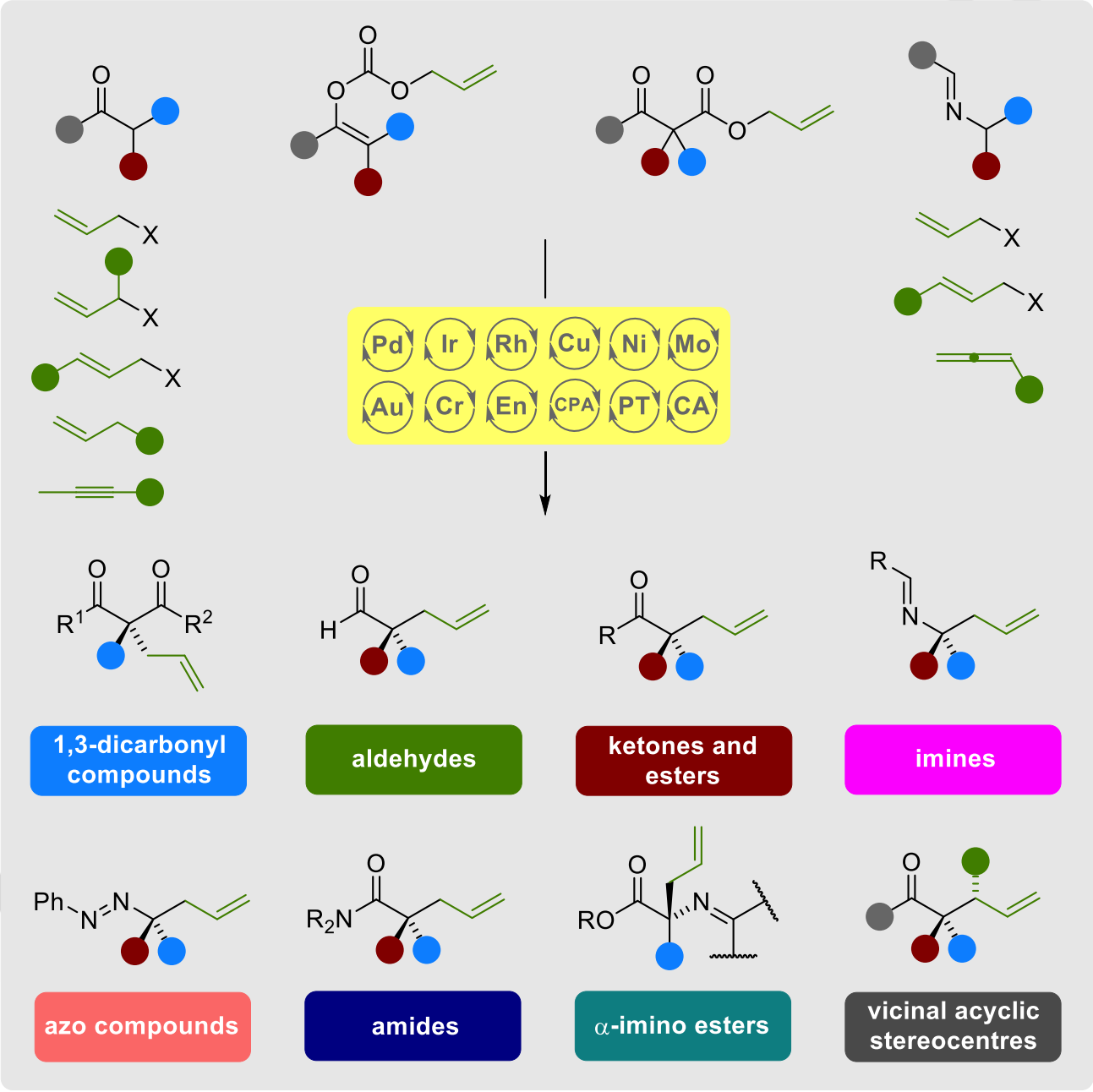
The Catalytic Asymmetric Allylic Alkylation of Acyclic Enolates for the Construction of Quaternary and Tetrasubstituted Stereogenic Centres

Connor M Griffiths,[a] and Vilius Franckevičius*[a]



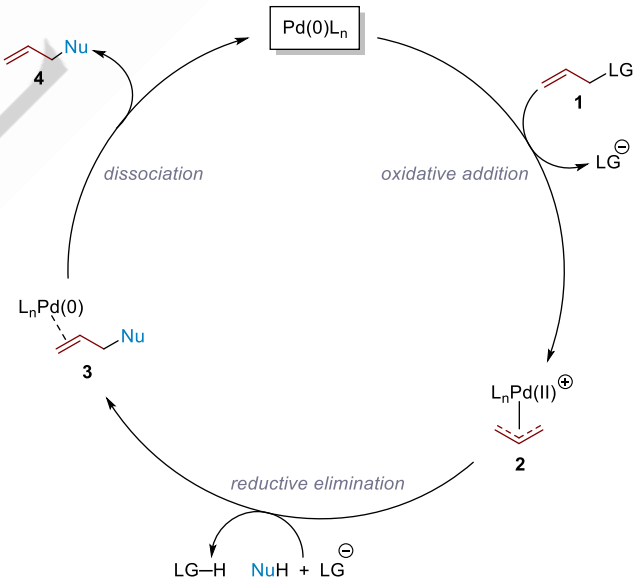
[a] Connor M Griffiths, Dr. Vilius Franckevičius
Department of Chemistry
Lancaster University
Lancaster LA1 4YB, U.K.
E-mail: v.franckevicius@lancaster.ac.uk

Abstract: To facilitate the discovery and development of new pharmaceuticals, the demand for novel stereofunctionalised building blocks has never been greater. Whilst molecules bearing quaternary and tetrasubstituted stereogenic centres are ideally suited to explore untapped areas of chemical space, the asymmetric construction of sterically congested carbon centres remains a longstanding challenge in organic synthesis. The enantioselective assembly of acyclic stereogenic centres is even more demanding due to the need to restrict a much wider range of geometries and conformations of the intermediates involved. In this context, the catalytic asymmetric allylic alkylation (AAA) of acyclic prochiral nucleophiles, namely enolates, has become an indispensable tool to access a range of linear α-quaternary and α-tetrasubstituted carbonyl compounds. However, unlike the AAA of cyclic enolates with a fixed enolate geometry, to achieve high levels of stereocontrol in the AAA of acyclic enolates, the stereoselectivity of enolisation must be considered. The aim of this review is to offer a comprehensive discussion of catalytic AAA reactions of acyclic prochiral enolates and their analogues to generate congested quaternary and tetrasubstituted chiral centres using metal, non-metal and dual catalysis, with particular focus given to the control of enolate geometry and its impact on the stereochemical outcome of the reaction.

1. Introduction

Commercial compound screening libraries used in drug discovery campaigns have historically been populated with sp^2-rich, flat heteroaromatic compounds.[1] This tradition is largely a result of the relative simplicity of functionalisation of sp^2-rich compounds using rigorous $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–X cross-coupling chemistries without the need for further stereochemical considerations.[2] Unfortunately, sp^2-rich compounds can be associated with unfavourable solubility and bioavailability profiles as a result of π-stacking interactions, culminating in a high rate of attrition during drug development.[3] Overuse of flat molecules in library design also results in diminished structural novelty, diversity and 3-dimensional complexity, which dampens the opportunities to identify new binding targets and, ultimately, lessens the efficiency of the screening campaign. As such, there is a clear interest in preparing novel, more architecturally complex, sp^3-rich molecules in an effort to enhance structural diversity within screening libraries. sp^3-Rich small molecules containing a chiral quaternary centre – a carbon centre containing four carbon substituents – or a chiral tetrasubstituted centre – a carbon centre bonded to four non-hydrogen substituents, at least one of which is a heteroatom – are of particular interest as they allow for maximal exploration of 3D chemical space.[4] Indeed, the presence of a chiral, tetrasubstituted $C(sp^3)$ centre in bioactive molecules has been shown to increase both the selectivity of binding and the metabolic stability of the compound owing to its 3-dimensional complexity and enhanced steric hindrance surrounding the chiral centre.[5] The most efficient approach to the construction of chiral, sp^3-rich compounds exploits enantioselective catalysis so as to remove time-consuming chiral separation, which would otherwise limit their broader applicability. However, the assembly of novel structures enantioselectively can be very challenging, often demanding the development of new catalytic asymmetric methods. The challenge of constructing quaternary or tetrasubstituted chiral centres is greater still due to the concurrent requirement to overcome the high energetic barrier associated with the formation of a sterically hindered bond.[6]

The palladium-catalysed allylic alkylation reaction, also known as the Tsuji-Trost process, has been shown to be an effective means to functionalise nucleophiles in the presence of allylic electrophiles (Scheme 1).[7] In general terms, the reaction begins with an oxidative addition of allylic electrophile **1** to palladium(0) to give π-allylpalladium(II) intermediate **2**. A nucleophile then reacts with **2** in a reductive elimination step to afford **3**, which subsequently dissociates from palladium(0) to form allylated product **4**. When a chiral ligand is used for palladium, the allylic alkylation process can become enantioselective if either the allylic electrophile or the nucleophile is prochiral, or both. Crucially, over the years, it has been clearly demonstrated that a number of other metals beyond palladium, such as iridium, nickel, copper, amongst others, can also successfully catalyse asymmetric allylic alkylation (AAA) reactions.[8]

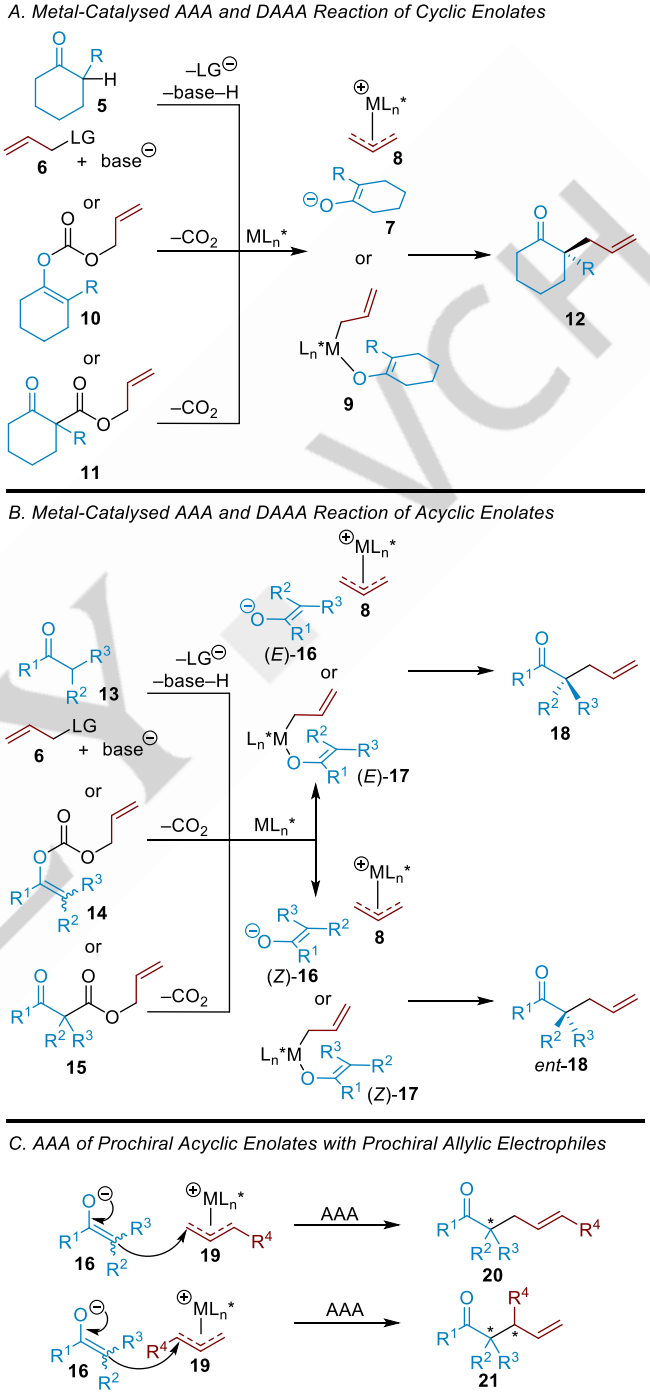


Scheme 1. The catalytic cycle of the palladium-catalysed allylic alkylation reaction.

The metal-catalysed AAA and the metal-catalysed decarboxylative asymmetric allylic alkylation (DAAA) reaction of prochiral enolates in particular are well-established approaches to generate quaternary and tetrasubstituted stereogenic centres (Scheme 2). However, research focus has traditionally been given to cyclic enolates due to their fixed alkene geometry (A, Scheme 2).[9] Considering the AAA reaction of cyclic carbonyl **5**,

deprotonation of **5** with a base alongside oxidative addition of the metal catalyst to allylic electrophile **6** generates prochiral cyclic enolate **7** and π-allylmetal intermediate **8** or a covalently-bound metal enolate **9** *in situ*. In the analogous DAAA reaction, the same intermediates are accessed from either allyl enol carbonate **10** or β-keto allyl ester **11** by means of oxidative addition, followed by decarboxylation. The facial selectivity of alkylation of the prochiral enolate either in an outer-sphere mechanism from **7** or in an inner-sphere mechanism from **9** is determined by the chiral ligand framework surrounding the metal catalyst, resulting in an enantioselective formation of **12**, bearing a quaternary chiral centre. A variety of cyclic carbonyl compounds, such as ketones and lactams, among others, have been shown to successfully undergo enantioselective allylation in both AAA and DAAA processes.

In contrast to the alkylation of cyclic enolates, examples of the metal-catalysed AAA/DAAA reaction of *acyclic* enolate intermediates as a means of constructing quaternary and tetrasubstituted chiral centres are far less common (B, Scheme 2).[10] Specifically, acyclic carbonyl compound **13**, allyl enol carbonate **14** or β-carbonyl allyl ester **15** can give rise to either *E*-enolate intermediates (*E*)-**16** or (*E*)-**17** or *Z*-enolates (*Z*)-**16** or (*Z*)-**17**. Given that the absolute stereochemical outcome of allylic alkylation is determined by the chiral ligand, it is likely that *E*-enolates (*E*)-**16** and (*E*)-**17**, and *Z*-enolates (*Z*)-**16** and (*Z*)-**17** will afford opposite enantiomers of alkylated product **18** and *ent*-**18**, respectively. Since deprotonation of **13** or decarboxylation of β-carbonyl allyl ester **15** is likely to result in a mixture of *E*/*Z* enolates (*E*)-**16**/(*Z*)-**16** or (*E*)-**17**/(*Z*)-**17**, allylic alkylation would also afford a mixture of **18** and *ent*-**18**, leading to diminished enantioselectivity. As such, the asymmetric allylic alkylation of acyclic prochiral enolates in both the direct and decarboxylative manner is substantially more challenging than that of cyclic enolates as not only does the allylic alkylation step need to be stereoselective, but stereocontrol in the preceding enolisation step also becomes essential. Similarly, while pre-formed allyl enol carbonates **14** can be utilised in DAAA reactions in geometrically pure form, either stereoselective enolisation to make the enol carbonate or chromatographic separation of *E*/*Z* enol carbonate isomers is still required prior to the allylic alkylation process. Notwithstanding these challenges, there are a growing number of reports of successful and highly enantioselective metal-catalysed AAA and DAAA reactions of acyclic enolates as new ways to control the enolate geometry are developed. This review aims to discuss catalytic AAA and DAAA reactions of acyclic prochiral nucleophiles, namely, but not exclusively, enolates, for the construction of quaternary and tetrasubstituted stereogenic centres, with a particular focus on how controlled enolisation is achieved in order to enable high levels of stereocontrol in the alkylation step. The majority of the reports centre around metal-catalysed AAA and DAAA reactions, albeit metal-free catalytic AAA methodologies are also discussed. A further level of complexity is introduced through the use of a substituted allylic electrophile, resulting in prochiral π-allylmetal intermediate **19** (C, Scheme 2). If enolate **16** attacks the less substituted terminus of electrophile **19**, then an α-quaternary stereogenic centre in **20** is formed in the usual way. If, however, alkylation occurs at the more substituted position of intermediate **19**, two contiguous stereogenic centres arise in **21**, requiring the control of both diastereo- and enantioselectivity. There have been a number of reports of the successful construction of vicinal stereogenic centres in products of type **21**, which are also discussed in this review.



Scheme 2. Comparison of AAA and DAAA reactions of cyclic and acyclic enolate intermediates.

Connor M. Griffiths received his MChem from Lancaster University in 2022. He is currently pursuing his PhD at Lancaster University under the supervision of Dr Vilius Franckevičius with a research focus on the development of asymmetric synthetic strategies towards novel building blocks utilising palladium catalysis.

Dr Vilius Franckevičius completed his PhD in 2008 in the group of Professor Steven Ley at the University of Cambridge, UK. Following post-doctoral positions with Professor Dirk Trauner at the Ludwig Maximilians University of Munich, Germany, and Professor Richard Taylor at the University of York, UK, he started his independent academic career in 2013 at Lancaster University, UK. His research interests concern the development of asymmetric catalytic methodologies for the synthesis of novel building blocks for medicinal chemistry applications.

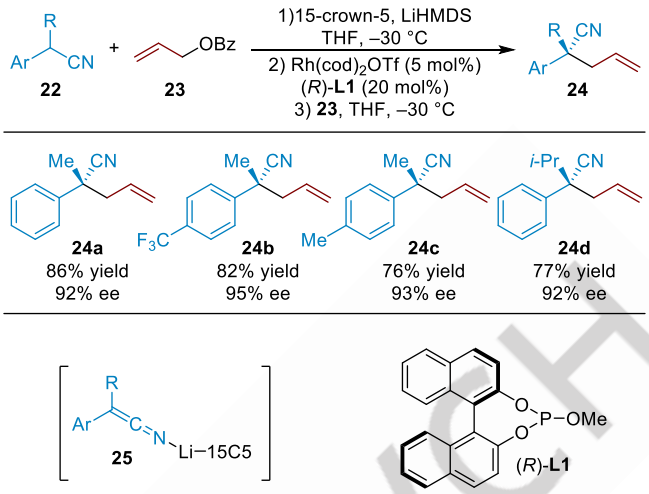
2. The AAA Reaction of Acyclic Prochiral Nucleophiles Lacking *E*/*Z* Isomerism

When considering AAA reactions of acyclic nucleophiles, the simplest case arises when the formation of the prochiral enolate or enolate-like species requires no stereocontrol due to the lack of *E*/*Z* geometrical isomerism associated with the nucleophile, namely α-nitrile anions, enolates of carboxylates and nitronate anions. The AAA processes of this type of nucleophile are discussed in this section.

2.1. The AAA Reaction of Nitriles

The α-nitrile anion is one such example of linear prochiral nucleophile that has no *E*/*Z* isomers associated with it. In 2015, the Evans group developed a rhodium-catalysed AAA reaction of nitriles **22** (Scheme 3).[11] The reaction gave a range of α-quaternary products **24a-d** with high levels of enantioselectivity (92-95% ee). The reaction proceeds *via* the AAA reaction of α-nitrile anion **25** with a π-allylrhodium(III) intermediate. The use of 15-crown-5 improved the enantioselectivity, presumed to result from the slower rate of equilibration between the *C*- and *N*-metallated forms of **25**.

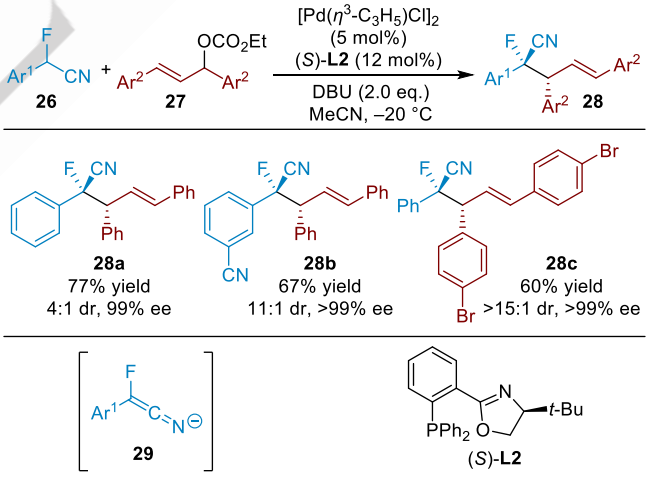
Evans and co-workers (2021)



Scheme 3. The rhodium-catalysed AAA reaction of nitriles.

More recently, Wolf described the palladium-catalysed AAA reaction of arylfluoroacetonitriles **26** (Scheme 4).[12] Using substituted allylic electrophiles **27**, DBU as the base and chiral ligand (*S*)-**L2** for palladium, a library of allylated products **28a-c** bearing two contiguous stereogenic centres could be accessed with moderate to high diastereoselectivity and excellent enantioselectivity (4:1 to >15:1 dr and ≥99% ee). Mechanistically, α-deprotonation of nitrile **26** gives prochiral nucleophilic intermediate **29** that then undergoes allylation with a π-allylpalladium(II) intermediate.

Wolf and co-workers (2022)

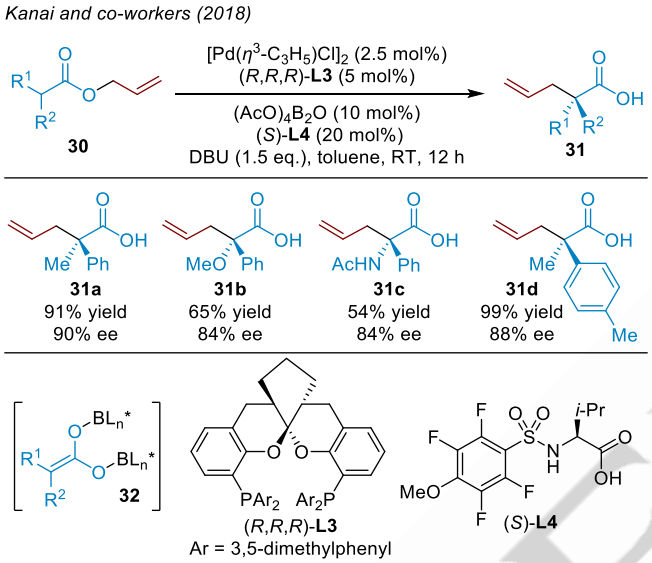


Scheme 4. The palladium-catalysed AAA reaction of arylfluoroacetonitriles.

2.2. The AAA Reaction of Carboxylic Acids

The second class of acyclic nucleophile that lacks *E*/*Z* isomers concerns symmetrically 1,1-disubstituted enolates of carboxylates. In this context, in 2018, Kanai developed a palladium/boron dual-catalysed AAA reaction of α-tertiary allyl esters **30** to give enantioenriched carboxylic acids **31** containing an α-quaternary centre in the presence of ligand (*R*,*R*,*R*)-**L3** for palladium and (*S*)-**L4** for boron (Scheme 5).[13] The reaction gave high enantioselectivity for α-alkyl, α-oxy and α-amido groups, affording **31a-c** with 84-90% ee. Substitution at the α-aryl group

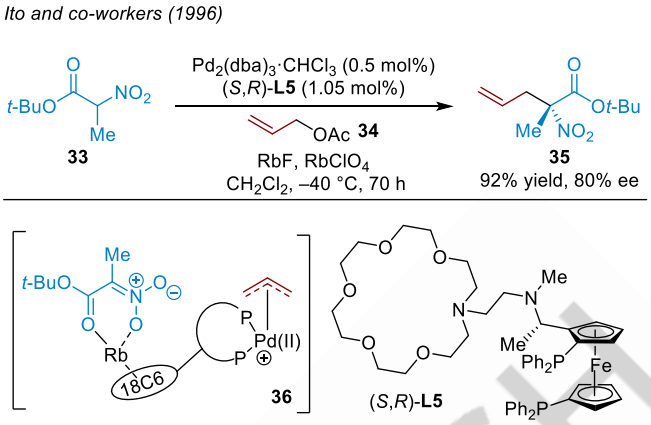
was also tolerated, giving *p*-tolyl **31d** with 88% ee. The authors postulated that allyl ester **30** undergoes oxidative addition to palladium(0) resulting in a carboxylate anion that is trapped and enolised by the boron catalyst, generating boryl enediolate intermediate **32**. The AAA reaction of **32** with the π-allylpalladium(II) intermediate then follows, forming allylated α-quaternary carboxylic acid **31**. The high levels of enantioselectivity observed in the formation of an acyclic quaternary centre in **31** is a result of cooperative effects of the two chiral catalysts, creating a matched chiral environment and allowing for a high degree of enantioinduction. Given the symmetrical nature of boryl enediolate intermediate **32**, enolate geometry is not relevant in this case.



Scheme 5. Palladium/boron dual-catalysed AAA reaction of α-tertiary esters.

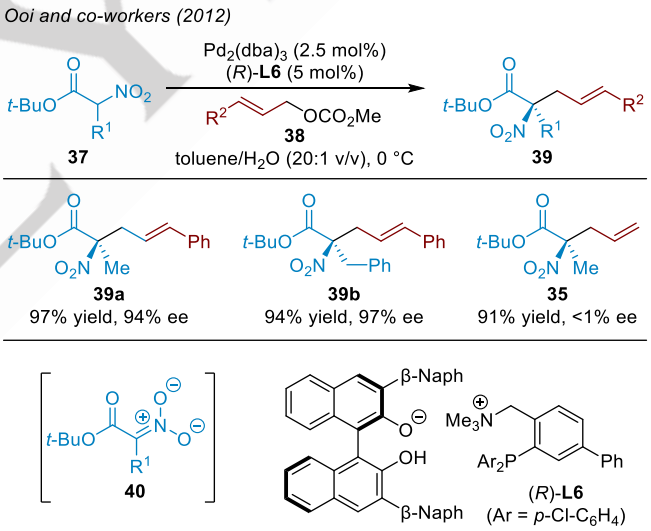
2.3. The AAA Reaction of Nitro Compounds

The third type of prochiral nucleophile free from *E*/*Z* isomerism is the nitronate anion. In 1996, the Ito group described the first palladium-catalysed AAA reaction of α-nitroester **33** with allyl acetate (**34**) using 18-crown-6-appended chiral ligand (*S*,*R*)-**L5** for palladium, rubidium fluoride as the base and rubidium perchlorate as an additive (Scheme 6).[14] The reaction proceeded well, giving **35** in 92% yield and 80% ee. The authors proposed that the rubidium cation fits into the 18-crown-6 (18C6) cavity within ligand (*S*,*R*)-**L5**. Following the formation of the π-allylpalladium(II) intermediate, the nitronate anion and ester carbonyl in **36** forms a chelate with the rubidium cation, thereby providing high levels of enantioselectivity in the AAA reaction that is essentially intramolecular in nature. It is noteworthy that the *tert*-butoxy residue in **33** was essential for selectivity as the analogous methyl and ethyl ester substrates gave poor enantioselectivity in the reaction (23% and 37% ee, respectively).



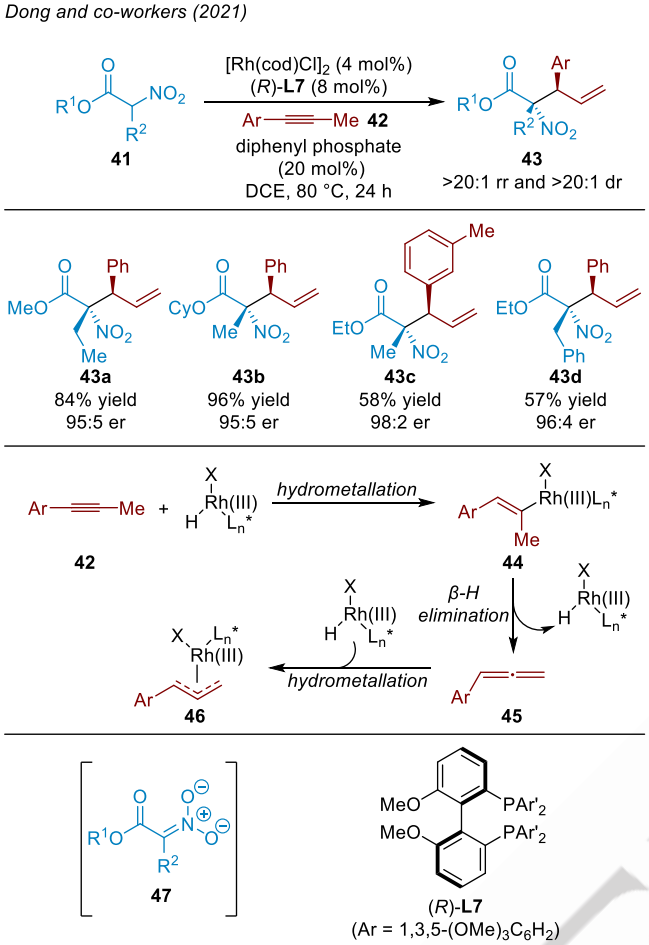
Scheme 6. The palladium-catalysed AAA reaction of an α-nitroester.

In 2012, the Ooi group described the palladium-catalysed AAA reaction of α-nitroesters **37** using ion-paired chiral ligand (*R*)-**L6** (Scheme 7).[15] The authors observed excellent enantioselectivity for a range of α-allyl products, including **39a** (94% ee) and **39b** (97% ee). Interestingly, when no substitution was present on allylic electrophile **38** (R^2 = H), the enantioselectivity was completely lost, forming **35** in racemic form. It was suggested that the prochiral nucleophile exists solely as nitronate anion **40**, thus, eliminating the need to consider geometric isomerism.



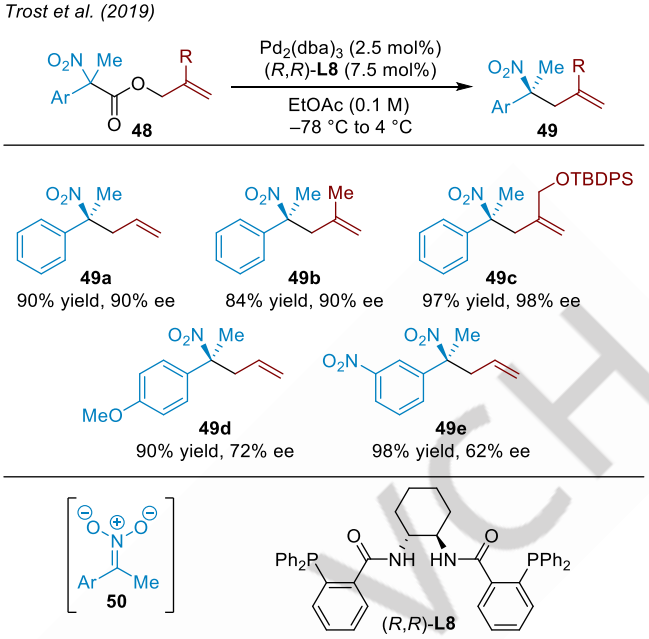
Scheme 7. The palladium-catalysed AAA reaction of α-nitroesters.

Expanding on the work by Ooi, the Dong group described the rhodium-catalysed AAA reaction of α-nitroesters **41** with alkyne **42** in the presence of diphenyl phosphate as the additive and ligand (*R*)-**L7** for rhodium to give allylated building blocks **43** with excellent branched to linear selectivity, diastereo- and enantioselectivity (Scheme 8).[16] Specifically, products **43a-d** were formed with >20:1 rr, >20:1 dr and 95:5-98:2 er. The authors proposed that hydrometallation of alkyne **42** with the rhodium hydride catalyst gives intermediate **44**, which, following β-hydride elimination, produces allene **45**. A second hydrometallation of allene **45** with the rhodium hydride catalyst results in π-allylrhodium(III) intermediate **46** as the electrophile.[17] The prochiral nucleophile (**47**), formed by deprotonation of **41**, is a nitronate anion, devoid of *E*/*Z* geometrical isomers.



Scheme 8. The rhodium-catalysed AAA reaction of α-nitroesters.

The Trost group reported the palladium-catalysed DAAA reaction of α-nitro allyl esters **48** using DACH phenyl Trost ligand (*R*,*R*)-**L8** (Scheme 9).[18] The reaction gave **49a** in 90% yield and 90% ee. When the allyl group was substituted, yields and enantioselectivity were largely unaffected, giving **49b** in 84% yield and 90% ee, and **49c** in 97% yield and 98% ee. However, if electron-donating or withdrawing aryl substituents were introduced, the enantioselectivity was lower, affording **49d** with 72% ee and **49e** with 62% ee. This process presumably proceeds *via* prochiral nitronate anion **50**, which does not have geometrical isomerism associated with it.



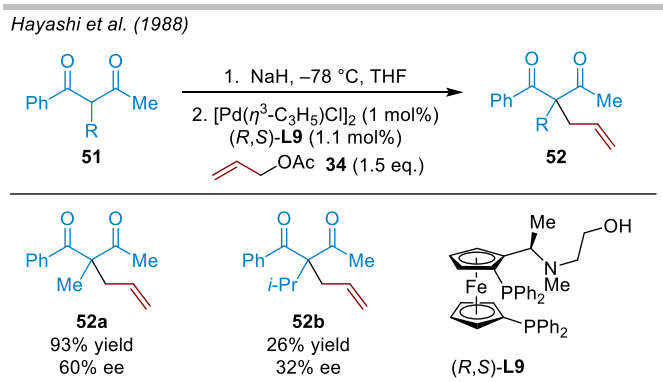
Scheme 9. The palladium-catalysed DAAA reaction of α-nitro allyl esters.

