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Lessons from Nature: Biomimetic Organocatalytic Carbon−Carbon Bond Formations[§]

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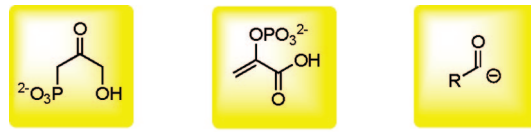

Nature utilizes simple C_2 and C_3 building blocks, such as dihydroxyacetone phosphate (DHAP), phosphoenolpyruvate (PEP), and the "active aldehyde" in various enzyme-catalyzed carbon−carbon bond formations to efficiently build up complex organic molecules. In this Perspective, we describe the transition from using enantiopure chemical synthetic equivalents of these building blocks, employing our SAMP/RAMP hydrazone methodology and metalated chiral α-amino nitriles, to the asymmetric organocatalytic versions developed in our laboratory. Following this biomimetic strategy, the DHAP equivalent 2,2-dimethyl-1,3-dioxan-5-one (dioxanone) has been used in the proline-catalyzed synthesis of carbohydrates, aminosugars, carbasugars, polyoxamic acid, and various sphingosines. Proline-catalyzed aldol reactions involving a PEP-like equivalent have also allowed for the asymmetric synthesis of ulosonic acid precursors. By mimicking the "active aldehyde" nucleophilic acylations in Nature catalyzed by the thiamine-dependent enzyme, transketolase, enantioselective *N*-heterocyclic carbene-catalyzed benzoin and Stetter reactions have been developed. Finally, based on Nature's use of domino reactions to convert simple building blocks into complex and highly functionalized molecules, we report on our development of biomimetic asymmetric multicomponent domino reactions which couple enamine and iminium catalysis.

1. Introduction

Since the beginning of organic synthesis, chemists have dreamed of preparing complex molecules in an elegance and efficiency similar to that of Nature. Examination of the chemical building blocks, modes of substrate activation, and biosynthetic pathways in Nature provides insight for achieving similar transformations by chemical synthesis. In doing so, chemists have designed many biomimetic natural product syntheses and biomimetic catalytic processes.[1,2] Over the past 20 years, our research group has been interested in the synthesis and application of chiral C_3 building blocks as chemical equivalents to Nature's dihydroxyacetone phosphate (DHAP, **1**) and phosphoenolpyruvate (PEP, **2**) in asymmetric synthesis (Figure 1). We have also been engaged in the development of biomimetic catalytic processes such as carbene-catalyzed benzoin-type reactions that involve "active aldehyde"-type intermediates **3**, shown as an acyl anion synthon, and multicomponent domino reactions. Combined, these biomimetic carbon−carbon bond-forming approaches have allowed for the synthesis of many

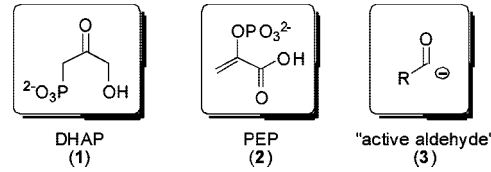

FIGURE 1. Some of Nature's simple chemical building blocks.

[§] Dedicated to Professor Elias J. Corey on the occasion of his 80th birthday.

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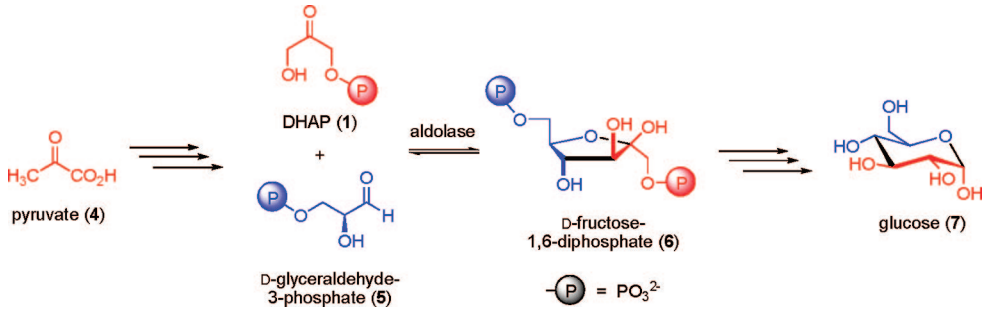


FIGURE 2. Gluconeogenesis via an enzyme-catalyzed aldol reaction of DHAP.

natural and non-natural products in a highly chemo-, regio-, and stereoselective manner. This Perspective details our efforts in these areas with emphasis on our inspiration from Nature.

2. Dihydroxyacetone Equivalents in Asymmetric Synthesis

Dihydroxyacetone phosphate (DHAP, **1**) is an intermediate in many biochemical pathways including the Calvin cycle, glycolysis, and gluconeogenesis. In the latter, DHAP (**1**) is an intermediate in the conversion of pyruvate (**4**) into glucose (**7**) and participates in an enzyme-catalyzed aldol reaction with D-glyceraldehyde-3-phosphate (**5**) to form fructose 1,6-diphosphate (**6**) (Figure 2).[3] To mimic the biosynthesis of glucose and other valuable compounds possessing similar structural motifs, we employed chiral hydrazones **8** derived from 2,2-dimethyl-1,3-dioxan-5-one (dioxanone) as a chiral synthetic equivalent to dihydroxyacetone (DHA). Dioxanone occupies a special position in the realm of DHA equivalents: it is easily prepared in multigram quantities, soluble in organic solvents, stable to basic and weakly acidic conditions, and conformationally constrained.[4] Furthermore, its 1,3-diol motif can be easily revealed in an acid-catalyzed acetal hydrolysis reaction.

Beginning in the late 1980s, dioxanone was first used in stoichiometric asymmetric synthesis employing the SAMP/RAMP hydrazone methodology.[5] Chiral hydrazones **8**, which can be considered as 3-carbon d^2 synthons **9**, were metalated to form their corresponding *aza*-enolates and a wide variety of electrophilic α-substitutions were performed in a highly diastereoselective fashion.[6] An analogous approach involved the use silyldioxanone **10** derived themselves from chiral hydrazones **8**.[7] The bulky α-silyl group acted as a "traceless" directing group and allowed high levels of asymmetric induction to be obtained in cases where the SAMP/RAMP methodology was less effective. Both methods were extensively studied and applied to the synthesis of many natural products and pharmaceutically relevant molecules (Figure 3).

2.1. Organocatalytic Asymmetric Synthesis of Carbohydrates. Having demonstrated that dioxanone was a useful C_3 building block in stoichiometric asymmetric synthesis, we were inspired by the biosynthesis of carbohydrates, which involves a catalytic aldol reaction, and the emergence of the field of organocatalysis. The seminal studies by List, Lerner, and Barbas III on the proline-catalyzed intermolecular aldol reaction and its use by Northrup and MacMillan in their elegant $C_2 + C_2 + C_2$ total synthesis of the hexoses suggested that dioxanone could function as a useful building block in organocatalysis.[8] The biomimetic $C_3 + C_3$ strategy involving dioxanone (**12**) and a 3-carbon aldehyde **13** would represent a highly concise de novo synthesis of ketohexoses **11** (Figure 4). Furthermore, access to homologous carbohydrates and various derivatives thereof would

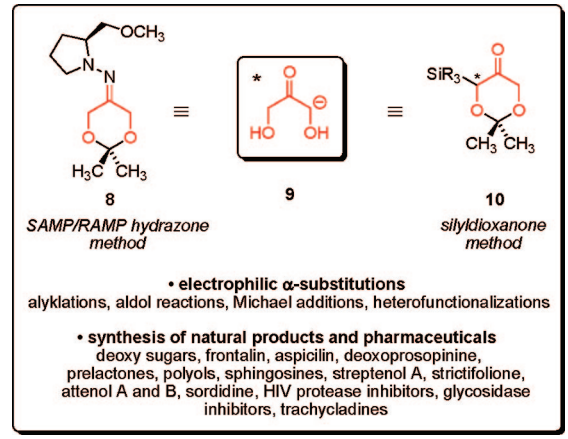


FIGURE 3. Stoichiometric asymmetric synthesis using SAMP/RAMP- and silyl-derived dioxanones as chiral DHA equivalents.

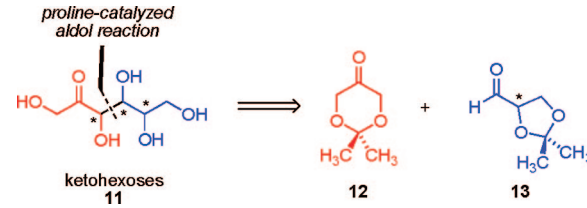


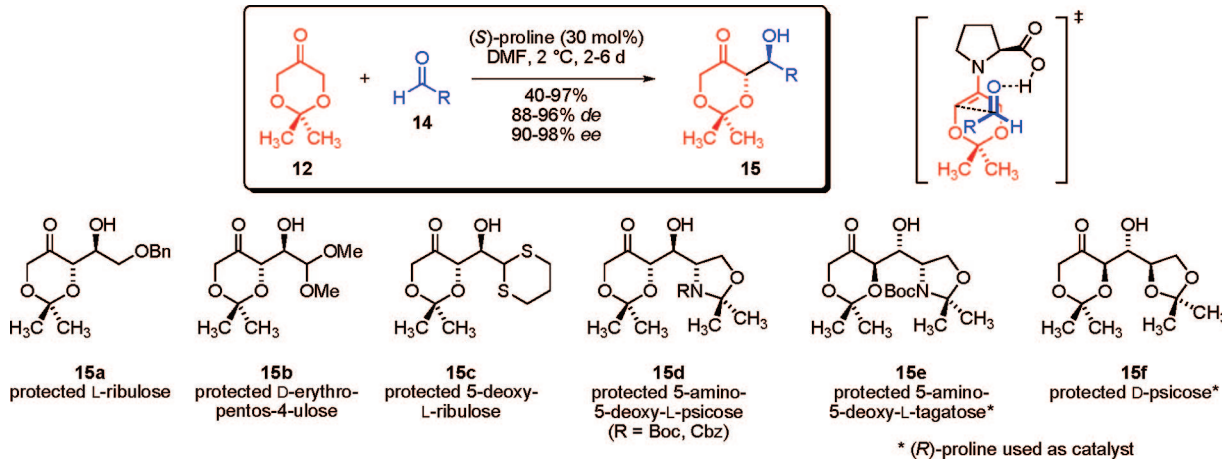
FIGURE 4. Retrosynthetic analysis of proline-catalyzed aldol synthesis of ketohexoses from dioxanone: a $C_3 + C_3$ approach.

be possible by employing aldehydes of various chain lengths (C_n) and heteroatom substitution patterns.

