Organocatalysis

International Edition: DOI: 10.1002/anie.201503920
German Edition: DOI: 10.1002/ange.201503920

The Diarylprolinol Silyl Ethers: Ten Years After

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aminocatalysis · diarylprolinol silyl ethers · organocatalysis

Asymmetric organocatalysis has experienced an incredible development since the beginning of this century. The expansion of the field has led to a large number of efficient types of catalysts. One group, the diarylprolinol silyl ethers, was introduced in 2005 and has been established as one of the most frequently used in aminocatalysis. In this Minireview, we will take a look in the rear-view mirror, ten years after the introduction of the diarylprolinol silyl ethers. We will focus on the perspectives of the different activation modes made available by this catalytic system. Starting with a short introduction to aminocatalysis, we will outline the properties that have made the diarylprolinol silyl ethers a common choice of catalyst. Furthermore, we will describe the major tendencies in the activation and reaction concepts developed with regard to reactivity patterns and combinations with other activation concepts.

1. Introduction

1.1. General Introduction

When the spermatozoon enters the egg in the uterus, life is generated. Life as we know it is based on a large number of catalytic reactions, and these are the origin of asymmetry in our body and culture.[1] The catalysts for these reactions are enzymes, which have also been the prime catalysts in academia and industry for over a century.[2]

Owing to the importance of the chiral molecules formed by asymmetric catalysis, such reactions have been of great value since the birth of modern chemistry. Catalytic asymmetric methods have expanded beyond the application of enzymes, and in the last decades of the 20th century, transition-metal complexes dominated the field.[3] Since the turn of the century, organocatalysis has been established as the third pillar of asymmetric catalysis.[4]

The development and application of organocatalysis have expanded from academia to industrial processes, from simple functionalizations to cascade, domino, and tandem reactions, and also cover combinations of organocatalysis with other activation concepts. This progress is based on the development of a large number of different catalytic systems, and in this Minireview, we will focus on one such class of catalysts—the diarylprolinol silyl ethers. These catalysts were introduced in 2005 and have been shown to be able to activate aldehydes by "classical activation concepts" and integrate the relevant intermediates in catalytic processes. Furthermore, they have paved the way for hitherto unknown activation concepts for aldehydes and allowed for the development of a variety of new asymmetric reactions achieving unprecedented molecular complexity. Finally, these catalytic processes have now been integrated in the total synthesis of optically active molecules.

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1.2. Focus of this Review

In the following, we will describe the lessons learned during the ten-year development of the diarylprolinol silyl ethers as organocatalysts in an unconventional manner. In Section 4, we will describe the major tendencies in the different activation concepts with a focus on the first examples of a given reactivity pattern. In Sections 5 and 6, we will present method developments based on more elaborate systems, including cascade reactions, one-pot methods, and combinations with other catalytic systems, again highlighting the first ventures within these areas. Section 7 covers recent examples of unforeseen reactivities. Therefore, this Minireview will not be a comprehensive enumeration of the large number of reactions and methods that apply diarylprolinol silyl ethers. Instead, an exploration of the opportu-

nities introduced by the diarylprolinol silyl ethers will hopefully allow for new avenues to be paved.

2. The Renaissance of Organocatalysis

The millennium started with the birth of a "new field" in catalysis—asymmetric organocatalysis. Asymmetric reactions applying small organic molecules as catalysts had previously been reported;[5] however, the potential of the field had not been realized prior to the publications by the groups of List[6] and MacMillan.[7] These reports applied the two fundamental and well-known activation modes for aldehydes and α,β-unsaturated aldehydes to provide enamine and iminium ion intermediates, respectively, which were integrated into catalytic cycles.[8] The formation of the enamine and iminium ion intermediates generates nucleophilic and electrophilic carbon atoms, respectively, according to the HOMO-raising and LUMO-lowering principles (Figure 1).

It was demonstrated that proline and imidazolidinones, which were some of the most popular organocatalysts in the first years, could be applied in catalytic reactions involving enamine and iminium ion intermediates. These catalysts were typically applied in conceptually simple and fundamental bond-forming reactions for a limited number of functional groups. For reactions involving enamine catalysis, the initial focus was on the asymmetric α-functionalization of aldehydes by addition to polarized π-systems. These reactions include aldol reactions,[6,9] Mannich reactions,[10] conjugate additions,[11] α-aminations,[12] and α-oxygenations.[13] Subsequently, it was discovered that [4+2] cycloadditions of enamines were possible, leading to α,*ipso*-functionalized products.[14] This discovery highlighted that aminocatalysis could be used in an efficient and selective manner to build more complex structures than those achieved in the initial investigations.

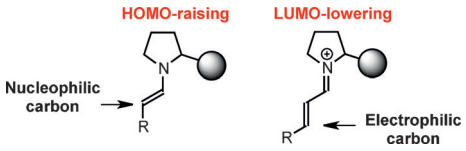

Figure 1. Enamine and iminium ion intermediates.

Interestingly, iminium ion catalysis has taken a different path in terms of method development. It was recognized early on that this activation mode could facilitate various types of reactions. It was demonstrated that α,β-unsaturated aldehydes could be activated by iminium ion catalysis for asymmetric Diels–Alder reactions with dienes leading to α,β-functionalized products.[7] Soon after, a 1,3-dipolar cycloaddition reaction was described, in which α,β-unsaturated aldehydes were reacted with nitrones.[15] The iminium ion activation concept (Figure 1) parallels the activation mode in Lewis acid catalyzed reactions of α,β-unsaturated carbonyl compounds.[16]

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Although in the early years of the new millennium, an impressive development of organocatalytic methods could be observed, the investigations also revealed limitations and challenges. The lack of a general catalyst system necessitated extensive screenings of reaction conditions and catalysts for the development of new reactions. An important challenge was thus the discovery of a general catalyst that could not only improve well-known transformations, but, more importantly, reveal novel reaction concepts.

3. The Introduction of the Diarylprolinol Silyl Ether Catalysts

3.1. Initial Work and Inspiration

The inspiration for the development of the diarylprolinol silyl ethers came from two related compounds, namely, diarylmethylpyrrolidine and diarylprolinol, which were found to be efficient catalysts for [4+2] cycloadditions of enamines, for example.[14,17] These catalysts displayed orthogonal behavior in terms of activity and stereoinduction. The diarylmethylpyrrolidines generally provided high catalytic turnover at modest selectivity, whereas the diarylprolinols performed well in terms of stereocontrol; however, low reaction rates were achieved. Whereas the lack of stereocontrol for the diarylmethylpyrrolidines was hypothesized to arise from insufficient steric shielding, the lack of catalytic turnover for the diarylprolinols was more puzzling. It was found that a parasitic equilibrium existed, with formation of an oxazolidine species. A simple silyl protection circumvented this problem, and therefore, the diarylprolinol silyl ether catalysts were developed (Figure 2).[18]

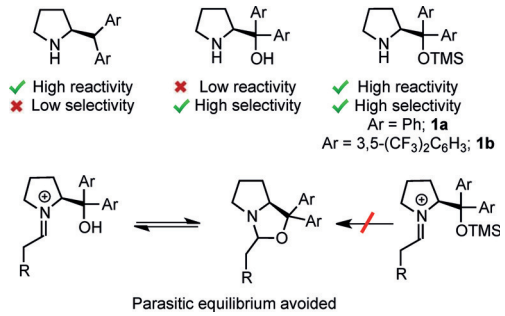


Figure 2. The diarylprolinol silyl ethers and related catalysts.