The AAA reactions discussed so far concerned the use of acyclic prochiral nucleophiles that lack *E*/*Z* geometrical isomerism. However, to generate quaternary and tetrasubstituted stereogenic centres *via* the AAA reaction of non-symmetrically 1,1-disubstituted acyclic enolates, in addition to achieving high levels of enantioselectivity in the allylic alkylation step, the stereocontrol of enolisation to either the *E* or the *Z*-isomer of the prochiral enolate intermediate prior to allylation must be considered. In particular, mechanisms that ensure stereoselective enolisation are often essential, most often enabled by the judicious choice of a sterically-biased substrate or one that permits chelation. Nonetheless, examples where non-stereoselective enolisation can still afford high levels of enantioselectivity of allylic alkylation have also been reported. This topic concerns the remainder of this review.

3. The AAA Reaction of 1,3-Dicarbonyl Compounds

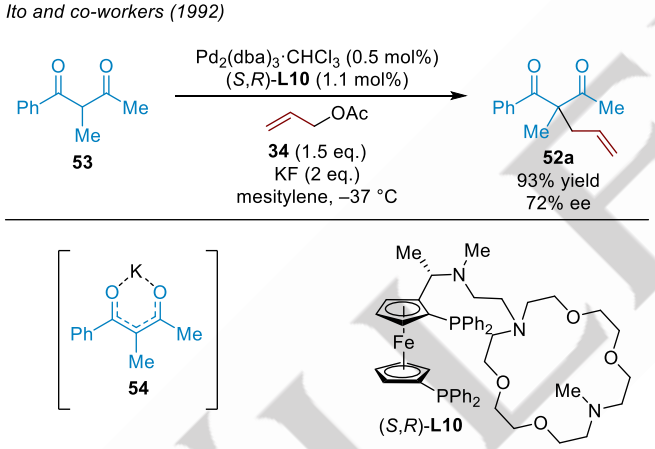
3.1. Palladium Catalysis

In 1988, Hayashi *et al*. reported the first palladium-catalysed AAA reaction of acyclic α-substituted 1,3-diketone substrates **51** (Scheme 10).[19] Using chiral ferrocene-based ligand (*R*,*S*)-**L9** for palladium, sodium hydride as the base and allyl acetate (**34**) as the electrophile, formation of α-quaternary product **52a** (R = Me) was achieved with moderate enantioselectivity (60% ee). When a more sterically congested substrate was used (R = *i*-Pr), the reaction efficiency and enantioselectivity were reduced significantly, giving rise to **52b** in 26% yield and 32% ee.



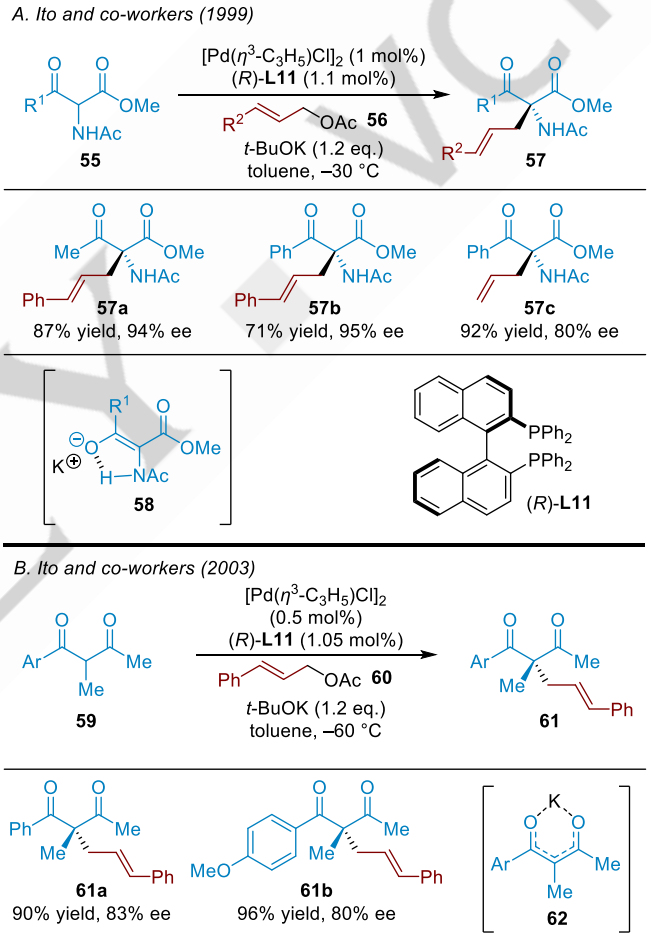
Scheme 10. The first palladium-catalysed AAA of acyclic 1,3-diketone substrates.

Following this seminal report of the palladium-catalysed AAA reaction of prochiral acyclic enolates, in 1992, Ito and co-workers improved upon the enantioselectivity achieved by Hayashi in the palladium-catalysed AAA reaction of acyclic 1,3-diketone substrate **53** (Scheme 11).[20] The authors showed that, when using chiral ligand (*S*,*R*)-**L10** for palladium, the AAA reaction of **53** with allyl acetate (**34**) gave **52a** in 93% yield with a higher 72% ee (*vs* 60% ee, *vide supra*, Scheme 10). Due to the 1,3-arrangement of the oxygen atoms, enolate geometry is likely controlled by chelation in **54**.



Scheme 11. Improved AAA of a 1,3-diketone.

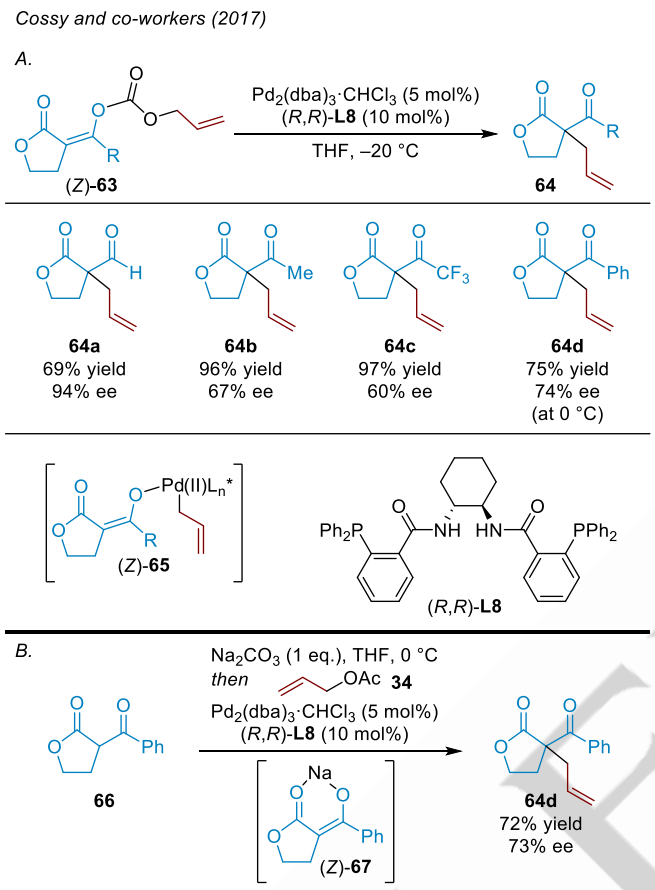
In 1999, Ito and co-workers described the palladium-catalysed AAA reaction of β-ketoesters **55** bearing an α-acetamido group (A, Scheme 12).[21] The reaction was shown to be highly enantioselective when using (*R*)-BINAP (*R*)-**L11** as the ligand and phenyl-substituted allylic electrophile (R^2 = Ph in **56**), giving **57a** and **57b** with 94% and 95% ee, respectively. In the case of an unsubstituted allylic electrophile (R^2 = H in **56**), the enantioselectivity was notably lower, affording **57c** with 80% ee. This observation suggests that, under these conditions, a terminal substituent on the π-allylpalladium(II) intermediate was essential for high enantioselectivity. The team also observed that, when using a substituted allyl electrophile, addition of the enolate occurs exclusively at the less substituted position for steric reasons, and the *E*-alkene geometry in the product is always maintained, a reactivity profile that is commonly observed in palladium-catalysed allylic alkylation reactions. The high enantioselectivity obtained in this process was proposed to result from hydrogen-bonding between the oxyanion of the enolate and the N–H of the α-acetamido group in intermediate **58**, enabling stereocontrolled enolisation. The authors also later attempted the reaction with 1,3-diketones **59** that do not contain an α-acetamido substituent (B, Scheme 12).[22] Surprisingly, under similar reaction conditions, the enantioselectivity was still high, giving **61a** in 83% ee and **61b** in 80% ee. Presumably chelated potassium enolate **62** is formed *in situ*, thereby controlling the enolate geometry and affording high levels of stereoselectivity in the alkylation step. Given the *trans* arrangement of the oxygen atoms in enolate **58** and the *cis* arrangement in enolate **62**, the same facial selectivity of alkylation with (*R*)-BINAP (*R*)-**L11** as the ligand gives the opposite absolute stereochemical outcome in **57** and **61**, as expected.



Scheme 12. The palladium-catalysed AAA reaction of α-acetamido β-ketoesters and 1,3-diketones.

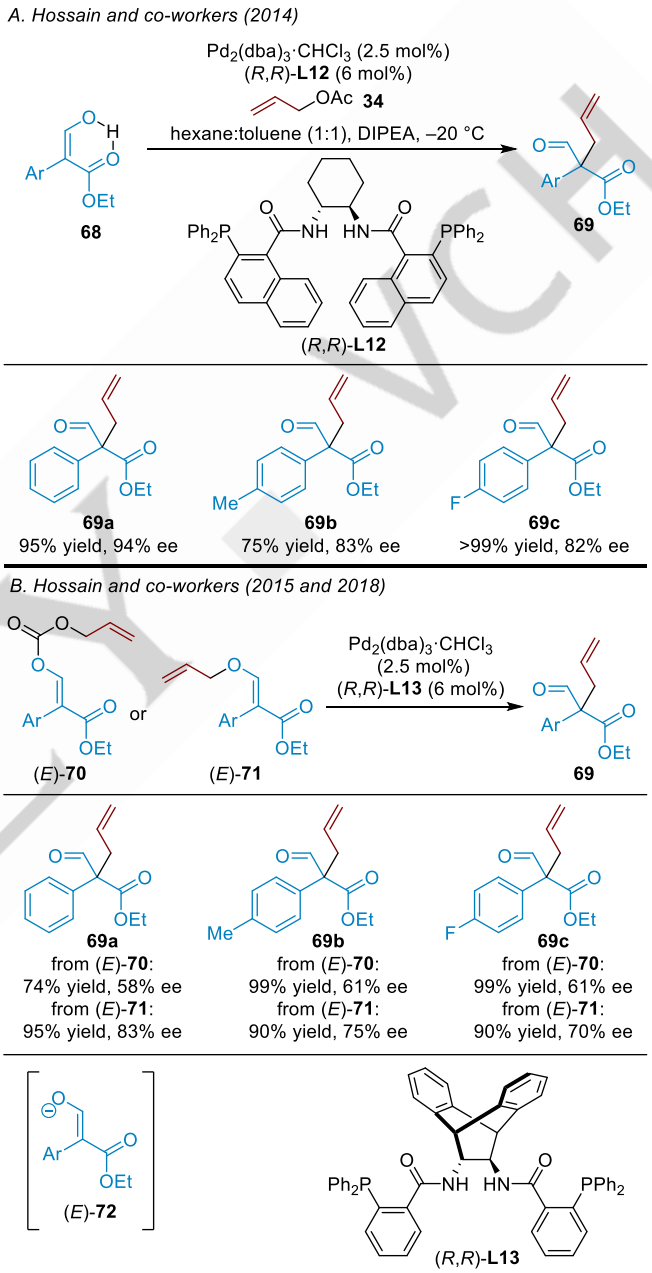
In 2017, Cossy and co-workers described the palladium-catalysed DAAA reaction of *Z*-allyl enol carbonates (*Z*)-**63** derived from α-acyl-γ-butyrolactones (A, Scheme 13).[23] The use of (*R*,*R*)-DACH phenyl Trost ligand (*R*,*R*)-**L8** for palladium afforded allylated products **64a-d** with moderate to high enantioselectivity. While the *Z*-enolate geometry in (*Z*)-**65** is defined by the geometrically pure *Z*-enol carbonate substrates (*Z*)-**63**, purification of the *Z*-isomer of **63** by recrystallisation prior to the DAAA reaction was required. When the authors carried out the analogous AAA reaction using β-keto lactone **66** in the presence of sodium carbonate as the base and allyl acetate (**34**) as the externally added electrophile, an intriguing observation was made

(B, Scheme 13): **64d** was formed with the same level of enantioselectivity (73% ee) when compared with the DAAA strategy (74% ee). This result suggests that enolisation of **66** with sodium carbonate may be stereoselective for the *Z*-enolate (*Z*)-**67** due to chelation to sodium, making the direct and decarboxylative processes complementary.



Scheme 13. The palladium-catalysed DAAA reaction of allyl enol carbonates.

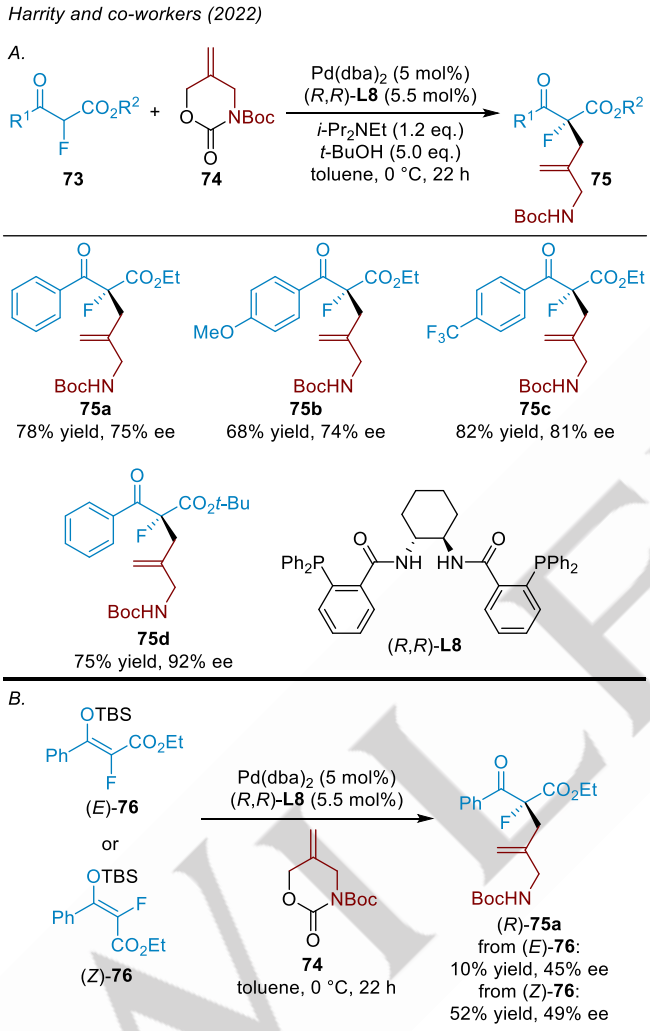
In 2014, Hossain and co-workers reported the palladium-catalysed AAA reaction of enols of β-aldehyde esters **68** in the presence of allyl acetate (**34**) and DACH naphthyl Trost ligand (*R*,*R*)-**L12** (A, Scheme 14).[24] The reaction gave α-quaternary β-aldehyde ester product **69a** in an excellent 94% ee owing to the control of enol geometry in **68** *via* hydrogen-bonding. The enantioselectivity remained high with aryl substitution, giving **69b** with 83% ee and **69c** with 82% ee. Subsequently, the same group carried out the analogous decarboxylative reaction of geometrically pure *E*-allyl enol carbonates (*E*)-**70** (B, Scheme 14).[25] The authors found that, in comparison to the aforementioned AAA reaction of enols (*Z*)-**68**, there was a significant reduction in the enantioselectivity of alkylation in the decarboxylative process, giving **69a**, **69b** and **69c** with 58%, 61% and 61% ee, respectively. In addition, they expanded on their work by exploring *E*-allyl enol ethers (*E*)-**71** as substrates, made stereoselectively by *O*-allylation of **68** with allyl bromide.[26] The reaction was shown to give a moderate improvement in the enantioselectivity compared to the DAAA reaction of the equivalent *E*-allyl enol carbonate substrates (*E*)-**70**, affording products **69a**, **69b** and **69c** with 83%, 75% and 70% ee, respectively. Mechanistically, upon decarboxylation, *E*-allyl enol carbonates (*E*)-**70** and *E*-allyl enol ethers (*E*)-**71** would be expected to result in the opposite *E*-enolate geometry to that of *Z*-enol **68**, and allylation thereof should, in principle, afford enantiomeric products. Although the authors did not determine the absolute configuration of **69** during their investigations, such a study in the future may shed more light on the origins of stereoselectivity in this reaction.



Scheme 14. The palladium-catalysed AAA of enols, allyl enol carbonates and allyl enol ethers.

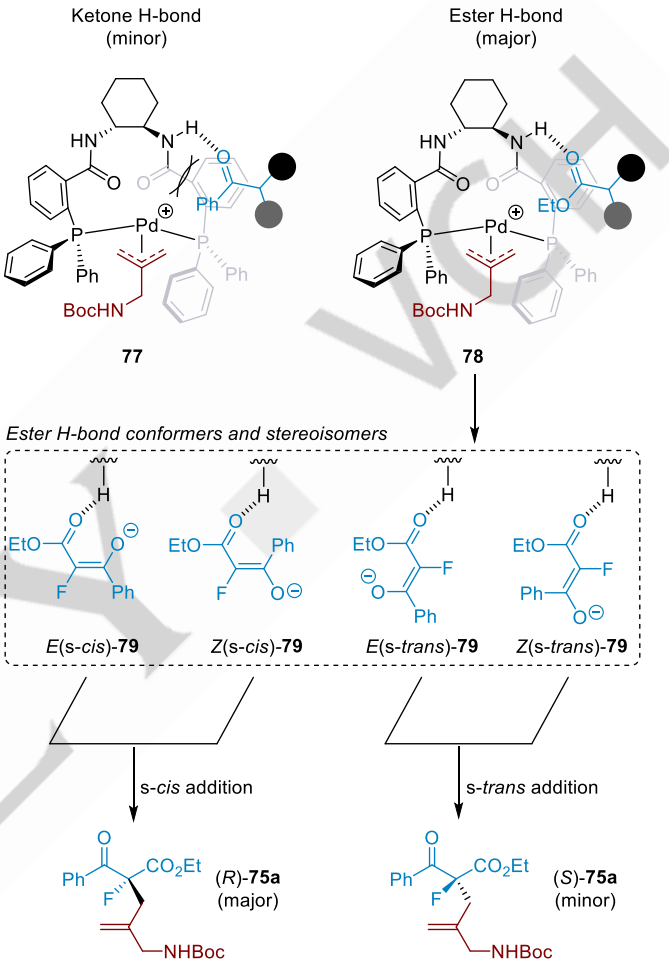
In 2022, Harrity and co-workers reported the palladium-catalysed AAA reaction of acyclic α-fluoro-β-ketoesters **73** with cyclic carbonate **74** as the electrophile (A, Scheme 15).[27] In the presence of (*R*,*R*)-DACH phenyl Trost ligand (*R*,*R*)-**L8**, product **75a** was formed in 78% yield and 75% ee. The reactivity and enantioselectivity did not change significantly when varying the electronics of the ketone aryl substituent, giving **75b** in 68% yield and 74% ee, and **75c** in 82% yield and 81% ee. Notably, the

analogous reaction of the more sterically demanding *tert*-butyl ester substrate improved the enantioselectivity (**75d**, 92% ee). A mechanistic investigation using geometrically pure, pre-formed silyl enol ethers (*E*)-**76** and (*Z*)-**76** independently in the reaction was attempted (B, Scheme 15). (*E*)-**76** gave (*R*)-**75a** in 10% yield and 45% ee, whereas (*Z*)-**76** produced **75a** in an improved 52% yield and 49% ee, with (*R*)-**75a** also being the major enantiomer. Although one would typically expect the absolute stereochemical configuration of the major enantiomer of allylated products from the *E*- and *Z*-enolates to be opposite, in this case, regardless of the geometry of the enolate, the major enantiomer resulting from both (*E*)-**76** and (*Z*)-**76** was the same.



Scheme 15. The palladium-catalysed AAA of α-fluoro-β-ketoesters.

To explain how both (*E*)-**76** and (*Z*)-**76** afford the same absolute stereochemical configuration of the major isomer of **75a**, the authors suggested that the Lloyd-Jones and Norrby model may offer a suitable rationale (Scheme 16).[28] In this model, the oxygen atom of either the ester or ketone carbonyl in **73** can hydrogen bond to the N–H of the chiral ligand, forming either intermediate **77** or **78**. The ester is more likely to hydrogen bond as this arrangement (**78**) places the less bulky ester residue close to the catalyst backbone (cf. the bulkier aryl substituent of the ketone in **77**), resulting in minimised steric interactions. As such, the lower energy intermediate **78** predominates. Enolisation of **78** results in the formation of an *E*/*Z*-enolate pair that can adopt either the s-*cis* or the s-*trans* conformation, giving four reactive states of **79**: *E*(s-*cis*)-**79**, *Z*(s-*cis*)-**79**, *E*(s-*trans*)-**79** and *Z*(s-*trans*)-**79**. In order to explain the observed stereoselectivity in the formation of (*R*)-**75a** as the major enantiomer, it was proposed that the two s-*cis* states of **79** are the major occupied conformations that result in the same major enantiomer of **75a** regardless of whether the enolate is in the *E*- or *Z*-geometry.

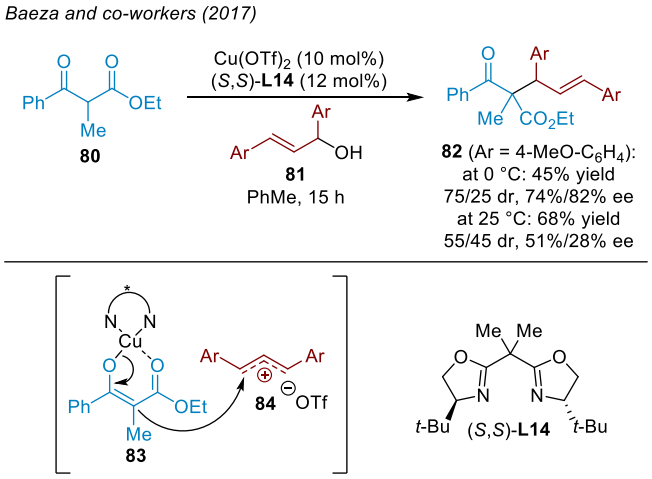


Scheme 16. Explanation for the enantioselectivity observed by Harrity and co-workers.

3.2. Copper Catalysis

Whilst palladium-catalysis in AAA processes is the most popular, Baeza developed the copper-catalysed AAA reaction of β-ketoesters with substituted allylic alcohols (Scheme 17).[29] This study was primarily concerned with cyclic substrates and the assembly of α-trisubstituted products; however, a single example of acyclic α-quaternary centre formation was reported using β-ketoester **80** and allylic alcohol **81** as substrates in the presence of BOX ligand (*S*,*S*)-**L14** for copper. Product **82** was isolated with a modest 75:25 dr, with each respective diastereoisomer formed with 74% and 82% ee. It was proposed that the reaction proceeded *via* copper-chelated enolate **83**, which undergoes allylic alkylation with symmetrical carbocation intermediate **84**. Although the stereoselectivity was moderate, further development of this methodology to generate products with higher diastereo- and enantioselectivity could unlock the potential for the use of

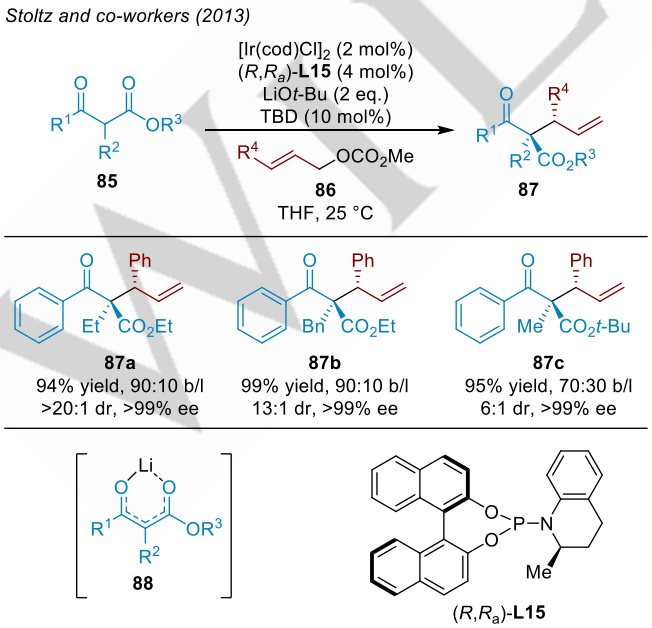
more sustainable metal catalysts in enantioselective allylic alkylation processes.



Scheme 17. The copper-catalysed AAA of a β-ketoester.

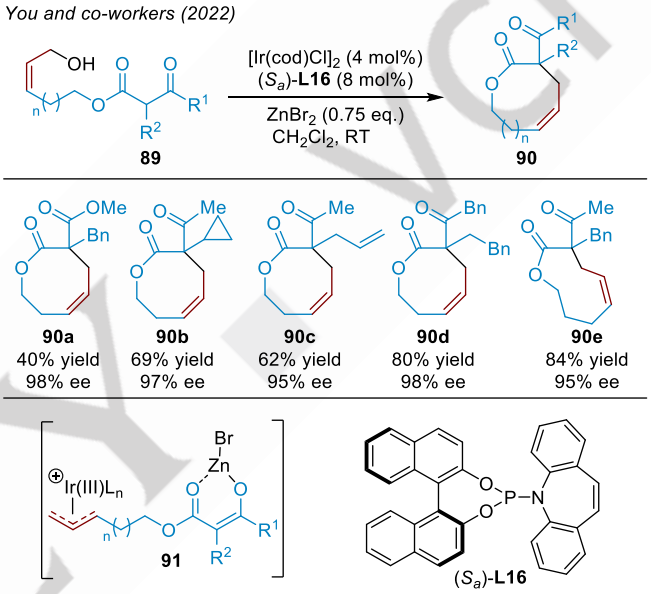
3.3. Iridium Catalysis

Iridium catalysis has also found utility in the AAA reaction of 1,3-dicarbonyl compounds. In this context, in 2013, the Stoltz group reported the iridium-catalysed AAA reaction of β-ketoesters **85** with substituted allylic electrophiles **86** (Scheme 18).[30] Allylated products **87**, bearing vicinal α-quaternary and β-tertiary stereogenic centres, were generated with high levels of branched to linear (b/l) selectivity, diastereo- and enantioselectivity, forming **87a-c** with 90:10 to 96:4 b/l, 12:1 to >20:1 dr, and 95% to >99% ee. In this process, enolate geometry is believed to be controlled by chelation to lithium in **88**, whereas nucleophilic addition regioselectively at the more substituted terminus of the π-allyliridium(III) intermediate is a common observation in iridium-catalysed AAA reactions.[31]



Scheme 18. Iridium-catalysed AAA reaction of β-ketoesters.

The You group described a similar iridium-catalysed AAA reaction of linear β-ketoester substrates **89** but in an intramolecular fashion (Scheme 19).[32] The authors used ligand (S_a)-**L16** for iridium alongside zinc bromide as an additive to produce medium-ring β-keto lactones **90a-e** with excellent enantioselectivity (95-98% ee). Zinc bromide is thought to be responsible for the selective formation of a chelated *Z*-enolate **91**, which then undergoes an intramolecular AAA reaction with the π-allyliridium(III) electrophile. Unusually for iridium catalysis, a regioselective *endo* cyclisation at the less substituted terminus of the π-allyliridium(III) electrophile to form a medium ring, rather than an *exo* cyclisation at the more substituted terminus of the electrophile to afford a smaller ring, predominates.

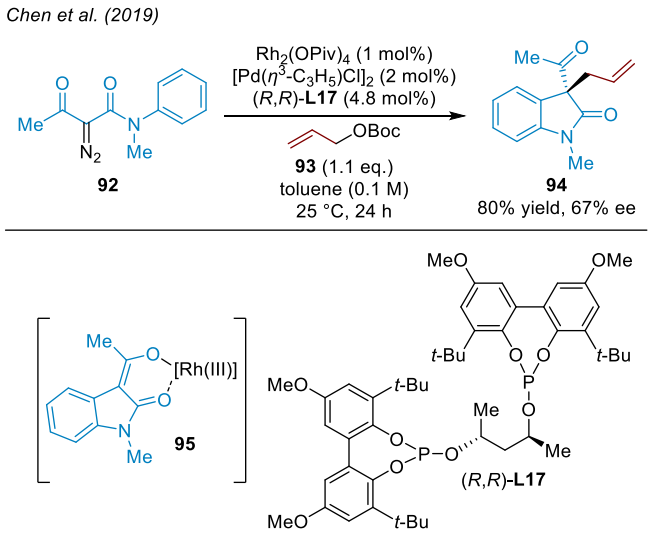


Scheme 19. The intramolecular iridium-catalysed AAA of β-ketoesters.

3.4. Dual Metal Catalysis

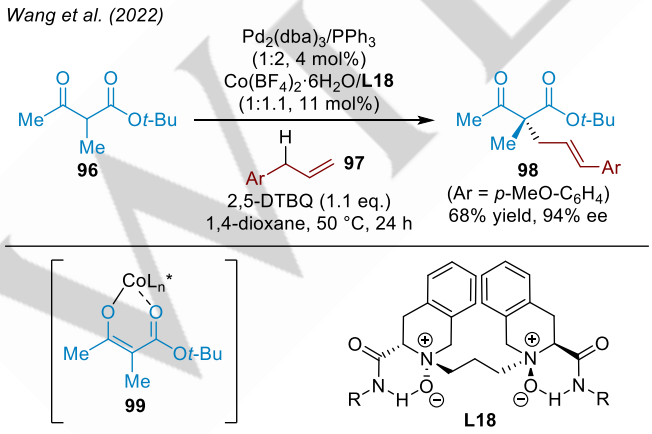
The use of two metal catalysts has also been shown to be an effective strategy in achieving highly selective AAA reactions of 1,3-dicarbonyl compounds. In these processes, either one of the two catalysts generates a chiral π-allylmetal electrophile in the presence of an achiral enolate of the second catalyst, or a chiral metal enolate undergoes an AAA reaction with an achiral allylmetal electrophile. Concerning the former approach, in 2019, Chen *et al*. described a chemoselective rhodium/palladium dual-catalysed one pot synthesis of α-quaternary allylic oxindoles from *N*-aryl-α-diazo-β-ketoamides (Scheme 20).[33] Although the aim of the research was to optimise the reaction efficiency in pursuit of high yields of products, the authors did report a single mildly enantioselective example of the reaction using substrate **92**, allyl carbonate **93** and chiral ligand (*R*,*R*)-**L17** for palladium, giving β-keto oxindole **94** in 80% yield and 67% ee. The diazo 1,3-dicarbonyl **92** undergoes an intramolecular aryl C–H insertion, followed by deprotonation to give a chelated rhodium(II)-enolate **95**, which takes part in the AAA reaction with the π-allylpalladium(II) electrophile to give α-quaternary product **94**. Although the development of an enantioselective variant of this synthetic strategy is in its infancy, this report offers promising scope for future work towards the development of efficient, one-

pot syntheses of stereofunctionalised heterocycles from linear building blocks.



Scheme 20. Rhodium/palladium-catalysed AAA of *N*-aryl-α-diazo-β-ketoamides.

