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Synthesis of *syn*-vicinal diamines *via* the stereoselective allylation of acyclic chiral α-amino aldimines

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ABSTRACT

The stereoselective allylation of acyclic chiral α-amino aldimines affording vicinal diamines, mediated by various Lewis acids ($TiCl_4$, $SnCl_4$, $MgBr_2{\cdot}OEt_2$, $BF_3{\cdot}OEt_2$, $ZnCl_2$), is described. The $TiCl_4$-mediated allylation of an α-*N*-Boc aldimine afforded the allylation product with *syn*-selectivity, which in turn was used for the synthesis of an intermediate of an oseltamivir derivative.

Introduction

1,2-Diamino functionalities are prevalent structural motifs in natural products. Due to their potent biological activities, several vicinal diamine compounds have been employed as medicinal agents (Fig. 1) [1]. It is believed that the amine functionality plays an important role in hydrogen bonding and enzyme folding [2]. Biotin (or vitamin H), which features a 1,2-diamino functionality in an imidazolidinone ring, is an important cofactor for carboxylase enzymes. Penicillins and cephalosporins are well-known antibiotics possessing a 2,3-diamino carboxylic acid moiety [1b]. Oxaliplatin is a cancer medication that features a Pt(II) center and a bidentate 1,2-diaminocyclohexane. Oseltamivir and zanamivir, which also bear 1,2-diamino functionalities, are neuraminidase inhibitor antiviral agents used for the treatment and prevention of influenza [2,3]. Vicinal diamine functionalities can also be found in various natural alkaloids, ranging from small and simple molecules to large and structurally intriguing ones [4]. They have become important synthetic targets not only because of their structural complexities but also due to their significant biological activities.

In order to obtain chiral 1,2-diamino compounds, the development of stereoselective diamination methods is necessary. General synthetic approaches to *syn*-vicinal diamines are illustrated in Fig. 2.

Classic methods, including reductive coupling and aziridine opening reactions, have been extensively studied and applied to the synthesis of various 1,2-diamino compounds [1b,4b]. Two methods are available for obtaining *syn*-vicinal diamines *via* the direct diamination of alkenes. One reliable method is asymmetric hydroxylation followed by displacement of the oxygen atoms by amines. In particular, osmium-based catalyzed reactions have been well-established by the Sharpless group [1b,5]. The other method, which is recently developed, involves a metal-catalyzed stereoselective diamination. Since the direct diamination can be regarded as the most straightforward and environmentally benign route, articles reviewing this methodology have frequently appeared [5,4] The diaza-Cope rearrangement [6] and aza-Michael addition [1b] are good alternatives to synthesize 1,2-diamine functionalities. Moreover, nitro-Mannich reactions, also known as aza-Henry reactions, are widely researched methods [7]. The stereoselectivity in such nitro-Mannich reactions strongly depends on the choice of chiral bulky ligands. On the other hand, the nucleophilic addition of α-amino aldimines has remained largely unexplored. The nucleophilic addition of α-amino aldimines derived from Garner's aldehyde has been reported by Fujisawa [8] and Chattopadhyay [9], while the nucleophilic addition of acyclic α-amino aldimines has been described by Reetz [10]. Despite

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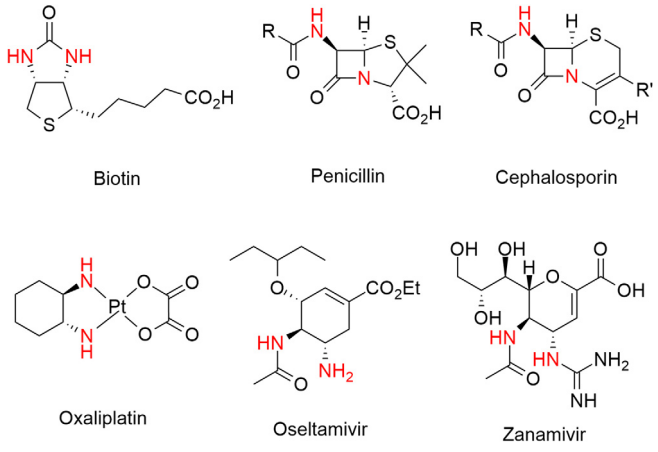
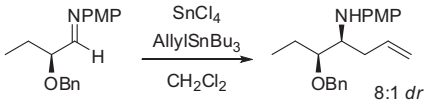


