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# The Diarylprolinol Silyl Ether System: A General Organocatalyst

KIM L. JENSEN, GUSTAV DICKMEISS, HAO JIANG,
ŁUKASZ ALBRECHT, AND KARL ANKER JØRGENSEN*
*Center for Catalysis, Department of Chemistry, Aarhus University, Denmark*

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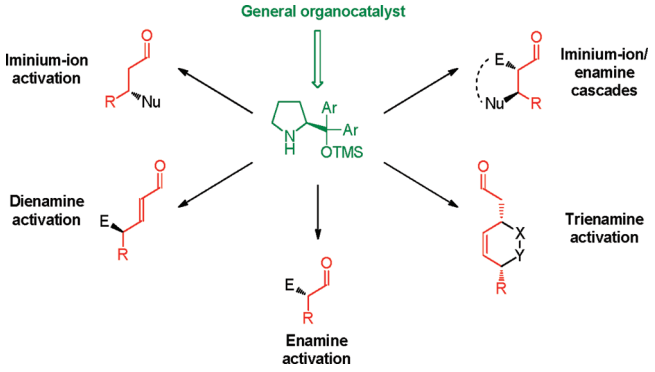
## CONSPECTUS




The past few decades have witnessed some of the most important and revolutionizing advances in the field of asymmetric catalysis. Chemists no longer rely solely on natural sources as the starting point of their synthetic strategy, as in chiral pool or auxiliary-based synthesis. Instead, naturally occurring chiral motifs are selected and, either unchanged or after modification, used in substoichiometric amounts as chiral catalysts or ligands. In this way, they effectively transfer their chirality to prochiral substrates, thereby rapidly amplifying and diversifying the arsenal of useful chiral building blocks available to the synthetic community.

A long-standing goal in the pursuit of new catalytic systems is the discovery of general catalysts. Ideally, such catalytic systems should be capable of promoting a large number of enantioselective reactions, via multiple modes of activation, with good substrate tolerance and high stereoselectivity. In this Account, we describe the synthetic usefulness, efficiency, selectivity, and robustness of the diarylprolinol silyl ether system as the catalyst in various reactions of aldehydes.

Based on the diarylprolinol silyl ether system, several studies on enamine-mediated transformations of saturated aldehydes have resulted in the introduction of different functionalities into the α-position of aldehydes in a highly stereoselective manner. This HOMO-activation concept was later extended to include α,*β*-unsaturated aldehydes, which after condensation with the aminocatalyst generate a dienamine species capable of undergoing stereoselective Diels–Alder-type reactions. As a result, the effective functionalization of the *γ*-position of the aldehyde is achieved. Recently, the activation principle was further developed to include 2,4-dienals, which form trienamine intermediates upon condensation with the aminocatalyst. The trienamines effectively react with carbon-centered dienophiles, forming aldehyde products having up to four contiguous stereocenters. Because of the concerted nature of the reaction and the efficient catalyst shielding of the *β*-position, the stereoinduction is achieved at the remote *ε*-position of the original aldehyde.

Complementary to the enamine-mediated activations, α,*β*-unsaturated aldehydes can also be efficiently functionalized by applying the diarylprolinol silyl ether system via conjugate addition through iminium-ion-mediated processes, that is, LUMO-activation. In such reactions, the aminocatalyst not only effectively shields one of the enantiotopic faces of the enal, it also ensures excellent chemoselectivity, affording 1,4-adducts as the only products. Several different carbon and heteroatom nucleophiles can be added in a highly stereoselective fashion. The ability of the catalysts to participate in various enamine- and iminium-ion-mediated processes also makes them ideal for the sequential addition of nucleophiles and electrophiles in a cascade manner. These cascade reactions thereby afford access to products having at least two stereocenters.

In the years to come, the diarylprolinol silyl ether catalysts will probably maintain their prominent position as general catalysts in the field of aminocatalysis. Moreover, recent efforts devoted to mechanistic studies might soon engender further advances with this versatile catalytic system, particularly in the areas of activation modes, catalyst loadings, and industrial applications.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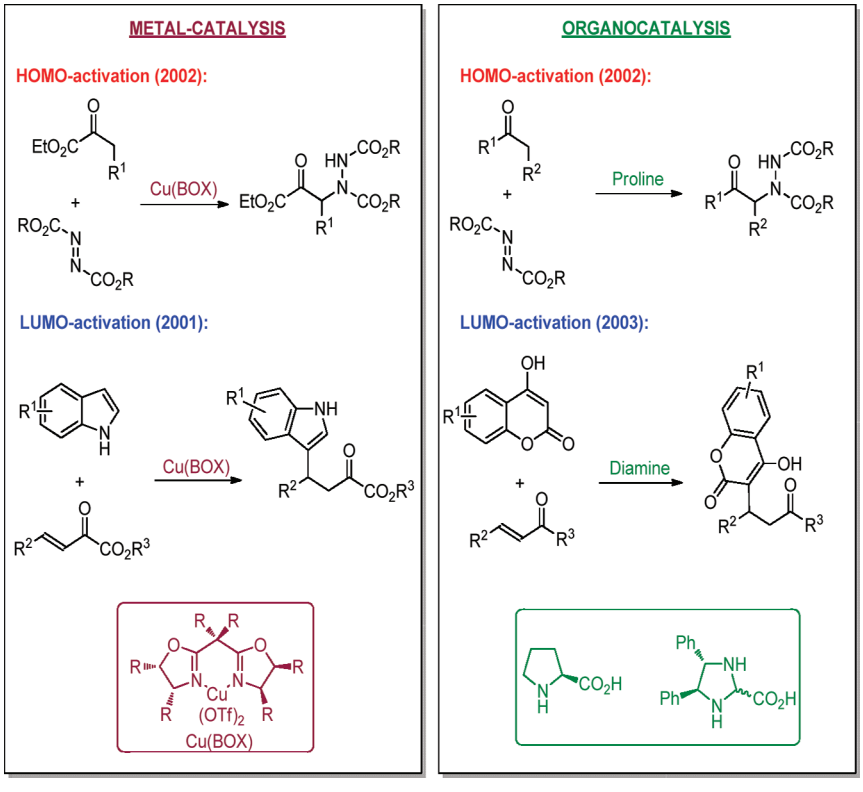
## Introduction and Background

Organocatalysis, now commonly viewed as the third pillar in the "trio of asymmetric catalysis"[1] (with the other two being biocatalysis and metal catalysis), has since its renaissance in 2000[2] proven to be a highly robust and useful tool in contemporary asymmetric synthesis. Already at its infancy, organocatalysis,[3] the use of small organic molecules as rate enhancers and chirality inducers, caught strong interest in our research group, which at that time mainly focused on the development of new metal-catalyzed methods for activation of carbonyls and imines toward nucleophilic, electrophilic, and cycloaddition reactions.[4] Seeing the direct resemblance between the well-studied metal-based catalytic systems and the ability of small molecules, such as chiral amines, to activate saturated and $\alpha,\beta$-unsaturated carbonyl compounds, a more detailed study of these newborn (or newly reborn) modes of activation was pursued (Scheme 1). The core of our studies focused on two issues: (i) to take well-studied metal-catalyzed reactions and probe the possibility of achieving similar or better results using organocatalysis; (ii) to challenge unsolved problems or traditionally difficult reactions by the application of organocatalysis.

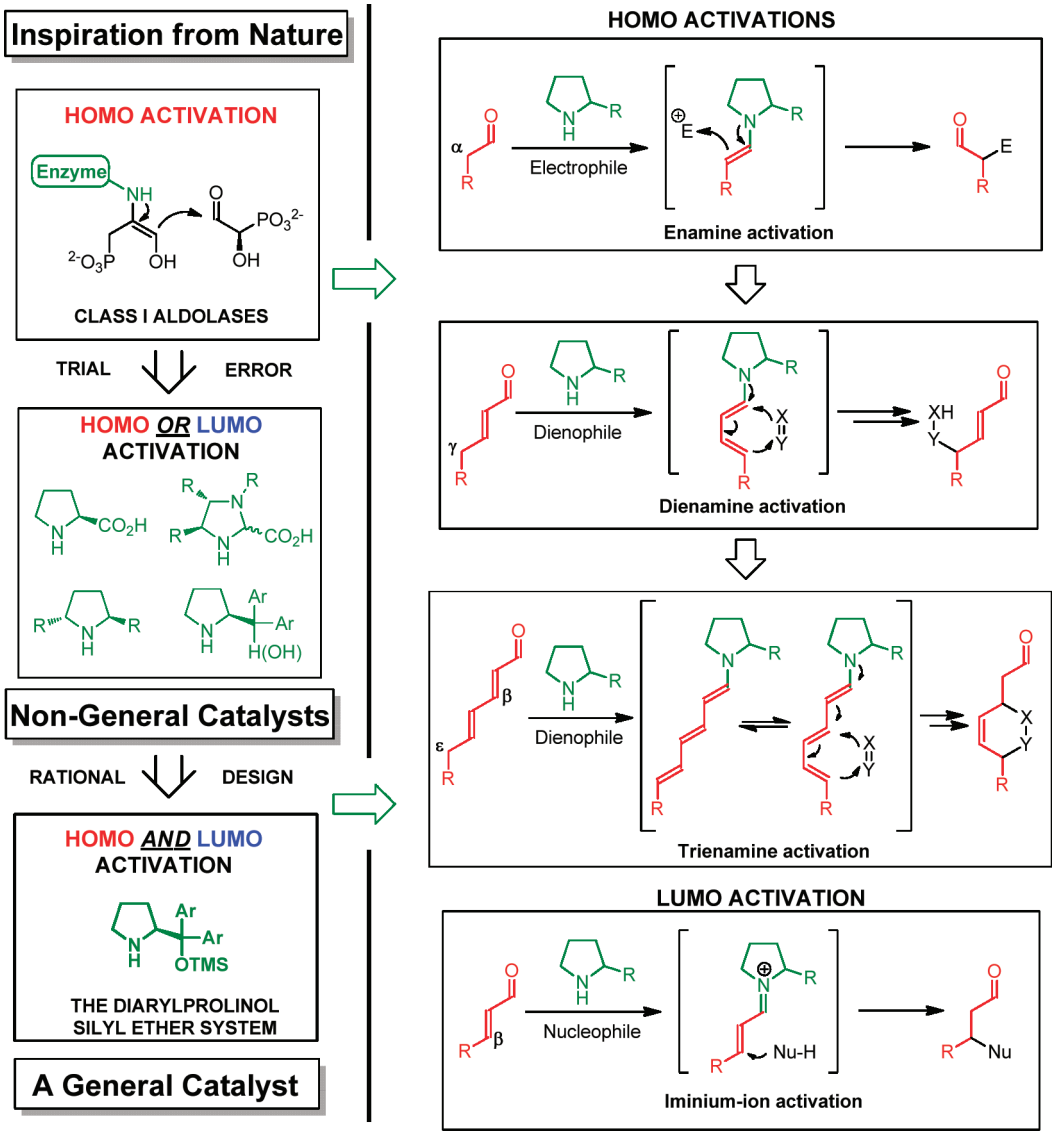
In 2002, the use of chiral Cu(BOX) (BOX = bisoxazoline ligands) as the catalytic unit in activation of $\alpha$-ketoesters by HOMO-activation via a metal-enolate species was achieved, furnishing enantioenriched $\alpha$-aminated products by the direct electrophilic addition of azodicarboxylates.[5] Based on the appearing overlap to facilitate HOMO-activation by enamine catalysis and, hence, $\alpha$-functionalizations of aldehydes and ketones, we prompted the possibility of employing azodicarboxylates as electrophiles in the proline catalytic system. Gratifyingly, this transformation proceeded in a highly stereoselective manner for both aldehyde and ketone substrates.[6]