3.2. Elucidation of the Stereoinducing Properties

Early studies revealed that the stereoselective properties of the diarylprolinol silyl ethers arise from steric shielding by the substituents at the carbon atom attached to the stereogenic center in the pyrrolidine ring.[18a] Several studies have contributed to elucidating the role of the individual moieties of the catalyst in terms of activation as well as stereoinduction. In order to fine-tune the system, the aromatic substituents or the silyl ether protection group are often varied. The two most popular diarylprolinol silyl ethers carry C_6H_5 (**1a**) or 3,5-$(CF_3)_2C_6H_3$ substituents (**1b**) as the aromatic moieties and a trimethylsilyl protecting group at the oxygen atom (Figure 2). In the initial work that introduced the diarylprolinol silyl ethers as a general catalyst system, the effect of the aromatic groups was investigated for the asymmetric α-sulfenylation of aldehydes.[18a] Catalysts carrying C_6H_5 (**1a**), 3,5-$(CH_3)_2C_6H_3$, or 3,5-$(CF_3)_2C_6H_3$ (**1b**) as the aromatic substituents were employed, and it was found that the enantioselectivity of the reaction was affected by these groups, as the three catalysts provided the product in 77, 90, and 98% *ee*, respectively. The authors showed that there was an approximately linear correlation between the Taft E_s values (steric substituent constants)[19] and the enantiomeric excess. This finding indicated that the steric rather than the electronic properties of the aromatic substituents influence the enantioselectivity of the reaction. The absolute stereochemistry of the product suggested that facial discrimination was achieved by steric shielding in the reactive enamine intermediates.

In order to gain further insight into the operating mechanism of enamine catalysis, the relevant intermediates were studied by several groups using various methods, including X-ray analysis,[20] NMR analysis,[21] and computational methods.[22] These studies were motivated by the observation that very high enantioselectivities can be achieved although several enamine intermediates may be present in solution, in which opposite faces of the nucleophilic system would be expected to be shielded (Figure 3). A study of the

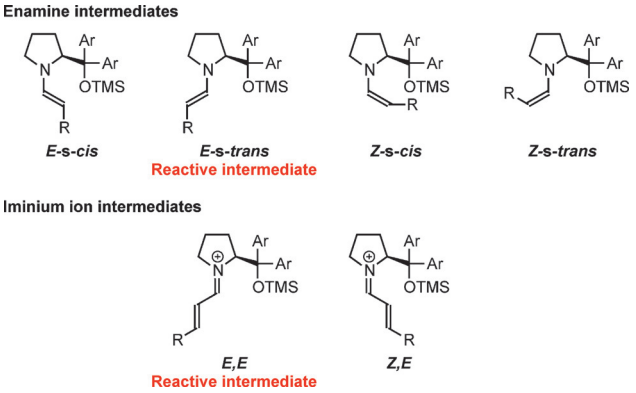


Figure 3. Relevant enamine and iminium ion intermediates.

distribution of the possible enamine intermediates and their reactivity using DFT calculations revealed that two enamine intermediates, both with *E* configuration, were similar in energy. However, the enamine with s-*cis* conformation gave rise to a transition state with a higher energy than the s-*trans* conformer owing to increased steric repulsion.[22a] The enamines with *Z* configuration were found to be higher in energy. Reaction through the *E*-s-*trans* enamine intermediate correlated with the observed product stereochemistry.

The enamine intermediates formed from the diarylprolinol silyl ethers were studied by Gschwind et al. by NMR analysis.[21] In these investigations, it was found that the *E*-s-*trans* enamine was primarily present in solution. Furthermore,

the studies revealed the influence of the aromatic substituent on the rate of enamine formation from organocatalyst and aldehyde. The reactive enamine intermediate was formed faster with the C_6H_5-substituted catalyst (**1a**) than with the 3,5-$(CF_3)_2C_6H_3$-substituted catalyst (**1b**). Furthermore, the bulk of the catalyst was found to influence the equilibrium between the condensed and hydrolyzed substrates resulting in a comparatively larger amount of the enamine intermediate being present in solution for the smaller phenyl-substituted catalyst.

Further attempts to describe and improve the understanding of the finer details of enamine catalysis have spurred investigations of the reactivity of these intermediates. In this regard, the nucleophilicity of a number of enamine intermediates, derived from relevant aminocatalysts, have been quantified by Mayr and co-workers.[22b] An enamine formed from catalyst **1a** displayed a nucleophilicity more than 1000 times higher than the corresponding enamine formed from the first-generation imidazolidinone-type catalyst. The high nucleophilicity of the enamine intermediate may account for the wide applicability of the diarylprolinol silyl ethers in enamine-catalyzed transformations.

The operating mechanisms in specific enamine-catalyzed α-functionalization reactions have also been investigated. In particular, the mechanism of the enamine-catalyzed addition of aldehydes to nitroolefins has come under scrutiny, as it has proven to be somewhat controversial. This reaction has been studied by the groups of Blackmond, Seebach, Hayashi, Pápai, and Pihko using various methods, including NMR spectroscopy, reaction calorimetry, reaction kinetics, and computational studies.[23] These investigations revealed that several distinct intermediates are formed during the reaction, including a cyclobutane and a 1,2-oxazine *N*-oxide, which are believed to affect the selectivity and kinetic profile of the reaction. These studies illustrated that although the underlying principles of aminocatalysis are based on straightforward concepts, the operating mechanisms may be complex, and the idea that aminocatalyzed transformations are mechanistically simple may be deceiving.

The iminium ion intermediates resulting from condensation of the diarylprolinol silyl ether system with α,β-unsaturated aldehydes have also been studied by a number of methods. With regards to reactivity, Mayr et al. found that the iminium ion formed from condensation of catalyst **1a** with cinnamaldehyde was approximately ten times less electrophilic than the corresponding iminium ion from the first-generation imidazolidinone-type catalyst.[24] Studies of the reactive iminium ion intermediates revealed that the steric shielding of one face of the reactive center(s) arises primarily from the silyl ether substituent, whereas the aryl substituents are predominantly positioned "on top" of the pyrrolidine ring, hereby forcing the silyl ether into close proximity with the reactive centers.[25] For iminium ions formed from catalyst **1b**, the *meta* substituents assist in this facial screening, which accounts for the increased selectivity observed with this catalyst in some reactions that proceed via iminium ion intermediates.

Interestingly, NMR studies have revealed that some iminium ion intermediates exist in an equilibrium between the *E*,*E* and *Z*,*E* isomers (Figure 3).[25a] Although reaction through these isomers would presumably provide opposite product enantiomers, leading to poor stereocontrol, excellent stereoselectivity is often observed. A plausible explanation for this is that nucleophilic attack to the *Z*,*E* isomer of the iminium ion intermediate is associated with increased steric repulsion in the transition state. Consequently, high enantioselectivities can be achieved by the preferential reaction through the *E*,*E* isomer in accordance with the Curtin–Hammett principle. This model is in agreement with the absolute stereochemistry of the products.

In a recent study, Hayashi, Seebach, and co-workers investigated the role of the silyl ether protecting group of the diarylprolinol silyl ethers in a series of reactions that proceed via enamine and iminium ion intermediates.[26] For the enamine reactions, excellent enantioselectivity was achieved with catalyst **1a**, which bears a trimethylsilyl substituent. As there was little room for improvement, the application of catalysts with bulkier silyl ether groups was somewhat futile in these cases. For the application of catalyst **1a** in β-functionalization reactions via iminium ion intermediates, high enantioselectivities were typically observed. In several examples, slight improvements of the enantioselectivities could be achieved by applying catalysts with bulkier silyl ether groups, although often at the cost of prolonged reaction times. It was found that conjugate additions relying on ionic interactions between the reagent and the iminium ion intermediate tend not to show this improvement in enantioselectivity on changing the catalyst. Furthermore, it was noted that for some transformations that involve highly activated substrates, improved yields were achieved with the more bulky catalyst, probably owing to the suppression of side reactions. Interestingly, iminium ion cycloadditions where both the α- and β-positions of the α,β-unsaturated aldehyde are functionalized did not display the same tendency as the iminium ion conjugate additions. In these cases, excellent enantioselectivities could be achieved with catalyst **1a**.

