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Proline-Catalyzed Asymmetric α-Amination in the Synthesis of Bioactive Molecules

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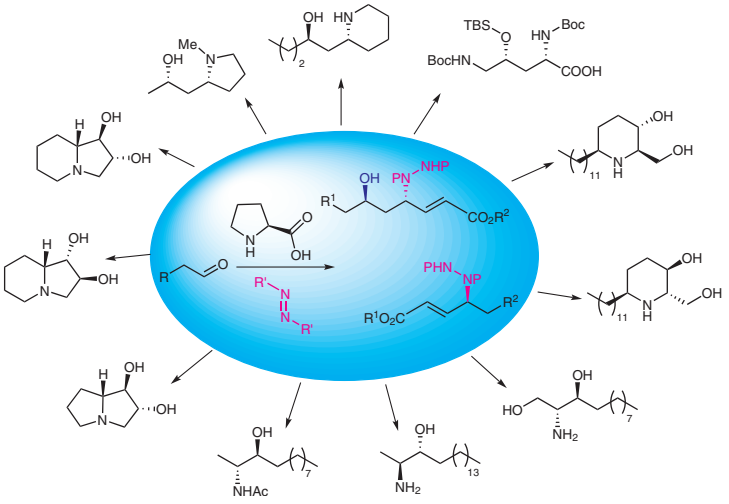

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Abstract The direct α-amination of carbonyl compounds using organocatalysts represents a powerful and atom-economical tool for asymmetric C–N bond formation. We describe a complete account of α-functionalization of carbonyl compounds, through iterative sequential α-aminoxylation/amination using electrophilic O and N sources, as well as sequential α-amination/HWE reaction for enantio- and diastereoselective synthesis of both *syn*- and *anti*-1,3-aminoalcohols and 1,3-diamines. Additionally this protocol is further extended for the easy construction of alkaloids such as indolizidine, pyrrolizidine, and quinolizidine fused-ring systems just by tuning the chain length of the aldehyde used as a starting material. This methodology provides further scope to extrapolate it for a variety of naturally occurring hydroxylated monocyclic and fused bicyclic pyrrolidine and piperidine based alkaloids such as lentiginosine, *epi*-lentiginosine, dihydroxypyrrolizidine, (+)-deoxoprosophylline and (–)-deoxoprosopinine alkaloids. Furthermore, we have also uncovered proline-catalyzed *anti*-selectivity for the synthesis of 1,2-amino alcohols in α-amination of aldehyde and one-pot indium-mediated Barbier type allylation of α-hydrazino aldehydes to accomplish the total synthesis of clavaminols, sphinganine and spisulosine with reduced number of steps and with high overall yields.

1 Introduction
2 Application in the Total Synthesis of Alkaloids
3 Conclusion

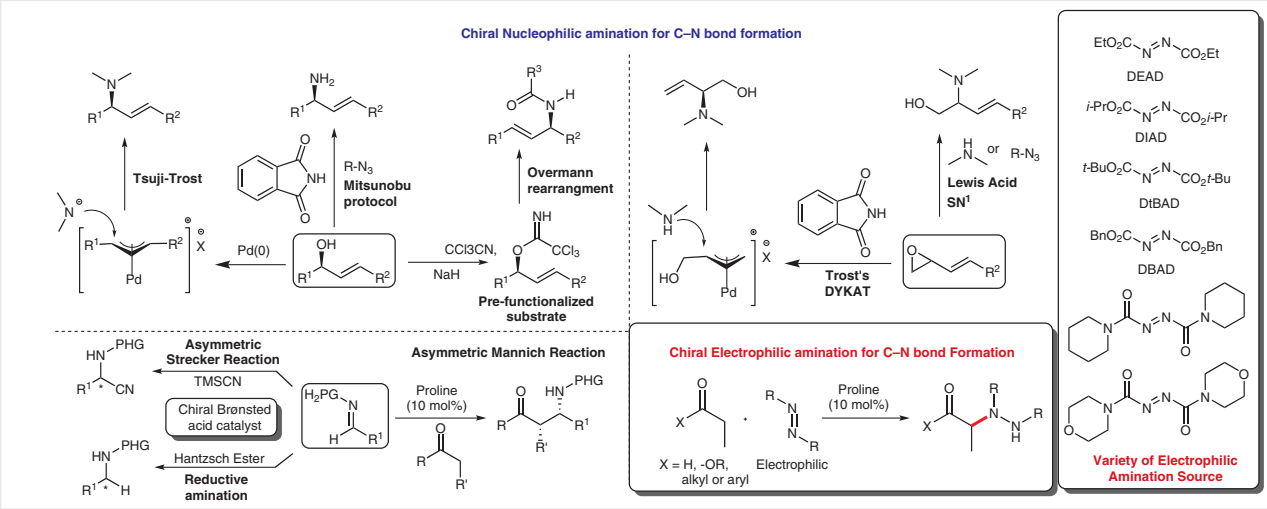
Key words natural products, alkaloids, organocatalysts, α-amination, C–N and C–O bond formation

1 Introduction

Natural products continue to be the biggest source of inspiration[1] for synthetic chemists towards the development of various methodologies for C–C and C–hetero bond formation. In this regard, chiral amines[2] have received wide attention in recent years because of their diverse applications as chiral auxiliaries,[3] organocatalysts,[4] chiral ligands for metal-catalysis,[5] and also for the synthesis of pharmaceutically active natural and unnatural products.[6] Classical methods for asymmetric C–N bond formation, including Sharpless aminohydroxylation, rely on nucleophilic amination reactions[7] (Scheme 1).

Later, electrophilic enantioselective α-amination reactions were developed with azodicarboxylates, using chiral auxiliary derivatized preformed enolates and enol ethers.[8] Despite the robustness of asymmetric C–N bond formation, all of the above methods require either substrate controlled chiral induction or pre-functionalized substrates. Recently, organocatalysis have played a major role in the development of one-pot asymmetric approaches for direct α-amination of prochiral aldehydes and ketones to access chiral α-branched amines in high enantiomeric excess,[9] using simple and readily available starting materials.

In this context, the enzyme mimetic ability of proline has elegantly been explored by List, Lerner, and Barbas III for asymmetric C–C bond formation in aldol reactions.[10] Working on the same grounds, List[11] and Jørgensen[12] for the first time unraveled, proline-catalyzed direct electrophilic α-amination of achiral carbonyl compounds with azodicarboxylates for asymmetric C–N bond formation with >95% ee. The merit of this protocol is the use of an inexpensive chiral catalyst and the easy access to gram-scale reactions that do not necessitate the maintenance of highly anhydrous conditions and proceeds with predictable stereochemical outcome based on the catalyst used. Later, Jørgensen and co-workers demonstrated that groups capable of hydrogen bonding are not prerequisites for high catalytic efficiency and enantioselectivity in reactions involving



Scheme 1 Methods for C–N bond formation

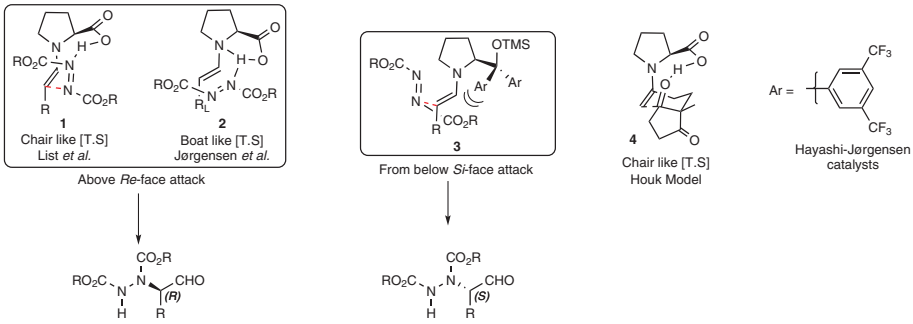
silyl-protected diarylprolinol catalyst.[13] Given that the reaction proceeds through an enamine mechanism,[14] the chair-like transition state **1** proposed by List closely resembles Houk's transition-state model **4** used for proline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction rather than the boat-like transition state **2** proposed by Jørgensen. On the basis of a series of calculations, Houk and co-workers showed that the N–H hydrogen bond with proline does not lower the transition-state energy.[15] Whereas, for a non-hydrogen-bonding catalyst the observed enantioselectivities originated from steric discrimination of two enamine faces formed as a result of interaction between the catalyst and carbonyl compound (transition-state model **3**; Scheme 2).

