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Old tricks, new dogs: organocatalytic dienamine activation of α,β-unsaturated aldehydes

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Chiral secondary amines are some of the most commonly used kinds of catalysts. They have become a reliable tool for the α- and β-activation of carbonyl compounds, *via* HOMO, SOMO or LUMO activation pathways. Recently, chemists have turned their attention to the development of novel organocatalytic strategies for remote functionalisation, targeting stereocentres even more distant from the catalyst-activation site, through dienamine, trienamine, and vinylogous iminium ion pathways (γ-, ε- and δ-positions, respectively). Here we outline and discuss the state-of-the-art in dienamine activation, classifying examples according to the different reactive activation pathways followed by the formed dienamine intermediate (1,3-, 1,5-, 2,5- and 4,5-functionalisation) and the reaction type developed, as determined by the structure and the nature of electrophiles and nucleophiles.

1. Introduction

In the past decade, organocatalysis has emerged as a powerful and environmentally benign strategy towards numerous organic transformations.[1] Since its renaissance it has been proven to be a robust and useful tool, and equally as competent as metal or enzyme catalysis. Organocatalysis can be sub-classified into covalent and non-covalent catalysis. In the covalent catalysis, the carbonyl group has played a central role and has allowed the introduction of several new modes of chemical activations with hundreds of newly developed reactions. Therefore, this bio-mimetic "organocatalytic revolution" has inspired the development of original activation modes, especially those concerning the carbonyl group. Among these, activation accomplished by chiral amines has been shown to be a particularly powerful tool due to the well-established methods of HOMO,[2] LUMO,[3] and SOMO[4] activations widely used in asymmetric synthesis.

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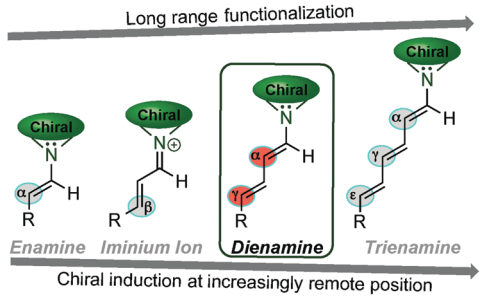
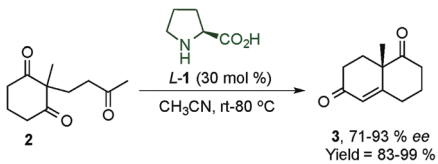


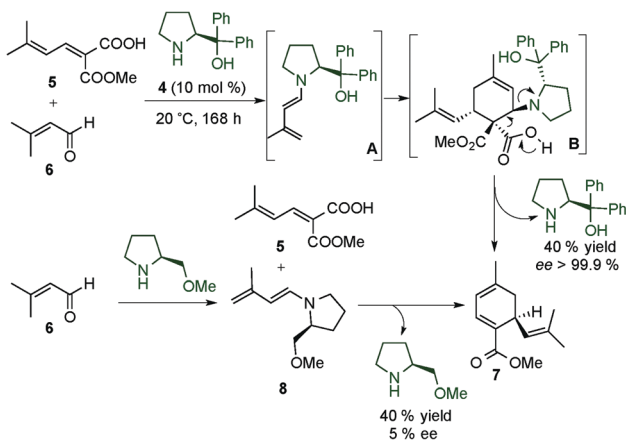
Fig. 1 Different long extended functionalisation of aldehydes.

In 2000, the concepts of LUMO[5]-lowering (iminium ion, Fig. 1) and HOMO-raising (α-functionalisation *via* enamine,[2a–f] Fig. 1) organocatalytic strategies were applied to the activation of both, unsaturated and saturated, carbonyl compounds. Since then, the application of asymmetric aminocatalysis to activate a more remote position has been under consideration, but it took several years for it to be accomplished[6] (in contrast to the remarkably quick advances in the field of the chiral auxiliaries[7]). From a historical point of view, the stoichiometric enamine preparation was first made practical by Mannich and Davidsen[8] and it was used for the first time, in a catalytic manner, in the well-known Hajos–Parrish–Eder–Sauer–Wiechert reaction (Scheme 1).[9]

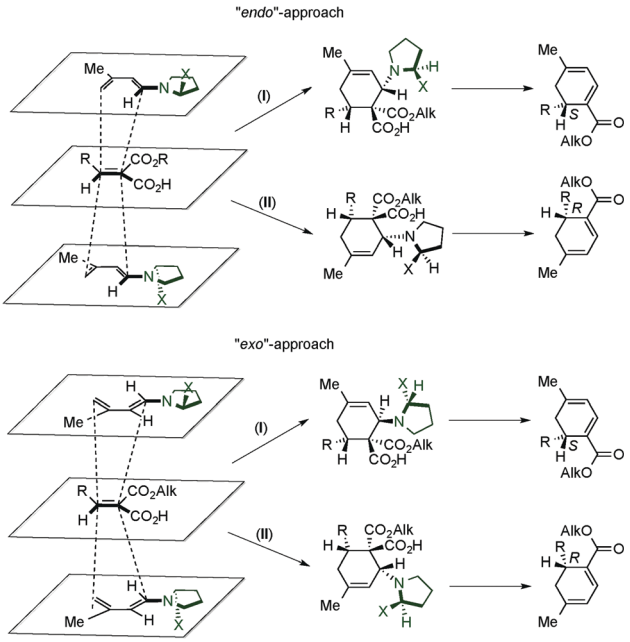
After this early example from the 70's, in 1993, Serebryakov and colleagues were the first to study the stoichiometric and organocatalytic dienamine activation of α,β-unsaturated aldehydes (Scheme 2).[10] In these works, the authors described the



Scheme 1 The first example of asymmetric organocatalysis using HOMO-raising activation.



Scheme 2 First asymmetric catalytic example using dienamine activation for the synthesis of cyclohexadienes.



Scheme 3 Proposed reaction mechanism and stereochemical model by Serebryakov *et al.*

synthesis of different polysubstituted cyclohexadienes, using the HOMO-raising activation of the dienamine system. The authors reported that after the formation of the chiral dienamine, a subsequent cycloaddition from its sterically less hindered face to a dienophile (*exo* or *endo* approach) can take place to give the final cycloadducts which, after hydrolysis and release of the catalyst, could give the polysubstituted cyclohexadienes. This mechanism was supported experimentally through the isolation of different chiral dienamine intermediates by condensation of an aldehyde with a chiral secondary amine and subsequently by the reaction of these dienamines with the dienophile in a two-step process (see the bottom, Scheme 2).

In addition, based on computational studies, the authors proposed some stereochemical models for the obtained results (Scheme 3).[10c] The plane accommodating the five backbone atoms of the delocalized system of a dienamine has sterically non-equivalent faces. Therefore, four favourably oriented complexes can be found; two are related to the *endo* approaches, whereas the other two correspond to the *exo* ones. The *endo*-**I** and *exo*-**I** approaches lead to the same *S* configuration of the final product (where the intermediate cycloadducts are epimers at the configuration of the C–N bond), resulted from the reaction of the dienophile by the "lower face". In an analogous manner, when the dienophile reacts through the "upper face", the *endo*-**II** and *exo*-**II** approaches allow the synthesis of the *R* configuration final product (where intermediates are again epimers at the C–N bond).

Whereas the level of control achieved in this early example was excellent, no representative examples were reported in this field until 2006 when Jørgensen *et al.* described the aza-1,5-functionalisation of α,β-unsaturated aldehydes.[11] In a parallel manner, the dienamine activation of α,β-unsaturated ketones

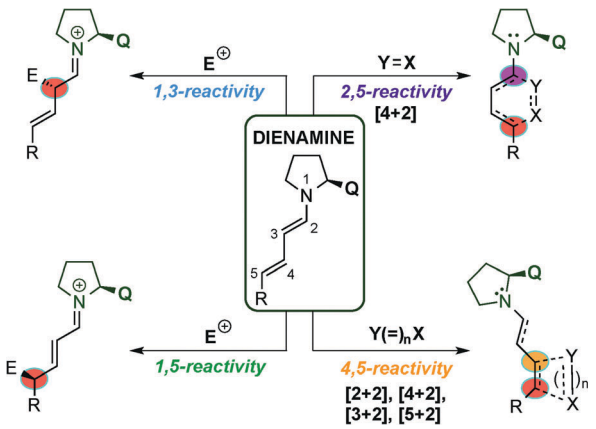
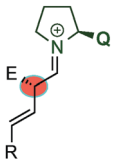


Fig. 2 Classification of different reactivity pathways of dienamine intermediates used in the present review.

was developed by Barbas III and Ramachary[12] and owing to the fact that it has been recently discussed in detail by other revisions,[13] only the functionalisation of enals *via* dienamine intermediates has been discussed in this review.

The dienamine intermediate formed (Fig. 2) presents different activation pathways to react by, and the pathway that the reaction takes is determined by the structure and the nature of electrophiles and nucleophiles (HOMO and LUMO coefficients). The simplest pathway undergoes 1,3-reactivity which allows the α-functionalisation of the aldehyde and leaves an unreacted double bond available for further modification (top-left, Fig. 2). The second reactivity relates to the 1,5-functionalisation, and was the first reported remote functionalisation (bottom-left, Fig. 2).[11] Thirdly, by taking into account that the normal Diels–Alder reaction usually proceeds with electron rich-dienes, the formed dienamine has a large tendency to react with dienophiles. Thus, a large number of publications have described using this strategy, in an intra- and inter-molecular manner, for the synthesis of enantio-enriched six membered rings (top-right, Fig. 2). In a final approach, inspired by the pioneer mechanistic studies carried out by Seebach and Blackmond,[14] in which a formal organocatalytic [2+2]-cycloaddition between enamine intermediates and nitroolefins was identified as an undesired reaction pathway leading to catalyst inhibition, the asymmetric synthesis of cyclobutanes at the more remote double bond of the dienamine intermediate *via* [2+2] cycloadditions (bottom-right, Fig. 2) has been developed. Following these seminal examples, other cycloadditions, such as [4+2], [3+2] and [5+2], have been achieved at the 4,5-position of the dienamine intermediate. In this review, we outline and discuss the state of the art in the emerging field of dienamine-mediated catalysis of unsaturated aldehyde derivatives, including the catalytic systems reported so far in this area, grouping them by the reactivity pathway followed by the dienamine intermediate (1,3-, 1,5-, 2,5- and 4,5-functionalisation, Fig. 2) and the type of reaction developed. Furthermore, we briefly comment on more complex cascade processes involving dienamine intermediates and we conclude by considering the outlook of this area in the future.

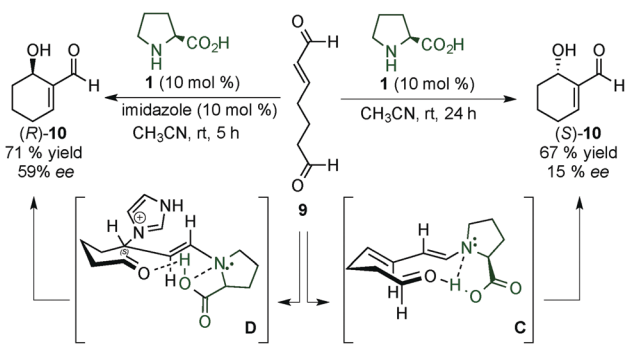
2. 1,3-Reactivity: α-functionalisation



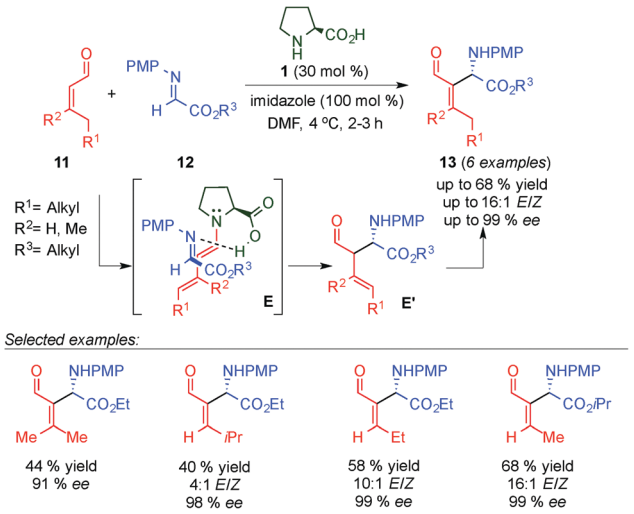
The early example of *in situ* generation of dienamine intermediates demonstrated by Serebryakov *et al.*[10] has inspired others to make use of these intermediates for the α-functionalisation of α,β-unsaturated aldehydes in a wide variety of reactions.

In 2005, Hong and colleagues described the first proline-catalysed enantioselective intramolecular Baylis–Hillman (BH) reaction of hept-2-enedial (**9**) through a dienamine intermediate from poor to good yield and from poor to moderate enantioselectivity (right, Scheme 4) depending on the reaction conditions.[15] Of interest is the reported inversion and enhancement of the stereoselectivity in the presence of imidazole due to the formation of an enamine intermediate (left, Scheme 4). In the proline catalysed reaction, enal **9** is activated with the catalyst to give the corresponding iminium ion, which evolves to form the dienamine intermediate. The enamine-aldol reaction proceeds preferentially through a Zimmerman–Traxler transition state (**C**), furnishing (*S*)-**10**. In contrast, the addition of a catalytic amount of imidazole proceeds from the Si-face of the iminium-ion intermediate, which facilitates the formation of the enamine intermediate **D** that suffers from the presence of an axial imidazolium group, leading to the formation of (*R*)-**10**.