In parallel, in 2001, studies demonstrated that Cu(BOX), in addition to the HOMO-activation, allowed reactions to occur via LUMO-activation of electron-poor olefins. Olefinic $\alpha$-ketoesters were activated toward catalytic enantioselective 1,4-additions of electron-rich aromatic compounds, providing the Friedel–Crafts products.[7] A similar organocatalyzed Friedel–Crafts reaction employing $\alpha,\beta$-unsaturated aldehydes was realized in 2002.[8] Following these preliminary reports, our laboratory turned the attention to the use of enones and 4-hydroxycoumarins as Michael acceptors and carbon-nucleophiles, respectively. By virtue of their vitamin-K antagonistic effects, 4-hydroxycoumarins are an important class of compounds used as anticoagulant drugs. The simplest synthetic 4-hydroxycoumarin used for therapeutic treatment is warfarin,

**SCHEME 1.** Metal-Catalysis and Organocatalysis



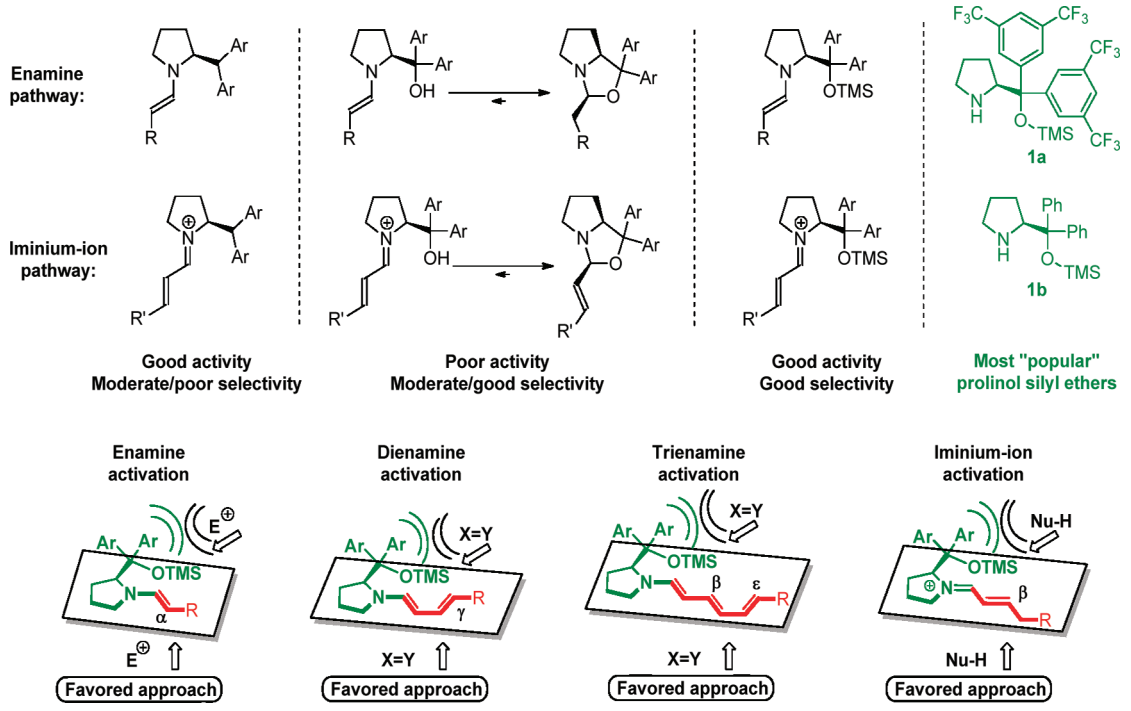
**SCHEME 2.** Activation Modes in Aminocatalysis




formed by addition of the enol nucleophile to methyl styryl ketone. It was demonstrated that, by LUMO-activation of enones using a chiral diamine, highly enantioenriched warfarin or warfarin-like compounds can be accessed.[9]

Encouraged by these initial studies, where it was demonstrated that experiences from the "metal catalysis world" could be successfully transferred to asymmetric organocatalysis, our attention gradually shifted toward the second core issue: to challenge the system with less-studied reactions in order to develop unique bond-formations. The first and by far the most crucial challenge faced in this endeavor was catalyst selection and development. In metal catalysis, decades of intensive research had led to the discovery of fairly general catalytic systems. On the contrary, similar information with respect to useful organocatalysts was, at the time, basically nonexisting, leaving trial-and-error as the only approach. Nevertheless, by joint efforts of the chemical community, some nongeneral, yet useful catalytic motifs appeared in a relatively short time span (Scheme 2, left). The original aminocatalyst, proline, performed well in enamine-mediated pathways; however, the success was usually correlated with the hydrogen-bond-acceptor ability of the approaching electrophile. A class of $C_2$-symmetric pyrrolidines seemed to be more general governing bodies, which via steric shielding provided good results in a range of enamine-mediated reactions. The only disadvantage was the necessity of fine-tuning of the R-substituent for each individual reaction. In comparison, general catalysts capable of facial differentiation in iminium-ion-mediated

**SCHEME 3.** Catalyst Design Plan and Modes of Stereoinduction



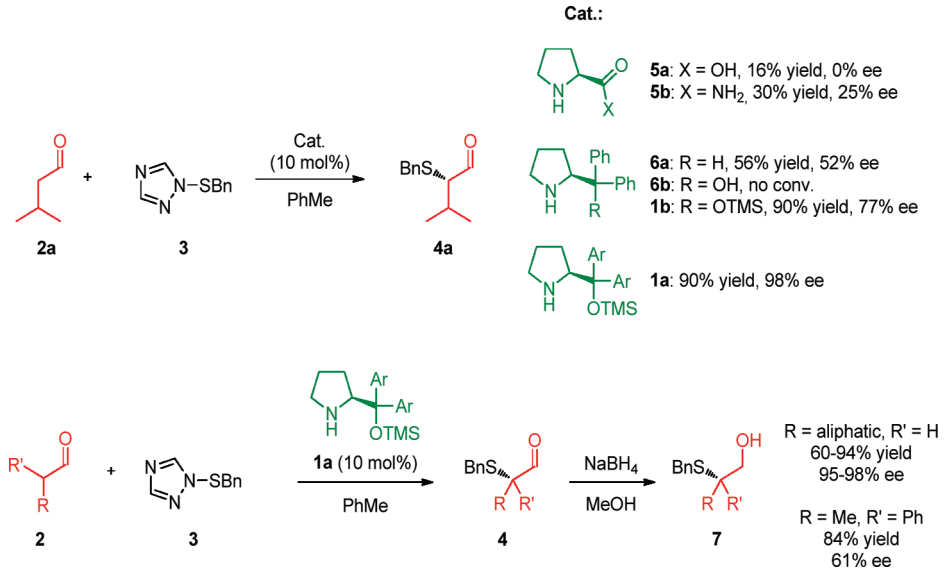

pathways were rare. Diamine catalysts displayed good activity and some generality for enone substrates; however, prolonged reaction times sometimes prevailed.[9] Moreover, at that time, no single catalyst showed good and consistent activity/selectivity in both the HOMO and LUMO pathways. The most general catalysts at that time were MacMillan's imidazolidinone-based catalysts.[10] Although applicable to a range of reactions, ultimate fine-tuning of the substituents was often required to reach the desired selectivities (>90% ee).