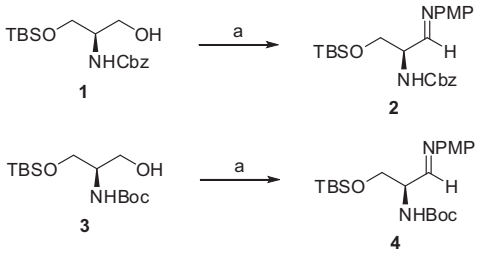
Fig. 1. Various medicinal compounds containing vicinal diamino functionality.

the utility and efficiency of these reactions, only a few examples have been demonstrated.

We have previously reported the stereoselective allylation of *N*-*p*-methoxyphenyl (PMP)-substituted α-hydroxy aldimines (Scheme 1) [11], where the addition of an allyl group generates a new stereocenter and affords a *syn*-vicinal amino alcohol. Nucleophilic addition to aldimines requires particular conditions due to their lower reactivity compared to that of carbonyl compounds [12]. In the case of less reactive aldimines, an electron-donating group can strengthen the coordination between the Lewis acid and the imino nitrogen [10a]. Diastereoselective nucleophilic additions to aldimines are stereocontrolled according to the Felkin-Anh model and chelation [13] mediated by Lewis acids [14]. As part of our ongoing research, herein we report a new approach to *syn*-vicinal diamines *via* stereoselective allylations of acyclic chiral α-amino aldimines, and its application to the synthesis of an intermediate of an oseltamivir derivative.



Scheme 1. Previous work [11].



Scheme 2. Preparation of α-*N*HCbz-aldimine **2** and α-*N*HBoc-aldimine **4**. Reagents and conditions: (a) i. Dess-Martin Periodinane, CH_2Cl_2, rt; ii. *p*-anisidine, $Ti(OiPr)_4$, CH_2Cl_2, rt, 87–90%.

Results and discussion

Enantiomerically pure *N*-Cbz-protected α-amino alcohol **1** and *N*-Boc-protected α-amino alcohol **3** were prepared using a previously reported method [15]. Primary alcohols **1** and **3** were converted to the corresponding *N*-PMP-protected α-amino aldimines **2** and **4** using a previously reported method (Scheme 2) [11].

The results of the allylation reactions with different allyl reagents using various Lewis acids are shown in Table 1. The allylation mediated by $SnCl_4$ gave *syn*-compound **5a** with a 6:1 ratio in 66% yield (Entry 1). In the presence of $TiCl_4$, the ratio was decreased (Entry 2). In the presence of $MgBr_2{\cdot}OEt_2$ the reaction did not occur (Entry 3). The allylation mediated by $BF_3{\cdot}OEt_2$

