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ARTICLE TYPE

Linear dialdehydes as promising substrates for aminocatalyzed transformations

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Organocatalytic domino reactions involving amine activation of carbonyl compounds have become the latest chemical technology towards the designing and development of useful synthetic methods. In this direction, linear dialdehydes such as succinaldehyde, glutaraldehyde, and other homologous compounds have attracted considerable attention as suitable substrates for amine catalyzed transformations. Due to their unique structural features, dialdehydes can easily engage in recreation of cascade/tandem transformations for the synthesis of valuable natural products and drug molecules. In this review article we discuss the current scenario and potential application of linear dialdehydes as adequate synthetic substrates for amine catalyzed transformations to access biologically important complex scaffolds.

1. Introduction

The development of efficient protocol for carbon-carbon and carbon-heteroatom bond formation and rapid construction of small to complex molecular frameworks is an enduring challenge in modern organic chemistry. This challenge can be accomplished through the use of catalytic cascade/tandem reactions, where two or more bonds can be formed in a sequential manner. These transformations further reduced the use of ecologically hazardous chemicals and generally carried out in one-pot process, have happen to be the major target of synthetic chemists today.[1] In this context, organocatalysis remained as one of the most explored area in chemistry during last decade, since its renaissance at the beginning of this century.[2] Organocatalytic cascade/tandem reactions are highly efficient in one-pot operation and gaining rapid interest because of easy availability, robust, nontoxic nature of catalysts, saving time and solvents that is required for multistep processes. These transformations provides a rapid path to access complex molecules which could not be achieved by using conventional metal catalysis while maintaining "pot economy" in synthesis.[3] Among various modes of activation applicable for organocatalysis, amine catalysis proceed through enamine (HOMO)[4] and iminum-ion (LUMO)[5] activations have emerged as a major contributor in the exponential growth of this area (Figure 1). Enamine (HOMO)-activation for the α-functionalization of carbonyl compounds has already been expanded to "dienamine"[6] and recently to "trienamine"[7] modes of activation for functionalization at γ- and ε-positions respectively. In addition, an elegant amine catalyzed SOMO-activation mode has also been developed and applied successfully for several transformations.[8] These strategic expansion further enhance the synthetic utility and acceptability of amine catalysis for cascade or tandem reactions with different dienophiles (X=Y). Besides asymmetric transformations, amine catalysis has also been applied successfully for several non-asymmetric transformations.[9]

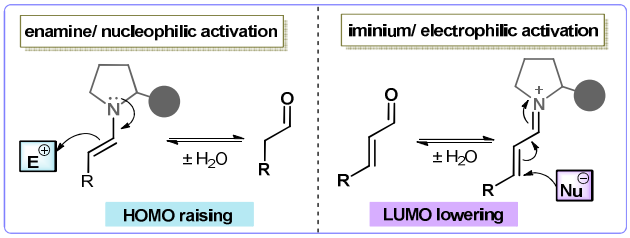

Figure 1: Activation of carbonyls through amine catalysis

On the other hand, a vital demand for finding suitably substituted bi- or tri-functionalized substrates that can participate in similar transformations with different dienophiles (X=Y) under metal free process is still exist. In this context, dialdehydes have recently emerged as suitable substrates for the development of amine catalyzed one-pot cascade transformations. Linear dialdehydes have been utilized for various transformations such as aldol/Mannich/Michael/Henry/Baylis-Hillmann reactions in inter- and intramolecular fashion. Linear dialdehydes and their derivatives have been recognized as important substrates in the area of synthetic organic chemistry.[10] Hence, the aim of this article is to highlight the importance of linear dialdehydes as promising substrates for the quick synthesis of important skeletons with molecular complexity and high selectivity through amine catalysis. Some of the "privileged" cyclic secondary amines, in particular proline and its derivatives, including diarylprolinol and diarylprolinol ethers utilized as catalysts in these transformations are shown in Figure 2. This review is

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organized according to the suitability of different linear dialdehydes *i.e.*, succinaldehyde, glutaraldehyde and other miscellaneous examples in various amine catalyzed transformations (Figure 3). In the first part, we will discuss amine catalyzed transformations of succinaldehyde and glutaraldehyde with various X=Y (C=C, C=N, C=O), whereas in the second part reactions of other higher homologated saturated or unsaturated dialdyhydes in intramolecular fashion will be presented as miscellaneous examples.

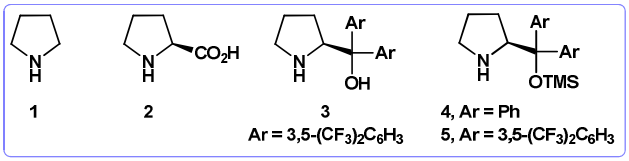


Figure 2: Some representative secondary amine catalysts

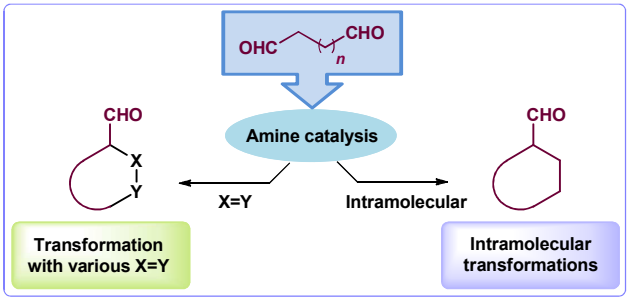
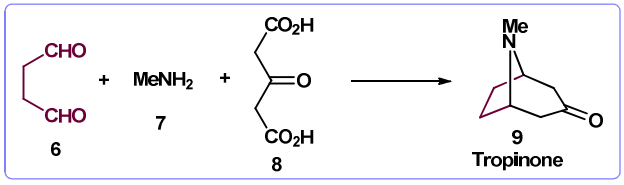


Figure 3: Linear dialdehydes as suitable substrates for amine-catalyzed transformations

2. Transformation with various X=Y (C=C, C=N, C=O)

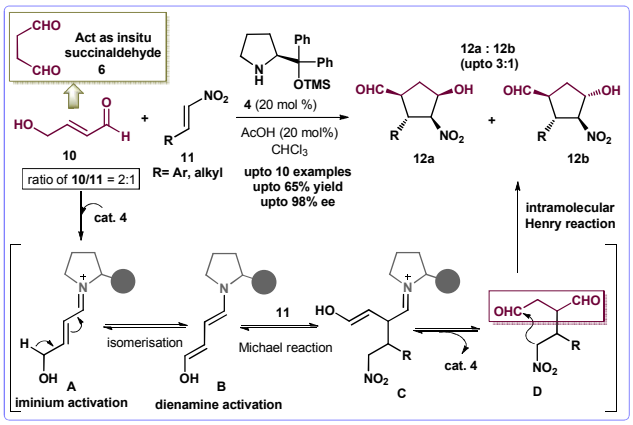
2.1. Succinaldehyde

Succinaldehyde **6** is a very simple 1,4-dialdehyde compound which undergoes polymerization in neat form, whereas reasonably stable in aqueous solution. The early utilization of succinaldehyde **6** to synthesize tropinone, by Sir Robinson in 1917, within a test tube is still an exciting example of total synthesis that illustrated a new way of synthetic creativity. This transformation showed the original application of dialdehydes in biogenetic-type synthesis, because nature uses the identical materials to make similar compounds. This one-pot tandem strategy utilized succinaldehyde **6** as a valuable synthetic substrate along with amine **7** and acetone dicarboxylic acid **8** through double Mannich condensation followed by decarboxylation to furnished the bicyclic tropane skeleton **9** (Scheme 1).[11] In addition, succinaldehyde **6** has also been applied successfully for the synthesis of various heterocyclic ring systems as well as natural products.[12]



Scheme 1: Classical example of tropinone synthesis from succinaldehyde through cascade process

In 2012, Hong and co-workers initially developed an organocatalytic Michael-Henry cascade reaction of various nitroalkenes **11** with masked dialdehyde **10** to synthesize cyclopantane carboxaldehyde **12** decorated with four consecutive stereogenic centres (Scheme 2).[13] This [3 + 2] cycloaddition proceed through amine **4** catalyzed Michael addition of in situ generated dienamine **B** from hydroxy enal **10** with nitroalkenes **11** to give intermediate **C**. Further tautomerization of **C** and intramolecular Henry reaction gave diastereomeric mixture of **12** with excellent enantioselectivity (up to 98%). In this overall process hydroxy enal **10**, for the first time, utilized as source of succinaldehyde in situ as understood by intermediate **D**. Interestingly, a complex reaction mixture was observed with this transformation was carried out between succinaldehyde **6** and nitroalkene **11** under similar reaction conditions. Therefore, hrdroxy enal **10** provides a suitable alternative to succinaldehyde **6** *via* dienamine intermediate **B** under amine catalysis.