At this time, we started the pursuit for a general organocatalyst, with the capacity to promote both enamine- and iminium-ion-mediated reactions with good stereoselectivities. The lead structures were diarylmethylpyrrolidine and diarylprolinol, which previously had been shown to exhibit amino-catalytic acitivity; however, no application in asymmetric catalysis was reported.[11] Interestingly, our studies showed that these catalytic systems displayed "orthogonal" characteristics regarding catalytic activity and selectivity (Scheme 3, top). The level of steric shielding provided by diarylmethylpyrrolidines was usually insufficient and provided only in rare cases high enantioselectivities, although good reactivity was observed for a range of different transformations. Contrarily, the prolinol system often promoted good stereocontrol while lacking the ability to provide sufficient catalyst turnover. The formation of a "parasitic" oxazolidine species was rationalized as the main reason of catalyst inhibition.[12] In order to circumvent this inhibitory pathway, a silyl-protected version of the diarylprolinol catalyst was designed and synthesized.[13] Gratifyingly, this turned out to be the final adjustment required to furnish a sterically demanding, yet highly active and general organocatalyst. Excellent face-differentiation and enantiocontrol (Scheme 3, bottom) are provided by the bulky side-chain of the catalyst, forcing the reacting electrophile/nucleophile/dienophile to approach from the least sterically hindered side of the catalyst-bound intermediate (enamine/dienamine/trienamine/iminium-ion). From a library of synthesized diarylprolinol silyl ethers (TMS = trimethylsilyl), two of them, **1a** (Ar = 3,5-$(CF_3)_2C_6H_3$) and **1b** (Ar = Ph), proved to be the most successful catalysts (Scheme 3, right). A wide range of enantioselective reactions via four distinct reaction pathways, named as enamine-, dienamine-, trienamine- and iminium-ion activation were realized (Scheme 2, right). Herein, some of the most significant contributions in these areas are described.[14]

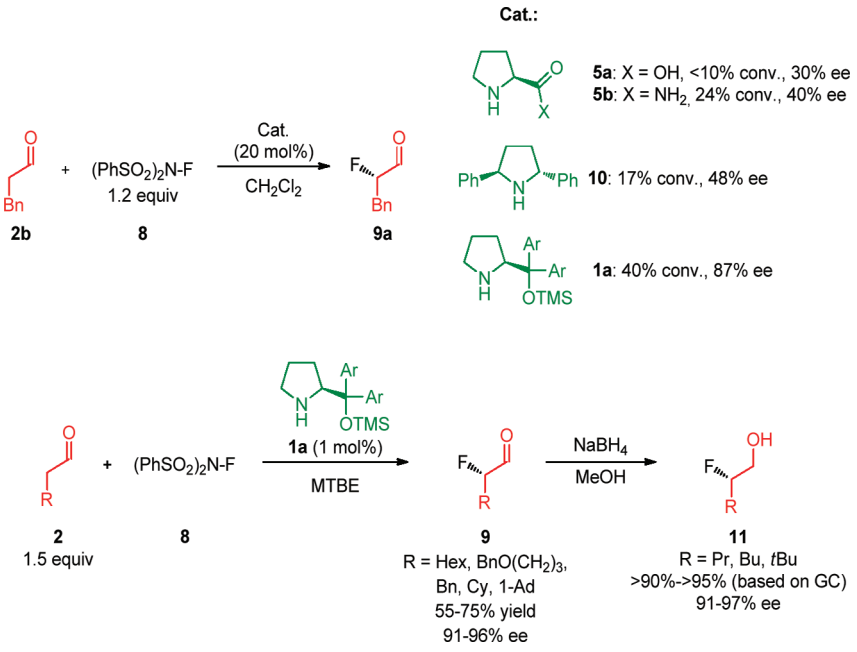
## Enamine-Mediated Catalysis

The TMS-protected prolinol catalyst **1a** was initially developed for the asymmetric α-sulfenylation of aldehydes **2** (Scheme 4, top).[13] In the model reaction, L-proline **5a**, L-prolinamide **5b**, and the secondary amine catalysts **6a** and **6b** proved to be unreactive and/or nonselective (up to 56% yield and 52% ee). However, with the TMS protection of the

**SCHEME 4.** α-Sulfenylation of Aldehydes




**SCHEME 5.** α-Fluorination of Aldehydes




hydroxyl-group, a highly reactive and selective system was obtained. With catalyst **1b** (which was later independently applied by Hayashi et al. in the Michael addition to nitroalkenes, vide infra), a significant increase of both reactivity and selectivity was observed (90% yield, 77% ee). Further catalyst modification to the more bulky aryl-groups of **1a** afforded a remarkable increase of selectivity (90% yield, 98% ee).

The reaction setup was tested on several aliphatic aldehydes and afforded the resulting sulfenylated products **4** with excellent enantioselectivity determined after reduction to the alcohol **7** (Scheme 4, bottom). Applying an α,α-disubstituted aldehyde, however, resulted in diminished stereocontrol.

With these intriguing results, we continued to investigate the potential of the new catalytic system in the asymmetric α-fluorination of aldehydes (Scheme 5).[15] An intrinsic challenge of this reaction is the increased acidity of the α-proton of the fluorinated product **9**, which may cause the product to racemize or react further to yield undesired difluorinated product. Again, L-proline **5a**, L-prolinamide **5b**, and $C_2$-symmetric catalyst

**10** produced inferior results in terms of selectivity and conversion, when carrying out the model reaction with NFSI **8** as the fluorinating agent. However, when utilizing the prolinol ether **1a**, high levels of stereoinduction were observed, despite the occurrence of substantial difluorination. Nevertheless, this could be circumvented by changing the solvent, reducing the catalyst loading to 1 mol %, and applying excess aldehyde. Utilizing this protocol, monofluorinated products were obtained in good isolated yields and with high levels of stereocontrol.

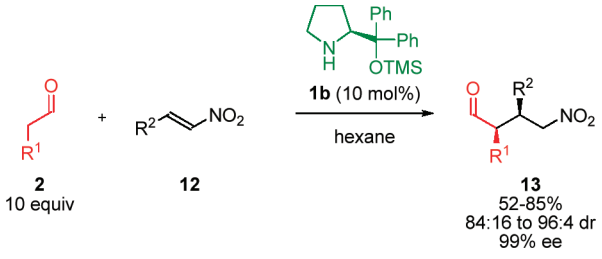
Shortly after these studies, the first α-C−C-bond forming reaction implementing the diphenylprolinol ether system was demonstrated by Hayashi et al. in the Michael addition of aldehydes to nitroalkenes (Scheme 6).[16] These well-recognized Michael acceptors are good reaction partners for the direct Michael addition of unmodified aldehydes proceeding via enamine catalytic species as presented by Barbas and Betancort.[17] With various aliphatic aldehydes, the reaction was demonstrated for a series of nitroolefins **12** with excellent stereocontrol both in terms of enantio- and diastereoselectivity (99% ee, up to 19:1 dr).

One of the most remarkable features of the diarylprolinol silyl ether system is its generality. Prior to 2005, organocatalytic procedures for α-aminations **14**,[6] α-brominations **15**,[18] α-addition to vinyl ketone providing **16**,[19] and Mannich reactions **17**[20] had all been described; however, the optimal catalytic system varied for each reaction, necessitating extensive catalyst screening. At this point, a study was performed underlining the usefulness and generality of the diarylprolinol silyl ether **1a** for all of the above-mentioned reactions (Scheme 7).[12] The results demonstrated a remarkable selectivity and efficiency in all cases delivering the products in 71−88% yield and 90−98% ee. It should be noted that when carrying out the α-amination and Mannich reaction with **1a**, the absolute configuration showed to be opposite to the configuration when L-proline **5a** was applied, due to a change in the mode of catalyst stereoinduction.[21]

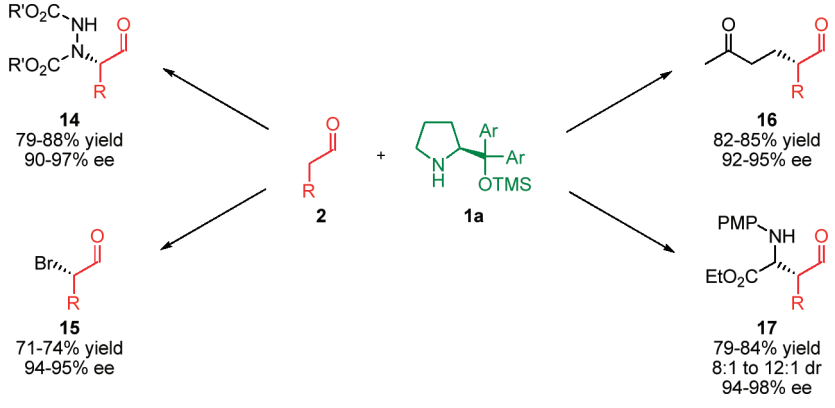
Over the following years, many important contributions were made which manifested the diarylprolinol silyl ethers as privileged catalysts for α-functionalizations of aldehydes. In this course, we became interested in the α-arylation reaction, due to the challenge of effectively introducing a $C(sp^3)-C(sp^2)$ bond in the α-position (Scheme 8).[22] The developed method relied on applying quinones **18** as the aromatic partner to afford optically active α-arylated aldehydes with electron-rich aromatic moieties. Following the addition/aromatization sequence, subsequent phenol cyclization with the aldehyde afforded the isolated hemiacetal 2,3-dihydrobenzofuran products **19**. Surprisingly, the bulky catalyst **1a** showed no activity in this transformation. However, the application of diphenylprolinol ether **1b** proved successful and a series of quinones and aldehydes were employed, affording the products in moderate to excellent yields and with excellent enantioselectivities.

