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Enantioselective Synthesis of *syn*/*anti*-1,3-Amino Alcohols via Proline-Catalyzed Sequential α-Aminoxylation/α-Amination and Horner−Wadsworth−Emmons Olefination of Aldehydes†

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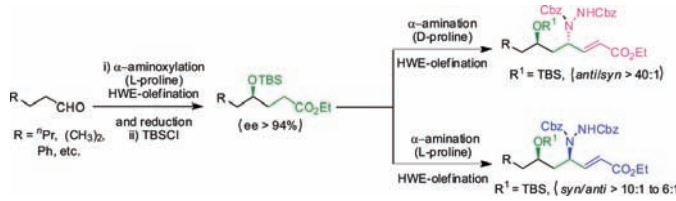
ABSTRACT



A novel and general method for asymmetric synthesis of both *syn*/*anti*-1,3-amino alcohols is described. The method uses proline-catalyzed sequential α-aminoxylation/ α-amination and Horner−Wadsworth−Emmons (HWE) olefination of aldehydes as the key step. By using this method, a short synthesis of a bioactive molecule, (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol, is also accomplished.

1,3-Amino alcohols are key structural components in many natural products,[1] potent drugs,[2] and numerous bioactive compounds, viz., HIV-protease inhibitors,[3] μ-opioid receptor antagonists,[4] potent antibiotic negamycin,[5] serotonin reuptake inhibitor, and antidepressants.[6] Additionally 1,3-amino alcohols have also been used as ligands for asymmetric catalysis, as chiral auxiliaries, as resolving agents, and as phase transfer catalysts.[7] Despite the importance of 1,3-amino alcohol, there are relatively fewer methods for their stereoselective synthesis.[8,9] Currently the most common strategy

† Dedicated to Professor Dr. Richard R. Schmidt on the occasion of his 75th birthday.

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for their synthesis is based on the diastereoselective reduction of an enantiomerically pure substrate, whereby the chirality of the substrate controls the formation of the new stereogenic center.[9a−d] Recently there has been a report of a reagent-controlled synthesis of *anti*-1,3-amino alcohol using rhodium as a catalyst.[9e] However, all these reports suffer from one or more disadvantages such as they (a) give predominantly one of the two isomers *syn* or *anti*, (b) require specially modified starting materials (β-keto alcohols, β-amino ketones), and (c) use toxic metal catalysts like Rh((COD)dunphos)BF_4, SmI_2, Ti(^{i}OPr)$_4$, and Pd(OAc)$_2$, etc.

Proline in the recent past has been defined as a "universal catalyst" because of its utility in different reactions providing rapid, catalytic, atom-economical access to enantiomerically pure products.[10] Similarly, organocatalytic tandem reactions are characterized by high efficiencies. They often proceed with excellent stereocontrol and are environmentally friendly.[11]

Recently, we developed an iterative approach to enantiopure synthesis of *syn*/*anti*-1,3-polyols[12a] which is based on proline-catalyzed sequential α-aminoxylation and Horner−Wadsworth−Emmons (HWE) olefination of aldehydes reported by Zhong et al.[12b] As a part of our research interest on developing new methodologies and their subsequent application to bioactive compounds,[12c,d] we envisioned that the proline-catalyzed α-aminoxylation[13a,b] and α-amination[13c] could easily give us stereocontrolled synthetic access to 1,3-amino alcohols. Since the α-amino aldehydes are prone to racemization, they have been sucessesfully trapped in situ by various methods to furnish 1,2-amino alcohol, γ-amino-α,β-unsaturated ester, β-amino alcohol etc.[13c,14] We chose to trap them by HWE olefination to furnish γ-amino-α,β-unsaturated ester using a mild procedure developed by Sudalai et al.[14a] It is noteworthy that γ-amino-α,β-unsaturated ester, an allylic amine, can serve as a useful building block and can further be elaborated to the synthesis of a variety of compounds of biological importance.

Our strategy for the synthesis of 1,3-amino alcohol is outlined in Figure 1.