1,3-Polyol containing compounds constitute a large number of natural products with a wide variety of potent biological activities.[16] As part of our ongoing studies on proline-mediated reactions, our group has developed an iterative approach for α-aminoxylation[17] and showed its application for the synthesis of various 1,3-skipped polyol containing natural products.[18] Working on the same lines,

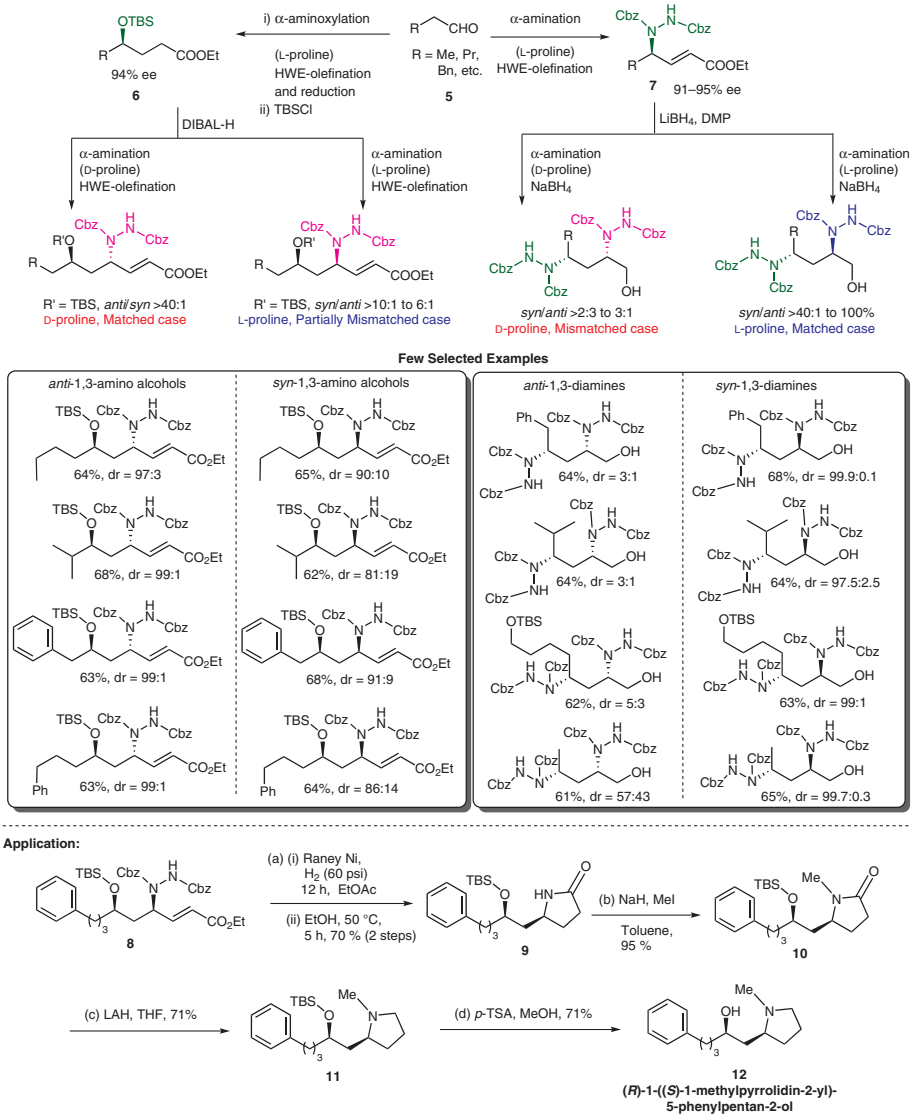
Biographical Sketches

Pradeep Kumar was born and grew up in India. He obtained his Ph.D. degree from BHU (Varanasi), UP. He undertook his post doctoral studies with Prof. Richard R. Schmidt as an AvH fellow at the University of Konstanz, Germany. He served as chief scientist and former Head of the Organic Chemistry Division, CSIR-National Chemical Laboratory Pune. Currently, he is working as INSA senior scientist in CSIR-NCL, Pune. He is a fellow of the National Academy of Sciences, India (2007) and Indian National Science Academy (2015). He is a recipient of the CRSI bronze medal (2010), OPPI Scientist Award (2012). His research interests include asymmetric synthesis and total synthesis of natural products.

Brijesh M. Sharma was born in 1989 in Khopoli (Maharashtra), India. He received his M.Sc in the Chemistry from the Department of Chemistry, University of Mumbai in 2011. He has been awarded a National fellowship for pursuing his doctoral studies in CSIR-National Chemical Laboratory under the supervision of Dr Pradeep Kumar. His research interest centers around the development of highly selective C–C bond-forming reactions and total synthesis of biologically active natural products.



Scheme 2 Proposed transition state for C–N bond formation



Scheme 3 Synthesis of 1,3-amino alcohols and 1,3-diamines via an iterative strategy

our group has also explored the efficacy of proline-catalyzed asymmetric α-amination in the stereoselective synthesis of 1,3-diamines,[19] employing sequential α-amination and Horner–Wadsworth–Emmons (HWE) olefination of aldehydes,[20] maintaining high *ee* as well as good *dr* during each iteration. The approach furnished >40:1 *dr* for *syn*/*anti* 1,3-diamines using L-proline (matched case), whereas poor to moderate (2:3 to 3:1) *dr* ratio was found for *anti*/*syn* 1,3-diamines using D-proline (mismatched case) (Scheme 3).[19] The *syn*/*anti* 1,3-diamines, however were found to show contrasting results compared with *syn*/*anti* 1,3-diol.[17] A plausible reason for poor diastereoselectivity could be accounted for by the steric as well as hydrogen-bonding influence of the existing chiral center in the substrate on the incoming electrophilic amine source. On the other hand, proline-catalyzed sequential α-aminoxylation/α-amination and HWE olefination of aldehydes lead to the formation of enantiomerically pure *anti*/*syn* 1,3-amino alcohols with a high degree of diastereoselectivity (Scheme 3).[21] Thus, the use of either D- or L-proline in the α-aminoxylation/α-amination step determines the outcome of the *syn*/*anti* configuration of 1,3-amino alcohol moiety. The potential of this methodology is further demonstrated in the short synthesis of a cyclic amino alcohol derivative; namely, (*R*)-1-((*S*)-1-methylpyrrolidin- 2-yl)-5-phenylpentan-2-ol (**12**; Scheme 3).[22] Compound **12** and its analogues have recently been shown to possess promising therapeutic potential in the treatment of Alzheimer's, Parkinson's, and Huntington's diseases, and several other neurological disorders, including spinal cord injuries and strokes. This account highlights our laboratory's ongoing program and accomplishment on proline-catalyzed iterative α-amination and α-aminoxylation or a combination of both, for asymmetric C–N and C–O bond formation. We have also covered the methods of closely related work carried out by others in the last five years. In principle, using this iterative strategy along with a judicious choice of proline catalyst and electrophilic 'O' or 'N' source, all possible combinations of 1,3-diamines as well as amino alcohols can be accessed. We have demonstrated the potential and broad scope of the strategy, by accomplishing the total synthesis of various alkaloids and bioactive compounds having 1,3-amino alcohols/1,3-diamines framework.