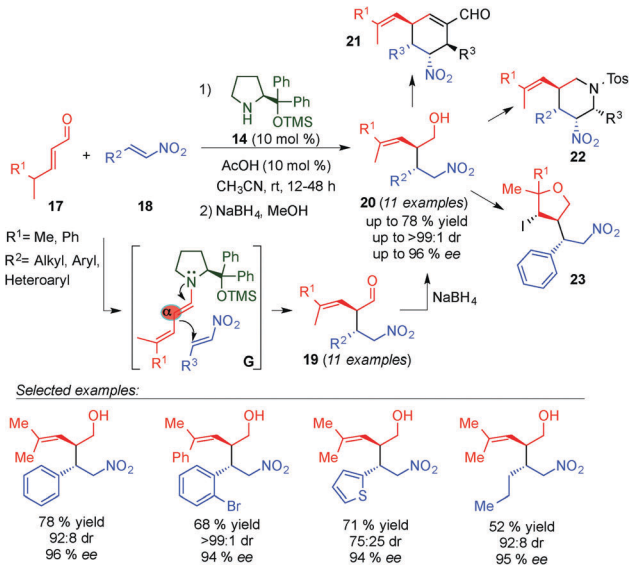
Barbas III and co-workers reported a highly enantioselective organocatalytic aza-Morita–Baylis–Hillman (aza-MBH) reaction of β-mono- and di-substituted α,β-unsaturated aldehydes (**11**) and *N*-PMP-protected α-imino esters **12** (Scheme 5)[16] catalysed by proline and imidazole, affording the corresponding *E*-β-amino aldehydes **13** as major isomers with moderate to good yields and excellent enantioselectivities. Through several conclusive ^{1}H-NMR experiments, the authors demonstrated that this reaction proceeds through a Mannich-type mechanism *via* the dienamine intermediate (**E** transition state) followed by isomerisation of the double bond (**E′**). In the same year, Córdova's group described a similar approach for the catalytic enantioselective formation of aza-MBH-type products *via* the dienamine



Scheme 4 Intramolecular BH reaction through a dienamine (**C**)-or enamine (**D**) intermediate.



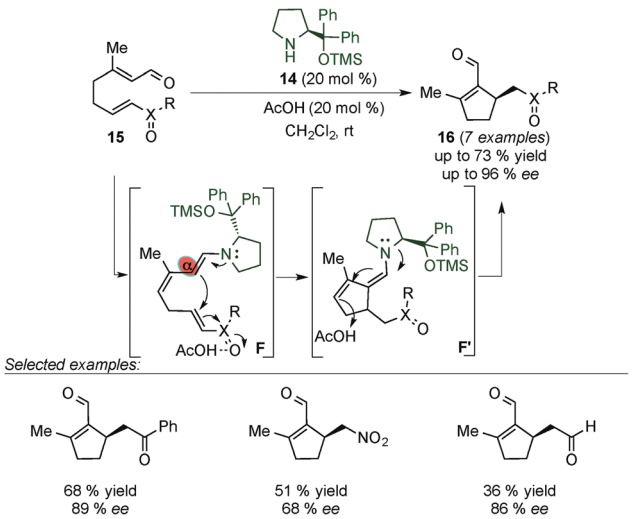
Scheme 5 Intramolecular aza-MBH reaction through a dienamine activation pathway.



Scheme 7 Dienamine-catalysed Michael addition and its application to the synthesis of cyclic compounds.

intermediate using L-proline/DABCO as a catalytic system. The authors explored the reaction of β-substituted α,β-unsaturated aldehydes with *N*-Boc-protected imines which afforded the corresponding amino aldehydes with moderate to good yields, *E*/*Z* ratios and excellent enantioselectivities.[17]

Christmann *et al.* successfully applied this activation pathway to the formation of chiral cyclopentenals (**16**) with moderate to good yields and enantioselectivities. These compounds were obtained by an intramolecular Rauhut–Currier cyclisation reaction of acyclic precursors (**15**) which bear within their structure an α,β-unsaturated aldehyde and a Michael acceptor (Scheme 6).[18] The authors proposed a catalytic cycle that starts with the activation of the enal and the Michael acceptor units of **15** with the catalyst and acetic acid, respectively, leading to the formation of a carbon–carbon bond through the electron rich dienamine intermediate **F**. Compound **16** was obtained by



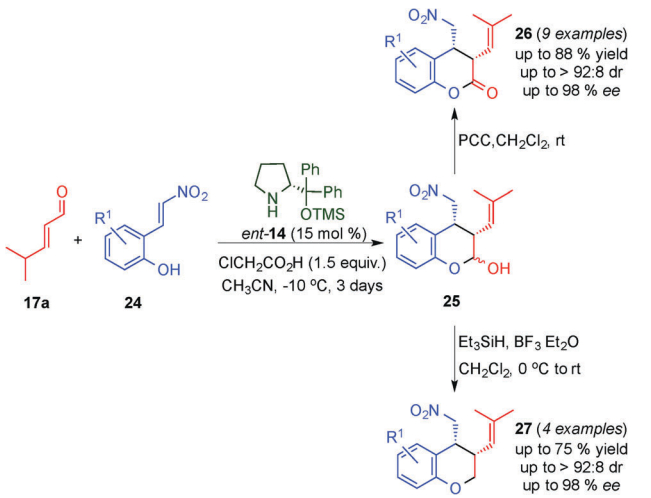
Scheme 6 Intramolecular Rauhut–Currier cyclisation *via* the dienamine intermediate.

protonation of **F′** at the γ-position followed by the release of the catalyst upon hydrolysis of the corresponding iminium ion intermediate. With the aid of sterics the reaction proceeds with complete α-regioselectivity.

In 2009, Chen and colleagues reported the first direct chemo-, regio-, and stereoselective Michael addition of γ,γ-disubstituted α,β-unsaturated aldehydes (**17**) to nitroolefins (**18**) through *in situ* generation of the dienamine intermediate (**G** transition state) using the Jørgensen–Hayashi catalyst **14** (Scheme 7).[19] The corresponding alcohols **20** were obtained with excellent yields, diastereo- and enantioselectivities in a broad substrate scope after *in situ* reduction using $NaBH_4$. The total α-regiocontrol is due to steric hindrance at the γ-position of the enals. Moreover, the authors demonstrated the utility of this methodology for the synthesis of optically pure six-member cyclic frameworks with versatile scaffold diversity, such as cyclohexenes (**21**) and piperidines (**22**) obtained by postsynthetic modifications involving tandem iminium–enamine and nitro-Mannich reactions of the Michael adducts **19**, respectively. They further explored the synthetic utility of the methodology in affording a tetrahydrofuran (**23**) framework by an iodine-mediated cyclisation reaction of **20**.

Following a similar approach, the Enders group described the organocatalytic highly stereoselective synthesis of *cis*-3,4-difunctionalised chromans (**27**) and dihydrocoumarins (**26**) in moderate to good yields and high stereoselectivities *via* a domino Michael–hemiacetalisation process of *ortho*-nitrovinylphenols (**24**) and 4-methylpent-2-enal (**17a**), followed either by dehydroxylation or oxidation of the *cis*-3,4-disubstituted chromanols (**25**) (Scheme 8).[20] Furthermore, using this protocol, the authors provided an efficient and stereoselective approach to the synthesis of a benzopyrano pyrrolidine which is a tricyclic heterocycle present as a subunit in fiduxosin, a potential drug for the treatment of benign prostatic hyperplasia.[21]

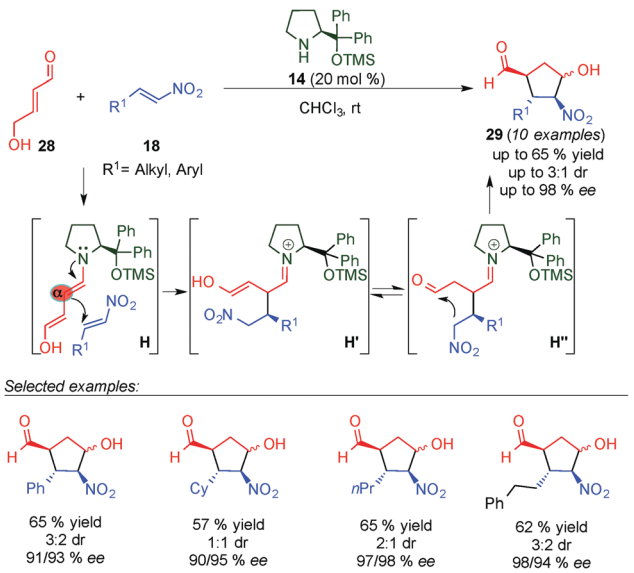
In a related study, Hong and colleagues reported formal [3+2] cycloadditions of 4-hydroxybut-2-enal (**28**) and nitroalkenes (**18**) for



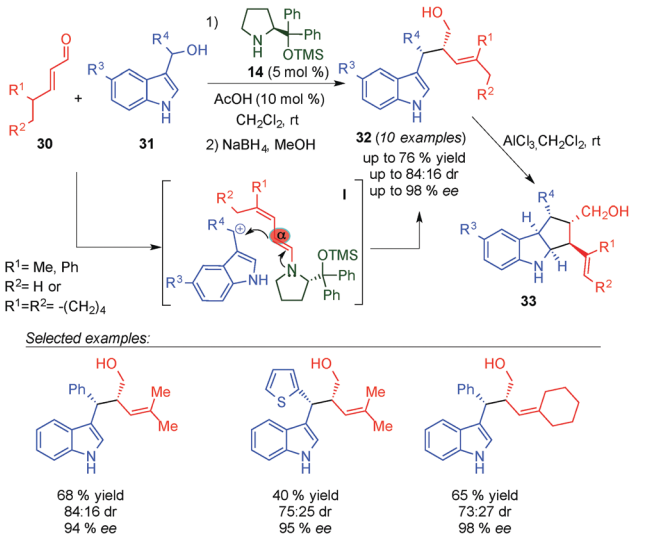
Scheme 8 Tandem Michael–hemiacetalisation reaction through dienamine activation followed by either oxidation or dehydroxylation reaction.

the synthesis of cyclopentanecarbaldehydes (**29**), containing four consecutive stereogenic centres in good yields and high enantioselectivities through a tandem Michael–Henry reaction (Scheme 9).[22] To explain the results obtained, the authors proposed a plausible mechanism based on the iminium ion activation of **28** with the catalyst, followed by deprotonation to give a dienamine intermediate which then undergoes nucleophilic attack by the nitroalkene (**H**). Subsequently, tautomerization of **H′** and a Henry reaction (**H″**) lead to **29** as a major diastereomer of the reaction. This work represents a noteworthy example of the use of a succinaldehyde surrogate in dienamine-mediated catalytic reactions.

Chen and colleagues reported the first alkylation reaction between 3-indolylmethanols (**31**) and γ,γ-disubstituted α,β-unsaturated aldehydes (**30**) through a dienamine intermediate



Scheme 9 Organocatalytic formal [3+2] cycloaddition by a tandem Michel–Henry process.

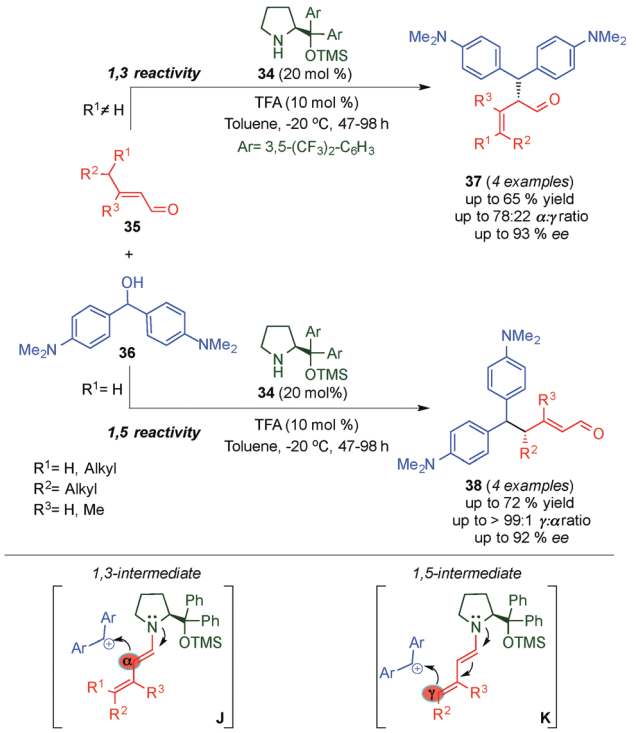


Scheme 10 α-Site selective S_N1-alkylation of γ,γ-disubstituted α,β-unsaturated aldehydes and 3-indolylmethanols.

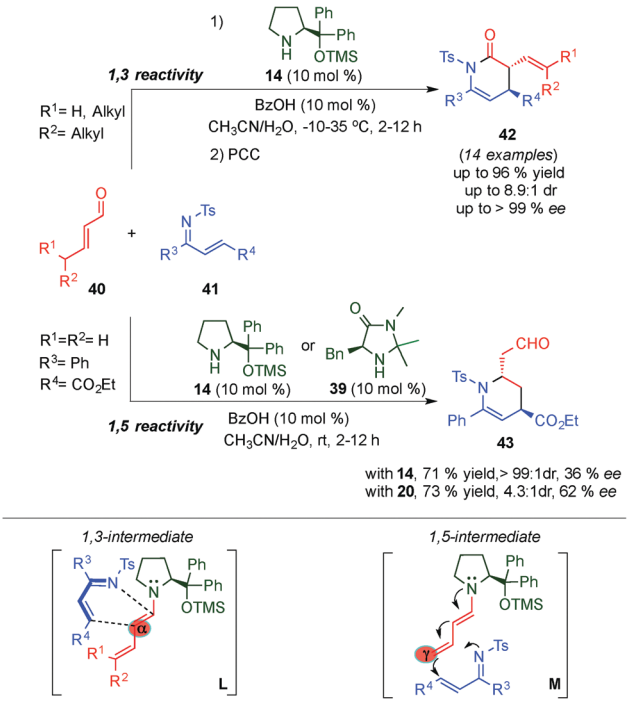
(**I** transition state), using **14** and AcOH as the catalytic system (Scheme 10).[23] The corresponding Michael adducts **32** were obtained in a broad substrate scope with excellent diastereo- and enantioselectivity. Complete control at the α-position was achieved with the use of γ,γ-disubstituted enals. Subsequently, in the presence of a Lewis acid ($AlCl_3$), the corresponding indole products (**32**) evolved to cyclopentyl[*b*]indoline derivatives (**33**) through an unusual intramolecular imino-ene reaction with excellent yields and enantioselectivities. This novel reaction proceeded through a key Lewis acid catalysed enamine–imine isomerisation step, which followed the Lewis acid mediated ene cyclisation.