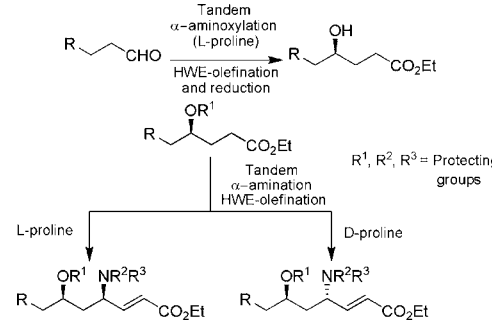
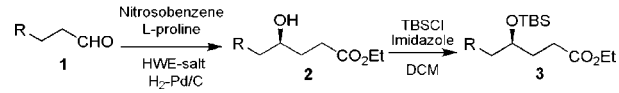


Figure 1. General strategy for the synthesis of 1,3-amino alcohol.

Toward the synthesis of 1,3-amino alcohols, our first goal was to synthesize various protected γ-hydroxy esters by the protocol developed recently by us.[12a] Thus, commercially available aldehydes **1a**−**e** on sequential α-aminoxylation using nitroso benzene as the oxygen source and L-proline as catalyst and subsequent HWE olefination using triethyl phosphonoacetate, followed by hydrogenation using a catalytic amount of Pd/C, furnished the γ-hydroxy esters **2a**−**e** in good yields (65−73%) and excellent enantioselectivities (94 to >99%) (Scheme 1, Table 1).

Scheme 1. Synthesis of γ-Hydroxy Esters



The free hydroxy group of γ-hydroxy esters **2a**−**e** was protected as TBS ether using TBSCl to furnish compounds **3a**−**e** in excellent yields (Table 1). With TBS-protected γ-hydroxy esters **3a**−**e** in hand, the stage was set for the introduction of amine functionality at the 3-position with respect to the hydroxy group. As illustrated in Scheme 2, the DIBAL-H reduction of ester **3a** furnished the corresponding aldehyde

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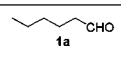
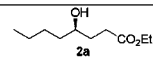
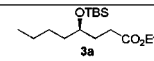
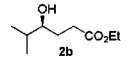
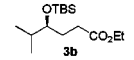
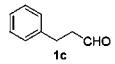
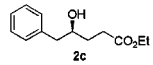
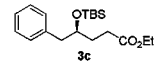
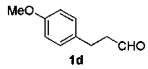
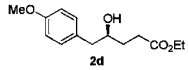
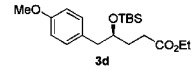
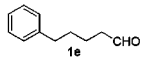
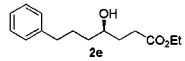
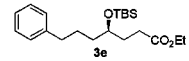
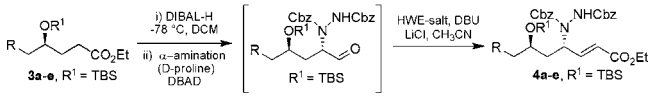
Table 1. Synthesis of TBS-Protected γ-Hydroxy Esters (**3a**−**e**)

entry	1	2	yield (%)	ee (%)	3	yield (%)
1	 **1a**	 **2a**	65	94[a]	 **3a**	92
2	 **1b**	 **2b**	69	98[b]	 **3b**	89
3	 **1c**	 **2c**	71	98[a]	 **3c**	91
4	 **1d**	 **2d**	73	99[a]	 **3d**	92
5	 **1e**	 **2e**	68	99[a]	 **3e**	90

[a] ee was determined by chiral HPLC/chiral GC analysis. [b] ee was determined by optical rotation. See Supporting Information.

which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D-proline as a catalyst to furnish the α-amino aldehyde, which on in situ trapping by triethyl phosphonoacetate (HWE olefination) in the presence of DBU furnished the *anti*-1,3-amino alcohol **4a**[15] in 64% yield and 97:3 diastereomeric ratio as determined from HPLC analysis (Scheme 2).