4. Applications of the Diarylprolinol Silyl Ethers

4.1. Activation Concepts

The diarylprolinol silyl ethers have allowed for significant progress within the well-established activation modes, enamine and iminium ion catalysis, aside from playing a key role in the development of new activation modes. Figure 4 outlines the new activation modes that have become available with the introduction of the diarylprolinol silyl ethers along with the previously established concepts.

For saturated aldehydes, condensation with the diarylprolinol silyl ethers provides enamine intermediates, which represents a HOMO raising of the system. The application of the catalytic system for the activation of α,β-unsaturated aldehydes corresponds to a novel dienamine activation mode by the HOMO-raising principle. For the same class of substrates, the LUMO-lowering principle can also be applied by iminium ion activation. When 2,4-dienals are employed in combination with the diarylprolinol silyl ethers, two new

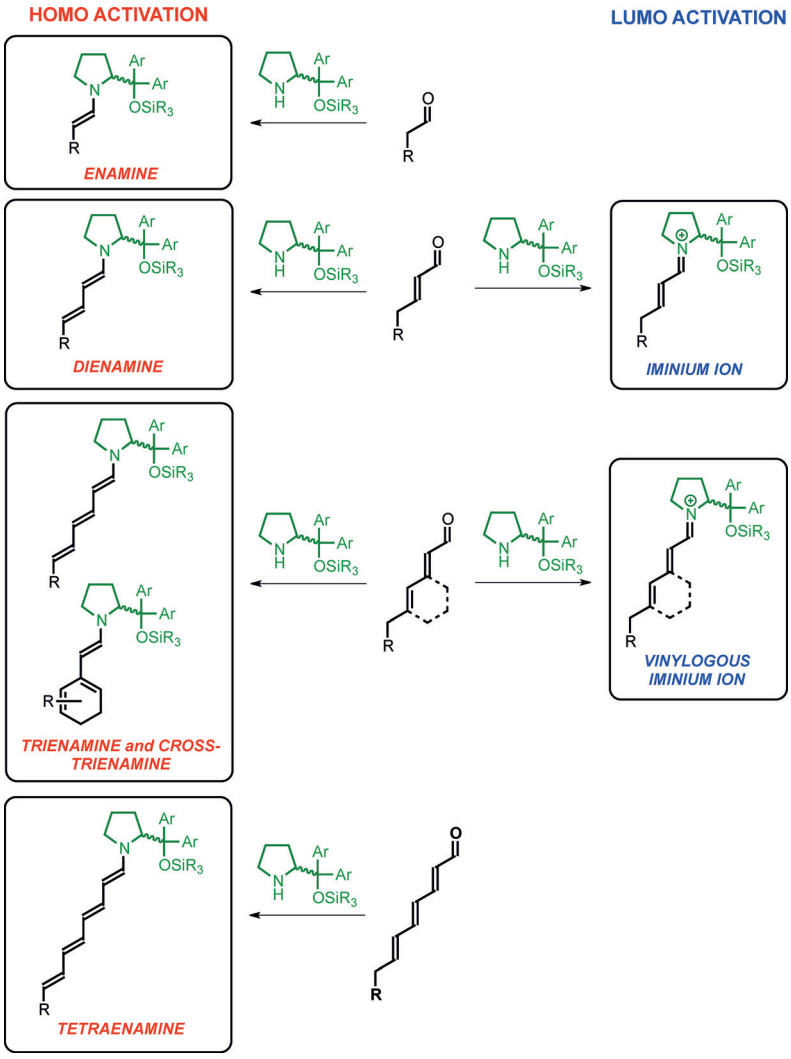


Figure 4. Reactive intermediates in aminocatalysis.

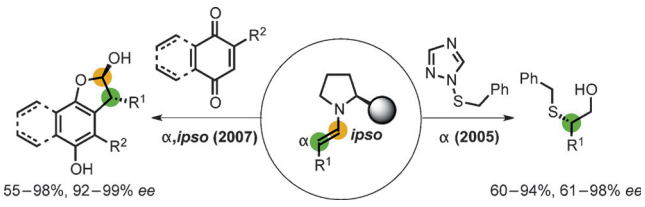
HOMO-raising activation modes are possible, which proceed via trienamine and cross-trienamine intermediates. The same substrates could also be activated by the LUMO-lowering strategy via the vinylogous iminium ion intermediate. Finally, the diarylprolinol silyl ethers have also allowed for the activation of higher classes of unsaturated aldehydes, including those leading to tetraenamines, either as linear or cyclic intermediates.

In the following Sections, these activation modes will be described in general terms, focusing on reactivity patterns by highlighting pioneering work. For extensive discussions of these activation modes, we refer to more comprehensive reviews.[4,27]

4.2. Activation Modes Applying a HOMO-Raising Strategy

4.2.1. Enamine Catalysis

The diarylprolinol silyl ethers were introduced in the development of the α-sulfenylation of aldehydes (Scheme 1, right).[28] In this work, an electrophilic sulfur reagent carrying a triazole as a nucleofuge was applied. When this reagent was combined with aldehydes and catalyst **1b**, α-sulfenylated products were formed in 60–94% yield and 61–98% *ee*. This development highlighted the complementarity of organo- and metal catalysis, as the corresponding transformation had not been achieved using metal catalysis. The general applicability of the diarylprolinol silyl ethers was quickly realized as they showed superior or equal performance in a range of α-functionalization reactions that had been developed using various catalysts.[18a] A wide range of enantioselective aldehyde α-functionalizations have been achieved using the



Scheme 1. Selected examples of enamine catalysis.

diarylprolinol silyl ethers. Among the carbon–carbon bond-forming reactions, conjugate additions to electron-deficient alkenes,[18a,29] aldol,[30] Mannich,[18a,31] α-alkylation,[32] and α-arylation[33] reactions should be mentioned. Furthermore, a broad variety of carbon–heteroatom bond-forming reactions have been developed, including α-fluorination,[34] α-bromination,[18a] α-amination,[18a,35] α-oxygenation,[36] α-sulfenylation,[28] and α-selenylation.[37] Another noteworthy feature of the diarylprolinol silyl ethers is that they can be employed for α-functionalizations relying on substitution reactions, of which only a very limited number had been reported previously.[38] Therefore, enamine intermediates were now able to undergo not only addition reactions to polarized π-systems but also substitution reactions. A key element in this development was the application of a steric shielding strategy,[9e] which could be applied in a general sense, in contrast to, for example, proline, which required a polarized π-system in the reagent in order for this functional group to be activated. Furthermore, the omission of a hydrogen-bond donor site in the catalyst suppressed the tendency of the aldehydes to undergo self-aldol condensation, which increased the general applicability of the catalyst.[39]

Following the development of various aldehyde α-functionalization reactions, it was found that the diarylprolinol silyl ethers could also facilitate formal cycloadditions leading to α,*ipso* functionalization of the aldehyde. This was illustrated by the α-arylation of aldehydes, in particular with the addition of enamine intermediates to quinones.[33] Subsequently, the phenol oxygen atom added to the aldehyde forming a hemiacetal (Scheme 1, left). Hereby, asymmetric α,*ipso* functionalization reactions were added to the arsenal of organocatalytic transformations, highlighting that enamine catalysis could be used to build increasingly complex structures in a selective and predictable manner.

