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One-Pot Highly Enantio- and Diastereoselective Synthesis of *anti,anti* Vinylic 3-amino-1,2 diols *via* Proline Catalyzed Sequential α-Amination/ Benzoyloxyallylation of Aldehydes †

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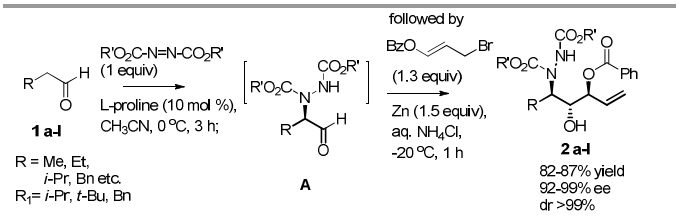
The first direct asymmetric synthesis of *anti,anti* vinylic 3-amino-1,2-diols from aldehydes is described *via* one-pot sequential L-proline catalyzed α-amination/ benzoyloxyallylation protocol. The reaction proceeds with exceptionally high diastereoselectivity (> 99 %) as can be explained based on Felkin-Ahn transition state model. Its effectiveness is proven unambiguously by demonstrating a short asymmetric synthesis of D-*ribo*-phytosphingosine tetraacetate (93% ee).

The vicinal amino diol subunits with three contiguous, heteroatom–bearing chiral carbons, constitute an important stereotriad pattern found in numerous pharmaceuticals and bioactive natural products.[1] The majority of synthetic strategies to these motifs often employ starting materials from the chiral pool[2a-b] or utilize the ring–opening of chiral epoxy alcohols with amine nucleophiles.[2c] A number of diastereoselective synthesis of these molecules have also been reported; some recent examples include the addition of Grignard reagents onto α-substituted nitriles,[2d] imines[2e] or catalytic processes involving dihydroxylation of allylamines,[2f] pinnacol coupling of chiral α-amino aldehydes[2g] and oxidation/reduction sequence of bicyclic methyleneaziridines.[2h] However, the efficient construction of vicinal amino diol units with well-defined stereochemistry and derivatizable functional group remains a challenge in organic synthesis. To the best of our knowledge, a direct method of synthesis of these stereotriads utilizing aldehydes as precursor remains elusive.

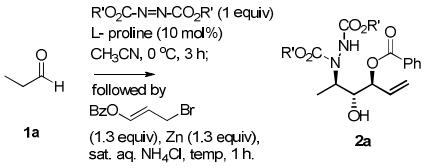
The synthetic methodology leading rapidly to structural complexity from readily available starting material through one-pot reaction sequence is widely recognized.[3] In particular, proline catalyzed *sequential* reaction such as α-amination of aldehydes[4] followed by Wittig,[5a-b] aldol,[5c] or Corey-Chaykovsky[5d] have gained more prominence in recent years. This is necessitated because α-aminated aldehyde is prone to racemisation during isolation. In this communication, we wish to describe a one-pot procedure for a tandem α-amination/benzoyloxyallylation of aldehydes **1a-j** that proceeds to give vicinal amino diols **2a-j** in a highly enantio- and diastereoselective fashion (Scheme 1).



Scheme 1. *in situ* Trapping of α-Amino Aldehydes (**A**) with Benzoyloxyallyl bromide

In the initial study, propanal **1a** was α-aminated with diisopropyl azodicarboxylate (DIAD) catalyzed by L-proline (10 mol %) CH_3CN

Table 1. L-Proline Catalyzed Asymmetric Sequential α-Amination/ Benzoyloxyallylation Reaction of Propanal[a]



			Product (**2a**)		
no.	R'	T (°C)	yield (%)[b]	ee (%)[c]	dr[c]
1	*i*Pr	0	79	69	7:3
2	*i*Pr	-10	79	77	4:1
3	*i*Pr	-20	79	77	99:1
4	*t*Bu	-20	81	78	99:1
5	Bn	-20	84	93	99:1

[a]Propanaldehyde (5 mmol), amine ($R'O_2C$-N=N-CO_2.R') (5 mmol), L-proline (10 mol %), 3-benzoyloxyallyl bromide (7.5 mmol), Zn (7.5 mmol), saturated aq. NH_4Cl (10 mL). [b]Isolated yield. [c]from chiral HPLC analysis.

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†Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR, IR, and HRMS of new compounds. For ESI and crystalographic data in CIF or other electronic format see DOI: 10.1039/c

at 0 °C for 3 h that produced the corresponding α-aminated aldehyde (**A**) *in situ,* followed by the sequential addition of Zn powder (1.5 equiv), 3-benzoyloxyallyl bromide[6] (1.5 equiv) and saturated aq. NH_4Cl at 0 °C, gave *anti,anti* vinylic 3-amino-1,2-diol **2a** in 79 % yield (dr = 7:3). Also, its diastereoselectivity could be marginally improved to 4:1 when the reaction was conducted at -10 °C. Finally, at -20 °C, we observed that **2a** could be obtained as a single diasteromer with dr 99:1 and 77% ee. The subsequent investigation has shown that dibenzyl azadicarboxylate was found to be an excellent amine sources for this sequential reaction (entry 5)

Table 2. L-Proline-catalyzed Asymmetric Sequential α-Amination/Benzoyloxyallylation of Aldehydes[a]