Scheme 2: Amine catalyzed cascade strategy for cyclopentane synthesis using succinaldehyde surrogate

An another interesting and direct application of succinaldehyde **6** in amine catalyzed domino reaction through 'pot-economy' for asymmetric total synthesis of prostaglandins was developed by Hayashi and co-workers.[14] This innovative and practical approach involved direct Michael reaction of succinaldehyde **6** and nitroalkene **13** catalyzed by diphenylprolinol silyl ether *ent*-**4** (5 mol%) followed by intramolecular Henry reaction in presence of iPr$_2$EtN, as [3 + 2] cycloaddition and subsequent Horner–Wadsworth–Emmons reaction as one pot transformation furnished basic prostaglandin skeleton **16** with high yield and selectivity. Further functional group inter-conversion from common scaffold **18** with additional two pot sequence completed the enantioselective synthesis of PGA$_1$ methyl ester **19** and PGE$_1$ methyl ester **20** in 25% and 14% yields respectively (Scheme 3). The most fascinating part of this short and efficient synthesis was not only the use of inexpensive starting materials but to also complete synthesis in just three pot sequence with few purification steps, which further reduced the amount of solvent consumption and waste production. Interestingly, one-pot operations were found to be essential due to unstable nature of intermediates and therefore isolation was avoided to enhance the overall yields of the process.

Kumar and co-workers applied succinaldehyde **6** as bifunctionalized substrate for the quick synthesis of nitrogen

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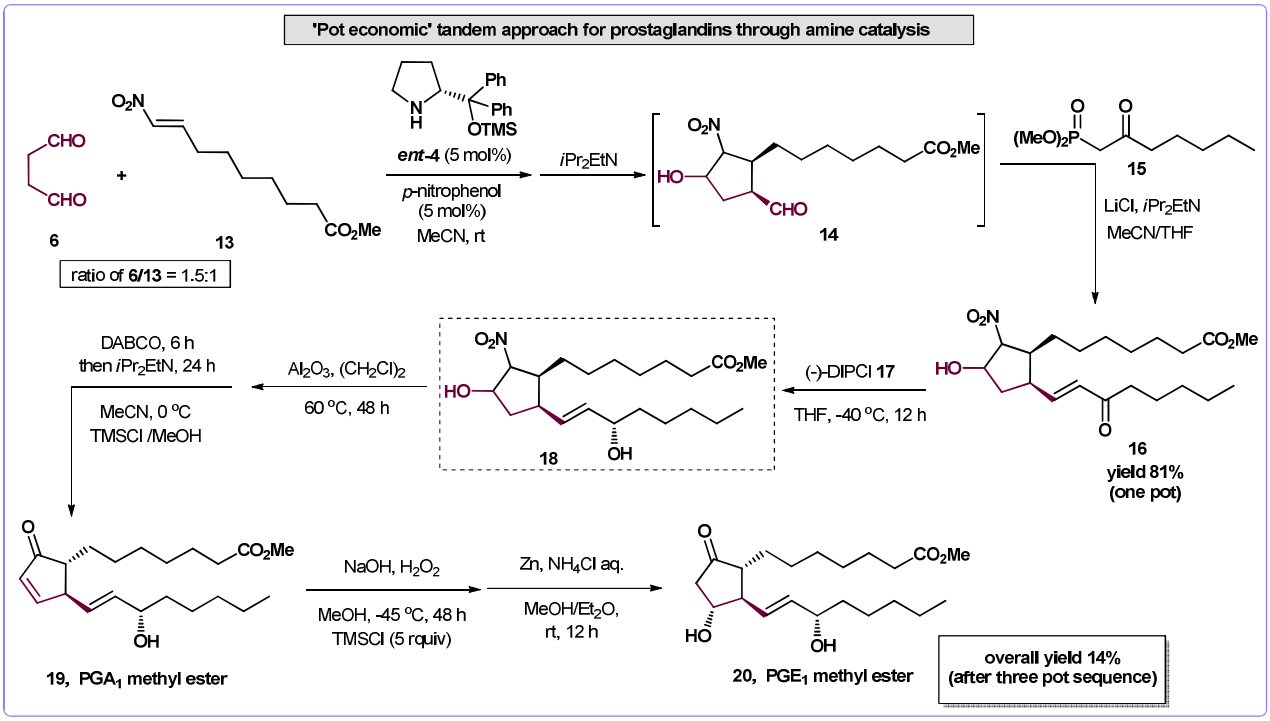
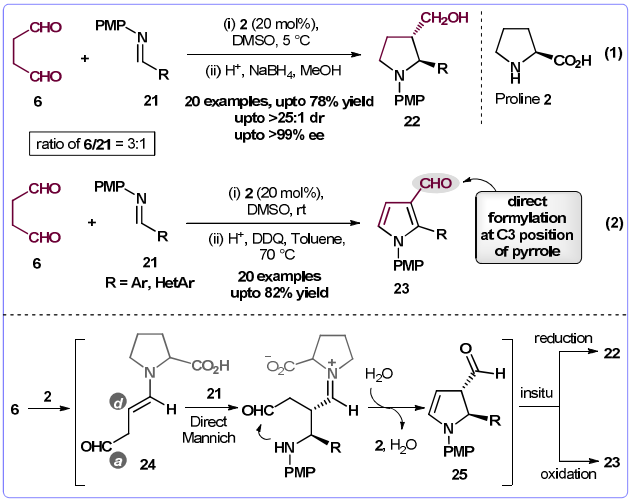


Scheme 3: Succinaldehyde as suitable substrate for Prostaglandins synthesis *via* amine catalysis



Scheme 4: Direct Mannich-cyclization tandem strategy for pyrrolidines and pyrroles from succinaldehyde

heterocycles through the amine catalysis. Initially, they developed a very simple and highly stereoselective one-pot synthesis of pyrrolidines **22** (eqn. 1, Scheme 4)[15] and then first direct synthesis of substituted pyrrole-3-carboxaldehydes **23** as a two step protocol was established (eqn. 2, Scheme 4).[16] These two very similar transformations as [3+2] annulation proceeds through proline **2** catalyzed Mannich reaction[17] between enamine **24** *in situ* generated from succinaldehyde **6** which serve as readily available 1,3-carbon D-A precursor, and imine **21**. The intermediate compound **25** was further reduced with $NaBH_4$ in presence of acid to furnish *trans*-2,3-substituted pyrrolidine **22** with high yields and excellent enantioselectivities (up to >99% ee), whereas oxidative aromatization of intermediate **25** with DDQ produced substituted pyrrole-3-carboxaldehydes **23** in good to high yields.

A spectacular example from Aggarwal and co-workers demonstrate the initial application of succinaldehyde in amine catalyzed cascade transformations for stereocontrolled synthesis of prostaglandin $PGF_{2\alpha}$ **30**.[18] The key step for the synthesis involves proline **2** catalyzed direct cross-aldol reaction of succinaldehyde **6** followed by intramolecular aldol condensation results the functionalized bicyclic enal **26** in one step with excellent enantiomeric excess (98%). Quick access to basic five membered skeleton **26** with well placed appropriate functionality makes this method quite attractive to synthesize prostaglandin-based drugs through synthetic manipulation by installing remaining groups as shown in Scheme 5. This gram scale and economic synthesis of $PGF_{2\alpha}$ **30** was completed in just six linear steps from succinaldehyde **6**, whereas most of the earlier methods were quite lengthy, consume time and energy and generate much waste.

