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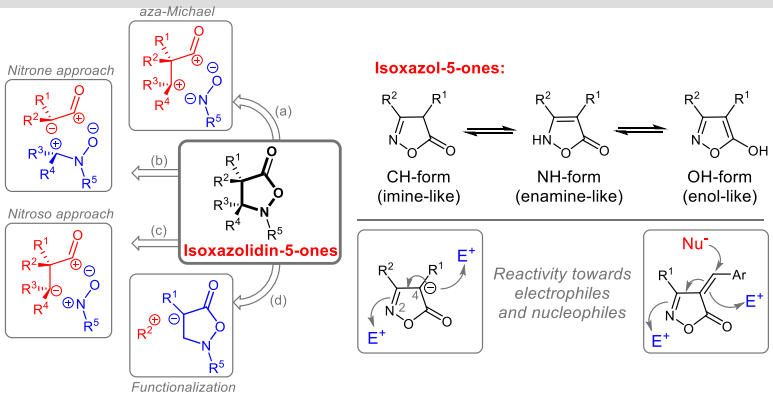

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Abstract. Isoxazol-5-ones and isoxazolidin-5-ones represent two important classes of heterocycles, with several applications as bioactive compounds and as versatile building blocks for further transformations. Unlike the parent aromatic isoxazoles, the presence of one or two stereocenters in the ring renders their asymmetric construction particularly important. In this review, starting from the description of general features and differences between these two related compound families, we present an overview on the most important enantioselective synthesis strategies to access these heterocycles. Both, chiral metal catalysts and organocatalysts, have been successfully employed for this task in the last years and some of the most promising approaches will be discussed herein.

Keywords: Asymmetric catalysis, organocatalysis, metal catalysts, heterocycles, chiral building blocks.

1) Introduction

Isoxazol-5-ones **2** and isoxazolidin-5-ones **3** are important classes of functional molecules belonging to a large family of heterocyclic compounds, the isoxazoles **1** (Figure 1). In particular, isoxazol-5-ones and isoxazolidin-5-ones have been found in a variety of natural products (Figure 2), isolated for example from lentil seedlings (compounds **4** and **6**)[1,2,3], bacteria (**5**)[4] marine sponges (**7**)[5] and chrysomeline larvae (**8**).[6] Besides the naturally occurring derivatives, a great number of (synthetic) products with very interesting biological activities has been reported (Figure 2). For example, some of them show anti-obesity activity (like compound **9**),[7] are used as anti-cancer agents (**10**)[8], were employed for the treatment of bladder over-activity in central nervous system (CNS) diseases (**11**)[9], or served as HNE (human neutrophil elastase) inhibitors with anti-inflammatory effects (**12**).[10] In addition they can show anti-bacterial (**13**)[11] and p38 MAP (mitogen-activated protein) kinase inhibition activity (**14**,[12] **15**[13]). Compound **16**[14] holds promise as an inhibitor of succinate dehydrogenase and derivatives **17** and **18**[15] are promising HDAC (histone deacetylases) inhibitors. Furthermore **19-21** and **26**[16] show anti-androgen activity as for blefoxatone and toloxatone and some derivatives also find applications as agrochemicals (**22-25**).[17,18,19,20,21,22]

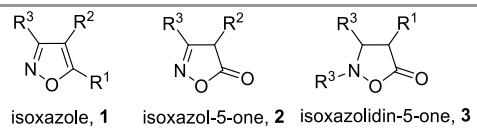


Figure 1. Isoxazole-based heterocycles.

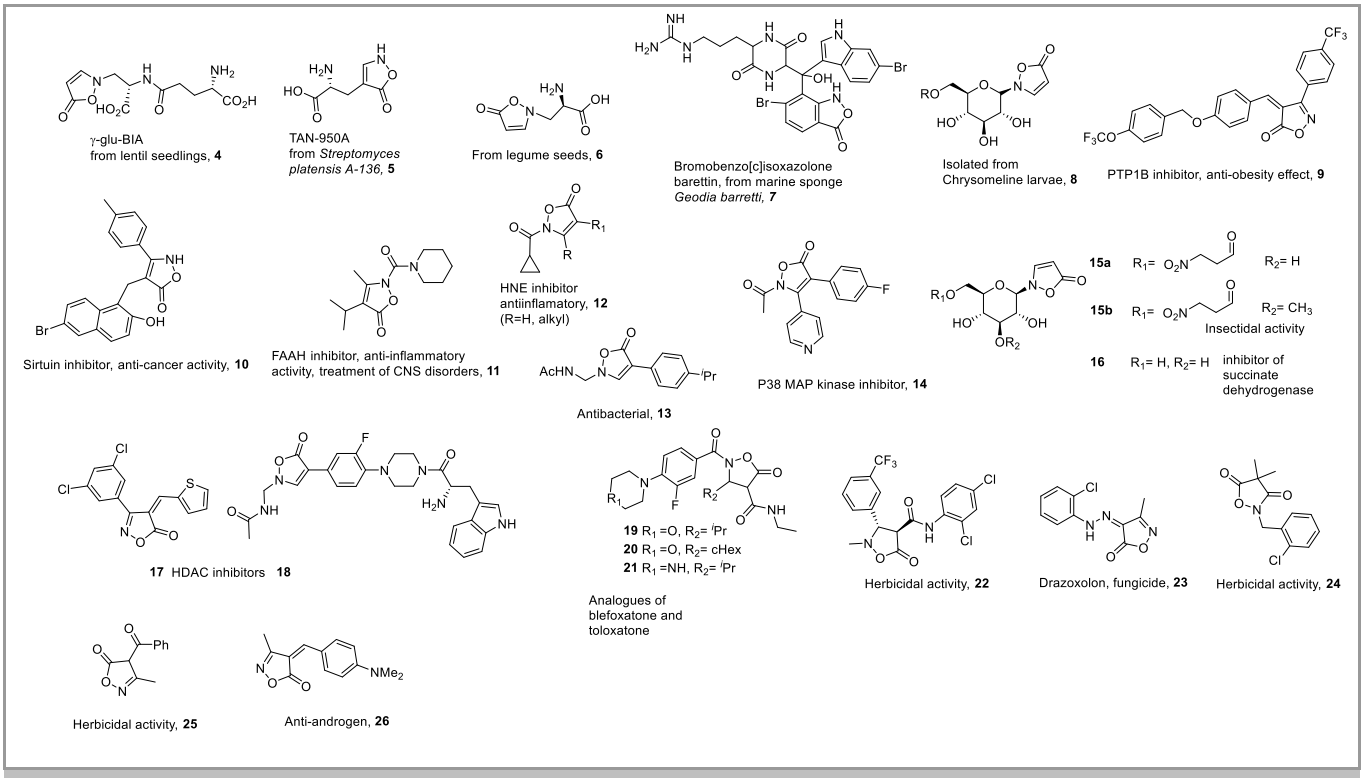
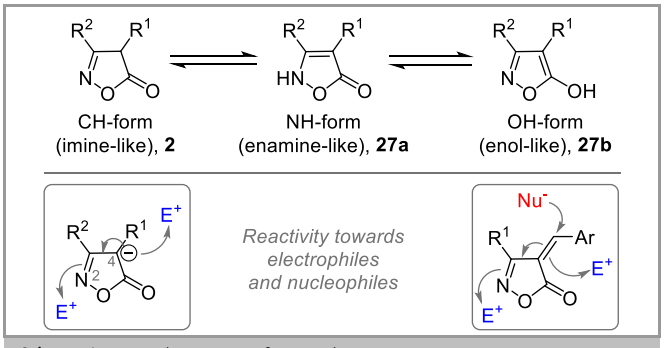


Figure 2. Selected natural and synthesis-derived biologically active derivatives.

Over the last years the development of asymmetric protocols for the syntheses of chiral isoxazol-5-ones **2** and isoxazolidin-5-ones **3** have attracted considerable attention, highlighting several similarities but also some peculiarities between these two related classes of heterocycles. In a recent review, Jurberg *et al.* have described the general features of isoxazol-5-ones chemistry, focusing mainly on their preparation and further transformations.[23] Most of this knowledge is also based on the seminal works proposed by the group of Zard.[24,25] In a complementary review, Brière and coworkers analyzed the properties and the asymmetric construction of the isoxazolidin-5-ones up to the beginning of 2017,[26] but it should be emphasized that most of the articles regarding the use of these heterocycles in enantioselective transformation processes have been published subsequently over the last 3-4 years.

Isoxazol-5-ones are characterized by relatively high acidity at C-4 because of resonance-stabilization of the resulting carbanion by the carbonyl and the imine group, thus resulting in pK_a values comparable to carboxylic acids. As depicted on Scheme 1, isoxazol-5-ones possess two main nucleophilic sites, N2 and C4, while the exocyclic carbonyl O atom is usually less reactive. Regioselectivity issues are challenging in this case and depends on several factors, while, in contrast, N-protected isoxazolidin-5-ones find applications as C-nucleophiles mainly. For both the heterocycles, the N–O bond is relatively weak[27] and a CO_2 molecule can also be eliminated under certain conditions.[24,25] Accordingly, a variety of transformations have been proposed giving access to more complex isoxazole-derived architectures or furnishing new acyclic building blocks like chiral alkynes and β-aminoacids. In addition, new heterocycles like piperidines and aziridines can be obtained by ring expansion or contraction, respectively. On the other hand, unsubstituted or 4-monosubstituted isoxazol-5-ones show complex tautomers **2** and **27** in equilibrium, due to the acidic C4-H of **2** and the relatively high stability of the conjugated NH-form **27a** in comparison to aromatic HO-form, **27b** (Scheme 1).

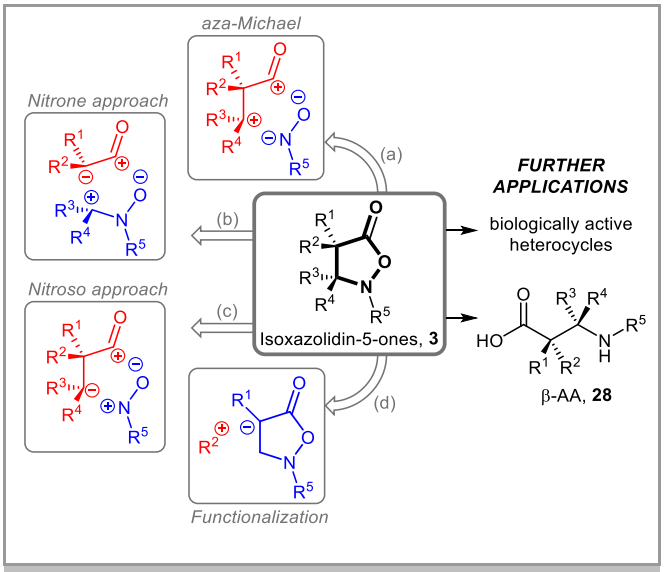


Scheme 1. General reactivity of isoxazole-5-ones.