2 Applications

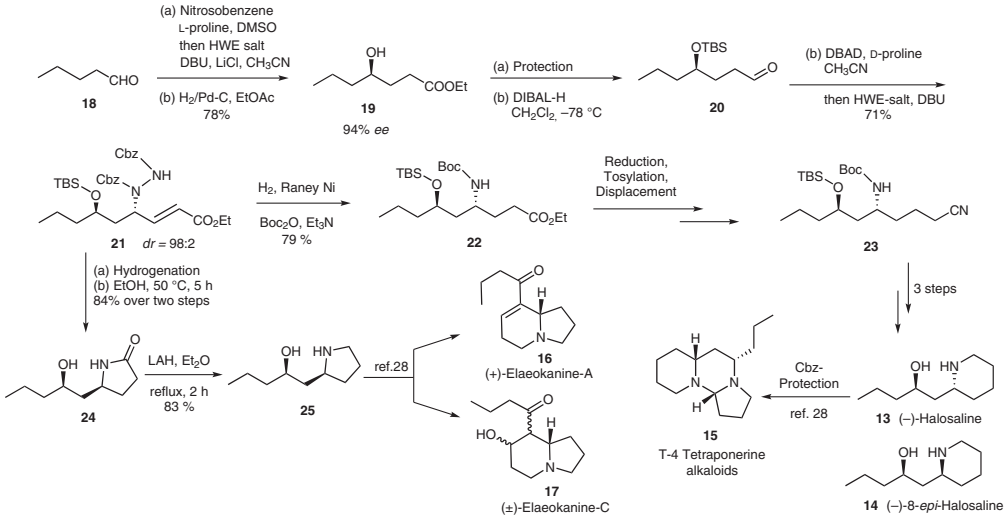
2.1 Total Synthesis of (–)-Halosaline, Formal Synthesis of (+)-Elaeokanine-A, (±)-Elaeokanine-C, and T-4 Tetraponerines Alkaloids

In a continuation of our work on asymmetric synthesis of substituted piperidine alkaloids using organocatalysis,[23] we further considered extending the above protocol to develop a general flexible approach for 2-substituted piperidines (–)-halosaline **13**,[24] (–)-8-*epi*-halosaline **14**,[25] T-4 tetraponerines **15**,[26] Elaeokanine A **16**, and Elaeokanine C **17**.[27] Synthesis of (–)-halosaline **13** started from the commercially available valeraldehyde **18**. It was subjected to α-aminoxylation using nitroso benzene and L-proline as catalyst. Subsequent Horner–Wadsworth–Emmons (HWE) olefination employing an ylide derived from triethyl phosphonoacetate and hydrogenation with Pd/C produced the γ-hydroxy ester **19** in 78% yield and 94% *ee*. The ester **19** was converted into aldehyde **20** through a silyl protection and reduction sequence. α-Amination of the corresponding aldehyde **20** using dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D-proline as catalyst furnished the α-amino aldehyde, subsequent in situ reaction of ylide generated from triethyl phosphonoacetate (HWE olefination) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) furnished *anti*-1,3-amino alcohol **21** in 71% yield and 98:2 diastereomeric ratio. 1,3-Amino alcohol **21** served as an important and versatile building block, which underwent N–N bond cleavage with concomitant reduction of the double bond, followed by Boc protection to furnish ester **22** in 79% yield. Compound **22**, on reduction using $LiBH_4$, tosylation, and NaCN displacement, produced the cyano compound **23** in 85% yield. After one-carbon homologation, cyano compound **23** was converted into the target molecule (–)-halosaline **13** by functional group interconversion, the latter can be converted into the target **15** by a known procedure.[28] Similarly, (–)-8-*epi*-halosaline **14** can be prepared by using L-proline during the α-amination reaction. Having achieved the synthesis of (–)-halosaline **13**, cyclic aminoalcohol **25** was considered as the next target for the formal synthesis of **16** and **17**.

For this purpose, 1,3-*anti*-aminoalcohol **21** was converted into lactam **24** under hydrogenation conditions, which, on LAH reduction, gave the key precursor **25** in 83% yield. Given that the conversion of compound **25** into target molecule **16** and **17** has been reported,[29] this constitutes the formal synthesis of target molecules Elaeokanine A and Elaeokanine C (Scheme 4).[30]

2.2 Synthesis of Protected (2*S*,4*R*)-4-Hydroxyornithine and (+)-Pseudohygroline

The nonproteinogenic amino acid (2*S*,4*R*)-4-hydroxyornithine **26** found in lentils[31] and pyrrolidine alkaloid (+)-pseudohygroline **27**[32a] isolated from *Carallia brachiata*, *Erythroxylon* coca, and *Schizanthus hookeri*[32b–d] showed potent biological activity and fascinating structural features. So we became interested in devising a strategy to access all these natural products from a single building block. To this end, the synthesis of the target molecule started from aldehyde **28**. Sequential α-aminoxylation in the presence of D-proline, followed by Wittig–Horner olefination and hydrogenation by Pd/C gave the γ-hydroxy esters **29** (**29a**: 68% yield, 96% *ee*; **29b**: 72% yield and 94%



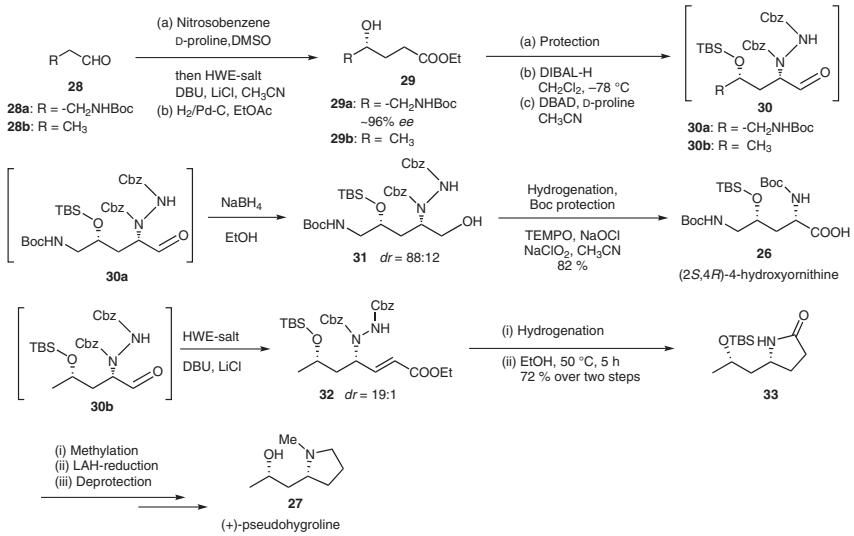
Scheme 4

ee). The γ-hydroxy esters **29**, on further silyl protection of hydroxy group, reduction and dibenzyl azodicarboxylate (DBAD) mediated α-amination in presence of D-proline, gave the product α-amino aldehyde **30**. Towards the synthesis of (2*S*,4*R*)-4-hydroxyornithine, aminoaldehyde **30a**, on $NaBH_4$ reduction, afforded the substituted hydrazine **31** as a separable diastereomers in 88:12 ratio. The N–N bond cleavage of **31** under hydrogenation followed by Boc protection and finally oxidation using TEMPO/NaOCl/$NaClO_2$ gave the desired protected (2*S*,4*R*)-4-hydroxyornithine **26** in 82% yield (Scheme 5).[33]

With an aim to synthesize (+)-pseudohygroline, aminoaldehyde **30b** was olefinated under HWE reaction conditions with ylide derived from triethyl phosphonoacetate to yield the *syn*-1,3-amino alcohol **32** in 19:1 diastereomeric ratio. Further N–N bond cleavage of **32** under hydrogenation conditions gave free amine, which was converted into lactam **33** smoothly in refluxing ethanol in 72% yield (over two steps). Methylation, reduction, and its subsequent desilylation furnished natural product **27** in 95% yield (Scheme 5). The target molecule **26** was synthesized in 22% overall yield; whereas **27** was synthesized in 24% overall yield from aldehyde **28a** and **28b**, respectively.