Reddy and co-workers have also found interesting application of succinaldehyde **6** for the synthesis of Diaportheone B **33** which is an anti-TB agent, through amine catalyzed process in a slightly different manner (Scheme 6).[19] The overall transformation was

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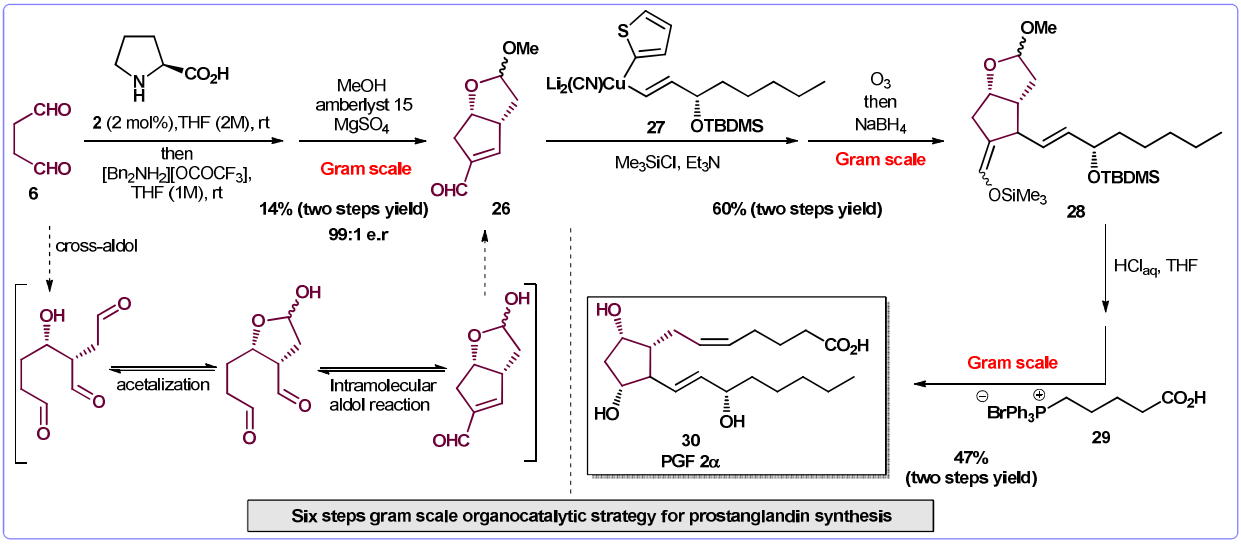
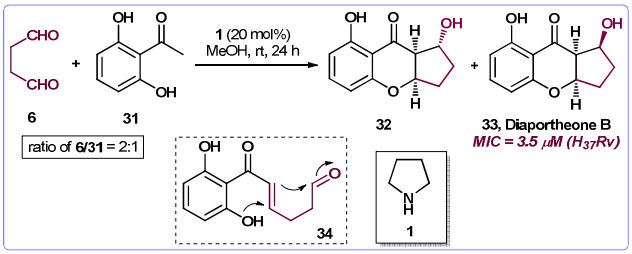
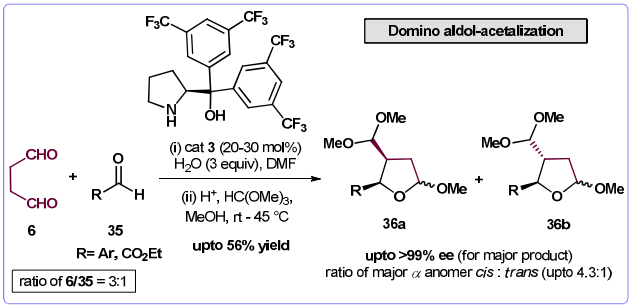


Scheme 5: The organocatalytic cascade strategy for Prostaglandins using succinaldehyde

proceeded through amine **1** catalyzed condensation of 2,6-dihydroxy acetophenone **31** and succinaldehyde **6** to a very reactive intermediate **34**, which subsequently cyclized through domino fashion offered Diaportheone B **33**. This one-pot process appeared as a quick route to synthesize this skeleton, however suffer from low yields and selectivity. The similar application of succinaldehyde **6** under amine catalysis was earlier reported by Mori and co-workers for the efficient synthesis of natural products coniochaetone A and B through domino aldol/cyclization reaction.[20]



Scheme 6: Amine catalyzed cascade strategy for Diaportheone B involving succinaldehyde

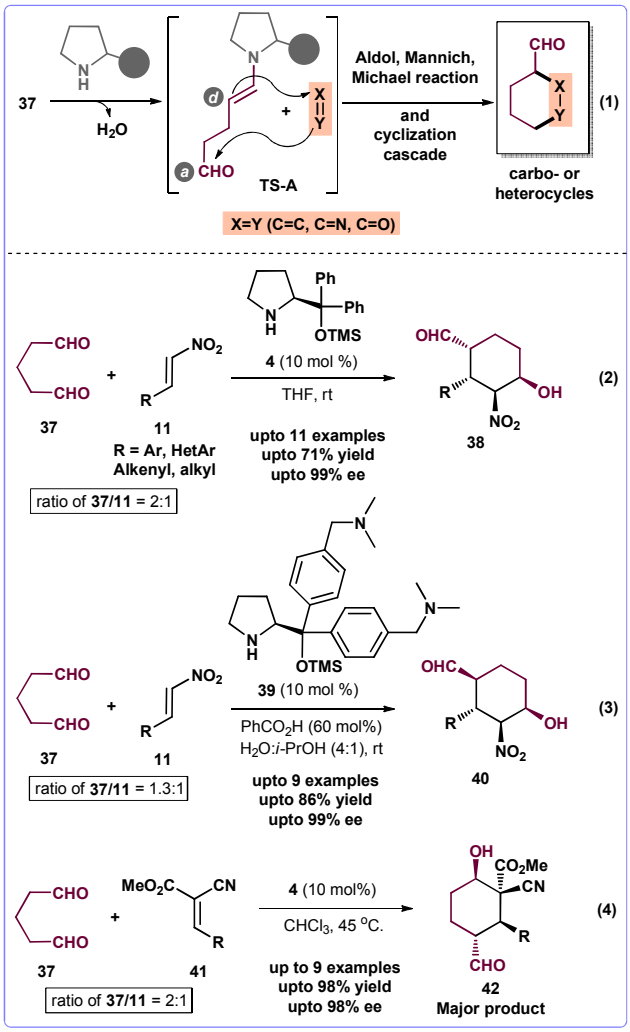


Scheme 7: Amine catalyzed domino aldol/acetalization as [3+2] cycloaddition using succinaldehyde

Very recently, Hayashi and co-workers also reported a domino approach for the asymmetric synthesis of tetrahydrofurans **36** through formal [3+2] cycloaddition of succinaldehyde **6** with other aromatic/activated aldehydes **35** (Scheme 7).[21] The overall process proceed through diarylprolinol **3** catalyzed direct aldol reaction of succinaldehyde **6** with various aldehydes **35**, followed by an intramolecular acetal-cyclization with good yields and high selectivity's (up to 99% ee).

2.2. Glutaraldehyde

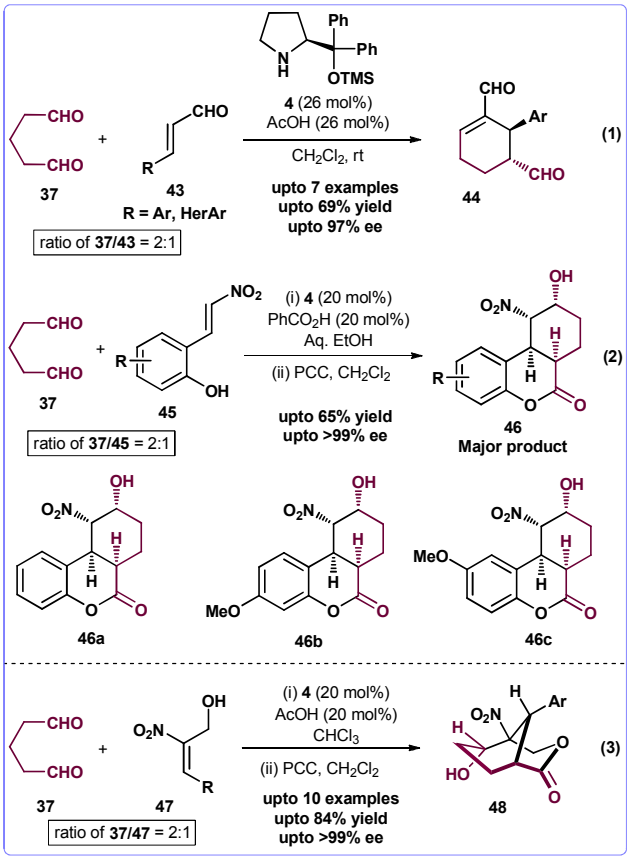
Glutaraldehyde **37**, 5-carbon dialdehyde, is a clear, colorless to pale straw-colored, pungent oily liquid that is soluble in all proportions in water and alcohol, as well as in organic solvents. This linear dialdehyde have had great success in synthesis because of its commercial availability and low cost in addition to its high reactivity. Glutaraldehyde act as suitable cross linking agent for the enzymes immobilization because it possesses unique chemical behavior in aqueous solution.[22] Additionally, glutaraldehyde has also been utilized successfully for the quick synthesis of small heterocyclic scaffolds as well as useful alkaloids.[23] The application of **37** in amine catalyzed domino transformation is quite obvious as it can give a rapid access to medium sized carbo-and heterocyclic ring systems depend on counterpart dipolarophile X=Y (C=C, C=N, C=O). In general, most of the amine catalyzed transformations of glutaraldehyde proceed through the enamine formation **TS-A** from one of the aldehyde group whereas another aldehydic moiety act as acceptor with various dipolarophile (X=Y), furnished carbocyclic /heterocyclic ring systems in one-pot operation without much protection-deprotection steps (eqn. 1, Scheme 8).