However, the prevalence of one tautomer strongly depends on the substitution pattern, on the solvent, and on the purification conditions. In most of the cases, mixtures of tautomers can be detected. This can be a limitation, not only for pharmaceutical applications, but it has also practical issues for product characterization, HPLC analysis and determination of diastereomeric and enantiomeric ratios.

With respect to asymmetric syntheses of isoxazol-5-ones, the currently established methods reflect the above described features and are mainly based on the use of preformed heterocycles. Depending on their substitution patterns, these can serve either as nucleophiles, developing regioselective N- or C-alkylations (Scheme 1, left side), or as Michael acceptors, even in domino reactions (Scheme 1, right side).

On the other hand, isoxazolidin-5-ones **3** show less diverse inherent reactivity tendencies (Scheme 2). Because of the absence of the imine group they are, first of all, less acidic than isoxazole-5-ones **2**. In addition, the usually protected nitrogen is not nucleophilic, and thus this class of molecules primarily reacts as C-nucleophiles. As a consequence of these features, the asymmetric synthesis of (functionalized) isoxazolidin-5-ones **3** is mainly based on two approaches. The historically well-established way to access isoxazolidin-5-ones relies on asymmetric annulation strategies of simple (prochiral) acyclic starting materials (strategies a-c).[28] In addition, over the last years, several reports described the asymmetric functionalization of racemic isoxazolidin-5-ones (strategy d, $R^{2\text{-}4}$ = H), which currently leads to relatively broad and diverse powerful synthetic strategies to access this valuable heterocyclic platform.



Scheme 2. General synthesis approaches to access chiral isoxazolidin-5-ones and most common applications of these heterocycles.

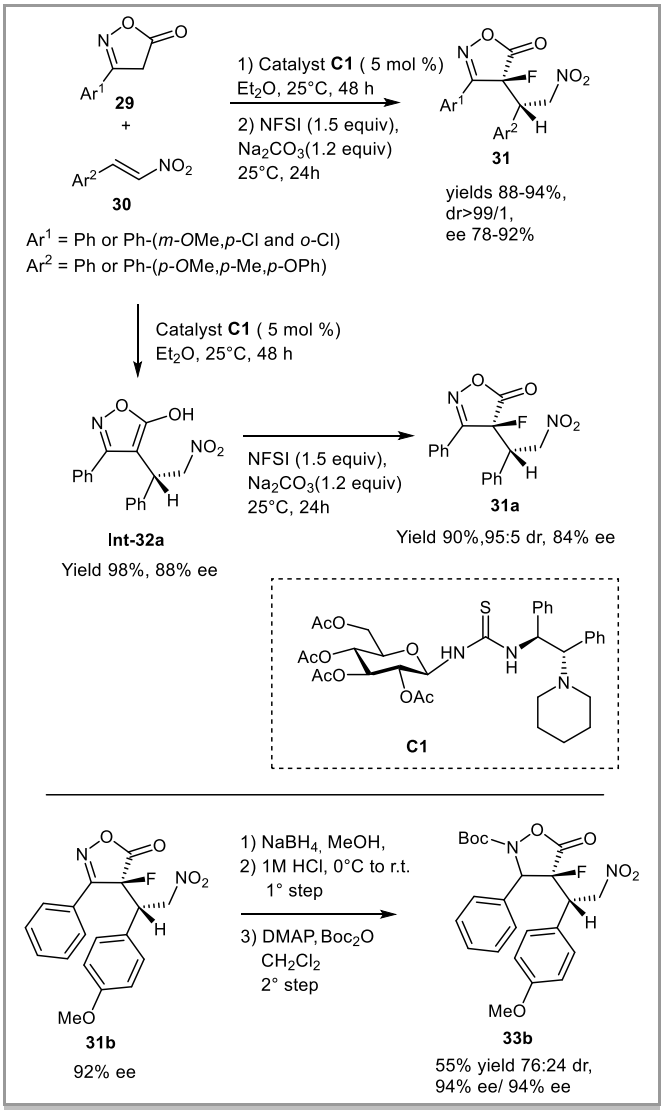
In this review we wish to provide an illustrative (but not encyclopedic) overview about the most relevant recent asymmetric synthetic strategies to access and/or to functionalize isoxazol-5-ones and isoxazolidin-5-ones. All the collected literature has been interpreted according to the above described features and we hope that the present review can inspire investigations toward the development of new methodologies and asymmetric transformations in this field. Therefore, besides discussing the fundamental concepts of the established approaches, we will mainly focus on recent emerging reports from the last few years within the following chapters.

2) Isoxazol-5-ones as C-nucleophiles

The existence of three potential nucleophilic sites (N2, C4 and the exocyclic carbonyl O atom in HO-form) usually gives rise to regioselectivity issues (see Scheme 1).[29] Epimerization and tautomerism limit the applications of the C-alkylations toward the synthesis of derivatives bearing a tetrasubstituted C-4 carbon. However, N-alkylations furnish stable derivatives in enamine-like form with a tertiary nitrogen atom and in these cases both 4-unsubstituted and 4-mono substituted isoxazol-5-ones have been utilized. Nevertheless, regioselective asymmetric C-alkylations and N-alkylations have been developed and the respective methodologies will be discussed in the following two sections.

2.1) Isoxazol-5-ones as C-nucleophiles

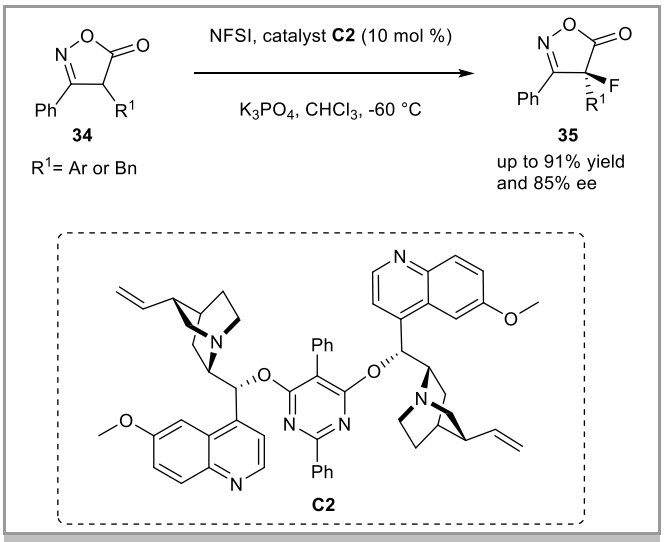
A facile one-pot sequential conjugate addition/dearomative fluorination transformation of isoxazol-5(4H)-ones with nitroolefins and *N*-fluorobenzenesulfonimide (NFSI) has been developed by Ma and coworkers (Scheme 3).[30] By using an acetylated *N*-glucoside chiral tertiary amino-thiourea catalyst **C1**, a series of chiral fluorinated isoxazol-5(4H)-ones **31** containing one fluorine-substituted quaternary stereocenter was obtained in high yields and with high diastereo- and enantio-selectivities.



Scheme 3. Asymmetric one-pot sequential conjugate addition/dearomative. fluorination.

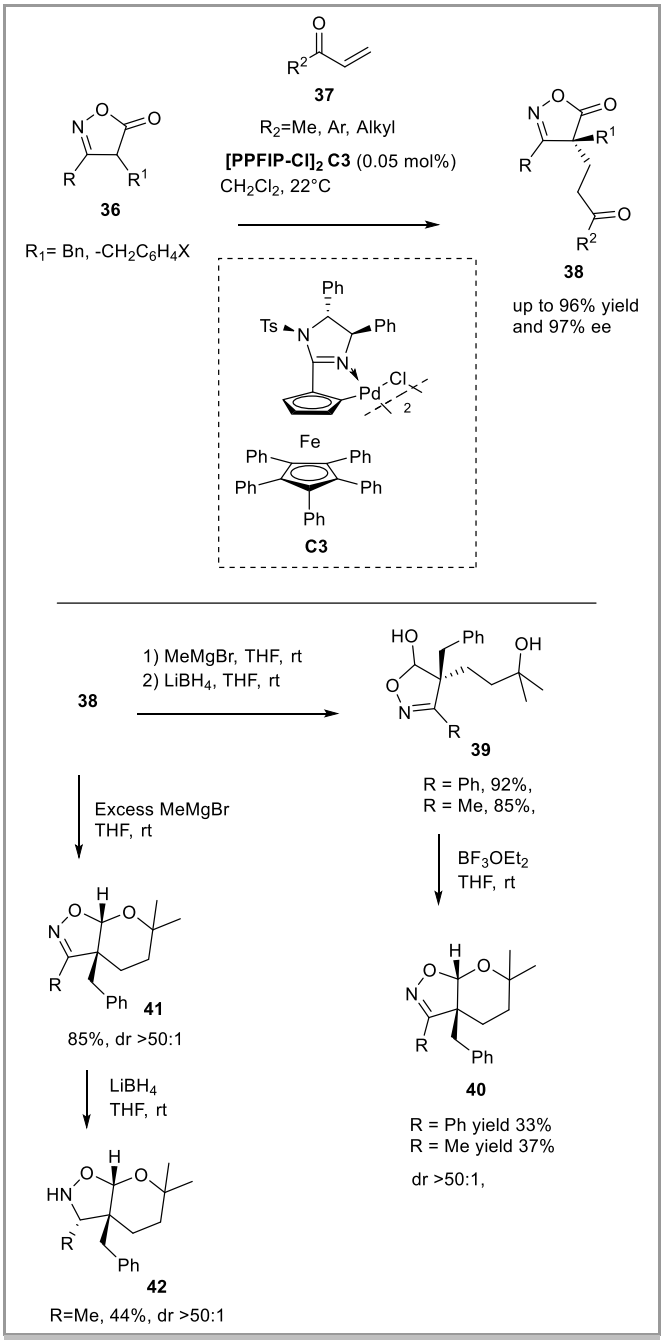
In order to obtain more information about this sequential transformation, several step-by-step control experiments have been performed. In the presence of the tertiary amino-thiourea catalyst **C1**, compound **29a** was transformed into the C-substituted intermediate **Int-32a** (Scheme 3), which was isolated in almost quantitative yield with 88% ee. Subsequent treatment of this intermediate **Int-32a** with Na_2CO_3 and NFSI in the absence of catalyst **C1** afforded the dearomatization–fluorination product **31a** in 90% yield with 95:5 dr and 84% ee. These results indicated that the chiral catalyst not only controls the first step, but also provides stereocontrol in the diastereoselective formation of the C–F bond in the subsequent transformation. In addition, sodium borohydride reduction of adduct **31b**, followed by Boc-protection allowed the synthesis of an isoxazolidin-5-one derivative **33b** with three contiguous stereocenters. In this case, only two diastereoisomers have been detected, even though with moderate diastereoselectivity (lower part of Scheme 3).