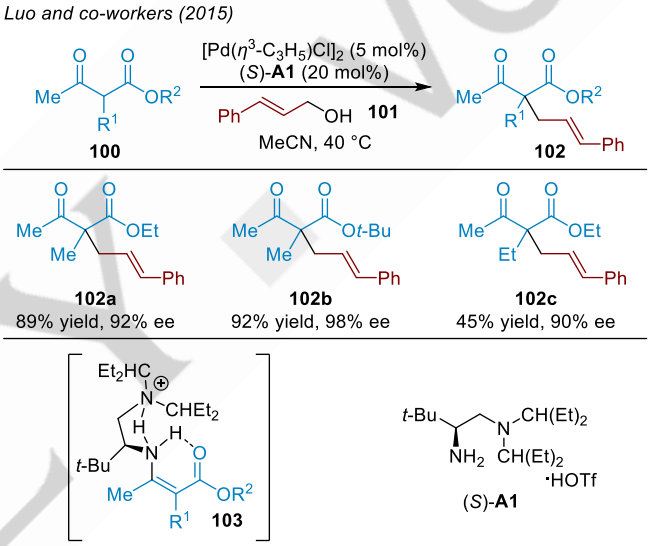
The second approach that exploits dual metal catalysis involves the alkylation of a chiral enolate species with an achiral allylic electrophile. In this context, in 2022, Wang *et al*. reported the use of unfunctionalised allyl electrophiles **97** in the palladium/cobalt-catalysed AAA reaction of β-ketoesters (Scheme 21).[34] The substrate scope comprised mainly cyclic substrates, albeit one acyclic example was also disclosed using substrate **96**. More specifically, 2,5-di-*tert*-butylquinone (2,5-DTBQ) as the oxidant facilitates C–H activation of simple allyl species **97** in order to produce an achiral π-allylpalladium(II) electrophile. The concomitant use of a cobalt catalyst as the Lewis acid in the presence of chiral ligand **L18** generated chiral chelated cobalt enolate **99**, which then underwent stereoselective allylation to afford α-quaternary linear product **98** in 68% yield and 94% ee.



Scheme 21. The palladium/cobalt-catalysed AAA.

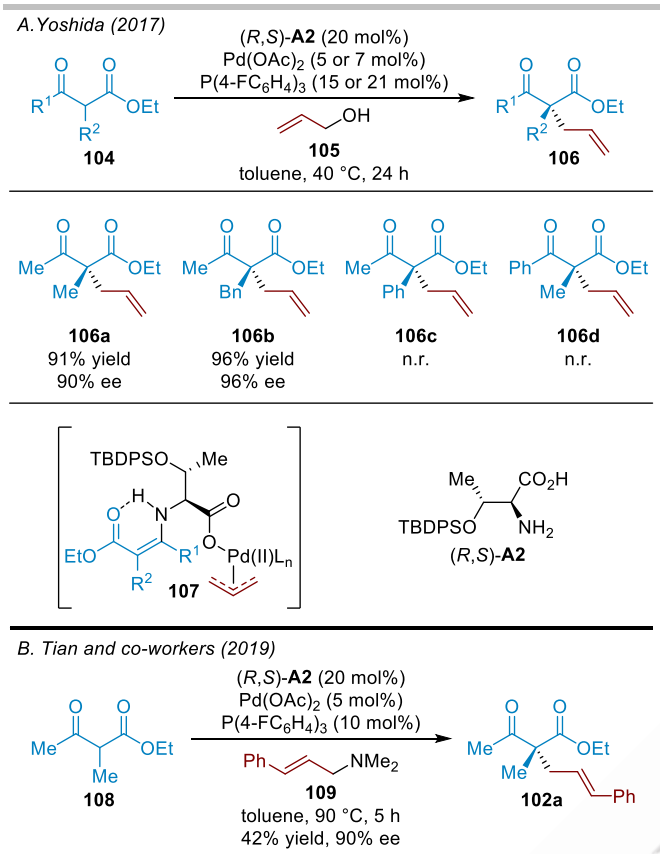
3.5. Enamine/Palladium Dual Catalysis

Palladium catalysis in conjunction with enamine activation of the ketone group in β-ketoester substrates has also allowed access to a number of α-quaternary products *via* the AAA reaction. In 2015, the Luo group described the first palladium-catalysed AAA reaction of β-ketoester substrates **100** *via* enamine activation using chiral amine catalyst (*S*)-**A1** (Scheme 22).[35] The reaction gave a range of products **102a-c** with excellent enantioselectivity (90-98% ee). The enamine geometry is controlled *via* hydrogen-bonding of the ester carbonyl group with the enamine N–H in intermediate **103**. The facial selectivity of allylation is then determined by steric effects exerted by the chiral enamine. The authors also proposed that the restricted conformation in **103** *via* additional hydrogen-bonding between the protonated tertiary amine and the enamine nitrogen atom improves the enantioselectivity. Two years later, the same group reported the analogous palladium-catalysed AAA reaction of β-ketocarbonyl substrates using allenes as electrophiles to form the π-allylpalladium(II) intermediate.[36]

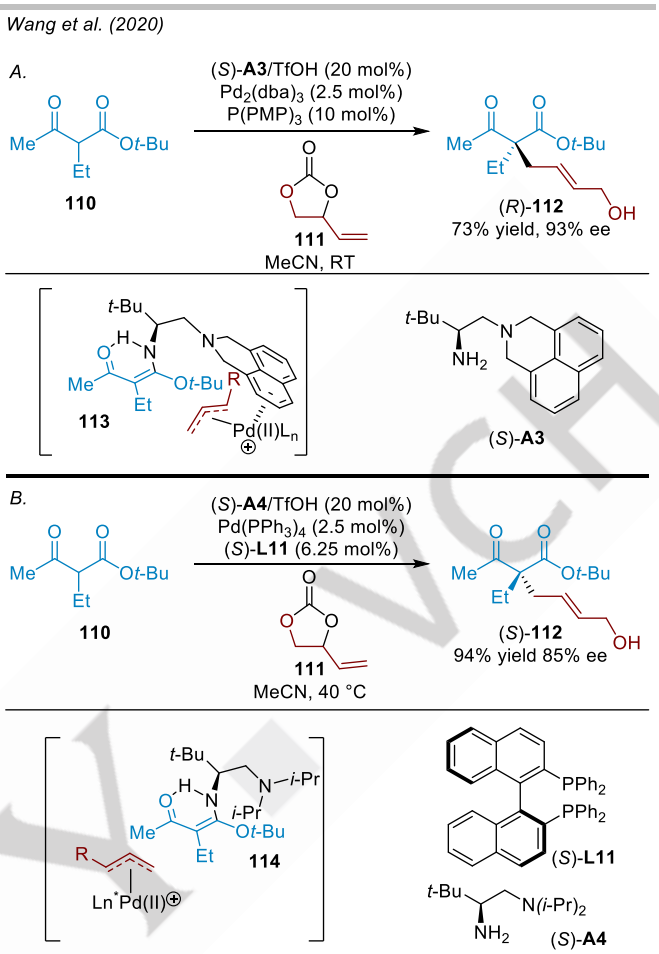


Scheme 22. The palladium-catalysed AAA reaction of β-ketoester substrates.

In 2017, Yoshida carried out a palladium-catalysed AAA reaction of β-ketoesters **104** with allyl alcohol (**105**) in the presence of α-amino acid catalyst (*R*,*S*)-**A2** (A, Scheme 23).[37] The reaction gave high enantioselectivity for products **106a** (90% ee) and **106b** (96% ee); however, no reaction was observed for products **106c** and **106d**, which the authors suggested was a result of increased steric hindrance at the α-centre and insufficient enamine formation from aromatic ketones, respectively. It was proposed that the reaction proceeded through intermediate **107**, whereby the enamine geometry is controlled *via* hydrogen-bonding to the carbonyl of the ester and facial selectivity arises from the intramolecular delivery of π-allylpalladium(II) intermediate through bonding to the carboxylate in **107**. Two years later, Tian and co-workers described a similar reaction using substrate **108** and allylic amine **109** as the electrophile, which afforded α-quaternary β-ketoester **102a** with equally high 90% ee (B, Scheme 23).[38]



Scheme 23. The palladium-catalysed AAA of β-ketoesters *via* enamine activation.

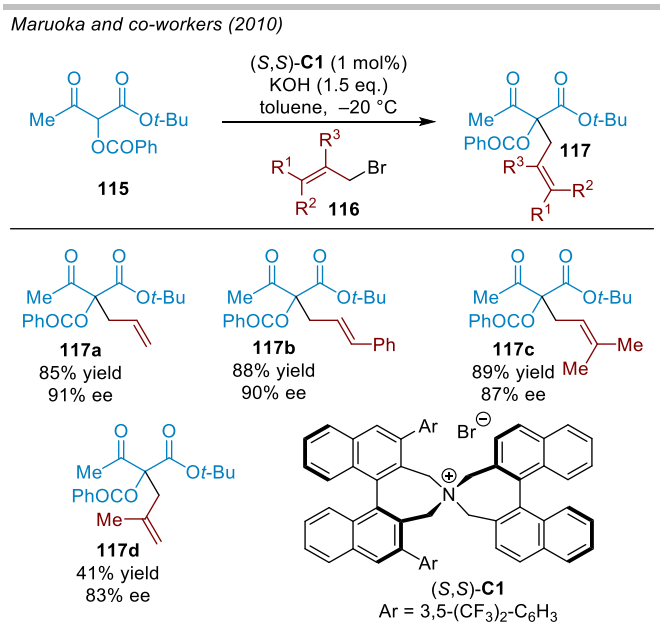


Scheme 24. Stereodivergent palladium-catalysed allylic alkylation *via* enamine activation.

In 2020, Wang *et al*. successfully developed a palladium and chiral amine catalysed AAA reaction to generate functionalised allylic alcohols in a stereodivergent manner (Scheme 24).[39] More specifically, with chiral amine catalyst (*S*)-**A3** and an achiral palladium catalyst, (*R*)-**112** was formed with 96% ee, with facial selectivity determined by π-coordination of enamine intermediate **113** to the palladium centre of the π-allylpalladium(II) electrophile, making the allylation step intramolecular (A, Scheme 24). In contrast, enantiomer (*S*)-**112** was formed with 96% ee using chiral amine catalyst (*S*)-**A4** that lacks the π-coordination ability and (*S*)-BINAP (*S*)-**L11** as the chiral ligand for palladium (B, Scheme 24). Without the potential for π-coordination, the facial selectivity is now governed by the combination of steric effects of the chiral amine and the palladium ligand. The authors were able to demonstrate the versatility of their methodology and produced a range of α-quaternary β-ketoesters with similarly high levels of enantioselectivity.

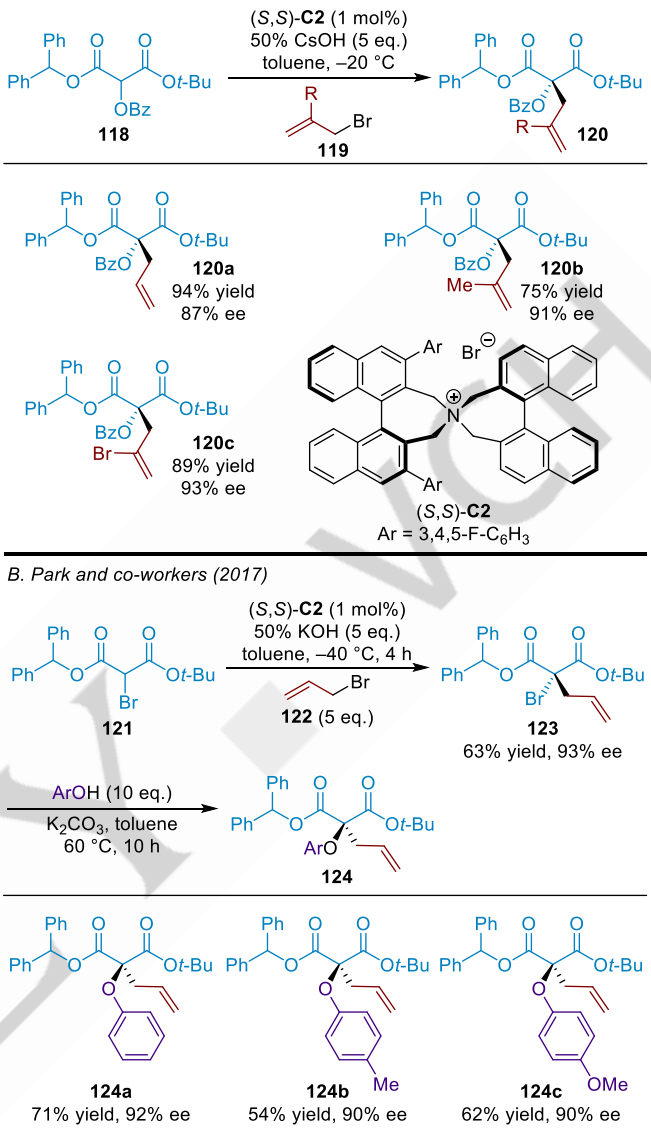
3.6. Phase-Transfer Catalysis

Although metal catalysis dominates the AAA research area, the use of phase transfer catalysts has also found success in AAA reactions in recent years. In this context, Maruoka developed an AAA reaction of linear α-oxy-β-ketoesters **115** using phase transfer catalyst (*S*,*S*)-**C1** (Scheme 25).[40] The reaction was found to give high levels of enantioselectivity for a range of allyl bromides **116**, affording **117a-d** with 83-91% ee. This method was also extended to a range of benzyl and propargyl bromide electrophiles, broadening the synthetic utility of the methodology. In light of the high enantioselectivity, stereoselective enolisation of **115** is likely to have occurred, albeit the stereoselectivity of enolisation or the effect of enolate geometry on the stereochemical outcome of the reaction were not investigated as part of this study.



Scheme 25. The phase-transfer-catalysed AAA reaction of α-oxy β-ketoesters.

More recently, Park and co-workers reported the phase-transfer-catalysed AAA reaction of benzoyl-protected α-oxygenated malonate **118** using chiral ammonium salt (*S*,*S*)-**C2** (A, Scheme 26).[41] The authors used allylic bromides **119** as electrophiles to obtain allylated products **120a-c** with high levels of enantioselectivity. This process was also expanded to benzylation reactions with similarly high levels of stereocontrol. Using this approach, the Park group carried out the phase-transfer-catalysed AAA of α-bromo malonate **121** to give product **123** in 63% yield and 93% ee using chiral catalyst (*S*,*S*)-**C2** (B, Scheme 26).[42] A subsequent S_N2 substitution reaction of **123** with phenols produced a range of α-oxygenated products **124a-c** with near complete retention of enantiopurity.



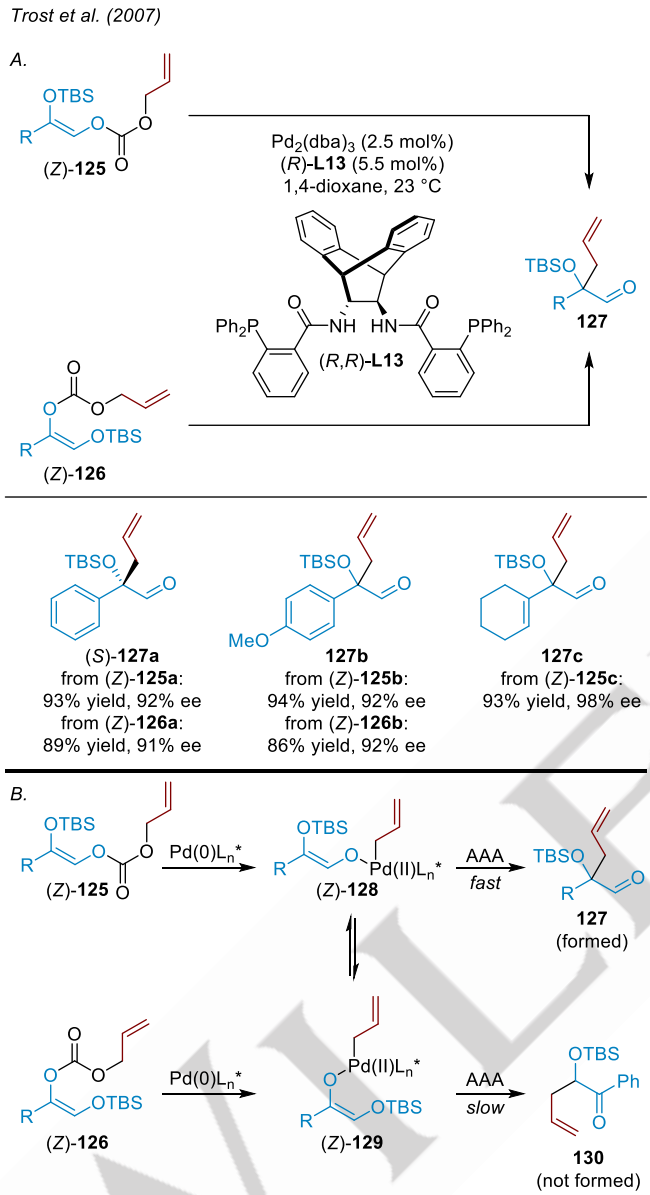
Scheme 26. The phase-transfer-catalysed AAA reaction of α-oxygenated and α-bromomalonates.

4. Aldehyde Enolates

4.1. Palladium Catalysis

In 2007, the Trost group reported the regioconvergent palladium-catalysed DAAA reaction of geometrically pure enol carbonates (*Z*)-**125** and (*Z*)-**126** to give aldehydes **127** with high levels of enantioselectivity (A, Scheme 27).[43] Using ANDEN phenyl Trost ligand (*R*,*R*)-**L13** for palladium, the reaction afforded (*S*)-**127a** in 93% yield and 92% ee from (*Z*)-**125**, and 89% yield and 91% ee from (*Z*)-**126**. The authors successfully isolated a number of α-tetrasubstituted aldehydes by varying the R group in (*Z*)-**125** and (*Z*)-**126**; for example, **127b** was formed in 94% yield and 92% ee from (*Z*)-**125**, and 86% yield and 92% ee from (*Z*)-**126**, whereas 1-cyclohexenyl substituted **127c** was formed in 93% yield and 98% ee from (*Z*)-**125**. Mechanistically, this process involves the rapid exchange between palladium enolate intermediates (*Z*)-**125** and (*Z*)-**126** as a result of the silyl protecting group shift (B, Scheme 27). Palladium enolate (*Z*)-**128** then undergoes allylic

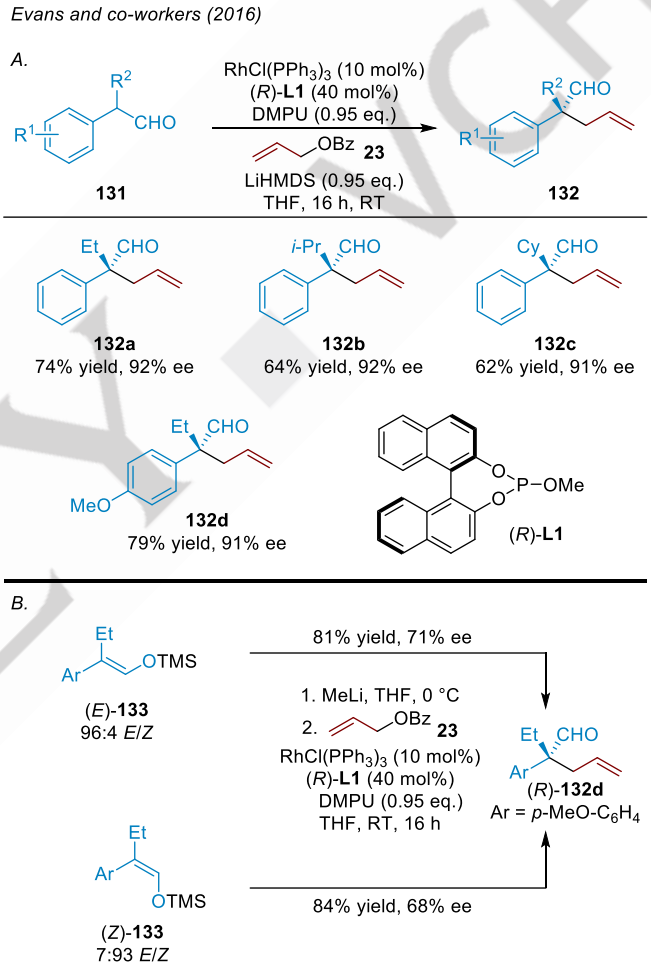
alkylation faster than (*Z*)-**129**, regioselectively affording aldehyde **127** bearing a tetrasubstituted α-stereogenic centre rather than ketone **130**. The *Z*-enolate geometry arises from geometrically pure substrates (*Z*)-**125** and (*Z*)-**126** and is preserved throughout the mechanism.



Scheme 27. The palladium-catalysed DAAA reaction of allyl enol carbonates derived from aldehydes.

4.2. Rhodium Catalysis

In 2016, Evans and co-workers reported the rhodium-catalysed AAA reaction of α-tertiary aldehydes **131** using phosphite ligand (*R*)-**L1** to afford α-quaternary aldehydes **132** (A, Scheme 28).[44] This rhodium-catalysed AAA reaction was shown to be tolerant of bulky alkyl α-substituents, giving **132a-c** in >90% ee. The enantioselectivity was also maintained when testing the electronic environment of the aryl group, affording **132d** with 91% ee. To ascertain the effect of enolate geometry on the reaction outcome, *E*-silyl enol ether (*E*)-**133** was reacted under the optimised conditions and produced (*R*)-**132** in 81% yield and 71% ee (B, Scheme 28). Astonishingly, when *Z*-silyl enol ether (*Z*)-**133** underwent the reaction, the same major enantiomer of **132** was formed in a similar 84% yield and 68% ee. Although the enantioselectivity was lower than the 91% ee observed when the lithium enolate was made with LiHMDS as the base (A, Scheme 28), the fact that the same major enantiomer of product is formed from both (*E*)-**133** or (*Z*)-**133** suggests that the enolate geometry is not important to obtain high enantioselectivity in this case. Further mechanistic investigation is warranted to establish why the *in-situ* deprotonation of aldehyde **131** with a base results in a more stereoselective allylic alkylation than the use of geometrically pure silyl enol ethers (*Z*)-**133** and (*E*)-**133**.

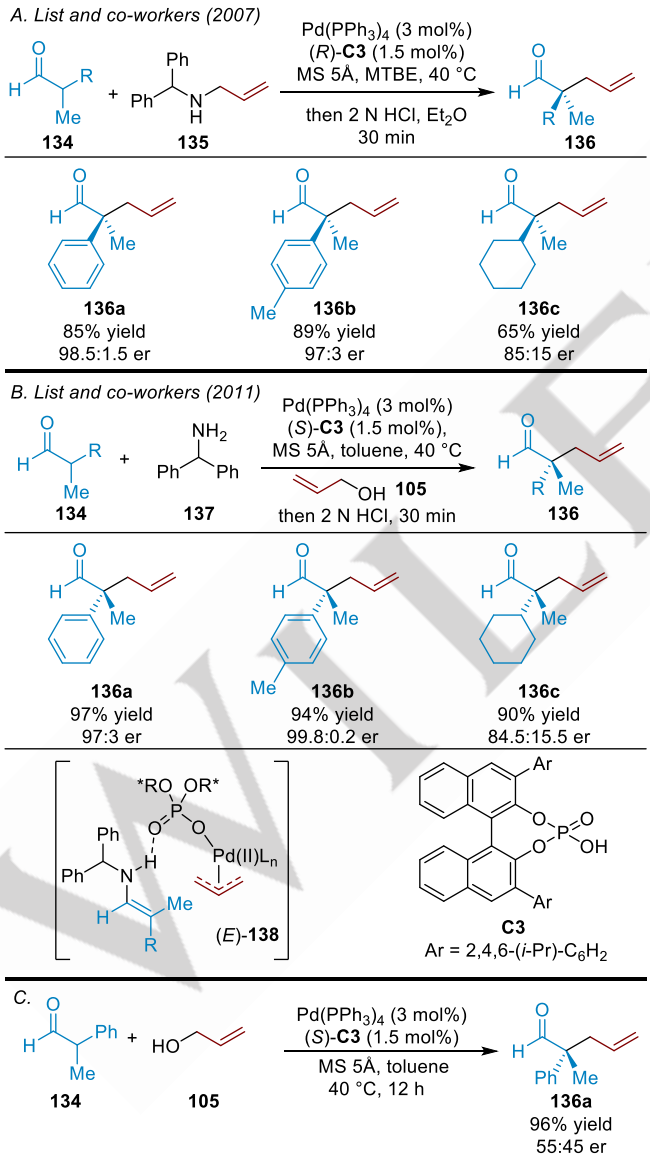


Scheme 28. The rhodium-catalysed AAA of aldehydes.

4.3. Enamine/Palladium Dual Catalysis

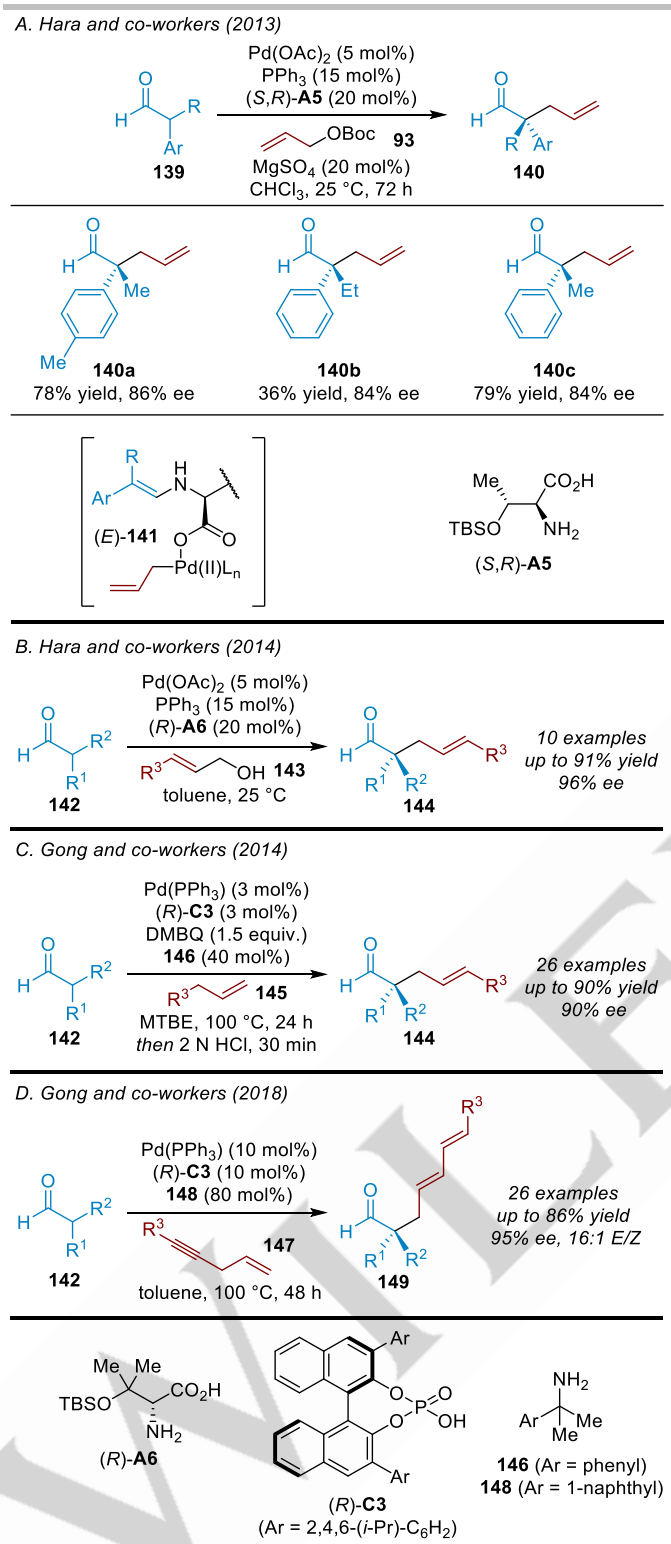
In addition to the AAA of aldehyde enolate intermediates, enamines have also been successfully used in AAA reactions as specific enol equivalents of aldehydes. In 2007, the List group was the first to report the enantioselective synthesis of α-quaternary aldehydes **136** *via* the palladium-catalysed AAA reaction of enamine intermediates (A, Scheme 29).[45] Using aldehydes **134**, allylic amine **135**, chiral phosphoric acid (CPA) catalyst (*R*)-**C3** and an achiral palladium catalyst, excellent enantioselectivity for a range of α-quaternary aldehydes **136a-c** was observed (85:15-98.5:1.5 er). The desired allylic alkylation was enabled by the simultaneous coordination of the CPA catalyst to the π-

allylpalladium(II) intermediate alongside hydrogen bond formation to the enamine in intermediate (*E*)-**138**. The impressive levels of enantioselectivity can be attributed to the selective *E*-enamine formation *in situ*. Subsequently, the same group disclosed the palladium-catalysed AAA reaction of aldehydes **134** using allyl alcohol (**105**) and amine **137** as independent reactants (B, Scheme 29).[46] The reaction was shown to proceed with good to excellent levels of enantioselectivity, forming α-quaternary products **136a**-**136c** with 84:16-99.8:0.2 er, respectively. In contrast, the analogous enolisation of aldehyde **134** in the absence of an amine additive is believed to result in a mixture of *E*/*Z* enols and, thus, low enantioselectivity of alkylation (55:45 er of **136a**) (C, Scheme 29). Bica-Schröder and co-workers also obtained high levels of enantioselectivity in the palladium-catalysed AAA reaction of tertiary aldehydes *via* enamine intermediates, but instead of using an achiral amine and a chiral phosphoric acid catalyst, the authors exploited a chiral amine in the presence of a racemic phosphoric acid.[47]



Scheme 29. The palladium-catalysed AAA of aldehydes *via* enamine intermediates.

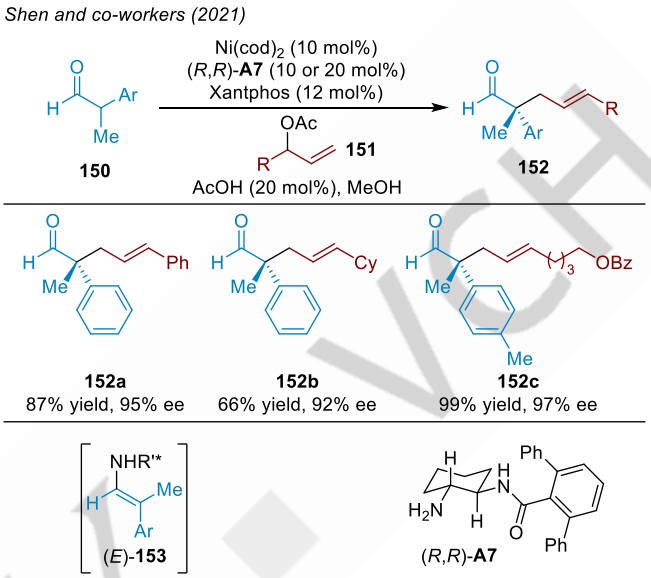
Hara extended the AAA reaction of aldehyde-derived enamines by using chiral amino acid (*S*,*R*)-**A5** in place of a CPA catalyst to both generate the enamine nucleophile and deliver the π-allylpalladium(II) intermediate to one face of the enamine *via* coordination of the palladium centre to the carboxylate anion in (*E*)-**141** (A, Scheme 30).[48] The reaction gave good levels of enantioselectivity, forming α-quaternary aldehyde products **140a-c** with 84-86% ee. In 2014, the same authors reported an analogous chiral amino acid and palladium co-catalysed AAA reaction of aldehydes **142** with substituted allylic alcohols **143** in place of pre-activated carbonate **93**, affording allylated α-quaternary aldehydes **144** with up to 96% ee (B, Scheme 30).[49] In the same year, the Gong group described the palladium-catalysed AAA of aldehydes using unfunctionalised allylic substrates **145**, 2,6-dimethylbenzoquinone (DMBQ) as the oxidant, amine **146** and CPA catalyst (*R*)-**C3** (C, Scheme 30).[50] The authors reported high levels of enantioselectivity of up to 90% ee in the formation of allylated aldehydes **144**. Subsequently, the same group extended this process to the use of allylic alkyne substrates **147** in the palladium-catalysed AAA reaction of aldehydes **142** in the presence of amine **148** and CPA catalyst (*R*)-**C3** (D, Scheme 30).[51] Aldehyde products **149** were formed with up to 95% ee and 16:1 *E*/*Z* ratio. During the preparation of this review, Córdova and co-workers also disclosed the palladium (and iridium) catalysed AAA reaction of aldehyde-containing sugars with allylic electrophiles *via* chiral enamine intermediates derived from Jørgensen–Hayashi prolinol-type catalysts.[52]



Scheme 30. Examples of palladium-catalysed AAA reaction of aldehydes *via* enamine activation.