In 2010, the α-arylation was further developed in a study applying electrochemical oxidative conditions for the in situ preparation of the electrophilic species from aminophenols (Scheme 9).[23] The study demonstrated the robustness of the

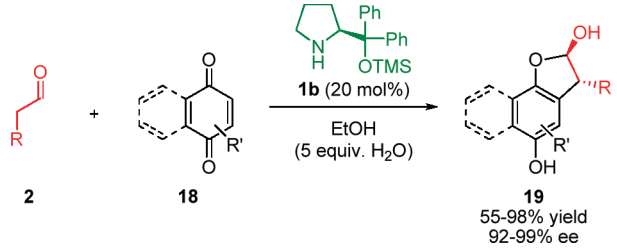
**SCHEME 6.** Michael Addition to Nitroalkenes



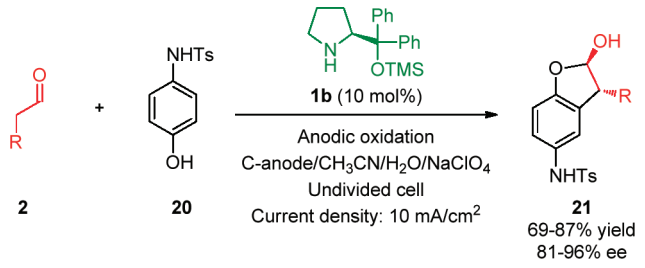

**SCHEME 7.** Early Demonstrations of the Generality of the Diarylprolinol Silyl Ether System



**SCHEME 8.** α-Arylation of Aldehydes




**SCHEME 9.** α-Arylation of Aldehydes under Anodic Oxidative Conditions




catalytic system as it continuously performed well in this setup. With various aliphatic aldehydes and *N*-tosyl-4-aminophenol **20** in an undivided cell equipped with carbon-rod and platinum-net electrodes, the resulting 2,3-dihydrobenzofurans **21** were synthesized in high yields and up to excellent enantiomeric excesses. Notably, the protocol delivers access to *meta*-alkylated anilines, which are usually not accessible by standard Friedel–Crafts alkylation methods.

## Dienamine- and Trienamine-Mediated Catalysis

Amino-substituted dienes are electron-rich conjugated systems, well-suited for Diels–Alder type reactions. In 2006, the HOMO-raising principle in enamine-mediated reactions was extended to α,β-unsaturated aldehyde **22** starting materials (Scheme 10).[24] This mode of activation proceeds via the intermediacy of a dienamine species, thus providing activation of the γ-position of the original aldehyde toward reaction with dienophiles. In this reaction, the catalyst serves a dual purpose: (i) formation of the catalytic dienamine; (ii) providing the required face-differentiation. Notably, the formation of catalytic dienamine species and application of these in formal asymmetric catalytic cycloaddition reactions have been studied by several groups, however, mainly focusing on the use of chiral amines and enones.[25] In our study, it was demonstrated that the catalyst-enal condensation product **24** was, upon formation, rapidly isomerized to the *s-trans* dienamine **25**, present as an *E*/*Z* mixture of the distant double bond. Single-bond rotation led to the *s-cis* intermediate, which readily reacted with the azodicarboxylate **23** in a concerted fashion. Consecutive hydrolysis/isomerization furnished the final γ-aminated enals **26** in moderate yields and high enantioselectivities.

More recently, the concept of HOMO-activation was further extended to incorporate the use of polyconjugated enals, such as 2,4-dienals **27**, which upon condensation with the diarylprolinol silyl ether form a trienamine species **A** (Scheme 11).[26] By density functional theory (DFT) calculations, it was shown that the rotational barrier of the C4–C5 single bond more distant to the steric bulk of the catalyst requires an energy of only 10 kcal/mol (forming **B**) and is slightly favored compared to the alternative C2–C3 rotation. Reaction of the *s-cis* diene motif, present in catalytic amounts, with a reactive dienophile such as olefinic azlactones **28** or oxindoles **29**, furnished cyclohexenes **30**/**31**, carrying up to four contiguous stereogenic centers. Due to the concerted mechanism of the Diels–Alder reaction, steric shielding at the C3-carbon (also forming a new bond) indirectly extends the chirality transfer from the catalyst to the remote C6-position (eight bonds away from the enantiocontrolling group), and as a result highly enantioenriched products are obtained.

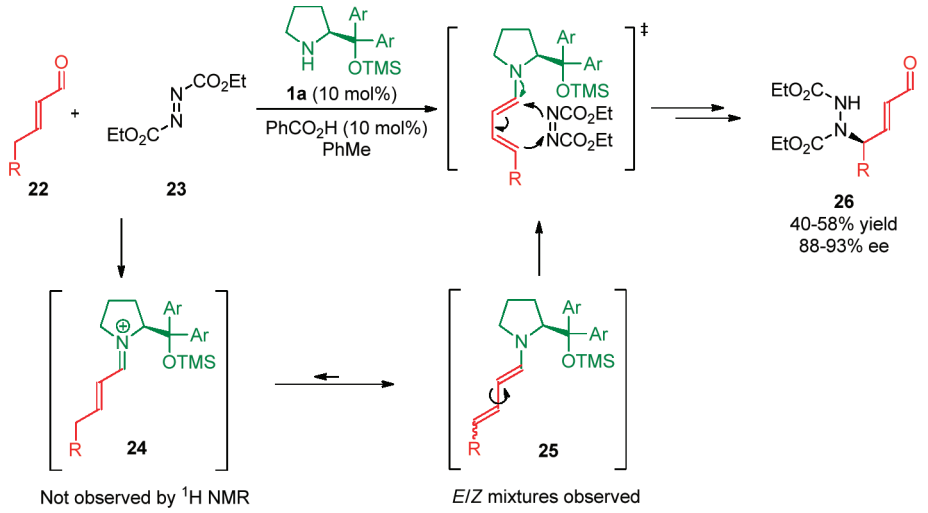
## Iminium-Ion-Mediated β-Functionalizations of α,β-Unsaturated Aldehydes

A main challenge often encountered in conjugate additions to α,β-unsaturated aldehydes is related to the possibility of 1,2-addition to the carbonyl group of the starting enal, which is especially pronounced in the case of hard nucleophiles. LUMO-activation of α,β-unsaturated aldehydes via formation of iminium-ion intermediates in a reaction between an aminocatalyst and a starting enal, an important activation pathway commonly utilized in the field of aminocatalysis, offers a possibility to overcome these difficulties. Among the multitude of aminocatalysts capable of iminium-ion formation, the diarylprolinol silyl ethers possess a great ability of enabling chemoselective 1,4-additions even when hard oxygen-centered nucleophiles are employed. Furthermore, high enantioselectivities arising from the aforementioned shielding effect of catalyst **1a**/**1b** are observed in most of the cases.

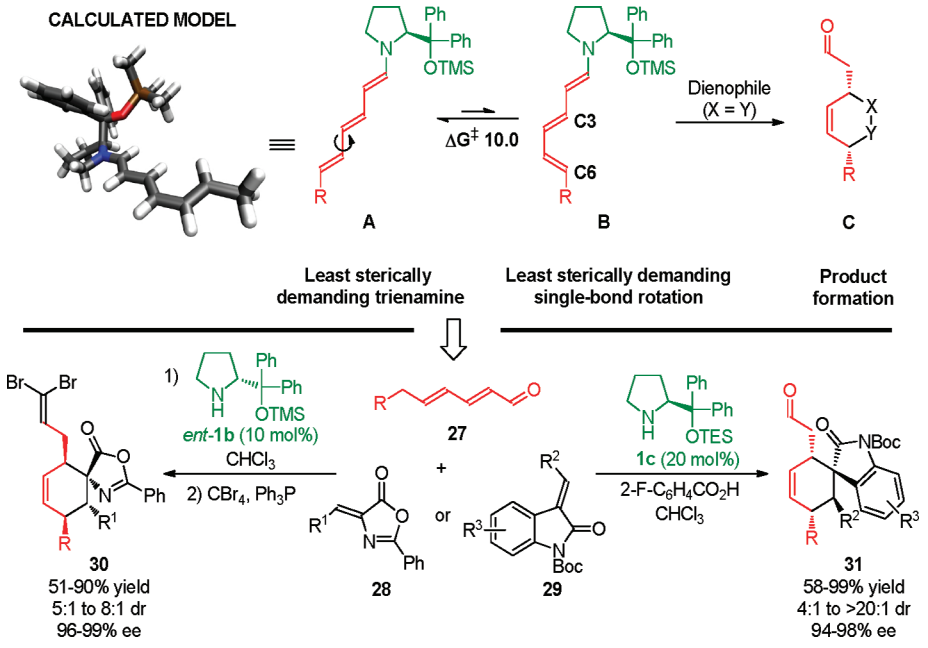
## Conjugate Additions of Heteronucleophiles

There are four main types of hetero-Michael additions that have been realized employing the diarylprolinol silyl ether systems, oxa-, aza-, sulfa- and phospha-Michael reactions,

**SCHEME 10.** Dienamine Activation




**SCHEME 11.** Trienamine Activation

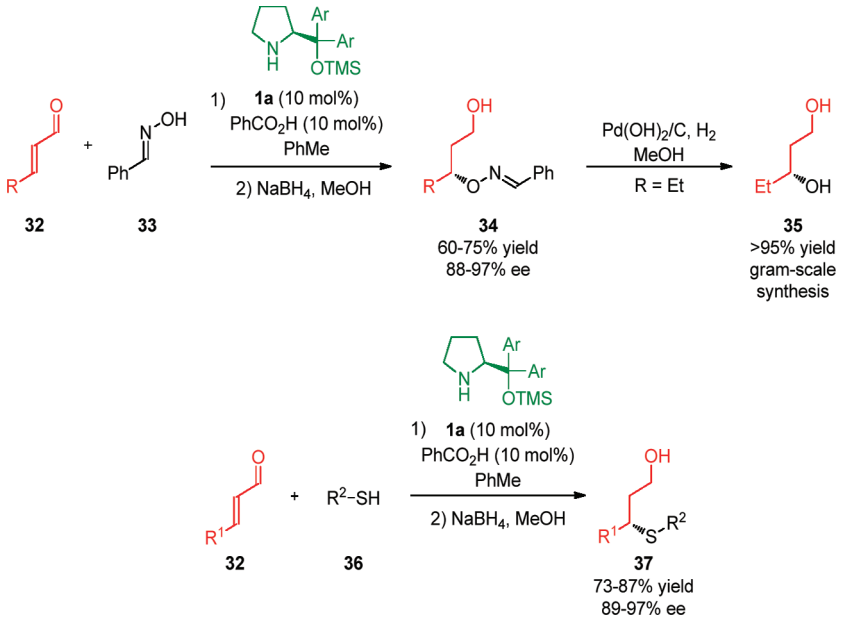



and different requirements must be fulfilled in order to achieve success in each case.