Asymmetric fluorination of 4-substituted isoxazol-5-ones **34** was also achieved by using a bis-cinchona alkaloid catalyst the $(DHQ)_2PYR$ **C2**.[31] A series of derivatives with a fluorine-containing tetrasubstituted stereocenter **35** was obtained in good to high yields and with good enantioselectivities as outlined in Scheme 4 (up to 91% yield, 85% *ee*).



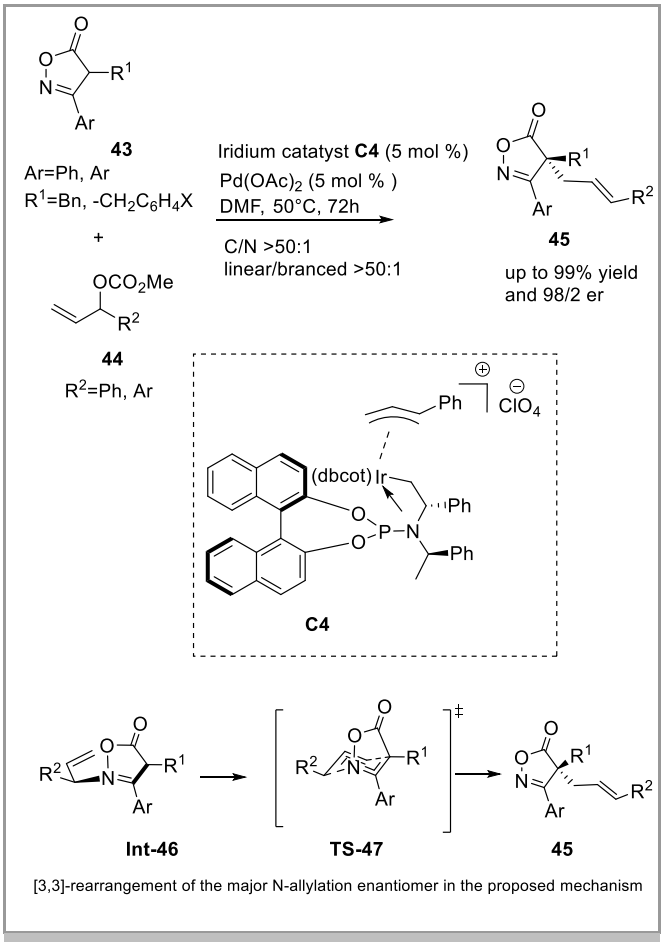
Scheme 4. Asymmetric fluorination of 4-substituted isoxazol-5-ones.

High regio- and enantio-selectivities have been achieved by Peters and co-workers[32] in the Michael reaction between 4-monosubstituted isoxazol-5-ones **36** with a series of vinyl ketones **37** in the presence of chiral palladium catalysts **C3**, leading to the synthesis of adducts bearing an all-carbon quaternary stereogenic center **38** (Scheme 5). Interestingly, very good yields and high C-regioselectivity were obtained using the bispalladacycle catalyst bearing a pentaphenylferrocene core. The proposed mechanistic models correlate the observed regioselectivity to the sterically demanding pentaphenylferrocene palladacycle catalyst (See Scheme 5). This directs the reactivity in the absence of a base nearly exclusively to the nucleophilic C atom, while at the same time it allows for high enantioselectivity and TONs up to 1900. The authors also reported further utilization of the hereby obtained Michael adducts for the asymmetric synthesis of **40** and **42** with a tetrahydro-4H-pyrano[3,2-d]isoxazole skeleton. These compounds are a motive of interest for the development of new herbicides (lower part of Scheme 5).



Scheme 5. Asymmetric palladium catalyzed Michael reactions of 4-monosubstituted isoxazol-5-ones and synthesis of new tetrahydro-4H-pyrano[3,2-d]isoxazole.

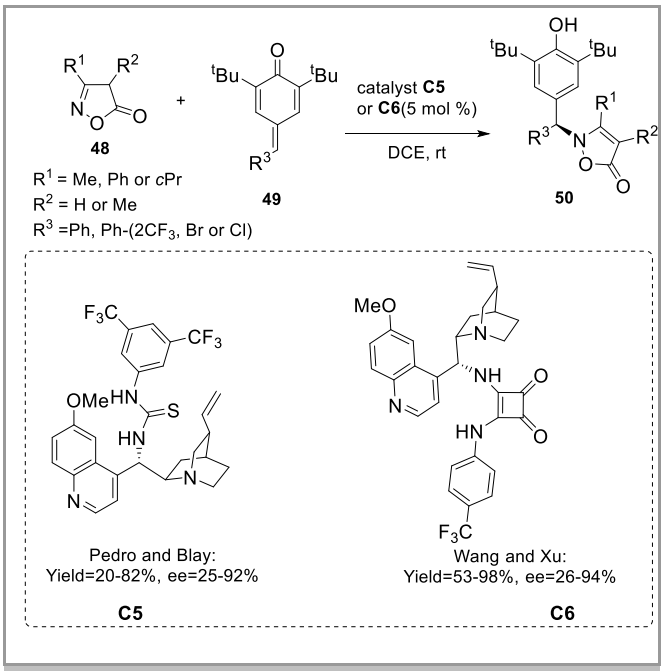
Later, the same group reported that a combination of chiral irridacycle phosphoramidite catalysts **C4** with $Pd(OAc)_2$ (5 mol%) as cocatalyst allowed the first regioselective catalytic asymmetric C-allylations of isoxazolinones **43** (Scheme 6).[29] The use of the co-catalyst guarantees the observed high C/N-regioselectivity. Interestingly, this method delivers the linear allylation products **45**, instead of branched ones. This was explained by a sequence of reactions starting from the regio- and enantio-selective N-allylation reaction to provide a branched allylic system **Int-46**, followed by a [3,3]-rearrangement with chirality translocation from the allyl part to the heterocycle via a chair-like transition state **TS-47** (Scheme 6).



Scheme 6. Iridium catalyzed regioselective asymmetric C-allylations of isoxazolinones.

2.2) Isoxazol-5-ones as N-nucleophiles

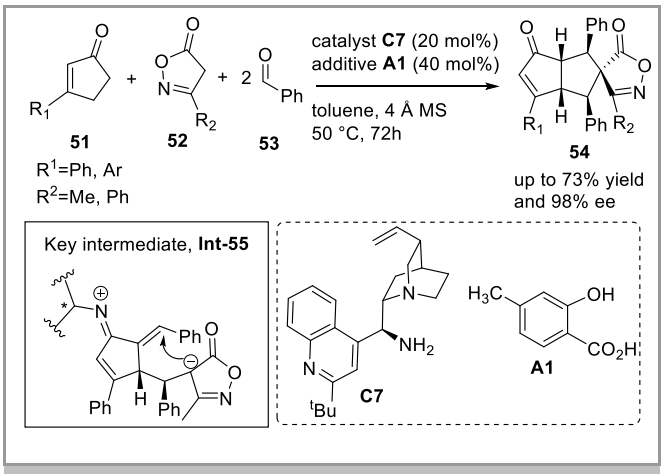
As described independently in 2020 by Pedro, Blay *et al.*[33] and by Wang, Xu and co-workers,[34] thiourea- and squaramide-containing Brønsted base bifunctional catalysts **C5** and **C6** allowed the enantioselective 1,6-*aza*-Michael addition of isoxazol-5-ones to *p*-quinone methides **49** to give isoxazol-5-ones **50** having a chiral diarylmethyl moiety attached to the nitrogen atom, with fair to good yields and enantiomeric excesses (Scheme 7). The protocol proved to be effective also on gram scale.[34] Even though both groups reported independently this first enantioselective N-alkylation which is effective even for C-4 unsubstituted isoxazol-5-ones (R^2=H), unfortunately no explanation has been given for the observed N-regioselectivity.



Scheme 7. Enantioselective 1,6-*aza*-Michael addition of isoxazol-5-ones to *p*-quinone methides.

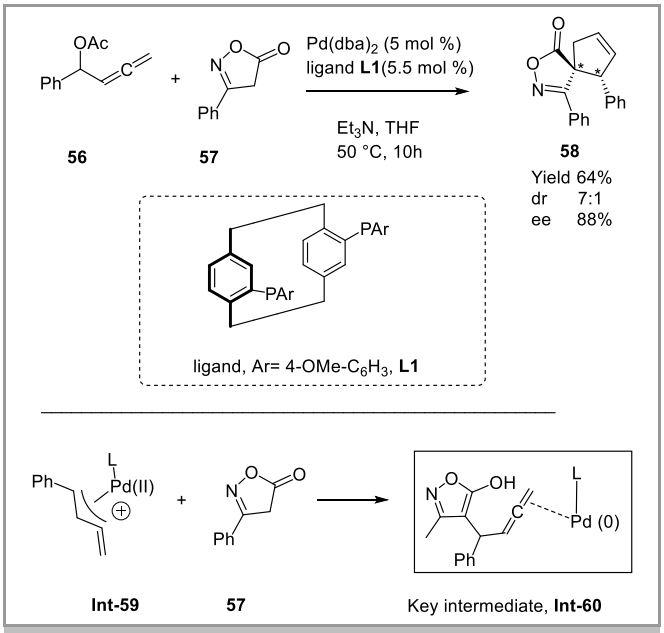
2.3) Isoxazol-5-ones as C-nucleophiles in cyclization processes

An asymmetric four-component (5+1+1+1) formal cycloaddition reaction of 3-substituted 2-cyclopentenones **51** has been developed by Chen, Du and coworkers (Scheme 8).[35] Activated methylene nucleophiles **52** and two molecules of aldehydes **53**, under chiral primary aminocatalysis, lead to various highly enantioenriched fused and spirocyclic frameworks **54** with high molecular complexity. Mechanistic studies indicate that the current reaction proceeds via a challenging cascade quintuple Knoevenagel condensation/Michael addition/retro-Michael addition/Michael addition/Michael addition sequence via diverse aminocatalytic modes, with the key intermediate **Int-55** as indicated in the lower part of Scheme 8.