4.4. Enamine/Nickel Dual Catalysis

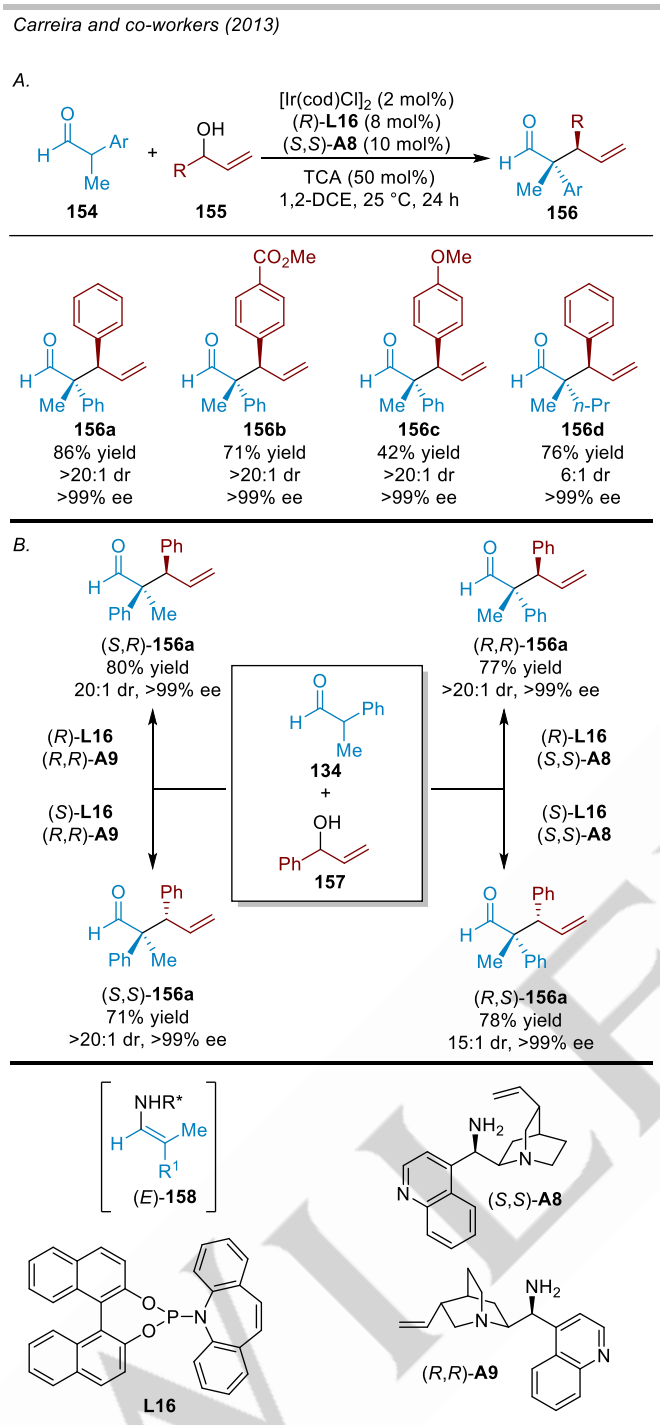
In 2021, Shen and co-workers reported the enamine/nickel dual-catalysed AAA reaction of aldehydes **150** in the presence of chiral amine (*R*,*R*)-**A7** (Scheme 31).[53] Chiral enamine intermediate (*E*)-**153** is formed *in situ*, which undergoes allylic alkylation with the π-allylnickel(II) intermediate to afford α-quaternary aldehydes **152**. The implication of enamine (*E*)-**153** in the reaction was proved by mass spectrometry. The reaction was highly enantioselective for a variety of aldehydes **150** and allylic acetates **151**, giving **152a-c** with >90% ee. High levels of stereocontrol are believed to arise directly from enamine intermediate (*E*)-**153** stereoselectively adopting the *E*-geometry.



Scheme 31. The nickel-catalysed AAA of aldehydes *via* enamine intermediates.

4.5. Enamine/Iridium Dual Catalysis

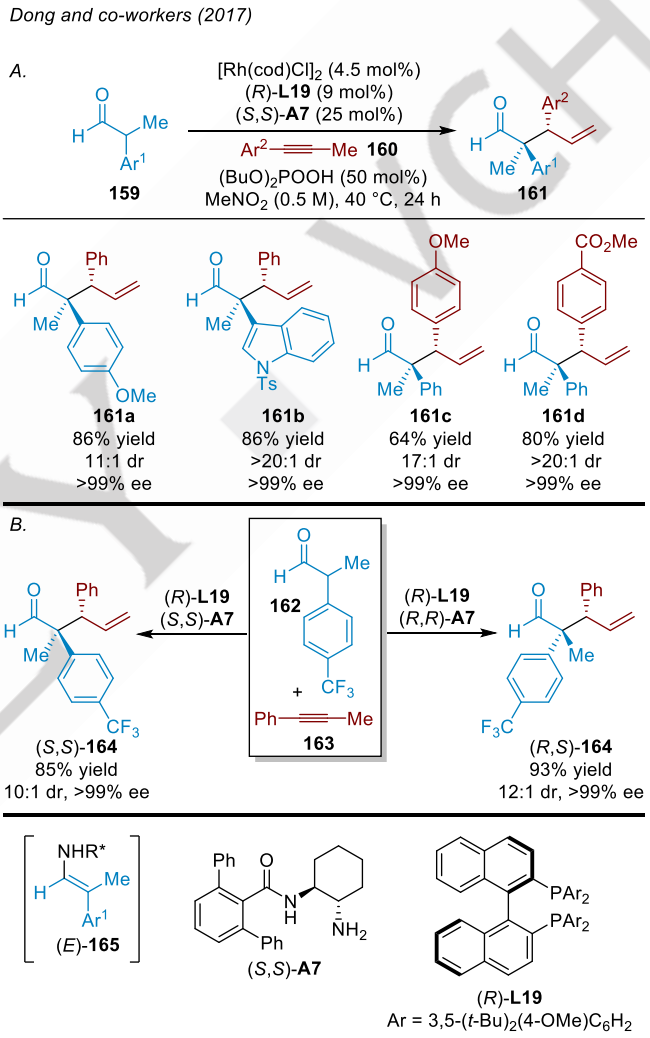
In 2013, Carreira and co-workers reported the dual iridium/chiral amine catalysed AAA reaction of α-branched aldehydes **154** with substituted allylic alcohols **155** to install two vicinal stereogenic centres in **156** with excellent levels of diastereo- and enantioselectivity using chiral ligand (*R*)-**L16** for iridium and chiral amine catalyst (*S*,*S*)-**A8** (A, Scheme 32).[54] A range of allylic electrophiles were used, giving **156a-c** with >20:1 dr and >99% ee. When both aldehyde α-substituents were alkyl groups, **156d** was formed with lower diastereoselectivity (6:1 dr), albeit the major diastereoisomer was isolated as a single enantiomer. The authors also demonstrated the stereodivergent nature of the process by accessing all four stereoisomers of **156a** with high levels of diastereo- and enantioselectivity when carrying out the AAA reaction of aldehyde substrate **134** with allylic electrophile **157** and combinations of ligand (*R*)-**L16** or (*S*)-**L16** for iridium alongside chiral amine (*S*,*S*)-**A8** or (*R*,*R*)-**A9** (B, Scheme 32). Consistent with previous reports, it is likely that selective formation of the *E*-enamine geometry in (*E*)-**158** allows for the observed excellent stereoselectivity of allylation. Synergistic iridium and enamine catalysis was subsequently exploited by Xiao and co-workers in formal asymmetric [4+2] cycloaddition reactions of aldehydes with vinyl aminoalcohols.[55]



Scheme 32. The dual iridium/chiral amine catalysed AAA reaction of aldehydes with substituted allylic alcohols.

4.6. Enamine/Rhodium Dual Catalysis

In 2017, the group led by Dong carried out the analogous rhodium/chiral amine-catalysed AAA reaction of aldehydes **159**, using alkynes **160** as electrophiles (A, Scheme 33).[56] The π-allylrhodium(III) intermediate is first generated from alkyne **160** *via* isomerisation and hydrometallation (*vide supra*, Scheme 8). The chiral enamine intermediate (*E*)-**165** then undergoes allylic alkylation at the more substituted position of the π-allylrhodium(III) electrophile, affording α-allylated aldehyde products **161** bearing adjacent α-quaternary and β-tertiary stereogenic centres. Indeed, excellent diastereo- and enantioselectivity was obtained for **161a-d** from a range of aldehyde and alkyne substrates **159** and **160**, respectively. The authors were also able to access both diastereoisomers (*S*,*S*)-**164** (10:1 dr and >99% ee) and (*R*,*S*)-**164** (12:1 dr, and >99% ee) when using chiral amine (*S*,*S*)-**A7** and (*R*,*R*)-**A7**, respectively (B, Scheme 33). The high levels of stereoselectivity observed in this process require the control of prochiral nucleophile geometry, likely resulting from the propensity of enamines to selectively form the *E*-isomer of **165**.



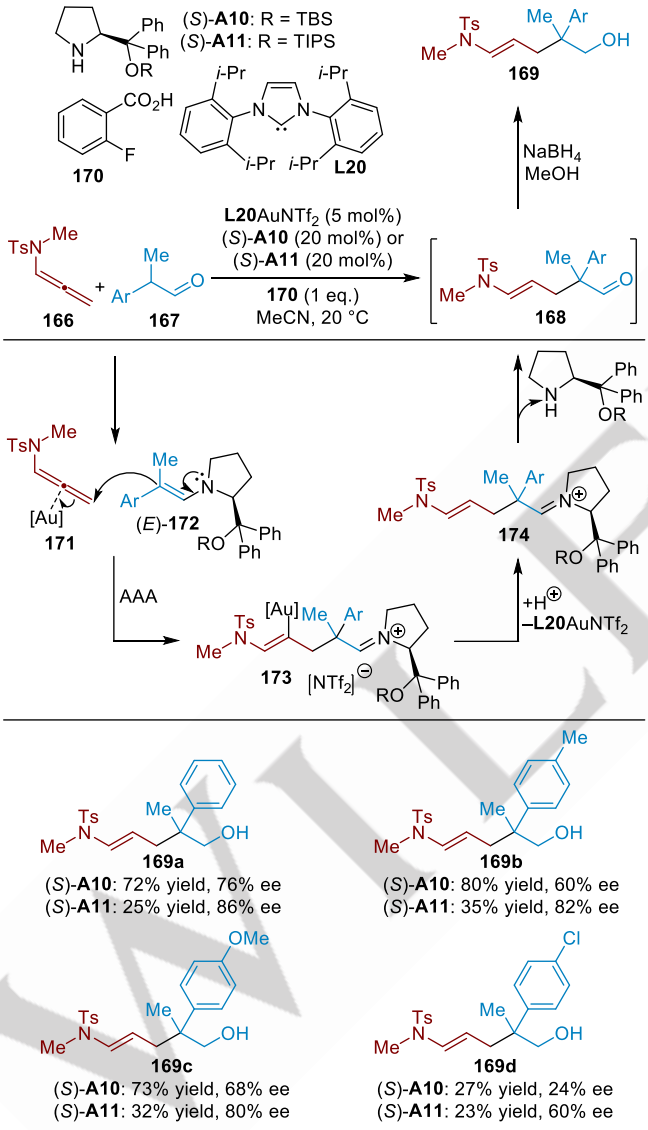
Scheme 33. The rhodium-catalysed AAA reaction of aldehydes *via* enamine activation.

4.7. Enamine/Gold Dual Catalysis

The González group was the first to describe a gold/chiral amine dual-catalysed AAA reaction of aldehydes **167** with allenamides **166** (Scheme 34).[57] Aldehyde products **168** were subsequently reduced to give chiral alcohols **169**. The authors proposed that the mechanism proceeded *via* the AAA of enamine (*E*)-**172**, generated from aldehyde **167** and Jørgensen-Hayashi catalyst (*S*)-**A10** or (*S*)-**A11**, with gold-activated allenamide electrophile **171** to give intermediate **173**. Benzoic acid **170** then facilitates the formation of iminium ion **174** by means of protodeauration, reforming the gold catalyst. Finally, hydrolysis of **174** gives α-

quaternary aldehyde **168** and regenerates the amine catalyst. Using chiral amine (*S*)-**A10**, products **169a-d** were formed in 27-80% yield and 24-73% ee. The use of chiral amine (*S*)-**A11** in the reaction improved the enantioselectivity; however, the reaction efficiency was significantly reduced, giving **169a-d** in 25-35% yield and 60-86% ee. Enamine **172** likely adopts the *E*-geometry in the s-*trans* conformation as is common in organocatalytic enamine activation with prolinol-derived catalysts.[58] Although the absolute configuration of the new quaternary centre in **169** was not established, facial selectivity of allylation presumably arises from the steric effects of the prolinol substituent blocking one of the faces of enamine (*E*)-**172**.

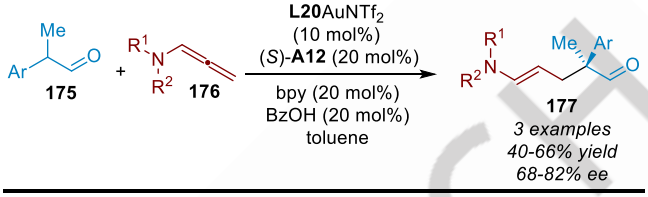
González and co-workers (2016)



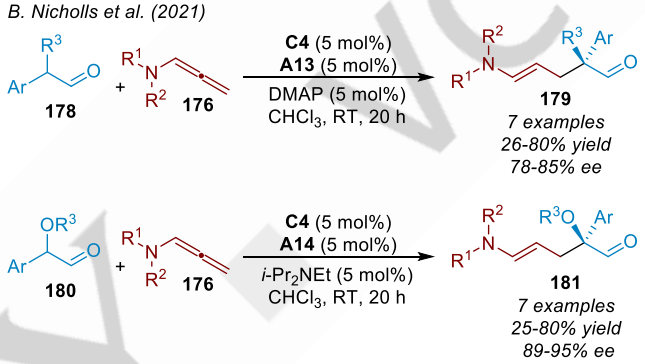
Scheme 34. The enamine/gold dual-catalysed AAA reaction of aldehydes using a chiral amine co-catalyst.

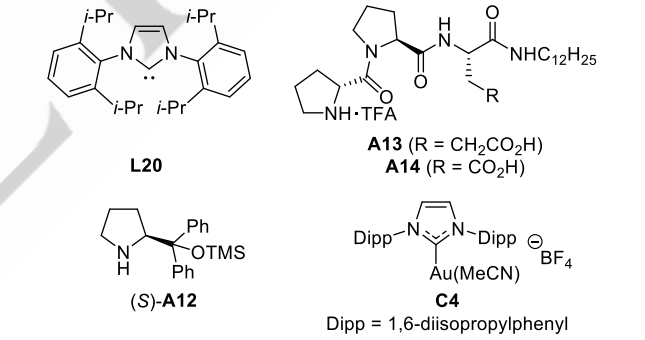
In the same year, Fernández-Casado *et al*. carried out the analogous gold-catalysed AAA reaction of aldehydes **175** using allenamides **176** in the presence of TMS-protected prolinol catalyst (*S*)-**A12** (A, Scheme 35).[59] The reaction afforded three examples of products **177** with 68-82% ee, presumably *via* the analogous *E*-enamine intermediate. Subsequently, Nicholls *et al*. were able to access a number of products **179** and **181** using the gold-catalysed AAA reaction of α-branched aldehydes **178** and **180** in the presence of chiral peptide catalysts **A13** and **A14**, respectively (B, Scheme 35).[60] α-Quaternary aldehydes **179** were formed in 26-80% yield and 78-85% ee, and α-oxy aldehydes **181** were generated in 25-80% yield and 89-95% ee.

A. Fernández-Casado et al. (2016)



B. Nicholls et al. (2021)

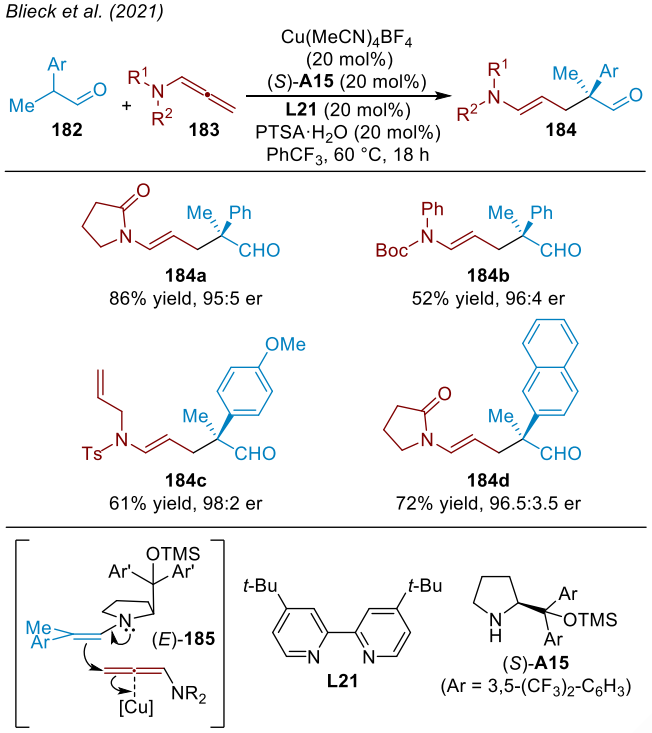




Scheme 35. Examples of the gold-catalysed AAA reaction of aldehydes using allenamide electrophiles

4.8. Enamine/Copper Dual Catalysis

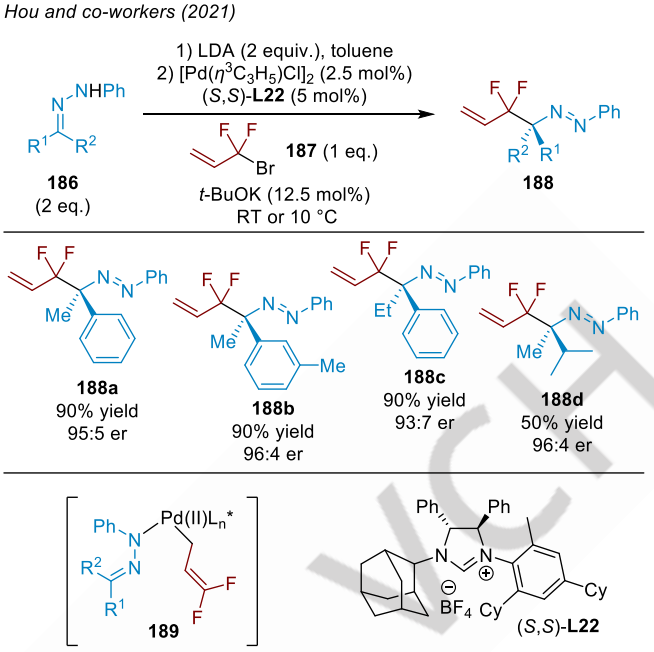
In 2021, Blieck *et al*. developed the analogous copper-catalysed AAA reaction of aldehydes **182** with allenamides **183** in the presence of chiral amine co-catalyst **A15** (Scheme 36).[61] By varying the α-aryl substituent of the aldehyde substrate (**182**) and the functionality at *N*-allene **183**, a number of products **184a-d** were formed with high levels of enantioselectivity (95:5 to 98:2 er). It was suggested that the prolinol substituent blocks the top face of *E*-enamine (*E*)-**185**, resulting in the observed facial selectivity of alkylation of the copper activated allene electrophile.



Scheme 36. Dual enamine-copper catalysed AAA reaction of aldehydes.

5. The AAA Reaction of Hydrazones

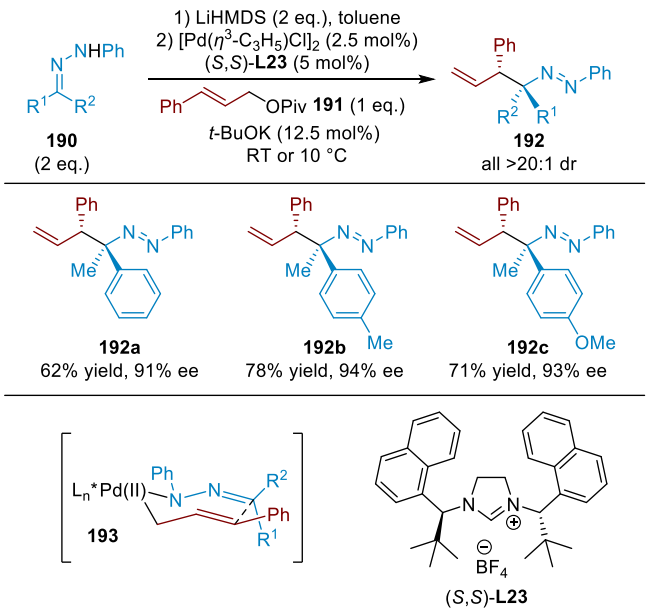
Anions of hydrazones, which structurally resemble enamines, have also been successfully utilised in AAA reactions using substituted allylic electrophiles. In this context, in 2021, Hou realised the palladium-catalysed AAA reaction of hydrazones **186** with fluorinated allyl electrophile **187** to give α-tetrasubstituted azo compounds **188** with high levels of enantioselectivity (Scheme 37).[62] In this process, LDA was used as the base to make the anion of hydrazone **186** alongside *N*-heterocyclic carbene (NHC) ligand (*S*,*S*)-**L22** for palladium. The reaction proceeded well for a range of aryl substituents (R^1), giving **188a** and **188b** with 95:5 and 96:4 er, respectively. A larger ethyl group in place of the methyl substituent (R^2) slightly increased the enantioselectivity, yielding **188c** with 93:7 er. Substrates bearing two aliphatic substituents were also successful (96:4 er for **188d**). Mechanistic experiments led the authors to propose an inner-sphere alkylation mechanism that proceeds *via* *N*-bound σ-allylpalladium(II) intermediate **189**. The use of geometrically pure hydrazones ensured high levels of stereocontrol in the formation of the α-tetrasubstituted stereogenic centre in **188**.



Scheme 37. The palladium-catalysed AAA reaction of hydrazones.

The following year, Hou developed a synthesis of azo compounds **192** with high levels of enantioselectivity by means of a palladium-catalysed AAA reaction of hydrazones **190** with substituted electrophile **191**, LiHMDS as the base and (*S*,*S*)-**L23** as the NHC ligand for palladium (Scheme 38).[63] The enantioselectivity of the reaction was found to be excellent for a variety of aryl substituents (R^2) on **190**, giving **192a-c** with complete diastereoselectivity and 91-94% ee. The yields ranged from moderate to good as a result of competing *N*-alkylation, as well as *C*-alkylation at the less substituted position of the electrophile, giving rise to unwanted side-products. In an analogous manner, by carrying out a comprehensive mechanistic study, the authors proposed that an inner-sphere alkylation mechanism was taking place *via* *N*-bound σ-allylpalladium(II) intermediate **193**. Given that the prochiral nucleophile has a pre-set C=N geometry, high enantioselectivity of allylic alkylation is observed.

Hou and co-workers (2022)



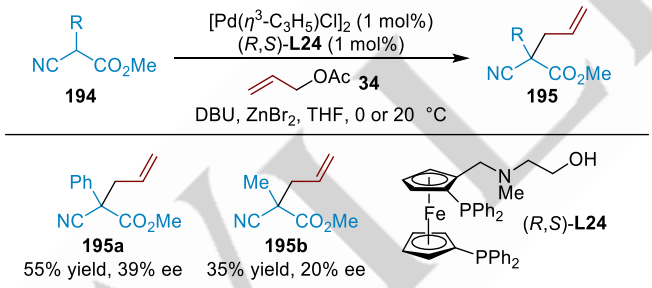
Scheme 38. The palladium-catalysed AAA of hydrazones.

6. The AAA Reaction of Ketones and Esters

6.1. Palladium Catalysis

In 1987, Ito *et al*. reported the first palladium-catalysed AAA reaction of α-cyanoesters **194** using chiral ferrocene-based ligand (*R*,*S*)-**L24** (Scheme 39).[64] Following optimisation of the reaction conditions, the authors reported low enantioselectivity of 39% and 20% ee for **195a** and **195b**, respectively.

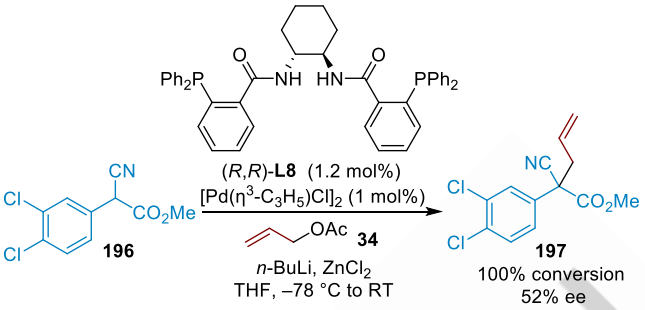
Ito et al. (1987)



Scheme 39. The first palladium-catalysed AAA reaction of α-cyanoesters.

In 2005, the group led by Agbossou-Niedercorn attempted the palladium-catalysed AAA of cyanoester substrate **196** in the presence of (*R*,*R*)-DACH phenyl Trost ligand (*S*,*S*)-**L8** (Scheme 40);[65] however, the authors observed only moderate enantioselectivity (52% ee) in the formation of **197**. This result highlighted the challenges in obtaining high levels of enantioselectivity in the allylation of α-quaternary cyanoesters using palladium-catalysed AAA methodology, where the difficulties associated with stereocontrolled enolisation may be partly to blame.

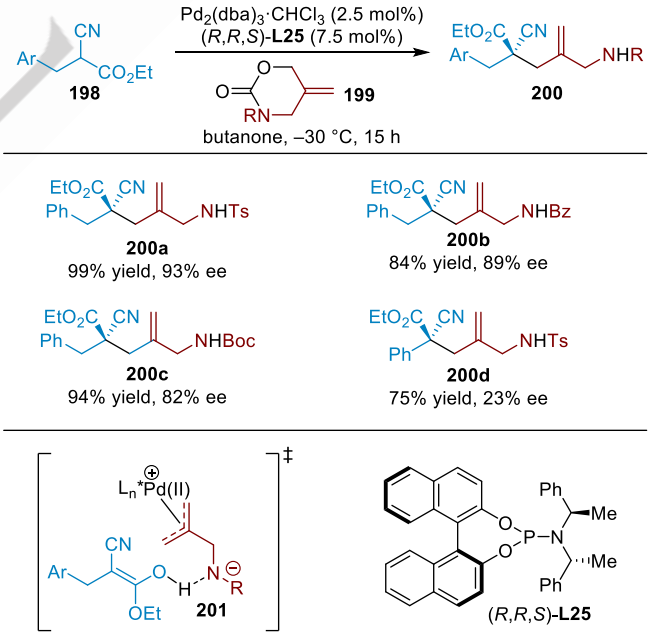
Agbossou-Niedercorn and co-workers (2005)



Scheme 40. The palladium-catalysed AAA of a cyanoester substrate.

More recently, in 2023, Bao *et al*. overcame these challenges and described the palladium-catalysed AAA reaction of α-benzyl α-cyanoesters **198** with cyclic allylic carbamates **199** (Scheme 41).[66] The authors reported high levels of enantioselectivity in the reaction, generating products **200a-c** with 82-93% ee. Nevertheless, when using the analogous α-phenyl α-cyanoester substrate, the reaction gave **200d** with a dramatically reduced 23% ee. The authors suggested that the reaction proceeds through transition state **201** whereby a hydrogen-bonding interaction between the OH of the enol and the nitrogen anion of the zwitterionic aza-π-allylpalladium(II) electrophile in **201** plays an important role in the enantioselectivity of the reaction. Although a single enol isomer in **201** is likely to be formed stereoselectively, further studies are required to ascertain whether the *Z*- or *E*-enol is involved in this reaction.

Bao et al. (2023)

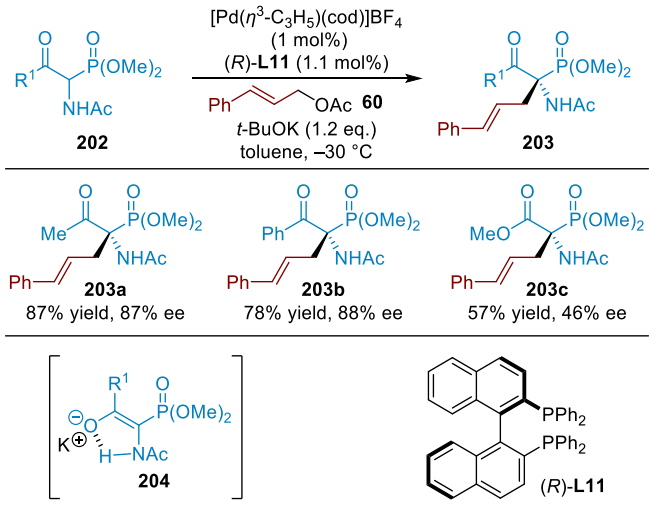


Scheme 41. The palladium-catalysed AAA reaction of α-benzyl α-cyanoesters.

Ito has described the AAA reaction of α-acetamido α-phosphono ketones **202** with allyl acetate **60** (Scheme 42).[67] The reaction gave products **203a** and **203b** with high enantioselectivity (87% and 88% ee, respectively). The enantioselectivity of the AAA reaction of the equivalent α-phosphono ester substrate (R^1 = OMe) was dramatically lower, giving **203c** with 46% ee. The α-

acetamido substituent is believed to be essential in the selective formation of enolate **204** that is stabilised by intramolecular hydrogen-bonding.

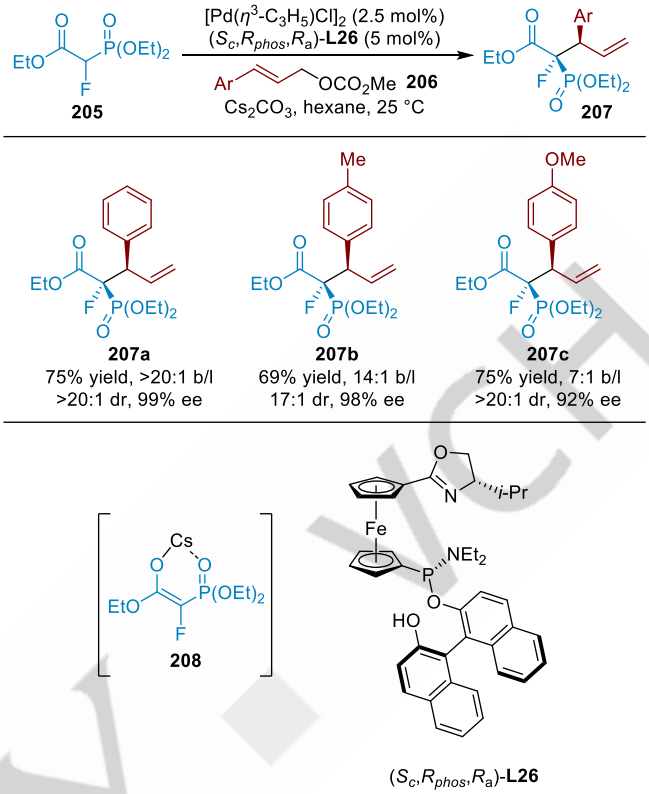
Ito and co-workers (1999)



Scheme 42. The palladium-catalysed AAA reaction of α-acetamido α-phosphonoketones.

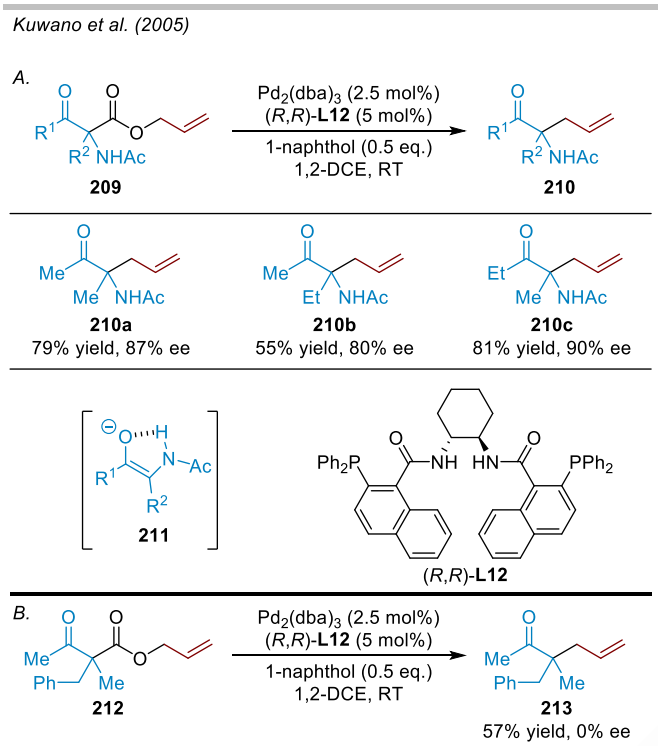
Huang *et al*. developed a palladium-catalysed AAA reaction of α-fluoro α-phosphonoesters **205** with substituted allylic electrophiles **206** in the presence of chiral ligand (S_c,R_{phos},R_a)-**L26** for palladium (Scheme 43).[68] The reaction proceeded with good to high levels of branched to linear selectivity, as well as excellent diastereo- and enantioselectivity for a number of examples (**207a-c**). Despite the lack of an α-acetamido group, present in the substrates utilised by Ito (*vide supra*, Scheme 42), the high levels of stereoselectivity observed in this process indicate excellent stereocontrol in the enolisation step, potentially resulting in chelated caesium enolate intermediate **208**, analogous to chelation in enolates of 1,3-dicarbonyls (*vide supra*, Section 3). The regioselectivity of allylic alkylation at the more substituted position is unusual for palladium catalysis that predominantly favours addition at the less hindered terminus of π-allylpalladium(II) electrophiles. The ferrocene-based ligand (S_c,R_{phos},R_a)-**L26** for palladium may play a role in this rare case of regioselectivity.