Scheme 8: Amine catalyzed domino transformations through glutaraldehyde

The very first application of glutaraldehyde **37** in amine catalyzed domino transformation was developed by Hayashi and co-workers for highly diastereo- and enantioselective synthesis of cyclohexane derivative **38** with nitro olefins **11** (eqn. 2, Scheme 8).[24] This domino sequence proceed through Michael/Henry reaction to generate four contiguous stereocenters, two in each of the carbon-carbon bond forming step. Among the four diastereomers, the major product **38** was obtained with high yields and enantioselectivity's (up to 99% ee), regardless to the substituents on the aromatic ring of **11**. The major diastereomer was also subjected to different isomerization conditions to access the complete formation of other diastereomers in good enantioselectivities. Consequently, the very similar approach for functionalized cyclohexanes **40** was developed by Ni and co-workers in aqueous solvents using the water soluble and recyclable organocatalyst **39** (eqn. 3, Scheme 8).[25] While, the catalyst loading (10 mol%) is same as Hayashi protocol but more costly synthesis of catalyst **39** as compare to **4** is the downside of the approach. Use of water as a safe and nontoxic solvent along with catalyst recycling from four to seven times without much variation in yields and selectivity make this protocol more practical.

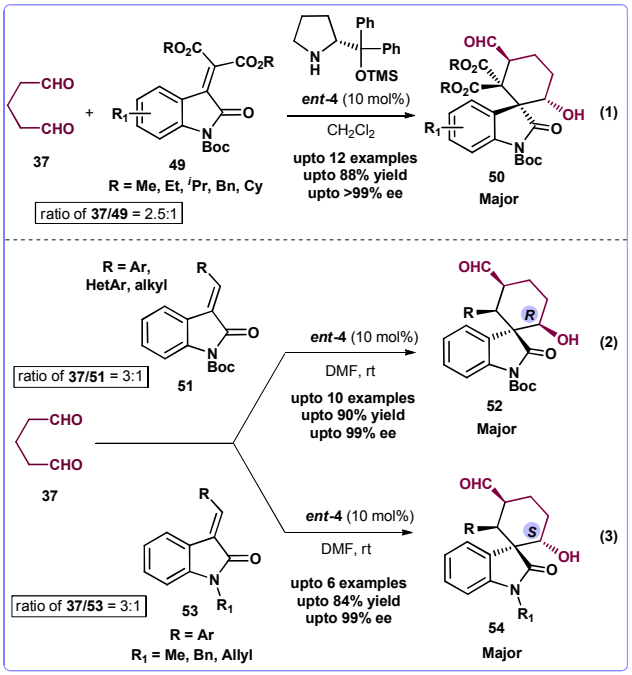
In an another effort, Córdova and co-workers explored the highly enantioselective approach to access functionalized cyclohexanes **42** from linear dials **37** under amine **4** catalyzed domino Michael/aldol procedure (eqn. 4, Scheme 8).[26] These functionalized chiral products **42** well decorated with cyano, formyl, hydroxyl, and ester groups, were generated with high yields and enantioselectivities (up to 98% ee) with various alkylidenemalonates **41** as suitable dipolarophiles. The resulting products contained four contiguous chiral centres including one quaternary centre, could be useful intermediates in synthesis. Theoretical mechanistic studies in this direction further support the suitability of glutaraldehyde **37** or its derivatives for amine catalyzed two component domino reactions with (i) nitroalkenes, or (ii) α,β-unsaturated carbonyl compounds.[27]



Scheme 9: The amine catalyzed Michael-cascade strategies through glutaraldehyde

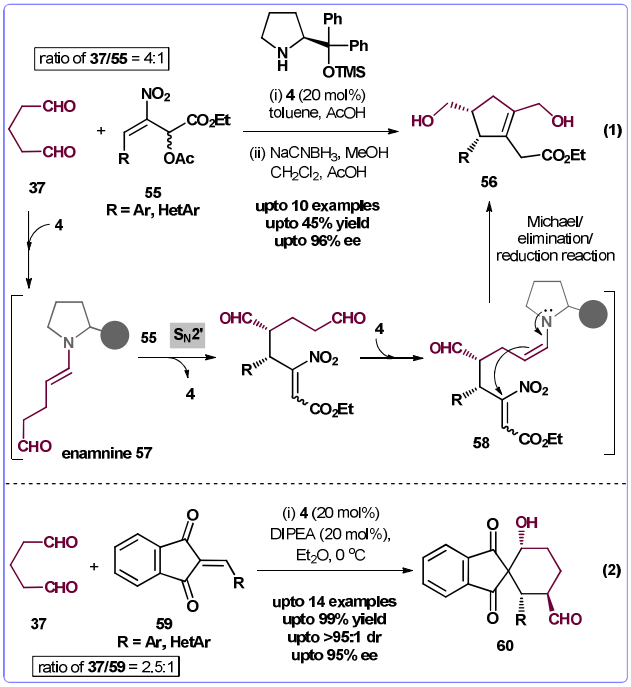
Hong and co-workers have made significant contribution in the development of amine catalyzed asymmetric cascade transformations, where linear dialdehydes attained enormous importance in the construction of complex molecules. The initial application of glutaraldehyde **37** in the quick synthesis of functionalized cyclohexene derivatives **44** as domino strategy was developed (eqn. 1, Scheme 9).[28] The reaction involved amine **4** catalyzed Michael reaction of glutaraldehyde **37** with 3-arylpropenal **43** followed by intramolecular aldol condensation to access **44** in high yields and excellent enantioselectivity (up to 97% ee). Soon after this group established an amine **4** catalyzed domino Michael-acetalization-Henry reaction between easily available glutaraldehyde **37** and *ortho*-hydroxynitrostyrenes **45** to

synthesize complex tetrahydro-6*H*-benzo[*c*]chromen-6-ones **46** in asymmetric fashion (eqn. 2, Scheme 9).[29] Interestingly, this cascade process performed exceptionally well when carried out "on water" and generated four contiguous chiral centers through three bonds forming steps with excellent stereoselectivity (up to 99% ee). Very recently, the same group explored another interesting application of glutaraldehyde **37** in amine **4** catalyzed transformation to 3-oxabicyclo[3.3.1] nonan-2-ones **48** consisting four consecutive stereogenic centres (eqn. 3, Scheme 9).[30] This method involved organocatalytic cascade Michael-Henry acetalization-oxidation reaction of 3-aryl-2-nitroprop-2-enols **47** with **37**, furnished bridged bicyclic systems **48** with high yields and excellent selectivity (up to >99% ee). The quick synthesize of highly functionalized bicyclic systems under benign reaction conditions should be highly appreciated as this can find wide range of synthetic applications.