Scheme 2. Synthesis of *anti*-1,3-Amino Alcohol

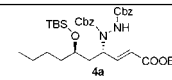
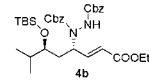
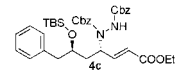
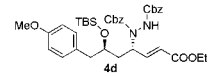
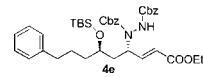


We examined the scope of this reaction using various aldehydes bearing different functional groups (Table 2). It was observed that the reaction sequence displayed a wide substrate scope and was compatible with functionalities such as the alkyl, aryl, and substituted aryl groups. Excellent diastereomeric ratio (dr 97:3 to 99:1) and good yields (63 to 68%) were obtained for all the substrates (Table 2).

Encouraged by the excellent *anti*-selectivities achieved, we next turned our attention toward the synthesis of *syn*-1,3-amino alcohol following a similar sequence of reactions as described for the preparation of *anti*-1,3-amino alcohols and using L-proline as a catalyst in the α-amination step.

As illustrated in Scheme 3, the DIBAL-H reduction of TBS-protected γ-hydroxy ester **3a** furnished the corresponding aldehyde which was then subjected to α-amination using DBAD and L-proline as catalyst followed by HWE olefination to give *syn*-1,3-amino alcohol **5a**[15] in 65% yield and 9:1 diastereomeric ratio as determined from HPLC analysis. We were able to separate the major diastereomerically pure *syn*-1,3-amino alcohol by silica gel column chromatography.

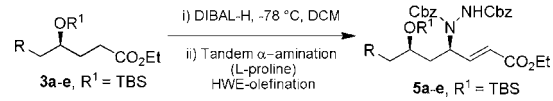
Table 2. D-Proline-Catalyzed Asymmetric Tandem α-Amination/HWE Olefination: Synthesis of *anti*-1,3-Amino Alcohol

entry	3	*anti*-1,3-amino alcohols **4**	yield (%)[a]	dr[b]
1	**3a**	 **4a**	64	97: 3
2	**3b**	 **4b**	68	99: 1
3	**3c**	 **4c**	63	99:1
4	**3d**	 **4d**	64	97: 3
5	**3e**	 **4e**	63	99:1

[a] Isolated yield of diastereomerically pure material. [b] Diastereomeric ratio was determined by HPLC analysis. See Supporting Information.

We further examined the scope of this reaction using the same set of aldehydes, and the results obtained are summarized in Table 3. The results were more or less comparable with 1,3-*anti* amino alcohol with regard to the substrate scope and functional group compatibility. However, selectivity in the case of the *syn*-isomer was less as compared to the corresponding *anti*-isomer.

Scheme 3. Synthesis of *syn*-1,3-Amino Alcohol



Overall these findings are in correlation with those observed for the synthesis of *syn*/*anti*-1,3-diols from γ-hy-

(15) The relative stereochemistry of amino alcohols **4** and **5** was determined by NMR and also on the basis of NOESY studies of the cyclic carbamates **14** and **17** derived from *anti*-**4a** and *syn*-**5a**, respectively (see Supporting Information).

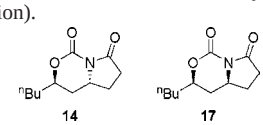
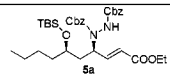
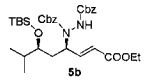
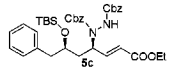
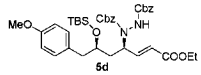
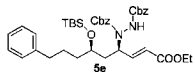


Table 3. L-Proline-Catalyzed Asymmetric Tandem α-Amination/HWE Olefination: Synthesis of *syn*-1,3-Amino Alcohol

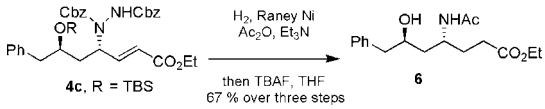
entry	3	*syn* -1,3-amino alcohols **5**	yield (%)[a]	dr[b]
1	**3a**	 **5a**	65	90:10
2	**3b**	 **5b**	62	81:19
3	**3c**	 **5c**	68	91:9
4	**3d**	 **5d**	66	88:12
5	**3e**	 **5e**	64	86:14

[a] Isolated yield of diastereomerically pure material. [b] Diastereomeric ratio was determined by HPLC analysis. See Supporting Information.

droxy esters[12a] where the asymmetric induction for the *anti*-isomer was greater as compared to the s*yn*-isomer. Presumably, the considerable steric bulk on the incoming nitrogen source coupled with the steric bulk of the silyl protecting group on the hydroxy group might be the possible cause for lowering the selectivities.