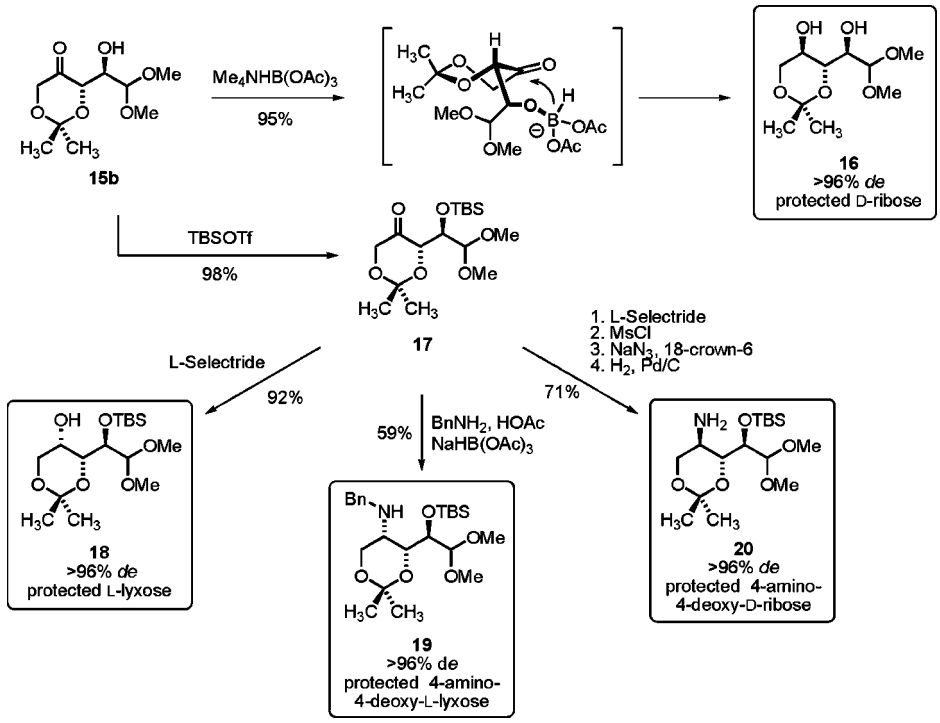
In the first study, we found that (*S*)-proline could catalyze the aldol reaction of dioxanone (**12**) and a variety of α-branched C_2- and C_3-aldehydes in moderate to excellent yields (40−97%) and high diastereo- and enantioselectivities (88−96% de, 90−98% ee, Scheme 1).[9] In doing so, synthetically valuable orthogonally protected pentoses and ketoses **15** could be prepared in one synthetic step. By varying the configuration of the catalyst and chiral aldehydes, further structural variation of the carbohydrate products was possible. Notably, unbranched aliphatic aldehydes and aromatic aldehydes were also tolerated in the reaction, albeit less efficiently (e.g., for *o*-chlorobenzaldehyde: 73% yield, ~80% de, 86% ee (*anti*), 70% ee (*syn*)). The parent sugar D-psicose could be readily prepared by deprotecting the doubly acetonide-protected D-psicose **15f** in an acid-catalyzed hydrolysis reaction. In accord with previous mechanistic proposals for proline-catalyzed aldol reactions, the reaction was *anti*-selective.[10]

In analogy to the "inverted" strategy of Whitesides and coworkers, stereoselective reduction of the ketone function of **15b** provided a direct entry to selectively protected aldopentoses,

SCHEME 1. Carbohydrate Synthesis: Proline-Catalyzed Aldol Reaction of Dioxanone and Various C_2- and C_3-Aldehydes



SCHEME 2. Elaboration of $C_3 + C_2$ Aldol Product into Protected D- and L-Aldopentoses and -Aminodeoxyaldopentoses



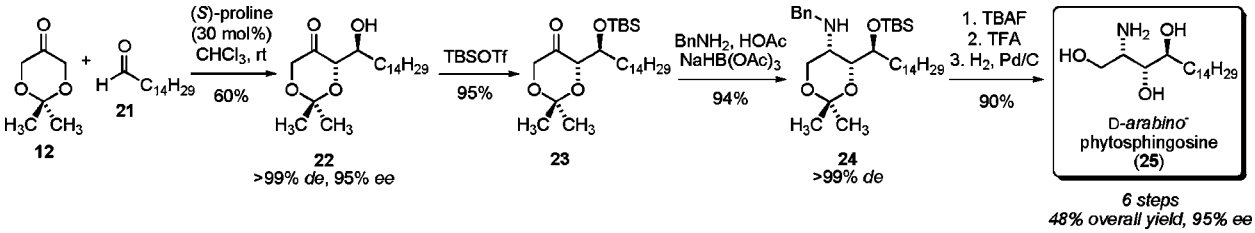
which greatly expanded the potential of this new protocol (Scheme 2).[11]

Thus, tetramethylammonium triacetoxyborohydride-mediated reduction gave *syn*-diol **16** that constitutes a protected D-ribose (95% yield, >96% de). To achieve an *anti*-selective reduction or reductive amination, the free hydroxyl group of aldol adduct **15b** was first silylated to give TBS-ether **17**. Treatment of TBS-ether **17** with L-Selectride or benzylamine in the presence of a reducing agent gave protected L-lyxose **18** and protected 4-amino-4-deoxy-L-lyxose **19**, respectively, both in excellent diastereoselectivity (>96% de). Protected 4-amino-4-deoxy-D-ribose **20** could also be synthesized efficiently in a reduction/azidation/reduction sequence.

2.2. Organocatalytic Asymmetric Synthesis of Sphingoids. Sphingoids are long-chain aliphatic amino alcohols that form the backbone of all sphingolipids (Figure 5). Glycosphingolipids, the major class of sphingolipids, are important structural constituents of the cell membrane and play a vital role in cellular signaling.[12] In addition, the oligosaccharide chains of glycosphingolipids serve as receptors for bacterial protein toxins and binding proteins of viruses. Phytosphingosines, one of the major subclasses of sphingoids, have been isolated and identified either separately or as parts of sphingolipids found in, for example, plants,[13] marine organisms,[14] and mammalian tissues.[15] Due to the physiological importance of these compounds, many syntheses of sphingoids and sphingolipids have been reported; however, most involve lengthy routes that rely on extensive protecting group strategies.[16]

In the past, our group established stoichiometric asymmetric approaches to the synthesis of sphingosines and sphinganines.[17] Recently, based on the proline-catalyzed aldol reaction of dioxanone developed in our laboratory, we devised a direct and flexible organocatalytic approach to two sphingoids; namely, D-*arabino*-phytosphingosine (**25**) and L-*ribo*-phytosphingosine (**27**).[18] Under optimized conditions, the proline-catalyzed aldol reaction of dioxanone (**12**) and pentadecanal (**21**) was found to proceed in good yield (60%) and excellent diastereo- and enantioselectivity (>99% de, 95% ee, Scheme 3). This proce-

SCHEME 3. Organocatalytic Asymmetric Synthesis of D-*arabino*-Phytosphingosine



dure allowed the preparation of gram quantities of acetonide-protected ketotriol **22**, which contained all of the required carbon atoms of the target phytosphingosines.

In order to establish the *anti*-1,3-amino alcohol configuration within D-*arabino*-phytosphingosine (**25**), the alcohol moiety of aldol product **22** was protected as a TBS-ether. Reductive amination of TBS-ether **23** proceeded readily and in excellent diastereoselectivity to afford the doubly protected 1,3-*anti*-amino alcohol **24** (>99% de). Of note, when a similar reductive amination was attempted on the aldol product **22**, the reaction was not diastereoselective (~1:1 *anti*/*syn*). In order to complete the synthesis of sphingosine **25**, a deprotection sequence was carried out. Thus, desilylation, hydrolysis of the acetonide and hydrogenolysis of the benzyl group afforded the target compound in six overall steps and excellent overall yield (48%).

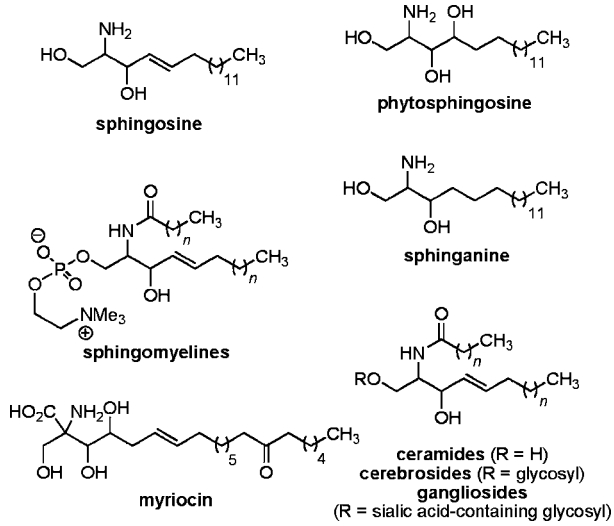
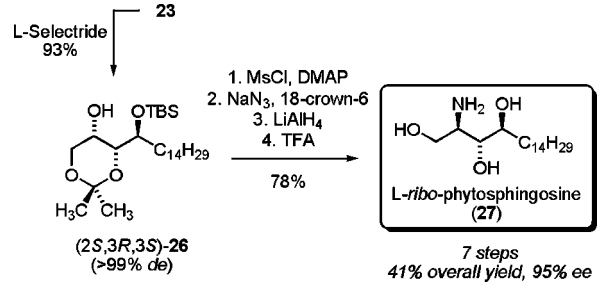


FIGURE 5. Sphingoids and related structures.

The total synthesis of L-*ribo*-phytosphingosine (**27**) could be achieved in an analogous and straightforward manner starting from the common intermediate, TBS-ether **23**. Here, reduction of the ketone moiety with L-Selectride afforded the *anti*-1,3-diol (2*S*,3*R*,3*S*)-**26** in excellent diastereoselectivity (>99% de) (Scheme 4). Subsequent azidation, reduction, and acetonide hydrolysis allowed the synthesis of L-*ribo*-phytosphingosine (**27**) to be completed in a total of seven steps and excellent overall yield (41%).