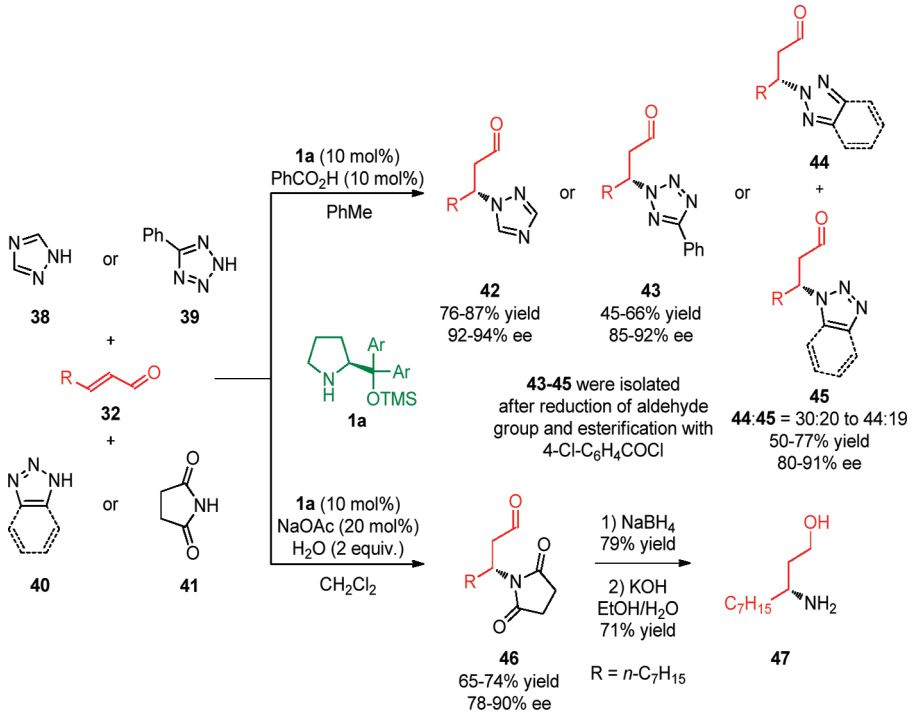
Due to the hardness of oxygen-centered nucleophiles, oxa-Michael additions to $\alpha,\beta$-unsaturated carbonyls are considered particularly challenging, as acetal or ketal formation often competes with the conjugate addition. In 2007, oximes **33** were identified as good protected oxygen-centered nucleophiles capable of circumventing these challenges (Scheme 12).[27] Catalyzed by **1a** conjugate addition of **33** to enals **32** proceeded efficiently in a highly enantioselective manner. Importantly, liberation of the hydroxyl group can be realized under hydrogenolytic conditions affording product **35**, and the whole procedure was performed on a gram scale, highlighting important practical aspects of this catalytic system. Under similar reaction conditions, conjugate thiol addition was realized, enabling for enantioselective introduction of C–S stereocenters **37**.[28]

Aza-Michael additions were also accomplished applying triazoles **38** and tetrazoles **39**[29] as well as succinimide **41**[30] as efficient nitrogen nucleophiles (Scheme 13). These C–N bond forming processes are characterized by their high enantioselectivities ensured by the diarylprolinol silyl ether

**SCHEME 12.** Enantioselective Oxa- and Sulfa-Michael Additions



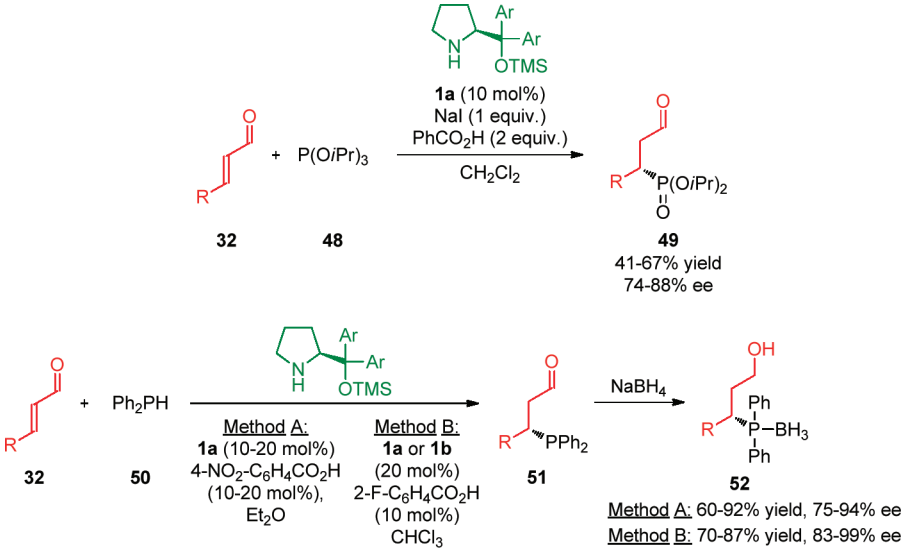

**SCHEME 13.** Enantioselective Organocatalytic Aza-Michael Reactions




catalyst. In the case of 1,2,3-triazole and 1,2,3-benzotriazole **40**, formation of two regioisomeric products **44** and **45** in up to a 2:1 ratio was observed. Notably, one of the benefits of using succinimide **41** relates to the possibility of deprotecting the amine functionality under hydrolytic conditions to afford 1,3-aminoalcohol **47**.

In a similar time frame, enantioselective P–C bond forming reactions were developed following an iminium-ion activation pathway (Scheme 14).[31−33] Two different P(III) species, phosphites and phosphines, were employed in these processes. In the case of phosphite addition, the proper choice of compatible nucleophilic additive enabling

**SCHEME 14.** Enantioselective P–C Bond Forming Reactions




P(III) to P(V) oxidation via an Arbuzov-type dealkylation reaction proceeding at one of the phoshite alkoxy moieties was crucial.[31] The direct $\beta$-phosphonylation of enals with triisopropyl phosphite **48** proceeded with the highest efficiency in the presence of stoichiometric amounts of benzoic acid and NaI as acidic and nucleophilic additives, respectively. Simultaneously, two independent reports on hydrophosphination of $\alpha,\beta$-unsaturated aldehydes with diphenylphosphine **50** using catalysts **1a** or **1b** were disclosed.[32,33] In both reports, Michael adducts **51** were reduced in situ to afford more stable alcohols **52**.