Huang et al. (2014)



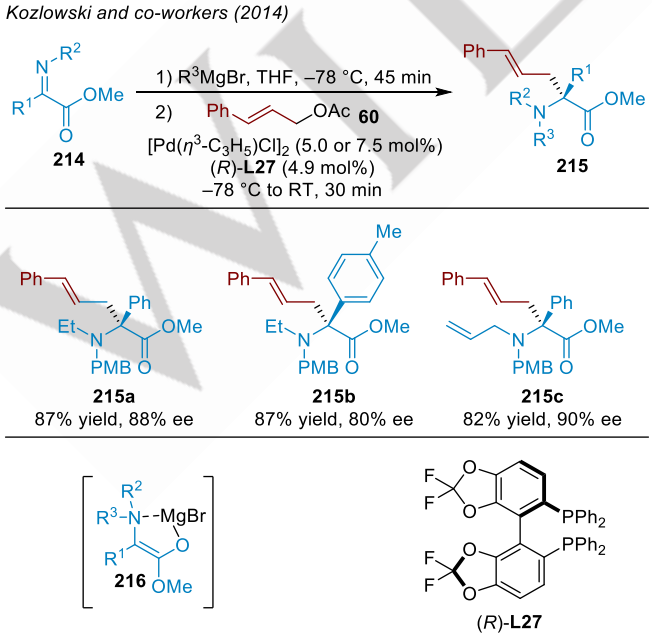
Scheme 43. The palladium-catalysed AAA of α-fluorophosphonates.

In 2005, Kuwano *et al*. reported the palladium-catalysed DAAA reaction of α-acetamido β-ketoesters **209** in the presence of (*R*,*R*)-DACH naphthyl Trost ligand (*R*,*R*)-**L12**, which enabled the installation of a tetrasubstituted α-stereogenic centre in **210a** with 87% ee (A, Scheme 44).[69] In an attempt to expand the reaction scope, the enantioselectivity was found to be lower with increasing steric bulk of the α-substituent, forming **210b** with 80% ee. Replacing the methyl ketone with an ethyl ketone in **210c** maintained the enantioselectivity (90% ee). In this process, a 1-naphthol additive was essential to achieve high levels of stereocontrol. It is likely that, similar to the AAA reaction of α-acetamido 1,3-dicarbonyls (*vide supra*, Scheme 12), and α-acetamido α-phosphono ketones (*vide supra*, Scheme 42), the acetamide substituent in **209** ensures the stereoselective formation of enolate **211**, enabling an enantioselective allylic alkylation. Indeed, when the reaction was carried out with the analogous substrate **212** lacking an α-acetamido group, ketone **213** was isolated in racemic form (B, Scheme 44).



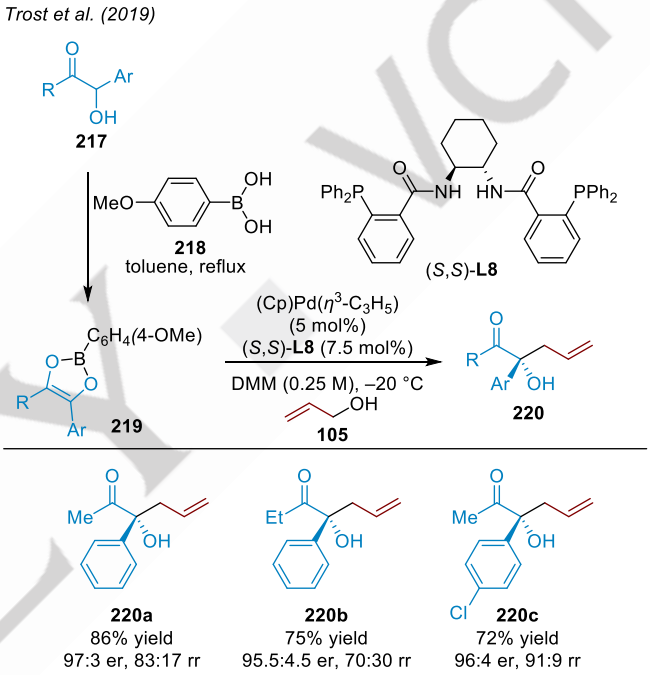
Scheme 44. The palladium-catalysed DAAA reaction of α-acetamido β-ketoesters.

In 2014, Kozlowski and co-workers described the palladium-catalysed AAA reaction of ketiminoesters **214** using a two-stage process (Scheme 45).[70] The reaction commences with an *N*-alkylation of **214** with a Grignard reagent, affording chelated enolate intermediate **216**, which then reacts with the π-allylpalladium(II) electrophile. This process gave high levels of enantioselectivity for a range of aryl substituents on **60**, forming **215a** and **215b** with 88% and 80% ee, respectively. The use of allylmagnesium bromide in place of ethylmagnesium bromide generated **215c** with 90% ee.



Scheme 45. The palladium-catalysed AAA reaction of ketiminoesters.

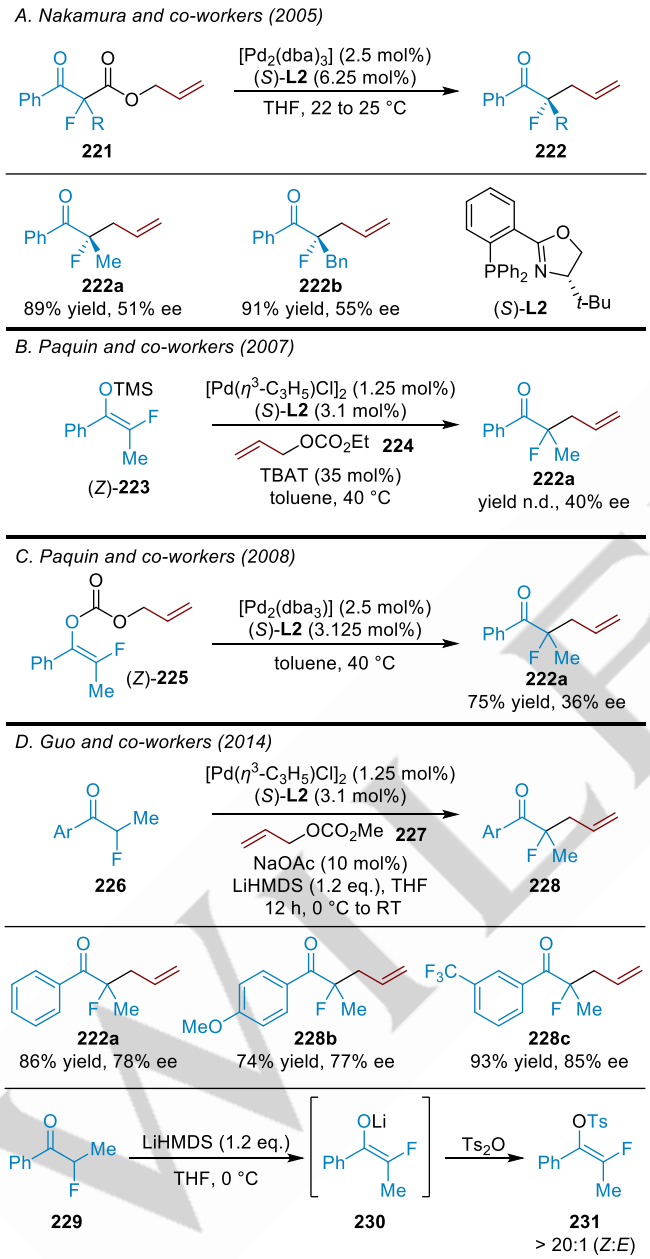
Trost *et al*. reported the palladium-catalysed AAA reaction of α-hydroxy ketones **217** using boronic acid **218** as the additive (Scheme 46).[71] The cyclic nature of 1,3-dioxaborole **219** ensures the formation of a *Z*-enolate. The palladium-catalysed AAA reaction of **219** then generates allylated α-hydroxy ketone products **220**. Although this methodology enables fully stereocontrolled enolisation, there are now two potential sites for alkylation in **219**, thus, requiring a regioselective reaction. The authors reported high enantioselectivity for a number of substrates, such as **220a-c**, which were formed with 95.5:4.5 to 97:3 er. The regioselectivity of the reaction, however, was found to be more variable.



Scheme 46. The palladium-catalysed AAA of 1,3-dioxaboroles.

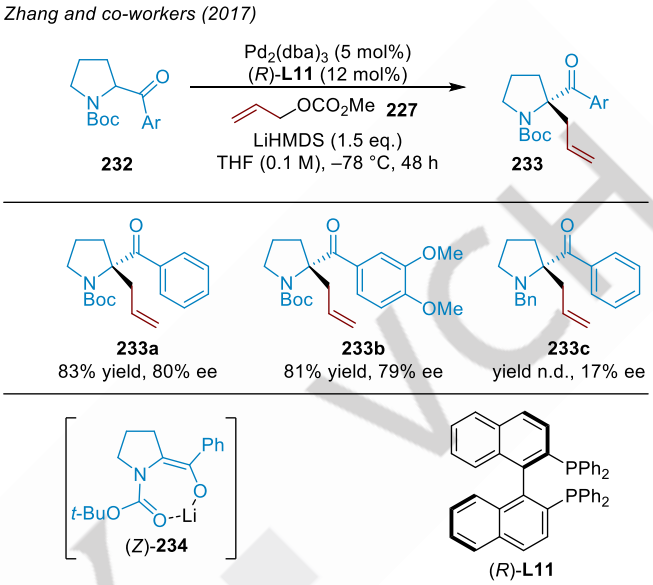
In the 2000s, efforts to develop a palladium-catalysed AAA reaction for the formation of simple, linear α-fluoroketones were met with low to moderate enantioselectivity. In 2005, Nakamura utilised the decarboxylative strategy using α-fluoro β-keto allyl esters **221** as substrates in the presence of PHOX ligand (*S*,*S*)-**L2**, and products **222a** and **222b** were formed with 51% and 55% ee, respectively (A, Scheme 47).[72] The group led by Paquin attempted the palladium-catalysed AAA reaction of geometrically pure *Z*-silyl enol ether (*Z*)-**223** (B, Scheme 47),[73] as well as the palladium-catalysed DAAA reaction of geometrically pure *Z*-enol carbonate (*Z*)-**225** (C, Scheme 47).[74] In both cases, the enantioselectivity was relatively low, giving **222a** in 40% ee from (*Z*)-**223** and 36% ee from (*Z*)-**225**. Given that it is likely that in both cases a *Z*-configured enolate would be generated in geometrically pure form, the allylic alkylation step itself is not particularly enantioselective under the conditions described. In 2014, Guo and co-workers reported the synthesis of α-tetrasubstituted α-fluoro ketones **228** from lithium enolates of **226** in the palladium-catalysed AAA reaction with much higher enantioselectivity despite using the same PHOX ligand (*S*)-**L2** (D, Scheme 47).[75] Specifically, the lithium enolate was formed from **226** with LiHMDS as the base, and the AAA reaction thereof gave products

222a, **228b** and **228c** with good to high levels of enantioselectivity (77-85% ee). The cause for the higher levels of enantioselectivity was investigated by trapping lithium enolate **230**, formed from ketone **229** *in situ*, with *p*-toluenesufonic anhydride. Indeed, excellent stereoselectivity in the enolate formation step was observed, resulting in a >20:1 *Z*/*E* ratio of **231**. In contrast to the work by Paquin, where the use of geometrically pure enol equivalents gave lower enantioselectivity, the use of a lithium enolate specifically appears to exert a positive impact on the stereoselectivity of allylation in this case.



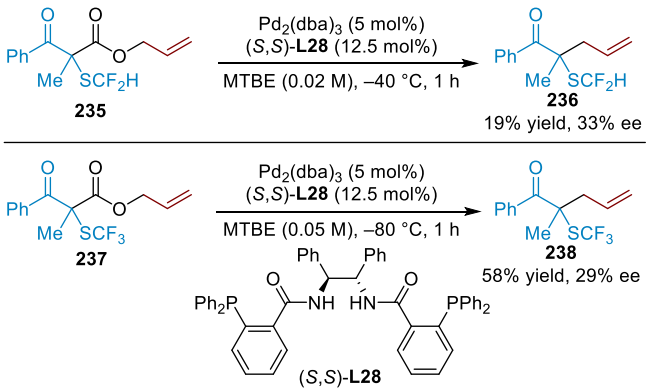
Scheme 47. The palladium-catalysed AAA and DAAA reaction of α-fluoroketones.

In 2017, Zhang and co-workers described the palladium-catalysed AAA reaction of α-pyrrolidinyl ketones **232** (Scheme 48).[76] The authors showed that, at low temperatures (–78 °C), good levels of enantioselectivity could be obtained for a number of aryl ketones, such as **233a** (80% ee) and **233b** (79% ee). The use of a benzyl-protected substrate resulted in the formation of **233c** with diminished enantioselectivity (17% ee). It was proposed that controlled enolisation arises from the chelation of the Boc protecting group to the lithium enolate in (*Z*)-**234**, thus also explaining the poor selectivity seen in the formation of **233c**.



Scheme 48. The palladium-catalysed AAA of α-pyrrolidinyl ketones.

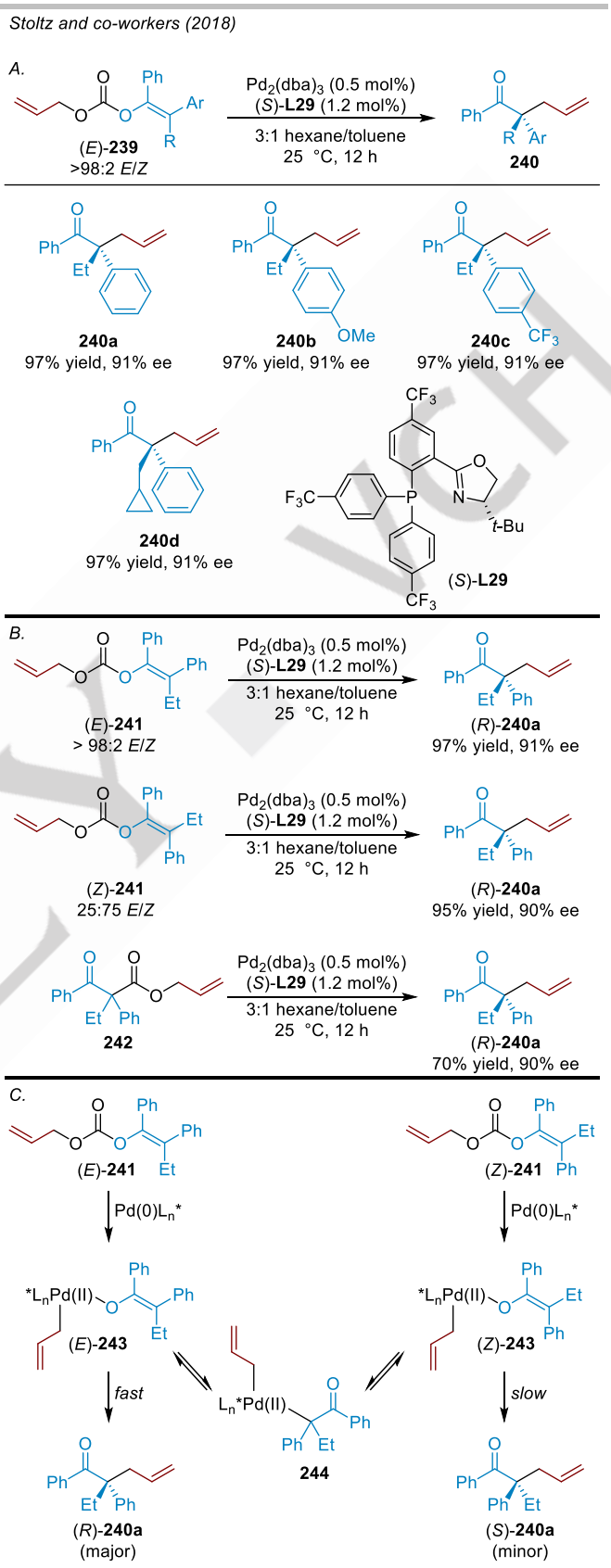
In 2018, Kondo *et al*. reported the asymmetric synthesis of α-tetrasubstituted α-difluoromethylthioether ketone **236** and α-trifluoromethylthioether ketone **238** using the palladium-catalysed DAAA reaction of β-keto allyl esters **235** and **237**, respectively in the presence of Trost ligand (*S*,*S*)-**L28** (Scheme 49),[77] albeit the enantioselectivity was low (33% and 29% ee, respectively). It was suggested that the lower reaction efficiency was a result of the increased steric hindrance associated with the formation of the tetrasubstituted carbon centre, whereas low levels of enantioselectivity were derived from poor stereocontrol of *in situ* enolate formation.



Scheme 49. The palladium-catalysed DAAA of α-thioether ketones.

Within the same year, Stoltz and co-workers developed the palladium-DAAA reaction of geometrically pure ketone-derived *E*-allyl enol carbonates (*E*)-**239** using electron-deficient PHOX ligand (*S*)-**L29** (A, Scheme 50).[78] The reaction showed excellent enantioselectivity for a range of substrates, installing an α-

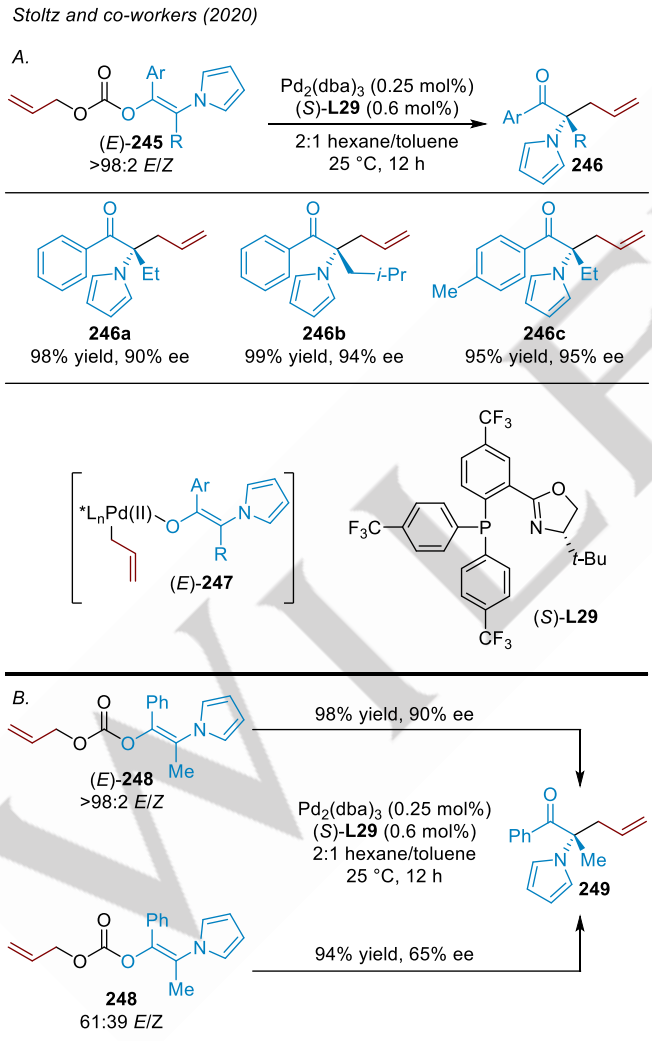
quaternary centre in **240a-d** with 91% ee. In addition, the outcome of the palladium-catalysed DAAA reaction of *Z*-allyl enol carbonate (*Z*)-**241** was compared to that of (*E*)-**241** (B, Scheme 50). Remarkably, both (*E*)-**241** and (*Z*)-**241** gave the same major enantiomer of **240a** with high ee. Furthermore, the reaction of racemic β-keto allyl ester **242** under the same conditions also afforded (*R*)-**240a** as the major enantiomer in 90% ee. It was postulated that *E*- and *Z*-enolate intermediates (*E*)-**243** and (*Z*)-**243** readily interconvert *via* a *C*-bound palladium enolate **244**, and that one enolate reacts faster in the allylic alkylation step than the other (C, Scheme 50). The resulting dynamic kinetic resolution of palladium enolates paves the way to high levels of enantioselectivity in the formation of (*R*)-**240a** irrespective of the initial geometry of the enolate following decarboxylation.



Scheme 50. The palladium-catalysed DAAA reaction of ketone-derived *E*-allyl enol carbonates.

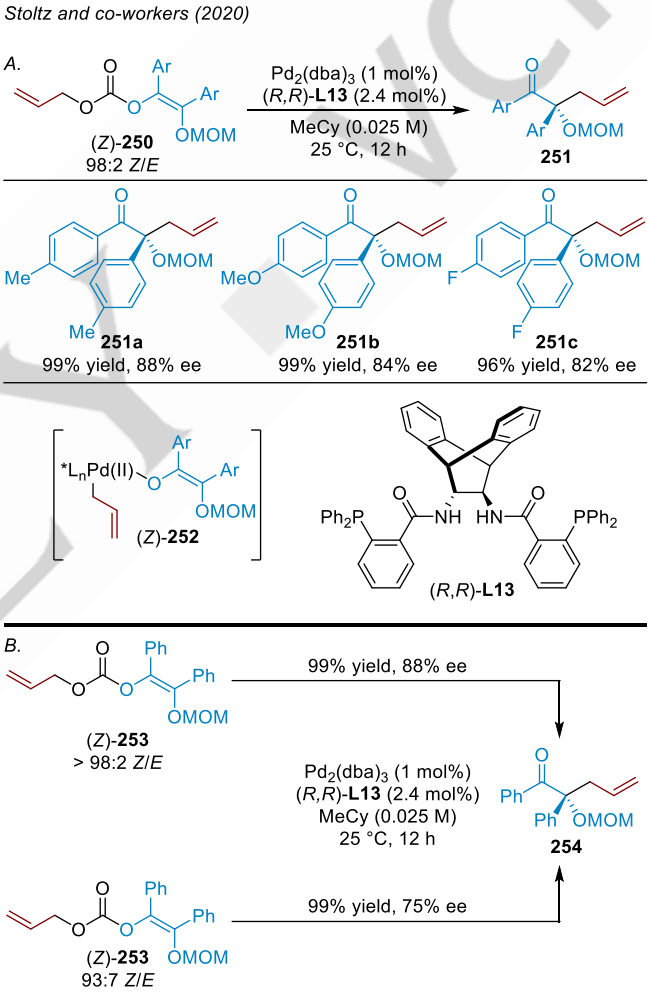
In 2020, Stoltz and co-workers developed a highly stereoselective synthesis of *N*-pyrrolyl-substituted *E*-allyl enol carbonates (*E*)-**245**

from retrospective ketones with >98:2 *E*/*Z* selectivity, thus avoiding any chromatographic separation (A, Scheme 51).[79] *E*-Enol carbonates (*E*)-**245** were then used in the palladium-catalysed DAAA reaction in the presence of chiral ligand (*S*)-**L29**. Indeed, given that geometrically pure enol carbonates (*E*)-**245** give rise to geometrically pure enolates (*E*)-**247** upon decarboxylation, the authors observed high to excellent enantioselectivities for a number of α-pyrrolyl ketone products **246a-c** (90-95% ee). Furthermore, the authors carried out two palladium-catalysed DAAA experiments with either geometrically pure (*E*)-**248** (>98:2 *E*/*Z*) or a 61:39 *E*/*Z* mixture of **248**, which gave ketone **249** in 90% ee and 65% ee, respectively (B, Scheme 51). These results demonstrated the importance of allyl enol carbonate purity to achieve high levels of enantioselectivity in this reaction, suggesting that allylic alkylation occurs faster than the potential interconversion of enolate intermediates. This observation is in stark contrast to that seen for acyclic ketones **241** (*vide supra*, Scheme 50), where the enolate geometry was inconsequential for obtaining high levels of enantioselectivity as a result of a dynamic kinetic resolution.



Scheme 51. The palladium-catalysed DAAA reaction of allyl enol carbonates of α-pyrrolyl ketones.

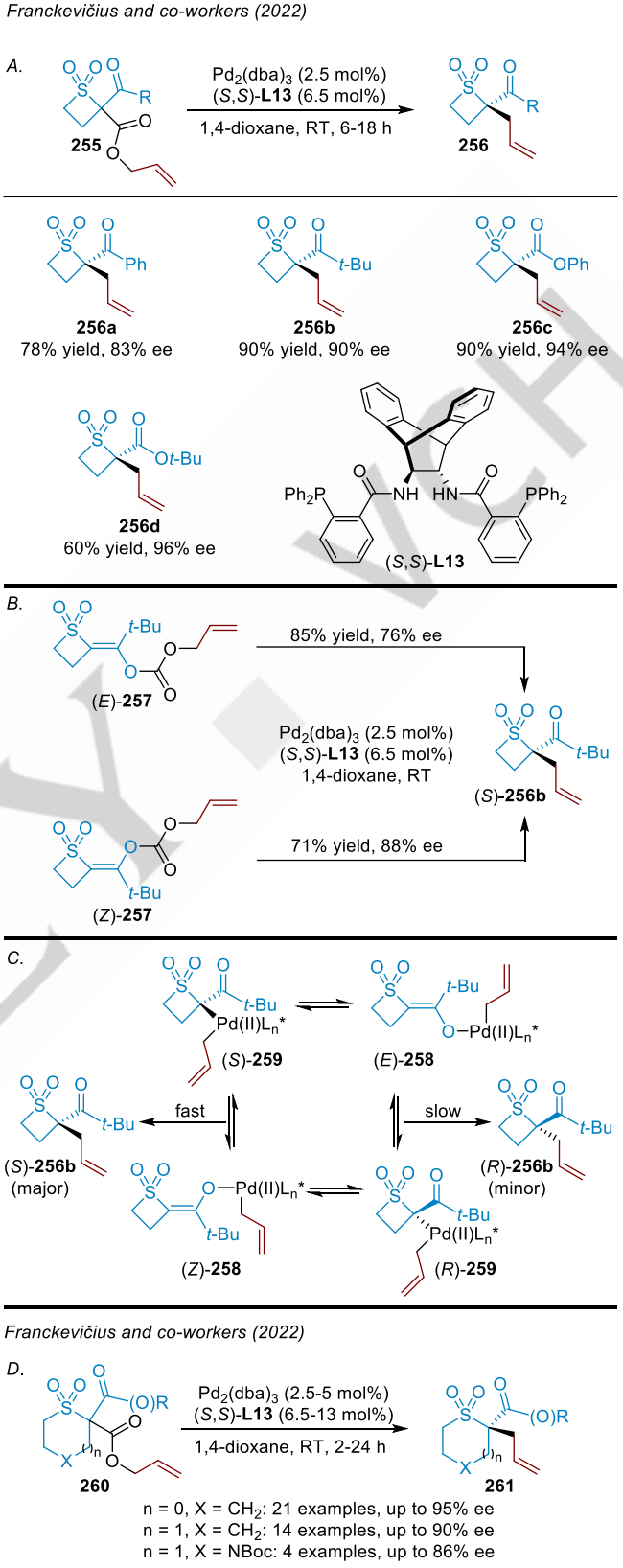
Subsequently, Stoltz and co-workers described the palladium-catalysed DAAA reaction of the analogous, geometrically pure α-oxygenated *Z*-allyl enol carbonates (*Z*)-**250** in the presence of (*R*,*R*)-ANDEN phenyl Trost ligand (*R*,*R*)-**L13** to give MOM-protected α-oxy ketones **251a-c** *via* *Z*-enolate intermediate (*Z*)-**252** with excellent reaction efficiency and high levels of enantioselectivity (82-88% ee) (A, Scheme 52).[80] Nevertheless, the authors observed a significant loss of enantioselectivity when reacting allyl enol carbonate (*Z*)-**253** with a slightly lower purity of geometrical isomers (B, Scheme 52). More specifically, **254** was formed in near-quantitative yield for both reactions, but with 88% ee for the 98:2 *Z*/*E* mixture of **253** and 75% ee from the 93:7 *Z*/*E* mixture of **253**. This observation indicates that high geometric purity of enol carbonate is again essential in order to achieve high enantioselectivity in this process, similar to that observed with *N*-pyrrolyl-substituted allyl enol carbonate **248** (*vide supra*, Scheme 51).



Scheme 52. The palladium-catalysed DAAA of α-oxygenated *Z*-allyl enol carbonates.

In 2022, Franckevičius and co-workers reported the palladium-catalysed DAAA reaction of linear enolates of ketones and esters appended with a thietane-1,1-dioxide unit (**255**) (A, Scheme 53).[81] Using (*S*,*S*)-ANDEN phenyl Trost (*S*,*S*)-**L13** as the ligand for palladium, the reaction afforded products **256** bearing a 2,2-disubstituted α-sulfonyl stereogenic centre. This work showed the successful asymmetric alkylation of a range of aryl and alkyl ketones, giving **256a** with 83% ee and **256b** with 90% ee. The enantioselectivity of allylic alkylation of ester substrates was shown to be even higher, affording **256c** and **256d** with 94% and

96% ee, respectively. Most notably, high levels of enantioselectivity were obtained despite the potential formation of a mixture of *E*- and *Z*-enolates *in situ*. It was shown that a dynamic kinetic resolution of enolates was responsible for ensuring a stereoselective reaction. More specifically, geometrically pure enol carbonates (*E*)-**257** and (*Z*)-**257** both gave (*S*)-**256b** as the major enantiomer in 76% and 88% ee, respectively, which is the same enantiomer of product as that derived from the analogous β-keto allyl ester **255** (B, Scheme 53). Therefore, regardless of the enolate geometry formed *is situ*, there is a rapid equilibration of palladium-bound enolates (*E*)-**258** and (*Z*)-**258** *via* *C*-bound enolate **259** (C, Scheme 53). Given that the allylic alkylation of (*Z*)-**258** was more selective than that of (*E*)-**258**, it is likely that the rate of allylic alkylation of *Z*-enolate (*Z*)-**258** to give enantiomer (*S*)-**256b** is faster than the rate of allylic alkylation of (*E*)-**258** to give (*R*)-**256b**. It is also plausible that *C*-bound palladium enolates (*R*)-**259** and (*S*)-**259** predominate so as to avoid placing a C(sp^2)-centre within the highly-strained four-membered ring. If this is the case, then reductive elimination may occur from *C*-bound enolate (*S*)-**259** faster than from diastereomeric (*R*)-**259**, resulting in an enantioselective reaction. The Franckevičius group further expanded the substrate scope of this methodology to 5- and 6-membered cyclic sulfones **260** (D, Scheme 53).[82] The analogous dynamic kinetic resolution was also found to operate, affording high levels of enantioselectivity for a range of 2,2-disubstituted α-sulfonyl-containing ketone and ester products **261** with up to 95% ee.

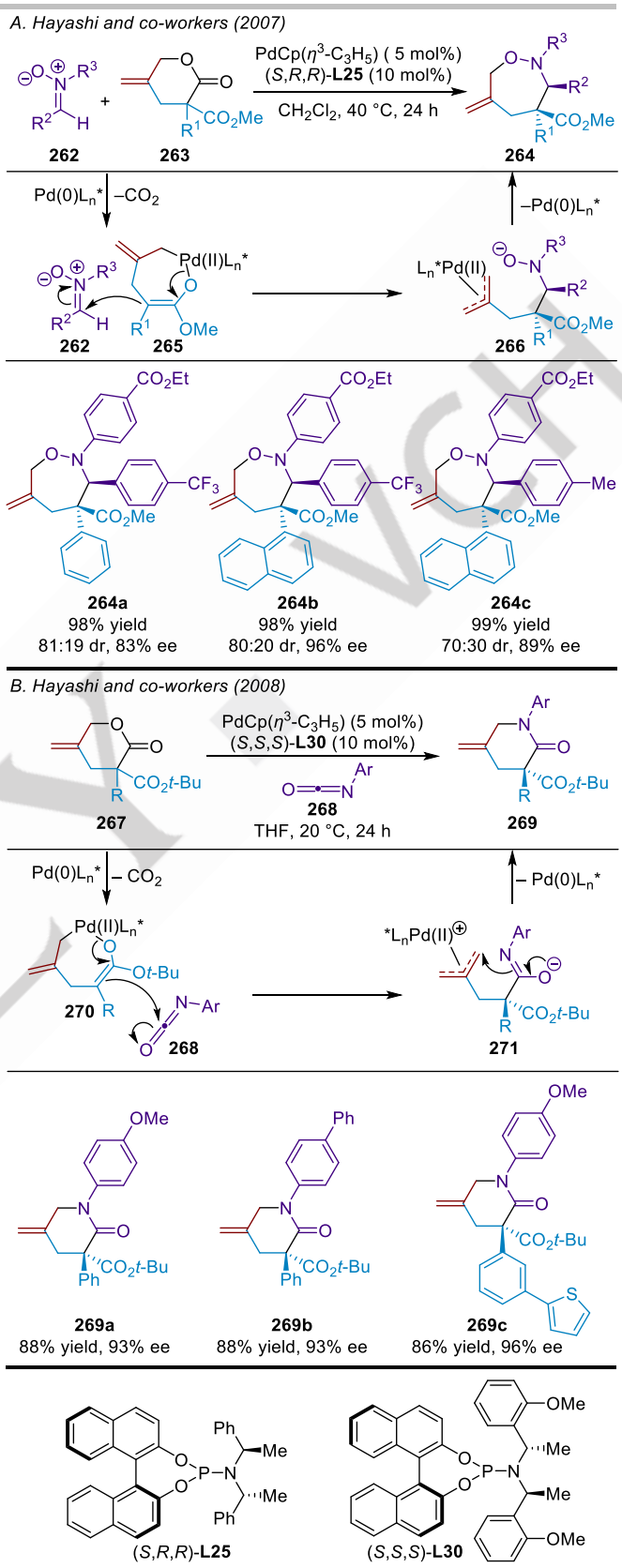


Scheme 53. The palladium-catalysed DAAA reaction of α-sulfonyl ketones and esters.