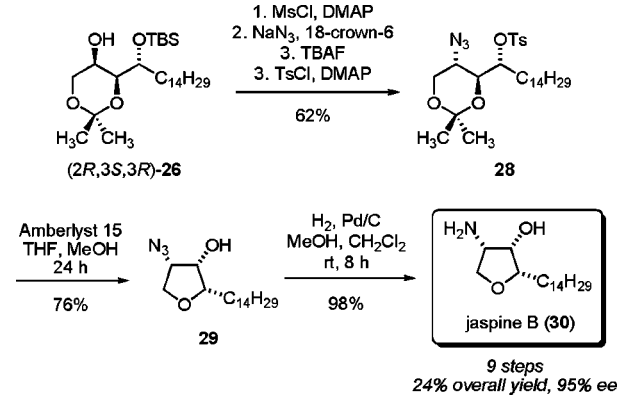
The total synthesis of jaspine B (**30**), a naturally occurring cyclic anhydrophytosphingosine derivative, was recently accomplished.[19] It involved the same key organocatalytic aldol reaction of dioxanone (**12**) and pentadecanal (**21**) used in our phytosphingosine synthesis, here, using the enantiomeric (*R*)-proline. With TBS-ether (2*R*,3*S*,3*R*)-**26** in hand, an azidation/tosylation sequence was performed to obtain intermediate **28** (Scheme 5). Treatment of tosylate **28** with an acidic resin

SCHEME 4. Organocatalytic Asymmetric Synthesis of L-*ribo*-Phytosphingosine via TBS-Ether 23 as a Common Intermediate



installed the tetrahydrofuran ring present in jaspine B. Mechanistically, the one-pot acid-catalyzed formation of tetrahydrofuran **29** likely involves an acid-catalyzed acetal solvolysis reaction within tosylate **28** to form a transient diol intermediate, which undergoes a subsequent intramolecular nucleophilic displacement reaction setting the appropriate relative and absolute configuration. To complete the synthesis, the azide group of the tetrahydrofuran **29** was subjected to a catalytic hydrogenation reaction, which afforded jaspine B (**30**) in a total of nine steps and good overall yield (24%).

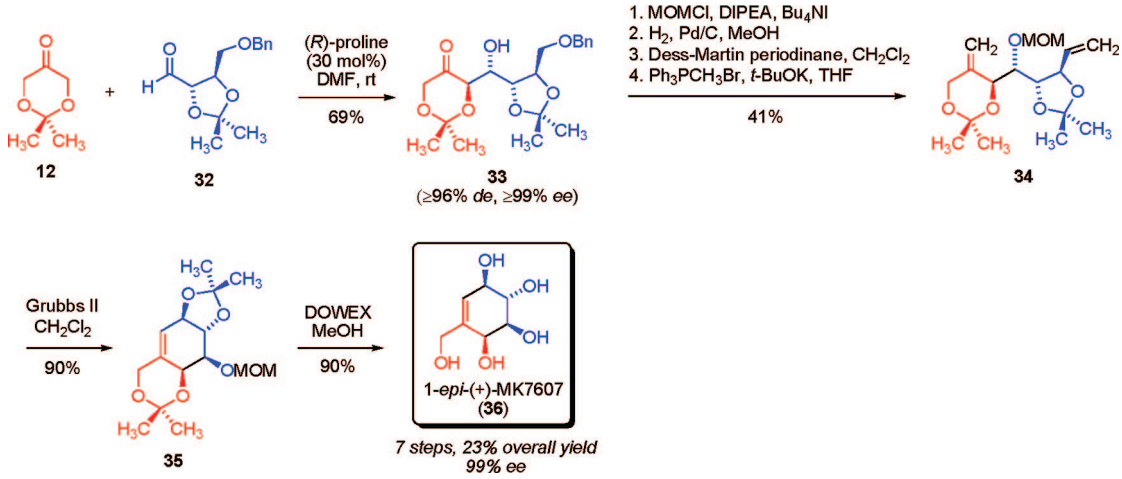
SCHEME 5. Organocatalytic Asymmetric Synthesis of Jaspine B



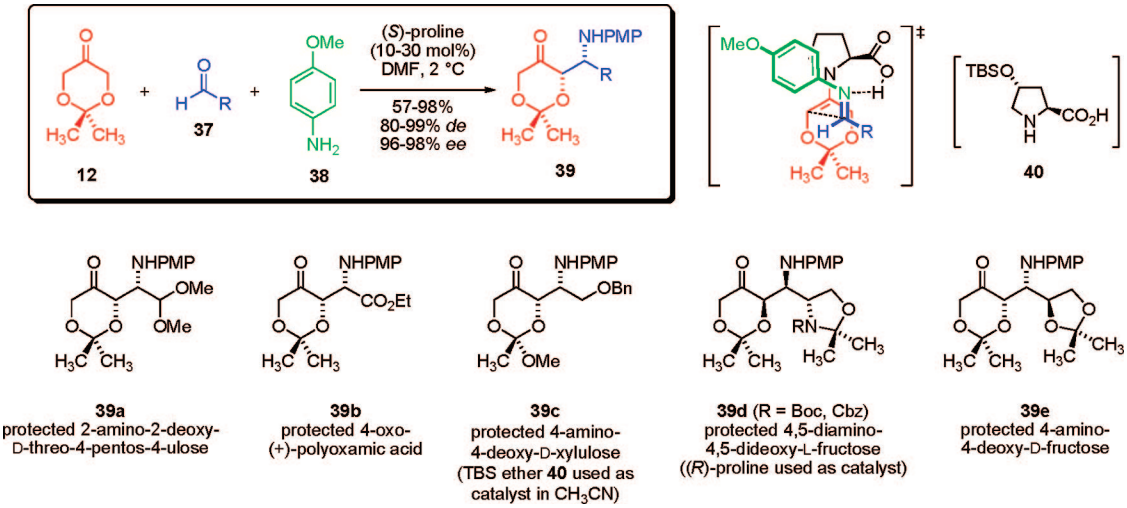
2.3. Organocatalytic Asymmetric Synthesis of Carbasugars. Carbocylic analogues of carbohydrates, namely carbasugars, lack the characteristic acetal moiety of the furanose/pyranose form of a carbohydrate preventing facile hydrolysis of the ring or pseudoglycosidic bonds.[20] As single components or constituents of more complex molecules, carbasugars possess a range of biological activities acting, for example, as glycosidase inhibitors, antibiotics, antivirals, or plant growing inhibitors. Many naturally occurring and synthetic carbasugars are known (e.g., carbagalactose,[21] bicyclo[4.1.0]heptylamine **31**,[22] mannostatin A,[23] neplanocine A,[24] and (+)-MK7607[25]) (Figure 6).

(+)-Streptol (also known as valienol) and (+)-MK7607 represent two naturally occurring diastereomeric cyclohexene-

SCHEME 6. Organocatalytic Asymmetric Synthesis of the Carbasugar 1-*epi*-(+)-MK7607



SCHEME 7. Direct Amino Sugar Synthesis: Proline-Catalyzed Three-Component Mannich Reaction of Dioxanone; *p*-Anisidine and Various C_2- and C_3-Aldehydes



based carbasugars of molecular formula $C_7H_{12}O_5$. (+)-Streptol is a plant-growth inhibitor, and its C-4 epimer, (+)-MK7607, has been demonstrated to have herbicidal activity. The C-1 epimer of streptol, 1-*epi*-MK7607, has been previously prepared in racemic form and shown to have a high affinity to the galactose-recognizing lectin ML 1.[26]

We developed the first asymmetric synthesis of 1-*epi*-(+)-MK7607 based on our proline-catalyzed aldol reaction of

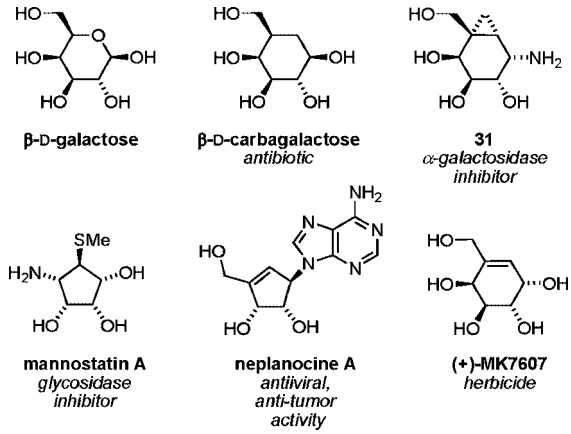
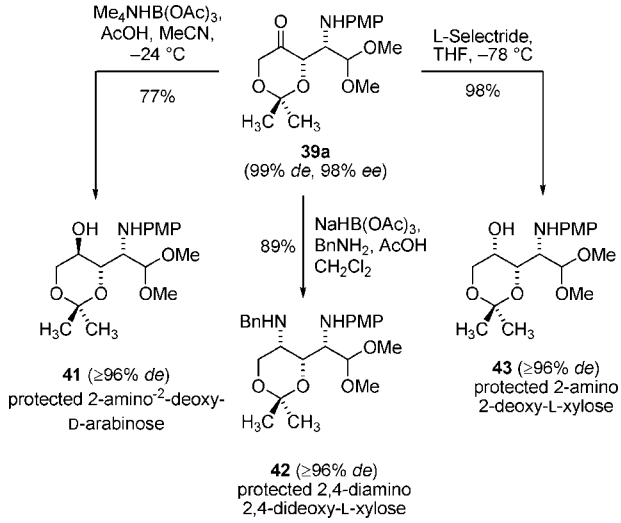


FIGURE 6. Representative biologically active carbasugars.

dioxanone.[27] The first step in the total synthesis of 1-*epi*-(+)-MK7607 (**36**) was the (*R*)-proline-catalyzed aldol reaction between dioxanone (**12**) and protected butanal derivative **32**, which was obtained from (2*S*,3*S*)-tartaric acid in four steps. The organocatalytic reaction was efficient and gave aldol adduct **33** in good yield (69%) and nearly perfect stereocontrol (≥96% de, >99% ee, Scheme 6). Protection of the secondary alcohol in aldol adduct **33** as a methoxymethyl (MOM) acetal and conversion of the protected primary alcohol into an aldehyde by deprotection and oxidation proceeded readily. Next, a double Wittig olefination of the ketone and aldehyde functions afforded the bis-alkene **34** in good overall yield (41% over four steps). The required carbocycle of the target compound was installed in a ring-closing metathesis reaction using the second-generation Grubbs' catalyst to give cyclohexenene **35**. Finally, a simple acid-catalyzed hydrolysis reaction of the protecting groups revealed 1-*epi*-(+)-MK7607 (**36**), which was formed in a total of seven steps and good overall yield (23%).