Scheme 8. Asymmetric four-component (5+1+1+1) formal cycloaddition reaction of 3-substituted 2-cyclopentenones.

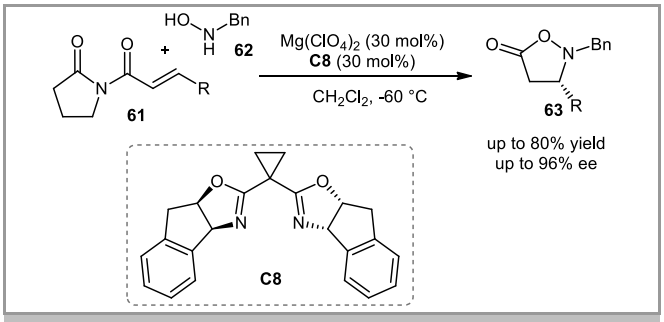
In a recent work Li, Shao and co-workers[36] have described a very interesting Pd-catalyzed asymmetric allenylic (4+1) formal cycloaddition, leading to the synthesis of 4-spiro isoxazol-5-one derivatives **58** (Scheme 9). The authors have demonstrated that tuning the Pd catalyst switched the reactivity toward an unprecedented (4+3) or (4+1) cycloaddition/cross-coupling in the case of pyrazolones, while only (4+1) reaction has been given for isoxazol-5-ones. A possible mechanism is proposed, suggesting two interesting catalytic cycles for the cycloaddition with palladium-butadienyls and the key intermediate **Int-59**, as described in Scheme 9.



Scheme 9. Pd-catalyzed asymmetric allenylic (4+1) cycloaddition.

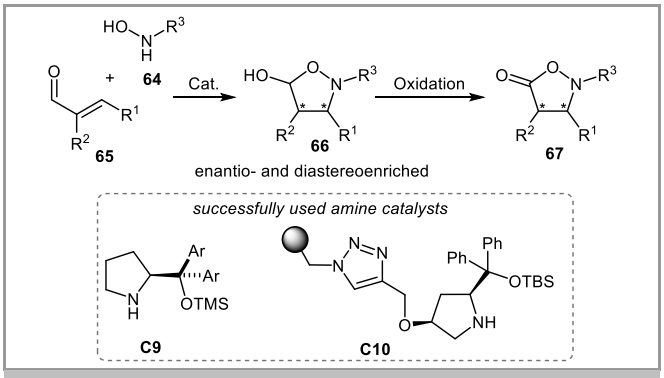
3.1) Asymmetric construction of isoxazolidin-5-ones

The pioneering (asymmetric) approaches to access isoxazolidin-5-ones relied on annulation reactions. First of all, racemic and chiral auxiliary controlled aza-Michael type additions of substituted (chiral) hydroxylamine derivatives to various Michael acceptors were reported almost 40 years ago by Baldwin's group.[28a] Over the years, this methodology allowed access to a variety of chiral β- or α,β-substituted isoxazolidin-5-ones, but the first asymmetric reports essentially relied on the use of chiral auxiliaries.[37] In the early 2000s, a variety of versatile asymmetric catalytic strategies were reported.[38,39,40,41] Sibi's group was the first to developed a powerful chiral Mg-complex-catalyzed protocol to facilitate enantioselective aza-Michael sequences by adding *N*-substituted hydroxylamines **62** to pyrrolidinone-containing amide Michael acceptors **61.** This strategy gave access to highly enantioenriched β-substituted isoxazolidin-5-ones **63** as shown in Scheme 10.[38]



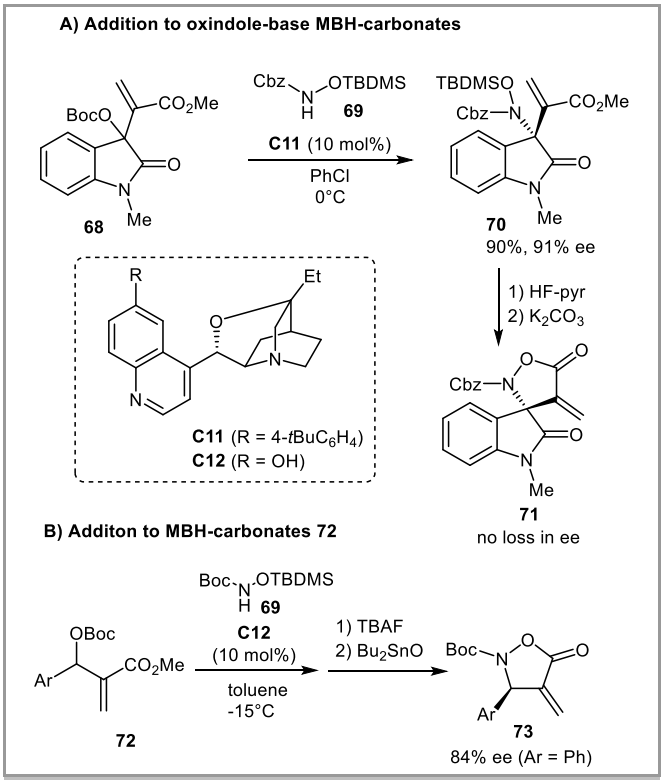
Scheme 10. First catalytic asymmetric isoxazolidin-5-one synthesis report by Sibi's group.

The following years then witnessed the introduction of a variety of alternative organocatalytic approaches. In this context impressive methods making use of chiral phosphoric acid catalysis,[39] chiral Brønsted base-mediated approaches,[40] and chiral iminium activation were introduced.[41] The majority of these reports were discussed in much detail in a recent review.[26] Iminium activation of α,β-unsaturated aldehydes with chiral secondary amine catalysts is also a very powerful methodology to obtain this heterocyclic platform (Scheme 11).[41] Hereby the classical Hayashi-Jørgensen catalyst **C9** turned out to be well-suited and could even be used in a one-pot two-step protocol where the enal **65** was accessed in situ by cross metathesis and then directly underwent the cyclization reaction with **64**, as demonstrated by Ge's group.[41c] More recently, immobilized catalyst derivatives like **C10** were also successfully used by Pericas and co-workers with high selectivities in batch and flow.[41d] Compared to other approaches, this iminium strategy is also very interesting as the primarily obtained enantioenriched isoxazolidin-5-ols **66** have not only been oxidized to isoxazolidin-5-ones **67**, but can also be directly utilized to access other molecules of interest, as demonstrated by Ge's group who synthesized sitagliptin phosphate monohydrate via such a strategy. [41e]



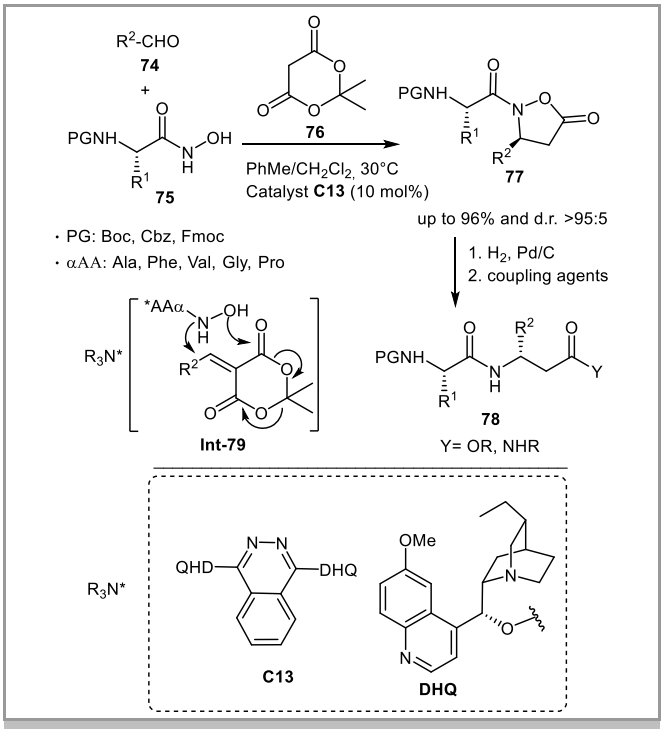
Scheme 11. The general concept of using iminium catalysis to control aza-Michael type-cyclizations to access compounds **66** (and **67** successively).

The addition of N-nucleophiles to Morita-Baylis-Hillman (MBH) carbonates **68** can be considered as a powerful alternative to classical aza-Michael addition chemistry and, in 2012, Chen and co-workers nicely demonstrated that such a strategy allows to access the chiral spiroisoxazolidin-5-one **71** with high enantioselectivity (Scheme 12-A).[42] In their organocatalytic approach they found that the β-isocupreidine derivative **C11** allows for high yield and enantioselectivity in the addition of the carbamate derivative to the MBH carbonate **68** (giving the formal aza-Morita-Baylis-Hillman product **70**). This compound can then be cyclized to the α-methylene isoxazolidin-5-one **71** without loss of optical purity by desilylation, followed by base-mediated transesterification. Similarly, Vesely and co-workers have recently shown that such a strategy afforded the chiral isoxazolidin-5-ones **73** with reasonable levels of enantioselectivity (Scheme 12).[43] In their approach β-isocupreidine (**C12**) turned out to be the catalyst of choice to control the N-addition of carbamate **69** to MBH carbonates **72**, followed by desilylation and a Bu_2SnO-mediated transesterification to access the α-methylene isoxazolidin-5-one **73** (Scheme 12-B).