2.3 Synthesis of (–)-Deoxoprosopinine and (+)-Deoxoprosophylline

Prosopis alkaloids such as deoxo analogues deoxoprosopinine **34** and deoxoprosophylline **35** isolated from the leaves of Prosopis afrikana Taub, containing 2,6-disubstitut-



Scheme 5

ed piperidin-3-ol framework, exhibit antibiotic, anaesthetic, analgesic and CNS stimulating properties. These alkaloids have unique structural features similar to the acyclic structure of sphingosine and safingol sphingolipids containing a hydrophobic aliphatic tail.[34] These sphingolipid mimics are required to facilitate transfer across the lipid membrane and a hydrophilic head group to enable glycosidase inhibition,[35] thus enhancing their therapeutic potential.

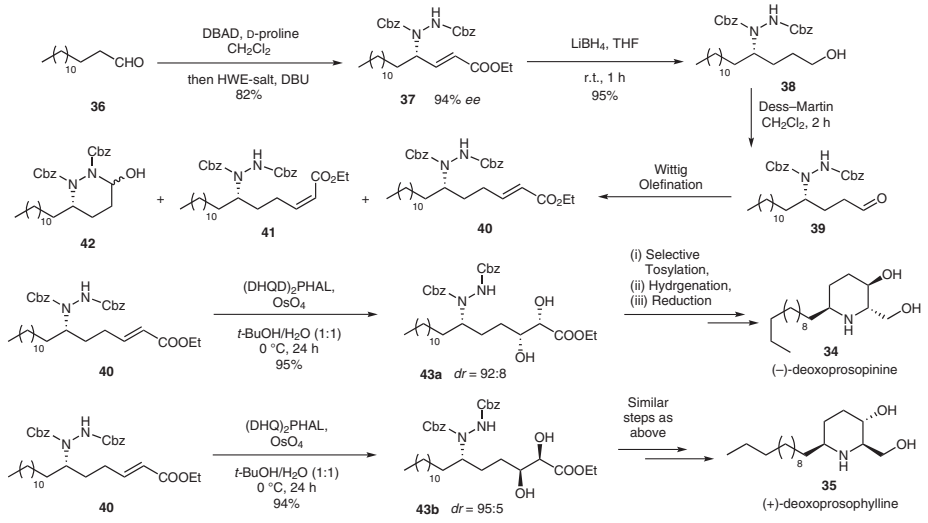
The stereoselective synthesis starts with myristyl aldehyde **36**. By following the protocol for α-amination of aldehyde using D-proline as discussed in the foregoing section, **36** gave the γ-amino-α,β-unsaturated ester **37** in 82% yield and 94% *ee*. Further reduction of **37**, with concomitant reduction of the double bond followed by Dess–Martin periodinane (DMP) mediated oxidation furnished aldehyde **39**. Subsequent Wittig olefination gave *trans*-olefin **40** as the major compound in 70% yield along with a small amount of *cis*-olefin **41** and cyclized product **42** (16% yield). The undesired cyclized product **42** was again converted back into valuable alcohol **38** using $LiBH_4$. Furthermore, olefin **40**, on asymmetric dihydroxylation with $(DHQD)_2PHAL$ ligand under the Sharpless AD conditions, furnished diol **43a** in 95% yield and 92:8 *dr* ratio. Regioselective monotosylation followed by Raney-Ni mediated N–N bond cleavage gave free amine, which, in the same pot, underwent nucleophilic displacement of α-tosylate to set the piperidine core of the molecule. Finally, reduction of the ester group attached to the piperidine framework using $LiBH_4$ produced (–)-deoxoprosopinine **34** in 96% yield with an overall yield of ca. 37%.[36] In a similar way, (+)-deoxoprosophylline **35** was synthesized with an overall yield of ca. 36% using $(DHQ)_2PHAL$ as a ligand in Sharpless AD step and following a similar set of reactions used for (–)-deoxoprosopinine (Scheme 6).

2.4 Synthesis of Indolizidine, Pyrrolizidine, and Quinolizidine Framework

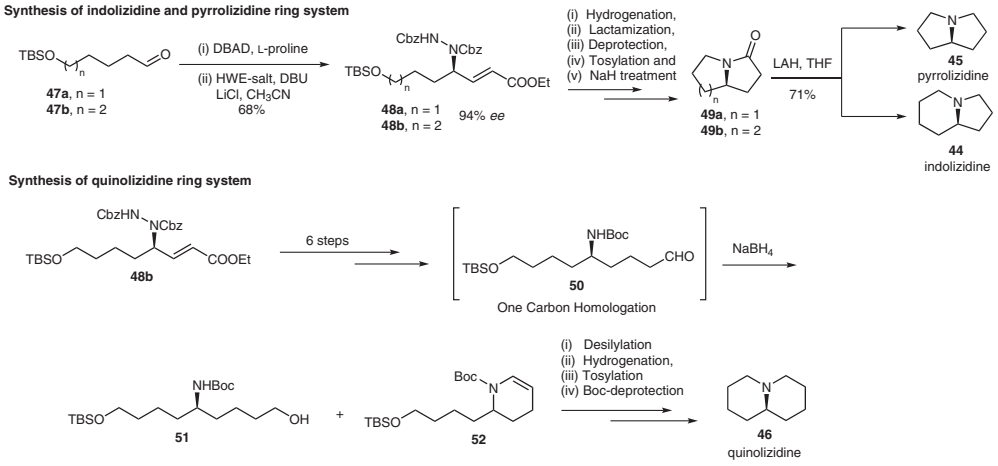
Indolizidine **44**, pyrrolizidine **45**, and quinolizidine **46** skeletons are important structural motifs found in diverse alkaloids, which exhibit a broad range of biological activity. As an extension of our work for the synthesis of alkaloids,[37] we considered developing a general strategy to access [5/5], [5/6] and [6/6] azabicyclic ring systems just by varying the number of carbon atoms of the aldehydes used as the starting material and the proper choice of organocatalyst employed.

As illustrated in Scheme 7, aldehydes **47a** and **47b**, on sequential L-proline catalyzed α-amination/HWE olefination sequence, gave the γ-amino-α,β-unsaturated esters **48a** and **48b** in excellent yields and high enantioselectivity. Compounds **48a** and **48b**, under reductive hydrogenation followed by subsequent lactamization deprotection, tosylation and finally base treatment, gave fused lactams **49a** and **49b** in 74% yield. Compounds **49a** and **49b**, on LAH reduction, gave pyrrolizidine **45** and indolizidine **44** ring systems. By following a reported procedure,[38] the fused lactam **49a** can be readily converted into pyrrolam.