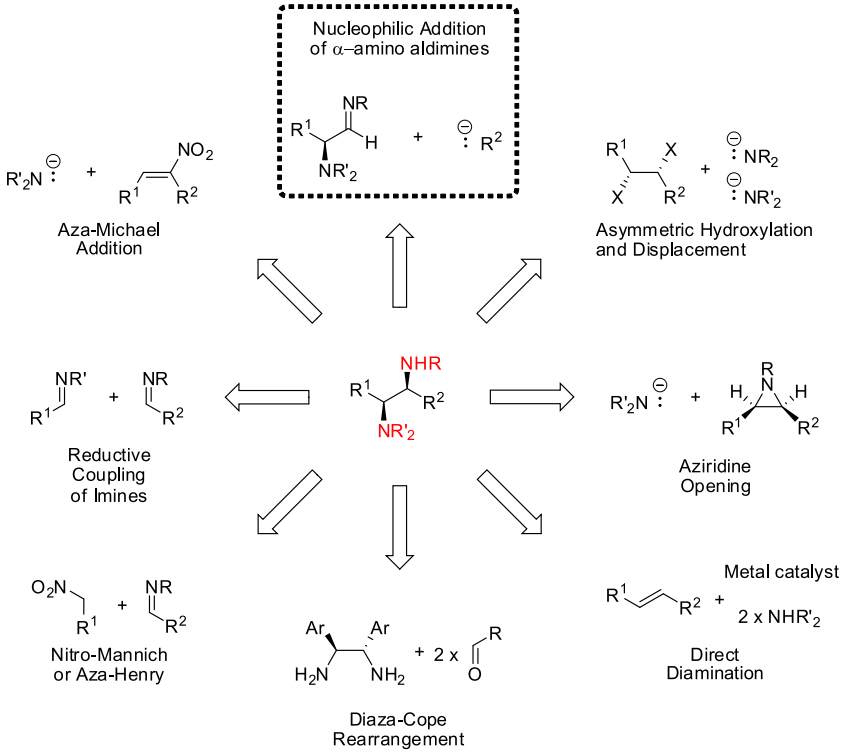


Fig. 2. General synthetic approaches to *syn*-vicinal diamines.

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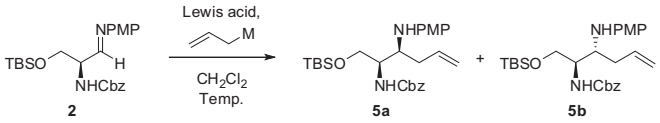
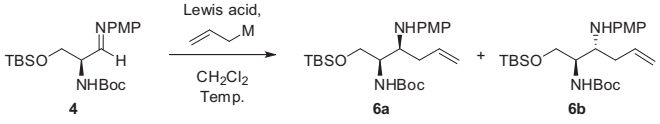
Table 1
Lewis-acid-mediated allyl addition reactions of α-*N*-Cbz aldimine **2**.



Entry	Lewis acid	Allyl reagent	Temp.	Ratio (*syn:anti*)[a]	Yield (%)[b]
1	$SnCl_4$	$AllylSnBu_3$	−78 °C	6:1	66
2	$TiCl_4$	$AllylSnBu_3$	−78 °C	2:1	69
3	$MgBr_2{\cdot}OEt_2$	$AllylSnBu_3$	0 °C	N.R.	N.R.
4	$BF_3{\cdot}OEt_2$	$AllylSnBu_3$	−78 °C	1:2	68
5	–	AllylMgBr	0 °C	2:1	44
6	$ZnCl_2$	AllylMgBr	0 °C	1.2:1	29
7	$SnCl_4$	$AllylSiMe_3$	−78 °C	N.R.	N.R.

[a] Ratio determined by integrating the relevant ^1H NMR resonances.
[b] Yields refer to isolated mixture of products over two-steps from the aldehyde derived from **1**.

Table 2
Lewis-acid-mediated allyl addition reactions of α-*N*-Boc aldimine **4**.



Entry	Lewis acid	Allyl reagent	Temp.	Ratio (*syn:anti*)[a]	Yield (%)[b]
1	$SnCl_4$	$AllylSnBu_3$	−78 °C	5:1	54
2	$TiCl_4$	$AllylSnBu_3$	−78 °C	8:1	77
3	$MgBr_2{\cdot}OEt_2$	$AllylSnBu_3$	0 °C	N.R.	N.R.
4	$BF_3{\cdot}OEt_2$	$AllylSnBu_3$	−78 °C	1:2	51
5	–	AllylMgBr	0 °C	1:1	81
6	$ZnCl_2$	AllylMgBr	0 °C	1.2:1	24
7	$SnCl_4$	$AllylSiMe_3$	−78 °C	N.R.	N.R.