It is clear from the reports by Stoltz and Franckevičius that a dynamic kinetic resolution of enolates is possible for the palladium-catalysed DAAA of acyclic ketones and esters (*vide supra*, Schemes 50 and 53). On the other hand, Stoltz has

reported examples where a dynamic kinetic resolution of enolates is not at play, resulting in diminished enantioselectivity when allyl enol carbonates with reduced geometric purity are used (*vide supra*, Schemes 51 and 52). Therefore, it is apparent that, although a dynamic kinetic resolution of linear enolates can be extremely advantageous, the circumstances under which this process operates is not yet understood.

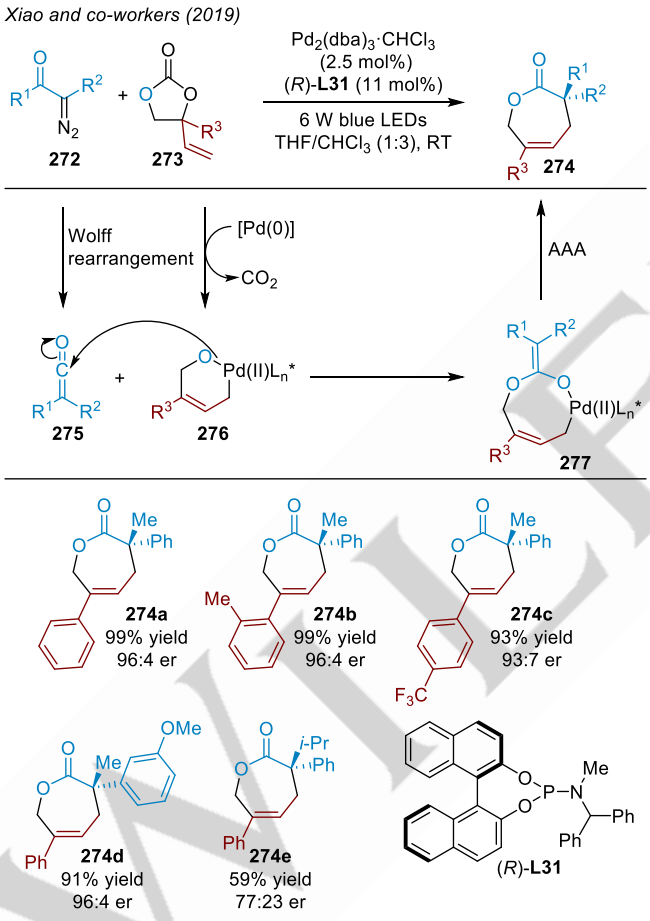
Alongside the conventional AAA reaction of enolates with allylic electrophiles to give allylated carbonyl compounds, there are several reports of AAA reactions of acyclic enolates that are intercepted by an additional reactant prior to alkylation. Such a process not only generates an α-quaternary stereogenic centre, but also substantially enhances the structural complexity of the products in a single step. In this context, Hayashi and co-workers disclosed an intercepted palladium-catalysed AAA reaction of β-ester allyl lactones **263** with nitrones **262** to pave the way to 7-membered heterocycles **264** (A, Scheme 54).[83] Mechanistically, ester palladium enolate **265**, derived from decarboxylation of substrate **263**, is intercepted with nitrone **262** to form intermediate **266**, which, following intramolecular *O*-allylic alkylation, paves the way to stereofunctionalised heterocyclic products **264**. The reaction gave good to high diastereo- and enantioselectivities, with **264a-c** formed with 70:30 to 86:14 dr and 83% to 96% ee. To enable chelation between the oxyanion of the enolate and the σ-allylpalladium(II) unit in **265**, the *Z*-geometry of the enolate is adopted. Subsequently, Hayashi carried out an intercepted palladium-catalysed DAAA reaction of similar β-ester allyl lactones **267** with aryl isocyanates **268** (B, Scheme 54).[84] Following decarboxylation, isocyanate **268** intercepts palladium intermediate **270**, generating a quaternary centre in **271**. Intramolecular *N*-allylic alkylation then affords β-ester lactam **269**. The enolate geometry in **270** is again believed to arise from the cyclic nature of palladium-bound nucleophile/electrophile complex. Using phosphoramidite ligand (*S*,*S*,*S*)-**L30** for palladium, high enantioselectivity for a range of products **269a-c** was observed.



Scheme 54. The intercepted palladium-catalysed AAA of β-ester allyl lactones.

The use of α-diazo esters can represent an alternative entry to enolate intermediates, diversifying the products accessible *via* the metal-catalysed AAA reaction. In 2019, the Xiao group disclosed an enantioselective strategy towards α-quaternary ω-lactones

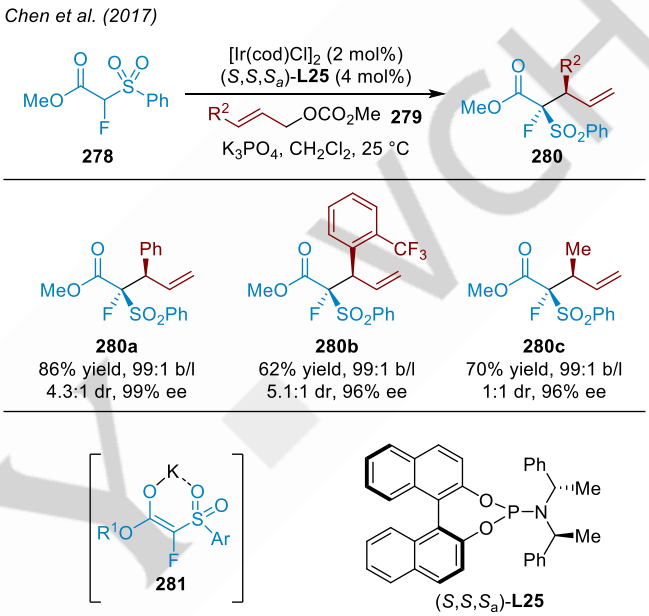
274 using the palladium-catalysed AAA reaction (Scheme 55).[85] This methodology uses diazocarbonyl substrates **272**, allylic carbonate electrophiles **273**, alongside phosphoramidite ligand (*R*)-**L31** for palladium. The mechanism commences with the *in-situ* formation of ketene **275** *via* a Wolff rearrangement of diazocarbonyl **272** with the concomitant generation of π-allylpalladium(II) intermediate **276** from oxidative addition of carbonate **273** to palladium(0). Nucleophilic addition of the alkoxide in **276** to ketene **275** then gives palladium enolate intermediate **277**. Finally, cyclisation of **277** *via* allylic alkylation provides α-quaternary lactones **274**. The reaction proved highly versatile, giving high levels of enantioselectivity for a range of products, including **274a-d**, which were formed with 93:7 to 96:4 er. Notably, when a bulkier alkyl ketone group was used in diazo substrate **272** (R^1 = *i*-Pr), the enantioselectivity was lower, giving **274e** with 77:23 er. The generally high levels of enantioselectivity in this reaction suggest that a geometrically pure enolate in **277** is involved in the allylic alkylation step.



Scheme 55. The palladium-catalysed AAA reaction of diazocarbonyl substrates.

6.2. Iridium Catalysis

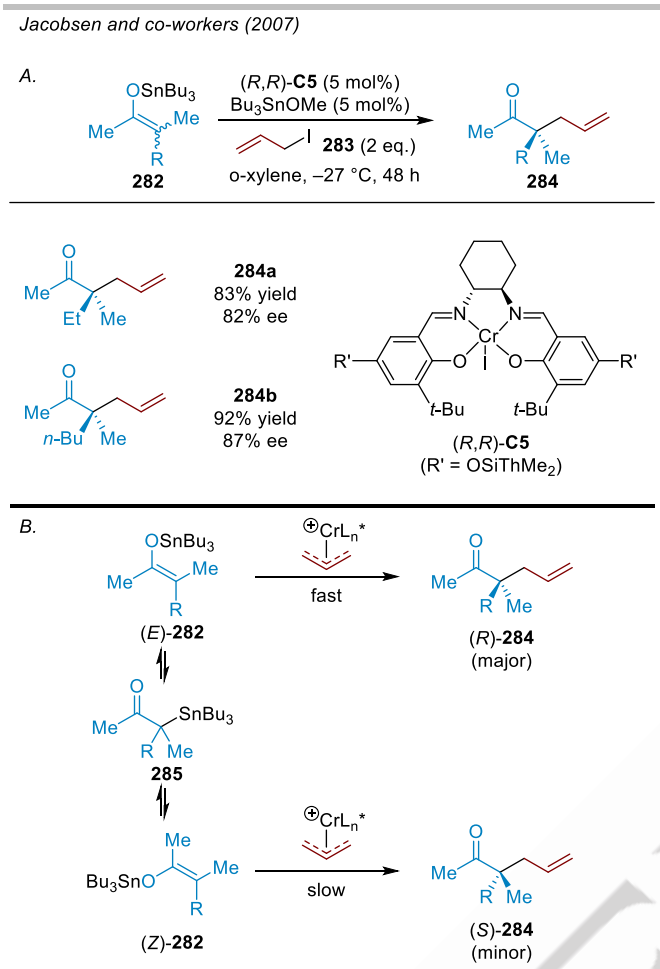
Alongside palladium, a number of other metals have also been shown to catalyse the AAA of ester and ketone enolates with high levels of stereocontrol. In this context, the AAA reaction of α-fluoro α-sulfonyl esters **278** with substituted allylic electrophiles **279** was reported by Chen *et al*. exploiting iridium catalysis (Scheme 56).[86] This process revealed excellent branched to linear product selectivity, moderate to good diastereoselectivity and high levels of enantioselectivity: products **280a** and **280b** were formed as branched regioisomers with 4.3:1 dr and 99% ee, and 5.1:1 dr and 96% ee, respectively. When the aryl group in electrophile **279** was replaced with a methyl substituent (R^2 = Me), the high level of branched to linear selectivity (99:1 b/l) and enantioselectivity (96% ee) for the formation of **280c** was retained; however, the reaction was not diastereoselective. In a similar fashion to α-phosphono carbonyl compounds (*vide supra*, Scheme 43), it is feasible that chelated enolate **281** is responsible for the high levels of stereoselectivity in the reaction.



Scheme 56. The iridium-catalysed AAA of α-fluorosulfones.

6.3. Chromium Catalysis

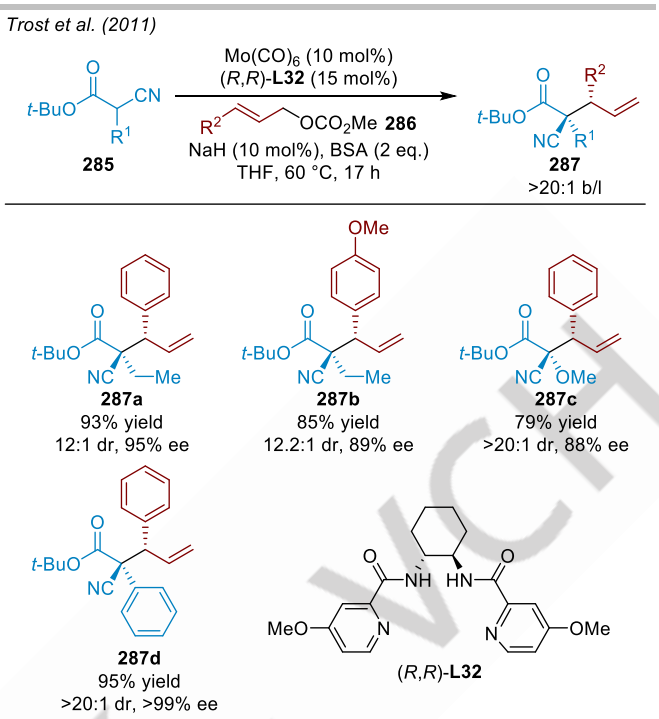
In 2007, Jacobsen reported the chromium-catalysed asymmetric AAA reaction of tin enolates **282** with allyl iodide (**283**) and chromium catalyst (*R*,*R*)-**C5** (A, Scheme 57),[87] where despite the use of a mixture of *E*/*Z*-tin enolates **282**, α-quaternary ketones **284a** and **284b** could be made with high levels of enantioselectivity (82% and 87% ee, respectively). Given that a mixture of *E*- and *Z*-enolates is expected to attenuate the stereoselectivity of the reaction, it was proposed that an equilibrium between enolates (*E*)-**282** and (*Z*)-**282** is set up, presumably *via* *C*-bound tin-enolate **285** (B, Scheme 57). Under the reaction conditions, if the rate of the allylic alkylation of one of the enolates, e.g. (*E*)-**282**, is substantially faster than that of (*Z*)-**282**, then a dynamic kinetic resolution of tin enolates occurs, resulting in enantioenriched (*R*)-**284** formation. This process appears to be analogous to the dynamic kinetic resolution of palladium enolates (*vide supra*, Schemes 50 and 53).



Scheme 57. The palladium-catalysed AAA reaction of tin enolates.

6.4. Molybdenum Catalysis

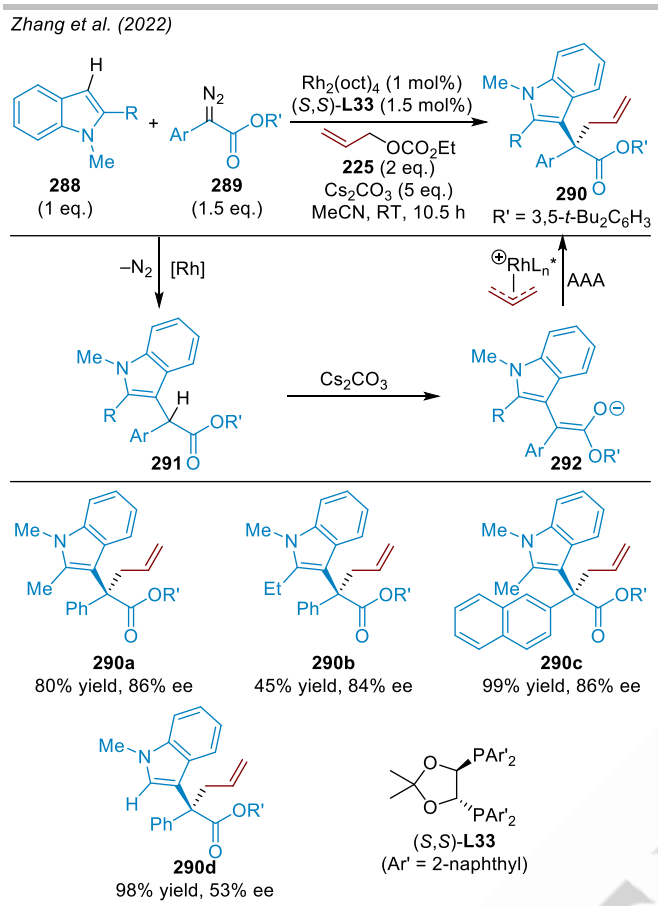
The first example of an asymmetric installation of vicinal quaternary/tertiary stereogenic centres using the molybdenum-catalysed AAA reaction of α-cyanoesters was reported by Trost *et al*. in 2011 (Scheme 58).[88] The authors demonstrated that the molybdenum-catalysed AAA reaction of cyanoesters **285** with substituted allylic carbonates **286** could give allylated products **287a-d** with excellent branched/linear selectivity (>20:1 b/l), diastereoselectivity (12:1 to >20:1 dr) and enantioselectivity (89% to >99% ee) in the presence of ligand (*R*,*R*)-**L32**. Although the effect of enolate geometry on the stereochemical outcome of the reaction was not discussed, given the high levels of stereoselectivity obtained in this process, enolate formation was also likely to have been selective.



Scheme 58. The molybdenum-catalysed AAA reaction of α-cyanoester.

6.5. Rhodium Catalysis

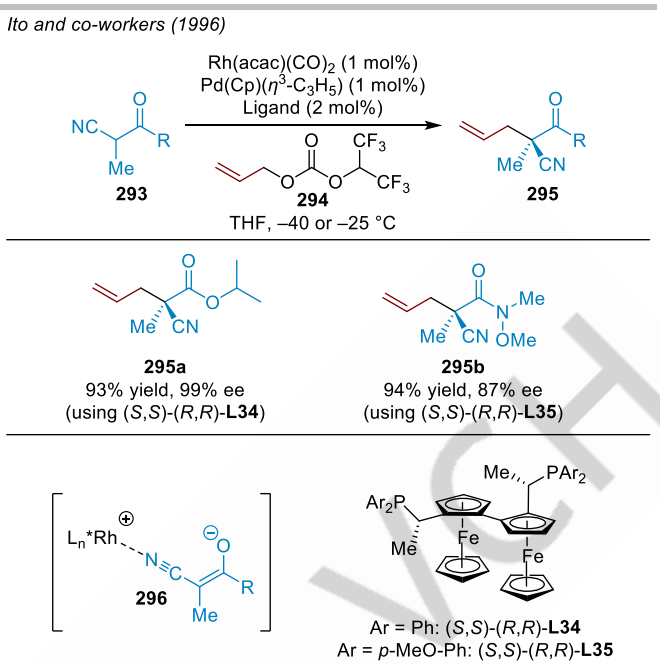
In 2022, Zhang *et al*. reported the relay rhodium-catalysed indole C–H functionalisation / asymmetric allylic alkylation from indoles **288**, diazocarbonyls **289** and allyl carbonate (**225**) (Scheme 59).[89] The reaction generated a range of α-indolyl α-quaternary ester products **290a-c** with high levels of enantioselectivity by varying the alkyl 2-substituent of the indole in **288** and the α-aryl group of the ester in **289**. The authors proposed that ester intermediate **291** is formed *via* a rhodium-catalysed C–H insertion of diazocarbonyl **289** to indole **288**. By deprotonation of ester **291** with caesium carbonate, enolate **292** is generated, which undergoes a rhodium-catalysed AAA reaction in the presence of chiral ligand (*S*,*S*)-**L33**. Although the geometry of enolate **292** was not established, the bulky indole substituent and ester residue likely adopt the *trans* geometry in **292** for steric reasons. The use of a smaller indole substrate that lacks a 2-substituent (R = H) gave **290d** with a significantly lower 53% ee, presumably as a result of a reduced steric distinction between the indole and phenyl substituents in **292**, producing a mixture of enolates, and thus, lower enantioselectivity in the formation of **290d**.



Scheme 59. The rhodium-catalysed relay C–H functionalisation / asymmetric allylic alkylation.

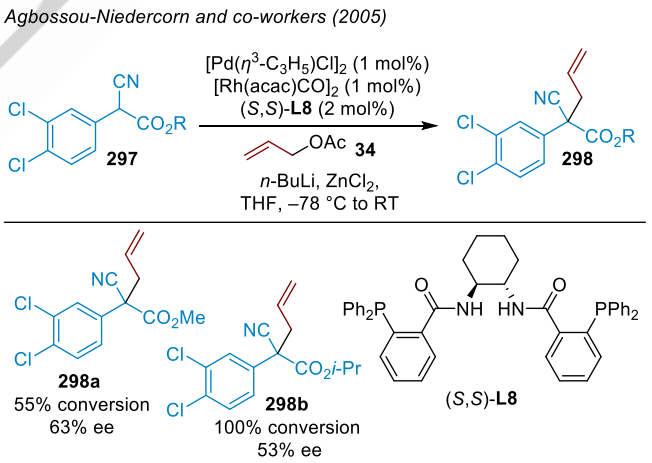
6.6. Dual Metal Catalysis

In 1996, Ito *et al*. reported the first palladium/rhodium dual-catalysed AAA reaction of a limited number of α-cyano carbonyl substrates **293** (Scheme 60).[90] Using chiral ligand (*S*,*S*)-(*R*,*R*)-**L34** or (*S*,*S*)-(*R*,*R*)-**L35** for rhodium, the authors were able to form α-cyano ester product **295a** with an impressive 99% ee, alongside α-cyano Weinreb amide **295b** with 87% ee. It was proposed that enolate **296** is formed *in situ*, which allows for *N*-coordination of the nitrile group to the rhodium metal. The rhodium centre also acts as the counter ion to the enolate ensuring that the oxyanion of the enolate is placed *cis* to the nitrile group due to favourable electrostatic attraction and, thus, resulting in the *Z*-geometry of enolate **296**. Allylic alkylation then forms product **295**, whereby facial selectivity of alkylation with a π-allylpalladium(II) electrophile is determined by the chiral rhodium-enolate complex **296**.



Scheme 60. The palladium/rhodium-catalysed AAA of α-cyano substrates.

In 2005, Agbossou-Niedercorn and co-workers attempted the palladium/rhodium co-catalysed AAA reaction of cyanoester substrates **297**, but the enantioselectivity was only moderate (Scheme 61).[91] Optimisation of the conditions resulted in the formation of **298a** with 63% ee using (*S*,*S*)-DACH phenyl Trost ligand (*S*,*S*)-**L8** for both the palladium and rhodium catalysts. Under the same conditions, the *iso*-propyl ester product **298b** was isolated with 53% ee.

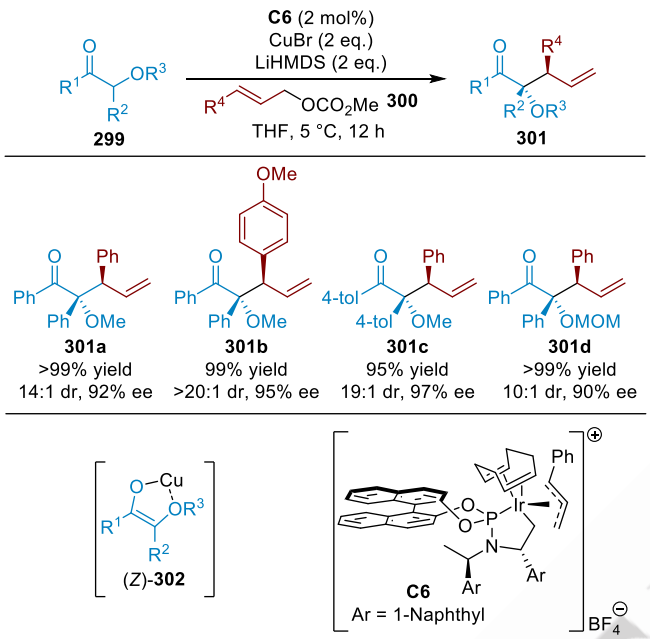


Scheme 61. The palladium/rhodium dual-catalysed AAA of cyanoester substrates.

To achieve high levels of stereoselectivity in AAA reactions of ketone and ester enolates, a copper co-catalyst has been successfully used as a means of ensuring chelation of the enolate intermediate, most commonly due to the presence of an additional α-heteroatom in the vicinity. In this context, Hartwig reported the iridium-catalysed AAA reaction of α-oxy ketones **299** with substituted allylic electrophiles **300** using iridium catalyst **C6**, LiHMDS as the base and copper bromide as an additive, albeit used in a superstoichiometric amount (Scheme 62).[92] The

reaction scope was shown to be broad, with a range of functionality at the allyl, ketone and α-position, giving products **301a-d** with high diastereo- and enantioselectivity. The authors proposed that the copper bromide additive allowed the control of enolate geometry *via* chelation to the α-oxygen substituent in (*Z*)-**302**.

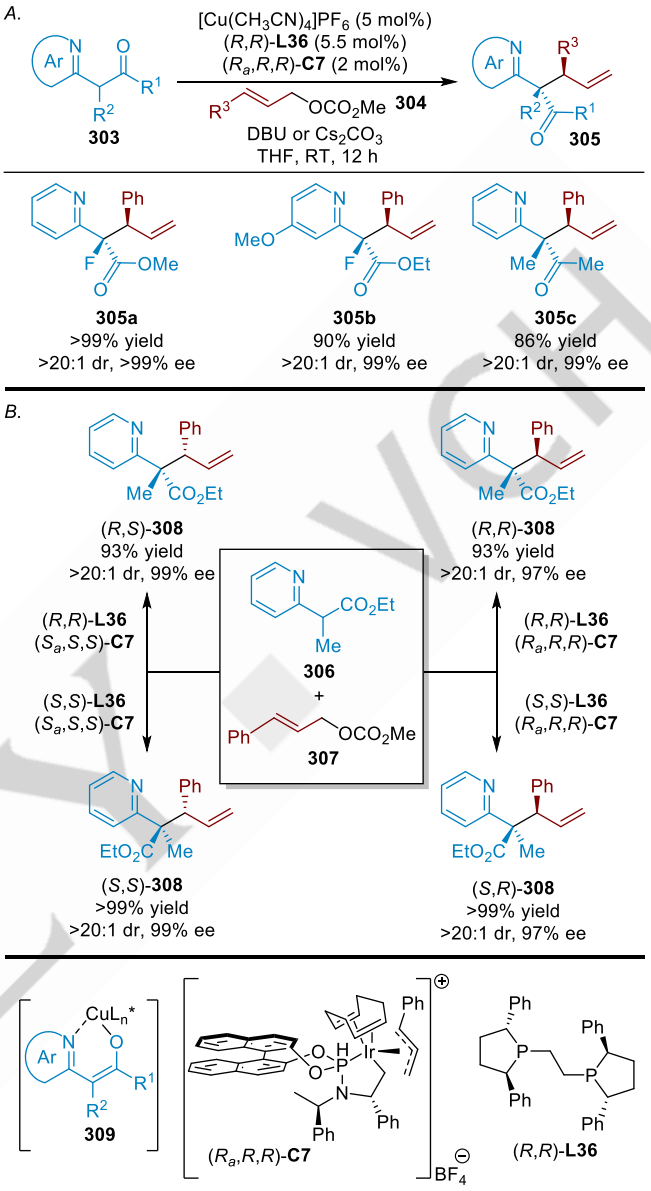
Hartwig and co-workers (2016)



Scheme 62. The iridium-catalysed AAA reaction of α-oxy ketones.

Often, however, catalytic amounts of copper can be used. As such, Hartwig reported a diastereo- and enantioselective AAA reaction of azaaryl carbonyl substrates **303** to afford products **305** bearing vicinal stereogenic centres using two chiral catalysts: iridium catalyst (*Ra*,*R*,*R*)-**C7** and ligand (*R*,*R*)-**L36** for copper (A, Scheme 63).[93] The results were excellent for a range of fluorinated and alkylated azaaryl esters and ketones, giving **305a-c** with >20:1 dr and ≥99% ee. The authors also demonstrated the stereodivergence of this process by accessing all four stereoisomers of **308** with high levels of diastereo- and enantioselectivity *via* the AAA reaction of **306** with **307** using different combination of enantiomers of catalyst **C7** and ligand **L36** for copper (B, Scheme 63). Control of enolate geometry in this case is achieved *via* chelated copper(I) enolate **309**. The following year, You and co-workers extended the iridium-catalysed AAA reaction of α-fluorinated acyclic ketones in the absence of a copper catalyst.[94]

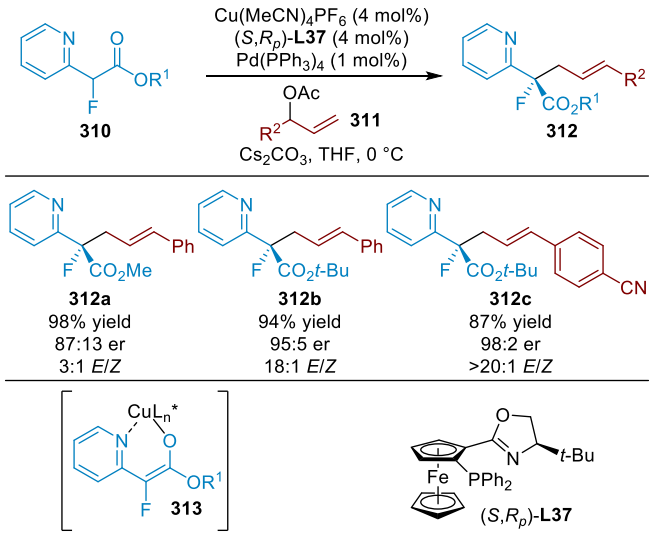
Hartwig and co-workers (2019)



Scheme 63. The iridium/copper-catalysed AAA reaction of azaaryl carbonyl substrates.

More recently, Liu described the palladium/copper dual-catalysed AAA reaction of α-pyridyl-α-fluoroesters **310** using allylic electrophiles **311**, an achiral palladium catalyst and chiral ligand (*S*,*Rp*)-**L37** for copper to afford α-fluorinated ester products **312**, containing a tetrasubstituted stereogenic centre (Scheme 64).[95] Unlike the previous iridium-catalysed AAA process (*vide supra*, Scheme 63), where regioselectivity for the branched product was observed, the palladium-catalysed allylic alkylation in this case afforded solely linear regioisomers **312**. The authors showed that increasing the steric bulk of the ester residue in **310** increased both the *E*/*Z* selectivity of the resulting alkene and the enantioselectivity of the reaction, producing **312a** and **312b** with 87:13 and 95:5 er, and an *E*/*Z* ratio of 3:1 and 18:1, respectively. The reaction was tolerant to a wide variety of allylic electrophiles **311**; for example, **312c** was formed with 98:2 er and an *E*/*Z* ratio of >20:1. The control of the enolate geometry is most likely derived from a chelated copper(I) enolate **313**.

Liu and and co-workers (2023)

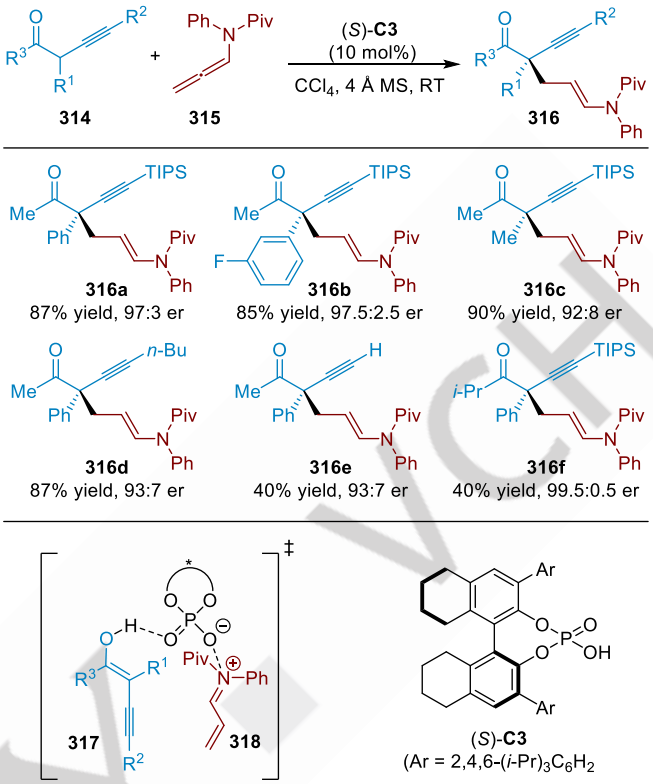


Scheme 64. The palladium/copper dual-catalysed AAA reaction of α-pyridyl-α-fluoroesters.

6.7. Chiral Phosphoric Acid Catalysis

Although AAA reactions of ketone and ester enolates that exploit metal catalysis are most common, in 2021, Yang and co-workers reported a unique asymmetric allylic alkylation of α-alkynyl ketones **314** with allenamides **315**, catalysed by chiral phosphoric acid (CPA) catalyst (*S*)-**C3**, to afford α-quaternary acyclic ketones **316** (Scheme 65).[96] The authors observed high levels of enantioselectivity of the reaction for a variety of α-substituents, as well as alkynyl and ketone functionality, giving **316a-f** in ≥92:8 er. After extensive studies, the authors proposed that enol **317** is more stable in the *E*-geometry as a result of minimised steric interactions between the linear alkyne and bulkier ketone substituent (R^3). Product **316** is then formed *via* a conjugate addition of *in situ* generated enol **317** to iminium ion **318** via the templating effect of the CPA catalyst (*S*)-**C3**.