Soon afterwards, Christmann's group investigated the asymmetric S_N1-alkylation of different γ,γ-disubstituted α,β-unsaturated aldehydes (**35**) through the dienamine intermediate with a stabilized carbocation derived from bis[4-(dimethylamino)methanol] (**36**) as an electrophile with catalyst **34** (Scheme 11).[24] The authors showed a substrate dependent α- and γ-alkylation procedure with moderate to excellent regio- and enantioselectivity. Using γ,γ-disubstituted α,β-unsaturated aldehydes, the reaction proceeded with either complete or high α-regioselectivity (products **37**) due to steric and electronic factors (**J**, Scheme 11). By contrast and as expected, linear α,β-unsaturated aldehydes afforded predominantly the corresponding γ-product (**38**) (**K**, Scheme 11). Almost simultaneously, Melchiorre *et al.* by using a different approach for the same reaction achieved the completely selective alkylation at the γ-position (see below, 1,5 Reactivity section).[25]

In 2009, a striking alternative approach to the normal electron demand Diels–Alder *via* dienamine activation was developed by Chen *et al.* They demonstrated the use of the formed dienamine intermediate as the dienophile, thus reporting the first highly regioselective and stereoselective inverse-electron-demand aza-Diels–Alder reaction between α,β-unsaturated aldehydes (**40**) and *N*-tosyl-1-aza-1,3-butadienes (**41**) for the asymmetric synthesis of piperidines **42** (Scheme 12).[26] The authors successfully demonstrated the possibility of using the HOMO-energetic



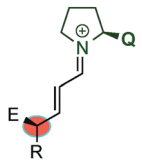
Scheme 11 α- *vs.* γ-site selective S_N1-alkylation of γ,γ-disubstituted α,β-unsaturated aldehydes.



Scheme 12 1,3- and 1,5-site-selective inverse-electron-demand aza-Diels–Alder reaction of α,β-unsaturated aldehydes and *N*-tosyl-1-aza-1,3-butadienes *via* dienamine intermediates.

destabilization of the *in situ* generated dienamine intermediate as a dienophile, with a broad scope of α,β-unsaturated aldehydes and *N*-tosyl-1-aza-1,3-butadienes, affording exclusively α-regioselective Diels–Alder adducts (**42**) with good yields and enantioselectivities through a 1,3-intermediate (**L** transition state, Scheme 12). The great preference towards the α-position is easily explained as the more proximal, regarding the aminocatalyst, of the dienamine double bonds, is the most reactive alkene. Intriguingly, crotonaldehyde exclusively afforded the corresponding γ-regioselective adduct **43** with moderate enantioselectivity using catalysts **14** or imidazolidinone catalyst **39** through a 1,5-intermediate (**M** transition state, Scheme 12), most likely due to steric factors. However, only poor or moderate selectivities were obtained in this example, the unique reactivity shown by crotonaldehyde laid the foundations for further developments of dienamine-mediated catalytic inverse-electron-demand Diels–Alder reactions, which will be covered in detail in Section 5.2.

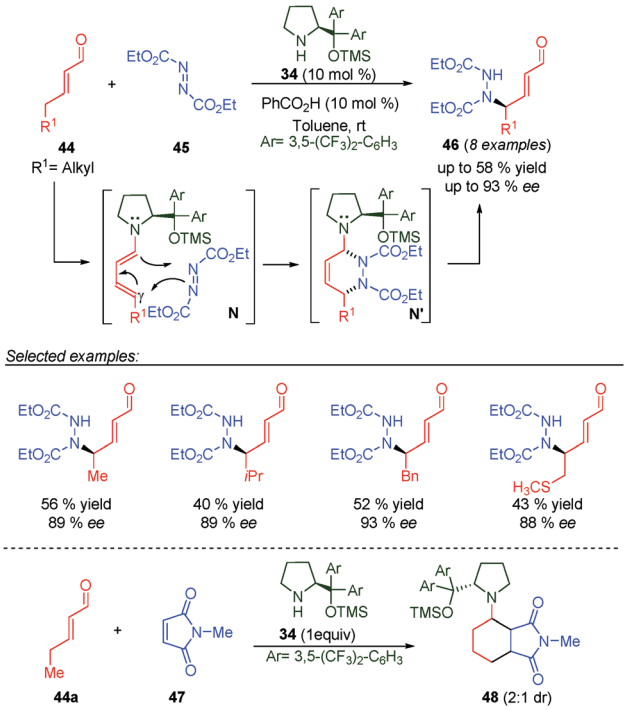
3. 1,5-Reactivity: γ-remote asymmetric functionalisation



In 2006, Jørgensen and co-workers reported the first example of an asymmetric vinylogous catalytic process through dienamine activation of γ-enolisable unsaturated aldehydes (top, Scheme 13).[11] They developed the γ-amination of different α,β-unsaturated aldehydes (**44**) with diethyl azodicarboxylate (**45**) under aminocatalysis using **34** with moderate yields and high enantioselectivities and perfect site selectivity for the γ position. To support the excellent stereo- and selectivity observed in the reaction, the authors reported experimental and theoretical studies that suggested a [4+2] cycloaddition path as the most probable reaction mechanism of the reaction. In this concerted mechanism, under these reaction conditions, the generated hetero-Diels–Alder adduct **N′** evolves into the final product **46** and the concerted transition state **N** proceeds *via* a dienamine *E*,s-*cis*,*E*, which is supported by the experimental stereochemical outcome obtained in the reaction. As further evidence of the Diels–Alder type pathway, the authors carried out reaction between 2-pentenal (**44a**) and *N*-methylmaleimide (**47**) in the presence of 1 equivalent of the aminocatalyst **34**, which afforded the Diels–Alder cycloadduct (**48**), leading to a dead end of a possible catalytic process (bottom, Scheme 13).

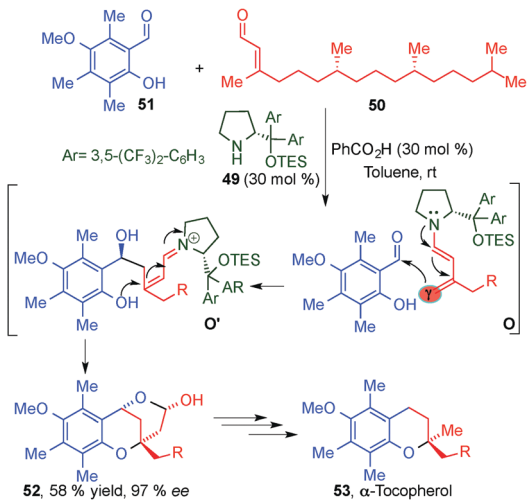
Afterwards, Brenner-Moyer *et al.* employed the above methodology to the synthesis of enantioenriched γ-amino alcohols and β-functionalised-γ-amino alcohols through a dienamine-iminium cascade reaction, which consisted of the γ-amination of α,β-unsaturated aldehydes followed by either conjugated reduction or nucleophilic addition of an oxime to **46**.[27]

This seminal work reported by Jørgensen's group inspired other groups to explore the potential of dienamine activation as a powerful tool for the direct asymmetric 1,5-functionalisation of α,β-unsaturated aldehydes. In 2008, Woggon and colleagues

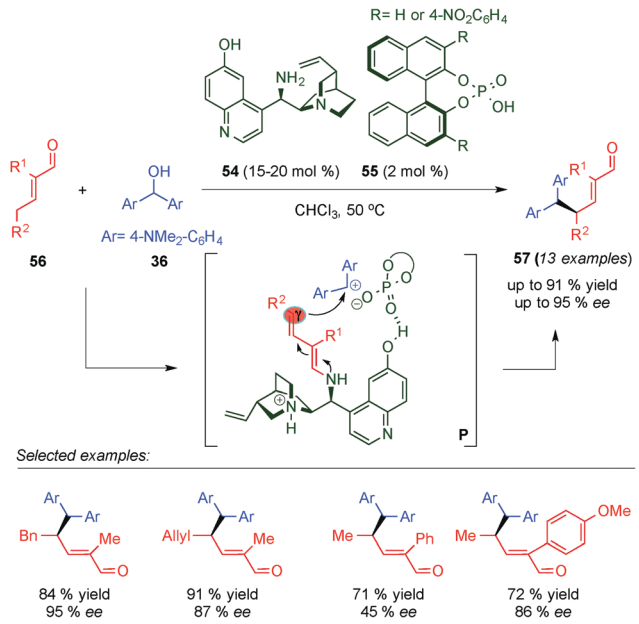


Scheme 13 γ-Amination of α,β-unsaturated aldehydes with diethyl azodicarboxylate.

reported an aldol/oxa-Michael cascade process *via* dienamine-iminium ion intermediates (**O**, **O**′), as a key step in the total synthesis of α-tocopherol (**53**), a member of the vitamin E family (Scheme 14).[28] The product obtained *via* the cascade sequence is subjected to a three step synthetic process based on ring opening *via* hydrogenation, decarboxylation and demethylation leading to the target molecule **53**. The dienamine catalysed reaction proceeded with a perfect γ-regioselectivity and can be considered an astonishing demonstration of the potential of the dienamine activation as a tool in the total synthesis of natural products.



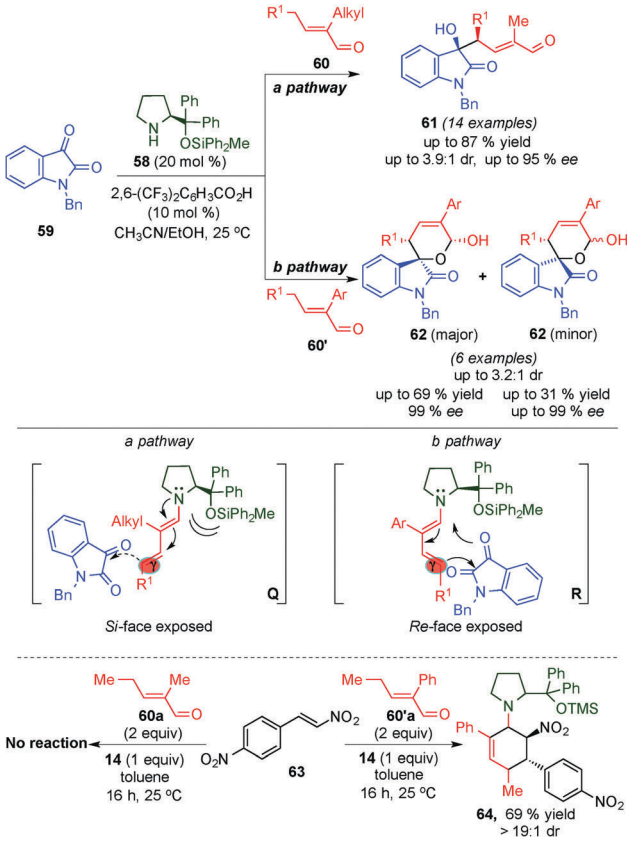
Scheme 14 Asymmetric total synthesis of α-tocopherol through an aldol dienamine mediated catalysed reaction.



Scheme 15 γ-Site selective S_N1-alkylation of α-branched enals through dienamine catalysis.

Targeting to develop discrete intermolecular nucleophilic additions of the remote γ-position of enals, concurrently and independent of Christmann's work (see Scheme 11, Section 2),[24] Melchiorre's group developed a cooperative catalytic system based on a combination of chiral primary amine **54** and chiral phosphoric acid **55**, which is able to promote the γ-site-selective alkylation of α-branched enals **56** *via* an S_N1 pathway (Scheme 15).[25a] The authors proposed that the reaction between α-branched enals and bis[4-(dimethylaminophenyl)methanol] (**36**) proceeds through a cooperative activation path that combines dienamine- and Brønsted-acid activation modes simultaneously. In the transition states (**P**), **55** participates in the formation of a chiral contact ion pair with **36**, which react with the chiral dienamine intermediate generated from condensation with **54**. Thus, through an interwoven of non-covalent interaction of the cooperative catalytic system and the reagents, the reaction furnishes exclusively **57** with excellent yields and enantioselectivities. As a following work, the same authors optimized the methodology using a more effective catalytic system based on a chiral secondary cyclic amine and saccharin, as an achiral acid additive, achieving better yields and enantioselectivities.[25b]

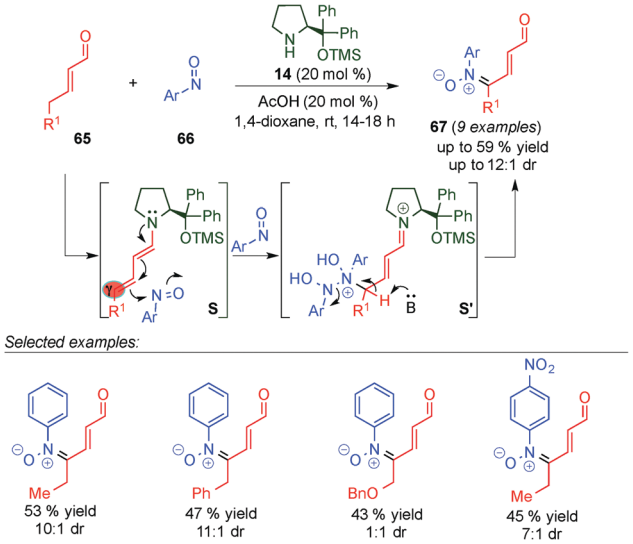
Seeking to extend the nucleophilic addition at the γ-position of the *in situ* generated dienamine intermediates with other electrophilic species, the same group reported the high stereoselective γ-site-selective aldol reaction between α-branched enals (**60** and **60**′) and isatin (**59**) (Scheme 16) *via* a dienamine intermediate using the sterically congested diphenylprolinol silyl ether **58** as a catalyst.[29] The authors observed that the nature of the α-branched enal's substituents led to different product outcomes, postulating two plausible divergent mechanisms for the reaction. Using α-alkyl substituted enals (**60**), the 3-substituted 3-hydroxyoxindole derivatives **61** were obtained with high stereocontrol and selectivity, which could be rationalized through a



Scheme 16 γ-Site-selective aldol reaction between α-branched enals and isatin *via* dienamine activation.