[a] Ratio determined by integrating the relevant ^1H NMR resonances.
[b] Yields refer to isolated mixture of products over two-steps from the aldehyde derived from **3**.

afforded **5a** and **5b** with a 1:2 ratio (Entry 4). The Grignard reactions, with or without Lewis acid, were not stereoselective (Entries 5 and 6). The reaction using a silyl allyl reagent mediated by $SnCl_4$ did not proceed (Entry 7); this result is in accordance with our previous work [11].

The Lewis-acid-mediated allylation of α-*N*-Boc aldimine **4** was similarly investigated (Table 2). The allylation mediated by $SnCl_4$ proceeded to give *syn*-product **6a** as the major compound (Entry 1). In the presence of $TiCl_4$, the *syn*-selectivity dramatically increased compared with the α-*N*-Cbz aldimine system (Entry 2). The reaction did not proceed in the presence of $MgBr{\cdot}OEt_2$ (Entry 3). The allylation mediated by $BF_3{\cdot}OEt_2$ afforded *anti*-product **6b** as the major stereoisomer with a 1:2 *syn*:*anti* ratio, which is in accordance with the α-*N*-Cbz aldimine system (Entry 4). The Grignard reactions proceeded to give non-selective products (Entries 5 and 6). When allyltrimethylsilane was employed as nucleophile, the $SnCl_4$-mediated reaction did not proceed (Entry 7).

Additionally, compounds with methyl, ethyl, phenyl, and benzyl groups instead of CH_2OTBS were examined under $TiCl_4$ and $allylSnBu_3$ conditions. When the phenyl containing substrate was used as a reactant, the reaction did not proceed. In the case of methyl, ethyl, and benzyl containing substrates, the reaction only afforded *syn*/*anti*-products with a 2:1 ratio and little α-chelation was observed.

The observed *syn*-selectivity in the allylation of α-*N*-protected-aldimines (Table 1, entry 2 and Table 2, entry 2) can be explained by α-chelation between the amido group and the aldimine nitrogen (Fig. 3A or B). Instead, the slightly *anti*-selective results (Table 1, entry 4 and Table 2, entry 4) can be accounted for by the Felkin–Anh model (Fig. 3C). To confirm the *syn*-configuration

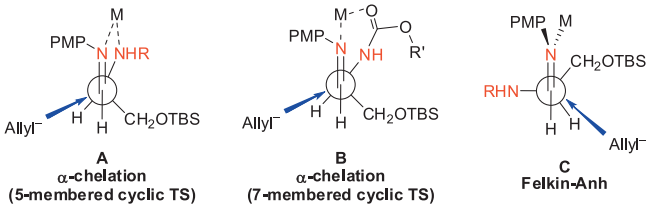


Fig. 3. Proposed mechanism for allylation.