2.4. Organocatalytic Asymmetric Synthesis of Amino Sugars. Based on our organocatalytic $C_3 + C_n$ concept for the synthesis of carbohydrates and the pioneering proline-catalyzed three-component Mannich reaction reported by List,[28] we developed a diastereo- and enantioselective Mannich reaction allowing for the direct synthesis of amino sugars. Amino sugars,

SCHEME 8. Divergent Synthesis of Protected Amino Aldopentoses from a Pentos-4-ulose Derivative



where an exocyclic hydroxyl function is replaced by an amine such as mannosamine and sialic acid, are subunits of many glycoproteins and glycolipids. The amine function can have a significant effect on the conformation, charge distribution, and biological effects on the sugar unit.[29]

In the first instance, (*S*)-proline was found to catalyze the three-component Mannich reaction of dioxanone (**12**), dimethoxyacetaldehyde (**37a**), and *p*-anisidine (**38**).[30] The Mannich adduct **39a**, which represents a protected 2-amino-2-deoxy-D-*threo*-pentos-4-ulose, was formed in excellent yield and diastereo- and enantioselectivity (91% yield, 99% de, 98% ee) (Scheme 7). Analogous conditions employed for other α-branched aldehydes also led to good yields and selectivities. In the case of linear aldehydes such as α-benzyloxyacetaldehyde (**37c**), (*S*)-proline was found to catalyze the reaction in excellent yield (94%) but lower selectivity (60% de, 82% ee). In this case, the related catalyst, silyl-protected hydroxyproline **40**, was more effective and the Mannich adduct **39c** could be synthesized in good yield (77%) and improved stereoselectivity (88% de, 96% ee). To prepare the L-fructose derivatives **39d**, (*R*)-proline was employed as catalyst without loss in reaction efficiency (63−67% yield, ≥96% de, ≥96% ee). In all cases, *syn*-configured Mannich products were observed, which is consistent with the transition state proposed by List and co-workers.[31]

In a divergent fashion, additional protected amino aldopentoses were accessible from the Mannich product pentose-4-ulose **39a** (Scheme 8). Reductive amination afforded the protected L-xylose derivative **42** in high diastereoselectivity. The C-2 epimers, D-arabinose derivative **41** and L-xylose derivative **43**, could also be synthesized using complementary reducing agents. Triacetoxyborohydride reduction was highly 1,3-*anti*-selective

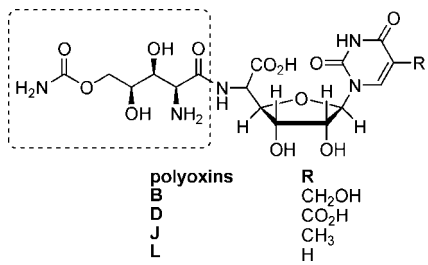
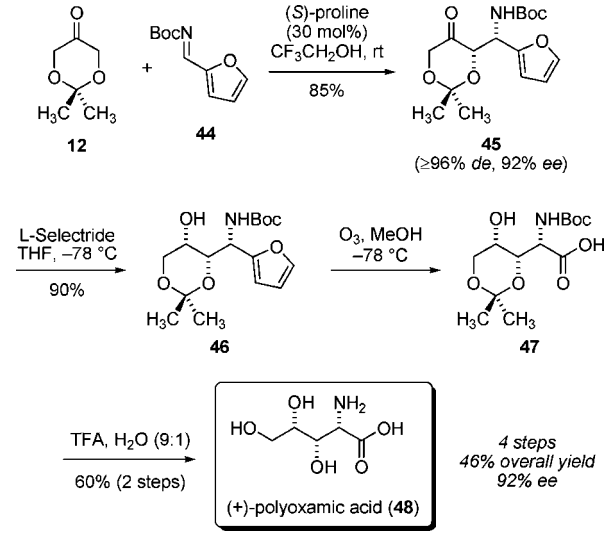


FIGURE 7. Several members of the polyoxin family.

SCHEME 9. Organocatalytic Synthesis of (+)-Polyoxamic Acid via a Proline-Catalyzed Mannich Reaction



giving the former in good yield (77%). L-Selectride reduction, in turn, was highly 1,3-*syn*-selective yielding the latter in excellent yield (98%).

2.5. Organocatalytic Asymmetric Synthesis of (+)-Polyoxamic Acid. The polyoxins are a family of naturally occurring crop protection agents isolated from *Streptomyces cacaoi* var. *asoensis*.[32] They act by inhibiting the synthesis of chitin, which constitutes an important component of the cell wall in fungi. They have also been found to be of potential therapeutic value against the human fungal pathogen *Candida albicans*.[33] A common motif of several members of the polyoxin family is 5-*O*-carbamoylpolyoxamic acid (highlighted in dotted rectangle), which is derived from (+)-polyoxamic acid (Figure 7). In the past three decades, numerous syntheses of (+)-polyoxamic acid have been reported.[34] Most are based on chiral pool methods, although several stereoselective approaches have also been developed.[35]

Based on our previously reported organocatalytic Mannich methodology, we developed a concise synthetic approach to (+)-polyoxamic acid (**48**) (Scheme 9).[36] To commence the synthesis of this α-amino acid, a proline-catalyzed Mannich reaction between dioxanone (**12**) and *N*-Boc-furyl imine **44**[37] was conducted. The Mannich adduct **45** could be prepared in multigram quantities and high stereoselectivities (≥96% de, 92% ee). Imine **44** was selected for two reasons: its furyl group acted as a masked carboxylic acid and the *N*-Boc protecting group could be cleaved under mild reaction conditions.[38] Previously, only anilines (e.g., *p*-methoxyaniline) had been utilized in proline-catalyzed Mannich reactions, which require harsh reaction conditions in order to liberate the free amine from the Mannich product.[39] Diastereoselective reduction of the ketone **45** using L-Selectride afforded the desired *syn*-1,3-amino alcohol **46** in high yield (90%) as a single diastereoisomer. To complete the synthesis, an oxidative cleavage of the furan ring was conducted, which revealed the carboxylic acid group within (+)-polyoxamic acid. Acid-catalyzed hydrolysis of the *N*-Boc protecting group was facile and afforded the natural product **48** in excellent overall yield (46%).

3. Phosphoenolpyruvate Equivalents in Asymmetric Synthesis

PEP (**2**) is an important biochemical acting as a high energy phosphate donor in glycolysis and C_3-building block in the

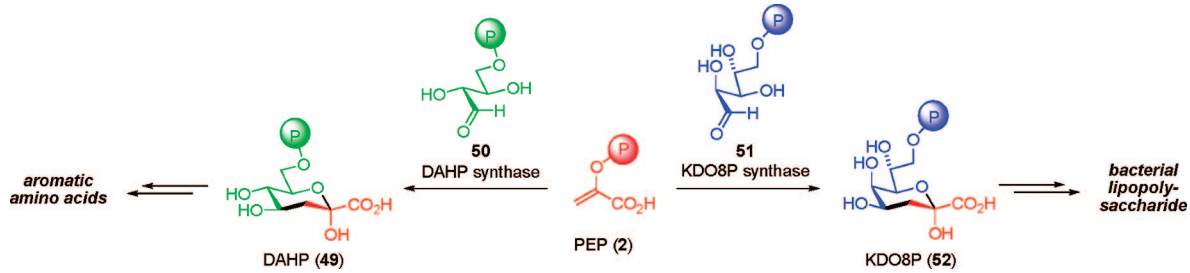


FIGURE 8. PEP as a C_3-nucleophile in Nature.

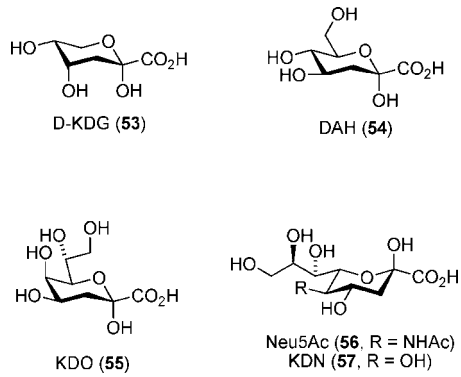


FIGURE 9. Representative six-, seven-, eight-, and nine-carbon-membered ulosonic acids.

biosynthesis of aromatic amino acids and ulosonic acids.[40] As a C_3-building block, PEP participates in enzyme-catalyzed aldol reactions with D-erythrose-4-phosphate (**50**) to form the ulosonic acid, 3-deoxy-D-arabinoheptulosonate-7-phosphate (DAHP, **49**), en route to the aromatic core of aryl amino acids in the shikimate pathway (Figure 8). The homologous ulosonic acid, 3-deoxy-D-*manno*-octulosonate-8-phosphate (KDO8P, **52**) is produced in an aldol reaction involving D-arabinose-5-phosphate (**51**), PEP (**2**), and the enzyme KDO8P synthase. In Gram-negative bacteria, KDO is incorporated into the lipopolysaccharide constituent of the protective outer membrane.

3.1. Organocatalytic Asymmetric Synthesis of Ulosonic Acid Precursors. Ulosonic acids are carbohydrates of varying chain length that contain an α-ketocarboxylic acid group (Figure 9). Their nine-carbon members, the sialic acids, are found in various organisms, particularly as terminal residues of cell surface glycoproteins and glycolipids.[41]As such, they are particularly important in various signaling events and have been implicated in the pathogenesis of microorganisms and viruses. Other ulosonic acids are involved in various biological processes/biochemical pathways (see Figure 8).

In recent years, a number of useful chemical and enzymatic methodologies have been reported to synthesize sialic acid, other ulosonic acids, and analogues thereof.[42] However, synthetic approaches have suffered from long reaction sequences involving many protecting group manipulations, and enzyme-catalyzed reactions have often lacked substrate scope. Consequently the need for short and practical synthetic routes remained a challenging endeavor of great interest.