Scheme 10: Amine catalyzed cascade for spiro-oxindoles using glutaraldehyde

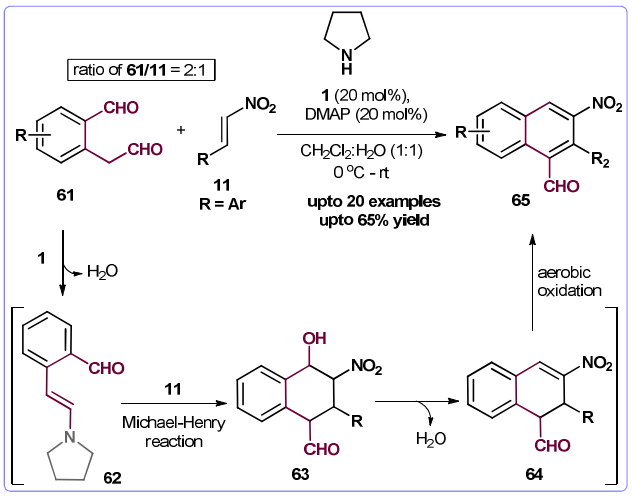
Spiro-oxindole motifs are an attractive three-dimensional structure often considered a privileged scaffold for the discovery of new medicinal compounds as well as found in many natural products.[31] Wang and co-workers exploited the ability of glutaraldehyde **37** in organocatalytic domino Michael/Aldol cyclization using isatin-derived alkenes **49** as Michael acceptors (eqn. 1, Scheme 10).[32] A series of functionalized spirocyclohexane oxindoles **50** decorated with formyl, hydroxy, and ester groups were synthesized in asymmetric fashion using amine *ent*-**4** (10 mol%) catalysis with high yields and excellent selectivity's (up to >99% ee). The present one-pot strategy also worked on the gram scale without affecting either the yield or the selectivity. In a very similar protocol, Ghosh *et al*. described the enantioselective synthesis of spirocyclohexane oxindoles **52** and **54** comprise of multiple stereocenters including a spiro-quaternary centre from the glutaraldehyde **37** in high yields and excellent enantioselectivities (up to 99% ee).[33] Interestingly, *N*-protecting groups on the oxindoles moiety played a critical role on aldol ring closure leading to ultimate stereochemical outcome of the hydroxyl centre. The oxindole **51** contained N-Boc as electron-withdrawing protecting group provided **52** with 6-(*R*)-hydroxy configuration in the presence of amine catalyst *ent*-**4** (eqn. 2, Scheme 10). While, oxindole **53** contained N-alkyl as electron-donating protecting group furnished **54** having 6-(*S*)-hydroxy configuration as major products (eqn. 3, Scheme 10).



Scheme 11: Amine catalyzed synthesis of cyclopentenes and spiro-carbocycles from glutaraldehyde

Chen and co-workers developed an amine catalyzed cascade transformation for the synthesis of functionalized cyclopentenes **56** from glutaraldehyde **37** and racemic nitroallylic acetates **55** (eqn. 1, Scheme 11).[34] In this process kinetic resolution of racemic **55** was accomplished through the S_N2' reaction followed by intramolecular Michael addition-elimination process with **37** in presence of diphenylprolinol silyl ether **4** gave tetrasubstituted-cyclopentenes **56** with satisfactory yields and high enantioselectivity (up to 96%). The less reactive enantiomeric substrate was generally recovered with good to excellent optical purities (up to 99% ee). In mechanism, enamine **57** generated from **37** and **4** gave S_N2' reaction with **55**, while another aldehydic moiety underwent intramolecular Michael addition-elimination through intermediate **58** to give **56** after in situ reduced with $NaBH_4$. Very recently, another interesting application of glutaraldehyde **37** for the synthesis of spirocyclohexane-carbaldehydes **60** using amine catalysis was developed by the same group (eqn. 2, Scheme 11).[35] The amine **4** catalyzed Michael/Aldol domino sequence between glutaraldehyde **37** and 2-arylideneindane-1,3-diones **59** as [4 + 2] annulations provided spirocyclohexane-carbaldehydes **60** with high yield and selectivity's (up to 95% ee). The overall selectivity of the reaction was found to be additive and temperature dependent, while **59** derived from aryl/heteroaryl groups were employed successfully.

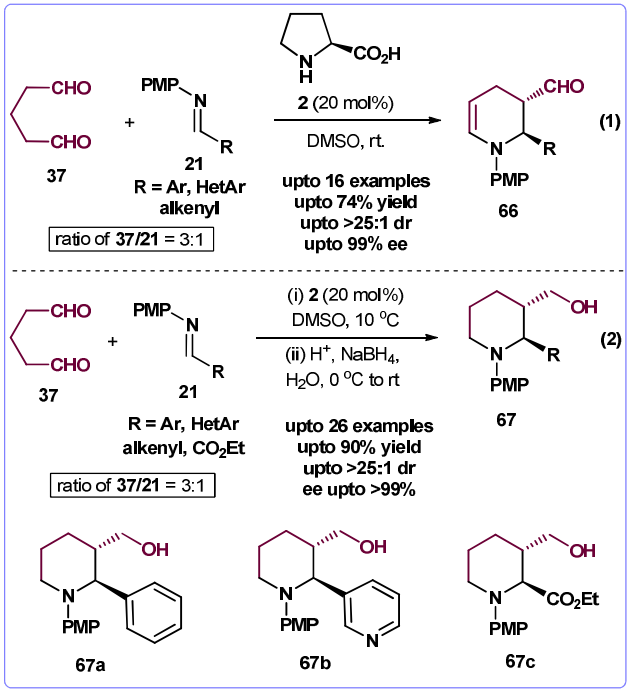
Xu and co-workers described a quick method for the synthesis of polysubstituted naphthalenes **65** from easily accessible linear dialdehyde such as 2-(2-oxoethyl)benzaldehydes **61** and nitroalkenes **11** in presence of pyrrolidine **1** (Scheme 12).[36] This transformation proceed through cascade Michael/Henry reaction of *in situ* generated enamine **62** with **11** gave intermediate **63**, which on further dehydration and oxidative aromatization as one pot four consecutive steps furnished the synthetically important naphthalene derivatives **65** in moderate yields (Scheme 12).



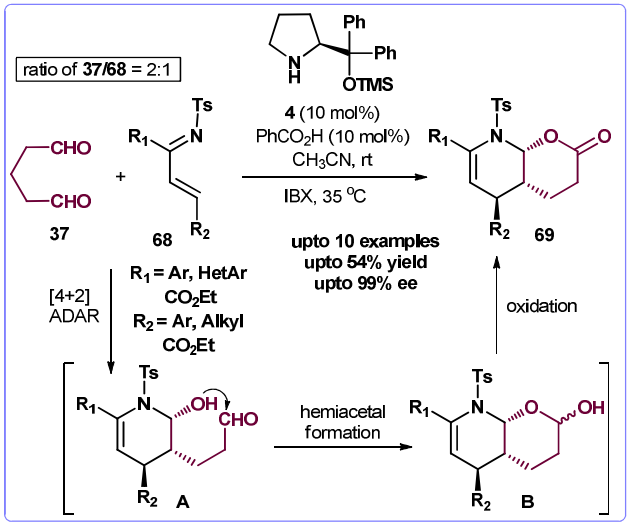
Scheme 12: The organocatalytic transformations of linear dials to access the naphthalene skeleton

Xu and co-workers anticipated the application of dials for the enantioselective synthesis of nitrogen heterocycles such as substituted tetrahdro-pyridines **66** through amine catalysis in high yields and excellent enantioselectivity's (up to 99% ee) (eqn. 1, Scheme 13).[37] This rapid approach involved aldimines **21** derived from aromatic/heteroaromatics/alkenyl aldehydes through proline **2** mediated direct Mannich reaction with glutaraldehyde **37** followed by intramolecular cyclization as one-pot transformation. Recently, Kumar and co-workers documented another interesting application of glutaraldehyde **37** for the asymmetric synthesis of 2,3-substituted piperidines **67** through the [4+2] annulation strategy (eqn. 2, Scheme 13).[38] This method involved the proline **2** catalyzed direct Mannich reaction of *N*-PMP aldimine **21** with readily available dialdehyde **37** followed by reductive cyclization as one-pot operation to synthesize various piperidines **67** with high yields and excellent enantioselectivities (up to >99% ee). This protocol was highly efficient for imines **21** derived from aromatic, heteroaromatics, CO_2Et, and alkenyl aldehydes but failed to give any transformation when electron rich aryl imine and aliphatic imines were employed under standardized conditions. The present one-pot strategy also worked on the gram scale without affecting either the yields or selectivity's.