Based on the development of a range of stereoselective transformations, enamine catalysis has been exploited in specifically designed systems en route to target molecules.[40] The synthesis of oseltamivir (Tamiflu), which has been a long-term focus of the Hayashi group,[41] illustrated the attractive features of applying organocatalysis in the stereodefining step of a total synthesis. The employment of enamine chemistry has also expanded beyond academic ventures, and a patent describes the addition of aldehydes to nitroalkenes as part of the asymmetric synthesis of aliskiren.[42]

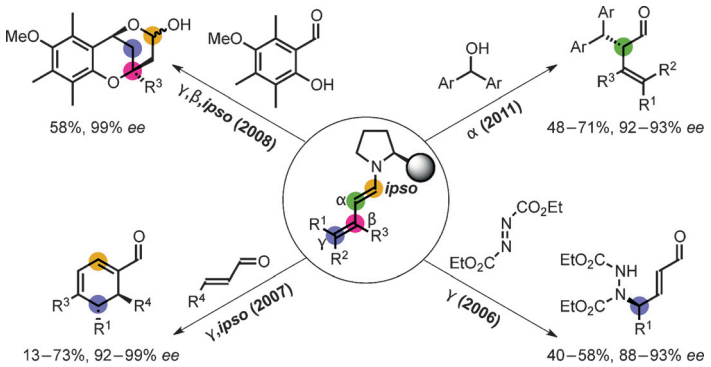
4.2.2. Dienamine Catalysis

In 2006, a novel catalytic concept for the activation of α,β-unsaturated aldehydes was introduced.[43] Applying a diarylprolinol silyl ether, dienamine activation was demonstrated, which opened up new types of reactivity. Notably, two nucleophilic sites, the α- and γ-carbon atoms, are present in the dienamine intermediate and can potentially compete in reactions with electrophiles. Furthermore, the dienamine is an electron-rich diene, applicable as the 4π electron component in [4+2] cycloadditions.

The original report described a direct γ-amination of α,β-unsaturated aldehydes that reacted with diethyl azodicarboxylate via a dienamine intermediate in the presence of organocatalyst **1b** (Scheme 2, bottom right). The γ-functionalization proceeded with complete regioselectivity and 88–93% *ee*. Investigations of the mechanism pointed to a reaction pathway involving a [4+2] cycloaddition forming a hetero-Diels–Alder adduct, which generated the γ-aminated aldehyde upon collapsing. However, this activation mode initially suffered from limited applications as it relied on collapse of the cycloaddition product for catalyst turnover.

This limitation was addressed in two papers that introduced dienamine activation as a general strategy for promoting asymmetric Diels–Alder reactions of α,β-unsaturated aldehydes, leading to γ,*ipso* functionalization (Scheme 2, bottom left). Applying a dienophile that leads to an all-carbon cycloadduct prone to elimination solved the issues regarding release of the catalyst.[44] An intermolecular reaction between α,β-unsaturated aldehydes has been reported, yielding the 2,4-dienal products in 13–73% yield and 92–99% *ee*.[44a]

Another strategy that facilitated catalyst release exploited the iminium ion intermediate formed in the γ-functionalization of the dienamine. By applying an electrophile with an incorporated nucleophilic center, β-functionalization followed the initial γ-functionalization. The first γ,β-functionalization of α,β-unsaturated aldehydes was developed as part of the synthesis of α-tocopherol (Scheme 2, top left).[45] In this

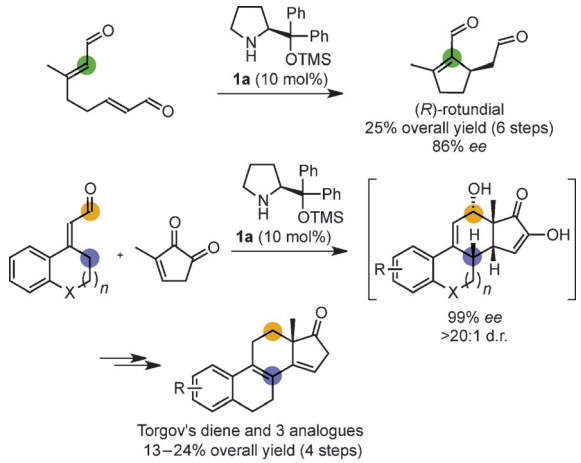


Scheme 2. Selected examples of dienamine catalysis.

case, hemiacetal formation at the *ipso* position followed and led to a tricyclic product in 99% *ee*. Further investigations reported the development of several γ,β-functionalization strategies.[46]

It has been observed that dienamines prefer to react through the least hindered position. This has been demonstrated in direct and selective γ-functionalization reactions of α-branched α,β-unsaturated aldehydes.[47] The same principle was exploited in the selective α-functionalization of γ-branched α,β-unsaturated aldehydes (92–93% *ee*; Scheme 2, top right).[48]

The new prospects offered by dienamine catalysis have been applied in the synthesis of attractive molecules (Scheme 3). One example is the synthesis of the mosquito repellent (*R*)-rotundial, where the stereochemistry is introduced in the final step of the synthesis by dienamine catalysis.[49] Another application of dienamine activation is the method developed for the enantioselective synthesis of



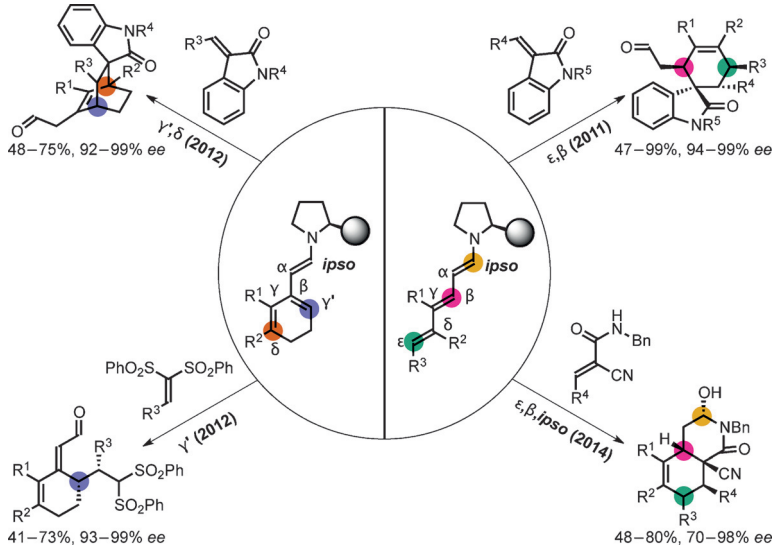
Scheme 3. Total synthesis of (*R*)-rotundial and synthesis of key intermediates for the construction of steroids using dienamine chemistry.

Torgov's diene and analogues.[50] Torgov's diene constitutes a key intermediate in the synthesis of naturally occurring steroids such as (+)-estrone, whereas the analogues can be employed for the synthesis of new steroids.

4.2.3. Trienamine Catalysis

In 2011, another HOMO activation mode employing the diarylprolinol silyl ethers was discovered: trienamine activation.[51] The development of asymmetric organocatalyzed processes with trienamine intermediates demonstrated the ability of the diarylprolinol silyl ethers to control the stereoselectivity at reactive centers even further away than in any hitherto known activation mode in organocatalysis. Notably, trienamines have several reactive sites and exist as several different conformers that are similar in energy, which could give rise to challenges regarding regio- and stereoselectivity. However, the trienamines can also display numerous reactivities. The addition of electrophiles to either the α-, γ-, or ε-position followed by either nucleophilic or electrophilic activation potentially leads to a large number of transformations. The first report utilized 2,4-dienals and olefinic oxindoles for the construction of chiral cyclohexene structures by a [4+2] cycloaddition over the ε,β-positions of the trienamine (Scheme 4, top right). Although the catalyst had to induce chirality over a distance of seven bonds, the products were formed in 94–99% *ee*. Furthermore, the risk of catalyst trapping in the product was avoided when 2,4-dienals were used, as compared to dienamine activation.