To mimic the biosynthesis of ulosonic acids, we introduced enantiomerically pure PEP (R = H) and homologous PEP (R = CH_3) equivalents, namely, chiral hydrazones **61**, which can be considered as 3- or 4-carbon d^2 synthons **60** (Figure 10). In the first instance, homologous PEP equivalent **61** (R = CH_3) was metalated and trapped with a variety of alkyl halides to afford, following auxiliary cleavage, 3-alkyl-2-ketoesters **58** (R^1 = CH_3) in high enantiomeric excesses.[43] The method was extended whereby metalation of PEP equivalent **61** (R = H), subsequent reaction with various aldehydes and auxiliary cleavage afforded 4-hydroxy-2-ketoesters **59** (R^1 = H) in high enantiomeric excesses, which could be elaborated into their corresponding cyclic hemiacetals.[44,45]

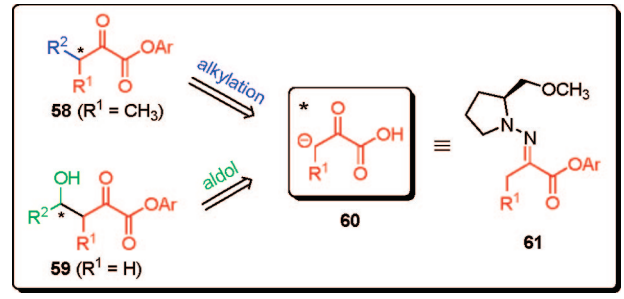
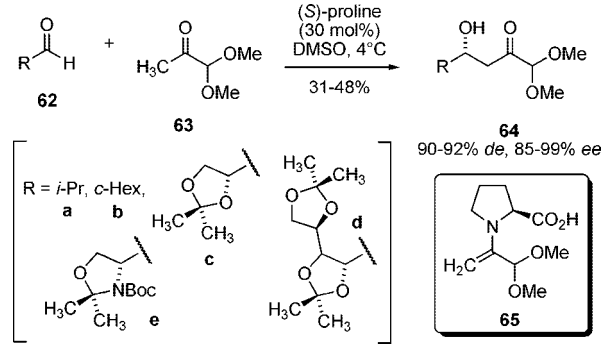


FIGURE 10. Stoichiometric asymmetric synthesis using SAMP-derived ketoesters as chiral PEP/homologous PEP equivalents.

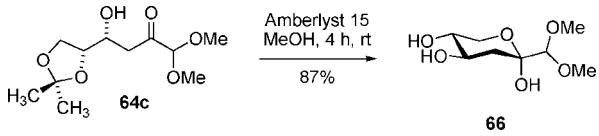
SCHEME 10. Ulosonic Acid Precursor Synthesis: Proline-Catalyzed Aldol Reaction of Aldehydes and Pyruvaldehyde Dimethyl Acetal



More recently, we investigated an organocatalytic asymmetric synthesis of sialic and ulosonic acids.[46] Our biomimetic approach relied on the reaction of pyruvic aldehyde dimethyl acetal (**63**) and (*S*)-proline to form enamine 65, which can be considered as a chiral PEP-like equivalent (Scheme 10). Initially, a variety of proline-derived catalysts were examined in a model reaction involving 2-methylpropanal (**62**, R = *i*-Pr) and ketoacetal **63**. (*S*)-Proline was the best catalyst, and under the optimized conditions, several *β*-hydroxy ulosonic acid precursors **64** could be prepared in moderate yields (31−48%) and high stereoselectivities (≥90% de, ≥85% ee). The yields are acceptable considering that competitive self-aldolization and Mannich/elimination pathways occurred and could not be suppressed completely.

Acid-catalyzed hydrolysis of the acetonide protecting groups of aldol adduct **64c** resulted in spontaneous cyclization to the pyranose-derivative **66** as a single anomer (Scheme 11). In theory, this compound could be easily elaborated into the C-4

SCHEME 11. Cyclization of Aldol Products En Route to Ulosonic Acids



epimer of D-KDG (**53**) via conversion of the acetal-protected aldehyde function into its corresponding carboxylic acid.

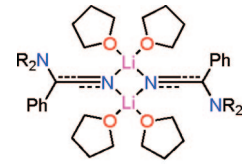
4. "Active Aldehyde" Equivalents in Asymmetric Synthesis

4.1. Enzymes as Archetypes. Transketolases are thiamine-dependent enzymes that catalyze the transfer of a two-carbon fragment from a donor ketose phosphate to an acceptor aldose phosphate and are involved in the biosynthesis of carbohydrates in plants (Calvin cycle) and the phosphate pentose pathway in animals.[47] Mechanistically, transketolases convert the ketose donor **68** into an "active aldehyde" **70** (i.e., a Breslow intermediate) in a 1,2-addition/fragmentation sequence involving a nucleophilic carbene **67** derived from the thiamine cofactor (Figure 11, left). 1,2-Addition to an aldose **71** followed by collapse of the tetrahedral intermediate **72** releases the product **73** and catalytic nucleophile for re-entry into the cycle. Schneider and co-workers recently obtained an X-ray structure of a transketolase enzyme in complex with an "active aldehyde": the thiamine-derived acyl anion donor **70** (Figure 11, right).[48]

4.2. Stoichiometric Chiral "Active Aldehyde" Equivalents. When an α-amino nitrile bears an α-hydrogen, deprotonation at this position using strong bases is possible. The resultant carbanion is capable of reacting nucleophilically with a number of electrophile classes.[49] In 1980, we began a research program concerning the use of chiral metalated α-amino nitriles as "active aldehyde" equivalents in asymmetric nucleophilic acylation reactions. After screening many chiral amine auxiliaries, (*S*,*S*)-2,2-dimethyl-5-*N*-methylamino-4-phenyl-1,3-dioxane (**77**) was found to induce the highest levels of asymmetric induction. In the first study, chiral 3-substituted 4-oxoesters **78** could be synthesized in three steps from various aromatic aldehydes via an asymmetric Michael addition of the metalated α-amino nitriles **Li-75** and α,β-unsaturated esters (Scheme 12).[50] The γ-aroylated products **79** were formed in good overall yields (47−71%) and excellent enantioselectivities (90-≥96% ee) following a mild Lewis acid promoted hydrolysis reaction of the amino nitrile function within the Michael adducts **78**. Subsequent studies revealed that cyclic enones and α,β-unsaturated lactones could be tolerated well in the protocol.[51] Furthermore, a tandem Michael addition/alkylation reaction using an analogous chiral reagent derived from aliphatic aldehydes was developed.[52]

The high asymmetric inductions observed for Michael additions using lithiated α-amino nitriles **Li-75** prompted a more detailed investigation of their solid- and solution-phase structures. In the solid state, lithiated **Li-75** (Ar = Ph) existed as a dimer with almost linear ketenimine units containing a four-membered Li_2N_2 ring and tetrahydrofuran molecules completing the lithium co-ordination sphere (Figure 12).

The measured bond lengths and angles point to an almost linear C−C−N unit with partial C−C double bond character and partial C−N triple bond character. The solid-state structure may therefore be formally represented by structure **80**. Based on IR, ^{1}H and ^{13}C NMR spectroscopy, and cryoscopic measurements, the lithiated α-amino nitriles exist as monomeric species in solution with slight ionic character. Based on this information, a transition state was proposed in order to account for the stereochemical outcome of the conjugate addition of such lithiated α-amino nitriles to α,β-unsaturated carbonyl compounds.



80

In collaboration with Fernandez, Lassaletta, and co-workers, we have used formaldehyde hydrazones derived from SAMP/RAMP as chiral synthetic equivalents of formyl and cyanide anion synthons.[53] In addition, our research group has investigated the use of α-amino nitriles derived from glyoxylates in stoichiometric and organocatalytic nucleophilic asymmetric glyoxylation reactions, respectively.[54] The latter, achiral α-amino nitrile **82**, which can be considered as a 2-carbon d^1 synthon **81**, was found to readily undergo an iminium-catalyzed Michael addition with several α,β-unsaturated aldehydes **83** in the presence of TMS-ether **84** (Scheme 13). This bioinspired use of "active aldehyde"-type glyoxylates **81** extends the synthetic repertoire of Nature, where glyoxylation reactions do not occur. The direct conversion of the Michael adducts **85** into the corresponding α-ketoester aldehydes by cleavage of the α-amino nitrile was problematic and only traces of the desired product could be isolated. Therefore, the crude Michael adducts **85** were subjected to a three-step reduction/protection/hydrolysis sequence after which glyoxylates **86** were isolated in good overall yields (30−30%) and enantiomeric excesses (83−87% ee). Aromatic and heteroaromatic enals **83** (R = Ph, furan-2-yl) were also tolerated in the reaction; however, the overall yields were lower and the initial Michael adducts **85** were prone to β-carbon epimerization.

4.2. Stable Carbenes. Carbenes exhibit remarkable and unique properties as ligands in metal complexes and reagents/catalysts in organic synthesis.[55] In 1995, our research group in collaboration with Teles and co-workers developed a novel stable triazolium-derived carbene **88** (Scheme 14).[56] Carbene **88** can be generated from precatalyst **87** via the 1,2-addition/α-elimination of methanol or deprotonation with base. Investigations of its reactivity revealed that it participated as a substrate in several chemical transformations and as a catalyst in a benzoin-type condensation of formaldehyde to form glycolaldehyde.[57] In this reaction, low catalyst loadings were possible (1.25 mol%) and the triazolium-derived catalysts were demonstrated to be far more active than their thiazolium and imidazolium-based counterparts. For example, under identical reaction conditions, a suspension of paraformaldehyde required 30−60 min to become clear in the presence of a thiazol-2-ylidene, whereas for triazol-5-ylidene **88**, the reaction became clear within seconds.