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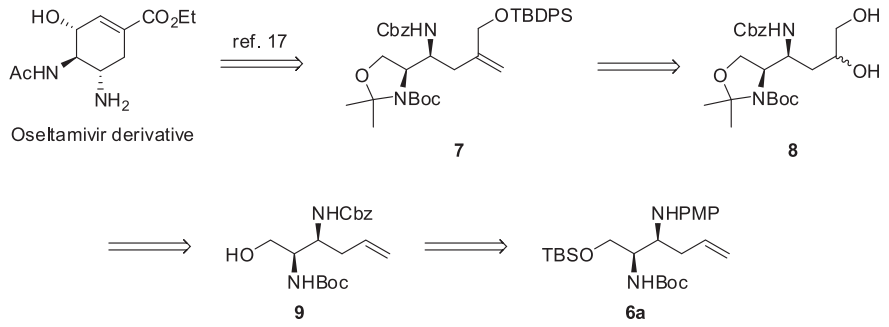
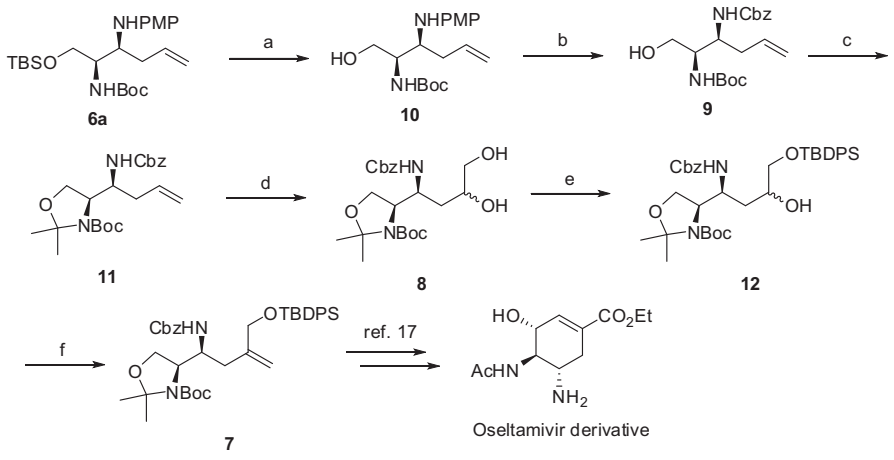


Scheme 3. Retrosynthetic analysis.



Scheme 4. Synthesis of **7**. Reagents and conditions: (a) 70% HF/Pyridine, Pyridine, THF, 0 °C to rt, 90%; (b) cerium(IV) ammonium nitrate, CH_3CN/H_2O, 0 °C then 0.6 M $NaHCO_3$, CH_2Cl_2, CbzCl, 30 °C, 56%; (c) PTSA, 2,2-dimethoxypropane, CH_2Cl_2, 40 °C, 80%; (d) OsO_4 (0.05 equiv.), NMO, acetone/H_2O, rt, 85%; (e) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 91%; (f) i. Dess-Martin periodinane, CH_2Cl_2, 82%; ii. Ph_3PCH_3Br, *n*-BuLi, THF, −78 °C to rt, 80%.

of the 1,2-diamine in **6a**, an intermediate of an oseltamivir derivative was synthesized.

The retrosynthetic analysis for oxazolidine **7**, which was reported in Yao's synthesis of an oseltamivir derivative [16], is shown in Scheme 3. The desired compound **7** can be prepared by Wittig olefination of diol **8**, which can be obtained from alkene **9** by dihydroxylation. Compound **9** can be obtained by selective deprotection and exchange of the amine protecting group in compound **6a**.

The synthesis of **7** is shown in Scheme 4. The silyl protecting group on **6a** was removed using Olah's reagent to afford primary alcohol **10**. Deprotection of the *p*-methoxyphenyl group was achieved using cerium(IV) ammonium nitrate and the carboxybenzyl protecting group was installed to give **9** in a one-pot procedure. Acetonide protection of **9** afforded compound **11**, and dihydroxylation with osmium tetroxide provided diol **8**. TBDPS protection gave alcohol **12**. Dess-Martin oxidation afforded the corresponding ketone, which was transformed into olefin **7** by Wittig olefination. The synthesis of the desired compound **7** was accomplished from amino alcohol **3** in 14% overall yield over 10 steps. The stereochemistry of the allylation product **6a** was confirmed by the synthesis of known compounds **8**, **12**, and **7**, whose data were in good agreement with the reported data in the literature [16].

Conclusion

In summary, we have developed a Lewis-acid-mediated, stereoselective allylation of α-amino aldimines. The reaction of an α-*N*-Boc aldimine mediated by $TiCl_4$ afforded the *syn*-selective product. A method for formation of the *syn*-vicinal diamines motif was developed, and its application was demonstrated by the synthesis of an intermediate of an oseltamivir derivative. Further experiments and the application of this methodology to total synthesis are in progress.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.12.021.

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