"steric control" transition state (a pathway, Scheme 16), which is based on the addition of isatin from the unshielded face of intermediate **Q** at the γ-position. In contrast, α-aryl substituted enals (**60′**) provided access to spirocyclic oxindole scaffolds **62**, with moderate diastereoselectivity, high enantioselectivity (pathway b, Scheme 16) and opposite configuration of the γ-stereocenter, which is indicative of a [4+2] cycloaddition transition state (**R**). To prove the two different transition states, **Q** and **R**, involved, the authors mixed enal **60a′** with a stoichiometric amount of catalyst **14** and nitrostyrene **63**, a dienophile that can react in a concerted pericycle reaction catalysed by **14**, leading to the Diels–Alder adduct **64**, with great stereocontrol. In contrast, under the same reaction conditions, enal **60** remains unreacted.

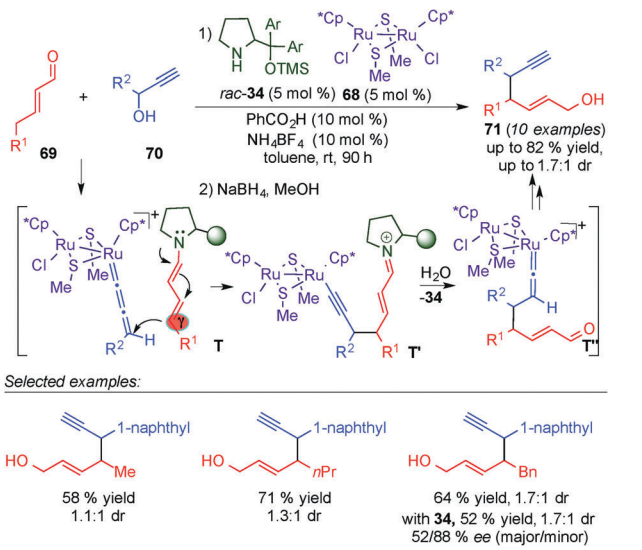
Very recently, Brenner-Moyer and colleagues reported the first γ-site-selective catalytic reaction to directly introduce nitrone functionality to α,β-unsaturated aldehydes *via* dienamine intermediate **S** using catalyst **14** (Scheme 17).[30] This work represents an unprecedented and useful example of an organocatalytic redox reaction, in which the alkyl and aryl substituted enal (**65**) is oxidized to the corresponding γ-nitrone (**67**) with moderate yields and diastereoselectivities, thereby reducing the corresponding nitrosoaryl derivative to *N*-arylhydroxylamine. Supported by experimental and theoretical studies, the authors proposed a plausible mechanism, in which the reaction starts with the condensation of the enal **65** with catalyst **14**, to form an iminium



Scheme 17 γ-Site-selective addition of nitrone to α,β-unsaturated aldehydes.

ion intermediate, which is in equilibrium with the dienamine intermediate (**S**) *via* the loss or gain of a proton. Subsequently, the *in situ* generated dienamine reacts with 2 equivalents of the nitrosoaryl compound (**66**), furnishing intermediate **S′**. However, there is no evidence to confirm whether an asynchronous or concerted transition state is involved. Finally, deprotonation of **S′** liberates the nitrone **67**, along with 1 equivalent of the product of reduction of **66**.

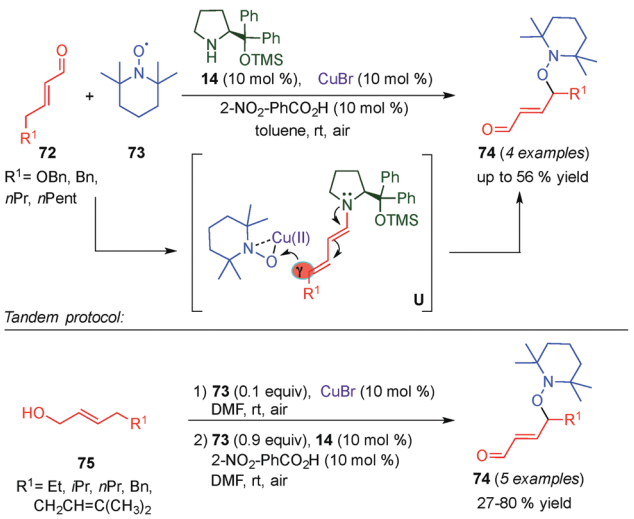
The extension of the asymmetric functionalisation at remote centers of enals by cooperative catalytic processes, involving the combination of dienamine activation with transition-metal catalysis, constitutes an exciting approach to provide a general synthetic technology for designing vinylogous reactions. Pursuing this prospect, the Nishibayashi group developed the γ-site-selective



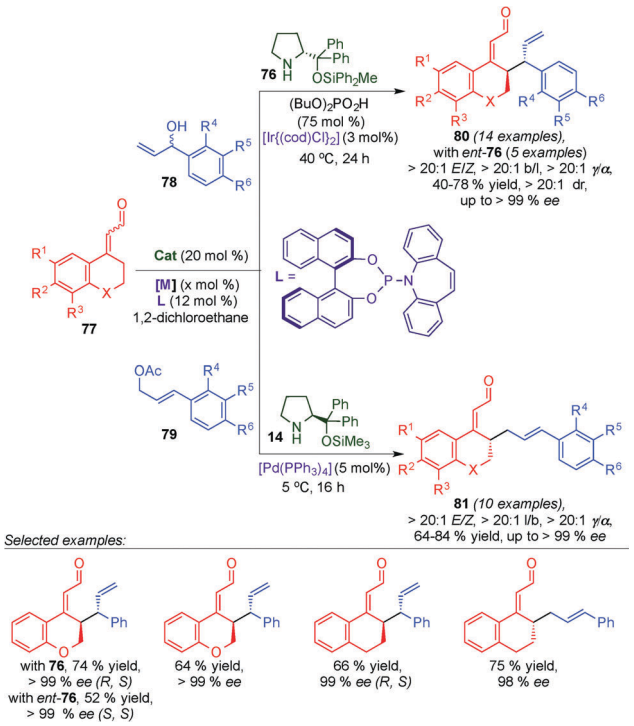
Scheme 18 γ-Propargylation reaction of α,β-unsaturated aldehydes through cooperative ruthenium-dienamine catalysis.

alkylation of γ-enolisable unsaturated aldehydes through cooperative dienamine–metal catalysis (Scheme 18).[31] The diruthenium complex **68** in combination with the chiral secondary amine **34** promoted the γ-selective propargylation of different α,β-unsaturated aldehydes (**69**) with a broad diversity of propargylic alcohols (**70**), with good yields, poor diastereoselectivities and moderate enantioselectivities. The author proposed a plausible reaction pathway which starts with the addition of the dienamine intermediate to the allenylidene complex formed by the reaction of the ruthenium complex with the propargyl alcohol (**T**, Scheme 18), leading to an alkynyl vinylidene complex intermediate *via* an alkynyl complex intermediate, which evolves into the γ-alkylated enal by ligand exchange with another propargylic alcohol (**70**). Compounds (**71**) were obtained by *in situ* reduction of the aldehydes using $NaBH_4$. Despite the poor diastereoselectivities and moderate enantioselectivities obtained, this example laid the foundations for further development of cooperative dienamine–metal catalysed methodologies.

In 2014, a second example of dual dienamine–metal catalysis was reported by Jang and colleagues.[32] They developed a multicatalytic reaction where a copper catalyst (CuBr) combined with aminocatalyst **14** was used to promote both the γ-oxyamination of α,β-unsaturated aldehydes (**72**) (top, Scheme 19). They also developed the one pot aerobic oxidation of allylic alcohols (**75**)/γ-oxyamination of α,β-unsaturated aldehydes (bottom, Scheme 19) using TEMPO (**73**) as an oxidative reagent. Various allylic alcohols and α,β-unsaturated aldehydes were converted to γ-oxyaminated α,β-unsaturated aldehydes with moderate to good yields. A plausible reaction mechanism for the tandem copper catalysed oxidation and copper–aminocatalysed oxyamination of α,β-unsaturated aldehydes was proposed. In the first step, copper–TEMPO complexes are used to oxidize **75**. The corresponding aldehyde (**73**) condensates with the aminocatalyst (**14**), forming the dienamine intermediate. Upon addition of the copper–TEMPO complex to the dienamine intermediate (**U**, Scheme 19), an iminium intermediate is formed, which due to the acidity of the γ-carbon isomerised to a dienamine



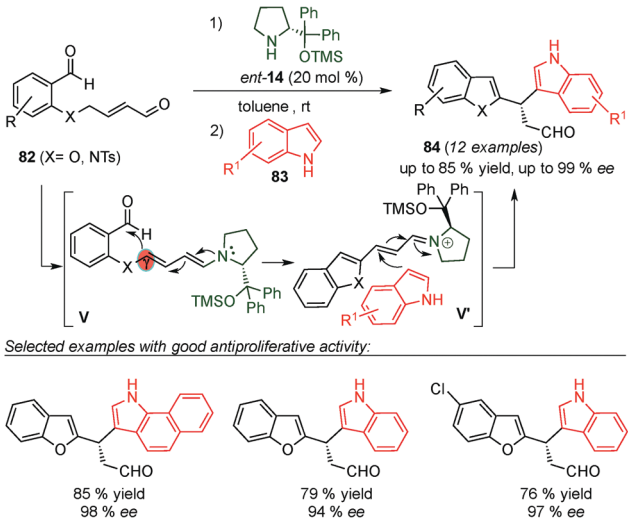
Scheme 19 γ-Oxyamination of α,β-unsaturated aldehydes and tandem oxidation/γ-oxyamination of allylic alcohols *via* copper-dienamine catalysis.



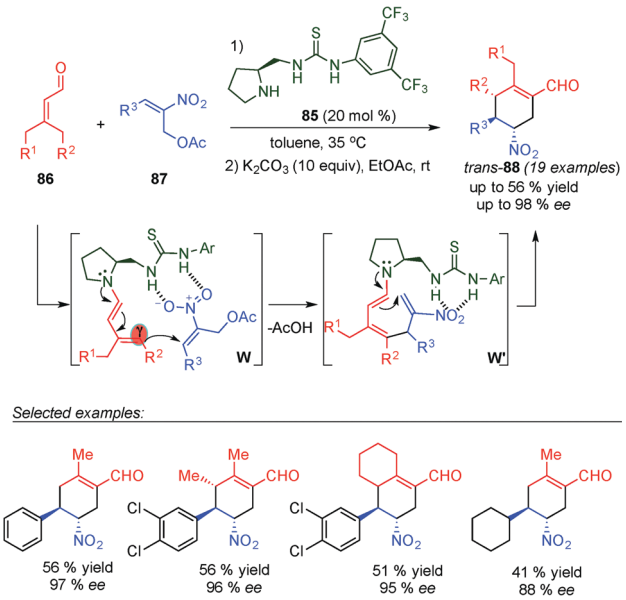
Scheme 20 γ-Allylation of cyclic α,β-unsaturated aldehydes by dual dienamine-transition metal catalysis.

intermediate, preventing further addition of nucleophiles at the β-position of the enal. After hydrolysis the desired product **74** is obtained. Although a chiral aminocatalyst (**14**) was used, stereocontrol was not observed, presumably, due to racemization at the γ-position of **74** during the reaction.

Recently, Jørgensen's group developed the asymmetric γ-allylation of α,β-unsaturated aldehydes based on the combination of dienamine-mediated catalysis and transition-metal catalysis (Scheme 20).[33] This transformation is associated with several potential selectivity issues; the regioselectivity (α- *versus* γ-allylation) of the α,β-unsaturated aldehyde due to the reactive dienamine intermediate contains two nucleophilic sites. Likewise, the activated π-allyl system has two electrophilic sites and the regioselectivity (branched *versus* linear products) of this intermediate also needs to be controlled. Moreover, the control of the *E*/*Z* ratio, the diastereomeric ratio (for branched products), and enantiomeric excess of the products are a challenge. To overcome the mentioned problems the authors developed a methodology, which provides access to all six isomers of the γ-allylated product (4 stereoisomers of branched products and 2 enantiomers of linear products) in a divergent fashion, in excellent selectivity, by choosing the appropriate combination of aminocatalysts, transition-metal catalysts, and ligands. By the use of aminocatalysts (**76**) in combination with an iridium catalyst, selective access to branched γ-allylated products (**80**) was achieved in excellent diastereo- and enantioselectivity. This approach is based on stereodivergent dual catalysis, and thus allows selective access to both diastereomers of **80** by using both enantiomers of **76**. Furthermore, by replacing the iridium catalyst with a palladium catalyst under otherwise similar reaction



Scheme 21 Synthesis of diheteroarylalkanals through a one-pot dienamine-iminium mediated catalytic process.