4.3. Asymmetric Benzoin Condensations. Based on the observed catalytic activity of triazol-5-ylidene **88** in a benzoin-type reaction, our research group designed and synthesized a series of chiral triazole-based catalysts for examination in the asymmetric benzoin condensation.[58] In the dimerization of benzaldehyde, precatalyst **91** provided (*R*)-benzoin ((*R*)-**90**, Ar = Ph) in good yield (66%) and enantioselectivity (75% ee) (Table 1). Electron-rich and electron-poor aromatic aldehydes

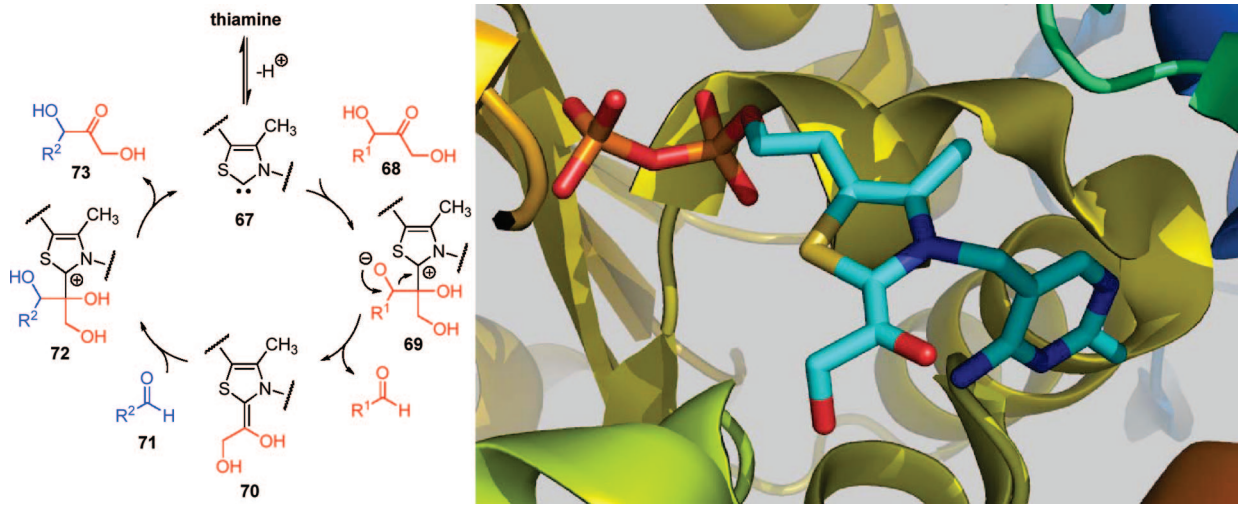
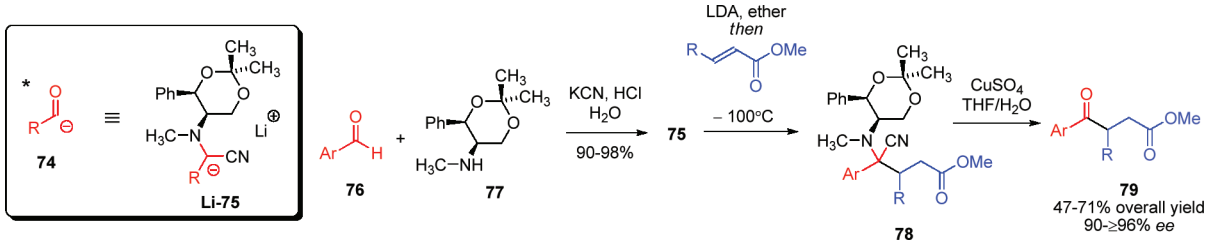
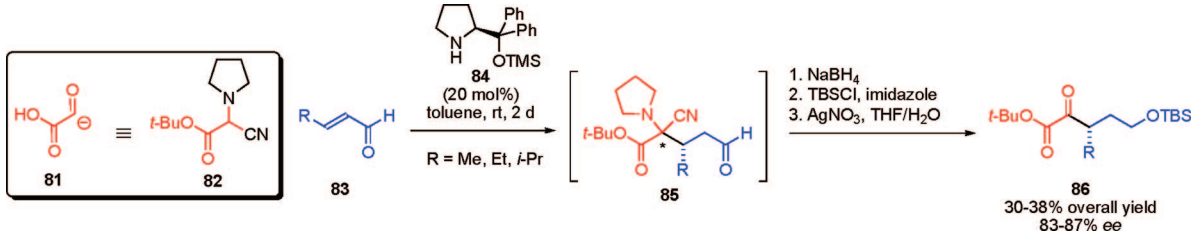


FIGURE 11. Simplified catalytic cycle (left) and crystal structure of thiamine-derived acyl anion donor **70** in the active site of *S. cerevisiae* transketolase (right).

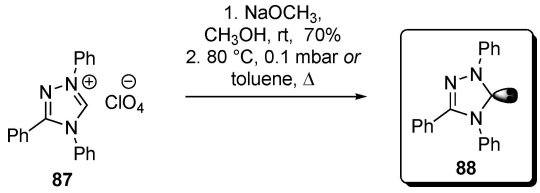
SCHEME 12. α-Amino Nitrile Anions as Chiral "Active Aldehyde" Equivalents and Use in Asymmetric Synthesis of 3-Substituted 4-Oxoesters



SCHEME 13. Asymmetric Organocatalytic Glyoxylations via α-Amino Nitrile-Derived Glyoxylates



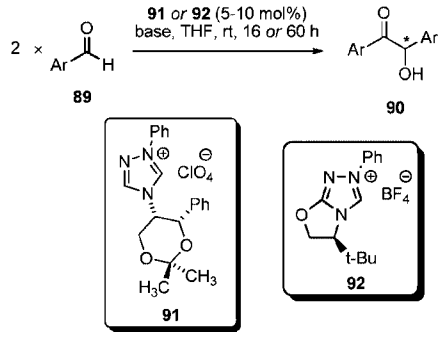
SCHEME 14. Preparation of 1,3,4-Triphenyl-4,5-dihydro-1*H*-1,2,4-Triazol-5-ylidene, a Stable Carbene



89 reacted to give their corresponding α-hydroxy ketones (*R*)-**90** in moderate to good yields and enantioselectivities. Inspired by the development of bicyclic thiazolium salts for the asymmetric benzoin condensation by Leeper and co-workers,[59] we developed a chiral bicyclic triazolium salt **92**, derived from (*S*)-*tert*-leucine.[60] With this precatalyst, (*S*)-benzoin ((*S*)-**90** (Ar = Ph)) was produced in a good yield (83%) and high enantioselectivity (90% ee) (entry 1). The condensation of various aromatic aldehydes **89** proceeded readily to afford α-hydroxy ketones (*S*)-**90** in generally good yields and moderate to high enantioselectivities (entries 2−9). Levels of asymmetric induction could be improved by lowering the reaction temperature to 0 °C. Compared to the first-generation precatalyst **91**, the bicyclic catalyst **92** was more active (16 h vs 60 h) and gave better yields and higher enantioselectivities.

Two possible transition states that account for the (*S*)-absolute stereochemical outcome of the asymmetric benzoin reaction involving bicyclic triazolium precatalyst **92** have been proposed (Figure 13). In both, the *Si*-face of the Breslow-type intermediate is assumed to be inaccessible due to steric shielding by the bulky *tert*-butyl group of the catalyst. In the first transition state **93**, a (*Z*)-enolamine geometry and orientation of the aldehyde from its *Re*-face with possible hydrogen bonding and π-stacking between the aromatic rings of the catalyst and substrate would account for the observed (*S*)-configured product (*S*)-**90**. Following a computational investigation of the reaction, a second proposal was made by Houk and co-workers.[61] In this transition state **94**, no π-stacking is present and the (*E*)-double bond isomer is reactive. The aldehyde approaches from its *Re*-face but its phenyl substituent is rotated *anti* to both phenyl groups in the Breslow-like intermediate. Furthermore, the authors suggested the possibility of a stabilizing π-interaction between the

TABLE 1. Carbene-Catalyzed Asymmetric Benzoin Condensation



		precatalyst **91**[a]		precatalyst **92**[b,c]	
entry	Ar	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	66	75	83	90
2	4-FC_6H_4	48	44	81 (61)	83 (91)
3	4-ClC_6H_4	51	29	80 (44)	64 (89)
4	4-BrC_6H_4	72	20	82 (59)	53 (91)
5	3-ClC_6H_4	n.a.[d]	n.a.	92 (85)	62 (86)
6	3-$CH_3C_6H_4$	54	76	70 (36)	86 (91)
7	4-$CH_3C_6H_4$	46	82	16	93
8	4-$CH_3OC_6H_4$	22	86	8	95
9	*o*-furyl	n.a.	n.a.	(100)	64

[a] Reaction performed using K_2CO_3 as base and 5 mol % of **91** in THF at rt for 60 h. [b] Reaction performed using KO-*t*-Bu as base and 10 mol % of **92** in THF at rt for 16 h. [c] Values in parentheses refers to reactions performed at 0 °C. [d] Not applicable (reaction).

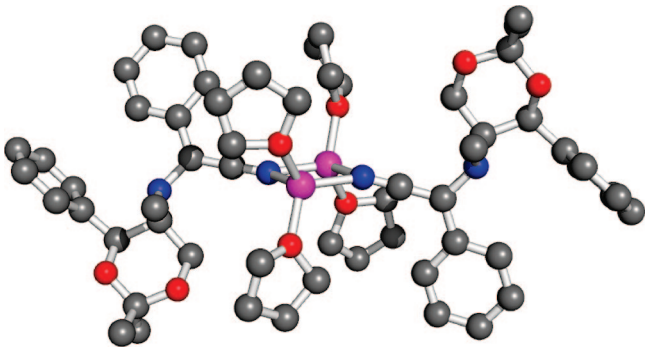


FIGURE 12. X-ray crystal structure of dimeric lithiated α-amino nitrile **Li 75** (gray, C; blue, N; red, O; magenta, Li).

developing iminium ion character with the heterocyclic core and the aryl residue of the aldehyde.

4.4. Asymmetric Intramolecular Crossed Benzoin Condensations. In 2004, our research group and Sukuki and co-workers independently developed the first carbene-catalyzed crossed benzoin condensation of ketoaldehydes to form various racemic five- and six-membered cyclic acyloins employing commercially available thiazolium salts as precatalysts.[62] Previously, ketone electrophiles had remained elusive in carbene-catalyzed nucleophilic acylation reactions. In 2006, the same groups developed the first *asymmetric* carbene-catalyzed crossed benzoin condensation.[63] Initially, we found that the carbene generated from bicyclic triazolium salt **92**, used previously in the enantioselective intermolecular benzoin condensation, was not catalytically active in the crossed benzoin condensation of ketoaldehyde **95** (Scheme 15). Therefore, several new precatalysts were prepared including the bi- and tetracyclic structures **98** and **99**. Precatalyst **99**, prepared in seven steps from 1-tetralone (7.1% overall yield), gave excellent results, and acyloins **96**, bearing a quaternary stereocenter, were synthesized

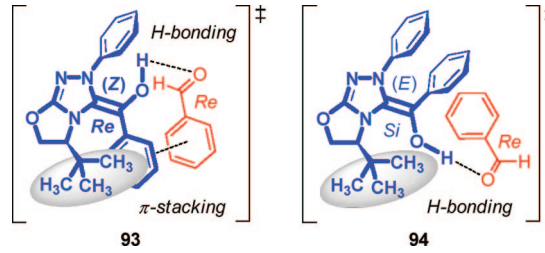
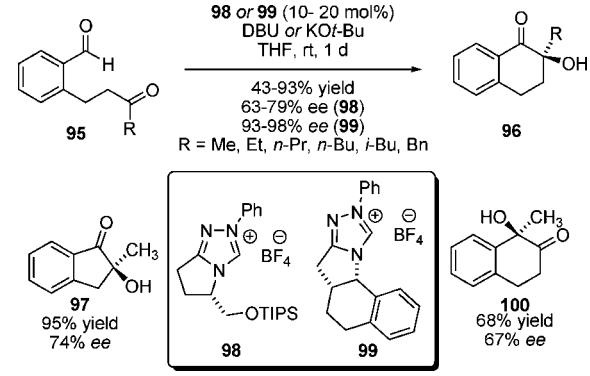


FIGURE 13. Possible transition states for the asymmetric benzoin condensation involving bicyclic triazolium precatalyst **92**.