Towards the synthesis of quinolizidine **46**, γ-amino-α,β-unsaturated ester **48b** was first subjected to N–N bond cleavage followed by Boc protection. Further reduction, tosylation, followed by one-carbon homologation using NaCN gave the cyano compound. Subsequent diisobutylaluminium hydride (DIBAL-H) reduction gave one-carbon homologated aldehyde **50**. Compound **50**, on subjection to $NaBH_4$ reduction, gave alcohol **51**, along with formation of **52** as a major product (Scheme 7). The double-bond reduction along with desilylation of compound **52** was achieved in one pot under hydrogenation conditions. Subsequent tosylation and Boc deprotection led to the formation of the amine. The nucleo-



Scheme 6



Scheme 7

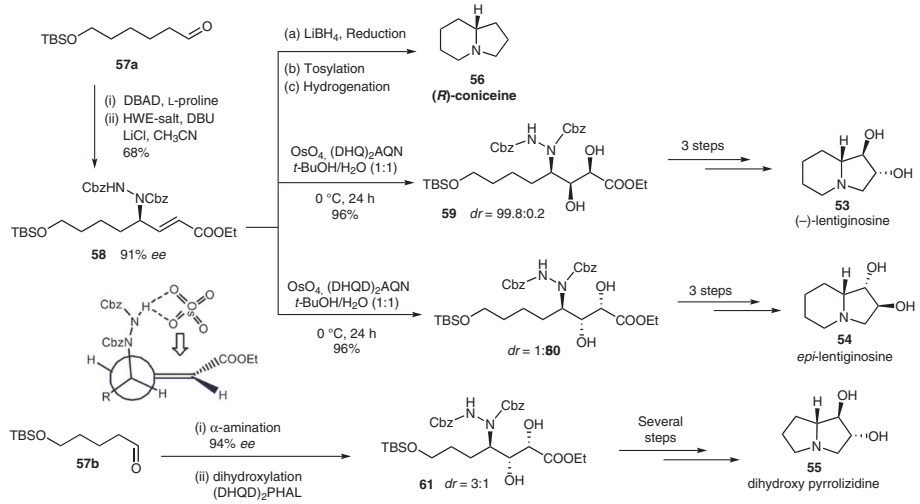
philic displacement of tosyl with the resultant amine in the presence of Hünig's base gave the quinolizidine ring system **46** (Scheme 7).[39]

2.5 Total Synthesis of (–)-Lentiginosine, (–)-*epi*-Lentiginosine, and Dihydroxypyrrolizidine

Lentiginosine **53**, isolated from astralaguslentiginosus,[40] is the most potent known inhibitor of amyloglycosidases, with IC_{50}=5 μg/mL, in addition to exhibiting excellent anti-HIV, anti-tumor and immunomodulating activities. Several other strategies employed for the synthesis of lentiginosine and its derivatives were tartaric acid, carbohydrates, nitrones, and amino acids etc. as a chiral pool starting material.

The synthesis started with aldehyde **57a**. By following the protocol for α-amination as discussed above, the γ-amino-α,β-unsaturated ester **58** was prepared in 68% yield and 91% enantioselectivity. Ester reduction and ensuing double bond reduction and desilylation of **58** using $LiBH_4$ in one step followed by di-tosylation and N–N bond cleavage employing Raney-Ni gave the free amine. Nucleophilic displacement of the di-tosylate resulted in the formation of indolizidine alkaloid (*R*)-coniceine **56** (Scheme 8).

Synthesis of target molecules (–)-lentiginosine **53** and its 1,2-*epimer* **54** started with γ-amino-α,β-unsaturated ester **58**. At this stage, the application of Sharpless AD reaction for embedding two hydroxyl groups in the substrate with the aim to install the three requisite stereocenters in a highly stereoselective manner paved to be a general synthetic route to the polyhydroxylated imino sugars. Dihydroxylation of **58** gave the predicted '*syn* facial selectivity' in the formation of the major product **59** in the absence of ligands. H-bonding between the OsO_4 and NCbz–NHCbz group could be a plausible reason, despite the steric effect of the allylic -NCbz substituent. Thus, by using $(DHQ)_2PHAL$ and $(DHQ)_2AQN$ ligands, high diastereoselectivity (*dr* ca.



Scheme 8

99:1) was achieved. The latter proved more effective in achieving the '*anti* facial selectivity', as the *dr* for the *anti* compound **60** increased to 3:1 based on exhaustive screening of other ligands.

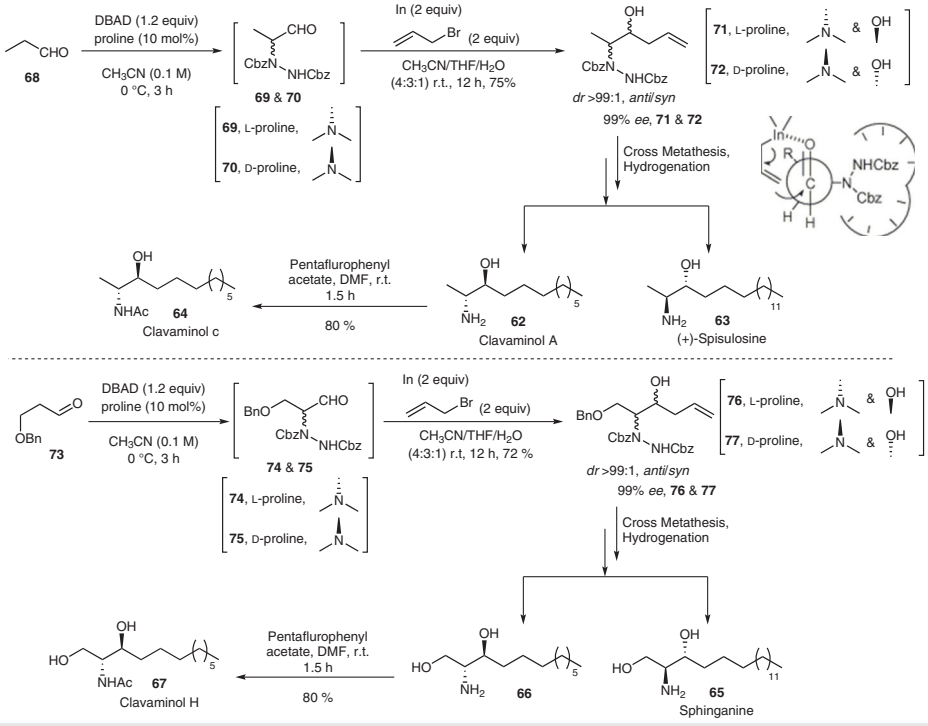
Diol **59** was reduced to tetrol followed by primary tosylation to give di-tosyl. Subsequent Raney-Ni hydrogenation conditions delivered the free amine. The nucleophilic displacement of di-tosylate under similar reaction conditions furnished the desired (–)-lentiginosine **53**. In a similar way, (–)-*epi*-lentiginosine **54** was synthesized from diol **60** by following a similar sequence of reactions (Scheme 8).

Successful synthesis of lentiginosine and its 1,2-epimer, further prompted us to generalize the strategy to other derivatives. Thus, by simple alteration of the chain length of the aldehyde, the synthesis of dihydroxy pyrrolizidine **55** was accomplished. The synthesis commenced with aldehyde **57b**, and by following the protocol for proline-catalyzed α-amination, as discussed above, the γ-amino-α,β-unsaturated ester was obtained in 68% yield and 94% enantioselectivity, as illustrated in Scheme 8. The olefinic compound, on subjecting to Sharpless asymmetric dihydroxylation conditions using $(DHQD)_2AQN$ as ligand, gave diol **61**. Diol **61** was converted into target compound **55** by using analogous reactions as described for the synthesis of **53** and **54**. Extension of this versatile methodology led us to complete all the three target molecules in an efficient and short synthetic steps.[41]

2.6 Synthesis of Clavaminols, Sphinganine, and (+)-Spisulosine, and a Theoretical Insight into the Stereochemical Aspects of the Reaction

The strategy developed to prepare long-chain α-amino-alcohols families such as clavaminol A-H, (+)-spisulosine, and sphinganine having potent bioactivities such as antitumor, immunostimulatory, immunosuppressant as well as neuronal proliferation, is summarized in Scheme 9. The synthesis began with proline-catalyzed α-amination of propanal **68** followed by indium-mediated Barbier type allylation to give homoallylic alcohol **71**/**72** in 75% yields with *dr* >99:1. The newly generated stereocenter will be *anti* and is contradictory to the result obtained with respect to that generated by using proline in case of tandem aminoxylation–allylation[42] reactions as well as chelation controlled allylation.[43] DFT calculations also showed a difference of 9.03 kcal/mole in favor of the *anti* transition state, leading to the preferential formation of the *anti* product (Figure 1). The bulky NCbz–NHCbz group[44] exerts steric effects thus decreasing the stability of the *syn* product.

