	2k	42	>20/1	96

^a Performed using an aldehyde (0.1 mmol) and **1** (0.2 mmol) in CHCl₃ (100 μ L) for 24 h at room temperature. ^b Isolated yield. ^c Determined by ¹H NMR spectroscopy. ^d The ee of the major diastereomer was determined *via* HPLC using a chiral column. ^e The ee was determined after benzylation.

reaction catalyzed by L-proline, was determined to be 2*S*,3*R* by comparison of the HPLC retention times of *syn*-2a ((2*R*,3*R*)-2a) and the epimer of *anti*-2a (for details, see the ESI[†]).

Based on the absolute configuration of the products, we would like to propose transition state models **TS2** and **TS3**

Table 3 *syn*-Selective Mannich reaction catalyzed by (S,R)-7^a



Entry	R ¹	R ²	R ³	Yield ^b (%)	<i>syn/anti</i> ^c	ee ^d (%)	
1	Bn	Pent	Me	2a	84	13/1	99
2 ^e	Me	Pent	Me	2b	84	>20/1	99
3 ^e	Bu	Pent	Me	2c	81	>20/1	99
4 ^e	Allyl	Pent	Me	2d	77	>20/1	99
5	(CH ₂) ₂ OBn	Pent	Me	2e	68	>20/1	99
6 ^{e,f}	(CH ₂) ₂ NHCOCF ₃	Pent	Me	2f	61	>20/1	99
7	Bn	Me	Me	2g	63	10/1	99
8 ^f	Bn	i-Bu	Me	2h	60	>20/1	99
9	Bn	Pent	Bu	2i	76	16/1	98
10 ^f	Bn	Pent	Ph	2j	71	15/1	99
11	Bn	Pent	TIPS	2k	80	20/1	99

^a Performed using an aldehyde (0.2 mmol) and **1** (0.1 mmol) in MeCN (100 μ L) for 48 h at 5 $^{\circ}$ C. ^b Isolated yield. ^c Determined by ¹H NMR spectroscopy. ^d The ee of the major diastereomer was determined *via* HPLC using a chiral column. ^e The ee was determined after benzylation. ^f Performed at 0 $^{\circ}$ C.



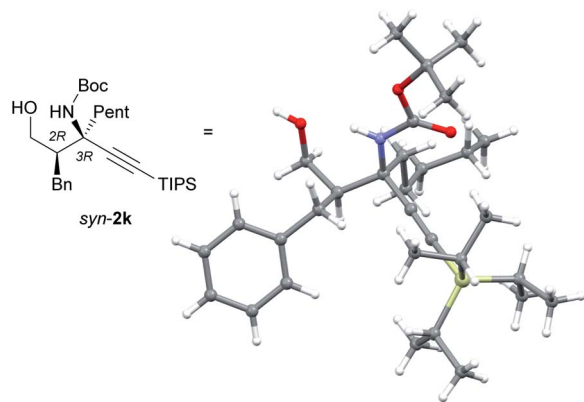


Fig. 1 X-ray crystal structure of *syn*-2k.

(Fig. 2). Since ketimines generally exist in an equilibrium between the *E* and *Z* isomers,¹⁹ a reaction of aldehydes with *in situ*-generated *E*-ketimines might occur. In transition state **TS1**, the *E*-ketimine approaches the *s-trans*-enamine, wherein the steric repulsion between the enamine moiety derived from the aldehyde and the carboxy group derived from *L*-proline is minimized, to give (2*S*,3*S*)-2. On the other hand, the Mannich product (2*S*,3*R*)-2 is formed from the *Z*-ketimine *via* transition state **TS2**. An analysis of the observed stereochemistry shows that the dominant *Z*-ketimine reacts with the *s-trans*-enamine (**TS2**). In the reaction catalyzed by (*S*,*R*)-7, both the *s-trans*-enamine and the *s-cis*-enamine can be formed, as the distal triflamide of (*S*,*R*)-7 does not cause steric repulsion with the enamine moiety. However, the reaction site of the *s-trans*-enamine is too far from the *Z*-ketimine activated by the triflamide group, and only the *s-cis*-enamine can react with the distant *Z*-ketimine to give predominantly *syn*-isomer (2*R*,3*R*)-2 (**TS3**).^{17,18} A computational study of the Mannich reaction of a ketimine using proline and a similar catalyst by Fu is consistent with the proposed transition state models **TS2** and **TS3**.²⁰