SCHEME 15. Carbene-Catalyzed Asymmetric Intramolecular Crossed Benzoin Condensation

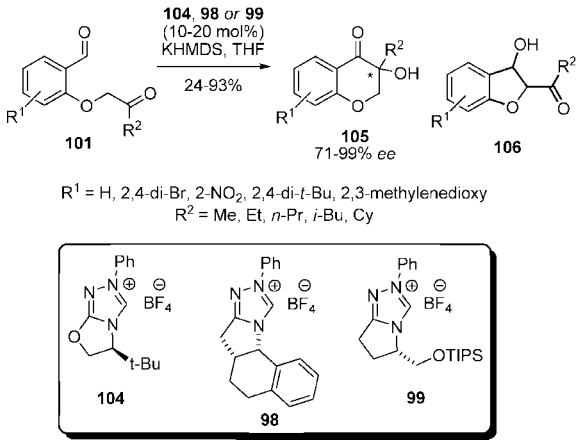


with good yields and excellent enantiomeric excess (93−98% ee). The precatalyst **98**, prepared in four steps from inexpensive L-pyroglutamic acid (21% overall yield), proved to be more active giving consistently excellent yields, albeit in lower enantiomeric excesses (63−84% ee). Homologous **97** and isomeric **100** acyloin products could also be synthesized efficiently using this protocol. The analogous study by Suzuki and co-workers utilized an aminoindanol-derived chiral triazolium salt developed by Rovis and co-workers[64] as precatalyst and gave comparable results. Importantly, these authors extended the reaction scope to include aliphatic and diaryl ketoaldehyde substrates.

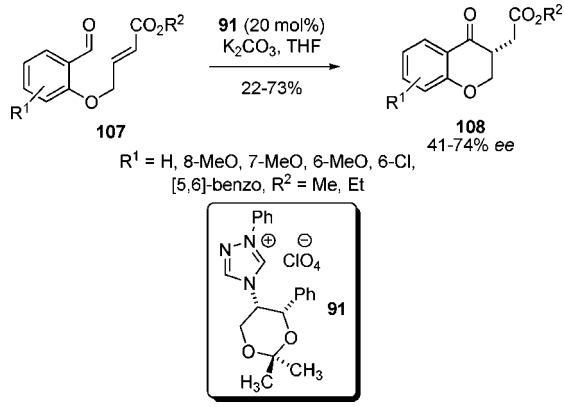
4.4. Chroman-4-ones via Asymmetric Intramolecular Crossed Benzoin Condensations. Chroman-4-ones are found in a wide variety of natural products with biological activities ranging from antibacterial to antiviral.[65] Recently, we applied the carbene-catalyzed intramolecular crossed benzoin reaction to the asymmetric synthesis of various 3-hydroxy-4-chromanones **105** (Scheme 16).[66] Undesired aldolization to form 2,3-dihydrobenzofuran derivative **106** was often a competing reaction manifold.[67] To circumvent this, several catalysts **104**, **98**, and **99** were employed, and in doing so, it was possible to maintain high enantioselectivities for a range of substrates while suppressing aldolization.

4.5. Asymmetric Intramolecular Stetter Reactions. The Stetter reaction involving the cyanide- or carbene-catalyzed generation of an "active aldehyde" for nucleophilic acylative 1,4-addition is a powerful method to synthesize 1,4-diketones, 4-ketoesters, and 4-ketonitriles.[68] In 1996, our research group developed the first enantioselective intramolecular Stetter reaction using our previously developed chiral triazolium salt **91** as a carbene precatalyst. The enantioselective synthesis of various 3-alkyl-4-chromanones **108** was possible in moderate to good yields (22−73%) and good enantiomeric excesses (41−74% ee) (Scheme 17).[69] Rovis and co-workers have made significant

SCHEME 16. Carbene-Catalyzed Asymmetric Synthesis of 3-Hydroxychroman-4-ones



SCHEME 17. Carbene-Catalyzed Asymmetric Synthesis of 3-Alkyl-4-chromanones



contributions in this field developing asymmetric variants involving new catalysts and Michael acceptors.[70]

5. Organocatalytic Asymmetric Domino Reactions

Nature uses many synthetic strategies to construct and break down complex molecules. In polyketide synthesis by type I polyketide-synthases, one enzyme catalyzes the *iterative* addition of acetyl or propionyl groups to the growing polyketide polymer.[71] In glycolysis, many enzymes work in *series*, the product of one enzymatic transformation becoming a substrate in the next, as glucose is converted into pyruvate.[40] In the synthesis of lanosterol, the precursor to all naturally occurring steroids, a synthase triggers a *domino* reaction within squalene epoxide.[72] Nucleophilic alkenes become and react with electrophilic carbocations as a series of ring forming events propagate across the molecule forming the tetracyclic adduct. This latter type, the domino reaction, has inspired many chemists since the origins of synthetic chemistry for pragmatic and aesthetic reasons.[73] The consumption of less reagents, solvents and energy is possible while increasing space-time yields. The combination of simple building blocks and one catalyst/reagent to chemo-, regio-, and stereoselectively synthesize a complex product can be considered be beautiful.

In 2006, we developed the first organocatalytic asymmetric triple domino reaction of simple achiral linear aldehydes **109**, nitroalkenes **110**, and α,β-unsaturated aldehydes **111** catalyzed by a simple chiral secondary amine **84** (Scheme 18).[74] This tandem Michael/Michael/aldol condensation reaction afforded

SCHEME 18. Organocatalytic Asymmetric Domino Reaction of Aldehydes, Nitroalkenes, and Enals

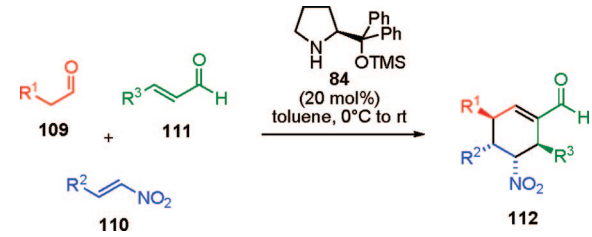


TABLE 2. Substrate Scope

entry	R^1	R^2	R^3	yield (%)	dr	ee (%)
1	Me	Ph	Ph	40	78:22	≥99
2	Me	Ph	H	50	86:14	≥99
3	Me	Ph	Me	25	68:32	≥99
4	Me	Ph	Et	18	77:23	≥99
5	Me	Ph	*n*-Bu	29	80:20	≥99
6	Me	Ph	$CH_3C{=}CH$	20	88:12	≥99
7	Me	furan-2-yl	H	47	77:23	97
8	Me	2-ClC_6H_4	Ph	51	84:16	≥99
9	Me	2-FC_6H_4	Ph	37	82:18	≥99
10	Me	4-BrC_6H_4	Ph	29	88:12	≥99
11	Me	4-$CH_3OC_6H_4$	Ph	39	83:17	≥99
12	Me	4-$NO_2C_6H_4$	Ph	33	71:29	≥99
13	Me	4-MeC_6H_4	Ph	38	83:17	≥99
14	Me	piperonyl	Ph	39	87:13	≥99
15	Me	furan-2-yl	Ph	23	87:13	≥99
16	Me	5-methylfuran-2-yl	Ph	37	89:11	≥99
17	Et	Ph	Ph	58	80:20	≥99
18	*i*-Pr	Ph	H	41	84:16	≥99
19	*i*-Pr	Ph	Ph	56	79:21	≥99
20	*n*-Pent	Ph	Ph	60	83:17	≥99
21	Bn	Ph	Ph	38	89:11	≥99
22	$TBSOCH_2$	Ph	Ph	54	99:1	≥99
23	AcO	Ph	Ph	18	71:29	≥99
24	$(MeO)_2CH(CH_2)_3$	Ph	H	47	65:35	98
25	$(MeO)_2CH(CH_2)_3$	Ph	Ph	60	78:22	≥99

highly functionalized chiral cyclohexene carbaldehydes **112**. Nearly stoichiometric amounts of propanal (**109**, R^1 = Me, 1.20 equiv), β-nitrostyrene (**110**, R^2 = Ph, 1.00 equiv), and cinnamaldehyde (**111**, R^3 = Ph, 1.05 equiv) were found to react in good yield (40%) and diastereomeric ratio (78:22 dr) and with near perfect enantioselectivity (≥99% ee) (Table 2, entry 1).

In the initial communication and subsequent full paper, the scope of the reaction was exhaustively investigated.[75] A range of substituted and unsubstituted, aromatic and heteroaromatic, aliphatic and olefinic substrates were viable components in the reaction which produced cyclohexene carbaldehydes **112** in moderate to good diastereomeric ratios (65:35−99:1 dr) and

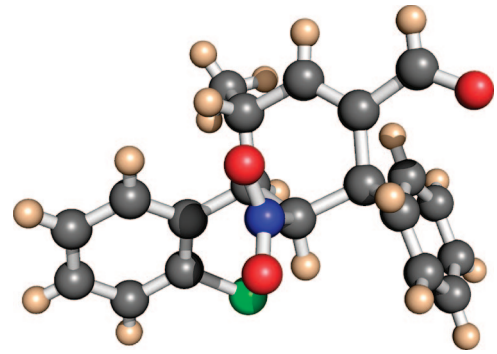


FIGURE 14. X-ray crystal structure of cyclohexene carbaldehyde **112** (R^1 = Me, R^2 = 2-ClC_6H_4, R^3 = Ph) (gray, C; wheat, H; blue, N; red, O; green, Cl).