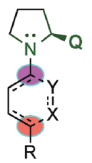
Scheme 22 Synthesis of *trans*-cyclohexene derivatives *via* a dienamine–dienamine mediated catalytic process.

conditions (aminocatalyst **14** instead of **76**) the linear products of the γ-allylation (**81**) were obtained in excellent enantioselectivity.

In 2015, Alemán and co-workers reported the synthesis of chiral diheteroarylalkanals (**84**) by aldol/Friedel–Crafts one-pot reaction (Scheme 21).[34] The one-pot process starts with the condensation of dialdehyde **82** with the catalyst (**14**) to form the dienamine intermediate (**V**) *via* isomerisation of the iminium ion intermediate, which then undergoes intramolecular aldol reaction (**V**, Scheme 21). Subsequently, the generated iminium ion intermediate (**V′**) reacts with the indole (**83**), leading to the diheteroarylalkanals (**84**) in good yields and enantioselectivities due to the classical ''steric control approach''. In addition, the authors carried out antiproliferative activity studies of these new diheteroarylalkanals in representative cancer tumor cell lines. Their structure-activity relationship indicated that with the appropriate substitution pattern, these compounds are as cytotoxic as Cisplatin.

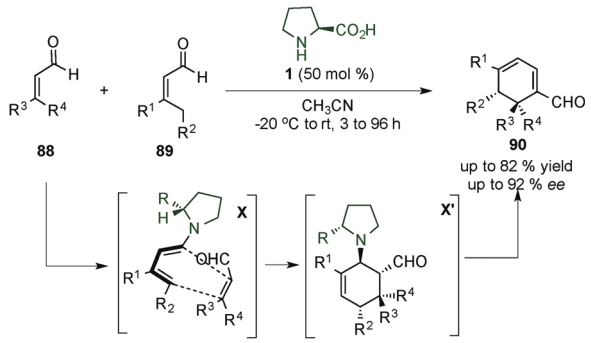
Very recently, Chen's group developed an asymmetric formal α,γ-regioselective [3+3] cycloaddition reaction of α,β-unsaturated aldehydes (**86**) and 2-nitroallylic acetates (**87**) using chiral bifunctional secondary amine–thiourea **85** as a catalyst *via* a cascade dienamine–dienamine mediated catalytic reaction (Scheme 22).[35] This cascade reaction proceeds through the generation of the dienamine intermediate (by condensation of **86** with the aminocatalyst **85**), which reacts with the nitroolefin acceptor (**87**) with complete γ-regioselectivity. Thus, this first Michael addition step generates the required second acceptor, through the elimination of a molecule of acid, favouring the subsequent α-site selective dienamine-mediated intramolecular catalytic Michael addition to furnish the cyclohexene structures. The formal [3+3] cycloaddition reaction produced cyclohexanes **88** in moderate yields, excellent enantioselectivities and poor diastereomeric ratios (*cis*/*trans*). Both diastereomers were obtained with identical ee values, indicating that the enantiocontrol is determined in the first γ-regioselective and the poor diastereocontrol is due to the protonation step. After a simple basic treatment second step, a *trans*-**88** diastereomer was obtained as a sole product of the reaction through epimerization of the chiral center adjacent to the NO_2 group of the major diastereomer (*cis*-**88**).

4. 2,5-Reactivity: [4+2]-Diels–Alder cycloadditions of electron-rich dienes

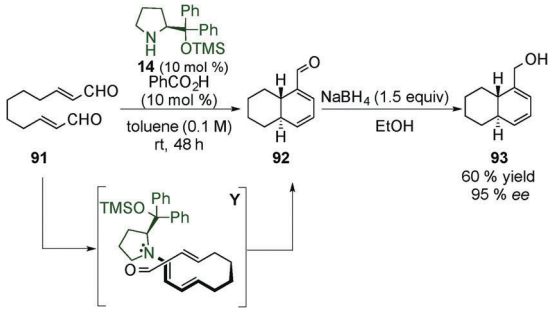


After the rediscovered reaction in the γ-functionalisation, Hong's group published the asymmetric Robinson annulation of α,β-unsaturated aldehydes[36] and subsequently applied this methodology to the total synthesis of (+)-palitantin.[37] In this work, the authors investigated eighteen different pyrrolidine-type catalysts and found that the best catalyst was the proline catalyst, obtaining a large number of six membered ring architectures (**90**) with, in some cases, excellent enantioselectivities (ee > 99%) (Scheme 23). Interestingly, they proposed a mechanism for the formation of a [4+2] adduct *via* a *cis*-dienamine intermediate and an alternative *via* a stepwise mechanism (*trans*-dienamine addition to an iminium ion intermediate followed by an intramolecular aldol reaction).

After this work, in 2008, Christmann *et al.* published the synthesis of mono- and bicycle derivatives *via* dienamine activation of α,β-unsaturated aldehyde (**91**).[38] The dienamine intermediate **Y** was easily formed using the Jørgensen–Hayashi catalyst (**14**), requiring benzoic acid as an additive. Once the intermediate **Y** was formed, an intramolecular Diels–Alder reaction can take place forming the bicyclic product (**92**) in



Scheme 23 First intermolecular [4+2] cycloaddition by Hong *et al.*

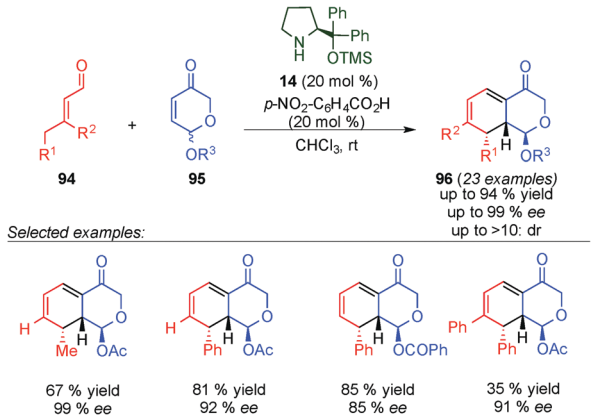


Scheme 24 First intramolecular [4+2] cycloaddition by Christmann *et al.*

good yield and enantioselectivity. The aldehyde was subsequently reduced to the alcohol **93** due to the easier isolation (95%) (Scheme 24). Based on this work, Gil Santo *et al.* studied Christmann's reaction development using DFT calculations.[39] They proved that the use of an external acid is necessary for both the initial enamine formation and also the final catalyst elimination steps. The enantioselectivity is related to the orientation around the C–N enamine bond during the cyclisation step, whereas the diastereoselectivity depends on the *syn*/*anti* configuration of the substituents on the final ring.

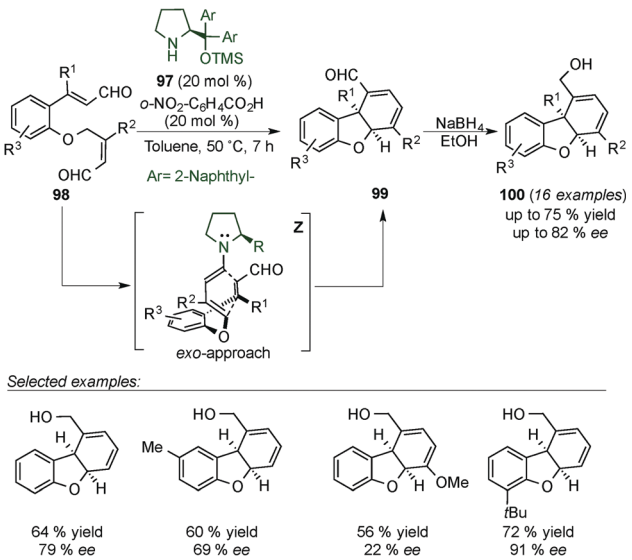
Later on, Vicario's group studied the dynamic kinetic resolution of 5-acyloxydihydropyranones (**96**) through dienamine activation.[40] Thus, they were able to react the racemic pyranones **95** with α,β-unsaturated aldehydes (**94**) in the presence of the Jørgensen–Hayashi catalyst (**14**, 20 mol%) and *p*-nitrobenzoic acid (20 mol%) (Scheme 25). The reaction proceeded through of a Diels–Alder/elimination cascade reaction, obtaining the final products (**63**) with excellent enantioselectivity.

Yang's group published the synthesis of dihydrodibenzofurans **99** by dienamine-mediated catalytic [4+2] cycloaddition reaction requiring a more sterically demanding catalyst **97** (Ar = naphthyl, Scheme 26).[41] Under these conditions, the authors generated a large number of different substrates, most of them with moderate ee (ranging from 22–80% ee) and only two examples with excellent enantiocontrol (91% ee). Aldehyde-dihydrodibenzofuran products (**99**) were subsequently reduced with $NaBH_4$ to their more stable corresponding alcohols **100** to ease isolation. The moderate enantiomeric excess achieved in most of the cases can likely be attributed to the highly strained concerted dienamine transition state (**Z**) (Scheme 26).

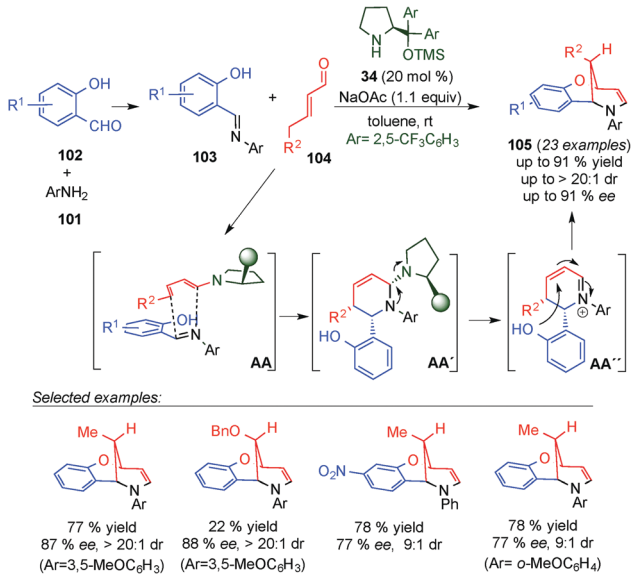


Scheme 25 Kinetic dynamic resolution of pyranones **96** and synthesis of dihydrodibenzofurans *via* dienamine catalysis.

In 2014, Albrecht, Jørgensen and co-workers described the multicomponent one-pot cascade approach for the synthesis of enantiomerically enriched methylene bridged benzo[1,5]oxazocines **105** (Scheme 27).[42] It utilizes initial condensation of the corresponding aniline (**101**) with salicylaldehyde derivatives (**102**) followed by a dienamine-mediated γ-selective Mannich-initiated cycloaddition reaction. Subsequent cyclisation *via* oxy-Michael addition furnishes **105** in good yields and with high stereoselectivities. The developed cascade allowed for direct γ,β,*ipso*-functionalisation of the employed α,β-unsaturated aldehydes. Based on the absolute configuration assignments established through the single crystal X-ray analysis of **105** a plausible reaction mechanism is proposed. The reaction is initiated by condensation of **101** with **102** to afford *N*-aryl imine **103**. Subsequently, a Mannich-initiated cyclisation reaction between **103** and the s-*cis* dienamine derived from the condensation of aminocatalyst **34** with **104** furnishes the cyclohexene framework



Scheme 26 Intramolecular Diels–Alder reaction for the synthesis of dihydrodibenzofurans.

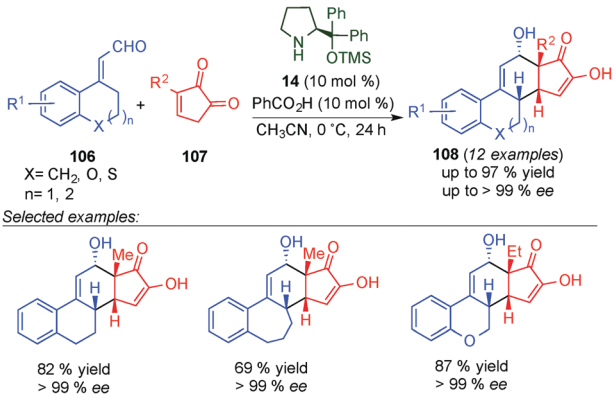


Scheme 27 Synthesis of bridged benzoxazocines through a multi-component one-pot cascade process.

(**AA**–**AA**′). The catalyst was eliminated to give the iminium ion intermediate and a subsequent intramolecular oxy-Michael addition (**AA**″) was carried out to yield **105**. In addition, the authors postulated that the employment of *N*-aryl imines possessing an extended electron-rich π-system might favour the [4+2]-cycloaddition pathway over a sequential reaction mechanism initiated by a γ-Mannich reaction involving an s-*trans*-configured dienamine intermediate.

The same group showed the potential of the dienamine intermediates as electron-rich dienes for the asymmetric synthesis of steroids.[43] This approach is based on the organocatalytic [4+2]-cycloaddition of cyclic enals (**106**) and diketone (**107**) using **14** and benzoic acid as a catalytic system. In most cases, the enantioselectivities were excellent (≥99% ee), providing β-steroid derivatives (**108**) with high yield in a broad substrate scope on the aromatic ring of the enal starting material (**106**). Furthermore, substrates with varying ring sizes and heteroatom incorporation were also synthesised (Scheme 28). In addition, post-synthetic transformation of **108** leading to the synthesis of Torgov's diene and its analogues was carried out in this work. This methodology was also applied to quinone-based dipolarophiles for the asymmetric synthesis of D-homosteroid products.