The synthetic utility of this method has been demonstrated *via* the transformation of the obtained Mannich product into

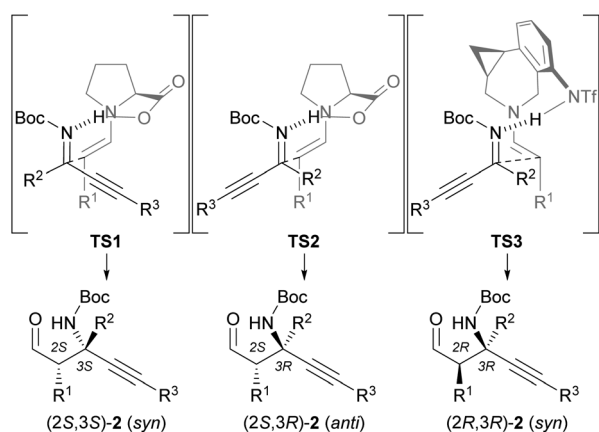
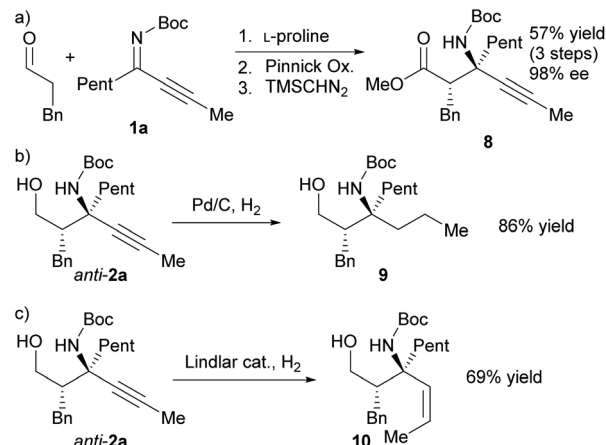


Fig. 2 Transition state models for asymmetric Mannich reactions catalyzed by *L*-proline (**TS2**) or (*S*,*R*)-7 (**TS3**).



Scheme 4 Transformations of the Mannich product *anti*-2a.

previously less-accessible chiral α -*tert*-amine derivatives. Pinnick oxidation of the *anti*-Mannich product and methylation with trimethylsilyldiazomethane (TMSCHN₂) provided the corresponding β -amino ester **8** without affecting the enantiomeric excess (Scheme 4a). Hydrogenation of *anti*-2a gave the chiral γ -amino alcohol derivative **9** with two similar alkyl groups (propyl and pentyl groups) (Scheme 4b). The chiral γ -amino alcohol **10**, which bears a *cis*-olefin moiety, was obtained from the semi-hydrogenation of *anti*-2a with Lindlar catalyst (Scheme 4c).

Conclusions

We have developed a diastereodivergent Mannich reaction of aldehydes with alkyl- and alkynyl-substituted *Z*-ketimines catalyzed by *L*-proline or the chiral phenylcyclopropane-based amine (*S*,*R*)-7. The newly synthesized *N*-Boc-protected ketimines, which cannot be accessed *via* conventional method, are effective for the present Mannich reaction. Hydrogenation of the obtained Mannich product provides access to less-accessible chiral α -*tert*-amine with two similar carbon chains. We believe that these results will find a broad range of applications in organic synthesis, enabling the preparation of valuable molecules for biological and pharmaceutical research.

Conflicts of interest

There are no conflicts to declare.

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