## Conjugate Additions of Carbon-Centered Nucleophiles

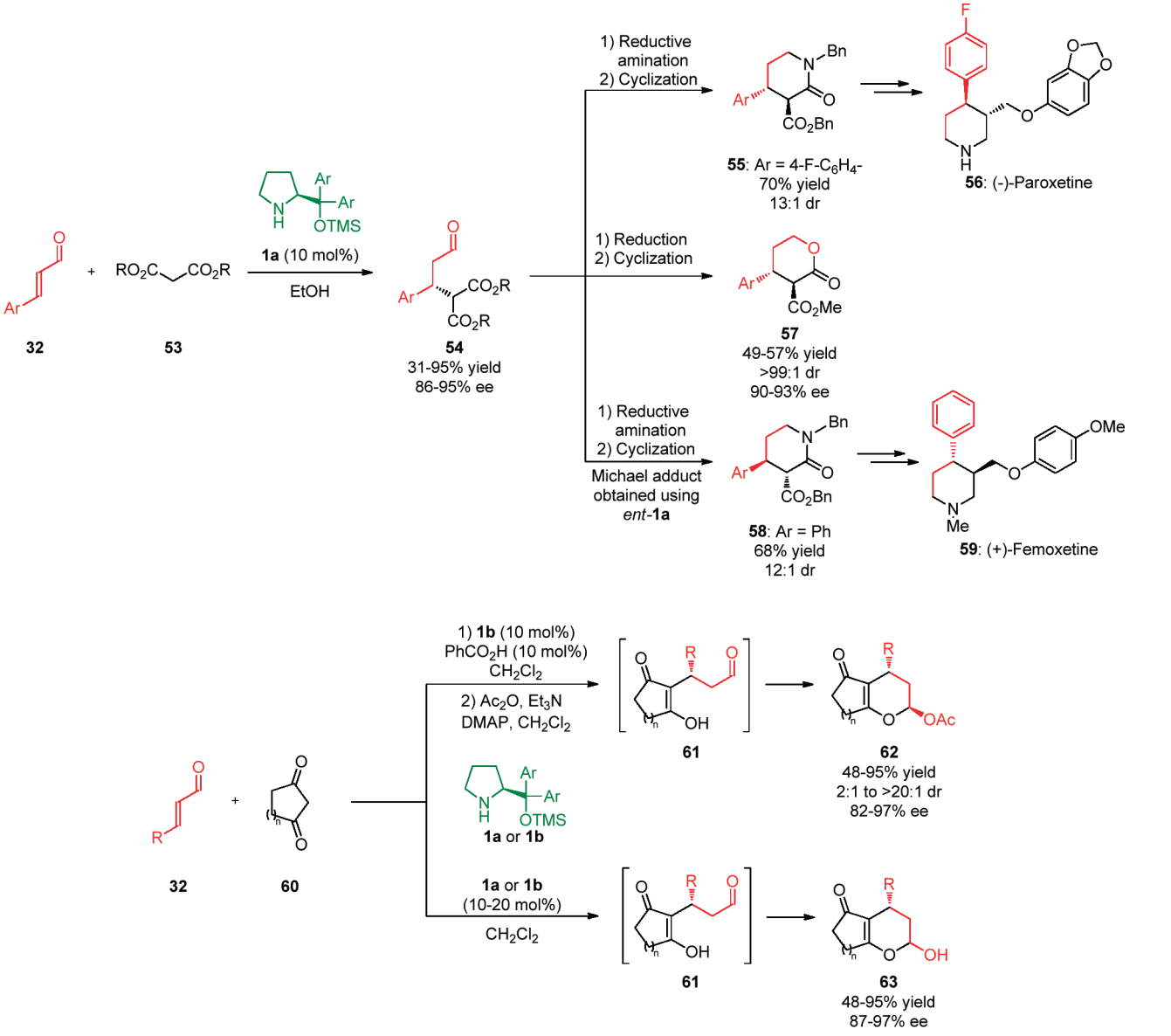
One of the very first carbon nucleophiles that was added in enantioselective fashion to iminium-ion-activated aromatic enals using the diarylprolinol silyl ether catalyst was dialkyl malonate **53** (Scheme 15).[34] The Michael adducts **54** obtained in this reaction can serve as versatile chiral building blocks for the synthesis of lactams **55** and **58**, lactones **57**, as well as various pharmacologically active compounds, such as (−)-paroxetine **56** and (+)-femoxetine **59**. Following this initial report, the catalyst was shown to promote various chemo- and stereoselective additions of different 1,3-dicarbonyl compounds to $\alpha,\beta$-unsaturated aldehydes. For instance, when 1,3-diketones **60** were employed as Michael donors, the originally formed Michael adducts **61** cyclized to give stable hemiacetal products **62** or **63**.[35,36]

Non-natural, $\alpha,\alpha$-disubstituted $\alpha$-amino acids constitute an important group of compounds easily accessible in a protected form via an enantio- and diastereoselective iminium-ion activation pathway when racemic $\alpha$-substituted oxazolones **64** are employed as carbon nucleophiles (Scheme 16).[37] Particularly high diastereoselectivities were obtained when a bulky benzhydryl substituent was present at C-2 of the oxazolone. DFT calculations indicated that the facial selectivity in the approach of the nucleophile is driven by steric repulsion between the C-2 substituent of oxazolone and the bis(3,5-bistrifluoromethylphenyl)trimethylsilyloxymethyl group of the iminium-ion-activated enal (Scheme 16, bottom).

Frequently, $\beta$-functionalizations are followed by the subsequent modification occurring at the carbonyl group, allowing for a facile introduction of various functional groups in a domino fashion. These strategies enable rapid access to various useful carba- and heterocyclic frameworks; for example, the [3 + 3]-annulations constitute a straightforward entry to differently functionalized cyclohexane or cyclohexene derivatives. In 2007, an example involving unprecedented tandem Michael/Morita–Baylis–Hillman reaction leading to the formation of $\alpha$-alkylidenecyclohexanones **70** was disclosed (Scheme 17).[38] Under the reaction conditions, Nazarov reagent **66** underwent iminium-ion-mediated Michael addition followed by an intramolecular Morita–Baylis–Hillman reaction. Importantly, mechanistic investigations revealed that diarylprolinol **1a** acts as the catalyst for the Morita–Baylis–Hillman step.

A highly stereoselective, organocatalytic Michael/Knoevenagel domino reaction of 4-diethoxyphosphoryl-3-oxobutanoates **71** with $\alpha,\beta$-unsaturated aldehydes constitutes another example of successful application of the diarylprolinol silyl

**SCHEME 15.** Enantioselective Conjugate Addition of 1,3-Dicarbonyl Compounds




ether catalyst for construction of highly enantiomerically enriched cyclohexenone derivatives **74** (Scheme 18, top).[39] In the case of aliphatic enals, the use of dihydroquinine **75** as a Brønsted base cocatalyst to facilitate the formation of the corresponding enol of **71** turned out to be necessary. It was postulated that the secondary aminocatalyst is involved in the intramolecular Knoevenagel condensation. Simultaneously, similar results from the Hayashi group utilizing dimethyl 3-oxopentanedioate **72** as a 1,3-dinucleophilic species were disclosed (Scheme 18, bottom).[40]

In 2007, a different cyclohexane-annulation strategy was developed (Scheme 19).[41] This time it was initiated by conjugate addition of 1,3-dinitroalkanes **78**. Subsequent Henry reaction furnished cyclohexanol framework **80**. In this domino reaction, starting 1,3-dinitroalkanes are efficiently desymmetrized, leading to the formation of densely functionalized cyclohexanols bearing five contiguous stereocenters. This example demonstrates an extraordinary potential of the catalytic system in assembling molecular and stereochemical complexity.

## Aminocatalytic Cascade Reactions

The ability of the diarylprolinol silyl ether catalysts to activate aldehydes and $\alpha,\beta$-unsaturated aldehydes via enamine and iminium-ion formation, respectively, makes the catalysts ideal for employment in cascade reactions, where $\alpha,\beta$-disubstituted aldehydes having at least two stereocenters

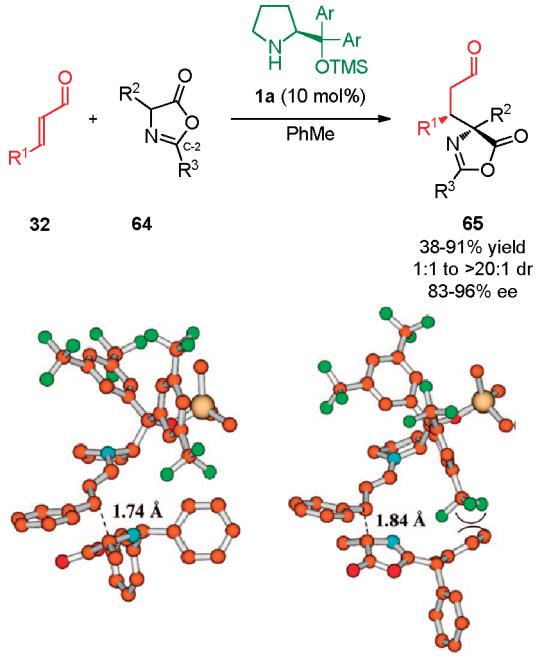
are afforded. Such reactions are based on conjugate addition of nucleophiles to α,β-unsaturated aldehydes followed by a functionalization at the α-position via the transient enamine intermediate. In 2005, it was demonstrated that the catalyst **1a** is able to catalyze the epoxidation of mono- and β,β-disubstituted α,β-unsaturated aldehydes (Scheme 20, top).[42]

The epoxidation reaction takes place under mild reaction conditions, employing hydrogen peroxide as the oxidant, and good to high yields and stereoselectivities were obtained for a series of α,β-unsaturated aldehydes. The mechanism involves a stereoselective addition of hydrogen peroxide to the iminium-ion furnishing β-peroxy enamine intermediate **82**, which forms the epoxide **83** by a nucleophilic displacement mechanism producing water as the only byproduct. A few years later, the analogous asymmetric aziridination of α,β-unsaturated aldehydes affording **85** was demonstrated employing catalyst **1b** and a protected hydroxylamine derivative as nitrogen source (Scheme 20, bottom).[43]

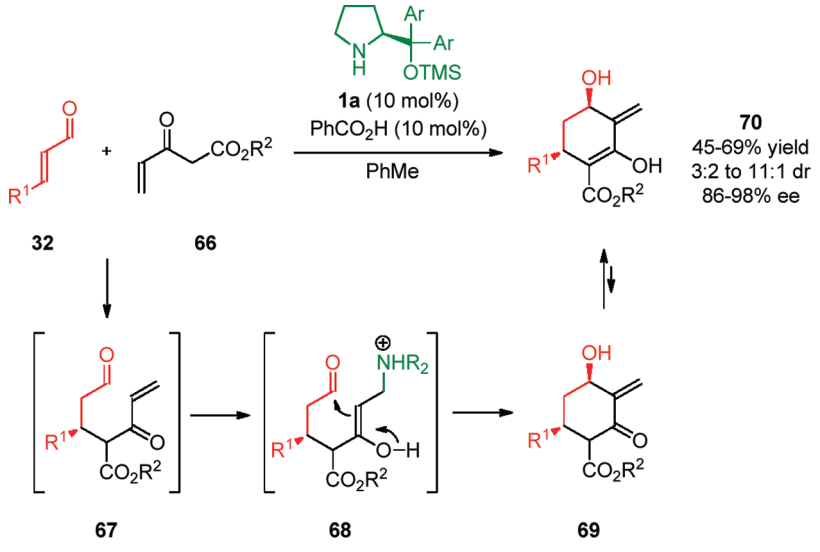
Shortly after the epoxidation reaction, it was also discovered that the iminium-ion/enamine concept could be exploited in reactions where the enamine step is intermolecular, hereby forming acyclic products. During the studies on a conjugate thiol addition to α,β-unsaturated aldehydes,[28] it was discovered that the conversion decreased as the reaction progressed. $^1$H NMR-spectroscopic studies revealed that the catalyst predominantly was bound as a stable enamine species to the thiol product, leaving only minor amounts of catalyst available for conjugate addition. By addition of azodicarboxylates **23** to the reaction, a multicomponent domino sequence was disclosed furnishing 1,2-aminothiols **86**. The products were isolated in good yields and excellent stereoselectivities after reduction of the aldehyde and sequential base-promoted carbamate formation **87** (Scheme 21, top).