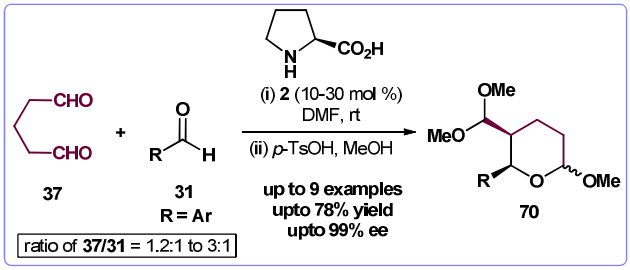
In another cascade transformation for the synthesis of nitrogen heterocycles from linear dialdehydes, Chen *et al*. reported the asymmetric synthesis of δ- and γ-lactones[2,3-*b*]piperidines **69** (Scheme 14).[39] This amine **4** catalyzed transformation involved inverse electron demand aza-Diels-Alder reaction of various *N*-Tos-1-aza-1,3-butadiene **68** with glutaraldehyde **37**, cyclization to hemi-acetal **B** and followed by IBX-oxidation furnished the complex nitrogen heterocyclic system **69** with high selectivity (up to 99% ee).



Scheme 13: The organocatalytic cascade strategy for tetrahydro-pyridine (1) and piperidine using glutaraldehyde (2)



Scheme 14: The organocatalytic cascade strategy involving glutaraldehyde in aza-Diels-Alder reaction



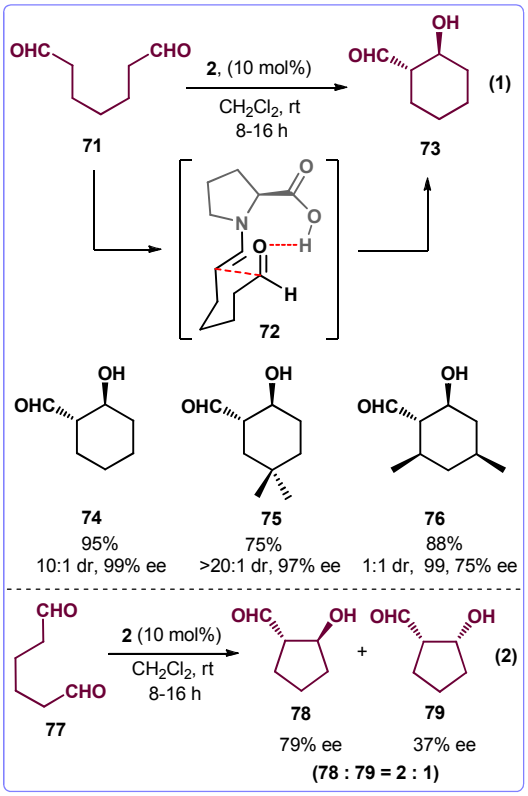
Scheme 15: Amine catalyzed synthesis of tetrahydropyran from glutaraldehyde

Hayashi and co-workers also developed amine catalyzed asymmetric synthesis of tetrahydropyrans **70** through domino transformations, in which glutaraldehyde **37** was considered as one of the important synthetic counterparts (Scheme 15).[40] This process involved proline **2** mediated direct aldol reaction of **37** with aromatic aldehydes **31**, followed by acid catalyzed acetalization reaction provided *cis*-tetrahydropyrans **70** with high selectivity's (up to 99% ee).

3. Intramolecular transformations

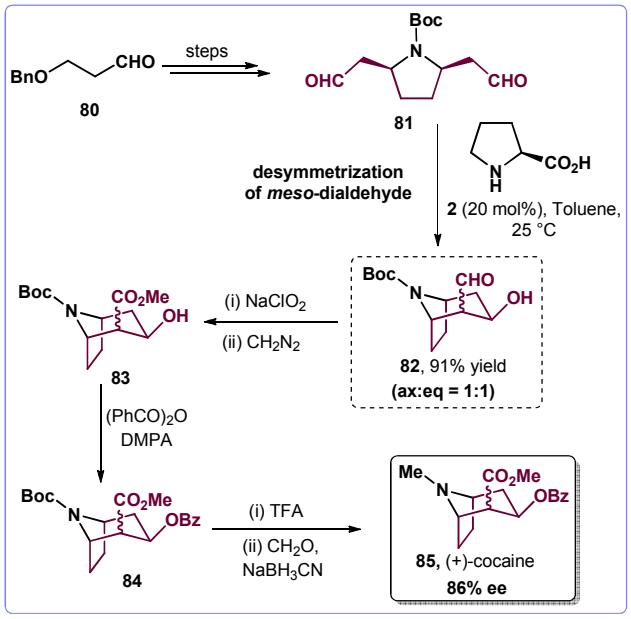
3.1. Miscellaneous examples

Dialdehydes not only act as suitable bifunctionalized substrates with various X=Y (C=C, C=N, C=O) under amine catalysis, but also reacts internally depending upon the length of the linear chain. Therefore, the intramolecular transformations are quite feasible when higher homologues linear dialdehydes having proper functionality are exposed to amine catalysis. These linear dialdehydes can undergo several intramolecular transformations such as Aldolization, Michael addtion, Baylis-Hillman reaction and several other transformations depends on the structural functionality of the parent compound. In this direction, the very first highly enantioselective intramolecular *enolexo*-aldolization of dialdehyde was developed by List and co-workers using proline catalysis in 2003.[41] Proline **2** (10 mol%) catalyzed intramolecular aldol reaction of different dialdehydic systems **71** through transition state **72** furnished chiral anti-cyclohexane carboxaldehydes **73** with good yields and high enantioselectivities (up to 99% ee), which are potential intermediates in the organic synthesis (eqn. 1, Scheme 16). The substrate scope of this reaction is not only limited to dialdehydes but also extended to ketoaldehydes. It was also mentioned that the corresponding 5-*enolexo*-aldolizations are less selective as compare to 6-*enolexo* variant. For example, proline catalyzed cyclization of hexanedial **77** provides the aldol products **78**/**79** with comparatively lower selectivities (eqn. 2, Scheme 16).

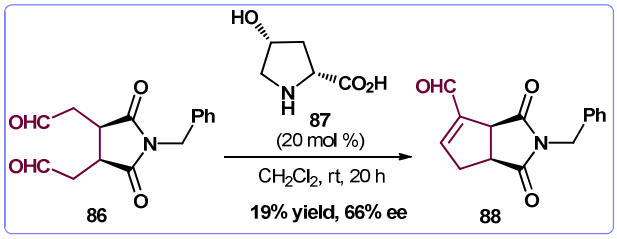


Scheme 16: Organocatalytic asymmetric *enolexo*-aldolization involving linear dialdehydes

The *enolexo*-aldolization process is particularly suitable for the desymmetrization of *meso*-compounds.[42] Therefore, Pearson and Mans reported an efficient and rapid access to (+)-cocaine **85** using amine catalyzed asymmetric desymmetrization of *meso*-dialdehyde **81** (Scheme 17).[43] The tropane skeleton **82** was established in 91% yield as 1:1 mixture of epimers by the reaction of dialdehyde **81** with proline **2** (20 mol%) through *enolexo*-aldolization, which was quickly converted to (+)-cocaine in additional five steps with over all high enantioselectivity (86% ee). This represents the first use of the intramolecular proline-catalyzed aldol reaction to generate aza-bridged bicyclic skeleton and additionally synthesis of various enantioenriched cocaine analogues could be achieved.