Yang and co-workers (2021)



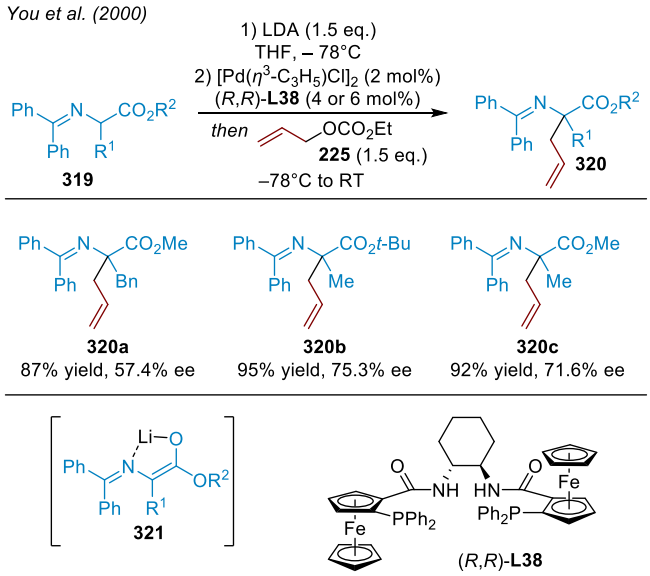
Scheme 65. The CPA-catalysed AAA of α-alkynyl ketones with allenamides.

7. The AAA reaction of α-Iminoesters

Catalytic AAA reactions of acyclic α-iminoester nucleophiles, a subclass of ester enolates, are relatively well developed, affording products with excellent enantioselectivities. These positive results stem predominantly from the propensity of α-iminoesters to form chelated enolate intermediates in the presence of additives, such as copper and zinc, which results in excellent stereocontrol of enolisation. This topic is discussed next.

7.1. Palladium Catalysis

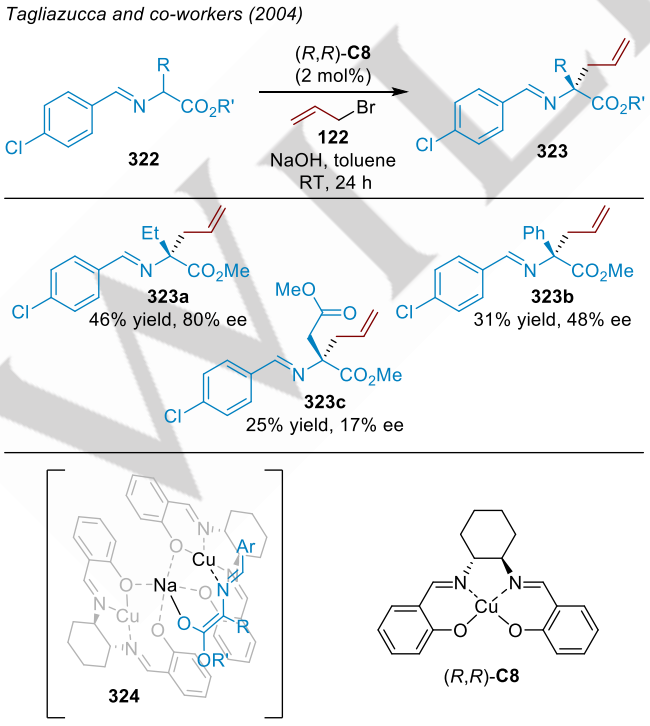
In 2000, You *et al*. disclosed the palladium-catalysed AAA reaction of linear α-iminoesters **319** with allyl carbonate (**225**) using LDA as the base and Trost ligand (*R*,*R*)-**L38** for palladium (Scheme 66).[97] The reaction proceeded smoothly to afford **320a-c** in up to 95% yield, and moderate to good enantioselectivity was observed. Stereocontrol of enolate geometry arises from the unique feature of α-iminoesters **319** to form a 5-membered chelate upon deprotonation, ensuring that enolate **321** is formed as a single geometrical isomer.



Scheme 66. The palladium-catalysed AAA of acyclic α-iminoesters.

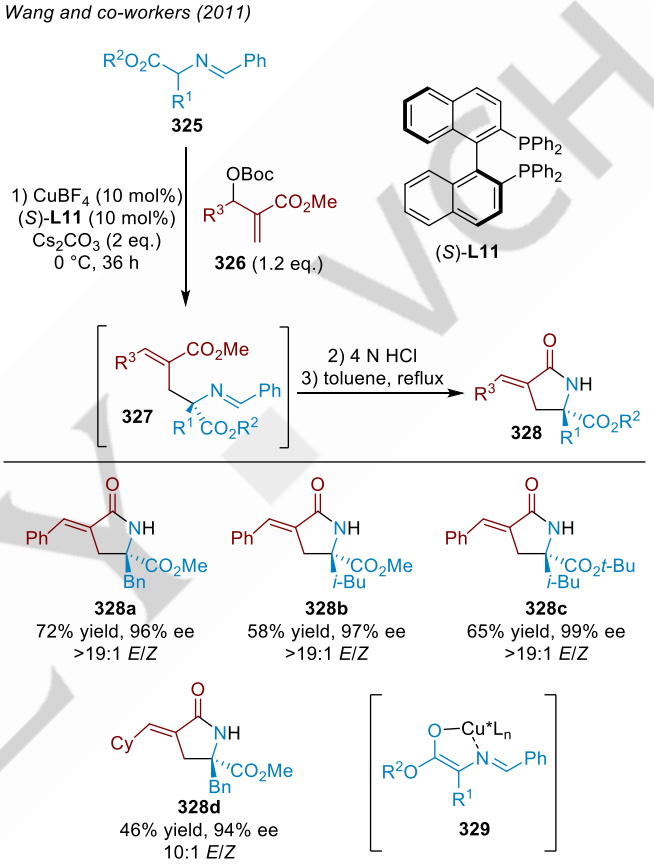
7.2. Copper Catalysis

In 2004, Tagliazucca and co-workers reported the use of copper(II) salen catalyst (*R*,*R*)-**C8** in the copper-catalysed asymmetric allylic alkylation of α-iminoesters **322** with allyl bromide (**122**) to install an α-tetrasubstituted stereogenic centre in **323** (Scheme 67).[98] It was shown that, under the optimised conditions, ethyl-substituted **323a** was formed in a modest 46% yield but with good enantioselectivity (80% ee). Nevertheless, the formation of phenyl- and alkyl-substituted **323b** and **323c**, respectively, was less selective. The authors suggested that the control of enolate geometry was a result of chelation, giving rise to enolate **324**.



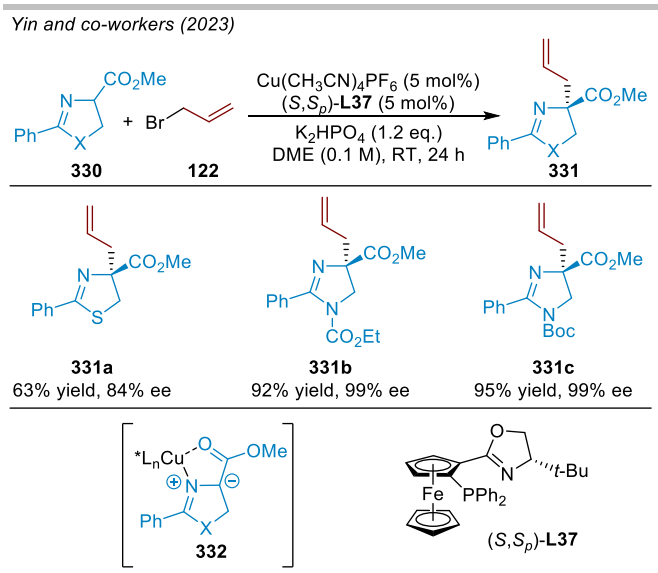
Scheme 67. A copper-catalysed AAA reaction of α-iminoesters.

Wang and co-workers expanded on this work by developing a copper-catalysed AAA reaction of α-iminoesters **325** with allylic carbonates **326** to give α-tetrasubstituted iminoesters **327** using caesium carbonate as the base and (*S*)-BINAP (*S*)-**L11** as the ligand for copper (Scheme 68).[99] Subsequent hydrolysis of **327** and cyclisation resulted in lactams **328a-d** with 94-99% ee. It is likely that chelation to copper ensures stereoselective formation of enolate **329**.



Scheme 68. Asymmetric synthesis of lactams *via* the copper-catalysed AAA of α-iminoesters.

More recently, the Yin group described the copper-catalysed AAA reaction of α-iminoesters **330** that comprise either an imidazoline or thioimidazoline unit (Scheme 69).[100] Indeed, it was shown that, by employing copper catalysis with (*S*,*Sp*)-*t*-Bu-FOXAP ligand (*S*,*Sp*)-**L37** alongside dipotassium phosphate as the base, allylated α-heterocyclic esters **331a-c** could be formed with 84-99% ee. The authors proposed that chelated copper enolate **332** was formed from α-iminoesters **330**, whereas allylation proceeded through an S_N2 substitution mechanism. In this study, the alkylation of α-iminoesters was also performed with alternative electrophiles, such as benzyl bromides, α-bromocarbonyl compounds and alkyl iodides, to afford a range of alkylated products with high levels of enantioselectivity.



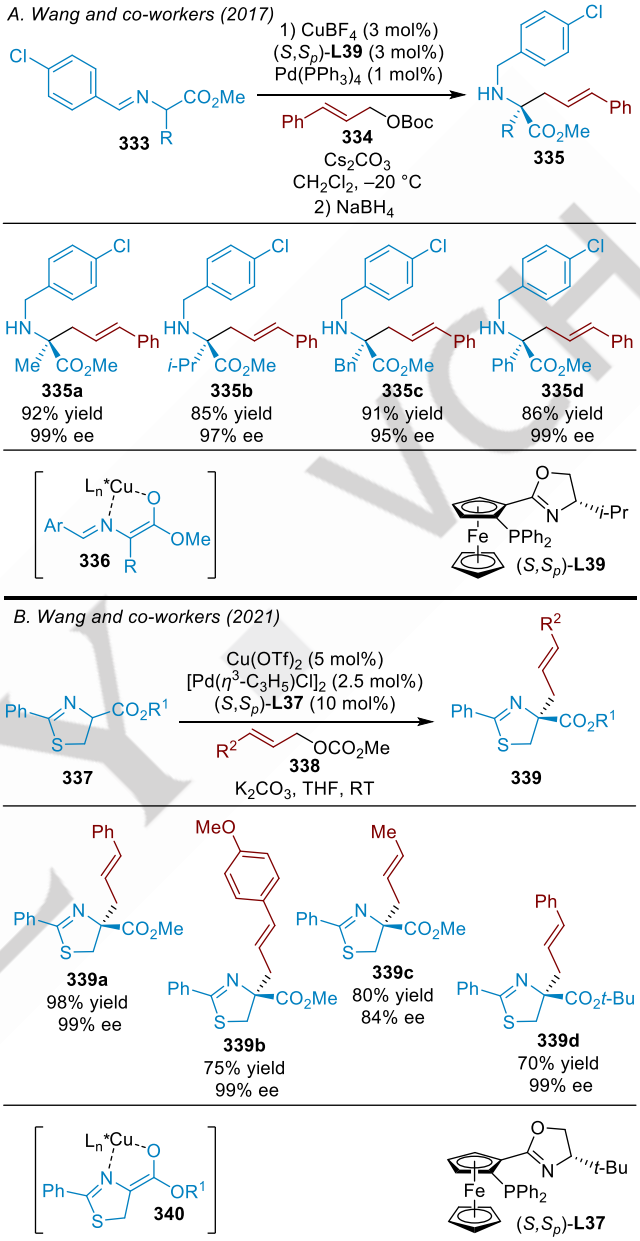
Scheme 69. The copper-catalysed AAA of α-iminoesters with allyl bromide.

While the examples of α-iminoester allylation discussed so far exploited a single catalyst, such as palladium or copper, dual-catalysed AAA reactions with α-iminoesters using copper and either palladium or iridium catalysts are more common. Reports typically utilise either a chiral ligand for copper to make a chiral copper enolate or a chiral ligand for palladium/iridium to make the respective chiral π-allylmetal intermediate. In some cases, by exploiting substituted allylic electrophiles and both a chiral copper enolate and a chiral π-allylmetal intermediate, a stereodivergent process can be achieved, whereby the use of different combinations of enantiomers of the ligand for copper and the ligand for palladium/iridium allows selective entry to all four stereoisomers of α-iminoester products that contain two adjacent stereogenic centres. The examples of copper/palladium, followed by copper/iridium, dual-catalysed AAA reactions are discussed next.

7.3. Copper/Palladium Dual Catalysis

In 2017, the use of a copper/palladium dual catalytic system for the allylic alkylation of α-iminoesters **333** was disclosed by Wang and co-workers (A, Scheme 70).[101] The authors exploited chiral ligand (*S*)-**L39** for the copper catalyst alongside the achiral tetrakis(triphenylphosphine)palladium(0) catalyst in the allylic alkylation of α-iminoesters **333** with allylic carbonate **334**. Subsequent reduction of the imine allowed access to α-amino ester products **335**. Overall, excellent enantioselectivity for **335a-d** was obtained (95-99% ee). It is likely that a copper-chelated enolate **336** is responsible for the high levels of enantiocontrol. More recently, Wang used a palladium/copper-catalysed AAA reaction of α-thiazoline esters **337** to access α-tetrasubstituted cysteine derivatives **339** (B, Scheme 70).[102] When α-iminomethylesters (R^1 = Me) **337** were reacted with aryl-substituted allylic electrophiles **338** (R^2 = Ar), the enantioselectivity was excellent, forming **339a** and **339b** with 99% ee. For alkyl-substituted **338**, the enantioselectivity was notably lower, giving **339c** with 84% ee. In the presence of a bulkier *tert*-butyl ester in α-iminoester **337** (R^1 = *t*-Bu), excellent enantioselectivity was maintained in the reaction (**339d**, 99% ee).

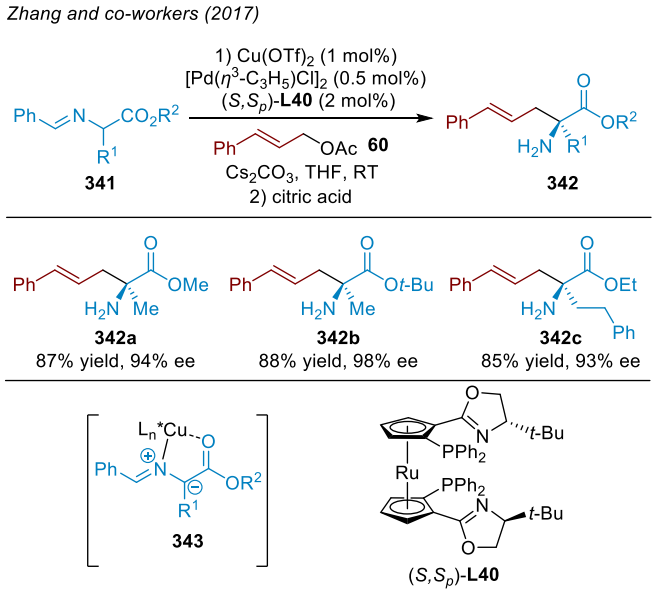
The high levels of enantioselectivity are again enabled by chelation to copper in enolate **340**.



Scheme 70. The copper/palladium-catalysed AAA of α-iminoesters with allyl carbonates.

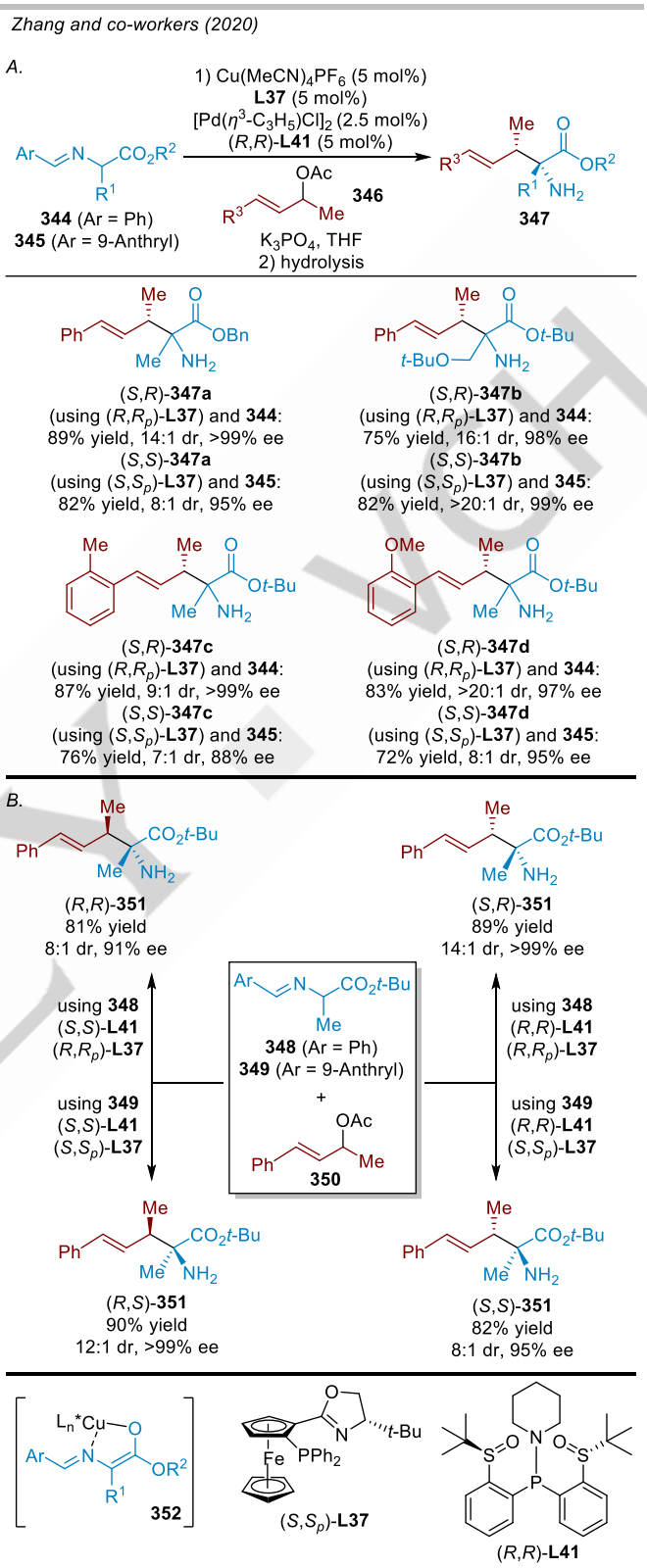
The use of allyl acetate (rather than carbonate) electrophiles has also been met with high stereoselectivity in the palladium-catalysed AAA of α-iminoesters. In this context, Zhang and co-workers reported a similar synergistic copper/palladium-catalysed AAA reaction of α-iminoesters **341** with phenyl-substituted allyl acetate (**60**) but using the chiral ligand (*S*)-**L40** for both copper and palladium (Scheme 71).[103] The alkylated imine was hydrolysed with citric acid to reveal α-tetrasubstituted amino esters **342**. The versatility of the reaction was demonstrated by successfully exploring both the ester and α-alkyl substituents, affording products **342a-c** with excellent enantioselectivity. The authors reasoned that the chiral copper complex forms α-chelated

azomethine ylide **343** that then undergoes stereoselective allylic alkylation with the π-allylpalladium(II) intermediate.



Scheme 71. The copper/palladium dual-catalysed AAA of α-iminoesters with monosubstituted allyl acetates.

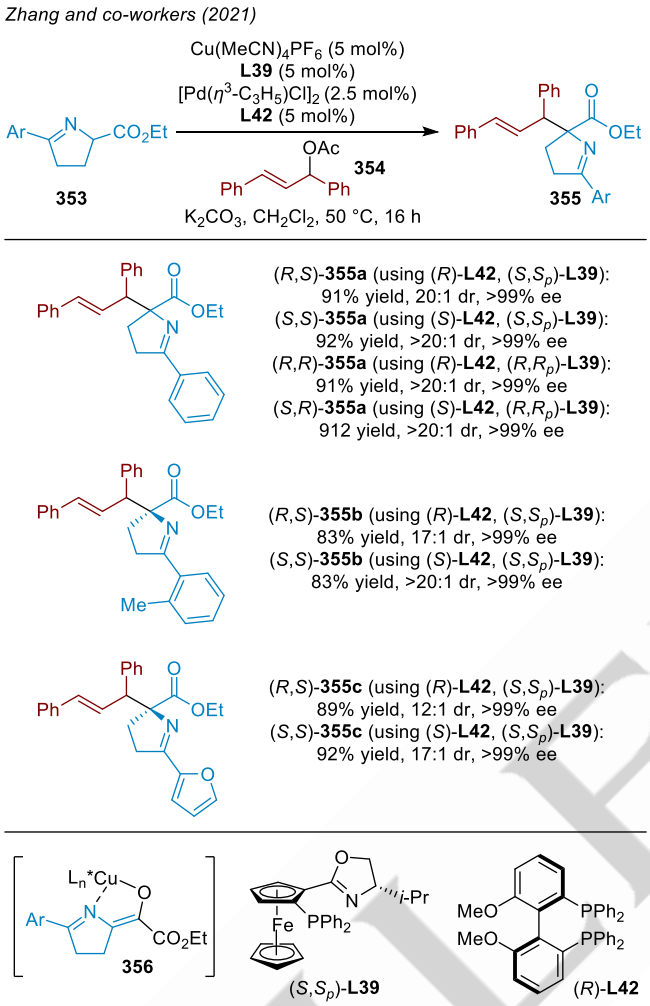
The Zhang group have also shown that, when employing disubstituted allyl acetate electrophiles **346** in the analogous copper/palladium-catalysed AAA reaction of α-aminoesters **344** and **345**, following subsequent hydrolysis, α-iminoesters **347**, containing vicinal stereogenic centres, can be accessed (A, Scheme 72).[104] The authors were able to obtain both (*S*,*R*)- and (*S*,*S*)-diastereoisomers selectively for a number of products **347a-d** (7:1->20:1 dr and 88->99% ee) by varying the enantiomer of ligand **L37** for copper. It was also demonstrated that, by varying the enantiomer of the ligand both for copper (**L37**) and for palladium (**L41**), access to all four stereoisomers of **351** could be obtained from the AAA reaction of α-iminoester **348** or **349** with allyl electrophile **350**, with 8:1-14:1 dr and 91->99% ee (B, Scheme 72). Again, chelation in copper enolate **352** is likely to be involved. In 2023, the Zhang and co-workers successfully developed an equally selective stereodivergent copper/palladium dual-catalysed AAA reaction of α-iminoesters with fluorinated allylic electrophiles.[105]



Scheme 72. Copper/palladium dual catalysed AAA of α-iminoesters using disubstituted allyl acetates.

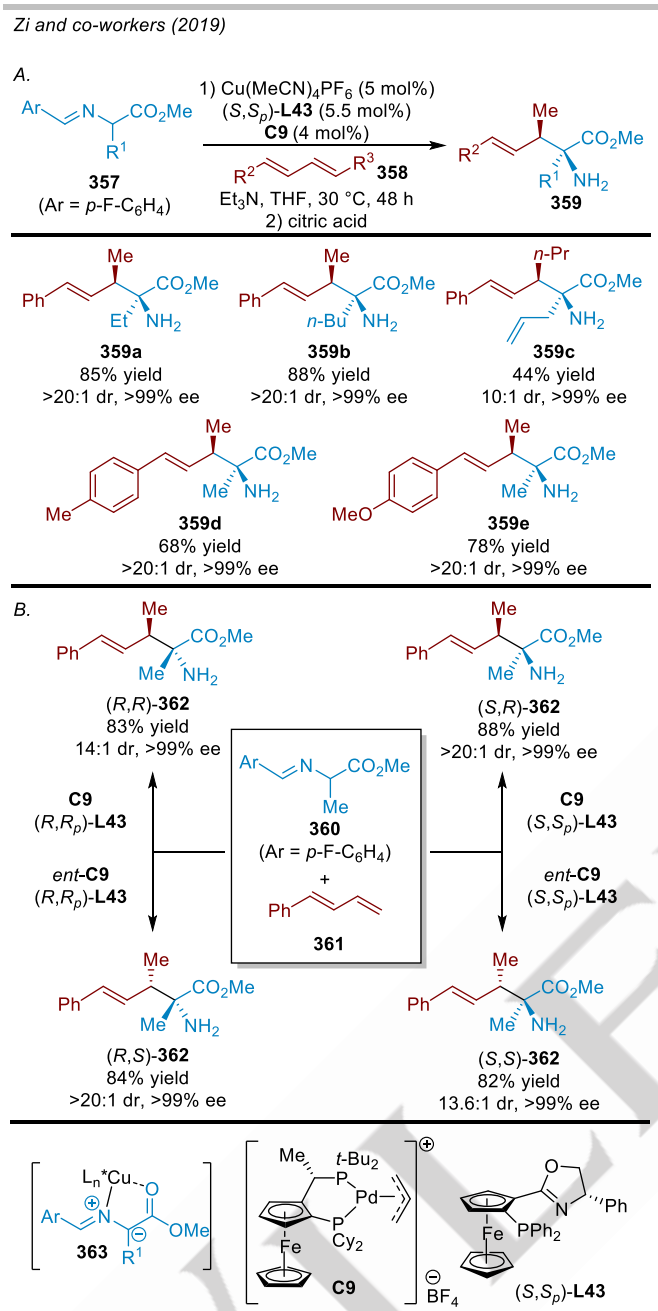
In addition, the Zhang group carried out the stereodivergent copper/palladium dual-catalysed AAA reaction of analogous α-iminoester substrates **353** bearing a cyclic imine with diphenyl substituted allyl acetate **354** (Scheme 73).[106] By varying the enantiomer of ligand **L39** for copper and **L42** for palladium, the

authors were able to access all four stereoisomers of **355a** with ≥20:1 dr and ≥99% ee. A number of products were obtained by changing the aryl functionality in **353**, such as (*R*,*S*)-**355b**, (*S*,*S*)-**355b** and (*R*,*S*)-**355c** and (*S*,*S*)-**355c**, which were formed with 12:1 to >20:1 dr and >99% ee. The excellent stereoselectivity is enabled by the formation of chelated copper enolate **356** *in situ*.



Scheme 73. The synergistic copper/palladium-catalysed AAA of α-iminoesters with diphenyl substituted allyl acetate.

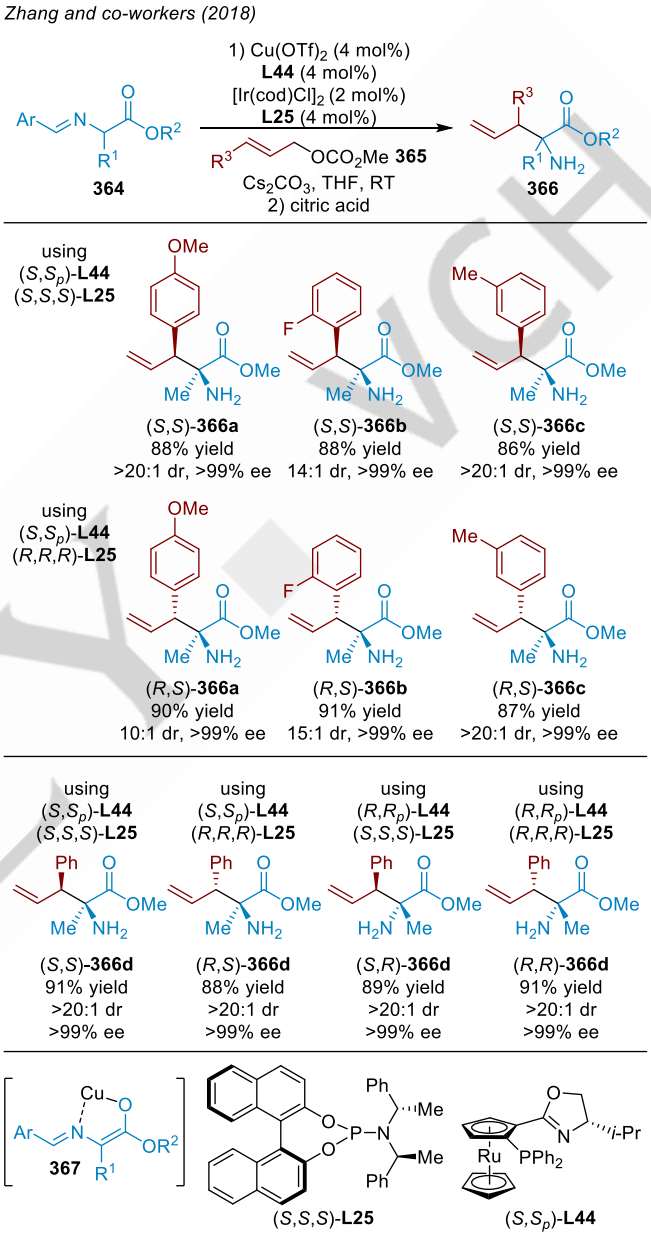
The use of activated allylic electrophiles, such as carbonates and acetates, allows the straightforward formation of the π-allylmetal intermediate as the allylating agent. However, it has been shown that simple unfunctionalised substrates can act as more cost effective and atom economical sources of allylic electrophiles in AAA reactions. In this context, Zi and co-workers described the copper/palladium dual catalysed AAA reaction of fluorophenyl-substituted α-iminoesters **357** with dienes **358** (A, Scheme 74).[107] Using palladium(II) catalyst **C9** and ligand (*S*,*S*$_p$)-**L43** for copper and, following hydrolysis of the imine product with citric acid, a number of α-amino esters **359** were produced bearing two contiguous stereogenic centres with excellent diastereo- and enantioselectivity. By varying the α-substituent (R^1) of α-iminoester **357**, products **359a** and **359b** were formed with >20:1 dr and >99% ee. When diene **358** was disubstituted, the reaction proceeded to give **359c** with reduced diastereoselectivity (10:1 dr), but the enantioselectivity was maintained (>99% ee). When aryl substituents of the diene electrophile were investigated, both the diastereo- and enantioselectivity were excellent (>20:1 dr and >99% ee of **359d** and **359e**). In all examples reported, the reaction was completely regioselective for the unsubstituted or alkyl-substituted side of diene **358** in favour of the aryl-substituted terminus. The authors also showed that, by using different combinations of enantiomers of catalyst **C9** and ligand **L43** in the AAA reaction of iminoester **360** with diene **361**, stereodivergent access to all four stereoisomers of **362** was possible with excellent diastereo- and enantioselectivity for each stereoisomer (B, Scheme 74). The high levels of stereoselectivity observed are enabled by the control of the enolate geometry *via* chelation in copper enolate **363**. A detailed mechanistic investigation and computational modelling for the ligand effects in stereodivergent copper/palladium dual-catalysed AAA reactions using α-iminoester substrates with substituted π-allylpalladium(II) intermediates was reported in 2023 by Dang and co-workers.[108]



Scheme 74. The copper/palladium-catalysed AAA reaction of α-iminoesters with simple dienes.

7.4. Copper/Iridium Dual Catalysis

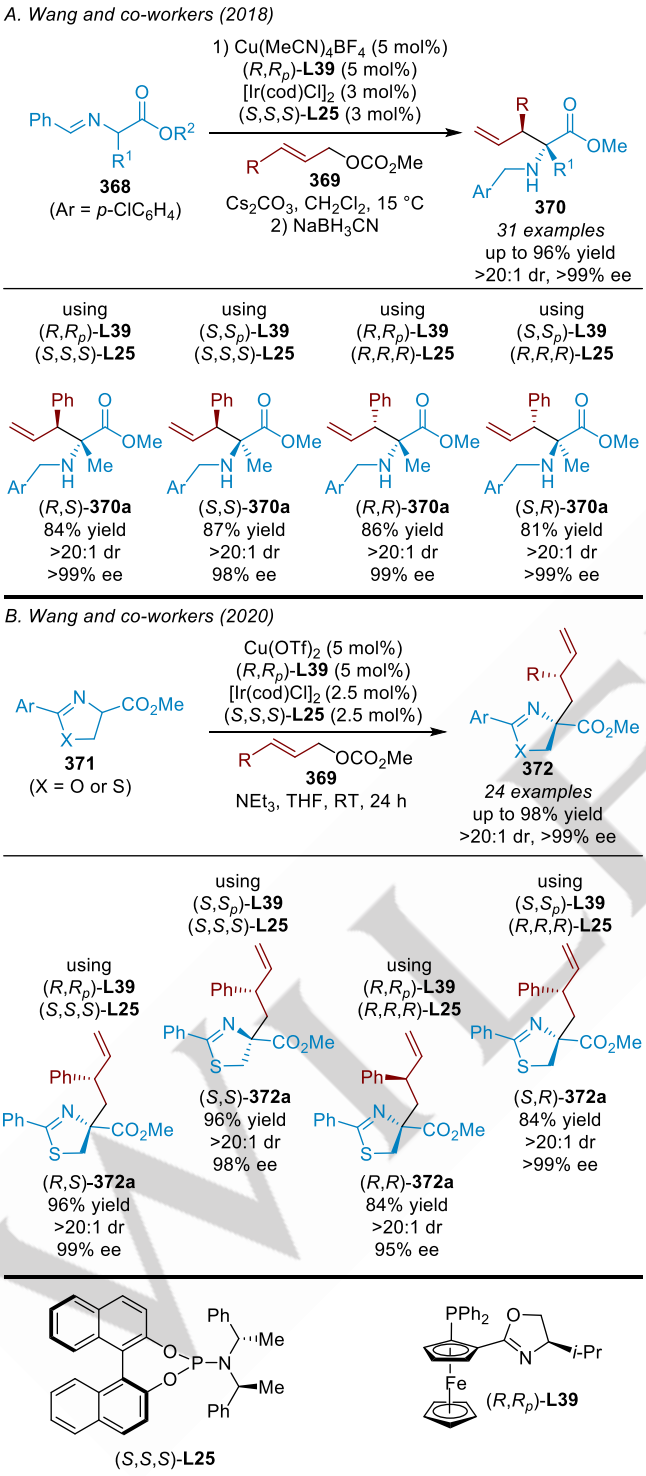
The use of synergistic copper/iridium-catalysed AAA reaction of α-iminoesters with substituted allyl electrophiles in the presence of chiral ligands for both iridium and copper has allowed entry to a wide range of building blocks containing both an α-tetrasubstituted and an adjacent β-tertiary centre with high levels of diastereo- and enantiocontrol. In this context, access to a library of α-iminoesters **366** using the copper/iridium-catalysed AAA reaction of α-iminoesters **364** with allyl carbonates **365** and subsequent imine hydrolysis was reported by Zhang and co-workers in 2018 (Scheme 75).[109] The group was able to obtain both the (*R*,*S*)- and the (*S*,*S*)-diastereoisomers with up to >20:1 dr and >99% ee for all products **366a-c** by varying the enantiomer of ligand **L25** for iridium. In addition, by varying the combination of the enantiomers of ligand **L44** for copper and **L25** for iridium, all four stereoisomers of **366d** were isolated with high levels of diastereo- and enantioselectivity. The cyclic nature of chelated copper enolate **367** is likely essential for the high levels of stereoselectivity observed in this reaction.