Since this seminal report, numerous papers on trienamine catalysis have been published. In 2012, two new applications of the trienamine activation mode were described (Scheme 4, left).[52] Cyclic dienals were found to exhibit unexpected reactivity compared to the acyclic aldehydes applied in earlier studies. The trienamines formed from cyclic dienals were most stable in their linear form, but most reactive as cross-trienamines. This enabled the formation of bicyclic systems in



Scheme 4. Selected examples of trienamine catalysis via linear trienamines or cross-trienamines. Bn = benzyl.

48–75 % yield and 92–99 % *ee*. Moreover, simple electrophiles reacted with trienamines in a selective manner, for example by addition of vinyl bis(sulfones) exclusively to the γ′-position.

A fourth application of the trienamines was discovered in 2014 (Scheme 4, bottom right).[53] The use of a dienophile with a nucleophilic site enabled a [4+2] cycloaddition with trienamines followed by ring closure, demonstrating an ε,β,*ipso*-reactivity pattern. The application of 2,4-dienals and cyanoacrylamides illustrated the high levels of molecular complexity that can be obtained with trienamine chemistry. The bicyclic molecules enabled the formation of five stereocenters and bicyclic structures in a one-pot reaction affording the products in 70–98 % *ee*. Recently, hetero-Diels–Alder reactions of trienamines were also reported,[54] enabling the synthesis of optically active heterocycles containing either sulfur or nitrogen (Scheme 5).

4.2.4. Tetraenamine Catalysis

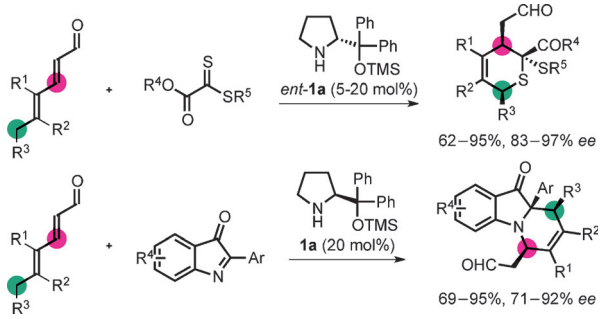
A further expansion of the HOMO-raising strategies was accomplished by the introduction of tetraenamine-mediated reactions.[55] The first report of this activation mode described a reaction based on a cyclic tetraenamine intermediate and olefinic oxindoles to synthesize spirocyclic structures (Scheme 6, right). The products were formed in 51–93 % yield and 68–95 % *ee*. One other application of tetraenamine catalysis has been reported (Scheme 6, left).[56] Chen and coworkers described the reaction of linear tetraenamines with olefinic oxindoles, which were shown to react over the ε,β-positions, favoring the same reactivity as often observed in trienamine activation. The products were obtained in 85–96 % *ee*.

4.3. Activation Modes Applying a LUMO-Lowering Strategy

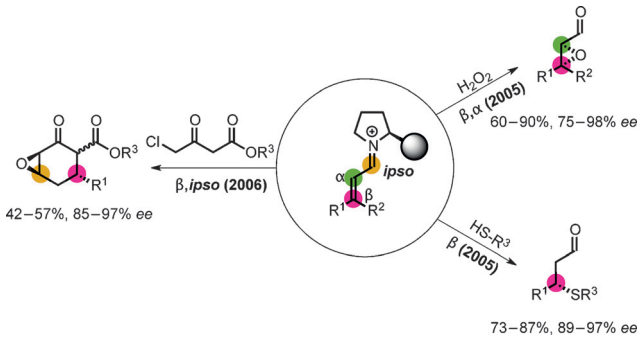
4.3.1. Iminium Ion Catalysis

Soon after the introduction of the diarylprolinol silyl ethers in enamine chemistry, it was realized that they could be used for the activation of α,β-unsaturated aldehydes via iminium ion intermediates.[57] In contrast to the HOMO-raising strategy exploited in the enamine intermediate, formation of an iminium ion intermediate represents a LUMO-lowering strategy, facilitating reactivity towards nucleophiles.

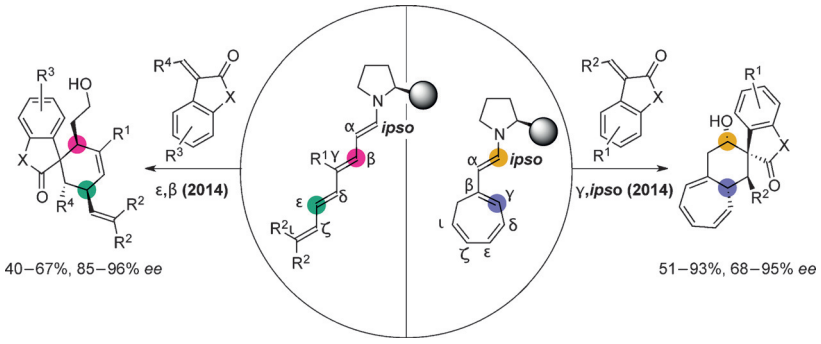
Starting from α,β-unsaturated aldehydes and hydrogen peroxide, α,β-epoxy aldehydes could be synthesized in 75–98 % *ee* (Scheme 7, top right). The β,α-functionalization of α,β-unsaturated aldehydes is not limited to the formation of epoxides. Subsequent reports have expanded the types of three-membered ring systems that can be formed to include chiral aziridines[58] and cyclopropanes.[59] The strategy of β,α-functionalization has also been applied in the synthesis of several different five- and six-membered hetero- and carbocycles.[60] Even though complex structures are of high value, fundamental methods for β-additions to the iminium ion are also desired. The β-addition of nucleophiles was disclosed in



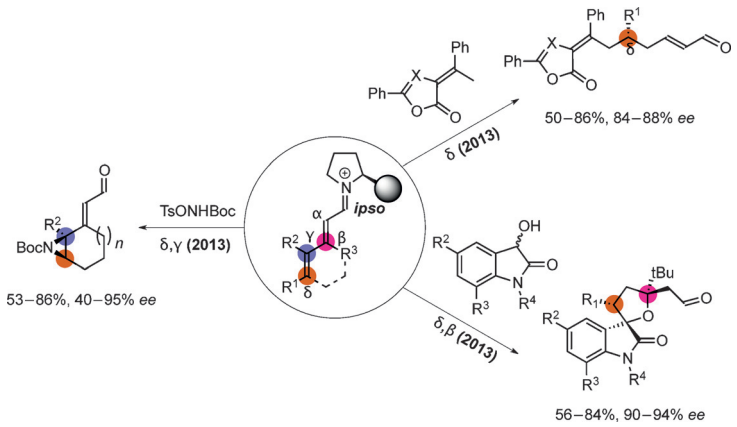
Scheme 5. Examples of heterocyclic structures obtainable by trienamine chemistry.



Scheme 7. Selected examples of iminium ion catalysis.



Scheme 6. Reported examples of tetraenamine catalysis.



Scheme 8. Examples of vinylogous iminium ion catalysis. Boc = *tert*-butyloxycarbonyl, Ts = *para*-toluenesulfonyl.