Wang's group also exploited the *in situ* generation of dienamine dienes for the synthesis of tricyclic benzopyrans **112**,[44] which can be found in important biologically complex natural products, such as cannabinoids and Murrayamine D, among others (Scheme 29). The synthesis is based on a two-step process: first, a [4+2] cycloaddition *via* dienamine activation, followed by a reduction/acid-catalysed intramolecular cyclisation. The first Diels–Alder reaction takes place by a [4+2]-cycloaddition pathway involving a *cis*-configured dienamine intermediate (**AB**), and it was proposed that the expulsion of CO_2 promotes the cycloaddition process (**AB**′ intermediate) to form **111** in line with Serebryakov's original postulation in the 90's.[10] The reaction proceeded quite

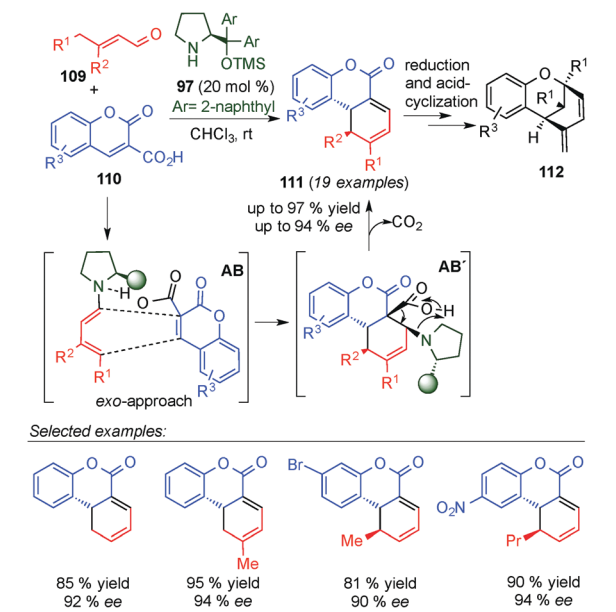


Scheme 28 Synthesis of steroids *via* dienamine-mediated catalytic [4+2]-cycloaddition reaction.

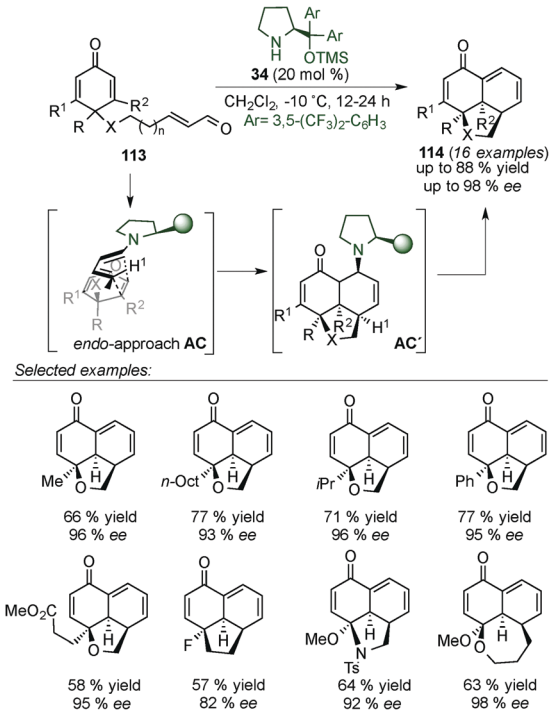
well for a large variety of cases (19 examples) in good yields and enantioselectivities.

In 2014, Alemán's group presented the synthesis of tricyclic derivatives (**114**) (which are present in different natural and biological products, *e.g.* momilactone A) by desymmetrisation of cyclohexadienones **113** *via* dienamine intermediate **AC** (Scheme 30).[45] The reaction tolerated a large variety of substituents at different positions of the cyclohexadienone **113** and different heterocyclic ring sizes can be achieved. Mechanistic studies by DFT calculations have shown that the reaction proceeds *via* an asynchronous [4+2] cycloaddition and not a stepwise reaction (intermediate **AC**).

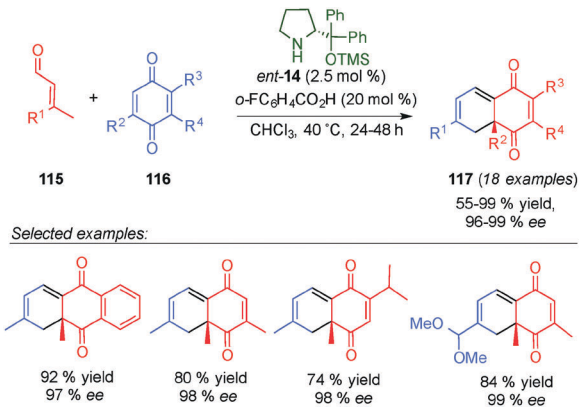
In a related study, Jørgensen *et al.* described the intermolecular [4+2]-cycloaddition reaction between quinone derivatives **116** and β-disubstituted enals **115** (Scheme 31).[46] The reaction tolerated different substituents at the β-position of the enals. Based on DFT calculations, the authors found that the Diels–Alder reaction



Scheme 29 Synthesis of tricyclic benzopyrans by a tandem dienamine-mediated catalytic Diels–Alder/ one-pot reduction/acid-catalysed cyclisation.



Scheme 30 [4+2]-cycloaddition for the desymmetrisation of cyclohexadienones.

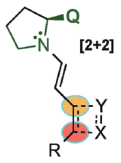


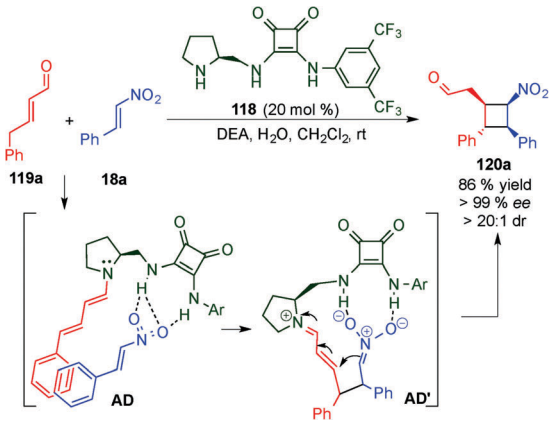
Scheme 31 Diels–Alder reaction between quinone derivatives and enals.

proceeded in a two-step manner with *endo*-selectivity due to a favourable electrostatic interaction in the formed zwitterionic intermediate.

5. 4,5-Reactivity: [2+2], [4+2] and [3+2] cycloaddition

5.1. [2+2] cycloadditions: strained ring formation



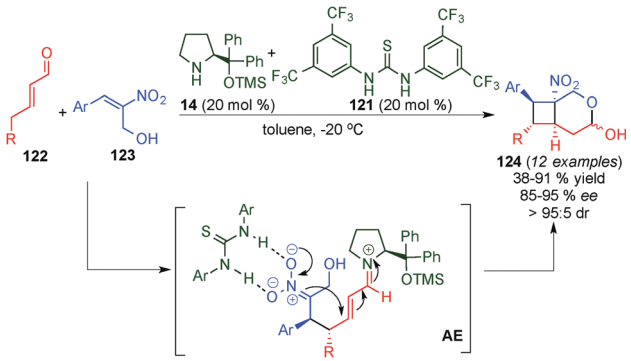


Scheme 32 Bifunctional H-bond directed dienamine catalysis.

With the aim of achieving higher levels of both reactivity and stereocontrol and, more importantly, overcoming the problem of site selectivity inherent to the remote functionalisation of enals through dienamine activation, Jørgensen *et al.* designed a bifunctional squaramide-based aminocatalyst (**118**), which simultaneously activates the two reaction partners (electrophile and enal) *via* H-bond and dienamine activations, respectively (Scheme 32).[47] As a proof of concept, catalyst **118** was applied to a formal [2+2]-cycloaddition of linear α,β-unsaturated aldehydes (**119**) with nitroolefins (**18**) leading to cyclobutane derivatives (**120**) in high yields and with excellent stereocontrol. In this example, the H-bonding interaction of the electrophile (**18a**) with the squaramide moiety arranged the amine protons with a *syn*/*syn* configuration. This conformation of the squaramide allows for three H-bonding interactions with the nitro group and a staggered π-stacking interaction between the phenyl rings of the nitroolefin and the dienamine (**AD**), which provide the proper positioning of the electrophile, and therefore allow for complete regio- and stereocontrolled functionalisation at the γ-carbon. The results were further supported by computational studies, and the authors concluded that a stepwise process would be the most plausible mechanism for this transformation (**AD′**, Scheme 32). Various cyclobutanes were efficiently synthesised by a formal [2+2] cycloaddition from aryl, heteroaryl and alkyl nitroalkenes (**18**) as well as 5-aryl (R^1 = H, R^2 = Ar) and 5-alkyl (R^1 = Me, R^2 = Me) substituted aldehydes (**11**).

Concurrently, Vicario *et al.* described a similar formal [2+2] reaction involving cooperative catalysis, utilising an aryl-prolinol ether (**14**) and a thiourea (**121**) that were used concomitantly to activate both reactants (Scheme 33).[48] In this case, it was necessary to have an α-hydroxymethyl-substitution on the nitroalkene (**123**) in order to push the reaction towards the hemiacetal product (**124**) with full conversion. This reaction provided a general protocol for a series of aryl-bearing either electron-rich [EDG] or electron-poor [EWG] substituents as well as heteroaryl and 5-alkyl substituted α,β-unsaturated aldehydes **122**. Whilst the presence of both EDGs and EWGs on the aryl ring of nitroalkene was tolerated, substitution with an alkyl chain was not described (Scheme 33).

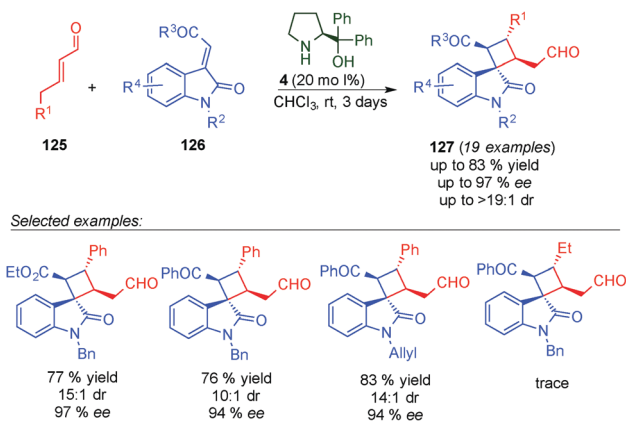
In 2014, Wang *et al.* described the synthesis of spirooxindole skeletons incorporating a cyclobutane moiety (**127**), which are



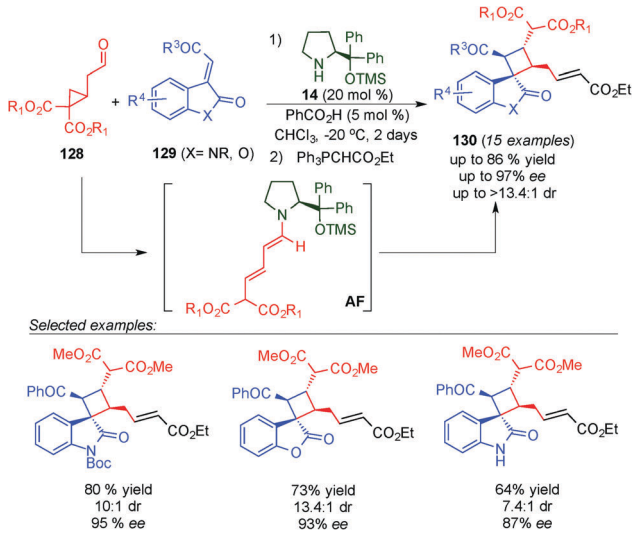
Scheme 33 Cooperative catalysis in the formal [2+2] cycloaddition.

quite common scaffolds in natural and pharmaceutical products, by using H-bond-directing dienamine activation.[49] By contrast, they found that the best catalyst was the diphenylprolinol **4** (20 mol%) in contrast to the one used by Jørgensen (squaramide **118** *vs.* prolinol **4**, Scheme 34). The reaction tolerated different groups at the dienamine functionality, however alkyl chains were not reactive enough to give the final product. In addition, the method allowed different aryl- and nitrogen-substitution groups on **126**.

One year later, Jørgensen's group described an alternative reaction for the synthesis of spirooxindole skeletons incorporating a cyclobutane moiety with a diverse substitution pattern (**130**) by using a novel approach to generate the dienamine intermediate (Scheme 35).[50] They found that cyclopropylacetaldehydes (**128**) can be condensed with aminocatalyst **14** to generate dienamine intermediate **AF**. This process is facilitated by a favourable orbital interaction between the π-orbital of the enamine and the σ* C–C orbital of the cyclopropyl ring. The latter intermediate (**AF**) reacted in a [2+2] manner to give similar cyclobutanes as Wang (compare Schemes 34 and 35).[49] Another plausible mechanism described by the authors is a [3+2] reaction followed by a ring-contracting rearrangement. However, based on the precedents in the literature, and the proof described by them, the [2+2] seems to be the more plausible one. As in Wang's case, the reaction tolerated a large number of substituents at the indol group (**129**),



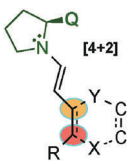
Scheme 34 Wang's [2+2] cycloaddition for the synthesis of spirooxindole skeletons.



Scheme 35 Jørgensen's [2+2] cycloaddition for the synthesis of spirooxindole skeletons.

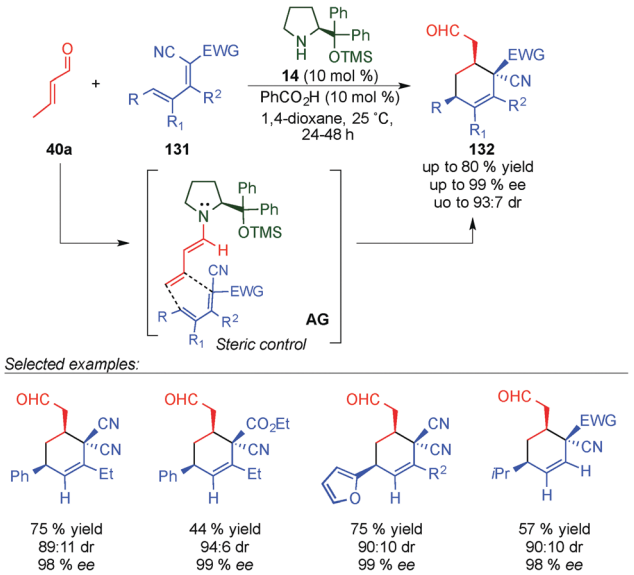
but in this case it was more restricted in the aldehyde reagent (**128**), as it required gem diester groups to achieve the ring opening (Scheme 35).