Finally, cross metathesis of homoallylic alcohols **71** and **72** with olefins with varying chain length such as oct-1-ene and tetradec-1-ene followed by N–N bond cleavage and reduction of the double bond furnished clavaminol A **62** and (+) spisulosine **63** in 99% yields. Next, the amine group of clavaminol A **62** was selectively acetylated in the presence of alcohols using pentafluorophenyl acetate to produce



Scheme 9

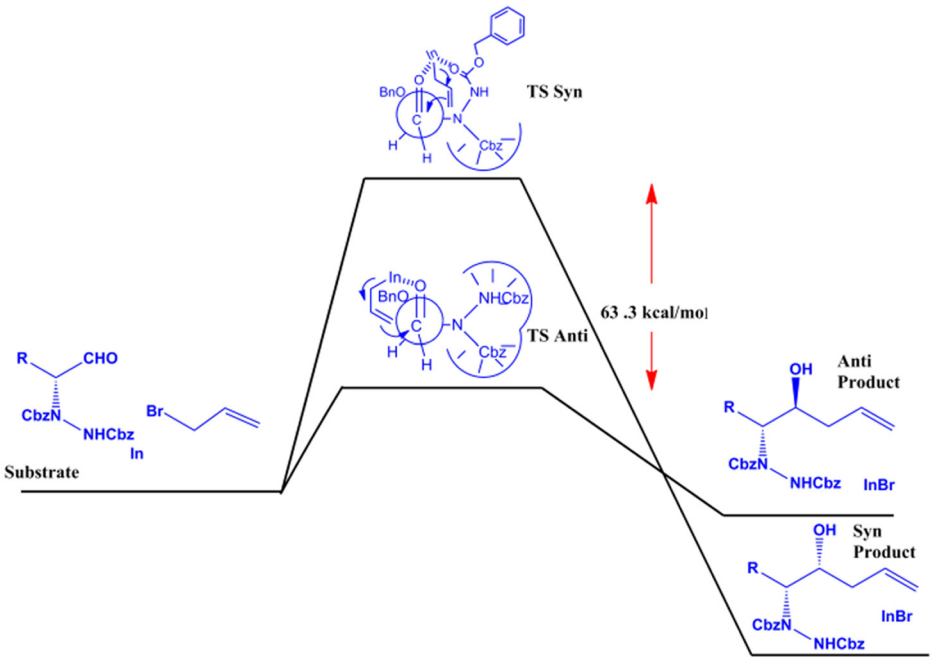


Figure 1 Chelation controlled reaction pathway showing the relative stability of the *syn* and *anti* transition state

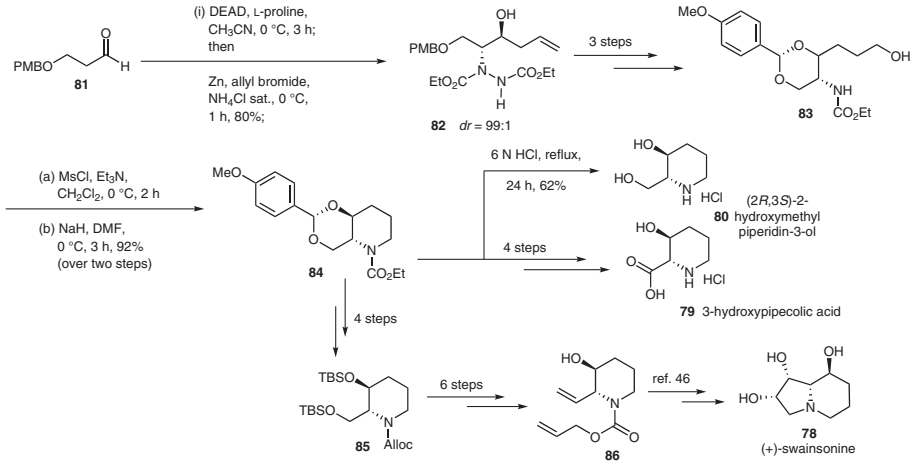
clavaminol C **64** in 80% yield. Thus, the total synthesis of clavaminol A **62** and (+)-spisulosine **63** was accomplished in 63% overall yield and clavaminol C **64** in 51% overall yield; better than the previously reported synthesis.

The synthesis of clavaminol H **67** and sphinganine **65** commenced from 3-(benzyloxy) propanal **73** using a similar reaction sequence, thus accomplishing the total synthesis of sphinganine **65** and clavaminol H **67** in three and four steps, respectively, with 61% and 45% overall yields (Scheme 9).[45]

2.7 Synthesis of (2*S*,3*S*)-3-Hydroxypipecolic Acid and Formal Synthesis of (+)-Swainsonine

Hydroxylated piperidines **79**, **80** and indolizidines such as swainsonine **78**, a potent α-mannosidase inhibitor, exhibit antiproliferative, immunomodulatory, antimetastatic, and anticancer activities making it an attractive synthetic target.

Sudalai et al. reported the synthesis of chiral piperidine **84** starting from known aldehyde **81**, which on L-proline-catalyzed α-amination followed by Zn-mediated Barbier



Scheme 10

allylation in situ furnished the hydrazino alcohol **82** in 80% yield (single diastereoisomer; 96% *ee*). The *anti* stereoselectivity can be accounted for on the basis of sterically controlled Felkin–Ahn transition state. The secondary alcohol **82** was subjected to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated intramolecular diastereoselective oxidative acetalization followed by N–N bond cleavage, which, on subsequent hydroboration–oxidation, gave primary alcohol **83** in 70% yield. Alcohol **83** was converted into mesylate, which underwent intramolecular N-alkylation, to give the piperidine core unit **84**, which on deprotection gave compound **80**. Similarly, compound **84** delivered 3-hydroxypipecolic acid **79** by four-step functional group transformation, which includes deprotection, protection, oxidation using cat. $RuCl_3$, $NaIO_4$ and its HCl salt formation (Scheme 10).[46]

Chiral piperidine **84** served as an important building block for the formal synthesis of (+)-swainsonine **78**. Piperidine **84** on hydrolysis of ethyl carbamate, followed by allyloxy protection and subsequent benzylidene acetal deprotection and silyl protection afforded di-TBS ether **85**. Selective deprotection of primary silyl ether, DMP oxidation and one-carbon Wittig olefination gave the required diene **86** in 65% yield. Since the transformation of **86** into (+)-swainsonine has been reported,[47] this constitutes a formal synthesis of target **78** (Scheme 10).

2.8 Synthesis of 4-Hydroxypyrazolidine Derivatives via Organocatalytic Sequential α-Amination/Corey–Chaykovsky Reaction

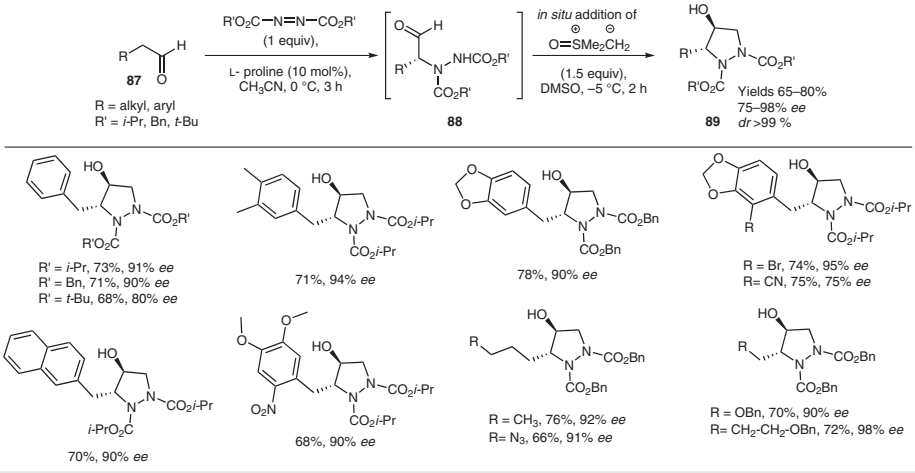
Chiral hydroxypyrazolidine derivatives serve as important building blocks for enantiopure 1,3-diamines as well as for the pharmaceutical industry. They are shown to exhibit a wide variety of biological activities such as anticonvulsant, antitumor and antidepressant properties.