2005 when different thiols were added to α,β-unsaturated aldehydes (Scheme 7, bottom right).[61] The scope of the enantioselective β-functionalization of α,β-unsaturated aldehydes was later expanded to include conjugate additions of hydride,[62] carbon,[63] nitrogen,[25b,64] and oxygen nucleophiles.[65] Interestingly, a third way of utilizing the iminium ion activation mode was described in 2006,[66] and was based on the annulation of γ-chloro-β-ketoesters with α,β-unsaturated aldehydes. The doubly nucleophilic nature of the γ-chloro-β-ketoesters allowed for a ring closure to the carbonyl group after the initial β-functionalization. Upon addition of base, the chloride was expelled, forming epoxy cyclohexanones in 85–97% *ee* (Scheme 7, left).

4.3.2. Vinylogous Iminium Ion Catalysis

Despite the interesting new activation concepts developed for the HOMO-raising strategy, novel modes of reactivity based on the LUMO lowering of aldehydes were only recently reported. The first successful merging of the classical activation mode of iminium ion catalysis with the principle of vinylogy was reported in 2013.[67] Upon condensation of a 2,4-dienal with a diarylprolinol silyl ether, a vinylogous iminium ion intermediate, bearing three electrophilic sites, was formed.

In the first report, olefinic azlactones and butyrolactones were added enantioselectively to aliphatic 2,4-dienals (Scheme 8, top right). The reaction proceeded with complete regioselectivity for the remote electrophilic carbon atom, and the δ-functionalized products were obtained in 84–88% *ee*.

Shortly after, a second application of vinylogous iminium ion intermediates was reported.[68] Cyclic 2,4-dienals were reacted with a protected hydroxylamine possessing a leaving group on the nitrogen atom, which led to remote aziridination of the aldehyde (Scheme 8, left). Using this method, the products were obtained in 53–86% yield and 40–95% *ee*.

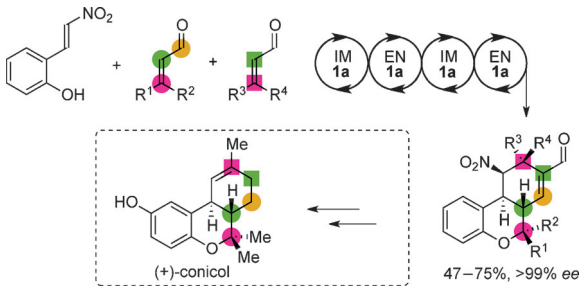
The enal moiety resulting from nucleophilic attack at the δ-carbon atom of a vinylogous iminium ion intermediate was also exploited in another process.[69] When a nucleophile with both a nucleophilic carbon atom and a nucleophilic oxygen atom was employed, a 1,4-addition followed the initial 1,6-addition (Scheme 8, bottom right). In this way, δ,β-functionalization of the aldehyde was achieved, giving the products in 56–84% yield and 90–94% *ee*.

5. Multicomponent and One-Pot Processes

The diarylprolinol silyl ether system has excelled in both HOMO-raising and LUMO-lowering activation, and this broad efficiency has been utilized in the development of a large number of cascade reactions. Combinations of the previously described activation modes have made complex chiral structures easily available, and these are often obtained with excellent enantioselectivities. The wealth of cascade and one-pot reactions described to date is not easily arranged into strict categories. Hence, a brief introduction to a few seminal reports is given here to showcase the synthetic possibilities of multicomponent reaction sequences facilitated by this catalytic system.

Several examples of two-component cascade reactions were already introduced in the discussion of activation modes with which multiple sites on aldehydes, α,β-unsaturated aldehydes, and 2,4-dienals are functionalized concomitantly (Section 4). In 2005, a three-component double cascade reaction was disclosed.[61] It involved an iminium/enamine sequence, doubly functionalizing α,β-unsaturated aldehydes in a thio-Michael/amination cascade process. Within a year, Enders and co-workers reported the first three-component triple cascade reaction forming enantiomerically enriched cyclohexene derivatives in a Michael/Michael/aldol condensation sequence.[70] Moving the concept even further, Hong et al. described the first three-component quadruple cascade reaction catalyzed by **1a** (Scheme 9).[71] An oxa-Michael/Michael/Michael/aldol condensation sequence gave rise to tetrahydro-6*H*-benzo[*c*]chromenes bearing five contiguous stereocenters in > 99% *ee*. During this reaction, one carbon–oxygen and three carbon–carbon bonds are formed, and the synthetic utility of the obtained products was later demonstrated by the synthesis of the natural product (+)-conicol.[72]

These examples serve to show the complex and interesting enantioenriched compounds that can be rapidly assembled by employing diarylprolinol silyl ethers and carefully chosen sets of substrates. Naturally, the more elaborate cascade reaction

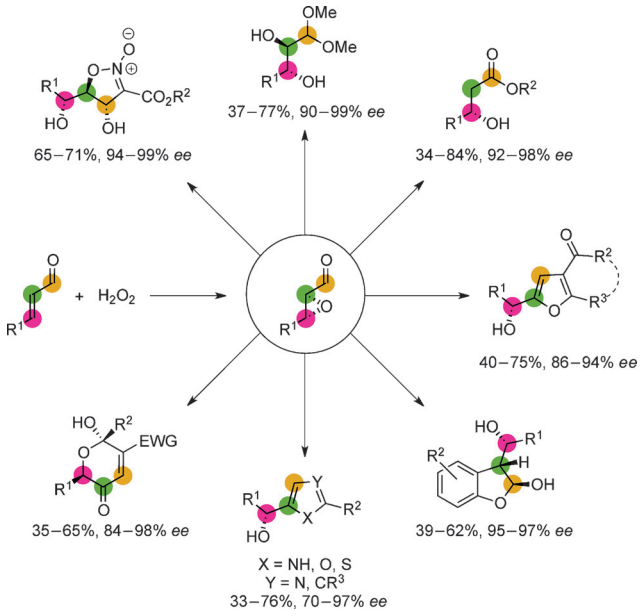


Scheme 9. Asymmetric quadruple cascade reaction to tetrahydro-6*H*-benzo[*c*]chromenes and application in the synthesis of (+)-conicol. IM = iminium ion, EN = enamine.

sequences rely on basic organocatalytic reactions, such as the Michael addition to nitroalkenes. In this symbiotic way, the procedures for forming complex molecules feed off of the principal α- and β-functionalization reactions, while studies of these underlying reactions are both tested and merited by their application in more advanced synthesis.

In contrast to the isolated cascade sequences, one-pot functionalizations refer to reactions in which new reagents are added to the reaction vessel after the first reaction has taken place. This strategy is well-suited for diversifying the product array of several diarylprolinol silyl ether catalyzed reactions. A popular starting point for one-pot functionalizations is the epoxidation of α,β-unsaturated aldehydes. From the common enantioenriched α,β-epoxy aldehyde formed by an iminium/enamine cascade reaction, a wide selection of interesting chiral building blocks has been made available as displayed in Scheme 10.[73]

In many of these studies, one-pot sequences initiated by stereoselective organocatalytic aziridination were also developed, further broadening the scope of these processes. The organocatalytic formation of the epoxide intermediate and



Scheme 10. Application of in situ formed α,β-epoxy aldehydes in various one-pot sequences.

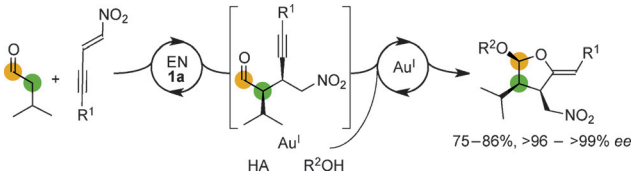
the compatibility of the system with the various subsequently added reagents demonstrate the applicability of aminocatalysis in diversity-oriented synthesis.