Later, the complementary amino-sulfenylation was disclosed and the reaction was accomplished by employing a masked nucleophile as the electrophilic sulfenylation reagent **88**, which is released upon reaction (Scheme 21, bottom).[44] Consequently, only catalytic amounts of nitrogen source **41** had to be added in order to initiate the domino

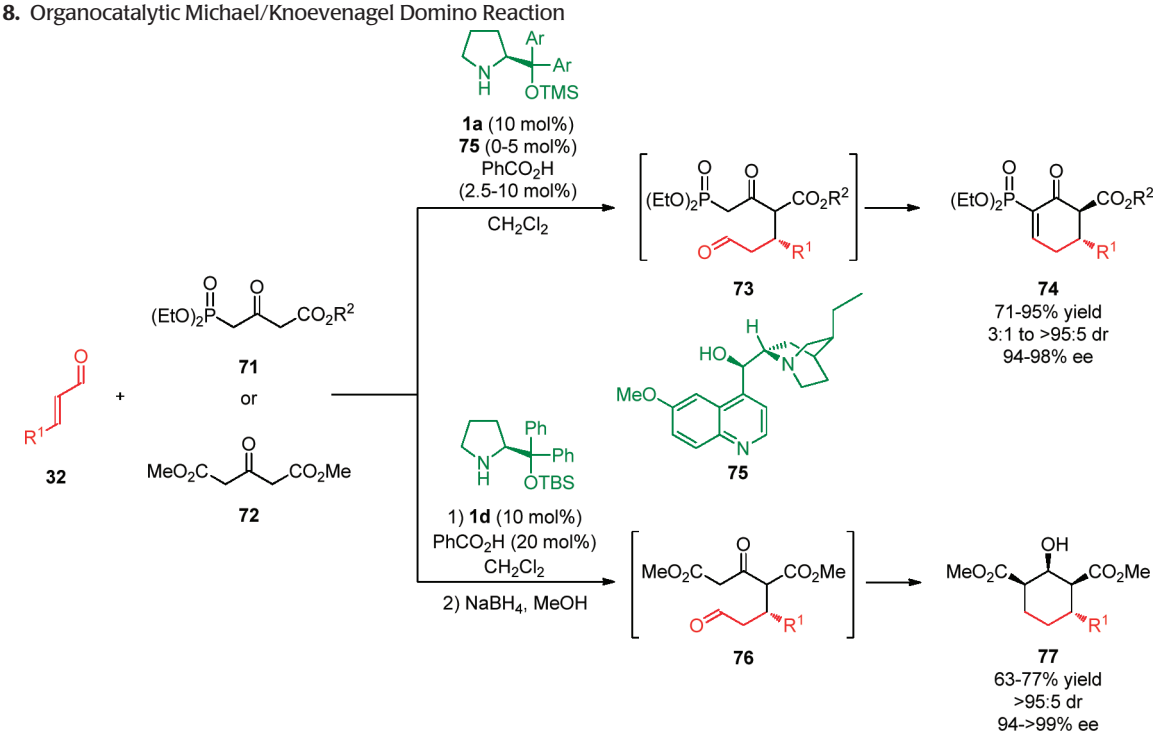
**SCHEME 16.** Enantioselective Synthesis of Protected α,α-Disubstituted α-Amino Acids



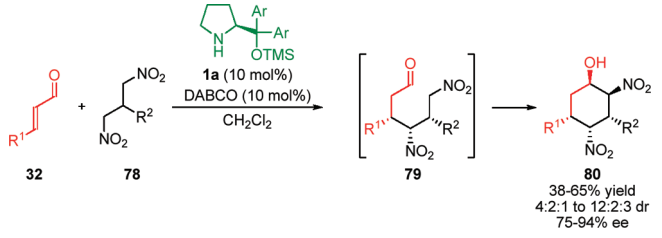

**SCHEME 17.** Enantioselective Michael/Morita–Baylis–Hillman Domino Reaction



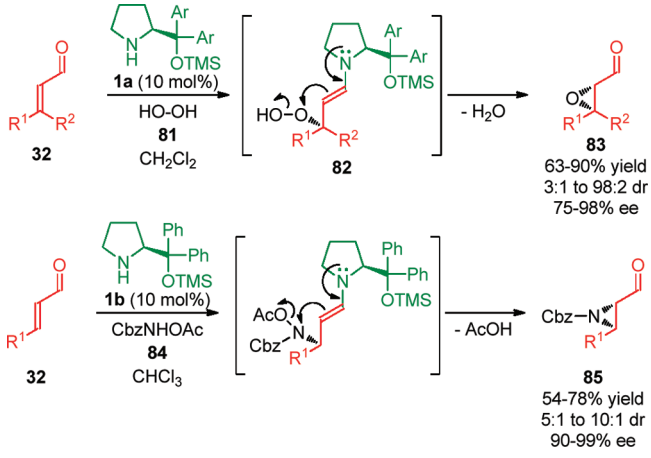
**SCHEME 18.** Organocatalytic Michael/Knoevenagel Domino Reaction




**SCHEME 19.** Enantioselective Michael/Henry Domino Reaction




**SCHEME 20.** Epoxidation and Aziridination of Aldehydes



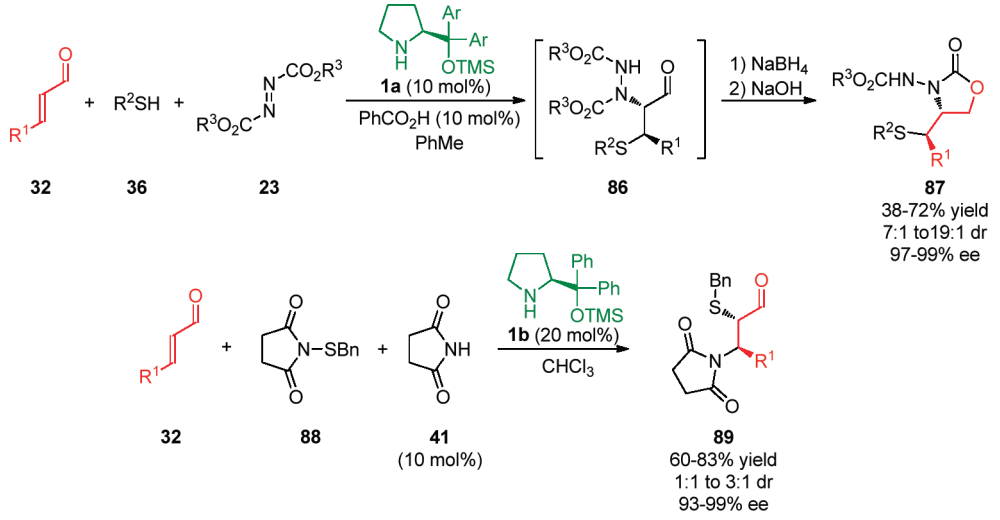

reaction furnishing the products **89** in good yields and excellent enantioselectivities but with poor diastereoselectivities.

In 2006, the combination of a thiol addition with an intramolecular aldol reaction for the highly stereoselective synthesis of tetrahydrothiophenes **91** having three stereocenters was documented (Scheme 22).[45] The catalyst is not only involved in the initial carbon−sulfur bond formation, but it is also believed to control the intramolecular aldol reaction. The obtained stereochemistry of the products suggests that the ring-closing reaction occurs via a highly organized intermediate **92** having the aldehyde substituent ($R^1$) in a pseudoequatorial position, while the phenyl substituent is placed opposite to the steric bulk of the catalyst. The reaction proceeds faster with benzoic acid as additive, and the increase in reaction rate is believed to be an effect of faster iminium-ion formation, as well as increased electrophilicity of the ketone in the aldol reaction by protonation.

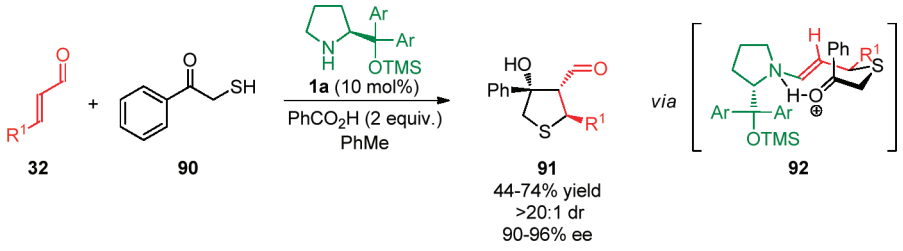
In 2006, Enders et al. developed a triple cascade reaction based on an enamine/iminium-ion/enamine-mediated sequence furnishing tetrasubstituted cyclohexene carbaldehydes **95** with four stereocenters (Scheme 23).[46] The reaction commences with an enamine-mediated addition of a saturated aldehyde to a nitroolefin derivative. The catalyst then activates an $\alpha,\beta$-unsaturated aldehyde toward conjugate addition of the nitroalkane **93**, resulting in an enamine intermediate **94** that cyclizes by an intramolecular aldol condensation.