In the past, various groups including our own have trapped reactive α-aminoaldehyde intermediates with various other nucleophiles.[48] Recently, Sudalai et al.[49] developed tandem α-amination/Corey–Chaykovsky reaction for in situ trapping of amino aldehyde **88** with Corey's sulfur ylide (dimethyloxosulfonium methylide) so as to access 4-hydroxypyrazolidine derivatives **89** in moderate to good yields (65–80%) with excellent enantio- and diastereoselectivities (Scheme 11). The reaction was compatible with a wide variety of aldehydes and electrophilic amine sources. The synthetic utility of this method was demonstrated in the synthesis of *anti*-1,2-aminoalcohol, which are common structural motifs present in phytosphingosines and HIV protease inhibitors.

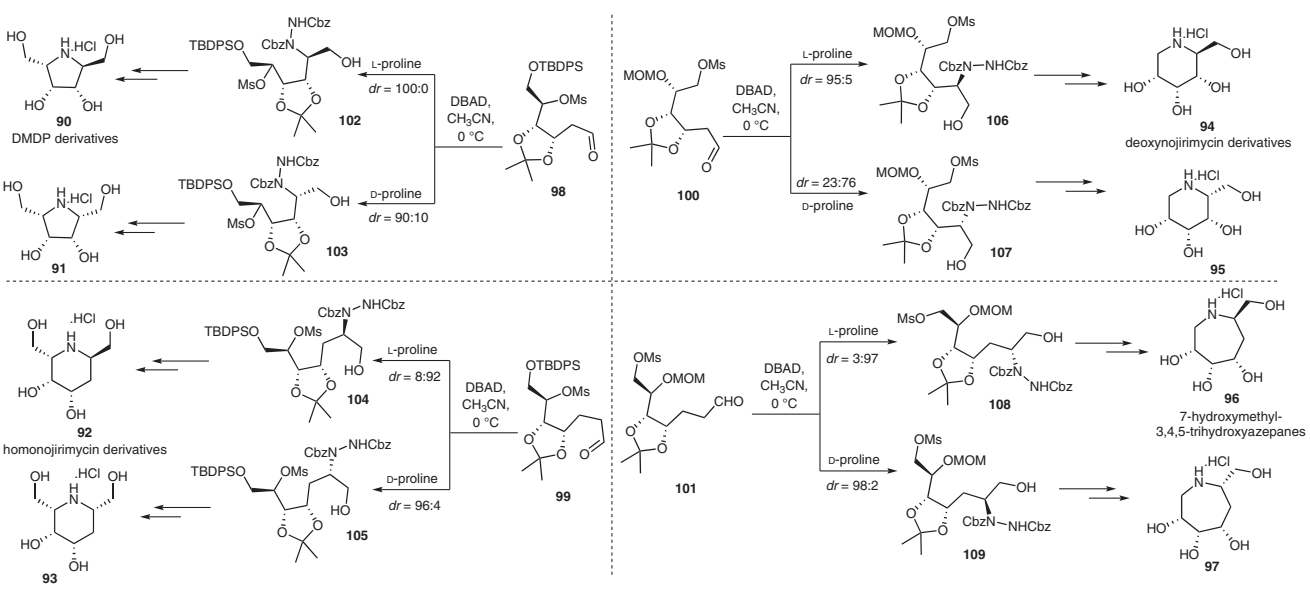
2.9 Synthesis of Diverse Iminocyclitols from D-Ribose

2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine (five-membered), 1- and 2-deoxynojirimycin derivatives (six-membered) and polyhydroxyazepane derivatives (seven-membered) are polyhydroxy *N*-heterocyclic frameworks that are generally referred to as iminosugars or azasugars. They are key building blocks for drug development against a number of diseases including cancer, diabetes, and viral infections such as AIDS. Ramapanicker et al. have developed a versatile and stereoselective strategy using proline-catalyzed α-amination as a key reaction to access this class of molecules.[50] Aldehydes **98**, **99**, **100**, and **101**, synthesized using chiral pool methods, have been successfully employed as starting materials for proline-catalyzed α-amination reaction to access five-, six-, and seven-membered azasugars after certain functional group transformation.

Aldehyde **98** gave DMDP derivatives **90** and **91**, aldehyde **99** gave homonojirimycin derivatives **92** and **93**, similarly, aldehyde **100** gave deoxynojirimycin derivatives **94** and **95** and finally aldehyde **101** gave azepanes derivatives **96** and



Scheme 11

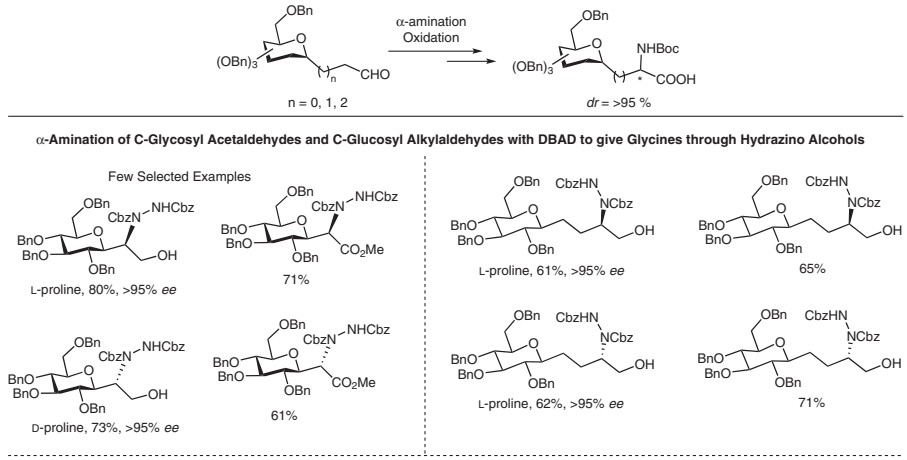


Scheme 12

97 depending on the choice of proline catalyst used. This hydrazino alcohol, on further functional group transformation, allowed easy access to iminocyclitols from D-ribose as a single starting material (Scheme 12).

2.10 Synthesis of C-Glycosyl Amino Acids via α-Amination of C-Glycosylalkyl Aldehydes

Non-natural *C*-glycosyl α-amino acids constitute ubiquitous building blocks of natural glycopeptides on co-translational modification and development of carbohydrate-based drugs. Dondoni and Massi et al. have developed a proline-catalyzed asymmetric synthesis of carbon-linked sugar amino acids.[51] The α-amination of sugar aldehyde with DBAD afforded the α-hydrazino aldehyde exclusively, in the presence of 30 mol% of L-proline as catalyst. This product can either be reduced to hydrazino alcohol using $NaBH_4$ or can be smoothly converted into the α-amino ester target by sequential Jones oxidation followed by esterification with diazomethane. A variety of substituted perbenzylated *C*-glycosyl acetaldehydes and *C*-glucosyl alkylaldehydes underwent efficient amination with good to excellent yields and high enantioselectivity >95% (Scheme 13).