For further synthetic manipulation, the *N*−*N* bond of substituted hydrazine **4c** was easily cleaved with concomitant reduction of the double bond using freshly prepared Raney-Ni, and free amine was converted into its acetate derivative using Ac_2O. Subsequent silyl deprotection using TBAF furnished compound **6** in 67% yield, over three steps (Scheme 4).

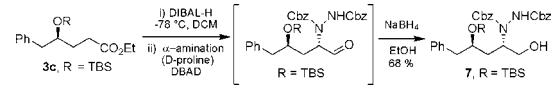
Scheme 4. Cleavage of the *N*−*N* Bond by Reductive Hydrogenation



In yet another synthetic manipulation, the α-amino aldehyde formed in the reaction can easily be reduced in situ by sodium borohydride in ethanol to furnish the 2-hydrazino alcohol. Thus, the DIBAL-H reduction of TBS-protected γ-hydroxy ester **3c** gave the corresponding aldehyde which was then subjected to α-amination using DBAD as a nitrogen source and D-proline as catalyst to furnish the α-amino aldehyde, which on treatment with $NaBH_4$ in ethanol afforded the *anti*-1,3-amino alcohol **7** in 68% yield (over three steps), thus offering considerable opportunities for further synthetic manipulations[16] (Scheme 5).

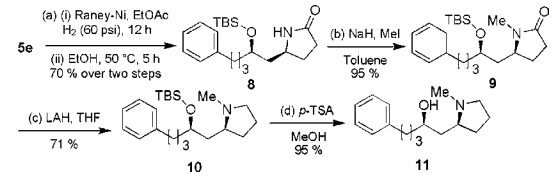
To further demonstrate the utility of this approach, we have developed a short synthesis of (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol (**11**), a cyclic amino alcohol derivative. Compound **11** and its analogues have recently been found to be useful for the treatment of various neurological disorders such as Parkinson's disease, Alzhemier's disease, Huntington's diseases, strokes, and spinal cord injuries, etc.[17]

Scheme 5. Synthesis of 2-Hydrazino Alcohol



As illustrated in Scheme 6, the reduction of the double bond and cleavage of the *N*−*N* bond in **5e** was achieved in one pot using freshly prepared Raney nickel. Subsequent filtration and reflux in ethanol afforded the lactam **8** in 70% yield over two steps. Monoalkylation of **8** using MeI and NaH furnished the N-methylated compound **9** in 95% yield. Finally, LAH reduction of amide to amine and TBS deprotection using *p*-TSA in methanol afforded the target compound **11** in 68% yield (over two steps).

Scheme 6. Synthesis of (*R*)-1-((*S*)-1-Methylpyrrolidin-2-yl)-5-phenylpentan-2-ol (**11**)



In conclusion, we have deverloped for the first time a practical, efficient, and organocatalytic approach to the stereocontrolled synthesis of both *syn*- and *anti*-1,3-amino alcohols from commercially available and inexpensive starting material using modified α-aminoxylation and α-amination reactions of an aldehyde. The synthetic utility of this protocol was further demonstrated by the asymmetric synthesis of (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol.

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Supporting Information Available: Experimental details and NMR spectroscopic data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For a review on 1,2-amino alcohols see: (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561. (b) Periasamy, M. *Pure Appl. Chem.* **1996**, *68*, 663.

(17) Mullican, M.; Lauffer, D.; Tung, R. US Patent 7105546B2.