6. Combinations with Other Catalytic Systems

6.1. Combinations with Metal Catalysts

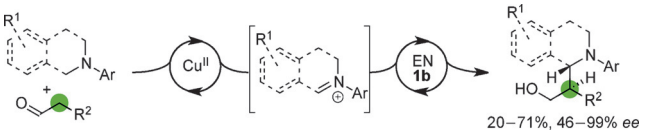
The field of transition-metal catalysis has been developed extensively over several decades, and a vast amount of important transformations have been described.[3] By merging metal- and aminocatalytic activation, it should be possible to attain unprecedented reactivity and selectivity. However, several issues must be addressed in the development of dual catalytic systems. Water is inherently present in aminocatalytic reactions, and this should be considered when choosing the metal catalyst. Furthermore, the aliphatic amine itself, being a relatively hard Lewis base, is capable of coordinating strongly to hard Lewis acidic metals, potentially obstructing any reactivity.

One strategy to circumvent the latter challenge is sequential dual catalysis where the reaction conditions are altered following the first catalytic step, in a so-called one-pot reaction. This type of combined catalysis was employed by Alexakis and co-workers in the formation of tetrahydrofuranyl ethers by enamine catalysis followed by a gold-catalyzed acetalization/cyclization sequence (Scheme 11).[74] In order to avoid deactivation of the Au^I catalyst, a strong Brønsted acid was added to protonate the diarylprolinol silyl ether after the first step. The one-pot procedure delivered cyclic acetals in 75 to 86% yield and 96 to >99% *ee*.



Scheme 11. An example of sequential dual catalysis.

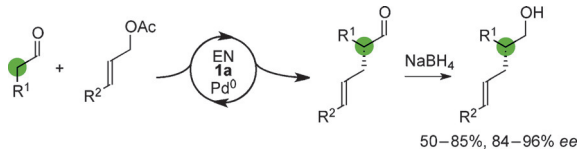
In relay processes, all substrates and catalysts are added at the beginning but the two catalytic cycles operate independently. An example of this is the oxidative cross-dehydrogenative coupling of tertiary amines and aldehydes described by Chi and co-workers (Scheme 12).[75] Initially, catalytic oxidation of the tertiary amine facilitated by Cu^{II} delivered a reactive iminium ion species, which reacted with an enamine formed from the aminocatalyst and the aldehyde. Following



Scheme 12. Example of a relay catalytic system.

reduction, the α-functionalized products were obtained in 20–71% yield and 46–99% *ee*.

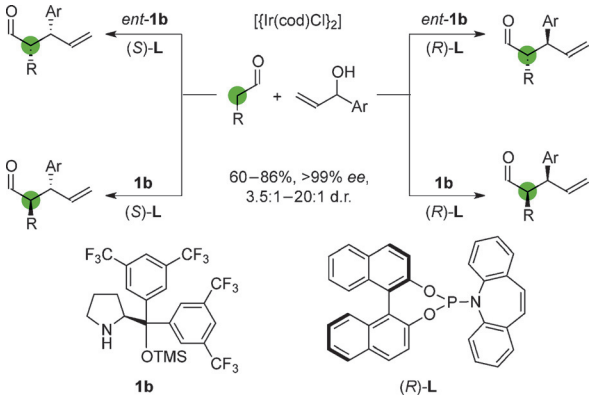
The first report of synergistic dual catalysis with a secondary amine and a transition metal in which the two catalytic cycles are intertwined was reported by Córdova and Ibrahem.[76] In this study, the α-allylation of aldehydes employing a combined pyrrolidine and $[Pd(PPh_3)_4]$ catalytic system was disclosed. An activated η^3 π-allyl palladium electrophile was formed from allyl acetate. This species was subject to nucleophilic attack to the least sterically hindered site from an enamine formed from the aldehyde and pyrrolidine. Later, the same group expanded the procedure to include a stereoselective version employing diarylprolinol silyl ether **1a**, furnishing α-allylated products in 55–85% yield and 84–96% *ee* (Scheme 13).[77]



Scheme 13. Synergistic/cooperative dual catalysis facilitating the enantioselective α-allylation of aldehydes.

Following these initial reports, the strategy of combining the enamine activation of aldehydes with the transition-metal activation of suitable electrophiles has resulted in a series of asymmetric α-functionalizations that would be difficult to achieve employing only one of the catalytic systems. Among others, these include alkylation[78] and propargylation reactions.[79]

A stereodivergent α-allylation was reported by the Carreira group (Scheme 14).[80] Employing an iridium catalyst and a chiral phosphoramidite ligand, they achieved the activation of allylic alcohols and an enantioselective reaction with linear aldehydes catalyzed by **1b**. The special feature of this system is the possibility to synthesize any of the four stereoisomers in excellent stereoselectivities (>99% *ee*, 3.5:1–>20:1 d.r.) by choosing the appropriate combination



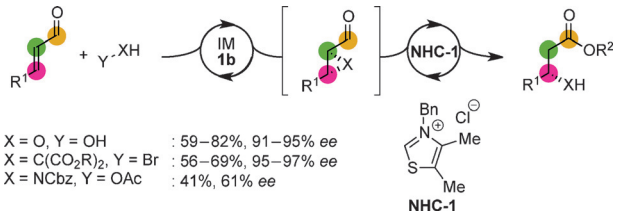
Scheme 14. Stereodivergent α-allylation by synergistic dual catalysis. cod = cycloocta-1,5-diene.

of enantiomers of the diarylprolinol silyl ether catalyst and the phosphoramidite ligand.

Córdova et al. have also developed combinatorial methods, employing iminium ion activation of α,β-unsaturated aldehydes with diarylprolinol silyl ethers and copper-mediated activation of boron-, carbon- and silicon-based nucleophiles for enantioselective β-functionalizations.[81]

6.2. Combinations with N-Heterocyclic Carbene Catalysts

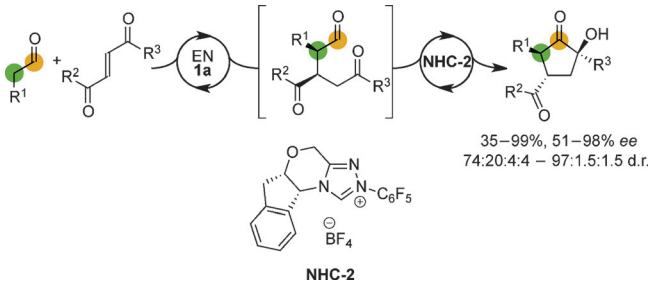
N-Heterocyclic carbenes (NHCs) are capable of reacting with aldehydes to form a Breslow intermediate, hereby leading to nucleophilic umpolung reactivity at the *ipso* position. This reactivity complements the α-reactivity of enamines, and NHC catalysis is a well-established area within organocatalysis.[82] Several combinatorial methods employing diarylprolinol silyl ethers along with NHC catalysts for the formation of interesting enantioenriched compounds have been disclosed. The first report by Córdova and Zhao described the sequential/one-pot synthesis of β-hydroxy-, β-malono-, and β-amino esters (Scheme 15).[73a]



Scheme 15. Sequential iminium ion and NHC-catalyzed formation of β-functionalized esters.

Following stereoselective iminium ion mediated formation of a three-membered cyclic intermediate, addition of the thiazolium salt **NHC-1** facilitated ring opening and esterification to yield the enantioenriched β-functionalized esters. Subsequently, a revised method employing alternative NHC catalysts and conditions have resulted in improvements of the efficiency, scope, and selectivity, especially for the β-amino esters.[73e]

An example of relay combinatorial catalysis reported by Rovis and Ozboya described interesting cooperative effects when **1a** and the chiral **NHC-2** were employed for a Michael/benzoin reaction cascade (Scheme 16).[83] When the intermediate formed by enamine catalysis was isolated and then submitted to NHC catalysis, lower diastereoselectivities were observed compared to the combinatorial process. The authors showed that one diastereoisomer of the intermediate is swiftly converted into the final product by **NHC-2** and proposed that **1a** mediates epimerization of the α-center of the intermediate, which would explain the cooperative effect.