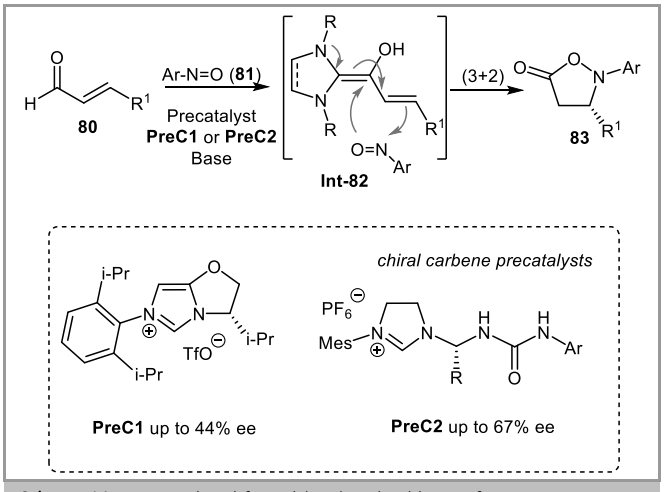
Scheme 12. Organocatalytic two-step isoxazolidin-5-one synthesis starting from Morita-Baylis-Hillman carbonates.

Very recently (Scheme 13),[44] utilizing Meldrum's acid **76**,[45] Brière and co-workers extrapolated the multicomponent Knoevenagel-aza-Michael-Cyclocondensation reaction to readily available hydroxamic acids **75** derived from naturally occurring α-amino acids (αAA). The thus obtained novel isoxazolidin-5-ones **77** proved to be useful platforms for the diversity-oriented synthesis of α/β-dipeptide derivatives **78**. The likely diastereoselective aza-Michael reaction, taking place onto the highly electrophilic in situ formed alkylidene Meldrum's acid intermediate **Int-79**,[45] turned out to be rather sensitive to the nature of the employed catalytic Brønsted base (R_3N), among them the $(DHQ)_2PHAL$ **C13** displayed the best outcome along with a significant match effect during a double induction process.



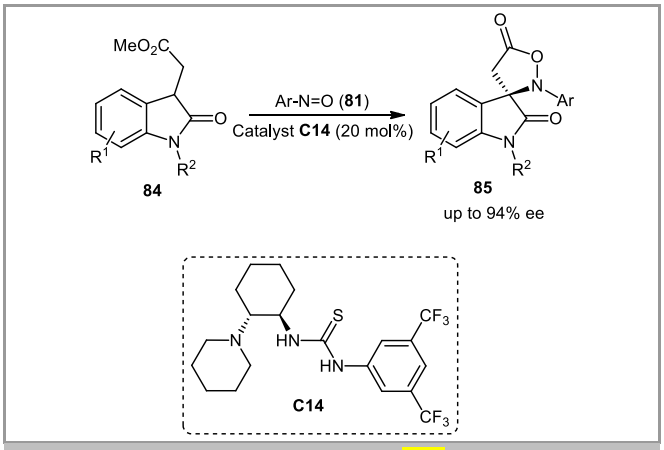
Scheme 13. Multicomponent organocatalytic synthesis of isoxazolidin-5-ones.

A rather general approach to access highly functionalized β-substituted isoxazolidin-5-ones **83** relies on formal (3+2) annulation reactions of nitroso compounds with suited three carbon building blocks.[46,47] The groups of Zhang and Ying and, subsequently, Rodriguez and Coquerel achieved the transformation of nitroso compounds based on the use of carbene precatalysts which activate enals **80** to perform (3+2) annulations via the formation of Breslow intermediates **Int-82**, (Scheme 14).[46]



Scheme 14. NHC-catalyzed formal (3+2) cycloaddition of nitroso reagents to access β-substituted isoxazolidin-5-ones.

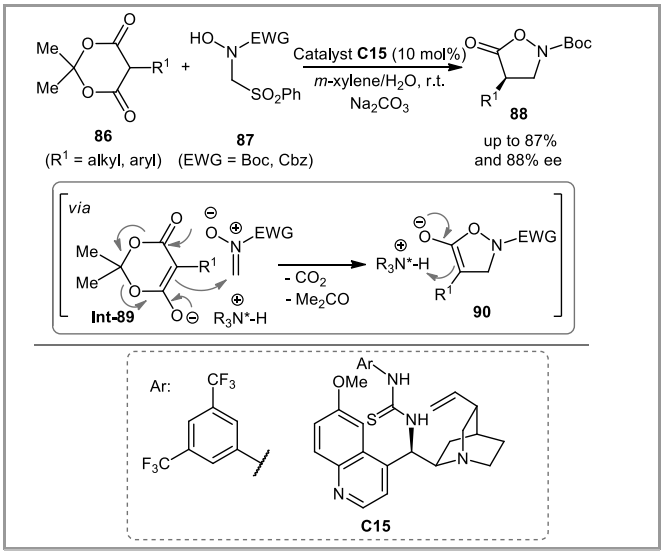
Alternatively, 1,4-dicarbonyl compounds like oxindole **84** were successfully used for nitroso aldol-esterification cascades under bifunctional thiourea catalysis to access the spirooxindoles **85** straightforwardly and with high enantioselectivities (Scheme 15).[47] Surprisingly however, to the best of our knowledge, no further developments of this concept have been reported anymore.



Scheme 15. A Brønsted base-catalyzed formal (3+2) cycloaddition of nitroso reagent to access β-substituted isoxazolidin-5-ones.

On the other hand, the use of nitrones as 1,3-dipolar building blocks in combination with suited two carbon synthons has been investigated in much details over the last years.[48,49] Since 2003, first reports by Shindo, Florio and others relied on diastereoselective approaches which led to high stereoselectivities with a limited scope however.[48]

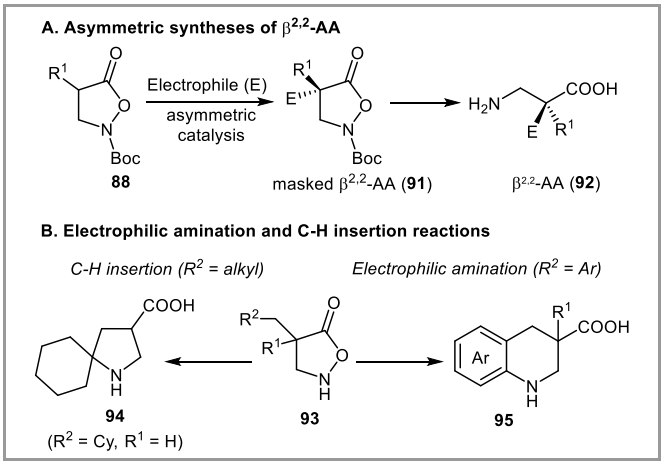
Over the last years, the group of Brière tackled the organocatalytic and asymmetric synthesis of chiral enantioenriched isoxazolidin-5-ones via a nitrone pathway starting from Meldrum's acid **76** and derivatives.[49] Especially, by utilizing the substituted Meldrum's acid **86** and *N*-hydroxy-sulfone **87**, under basic and biphasic conditions, a straightforward synthesis of α-substituted isoxazolidin-5-ones **88** occurred in high yields and with goods enantioselectivities (Scheme 16). It has been proposed that, upon a phase-transfer catalytic protocol, the Meldrum's acid anion **Int-89** would undergo a formal (3+2) cycloaddition to the in situ generated nitrone. Then, this domino sequence would be terminated by the enantioselective protonation reaction of the corresponding enolate intermediate, thanks to the bifunctional cinchona-derived catalyst **C15**. It is worth noting that α-substituted isoxazolidin-5-ones **88**, after hydrogenolysis of the N-O bond, afford an access to β²-AA, a highly versatile but difficult to access class of chiral β-AA (further applications of these targets to access β²,²-AA will be discussed in the next chapter).



Scheme 16. Catalytic stereoselective nitrone-based approaches to access α-substituted isoxazolidin-5-ones.

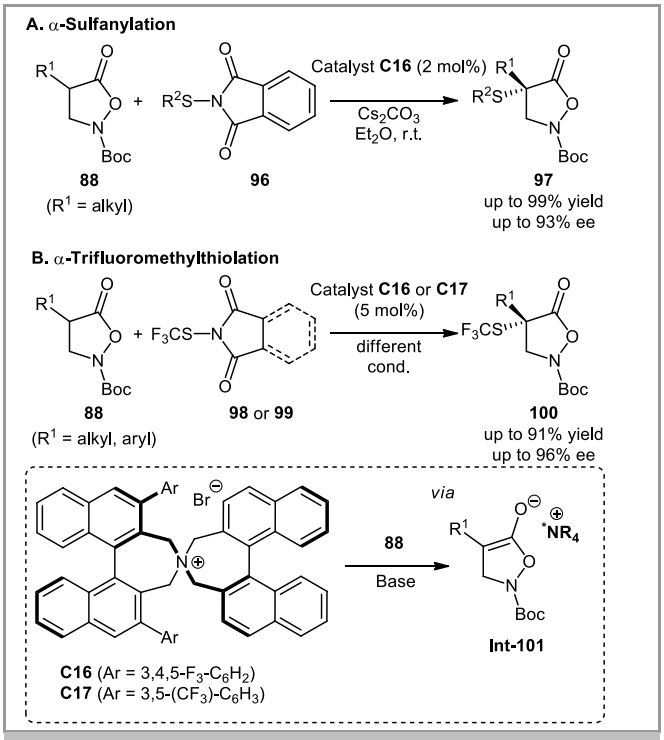
3.2) Enantioselective α-functionalizations of isoxazolidin-5-ones

Besides building the isoxazolidin-5-one motif via asymmetric cyclization strategies (as outlined above), the enantioselective modification of (racemic) isoxazolidin-5-ones **88**, i.e. via α-functionalization approaches, became a powerful methodology over the last years.[50,51,52,53,54] The thereby accessed chiral products **91** not only serve as versatile masked $\beta^{2,2}$-amino acid derivatives **92** (Scheme 17-A), but may also undergo further heterocycle forming reactions as demonstrated by Noda and Shibasaki very recently (Scheme 17-B).[55]



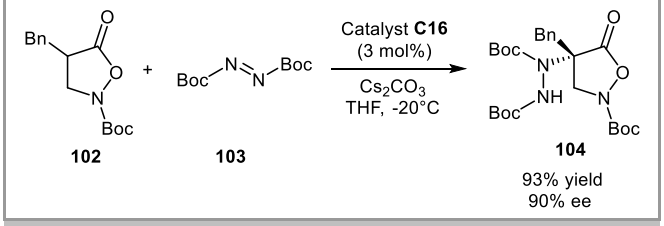
Scheme 17. (A) Isoxazolidin-5-ones to access (masked) $\beta^{2,2}$-AA and (B) to access cyclic β-amino acids via electrophilic amination or C-H activation methods.