Scheme 13

3 Conclusion

This Account unlocks the potential of proline for direct C–N bond formation through α-amination reactions and its successful utilization for the synthesis of complex natural products. We have developed proline-catalyzed sequential α-aminoxylation/α-amination and Horner–Wadsworth–Emmons olefination of aldehydes. Moreover, indium-mediated allylation of α-hydrazino aldehyde with *anti* selective outcome has also been uncovered. The protocol leads to easy access to 1,3-diamines, 1,3-aminoalcohols as well as 1,2-aminoalcohols in an iterative manner with high enantio- and diastereoselectivity. In addition, the role of N–H bonding directed Sharpless dihydroxylation has been studied. The proline-driven mild, robust and operationally simple reaction conditions presented in this Account are expected to find potential applications in organic chemistry and, especially, toward the synthesis of valuable alkaloids with potential bioactivities. In addition, exploration of proline-catalyzed bidirectional α-functionalization of dialdehyde, a second-generation approach, and its applications in the total synthesis of natural products appear to be future goals in this area.

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References

(1) (a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311. (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2016**, *79*, 629.
(2) (a) Li, W.; Zhang, X. *Stereoselective Formation of Amines*; Springer: Berlin, **2014**. (b) Ji, X.; Huang, H. *Org. Biomol. Chem.* **2016**, *14*, 10557.
(3) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894. (b) Roos, G. *Key Chiral Auxiliary Applications*; Academic Press: Amsterdam, **2014**. (c) Heravi, M. M.; Zadsirjan, V.; Farajpour, B. *RSC Adv.* **2016**, *6*, 30498.
(4) (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (b) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. (c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.
(5) (a) Cao, Z.-Y.; Brittain, W. D. G.; Fossey, J. S.; Zhou, F. *Catal. Sci. Technol.* **2015**, *5*, 3441. (b) Xu, Z.; Daka, P.; Budik, I.; Wang, H.; Bai, F.-Q.; Zhang, H.-X. *Eur. J. Org. Chem.* **2009**, 4581.
(6) (a) Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2014**, *31*, 1721. (b) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130. (c) Stevenazzi, A.; Marchini, M.; Sandrone, G.; Vergani, B.; Lattanzio, M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5349.
(7) (a) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (c) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947. (d) List, B. *Chem. Rev.* **2007**, *107*, 5413. (e) Raoufmoghaddam, S. *Org. Biomol. Chem.* **2014**, *12*, 7179. (f) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498.
(8) (a) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452. (b) Yamashita, Y.; Ishitani, H.; Kobayashi, S. *Can. J. Chem.* **2000**, *78*, 666. (c) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595.
(9) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917.
(10) (a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (b) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580. (c) Sunoj, R. B. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2011**, *1*, 920. (d) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8.
(11) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.
(12) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254.
(13) (a) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.
(14) (a) Clemente, F. R.; Houk, K. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 5766. (b) Rankin, K. N.; Gauld, J. W.; Boyd, R. J. *J. Phys. Chem. A* **2002**, *106*, 5155. (c) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5839. (d) Ashley, M. A.; Hirschi, J. S.; Izzo, J. A.; Vetticatt, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 1756.
(15) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911.
(16) (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2004**, *67*, 1216. (c) Weissman, K. J.; Muller, R. *Nat. Prod. Rep.* **2010**, *27*, 1276.
(17) Kondekar, N. B.; Kumar, P. *Org. Lett.* **2009**, *11*, 2611.
(18) Kumar, P.; Dwivedi, N. *Acc. Chem. Res.* **2013**, *46*, 289.
(19) Kumar, P.; Jha, V.; Gonnade, R. *J. Org. Chem.* **2013**, *78*, 11756.
(20) Kotkar, S. P.; Chavan, V. B.; Sudalai, A. *Org. Lett.* **2007**, *9*, 1001.
(21) Jha, V.; Kondekar, N. B.; Kumar, P. *Org. Lett.* **2010**, *12*, 2762.
(22) Mullican, M.; Lauffer, D.; Tung, R. US Patent 7105546B2, **2006**.
(23) (a) Kondekar, N. B.; Kumar, P. *Synthesis* **2010**, 3105. (b) Upadhyay, P. K.; Prasad, R.; Pandey, M.; Kumar, P. *Tetrahedron Lett.* **2009**, *50*, 2440.
(24) Michel, K.; Sandberg, F.; Haglid, F.; Norin, T. *Acta Pharm. Suec.* **1967**, *4*, 97.
(25) (a) Ahmad, V. U.; Nasir, M. A. *Phytochemistry* **1987**, *26*, 585. (b) Mill, S.; Hootelé, C. *J. Nat. Prod.* **2000**, *63*, 762.
(26) Merlin, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. *J. Chem. Ecol.* **1988**, *14*, 517.
(27) Hart, N.; Johns, S.; Lamberton, J. *Aust. J. Chem.* **1972**, *25*, 817.
(28) Airiau, E.; Girard, N.; Pizzeti, M.; Salvadori, J.; Taddei, M.; Mann, A. *J. Org. Chem.* **2010**, *75*, 8670.
(29) Tufariello, J. J.; Ali, S. A. *Tetrahedron Lett.* **1979**, 4445.
(30) Jha, V.; Kumar, P. *RSC Adv.* **2014**, *4*, 3238.
(31) Sulser, H.; Sager, F. *Experientia* **1976**, *32*, 422.
(32) (a) Bhosale, V. A.; Markad, S. B.; Waghmode, S. B. *Tetrahedron* **2017**, *73*, 5344. (b) Platonova, T.; Kuzovkov, A. *Med. Prom. SSSR* **1963**, *17*, 19. (c) Fitzgerald, J. *Aust. J. Chem.* **1965**, *18*, 589. (d) San Martín, A.; Rovirosa, J.; Gambaro, V.; Castillo, M. *Phytochemistry* **1980**, *19*, 2007.
(33) Jha, V.; Kumar, P. *Synlett* **2014**, *25*, 1089.
(34) Kolter, T.; Sandhoff, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 1532.
(35) (a) Asano, N. *Glycobiology* **2003**, *13*, 93R. (b) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199.
(36) Jha, V.; Kauloorkar, S. V. *Eur. J. Org. Chem.* **2014**, 4897.
(37) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Liddell, J. R. *Nat. Prod. Rep.* **2000**, *17*, 455. (c) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166.

(38) Majik, M. S.; Shet, J.; Tilve, S. G.; Parameswaran, P. S. *Synthesis* **2007**, 663.
(39) Kauloorkar, S. V.; Jha, V.; Kumar, P. *RSC Adv.* **2013**, *3*, 18288.
(40) Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886.
(41) Kauloorkar, S. V.; Jha, V.; Jogdand, G.; Kumar, P. *Org. Biomol. Chem.* **2014**, *12*, 4454.
(42) Zhong, G. *Chem. Commun.* **2004**, 606.
(43) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293.
(44) Lim, A.; Choi, J. H.; Tae, J. *Tetrahedron Lett.* **2008**, *49*, 4882.
(45) Pandey, M.; Chowdhury, P. S.; Dutta, A. K.; Kumar, P.; Pal, S. *RSC Adv.* **2013**, *3*, 15442.
(46) Aher, R. D.; Sudalai, A. *Tetrahedron Lett.* **2016**, *57*, 2021.
(47) Bates, R. W.; Dewey, M. R. *Org. Lett.* **2009**, *11*, 3706.
(48) (a) Oelke, A. J.; Kumarn, S.; Longbottom, D. A.; Ley, S. V. *Synlett* **2006**, 2548. (b) Chowdari, N. S.; Ramachary, D.; Barbas, C. F. *Org. Lett.* **2003**, *5*, 1685.
(49) Kumar, B. S.; Venkataramasubramanian, V.; Sudalai, A. *Org. Lett.* **2012**, *14*, 2468.
(50) Petakamsetty, R.; Jain, V. K.; Majhi, P. K.; Ramapanicker, R. *Org. Biomol. Chem.* **2015**, *13*, 8512.
(51) Nuzzi, A.; Massi, A.; Dondoni, A. *Org. Lett.* **2008**, *10*, 4485.