5.2. [4+2] cycloadditions of electron-rich dienophiles



In 2010 Chen's group developed a new regio- and stereoselective dienamine-mediated catalytic inverse-electron demand Diels–Alder reaction using α,β-unsaturated aldehydes as dienophiles.[51] This is the first case of using the double bond at the 4,5-position as a dienophile through a dienamine-activation strategy. It is of particular interest that even when six positions were removed from the chiral centre of the catalyst, the obtained enantiomeric excess was excellent (Scheme 36). The reaction tolerated a large number of variations at the diene (**131**), different aromatic and alkyl derivatives at the δ-position, and also some alkyl substitutions at β- and γ-positions with excellent enantioselectivities and good diastereomeric ratios in all cases (see selected examples, Scheme 36). However, in the case of the aldehyde, the scope was extremely limited and only crotonaldehyde (**40a**) was used for this study.

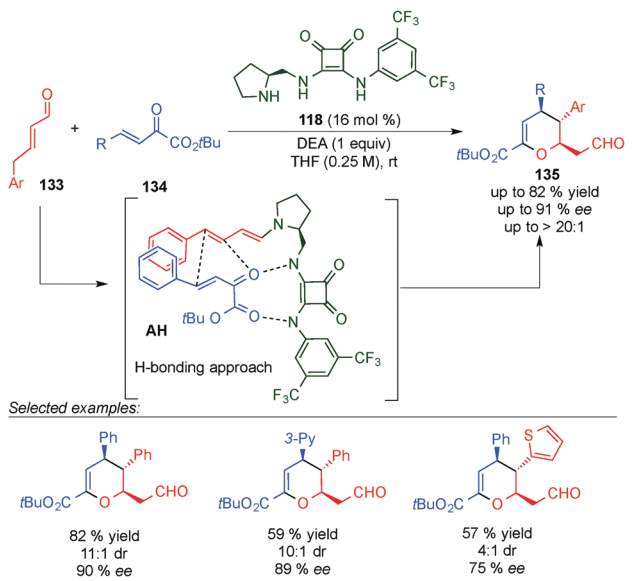
After two years, Jørgensen *et al.* described a similar dienamine-mediated catalytic inverse Diels Alder reaction pathway but instead of using a steric shielding strategy as Chen reported in his work, they described an aminocatalytic H-bond directing strategy (intermediate **AH**, Scheme 37).[52] Thus, the limitations that Chen found, such as the use of only crotonaldehyde as a nucleophile, were solved using this strategy. Only 4,5-reactivity was observed, high stereocontrol was found, and a broader scope was achieved, giving access to chiral dihydropyran frameworks



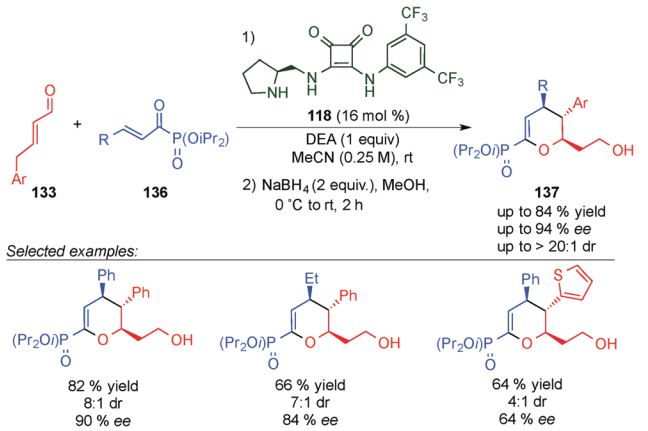
Scheme 36 First dienamine-mediated catalytic inverse-electron demand Diels–Alder reaction with crotonaldehyde.

(**135**). Thus, the reaction tolerated a large number of substituents at the 1,2-dicarbonyl electrophilic acceptors (**134**) with excellent ee values and diastereoselectivity. However, the scope at the aldehyde (**133**) was more limited and enantioselectivities from moderate to good were obtained (75% to 90% ee).

In an associated study, the same group developed the synthesis of enantioenriched dihydropyran phosphonates (**137**)[53] using acyl phosphonates (**136**) instead of the 1,2-dicarbonyl compounds (**134**) (compare Schemes 37 and 38). In this case, the products were also obtained with good ee values and yields, allowing even the use of alkyl acyl phosphonate derivatives.



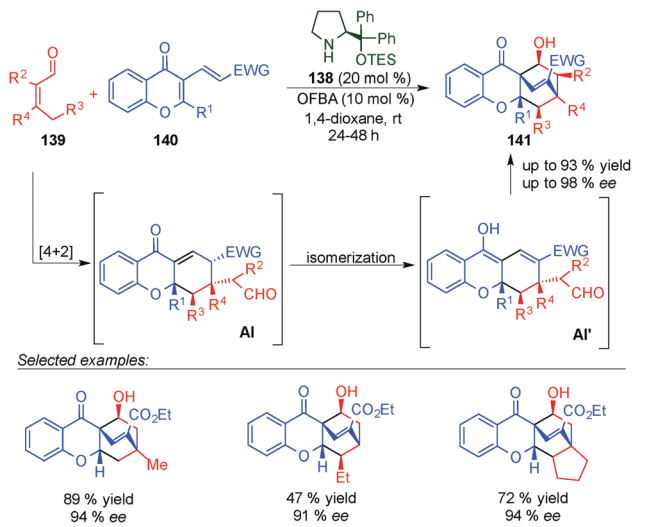
Scheme 37 First H-bond controlled dienamine-mediated catalytic inverse-electron demand Diels–Alder reaction.



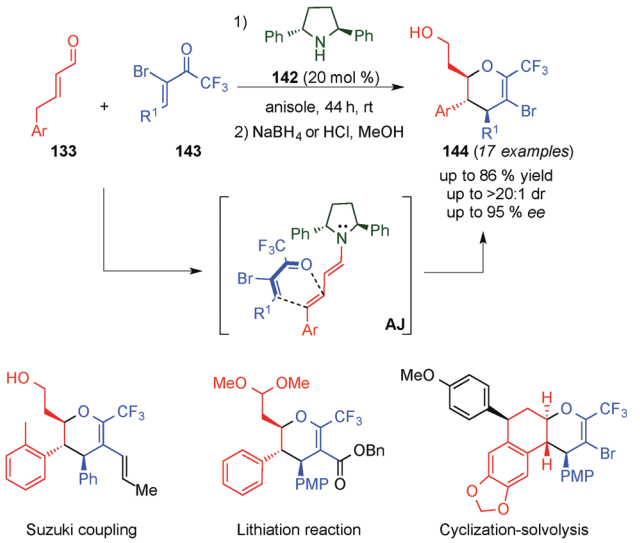
Scheme 38 H-bond controlled dienamine-mediated catalytic inverse-electron demand Diels–Alder reaction for the synthesis of dihydropyran phosphonates.

Later on, Chen described an asymmetric Diels–Alder reaction of β,β-disubstituted enals (**139**) and chromone-fused dienes **140** which gave access to different chiral tetrahydroxanthone based natural products **141** (Scheme 39).[54] This strategy is based on the HOMO-raising of the 4,5-double bond and represents the first use of β,β-disubstituted enals in dienamine activation. The Diels–Alder reaction was followed by a domino deprotonation-isomerisation-vinylogous aldol reaction to give the final bicyclo derivatives **141** (Scheme 39). The reaction tolerates a large number of aldehydes with different substitution (even at the α-position) and different chromone substrates. In all cases, only one diastereoisomer was detected and good yields and ee values were obtained.

Very recently, Jørgensen and colleagues reported the stereoselective formation of highly substituted CF_3-dihydropyrans (**144**),[55] which are important motifs in medical chemistry and in bioactive compounds, such as the antiviral agent zanamivir,[56]



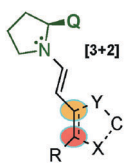
Scheme 39 Dienamine-mediated catalytic inverse-electron demand Diels–Alder reaction for the synthesis of tetrahydroxanthone based natural products.



Scheme 40 Inverse-electron demand hetero-Diels–Alder reaction.

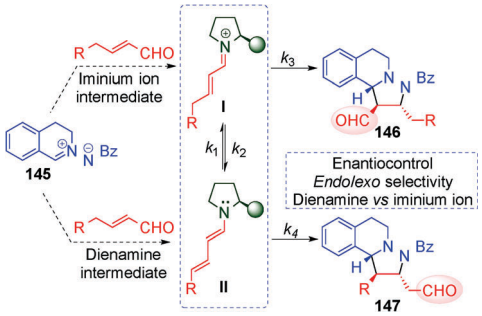
risugacin A50[57] and swertiamarin[58] (Scheme 40). Therefore, they developed the inverse-electron demand hetero-Diels–Alder reaction with a wide substrate scope of substituted 5-bromo-6-CF_3-dyhydropyrans **143** and γ-aryl substituted α,β-unsaturated aldehydes **133**, catalysed by C2-symmetric 2,5-diphenylpyrrolidine catalyst **142** with moderate to good yields and diastereoselectivities and excellent enantioselectivity. Additionally, the authors showed a further derivatisation of the Diels–Alder products (see the bottom, Scheme 40) by cross-coupling reactions and lithiation reactions, as well as an unexpected cyclisation protocol, which furnished optically active tetracyclic compounds.

5.3. [3+2] cycloadditions



In 2014, Wang's[59] and Alemán's[60] groups independently developed the [3+2] cycloaddition reaction between azomethine imines and α,β-unsaturated aldehydes through dienamine activation (Scheme 41). Despite the fact that the iminium ion is the previous intermediate for the formation of the corresponding dienamine and that both species are in equilibrium, there were no studies investigating the reactivity control of these two intermediates with their differing nucleophilic and electrophilic natures. In order to have complete control over the plausible equilibrium between the iminium–dienamine (k_1 *vs.* k_2) or over the reactivity of both reactions (k_3 *vs.* k_4), different reaction conditions were explored (Scheme 41).

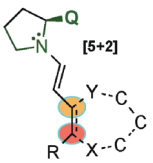
After screening conditions, Alemán's group found that complete control of the dienamine or iminium intermediates could be achieved by employing appropriate conditions.[60a] The use of catalyst **34**, TBAB as an additive and toluene as a solvent was the best conditions for iminium type products **146** (top Scheme 41).



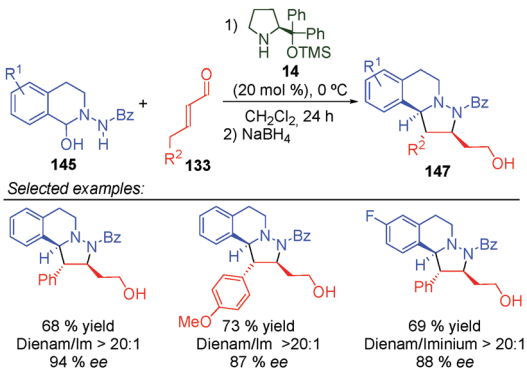
Scheme 41 [3+2] cycloaddition reaction: dienamine *vs.* iminium ion intermediates.

By contrast, the use of the hydrated dipole **145**, catalyst **14** and CH_2Cl_2 as a solvent is the best conditions so far to obtain dienamine products **147** (Scheme 42). With this work, Alemán's group was able to describe the first example of regio-control of an iminium ion intermediate *versus* a dienamine intermediate in the [3+2] cycloaddition of azomethine imines. Dienamine products (**147**) were achieved with good yield and good enantioselectivity in most cases, regardless of the nature of the aromatic ring used in the aldehydes (**133**) or the substituent on the aryl group of the azomethine imine (**145**) (Scheme 42).

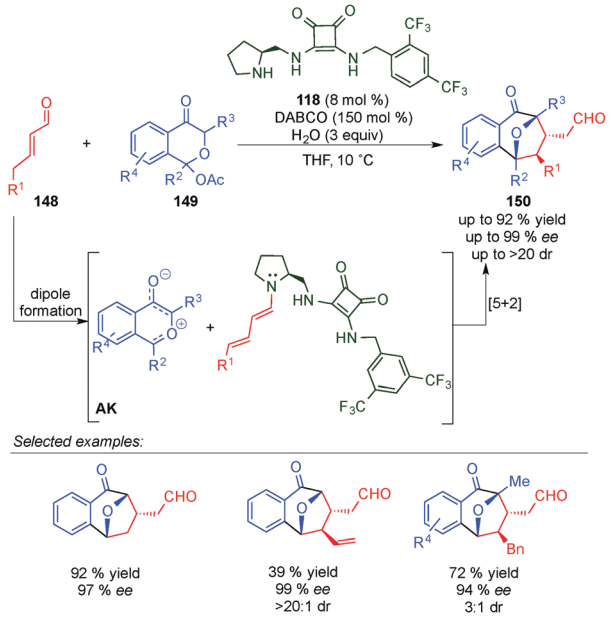
5.4. [5+2] cycloaddition



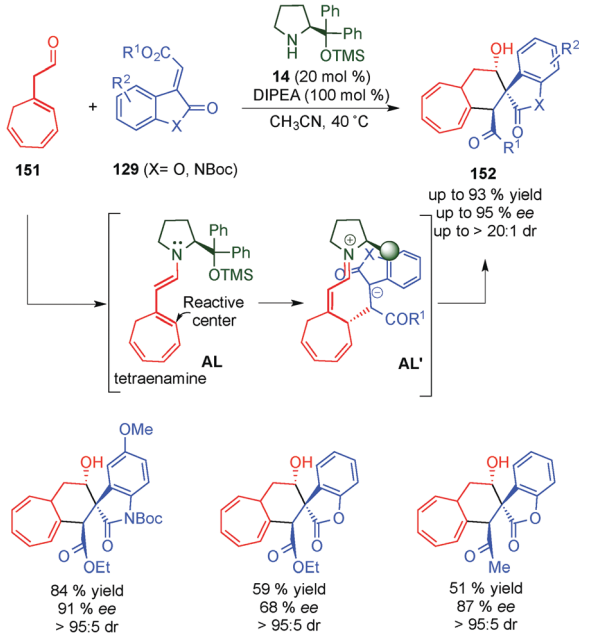
Vicario's group published the catalytic [5+2] cyclisation between oxidopyrylium ylides and enals (**148**) by dual hydrogen-bond dienamine activation (Scheme 43).[61] Thus, benzopyrylium ylides were generated from the acetoxy chromanone derivative **149** and, mediated by a squaramide secondary amine catalyst **118**, were able to react with the dienamine intermediate (**AK**). The reaction proceeds with moderate to excellent yields and good ee values in most cases, but with a low diastereomeric ratio in some cases. Unlike with [3+2] cycloadditions, the dienamine intermediate showed exclusively 4,5-reactivity, most likely due to the H-bond



Scheme 42 First examples of [3+2] cycloaddition *via* dienamine activation.