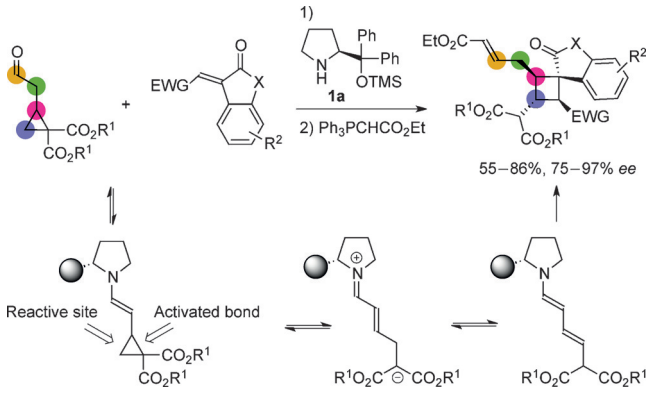


Scheme 16. Combining **1a** and a chiral NHC for the formation of chiral cyclopentanones.

7. "Unexpected Developments"

In this Section, we describe a few recently published transformations that can be considered unexpected either in terms of reactivity or as an unexpected development compared to the original role of the diarylprolinol silyl ether catalysts.

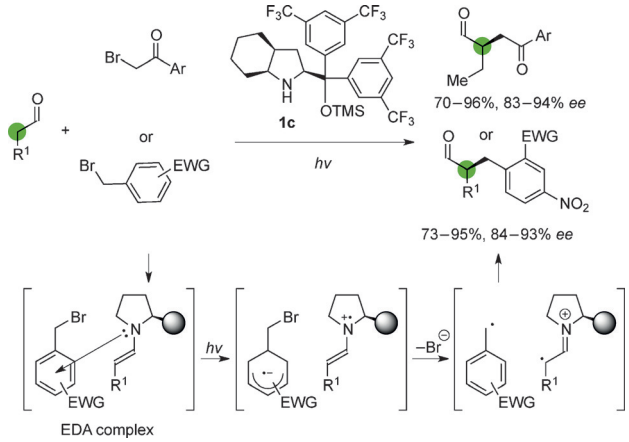
Recently, cyclopropyl activation by a HOMO-raising enamine strategy was demonstrated (Scheme 17).[84] It was



Scheme 17. Enamine-mediated activation of cyclopropane derivatives resulting in stereoselective [2+2] cycloadditions. EWG = electron-withdrawing group.

shown that diphenylprolinol silyl ether **1a** is able to open acetaldehyde cyclopropanes and facilitate the stereoselective formation of spirocyclobutaneoxindoles. The observed γ,β-reactivity pattern was not predicted. Reaction over the β,δ-positions in a [3+2] cycloaddition had been anticipated as breaking of the cyclopropane bond would lead to reactive sites at these positions. However, instead of the expected cyclopentane structures, cyclobutanes were formed, possibly through a [2+2] cycloaddition involving a dienamine intermediate.

The diarylprolinol silyl ethers were originally developed for α-functionalizations of simple aldehydes. Despite this fact, recently developed α-functionalizations of aldehydes by Melchiorre and co-workers can be classified as unexpected in terms of activation mode.[85] In 2013, the stereoselective α-functionalization of aldehydes with benzyl and benzoyl bromide derivatives utilizing diarylprolinol silyl ethers under visible-light irradiation was reported (Scheme 18). Compared

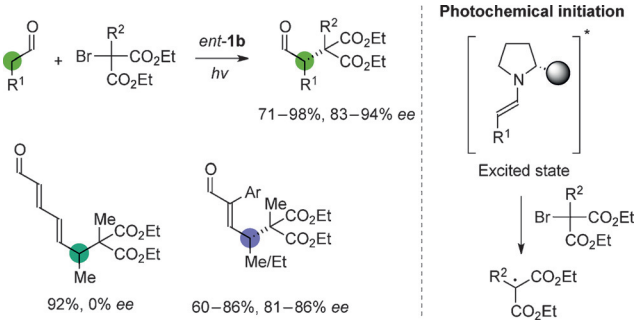


Scheme 18. Catalytic asymmetric α-benzylation and α-benzoylation of aldehydes under light irradiation.

to earlier combinations of aminocatalysis with photochemistry, the interesting feature of this system is that no photosensitizer was needed. Rather, the authors provided evidence for the formation of an electron donor–acceptor (EDA) complex between the enamine and the electrophile, which, after single electron transfer (SET), shaped a chiral radical ion pair leading to product formation.

A recent report from the same group unveiled that enamines formed with diarylprolinol silyl ether **1b** are directly susceptible to photoexcitation (Scheme 19). The authors suggested that the excited enamine species is able to undergo SET to bromomalonates, which, upon expulsion of bromide, can react with the ground-state enamine. In this fashion, α-alkylated products were obtained in high enantioselectivities (83–94% *ee*). Furthermore, stereoselective γ-alkylation of α,β-unsaturated aldehydes and racemic ε-alkylation of 2,4-dienals were also disclosed, showing that the direct photoexcitation is possible with both di- and trienamine chemistry as well. Although no enantioselectivity was observed in the latter case, the complete regioselectivity is noteworthy.

It is intriguing that the ability of the enamine intermediate to be activated by sunlight had not been discovered earlier, as this catalytic system has been employed for hundreds of studies. Such findings make one wonder which other unexpected events the future holds for the diarylprolinol silyl ethers.



Scheme 19. Direct photoexcitation of an enamine, which leads to activation of the electrophile for reaction with the ground-state enamine intermediate.

8. Outlook

Since the diarylprolinol silyl ethers were first employed as organocatalysts ten years ago, this class of catalysts has attained a dominant role in the field of organocatalysis, which has undergone a tremendous development in that period. In this Minireview, we have looked back on the developments achieved with these catalysts. We have shown how they appeared as novel catalysts providing unprecedented generality in known reactions, as well as facilitating a large number of new enantioselective transformations applying the well-established activation modes of enamine and iminium ion catalysis. Furthermore, it has been illustrated how these catalysts opened up new activation modes in organocatalysis, such as dienamine, trienamine, cross-trienamine, tetraenamine, and vinylogous iminium ion catalysis. The robustness of these catalysts has not only led to the development of multicomponent and one-pot processes, but also allowed for combinations with other catalytic systems, such as NHCs and transition metals, which have granted access to transformations not achievable by a single catalytic system. In the development of new methods, mechanistic investigations play a key role in increasing our understanding of the underlying principles of the operating system, and thus provide an improved platform for further developments. The most important mechanistic investigations concerning the diarylprolinol silyl ethers have therefore also been presented. Finally, examples in which the diarylprolinol silyl ethers have been applied in unexpected reactions have been outlined. These reports exemplify that the diarylprolinol silyl ethers are still prime candidates for the development of novel catalytic activation concepts and are therefore—hopefully—unlikely to lose popularity in the near future. We are excited to see in which area or combination the many creative and innovative scientists working in the field will be able to apply the diarylprolinol silyl ethers next.

Acknowledgements

This work was financially supported by Aarhus University, FNU, and the Carlsberg Foundation.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 13860–13874
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Received: April 29, 2015
Revised: July 22, 2015
Published online: October 1, 2015