Brière and co-workers were the first to demonstrate that α-alkylated isoxazolidin-5-ones **88** can undergo highly enantioselective α-functionalization reactions.[50] By using the commercially available Maruoka ammonium salt **C16** as catalyst,[56] they established a straightforward protocol for the highly enantioselective α-sulfanylation of **88** with the phthalimide-based S-transfer reagents **96** (Scheme 18-A). In this report, they also demonstrated that the chiral products may easily undergo ring-opening via reductive N-O bond cleavage, thus giving access to α-sulfanylated $\beta^{2,2}$-AA. Very interestingly, a broad variety of other commonly established chiral ammonium salt catalyst were tested as well,[57] but none of them allowed for any noteworthy selectivity. This exclusive potential of the Maruoka catalysts **C16** (and **C17** as well) to control the asymmetric ammonium salt-catalyzed transformations of compounds **88** was also described in other recent investigations (vide infra), but the exact reasons for this effect remain yet unknown. Very recently,[52] the groups of Della Sala and Aleman as well as the groups of Cahard and Waser independently reported the asymmetric α-trifluoromethylthiolation of α-alkyl and α-aryl-substituted substrates **88** using chiral ammonium salts **C16** or **C17** (Scheme 18-B). Further transformations of the products **100** like ring-opening reactions, direct KAHA (α-ketoacid–hydroxylamine)-type ligations[58] or S-oxidations to sulfone were successfully carried out, thus demonstrating the overall potential of this catalysis concept to access versatile chiral target molecules from a simple heterocyclic platform.



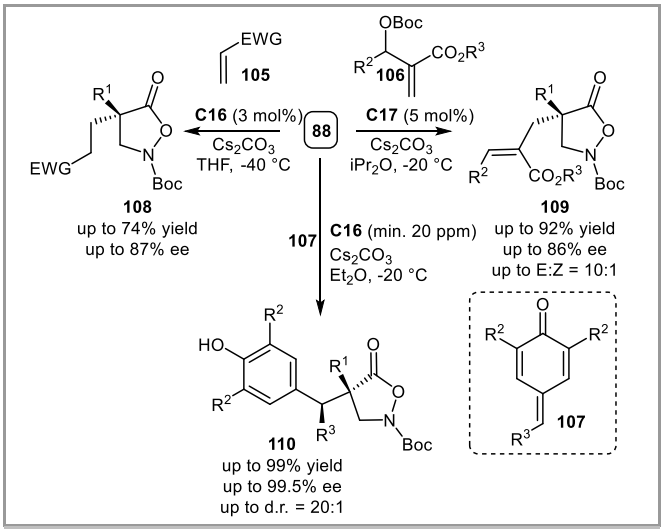
Scheme 18. Quaternary ammonium salt catalyzed asymmetric α-sulfanylation reactions.

With respect to further α-heterofunctionalization reactions of compounds **102**, it is fair to say that this approach is still in its infancy, and apart from the α-sulfanylation and α-trifluoromethylthiolation approaches only one example of an asymmetric α-amination reaction under asymmetric ammonium salt catalysis was reported by Brière so far (Scheme 19).[51a]



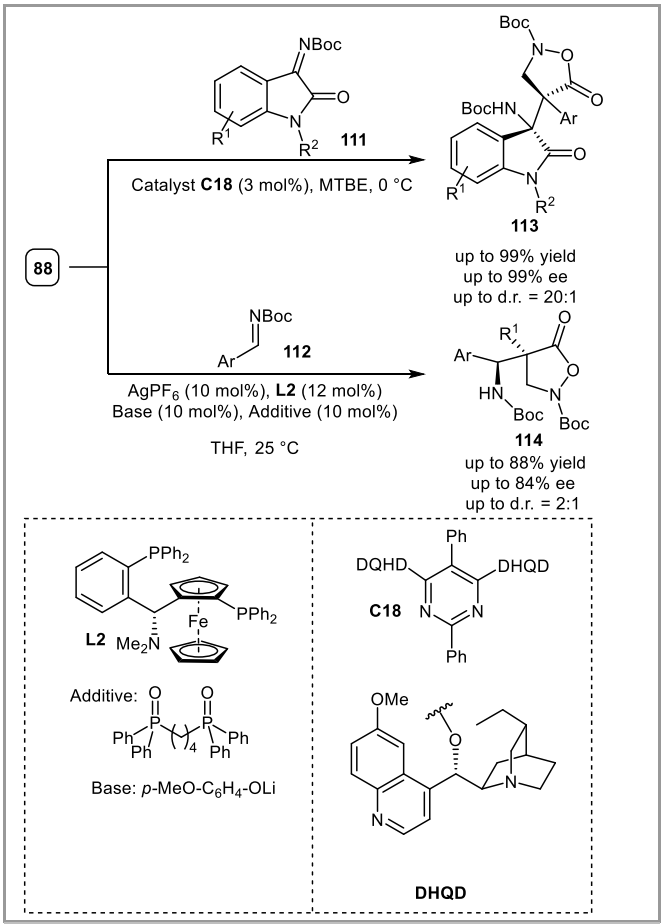
Scheme 19. Quaternary ammonium salt catalyzed asymmetric α-amination reaction.

Asymmetric C-C bond forming reactions of pronucleophiles **88** were carried out under a variety of different catalytic conditions over the last 2-3 years.[51,53,54] First, enantioselective conjugate addition reactions were investigated. The Michael acceptors **105-107** were found to be well tolerated under chiral ammonium salt catalysis (again with catalysts **C16** or **C17**), as demonstrated by Brière's group and Waser's group (Scheme 20).[51] Remarkably, while the addition of **102** to acrylates **105** and MBH-carbonates **106** required around 3-5 mol% of the catalysts, the reaction with *para*-quinone methides **107** could be carried out with as low as 20 ppm of the catalyst **C16**, which represents one of the lowest catalysts loadings reported in asymmetric organocatalysis so far.



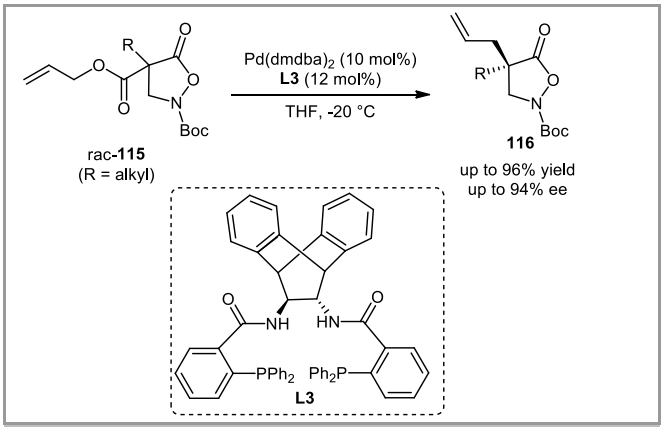
Scheme 20. Asymmetric conjugate additions of pronucleophiles 1 under asymmetric phase-transfer catalysis.

Noda and Shibasaki recently investigated asymmetric Mannich type reactions of compounds **88** (Scheme 21).[54] The addition of **88**, having an aryl (R^1) pendant, to the acceptor **111** was possible by using the commercially available organocatalyst **C18**, acting as a Brønsted base. In a single case,[54a] the authors also demonstrated that simple quinidine is also able to catalyze the asymmetric addition of **88** to nitrostyrene as Michael acceptor. On the other hand, the Mannich reaction with simple aldimines **112** and platform **88** with an alkyl (R^1) pendant, likely less acidic, required a very carefully optimized combination of $AgPF_6$ with ligand **L2**, a diphosphineoxide additive and a phenolate base to achieve good reactivity and ees. Unfortunately, however, the obtained diastereoselectivities were found to be relatively low in this last case.[54b]



Scheme 21. Asymmetric Mannich type reactions.

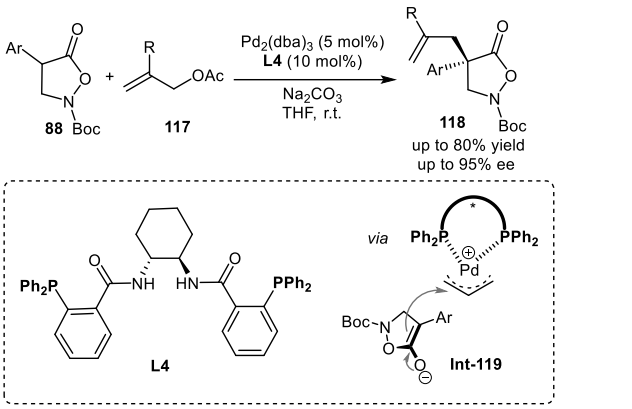
In 2018, Noda and Shibasaki also introduced a highly enantioselective decarboxylative Pd-catalyzed α-allylation protocol by starting from the racemic allyl esters **115** (Scheme 22).[53a] In this report, they first demonstrated that isoxazolidin-5-ones can be directly employed in KAHA-type ligations.[58] Since then, this methodology emerged as a very powerful strategy to directly access α/β-dipeptides from this heterocyclic platform and it was recently demonstrated to be rather generally possible for other isoxazolidin-5-one derivatives **116** as well.[51c,5252b,54]



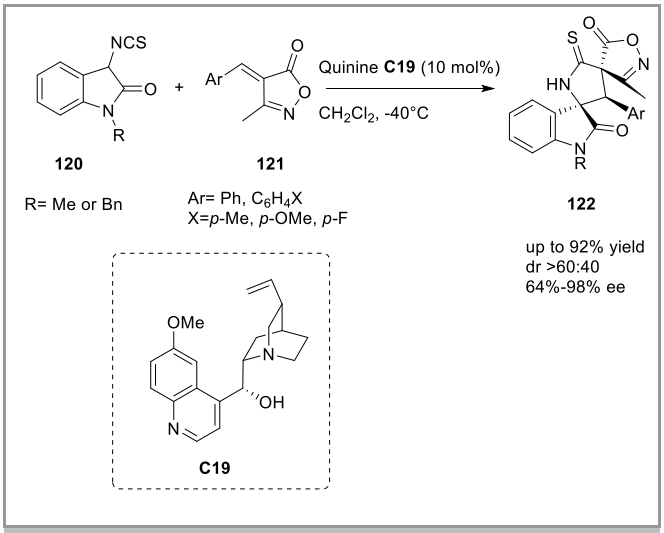
Scheme 22. Asymmetric decarboxylative α-allylation approach B.