Scheme 17: Organocatalytic access to (+)-cocaine through intramolecular *enolexo*-aldolization of *meso*-dialdehyde

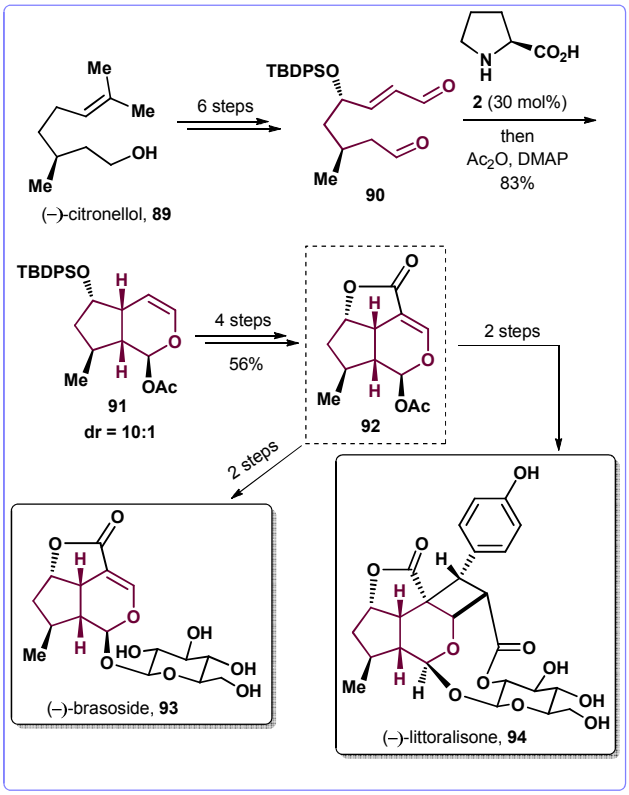


Scheme 18: Direct asymmetric intramolecular aldol condensation of 1,6-dialdehydes

In a very similar manner, Afonso *et al*. reported the synthesis of cyclopentene carboxaldehyde **88** through the direct asymmetric intramolecular aldol condensation reaction of *meso*-3,4-disubstituted 1,6-dialdehyde **86** using 4-hydroxyproline **87** (20 mol%).[44] The existence of hydroxyl group in the catalyst backbone showed better stereo-control (66% ee) among a number

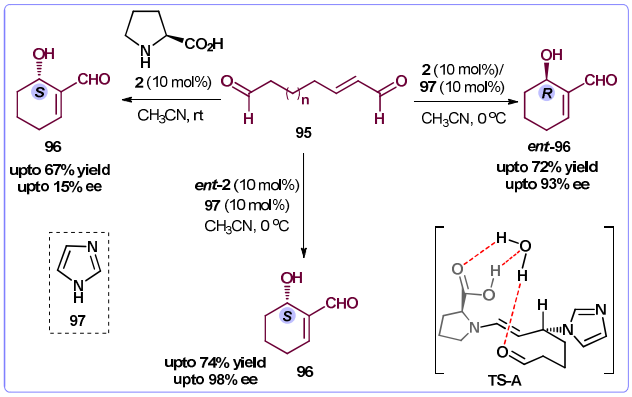
of other similar catalysts screened for this transformation (Scheme 18).

Recently, MacMillan's and Mangion's developed a very ingenious synthetic strategy for the synthesis of polyketide natural products such as brasoside and littoralisone, which displayed the profound use and potential of linear dialdehyde involving amine catalysis (Scheme 19).[45] Initially, they prepare dialdehyde **90** within six steps included a one-pot procedure consist of organocatalytic α-aminoxylation, Horner–Wadsworth–Emmons reaction and N–O bond methanolysis from (–)-citronellol **89**. (*S*)-proline **2** catalyzed intramolecular Michael reaction of linear dialdehyde **90** in DMSO yielded kinetic controlled cyclopentane product bearing the two aldehyde side chains in a *cis*-orientation, which on *in situ* acetylation afforded **91** in 83% yield. Compound **91** was elaborated into common iridolactone core **92** by a series of standard transformations. The synthesis of (–)-brasoside **93** and (–)-littoralisone **94**, was then completed in just two steps each from iridolactone **92** and with overall 13-steps from **89**.

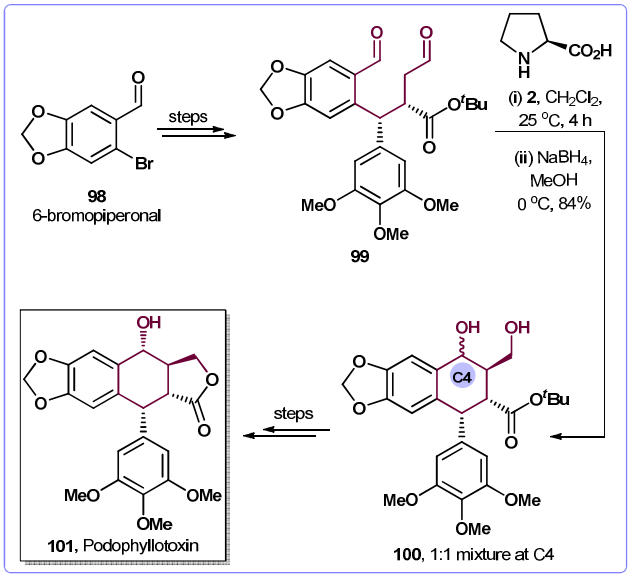


Scheme 19: Synthesis of (–)-brasoside and (–)-littoralisone through linear unsaturated dialdehyde

Hong and co-workers reported an efficient application of linear dialdehyde such as-hept-2-enedial **95** in proline **2** mediated enantioselective intramolecular Baylis-Hillman reaction to access 6-hydroxy-cyclohex-1-enecarbaldehydes **96**/*ent*-**96** with high selectivity's (Scheme 20).[46] Further, addition of imidazole **97** (10 mol%) to the mixture facilitated an inversion of selectivity. The reversal of selectivity in the presence of imidazole was explained through the formation of (*S*)-imidazolium in preferable transition state (**TS-A**) *via* intramolecular H-bonding which would lead to the formation of (*R*)-*ent*-**96**. These experimental results and



Scheme 20. The organocatalytic intramolecular MBH reaction involving linear α-β unsaturated dial



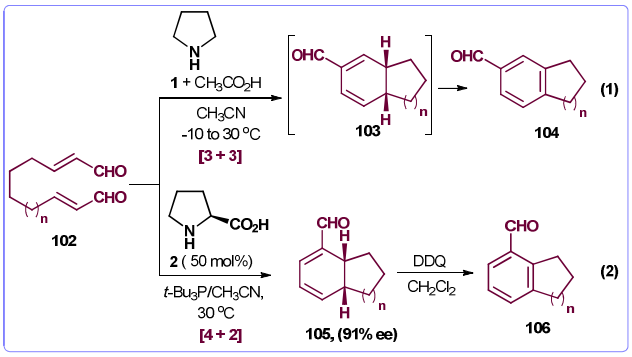
Scheme 21: Organocatalytic synthesis of podophyllotoxin through intramolecular aldolization of dialdehyde

reversal of selectivity in presence of imidazole was further supported by the computational study.[47]

Zhang and co-workers utilized linear dialdehyde in amine catalyzed intramolecular aldol reaction for the synthesis of natural product podophyllotoxin **101**, an important member of podophyllum family and potent inhibitor of microtubule assembly (Scheme 21).[48] The treatment of dialdehyde compound **97**, prepared in few steps from **98**, with proline **2** in dichloromethane followed by reduction gave core structure of podophyllotoxin **100** with 84% yield as 1:1 mixture of diastereoisomers at C4 position. This *enolexo*-aldol product **100** was then quickly transformed in to podophyllotoxin **101** following few synthetic steps.

Highly selective amine catalyzed intramolecular [4 + 2] and [3 + 3] cycloadditions of α, β-unsaturated aldehydes **102** to synthesize polysubstituted aromatic aldehydes **104**/**106** along with co-catalyst or additive effects were disclosed by Hong and co-workers in 2007.[49] Initially, the [3 + 3] cycloaddition product **104** obtained exclusively, when pyrrolidine **1** was employed as catalyst in presence of AcOH at low temperature followed by oxidative aromatization with DDQ. The intermediate adduct **103**

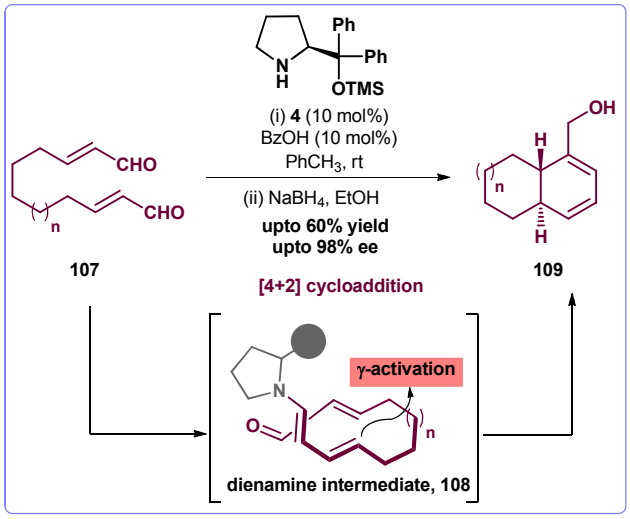
was found to be unstable under the reaction conditions (eqn. 1, Scheme 22), while intramolecular [4 + 2] cycloaddition product **106** obtained when the reaction of unsaturated dialdehydes **102** was carried out with proline **2**, followed by oxidation with DDQ. Interestingly, [4 + 2] cycloaddition adduct diene **105** was obtained in high selectivity (91% ee), when *t*-Bu_3P was used as additive along with proline **2** as amine catalyst (eqn. 2, Scheme 22).