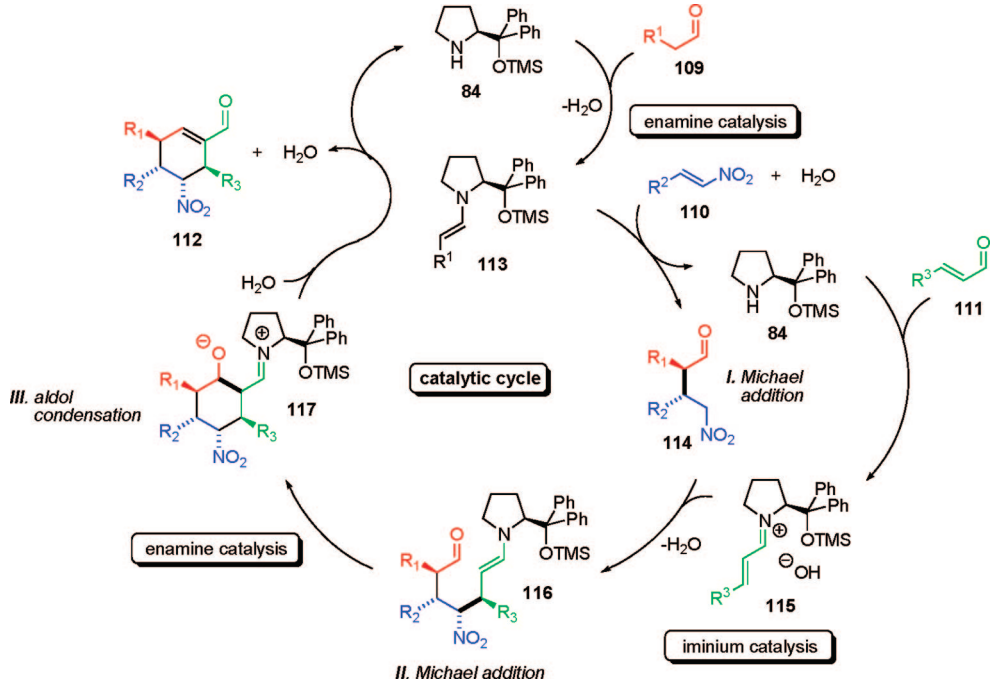


FIGURE 15. Proposed mechanism for the amine-catalyzed triple domino reaction.

excellent enantioselectivity (≥97% ee) (entries 1−25). The yields of the products were good (18−60%) considering the number of bond forming events in this process. The reaction was operationally simple: it could be performed at near ambient temperatures in a screw-cap or stopped flask without the need to rigorously exclude moisture or oxygen. In most cases ($R^1 = R^2 = R^3 \neq H$), tetrasubstituted cyclohexene carbaldehydes **112** were formed that contain *four contiguous stereogenic centers*. X-ray crystallographic analysis of cyclohexene carbaldehyde **112** (R^1 = Me, R^2 = 2-ClC_6H_4, R^3 = Ph) allowed its absolute configuration to be established (Figure 14).

We have devised a mechanistic proposal for this three-step domino reaction based on knowledge of the individual steps of the reaction and the observed reaction intermediates (Figure 15). The catalytic cycle is initiated when the catalyst **84** and aldehyde **109** react to form enamine **113**. The enamine **113** then reacts as a nucleophile with the reactive Michael acceptor, nitroalkene **110**, forming nitroalkyl aldehyde **114** upon hydrolysis. Nitroalkenes **110** are known to be among the most reactive Michael acceptors, explaining the chemoselectivity of the catalytic cycle's first step. The enamine **113** reacts much faster with this species than the alternate Michael acceptor, α,β-unsaturated aldehyde **111**.[76] The catalyst **84** then condenses with α,β-unsaturated aldehyde **111** to form the iminium ion **115**. Next, the iminium ion **115** participates as the electrophile in a second Michael addition with nitroalkyl aldehyde **114**, likely activated through deprotonation by the hydroxide counterion, to afford enamine intermediate **116**. In the third step, enamine intermediate **116** reacts as a nucleophile in an intramolecular aldol reaction, thus forming the six-membered ring of the domino product **117**. The final product **112** is formed following elimination of water and hydrolysis liberating the catalyst for re-entry into the cycle. Throughout the course of the reaction, only the first formed **114** and final **112** products could be detected by GC analysis. Thus, the rate-determining step of the reaction occurs after the formation of **114** and is likely the bimolecular iminium-catalyzed Michael addition. A more

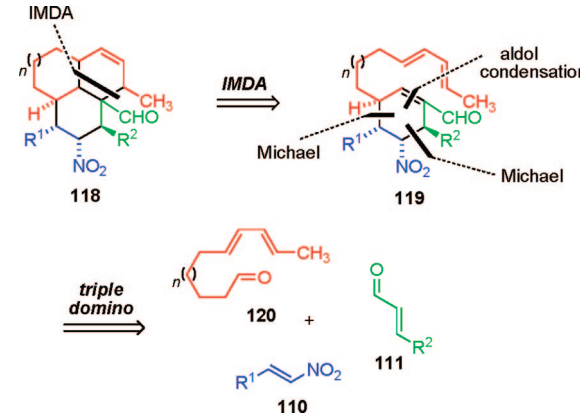


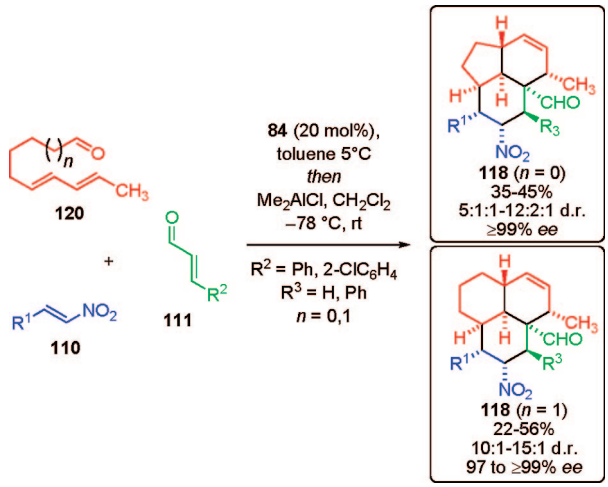
FIGURE 16. Retrosynthetic analysis of tricyclic carbaldehyes **118** (n = 0, 1).

detailed mass spectral investigation of the mechanism has recently been conducted and will be reported shortly.

Two variants of the asymmetric triple domino reaction were also developed in our laboratory. A simplified double-Michael/Michael domino reaction between γ-nitroketones and α,β-unsaturated aldehydes allowed for the synthesis of tetrasubstituted cyclohexenes containing two stereogenic centers in high enantiomeric excesses.[77] A more elaborate version permitted the synthesis of highly functionalized chiral tricyclic carbaldehydes **118** in one pot from linear aldehydes **120**, containing a diene function, nitroalkenes **110**, and α,β-unsaturated aldehydes **111** (Figure 16).[78] For this latter transformation, the initial synthetic strategy was based upon a quadruple domino reaction where the triple domino product **119** would react further in an intramolecular Diels−Alder reaction (IMDA). In theory, an iminium-ion-catalyzed IMDA would be feasible as the triple domino product **119** contains the requisite diene and α,β-unsaturated aldehyde components.

In the first instance, (5*E*,7*E*)-nona-5,7-dienal (**120**, n = 0), β-nitrostyrene (**110**, R^1 = Ph), and cinnamaldehyde (**111**, R^2 = Ph) were found to react in good yield (51% for major

SCHEME 19. One-Pot Amine-/Lewis Acid-Catalyzed Synthesis of Tricyclic Carbaldehydes 118 (n = 0, 1)



diastereomer **118**) and with near perfect enantioselectivity (≥99% ee). The reaction essentially stopped after the third step as only a small amount of the quadruple cascade product could be observed. This indicated that iminium-ion catalysis was not capable of effectively promoting the IMDA in this system. Nevertheless, an efficient one-pot amine/Lewis acid catalyzed procedure was developed. Diethylaluminium chloride (Et_2AlCl) was added to the reaction following completion of the triple domino reaction, and the desired tricyclic carbaldehyde **118** (n = 0) was formed in good yield (35%) and diastereoselectivity (5.1:1 dr) and excellent enantioselectivity (≥99% ee). Notably, the IMDA was completely diastereoselective and the diastereoselectivity represents that for the initial triple domino reaction. Furthermore, this process led to the formation of *five carbon−carbon bonds and eight stereogenic centers with complete enantiocontrol*. The reaction was amenable to various substrates and products containing 5- or 6-membered rings **118** (n = 0, 1) could be synthesized in good yields (35−56%) and diastereomeric ratios (5.1:1−15:1 dr) with excellent levels of asymmetric induction (≥99% ee) (Scheme 19).

6. Conclusions

In the synthetic laboratory, carbon−carbon bond formations can be rendered biomimetic by employing chemical building blocks or substrate activation modes that imitate those found in Nature. Based upon our SAMP/RAMP methodology, chiral hydrazones have been used as chiral DHAP and PEP equivalents in stoichiometric asymmetric carbon−carbon formations leading to a variety of useful chiral synthetic intermediates and natural products. Extension into the catalytic domain was possible via proline catalysis, which couples the mimicry of Nature's building blocks with a naturally occurring mechanism of substrate activation (e.g., enamine catalysis). In doing so, proline-catalyzed aldol and Mannich reactions of the DHAP equivalent, dioxanone, or a PEP-like equivalent allowed for the synthesis of many carbohydrates, azasugars, sphingoids, ulosonic acid precursors and other natural and pharmaceutically relevant products in concise and highly enantioselective fashions. Chiral α-amino nitriles and carbene catalysis mimic Nature's use of transketolase enzymes to generate the "active aldehyde" for use in nucleophilic acylation reactions. Thus, stoichiometric and catalytic asymmetric Michael additions, benzoin condensations, and Stetter reactions have been developed. Recent efforts in our laboratory culminated in the development of an organocatalytic triple domino reaction involving enamine and iminium catalysis. The highly substituted cyclohexene carbaldehydes typically contain four stereogenic centers, which are generated in three consecutive carbon−carbon bond formations with high diastereo- and complete enantiocontrol. Nature will inspire synthetic chemists and other scientists alike far into the future. Along this line, chemists will aspire to develop new biomimetic synthetic processes that eventually match the efficiency and elegance of Nature.

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