Scheme 43 [5+2] cycloaddition of oxidopyrylium ylides *via* dienamine activation.



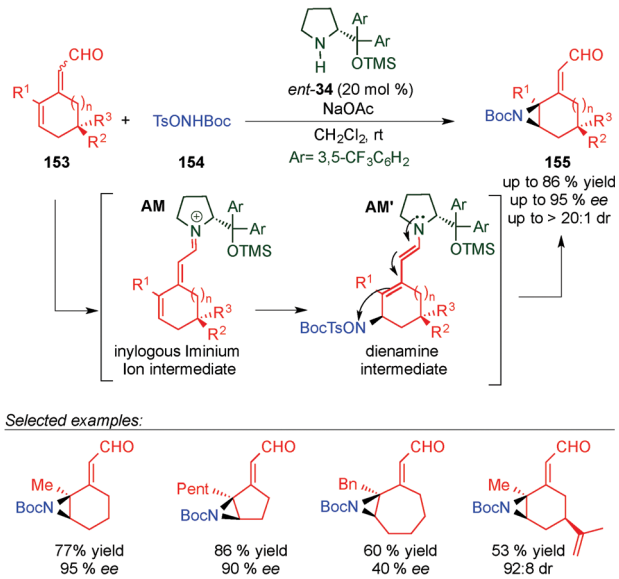
Scheme 44 Functionalisation of cycloheptatriene derivatives *via* the tetraenamine intermediate.

interactions of the bifunctional secondary-amine/squaramide catalyst, thus furnishing excellent regiocontrol.

6. Related dienamine and tandem processes

In 2014, Jørgensen's group used a tetraenamine intermediate (**AL**) to functionalise cycloheptatriene derivatives **151** (Scheme 44).[62] Once the tetraenamine **AL** is formed, it reacts with electrophile **129** *via* the dienamine intermediate from the less hindered prochiral face to afford intermediate **AL′**. The final cyclisation step of the anion to the iminium ion intermediate (**AL′**) takes place and leads to the corresponding spiro-compound **152**. Through DFT calculations the authors explained the high diastereomeric ratios that the authors obtained in the reaction.

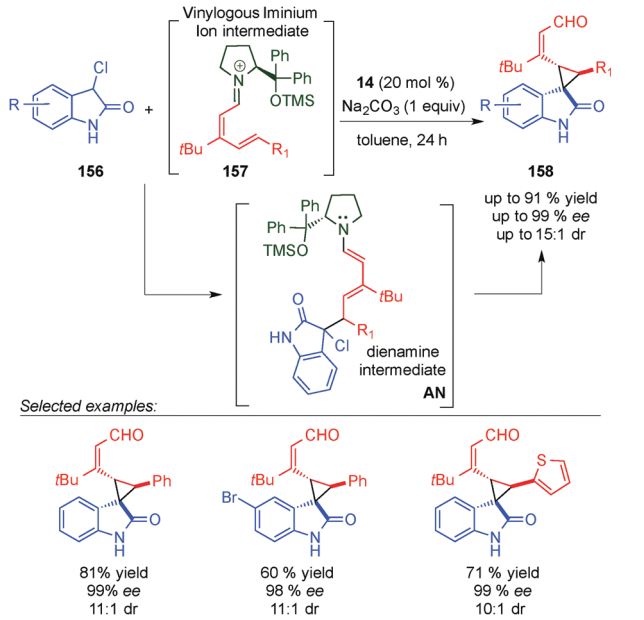
In 2013, the same group carried out the remote aziridination of 2,4-dienals (**153**) based on a vinylogous iminium ion/dienamine intermediate strategy (Scheme 45).[63] In this work, an iminium ion intermediate **AM** is attacked (*via* 1,6) by **154** to furnish a dienamine intermediate **AM′** that evolves through cyclisation (TSO^- as a leaving group) to **155** in good yields and excellent enantioselectivities.



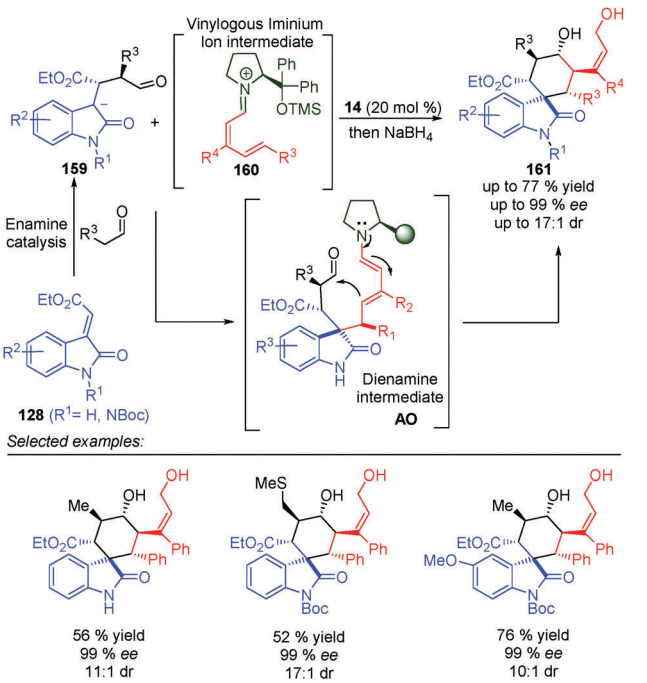
Scheme 45 Remote aziridination through dienamine intermediate **AM**.

The same concept was used by Melchiorre *et al.* in the 1,6-addition of an ambivalent compound **156** (a compound with both nucleophilic and electrophilic characteristics) to the vinylogous iminium ion **157**, to give an intermediate **AN** (Scheme 46).[64] The formed dienamine intermediate cyclises, *via* substitution of the chlorine atom at the benzylic position, and led to the final spiro-cyclohexane derivatives **158** in high enantiomeric excesses and good yields. Using dienamine intermediates, the same group published a triple vinylogous cascade reaction, *via* a Michael/1,6-addition/vinylogous aldol sequence (Scheme 47).[65] In this case, the key step was the formation of the dienamine intermediate **AO**, which presents the appropriate groups to promote the attack of the dienamine intermediate by the aldehyde to form the final alcohol **161** after reduction with $NaBH_4$.

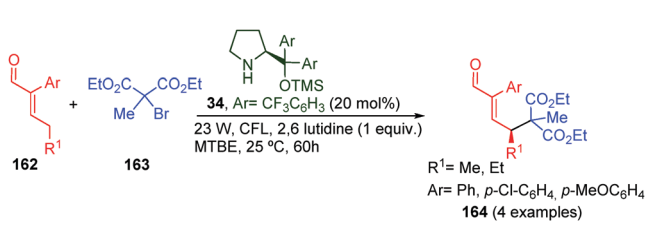
In 2015, Melchiorre *et al.* described the direct alkylation of enals **162** using various photocatalytic methodologies. Chiral dienamines, as well as enamines, have the ability to act as photosensitisers upon under light irradiation.[66] In this outstanding work, the reaction took place with complete γ-selectivity, but only α-substituted enals and tertiary bromo-alkanes were used as



Scheme 46 Remote cyclopropanation towards dienamine intermediate **AN**.



Scheme 47 Triple cascade reaction in the synthesis of six spiro-oxindolic cyclohexanes *via* a dienamine intermediate **AO**.



Scheme 48 Organocatalytic alkylation of enal by direct photoexcitation.

starting materials and four examples (**164**) were synthesised (Scheme 48).

7. Conclusions and outlook

As highlighted in this review, since the early examples of Serebryakov dienamines to their evolution during the organocatalytic age, dienamine activation has established itself as a powerful and reliable strategy for the functionalisation of α,β-unsaturated aldehydes. Several reactive dienamine intermediates have enabled the development of a large variety of new methodologies for the synthesis of complex molecules with excellent control over the regio- and stereoselectivity. By exploiting the broad variety of possible reactive dienamine intermediates, formed upon condensation of an aminocatalyst with an α,β-unsaturated aldehyde, the highly regio- and stereoselective generation of new stereogenic centres located at the 3- and 5-positions of the α,β-unsaturated aldehydes (α- and γ-functionalisation, respectively) has been successfully demonstrated.

With regard to regioselectivity, 1,3 *vs.* 1,5 reactivity, three main strategies have been used for regio-control: (i) In general terms, a delicate balance of electronic and steric effects is found in which the steric effect plays a predominant role in the reactivity of the dienamine intermediate with the electrophile. Therefore, the use of double substitution at C-5 (R^2 and $R^3 \neq H$) means that only 1,3 reactivity can take place (left, Fig. 3; see *e.g.* Scheme 11). (ii) The appropriate substitution at the α-position of the aldehyde ($R^1 \neq H$) changes the selectivity to the γ-position (middle; see *e.g.* Scheme 15). (iii) The third and final strategy is based on the design of the catalyst. Thus, the use of a bifunctional catalyst that approaches the electrophile at the second double bond (C-4 and C-5) provokes a large selectivity at this γ-position, with squaramide proline catalysts **118** being the most often employed (right Fig. 3; see *e.g.* Scheme 43).

Very recently, during the evaluation of this manuscript, Gschwind *et al.* have described a mechanistic study in the remote stereocontrol of the dienamine-mediated catalytic nucleophilic substitution reaction based on NMR and computational studies.[67] In this work, the authors reveal a plausible pathway in the *Z*/*E* dilemma, describing in detail the kinetics/thermodynamics in the formation of the dienamine and the latter reaction with an electrophile (S_N1 reaction with bis(4-dimethylamino-phenyl)(methanol) in the presence of acid). The enantioselectivity is directly correlated with the configuration of the second double bond (*Z* and *E*, Scheme 49). Thus, the *Z*

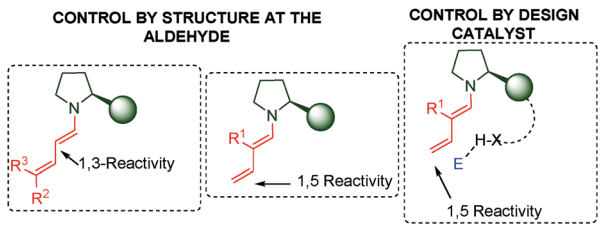
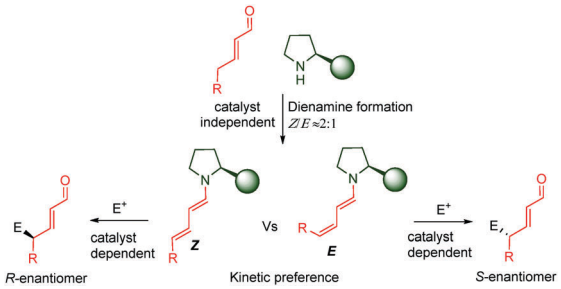


Fig. 3 Strategies for regiocontrol in the dienamine intermediate.



Scheme 49 Origin of the enantioselectivity in the dienamine-mediated catalysis.

configuration leads to the *R*-enantiomer whereas the *E* configuration yields the *S*-enantiomer. The study reveals the kinetic preference in the formation of the *Z*-isomer of the second double bond ($Z:E \approx 2:1$), which is independent of the structure of the catalyst (catalysts *e.g.* **14** and **34**). However, the reaction of the *Z* or *E* dienamine intermediate with the carbocation is catalyst dependent, and different interactions (CH-π, stacking) are the main factors responsible for the kinetic preference and faster reaction of *Z*-over the *E*-isomer. This is also corroborated by calculations and kinetic experiments.

Despite the great potential offered by dienamine catalysis in recent years, there are still challenging problems to solve and new potentially useful methodologies waiting to be discovered. For these reasons, the activation of α,β-unsaturated aldehydes *via* dienamine intermediates is expected to develop further in the near future with more and more diverse and ingenious findings. In our opinion, three main roads should be considered in the future: (i) New reactions, especially in the photocatalytic field, should be explored with different reagents (only one publication has been reported using photocatalytic conditions). (ii) New regioselective strategies for the control in 1,3 *vs.* 1,5 reactivity should be studied, especially concerning the use of bifunctional catalysts that could approach the electrophile at C-3 or C-5 regardless of the substitution of the enal. (iii) The combination of metal catalysis and organocatalysis in the dienamine functionalisation has not been fully explored and only a limited number of examples have been reported thus far.

Acknowledgements

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