The intermolecular Pd-catalyzed α-allylation of α-aryl isoxazolidin-5-ones was shortly after described by Arseniyadis and Cossy, giving access to a broad variety of highly

functionalized derivatives **118** with excellent selectivities as well via **Int-119** (Scheme 23).[53b]



Scheme 23. Asymmetric α-allylation approaches.



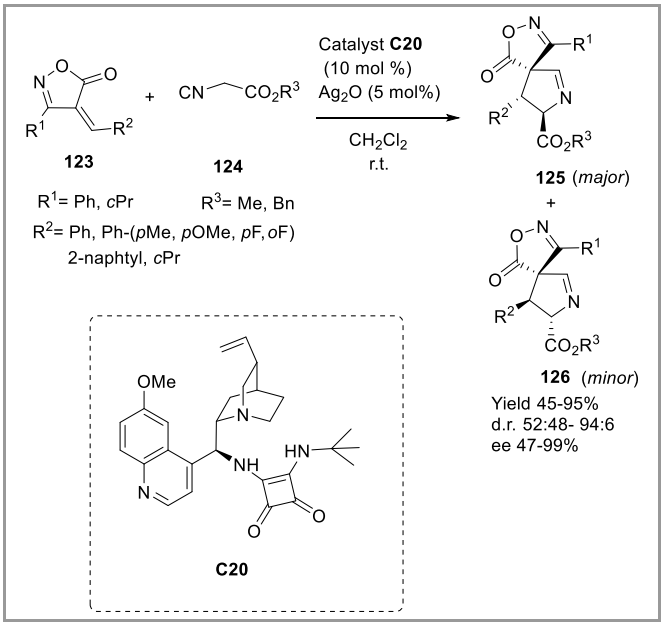
Scheme 24. Diastereo- and enantioselective cascade reaction between 3-isothiocyanato oxindoles and unsaturated isoxazolones.

4) Arylideneisoxazol-5-ones in conjugated addition

Despite the high reactivity of arylideneisoxazol-5-ones in conjugated additions,[23] the obtained Michael adducts suffer from tautomeric equilibria according to Scheme 1, as for isoxazol-5-ones mono-substituted at C-4 position. Therefore, a relatively limited number of applications has been described in this field. Most of them are directed toward the synthesis of derivatives with a tetrasubstituted carbon, exploiting in these cases the reactivity of the enolate intermediate in domino reactions[59] or otherwise the selective in situ entrapping/protection of the NH-tautomer of the respective Michael adducts is necessary.[60] In addition, the obtaining of complex molecular architectures has also been of great utility in further transformations of the Michael adducts allowing for example an entry to versatile alkynes.[61] Although a great number of synthesis methodologies of arylideneisoxazol-5-ones have been reported[23,59-66] and they have been sometimes represented with *E*-configuration, *Z* isomers are reported to be more stable.[62] X-ray structures confirm this outcome for a few derivatives.[61,62]

In one of the first reports, an efficient organocatalytic diastereo- and enantioselective cascade reaction between 3-isothiocyanato oxindoles **120** and unsaturated isoxazolones **121** has been described by Yuan[59] and co-workers in the presence of commercially available quinine as catalyst **C19**. This process consisting, of a domino Michael addition / cyclization sequence, has allowed the construction of spirocyclic oxindole derivatives **122** bearing two spiro quaternary centers and three consecutive stereocenters in high to excellent yields with moderate to high diastereo- and enantio-selectivities (Scheme 24).

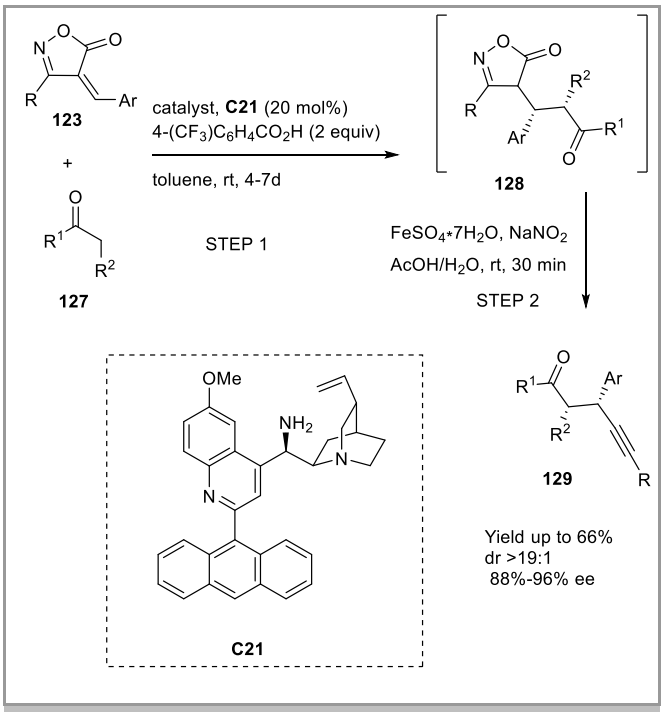
Very recently Pedro, Blay and co-workers reported a conceptually similar process in which enantioenriched spirocyclic compounds bearing three contiguous stereocenters were obtained from 4-arylideneisoxazol-5-ones **123** and isocyanoacetate esters **124** through a formal (3+2) cycloaddition reaction.[63] Interestingly, high enantioselectivity and only two diastereomers were obtained by means of cooperative catalysis combining a classical bifunctional organocatalyst derived from a Cinchona alkaloid and silver oxide as Lewis acid (Scheme 25).



Scheme 25. Enantioselective synthesis of spirocyclic compounds through a formal (3+2) cycloaddition reaction.

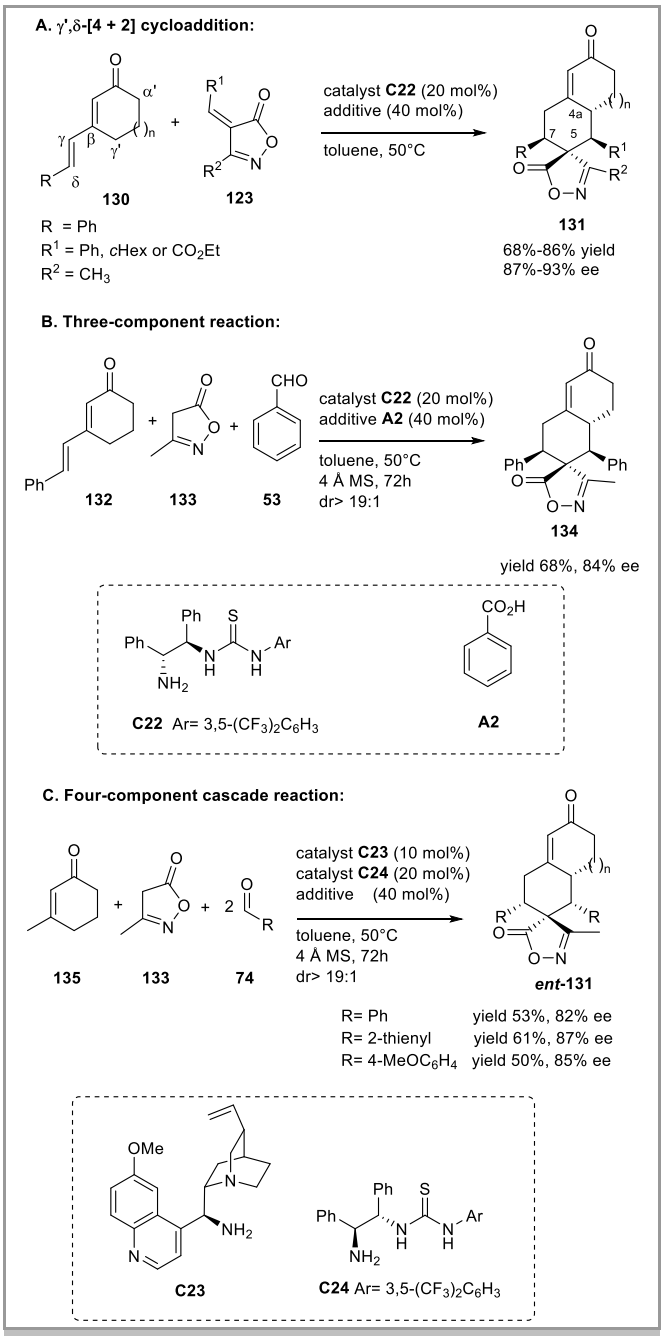
In 2017, Jurberg and co-workers[61] have developed an asymmetric Michael reaction of arylideneisoxazol-5-ones **123** with acyclic and cyclic ketones **127** in the presence of cinchona-derived aminocatalysts **C21** and substituted benzoic acids as co-catalysts (Scheme 26). The best results were obtained with modified catalysts bearing hindered substituents on the quinoline ring and mechanistic models have been proposed to explain the observed selectivity. Instead of their isolation, the Michael adducts **128**

were subjected to a controlled nitrosative degradation, according to Zard's conditions[24,25] leading to alkyne motifs **129** bearing two contiguous stereocenters.



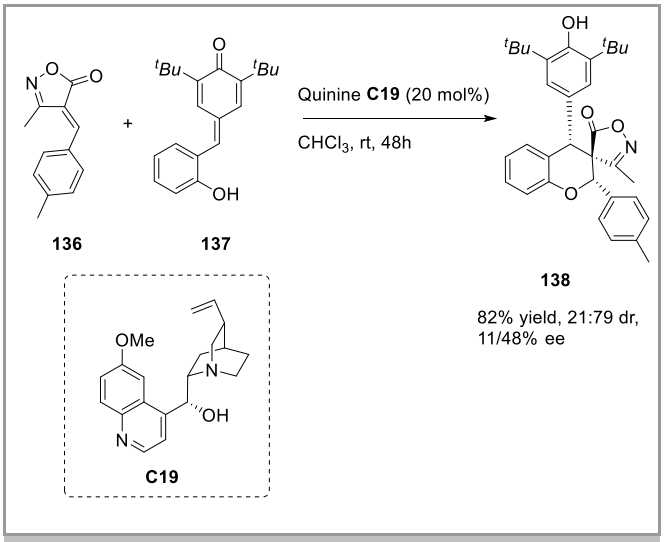
Scheme 26. Asymmetric Michael reaction of arylideneisoxazol-5-ones with ketones and further transformations.