A different triple cascade reaction based on an iminium-ion/iminium-ion/enamine sequence furnishing differently

**SCHEME 21.** Sulfenylation-Amination and Amino-Sulfenylation of Aldehydes




**SCHEME 22.** Formation of Tetrahydrothiophenes

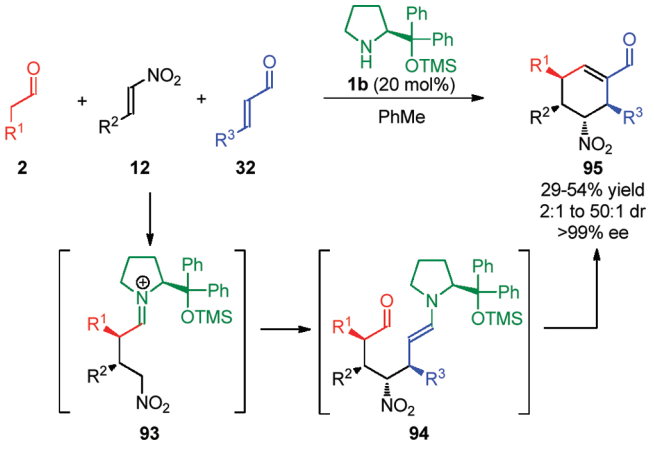



substituted cyclohexene carbaldehydes **99** was later disclosed (Scheme 24).[47] The reaction was realized by the combination of $\alpha,\beta$-unsaturated aldehydes and an activated methylene compound **96**. The products are formed via two consecutive conjugate additions of the carbon nucleophile, followed by an aldol condensation. Furthermore, products possessing an additional third all-carbon quaternary stereocenter could be obtained when malononitrile was substituted for cyano- or nitroacetate derivatives **96**.

In 2010, the reaction of $\alpha,\beta$-unsaturated aldehyde with alkyne-tethered carbon-based nucleophiles **100**, such as malononitrile and cyanoacetates, in a highly stereoselective iminium-ion/enamine/Lewis acid-catalyzed sequence furnishing cyclopentene carbaldehydes **103**/**104** was presented (Scheme 25).[48]

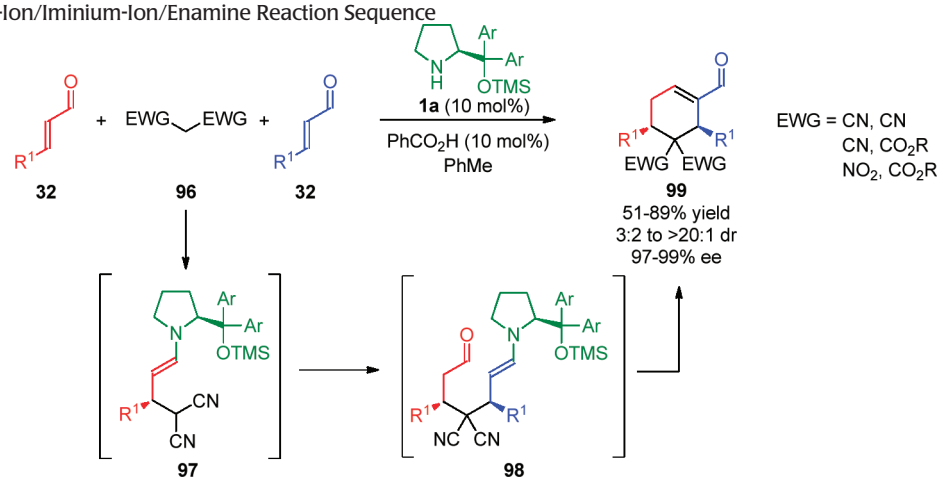
Mechanistic studies revealed a cooperative effect of organocatalysts and Lewis acid in the carbocyclization. When cyanoacetate derivatives were employed, the products **104** were obtained as essentially single isomers. $^1$H NMR spectroscopic studies showed that two diastereoisomers of

**SCHEME 23.** Triple Enamine/Iminium-Ion/Enamine Cascade Reaction

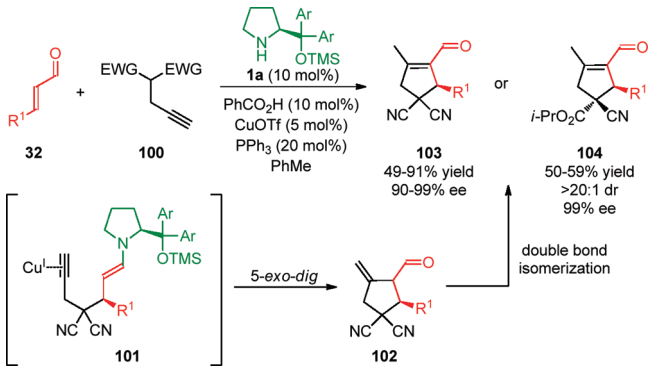



intermediate **101** are formed during the reaction, which eventually ring-close to give only one diastereoisomer of the product. The high selectivity is attributed to a highly diastereoselective catalyst-controlled cyclization of only one of the diastereoisomers, while the interconversion of the intermediates occurs via a retro-Michael reaction.

**SCHEME 24.** Iminium-Ion/Iminium-Ion/Enamine Reaction Sequence




**SCHEME 25.** Iminium-Ion/Enamine/Lewis Acid Reaction Sequence




## Summary and Outlook

The presented work describes the synthetic usefulness, efficiency, selectivity, and robustness of the diarylprolinol silyl ether system in various reactions of aldehydes. Several studies on enamine-mediated transformations of saturated aldehydes have resulted in the introduction of different functionalities in the α-position of aldehydes in a highly stereoselective manner. Later on, this HOMO-activation concept was extended to include α,β-unsaturated aldehydes. After condensation of aldehyde and aminocatalyst, a dienamine species is formed, which can undergo stereoselective Diels–Alder-type reactions with, for example, azodicarboxylates, hereby effectively functionalizing the γ-position of the aldehyde after hydrolytic cleavage of the catalyst. Recently, 2,4-dienals were found to form trienamine intermediates upon condensation with the aminocatalyst. The trienamine effectively reacts with carbon-centered dienophiles, forming aldehyde products having up to four contiguous stereocenters. Due to the concerted nature of the reaction and the efficient catalyst shielding of the β-position, the stereoinduction is achieved at the remote ε-positions of the original aldehyde. Complementary to the enamine-mediated activations, α,β-unsaturated aldehydes can be effectively functionalized via conjugate addition through iminium-ion-mediated processes. In such reactions, the aminocatalyst not only effectively shields one of the enantiotopic faces of the enal, it also ensures good chemoselectivity, affording 1,4-adducts as the only products. Several different carbon nucleophiles and heteronucleophiles have been added in a highly stereoselective fashion. Finally, the ability of the catalysts to participate in various enamine- and iminium-ion-mediated processes makes them ideal for the sequential addition of nucleophiles and electrophiles in a cascade manner, thereby giving access to products having at least two stereocenters. The authors believe that in the years to come the diarylprolinol silyl ether catalysts will maintain their prominent position as general catalysts in the field of aminocatalysis. In addition, it is our hope and expectation that further developments regarding activation modes, lower catalyst loadings, and industrial applications will be achieved. Recently, much effort has been devoted to mechanistic studies of these catalytic systems.[21,49] Different techniques, such as real-time NMR spectroscopy and X-ray crystallography, have been successfully employed for the identification of catalytic intermediates, providing a better understanding of the catalytic pathways. The mechanistic investigations could be beneficial for future developments of diarylprolinol silyl ether catalysis.

BIOGRAPHICAL INFORMATION

**Kim Lebek Jensen** was born in Svendborg, Denmark. He completed his M.Sc. degree in chemistry in 2010 at Aarhus University, Denmark. He is currently conducting on his Ph.D. research under

the supervision of Prof. Karl Anker Jørgensen at the Center for Catalysis, Aarhus University.

**Gustav Dickmeiss** was born in Tarm, Denmark. He obtained his M.Sc. degree in chemistry in 2009 at Aarhus University, Denmark. Currently, he is finishing his Ph.D. thesis performed under the guidance of Prof. Karl Anker Jørgensen at the Center for Catalysis, Aarhus University.

**Hao Jiang** was born in Shanghai, P. R. China. He studied chemistry at Aarhus University, Denmark and received his M. Sc. degree in 2009. He is currently pursuing his Ph.D. studies under the supervision of Prof. Karl Anker Jørgensen at the Center for Catalysis, Aarhus University.

**Łukasz Albrecht** was born in Łódź, Poland. He received his Ph.D. (2009) from the Technical University of Lodz, Poland working under guidance of Prof. Henryk Krawczyk. Currently, he is a postdoctoral fellow with Prof. Karl Anker Jørgensen at the Center for Catalysis, Aarhus University, Denmark.

**Karl Anker Jørgensen** received his Ph.D. from Aarhus University in 1984. He was a postdoc with Prof. Roald Hoffmann, Cornell University, 1985. In 1985, he became an Assistant Professor at Aarhus University, and in 1992 he moved up the ranks to Professor. His research interests are the development, understanding, and application of asymmetric catalysis.

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FOOTNOTES

*To whom correspondence should be addressed. E-mail: kaj@chem.au.dk.

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