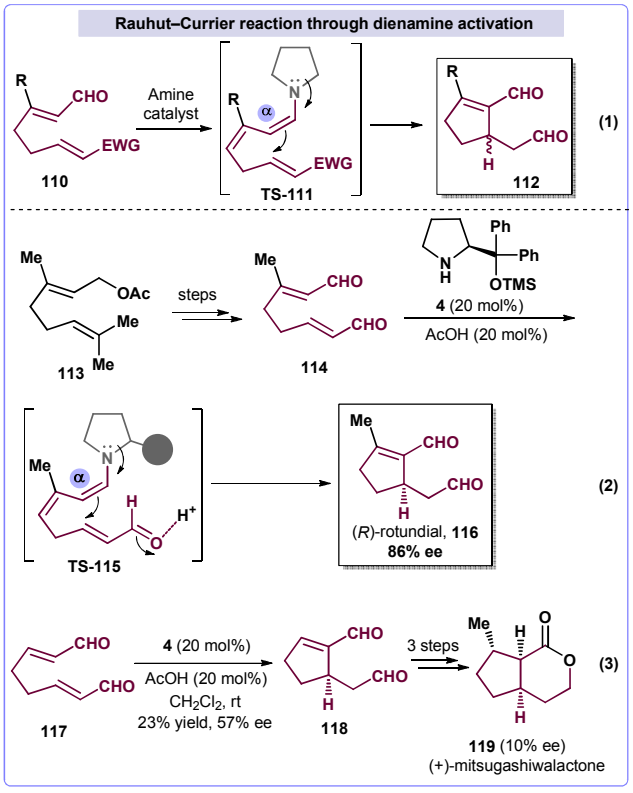
Scheme 22: Organocatalytic [3+3] and [4+2] cycloaddition of dials

In recent years, Christmann's group have contributed in the field of dienamine catalysis for the enantioselective construction of polycyclic compounds as a domino strategy from α, β-unsaturated dialdehydes. Initially, they reported the diversity oriented synthesis of novel mono- and bicyclic scaffolds by γ-activation of tethered unsaturated dicarbonyl **107** precursors. In this context, a series of products **109** were obtained in good yield and with excellent control of stereochemistry (up to 98% ee), after a subsequent $NaBH_4$ reduction of intermediate cycloadducts (Scheme 23).[50] This transformation was expected to proceed through the in situ formation of electron-rich dienamine intermediate **108** through the combination of dialdehydes **107** and amine **4** catalyst. Importantly, transition state intermediate **108** adopts a conformation that minimizes repulsive interactions with the bulky aryl substituents of catalyst and exposes the unshielded face of the π-system to an endo-approach of the enal, justified for high selectivity. The computational study in this direction further supported the application of dienamine catalysis to synthesize polycyclic scaffolds from unsaturated dialdehydes.[51]

Further potential application of the dienamine intermediate as a d2-synthon in a mechanistically distinct Rauhut–Currier-type reaction of unsaturated dialdehydes was developed by same group (eqn. 1, Scheme 24). The very first application of this methodology was shown for the synthesis of the mosquito repellent (*R*)-rotundial **116** (eqn. 2, Scheme 25).[52] The dialdehyde **114**, which was quickly prepared from the commercially available geranyl acetate **113**, underwent amine **4** catalyzed intramolecular Michael addition through electron-rich dienamine intermediate **TS-115** afforded natural product (*R*)-rotundial **116** with high enantioselectivity (86% ee). In another example amine **4** catalyzed Rauhut–Currier-type reaction of unsaturated dialdehyde **117**, furnished cyclized dialdehyde **118** with moderated selectivity (57% ee). The resulting dialdehyde **118** was rapidly converted to mitsugashiwalactone **119** with additional three synthetic steps (eqn. 3, Scheme 24). However, final product was obtained with low enantiomeric excess (10%).[53]



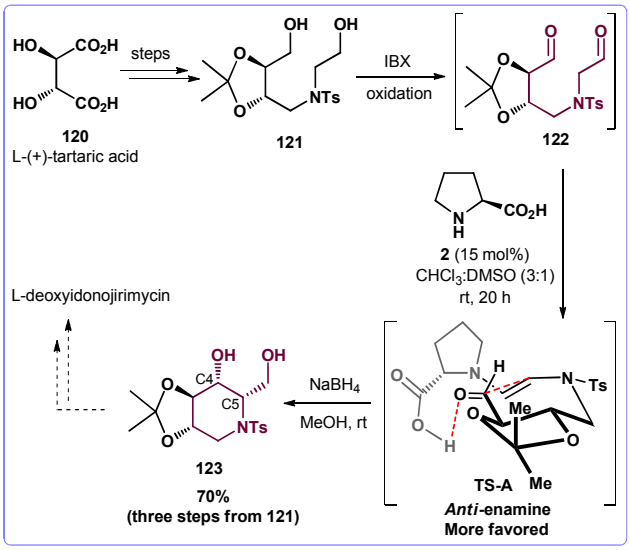
Scheme 23: Organocatalytic transformations of linear dials to access polycyclic compounds



Scheme 24: Rouhut-Currier reaction of unsaturated dialdehydes *via* dienamine activation

Kumar *et al.* demonstrated the application of linear dialdehyde in amine catalyzed intramolecular aldolization reaction to synthesize poly-hydroxylated imino-sugar skeleton (Scheme 25).[54] The key point of this 6-*enolexo* approach was to discriminate between two aldehyde moieties present in **122** by making this transformation diastereoselective. Surprisingly, high level of *syn*-selectivity (dr >10:1) was obtained in this intramolecular aldolization reaction, in contrast to the *trans*-selective 6-*enolexo*-aldolization observed by List group earlier.[42] This stereochemical outcome was explained through the *Ri*-facial attack on acceptor aldehyde by energetically more favored *anti*-

enamine *via* TS-**A**, in which equatorial positions were detained by acetonide moiety. Poly-hydroxyl piperidine unit **123** with *syn*-selectivity was obtained from linear diol **121** in two pot, three steps with overall 70% yield. This organocatalytic diastereoselective approach for the C–C bond formation between C4 and C5 provids a quick synthesis of imino-sugar skeletons.



Scheme 25: Amino-catalyzed intramolecular aldolization of dialdehyde for imino-sugar synthesis

Conclusions and outlook

In the present review article, we highlighted the recent advances in the direction of linear dialdehydes as promising substrates in amine catalyzed domino transformations. The suitability of dialdehydes for amine catalyzed domino transformation mainly rely on the easy availability or access of the compounds as well as the activation of aldehydic moiety through well established enamine or iminium-ion activation. This article is discussed in two parts; (i) *amine catalyzed reactions of succinaldehyde, glutaraldehyde or related dialdehydes with various X=Y (C=C, C=N, C=O)*, (ii) *miscellaneous examples, where higher homologues dialdehydes either saturated or unsaturated reacts intramolecular under amine catalysis*. It is obvious from the literature and one can easily imagine that these linear dialdehydes acts as donor-acceptor precursors with various dipolarophiles under amine catalysis *i.e.*, one of the aldehydic moiety form enamine (donor), while another moiety perform as acceptor. These aminocatalytic transformations with incomparable advantages further established the feasibility of dialdehydic compounds for the rapid and straightforward access to various cyclic and polycyclic skeletons with very high enantio- and diastereoselectivity. Additionally, this review article will make synthetic chemists familiar to the synthetic potential of dialdehydes and encourage them to design new synthetic methods for carbocyclic and heterocyclic ring systems with varied sizes. We also hope that in the coming time, linear dialdehydes will continue to serve as artistic substrates in the steady expansion of amine catalysis.

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