In 2018, the group of Chen and Ouyang[64] reported a diastereodivergent asymmetric formal (4+2) cycloaddition reaction, realized with Z-configured 4-alkylideneisoxazol-5-ones **123** and 2,4-dienone **130** in the presence of bifunctional chiral primary amine **C22** as catalyst in combination with benzoic acid (Scheme 27-A). As a previous mechanistic study suggested,[65] the γ',δ-(4+2) reaction might proceed via iminium ion catalysis in a stepwise cascade manner rather than a concerted Diels–Alder cycloaddition pathway. The authors also investigated a three-component reaction of 2,4-dienone **132**, 3-methylisoxazol-5(4H)-one **133**, and benzaldehyde **53** (Scheme 27-B).[64] This reaction was efficiently promoted under the catalysis of bifunctional **C22** and the acid **A2**, through a cascade Knoevenagel condensation / formal (4+2) cycloaddition process. The addition of 4 Å molecular sieves (MS) was beneficial for the enantioselectivity. These results also suggested the possibility to develop a more challenging and complicated four component cascade reaction process (Scheme 27-C),[64] involving condensations of simple 3-methyl-2-cyclohexenone **135** and 3-methyl-isoxazol-5(4H)-one **133** with aldehydes **74**, respectively, followed by the formal (4+2) cycloaddition. In this case the bifunctional amine-thiourea **C22** failed to deliver the desired product probably because it might not be effective for the formation of dienone **130**. However, the authors discovered that adding 10 mol % of cinchona-based amine **C23**, in combination with catalyst **C24**, could afford the cycloadducts *ent*-**131** in moderate yields with high enantioselectivity, probably proceeding in a relay aminocatalytic manner.



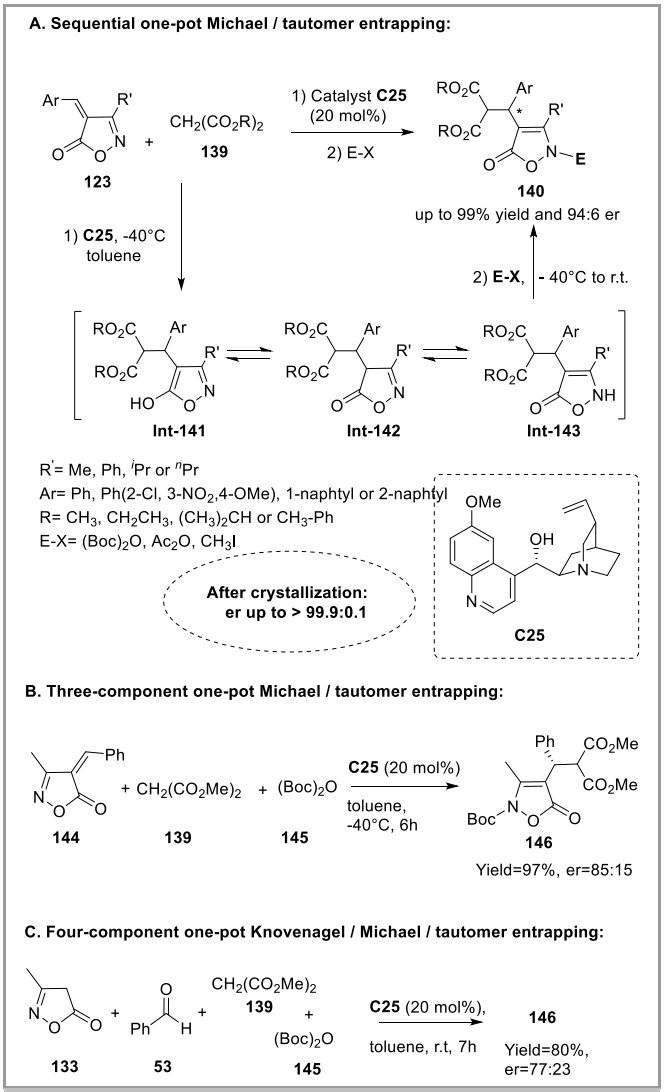
Scheme 27. Diastereodivergent, asymmetric formal (4+2) cycloaddition reaction.

In 2019, Yu, Zhou et al.[66] reported a domino oxa-Michael/1,6-addition reaction of orthohydroxyphenylsubstituted p-QMs **137** and unsaturated isoxazolones **136** (Scheme 28). Various new spiroisoxazolonechromans **138** were obtained in good yields (up to 89%) with excellent diastereoselectivities (>99:1 dr) in the presence of Et_3N, while preliminary investigation of asymmetric versions in the presence of quinine allowed the obtaining of the target compound in high yield and moderate diastereo- and enantio-selectivity.



Scheme 28. Domino oxa-Michael/1,6-addition reaction of orthohydroxyphenylsubstituted p-QMs and unsaturated isoxazolones.

On the basis of previous works in which the strategy of the entrapping of unstable intermediates allowed the isolation and transformation of challenging aldol adducts[67] or useful heterocycles,[68-70] very recently Massa *et al.* reported the first asymmetric Michael reaction of arylideneisoxazol-5-one **123** with 1,3-diesters **139** (Scheme 29).[60] Despite complex tautomer equilibria of the obtained Michael adducts (**Int-141-143**), as demonstrated by ^{1}H-NMR spectroscopy, the one-pot entrapping by the aid of different electrophiles/protecting groups (EX=$(Boc)_2O$, Ac_2O or CH_3I) led to the regioselective isolation of diverse *N*-substituted isoxazol-5-ones **140** in very high overall yield and with good enantioselectivities up to 94/6 er. The reaction can be performed in two ways: in a sequential fashion, carrying out the Michael addition first and then quenching with $(Boc)_2O$ or Ac_2O (Scheme 29-A), or in a truly one-pot procedure leading to comparable results in terms of yield and er (Scheme 29-B). Notably, the enantiopurity of several final products was further increased up to >99.9/0.1 er after a single crystallization in good overall yield. The use of quinidine **C25** as a cheap and readily available catalyst also allowed the development of one-pot four-component Knoevenagel / Michael / tautomer trapping (Scheme 29-C). Also, in this case the reaction was highly regioselective and, despite the lower yield **146** (80%) and the only moderate er (77/23), this procedure has the advantage to overcome the synthesis of the arylideneisoxazol-5-one **144**.



Scheme 29. Asymmetric one-pot Michael reactions/tautomer trapping of arylideneisoxazol-5 ones.

5. Conclusions

In this review we have presented the most common strategies for the asymmetric construction of isoxazol-5-one and isoxazolidin-5-one heterocyclic compounds. On the basis of the examples herein analyzed, several similarities but also some differences are shown between these two groups of heterocycles. These features not only affect the asymmetric synthesis strategies but also their further transformations to access other useful building blocks or different heterocycles. Even though both chiral metal catalysts and organocatalysts have been successfully used in the last years, it clearly appears that this is a research field still under-explored and it is easy to predict that the closer future will bring other asymmetric strategies and new transformations which will enlarge the chemical diversity and the applications of these fascinating organic molecules.

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Biosketches

Antonio Macchia was born in Potenza, Italy in 1992. He started studying chemistry at the University of Basilicata in 2011 and graduated in 2017 in the Dr. Paolo Lupattelli group. His Master's thesis focussed on the total synthesis of Myricanol. He moved at University of Salerno in the Prof. Massa group for PhD studies on enantioselective syntheses of isoxazol-5-ones and isoindolinones.

Andreas Eitzinger was born in Linz, Austria in 1993. He started studying chemistry at the Johannes Kepler University Linz in 2011 and graduated in 2017 in the Mario Waser group. His Master's thesis focussed on phosphine-catalysed annulation reactions of allenoates and azlactones. He stayed in the group and has since been carrying out PhD studies on enantioselective syntheses of fluorinated amino acids.

Dr Jean-François Brière (born in France in 1971) completed his PhD with Prof Guy Quéguiner (1998, France - heterocycles synthesis) and was a postdoctoral fellow with Prof Henk Hiemstra (1999-2001, the Netherlands - total synthesis) and Prof Istvan E. Markó (2001-02, Belgium, NHC in metallocatalysis) in collaboration with Rhodia Company. Recruited in 2002 (Caen Normandy University, France – Sulfur chemistry), Brière is currently CNRS senior research scientist in the Heterocycles team at laboratory COBRA (since 2007, Rouen Normandy University, France) and develops (organo)catalytic processes for the construction of bio-relevant chiral heterocycles.

Mario Waser was born in Steyr, Austria in 1977 and studied chemistry at JKU Linz, Austria where he obtained his Ph.D. in 2005 in the group of Prof. Heinz Falk. After a postdoctoral stay with Prof. Alois Fürstner (Max-Planck Institut für Kohlenforschung, Mülheim, Germany), he spent two years as an R&D chemist working for DSM. In 2009 he started his independent career at JKU Linz. In 2014 he obtained his habilitation (venia docendi) and became Associate Professor and in 2020 he became Full Professor for Organic Stereochemistry. His main research interests are on the design and application of asymmetric organocatalysts (i.e. ion pairing catalysts) and on the development of asymmetric organocatalytic synthesis methods.

Antonio Massa was born in Cava dei Tirreni, Italy in 1971. After obtaining his Ms degree in chemistry at University of Salerno (Italy) in 1996, he worked for three years in R&D in the company Montefibre. In 2003 he obtained his PhD in organic chemistry in Salerno (supervisor prof. A. Scettri). After post-doc, in 2004 he became assistant professor at University of Salerno. In 2002 he was visiting investigator at University of Glasgow (UK) in prof. Kočovsky's lab and in 2008 at the SCRIPPS in San Diego (USA) with a Fulbright scholarship in prof. Barbas III's lab. Since 2015 he is currently associate professor and in 2017 he obtained his habilitation as full professor. His main research interests are on the development of new synthetic methodologies and scale-up, in asymmetric catalysis and on the synthesis of bioactive compounds. He is involved in several collaborations and is consultant of pharma companies.

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