			Products (**2a-j**)		
no.	aldehydes (R) (1a-j)	amines (R')	yield (%)[b]	ee (%)[c]	de (%)[d]
1	methyl (**1a**)	Bn	84	93	>99
2	ethyl (**1b**)	*i*Pr	87	91	>99
3	*i*-propyl (**1c**)	*i*Pr	83	95	>99
4	*n*-propyl (**1d**)	*i*Pr	86	93	>99
5	3-(methoxymethoxy)-ethyl (**1e**)	*i*Pr	87	93	99
6	3-(benzyloxy)ethyl (**1f**)	*t*Bu	84	93	99
7	but-3-enyl (**1g**)	*i*Pr	82	95	>99
8	benzyl (**1h**)	*t*Bu	84	97	>99
9	4-methoxybenzyl (**1i**)	*t*Bu	81	99	>99
10	2-(benzyloxy)methyl (**1j**)	Bn	85	93	>99

[a]Aldehyde (5 mmol), amine ($R'O_2C$-N=N-CO_2-R') (5 mmol), L-proline (10 mol %), CH_3CN (25 ml), 0 °C, 3 h followed by 3-benzoyloxyallyl bromide (7.5 mmol), Zn (7.5 mmol), saturated aq. NH_4Cl (10 mL), -20 °C, 2 h. [b]Isolated yield. [c]from chiral HPLC analysis

To extend the scope of this one-pot reaction, a series of aliphatic aldehydes bearing different functionalities (alkyl, aryl, alkenyl, benzoyloxy or methoxy methyl) were examined under the optimized condition (Table 2). For all the cases studied, the products **2a-j** were indeed obtained in high yields (81-87%) and excellent enantioselectivity (91-99%) with de > 99%. The stereochemical assignment of this sequential reaction was made based on previously established absolute configuration of α-amino aldehydes.[4a] The anti,anti stereochemistry in **2a** was proven unambiguously from X-ray crystallographic analysis (Figure 1).

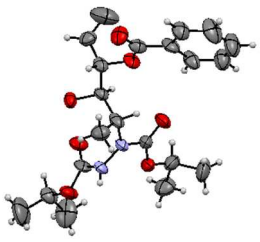


Fig. 1 ORTEP diagram of compound **2a**

To rationalize the observed high *anti,anti* diastereselectivity of vicinal amino diols, both Fekin-Ahn[6d] (**TS 1**) and six membered transition state (**TS II**) model have been proposed (Figure 2). *Anti* relationship at C_1-C_2 carbons is governed by the Felkin-Ahn model in which Zn atom of benzoyloxyallylzinc reagent is coordinated to the carbonyl oxygen and the nucleophilic attack of the corresponding reagent takes place at '*Si'* face predominantly perpendicular to the bulky R^1N-NHR^1 group. Also, *anti* relationship at C_2-C_3 carbons can be explained based on the six membered transition state model (**TS II**) in which hydrazino alkyl group of aldehyde and OBz group of nucleophile are oriented in the pseudoequatorial position to deliver anti diol.

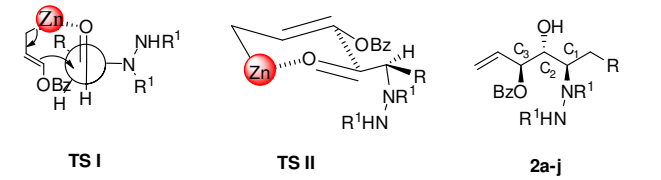
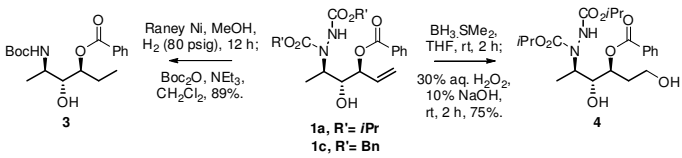


Fig. 2 Proposed transition state model (**R^1** = CO_2*i*Pr, CO_2*t*Bu, CO_2Bn; **R** = alkyl, alkyl aryl).

To further extend its synthetic utility **1a** was subjected to hydroboration/oxidation sequence that gave functionalized amino triol **3** in high yield. Also **1c** was hydrogenated over Raney Ni followed by its Boc protection giving **4** in 89% yield (Scheme 2).



Scheme 2 Oxidative and Reductive Transformations of *anti,anti* Vinylic 3-Amino-1,2-Diols.

Finally, a short enantioselective synthesis of D-ribo-phytosphingosine tetraacetate[7] (**7**) seemed attractive to us because it is a bioactive lipid that has potential antitumor properties[8] (Scheme 3). Its synthesis was achieved in 5 steps commencing from aldehyde **1j,** which was subjected to D-proline catalyzed sequential α-amination/benzoyloxyallylation protocol to afford vinylic aminodiol

Scheme 2 Synthesis of D-*ribo*-phytosphingosine tetraacetate (**7**)

***ent*-2j** (85%, 93% ee). The LiOH-mediated hydrolysis of ***ent*-2j** gave oxazolidinone **5** in 75% yield. The cross-metathesis of **5** with 1-tetradecene over Grubbs' catalyst produced **6** (72% yield). The catalytic hydrogenation [Raney Ni, H_2 (60 psig), 24 h] of **6** followed by basic hydrolysis (K_2CO_3, MeOH) and its acetylation (Ac_2O, py, DMAP) produced the target phytosphingosine **7** in 76% yield and 93% ee.

In conclusion, we have described an unprecedented, one-pot procedure for a sequential α-amination/benzoyloxyallylation of aldehydes that leads to the synthesis of vinylic-3-amino-1,2-diols **2a-l** in high yields with excellent enantio- and diastereoselectivities. This protocol generates three chiral centers consecutively with *anti,anti* relationship in a single step, and has been successfully applied to the short asymmetric synthesis of D-*ribo*-phytosphingosine tetraacetate, **7**. We believe this one-pot sequential method will find tremendous application in the synthesis of bioactive natural products and pharmaceutical substances.

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