Scheme 75. The synergistic copper/iridium catalysed AAA of α-iminoesters with allyl carbonate electrophiles.

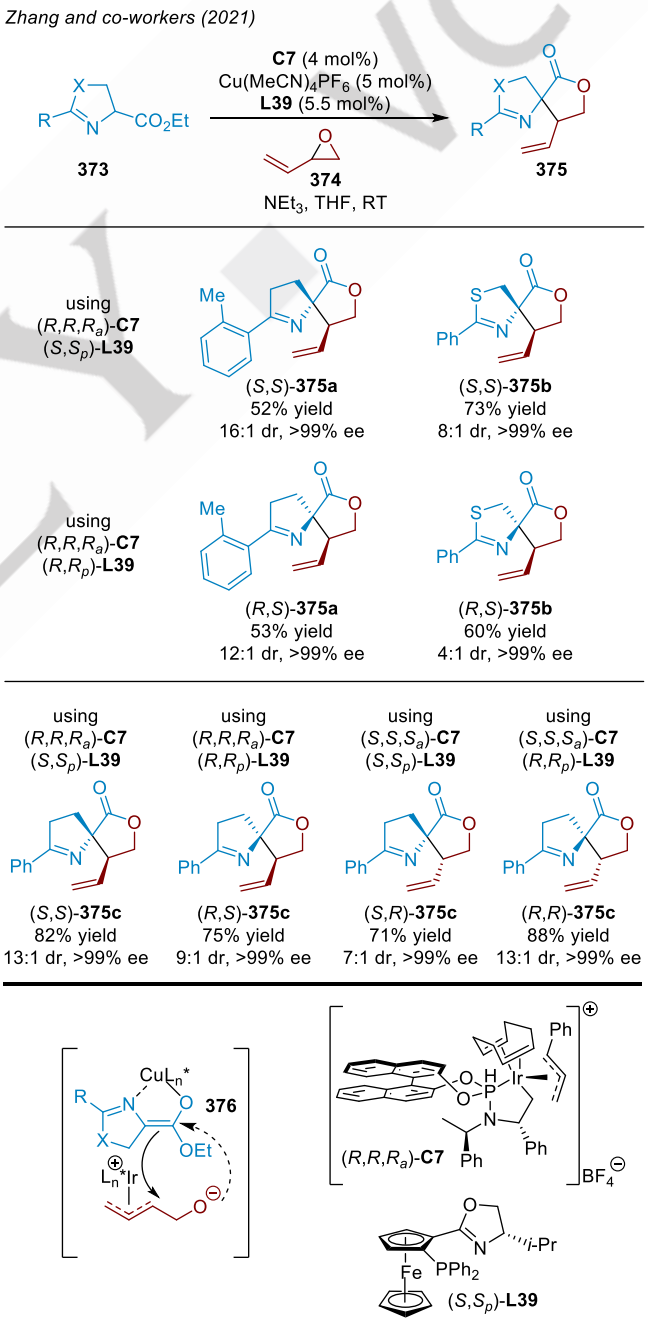
In the same year, Wang and co-workers described the analogous AAA process of α-iminoesters **368** with substituted allyl carbonates **369**, which, following imine reduction, gave amine products **370** with up to >20:1 dr and >99% ee (A, Scheme 76).[110] All four stereoisomers of product **370a** were accessed by varying the enantiomer of ligand **L39** for copper and **L25** for iridium, demonstrating the diastereo- and enantiodivergent nature of the reaction. The authors have also enabled entry to a range of α-thiazoline and α-oxazoline esters **372** bearing two stereogenic centres *via* the Ir/Cu-AAA reaction of **371** with substituted allylic carbonates **369** (B, Scheme 76).[111] Using ligand (*R*,*R*$_p$)-**L39** for

copper and (*S*,*S*,*S*)-**L25** for iridium, high levels of diastereo- and enantioselectivities were obtained. The group again demonstrated this process to be stereodivergent by isolating all four stereoisomers for a limited number of products, such as **372a**, by using different combinations of enantiomers of ligands **L39** for copper and **L25** for iridium in the AAA reaction.



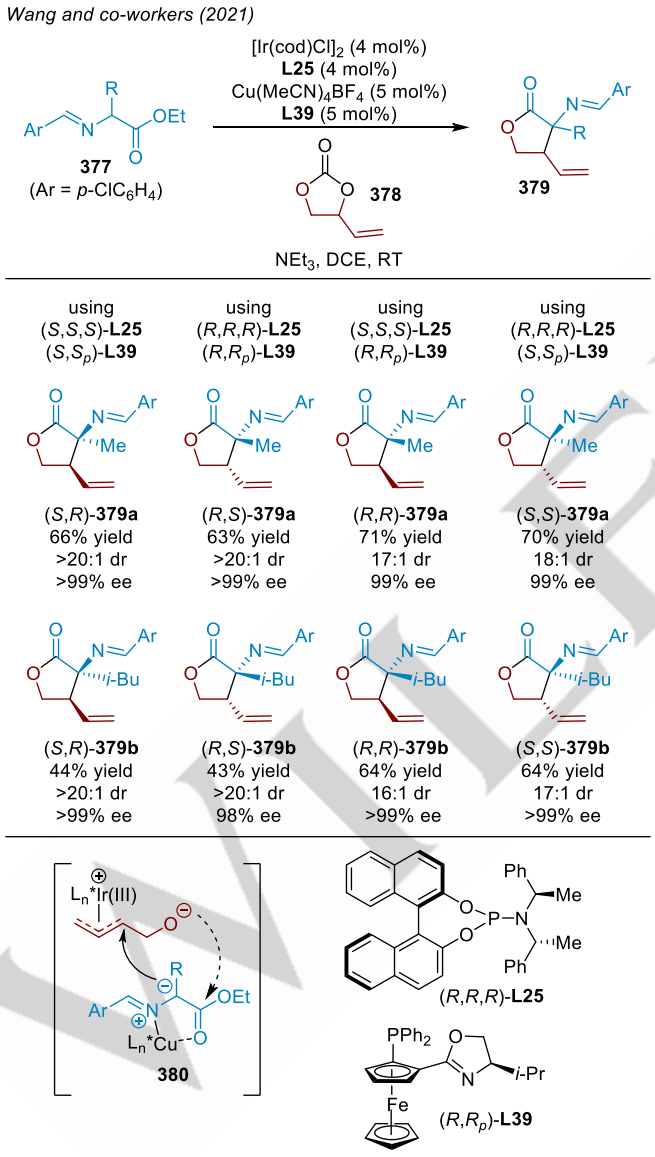
Scheme 76. The synergistic copper/iridium catalysed AAA of α-iminoesters with allyl carbonate electrophiles.

The Zhang group successfully demonstrated the use of allylic oxirane electrophile **374** in conjunction with α-iminoester substrates **373** in the diastereodivergent copper/iridium-catalysed AAA reaction using iridium catalyst (*R*,*R*,*R*$_a$)-**C7** and either chiral ligand (*S*,*S*$_a$)-**L39** or (*R*,*R*$_a$)-**L39** for copper (Scheme 77).[112] The chelated copper enolate **376** undergoes allylic alkylation with the π-allyliridium(III) intermediate regioselectively at the more substituted position, followed by subsequent lactonisation to afford spirocyclic products **375**. (*S*,*S*)-**375a** and (*S*,*S*)-**375b** were generated with 16:1 and 8:1 dr, respectively, each with >99% ee when using (*S*,*S*$_a$)-**L39** for copper. When (*R*,*R*$_a$)-**L39** was used in the AAA reaction, (*R*,*S*)-**375a** and (*R*,*S*)-**375b** were formed with 12:1 and 4:1 dr, respectively, each with >99% ee. The authors showed the reaction to be both diastereo- and enantiodivergent, gaining access to all four stereoisomers of **375c** with high levels of diastereo- and enantioselectivity by varying the enantiomer of ligand **L39** for copper, as well as of iridium catalyst **C7**.



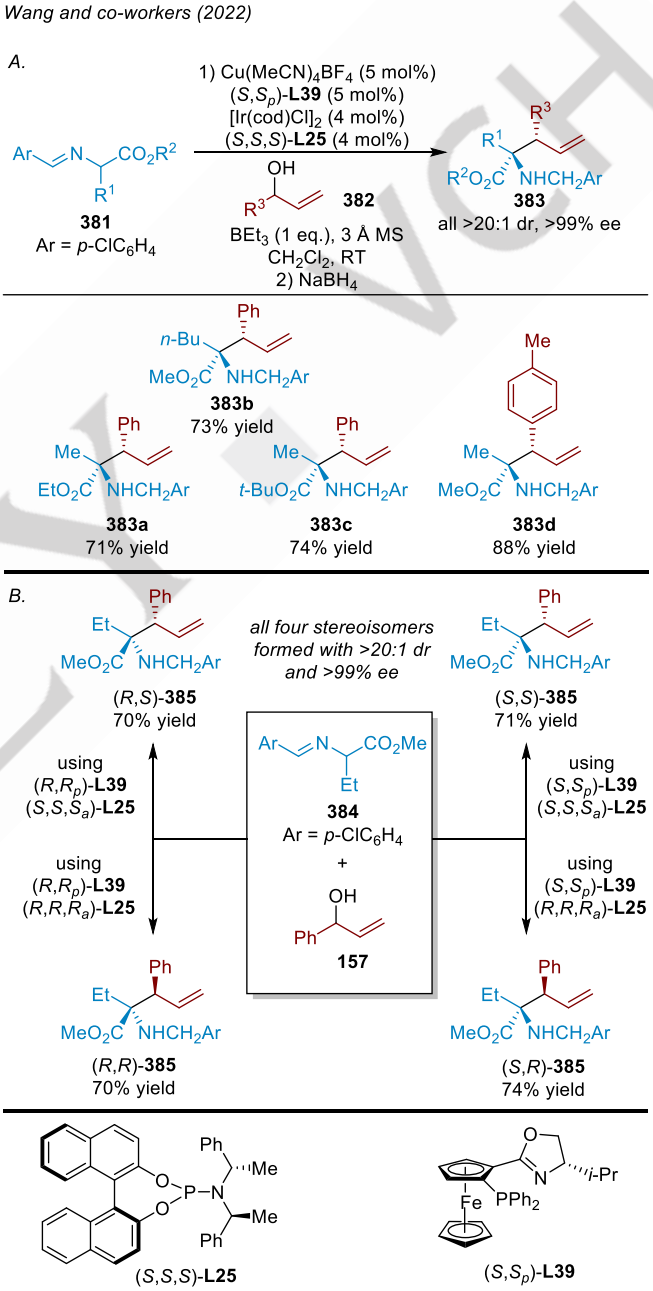
Scheme 77. Copper/iridium-catalysed AAA reaction of α-iminoesters with oxirane.

In 2021, Wang and co-workers disclosed the use of linear α-iminoesters **377** alongside vinyl ethylene carbonate **378** in the copper/iridium-catalysed AAA reaction in the presence of either ligand (*R*,*R*,*R*)-**L25** or (*S*,*S*,*S*)-**L25** for iridium and (*R*,*R*$_p$)-**L39** or (*S*,*S*$_p$)-**L39** for copper, giving rise to γ-butyrolactones **379** (Scheme 78).[113] Specifically, allylic alkylation of chelated enolate **380** with the π-allyliridium(III) intermediate is followed by an intramolecular transesterification to give α-iminolactone products **379**. The authors were also able to isolate all four stereoisomers of **379a** and **379b** with 17:1 to >20:1 dr and 98% to >99% ee by varying the enantiomer of ligands **L39** for copper and **L25** for iridium.



Scheme 78. Copper/iridium dual-catalysed AAA reaction of α-iminoesters with a cyclic carbonate allylic electrophile.

In 2022, the Wang group illustrated the use of allylic alcohol electrophiles **382** in the copper/iridium-catalysed AAA reaction of α-iminoesters **381** (A, Scheme 79).[114] Following the reduction of the resulting allylated imines, a large range of α-aminoesters **383** were formed by varying the α-substituent and the ester residue of iminoester **381**, as well as the allyl alcohol substituent (R^3 in **382**). For example, α-aminoesters **383a-d** were all formed with >20:1 dr and >99% ee. The authors also demonstrated that stereodivergent access to all four stereoisomers of **385** as single enantiomers was possible by varying the combination of ligands (*S*,*S*$_p$)-**L39** and (*R*,*R*$_p$)-**L39** for copper, as well as (*S*,*S*,*S*)-**L25** and (*R*,*R*,*R*)-**L25** for iridium in the AAA reaction of iminoester **384** with allyl alcohol **157** (B, Scheme 79).



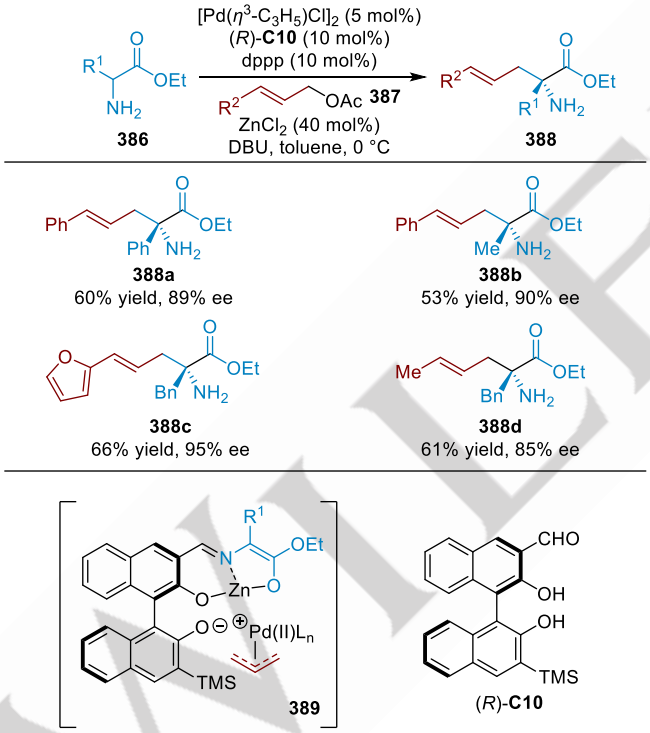
Scheme 79. The copper/iridium catalysed AAA reaction of α-iminoesters with allyl alcohols.

7.5. Chiral Aldehyde/Metal Catalysis

In addition to the use of cations of alkali metals and copper as chelating agents to selectively generate a chelated α-iminoester-derived enolate, zinc has also been found to be effective in

achieving this goal. In this context, Guo and co-workers developed a synthesis of α-tetrasubstituted esters **388** in good yields and high enantioselectivity *via* the chiral aldehyde/palladium/zinc-catalysed AAA reaction of unprotected α-amino esters **386** using zinc chloride as the additive and the aldehyde-containing axially chiral ligand (*R*)-**C10** (Scheme 80).[115] The reaction was highly enantioselective for aryl and alkyl substituents in **386** (R^1) and **387** (R^2), affording **388a-d** with 85-95% ee. Yields of product were generally moderate to good due to the formation of unwanted *N*-allylation side-products. To elucidate the mechanism of the reaction, a set of control experiments suggested that imine **389** is formed *in situ* from the aldehyde of catalyst (*R*)-**C10** and the α-amino group of **386**. In the presence of DBU, deprotonation of the naphthol units of (*R*)-**C10** allows for coordination to both zinc and the palladium centre of the π-allylpalladium(II) intermediate, whereas removal of the α-proton of the ester forms the chelated zinc enolate in intermediate **389**. Allylic alkylation of **389**, followed by either imine hydrolysis or imine exchange, then affords allylated α-aminoester product **388**. An analogous process was subsequently developed by Li and co-workers, which utilised a chiral ligand for palladium and an achiral aldehyde alongside a zinc additive.[116]

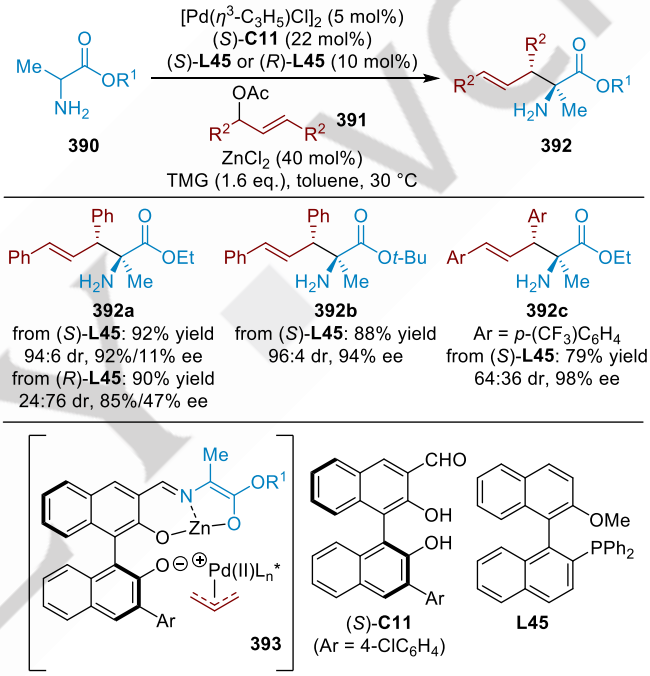
Guo and co-workers (2019)



Scheme 80. The chiral aldehyde/palladium/zinc-catalysed AAA of α-aminoesters.

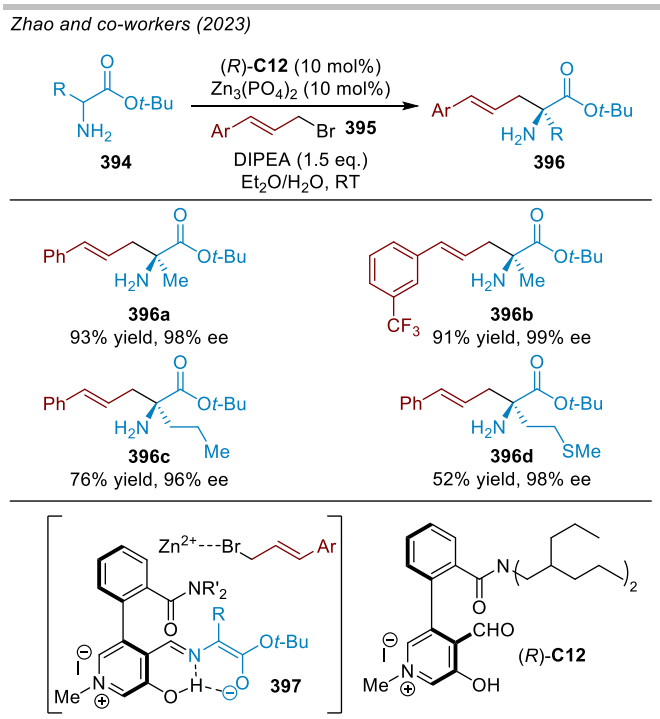
Guo continued to build on their work on chiral aldehyde/palladium/zinc-catalysed AAA reactions of α-aminoester substrates by exploiting disubstituted allylic electrophile substrates **391** in order to construct an additional stereogenic centre in allylated α-aminoester products **392** (Scheme 81).[117] The group found that matched chiral conditions required ligand (*S*)-**L45** for palladium alongside chiral aldehyde (*S*)-**C11**, which enabled the formation of **392a** with 94:6 dr, and each diastereoisomer was isolated with 92% and 11% ee, respectively. Good to excellent diastereo- and enantioselectivity was reported for a number of examples, such as **392b** and **392c** being formed with 96:4 dr and 94% ee, and 64:36 dr and 98% ee, respectively. Using the previously proposed model, the authors suggested that an *in situ* generated chelated zinc-iminoester enolate intermediate **393** is formed, leading to high levels of stereoselectivity of allylic alkylation. In 2023, the Guo group successfully extended this methodology to the use of 1,3-dienes and allenes as electrophiles, thereby reducing the amount of *N*-allylated side-product formation, and, by removing the need for a leaving group at the electrophile, paved the way to a highly atom-economical reaction process.[118]

Guo and co-workers (2023)



Scheme 81. The chiral aldehyde/palladium/zinc-catalysed AAA reaction of α-aminoesters with substituted allyl acetates.

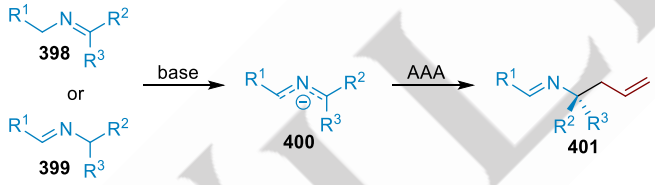
Exploiting a different axially-chiral aldehyde, Zhao and co-workers disclosed a chiral aldehyde/zinc-catalysed AAA reaction of α-amino esters **394** with allyl bromides **395** as S_N2 electrophiles to generate allylated α-tetrasubstituted α-amino esters **396** (Scheme 82).[119] Using aldehyde (*R*)-**C12** as the catalyst, allylated products **396a-d** were formed with excellent enantioselectivity (96-99% ee). The authors proposed that a hydrogen-bond-stabilised enolate intermediate **397** is formed *in situ*, which then undergoes alkylation with zinc-activated allyl bromide electrophile. The use of other alkylating agents, including aryl bromides and propargyl iodides, successfully expanded the substrate scope of this methodology.



Scheme 82. Chiral aldehyde-catalysed AAA of α-aminoesters.

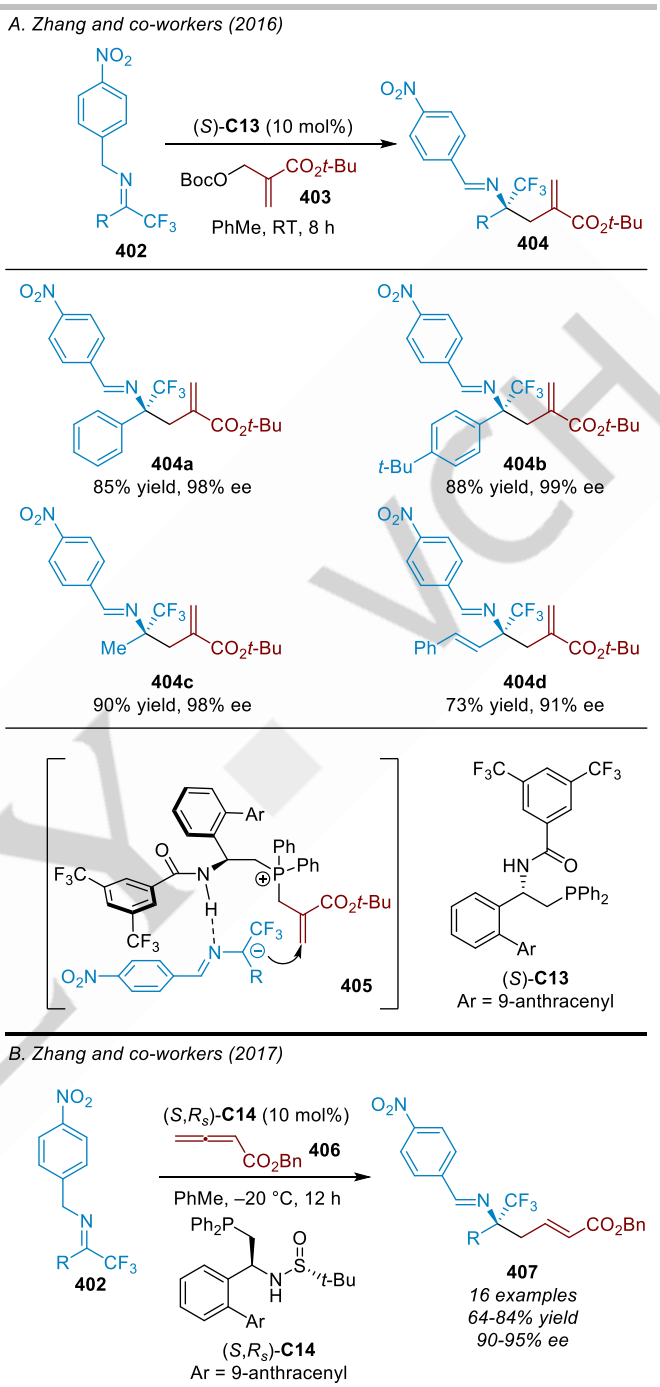
8. The Umpolung AAA Reaction of Imines

There are several examples of the umpolung AAA reaction of imine derivatives **398** and **399** *via* α-imino carbanion **400** that pave the way to nitrogen-containing tetrasubstituted stereogenic centres in allylated imine products **401** (Scheme 83). Although not an enolate, the geometry of α-imino carbanion **400** has to be controlled in the same manner as that of enolates if allylation is to proceed stereoselectively.



Scheme 83. The formation and AAA reaction of α-imino carbanions.

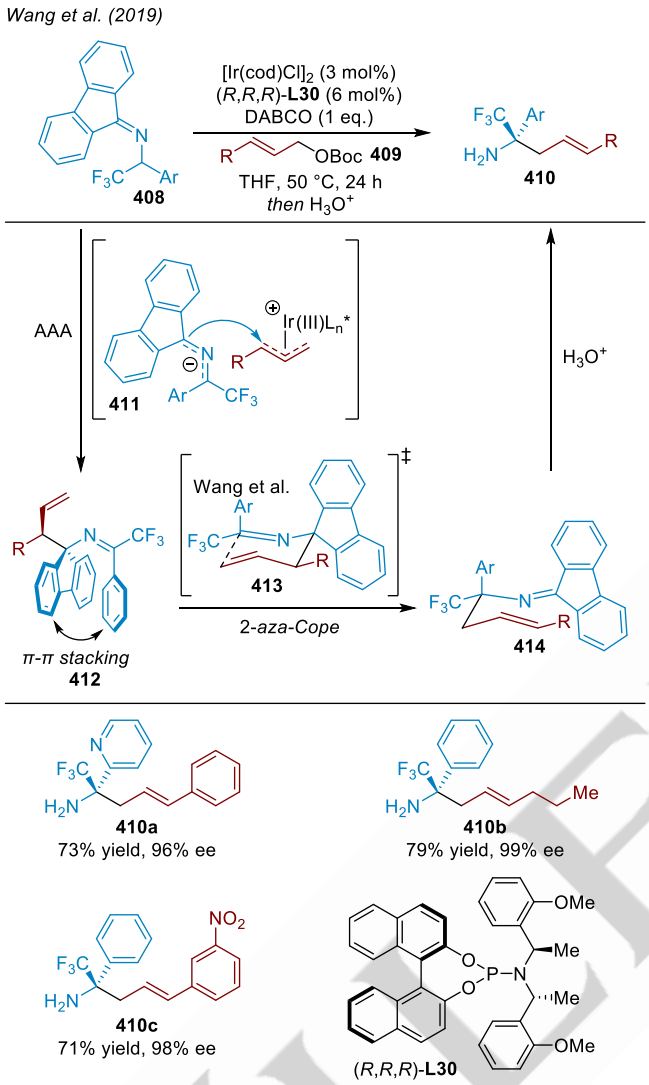
In this context, the Zhang group described the first chiral-phosphine-catalysed AAA reaction of imines **402** with allylic carbonate **403** in the presence of catalyst (*S*)-**C13** (A, Scheme 84).[120] The reaction scope was found to be broad, giving excellent enantioselectivity for a variety of aryl, alkyl and vinyl substituents in **404a-d** (90-99% ee). The prochiral α-imino anion **405** is likely to adopt the configuration that is pre-set by the geometry of imine **402** provided that any equilibration is slow. This process was subsequently extended to the AAA reaction of imines **402** with allenoate electrophile **406** in the presence of chiral phosphine catalyst (*S*,*R*$_s$)-**C14** (B, Scheme 84).[121] This reaction gave similarly high levels of enantioselectivity, forming enantioenriched imines **407** with 90-95% ee.



Scheme 84. The chiral-phosphine-catalysed AAA reaction of imines.

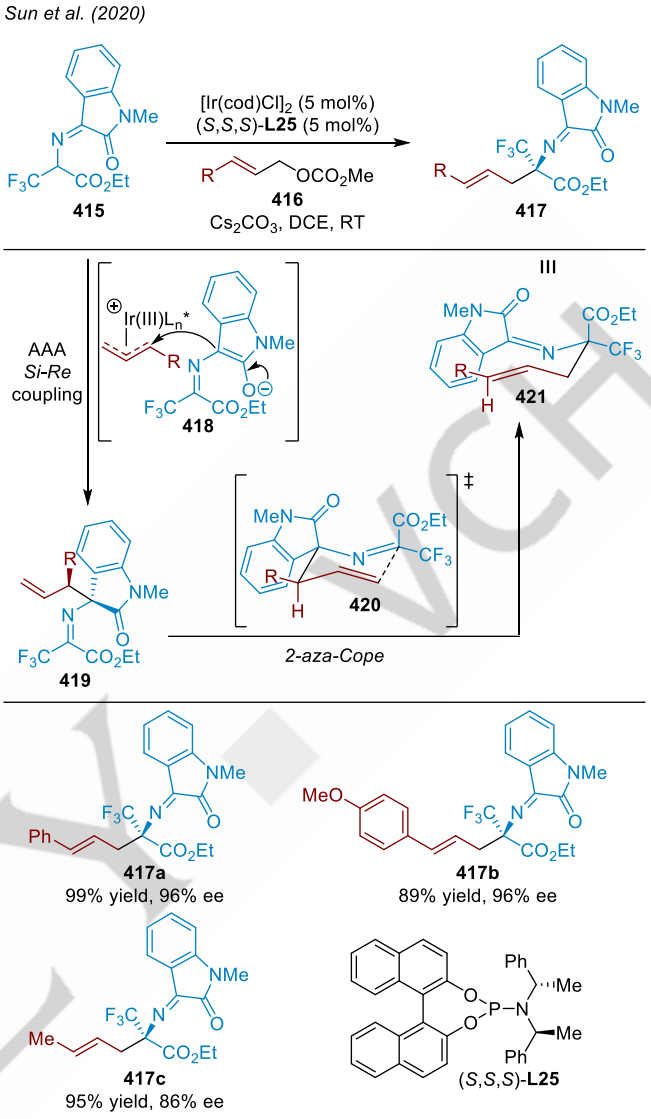
In 2019, Wang *et al*. described the iridium-catalysed AAA reaction of α-trifluoromethyl imines **408**, which, following subsequent hydrolysis, gave enantioenriched α-tertiary amines **410** (Scheme 85).[122] The mechanism commences with the formation of prochiral nucleophile **411** *via* deprotonation of **408** with 1,4-diazabicyclo[2.2.2]octane (DABCO), which undergoes a regio-, diastereo- and enantioselective allylic alkylation with the π-allyliridium(III) electrophile to give **412**, an intermediate that can be isolated. The imine geometry formed in **412** may be a result of stabilising π-π stacking interactions. Under the reaction conditions, a 2-aza-Cope rearrangement of **412** *via* chair-like transition state **413** takes place, whereas hydrolysis of imine **414** paves the way to amine **410**. The reaction gave excellent

enantioselectivity for a range products **410a-c** (96-99% ee). Given the stereospecific nature of the 2-aza-Cope rearrangement, selective formation of one geometrical isomer of the imine in **412** is essential in ensuring an enantioselective reaction.



Scheme 85. Sequential iridium-catalysed AAA/2-aza-Cope rearrangement of imines.

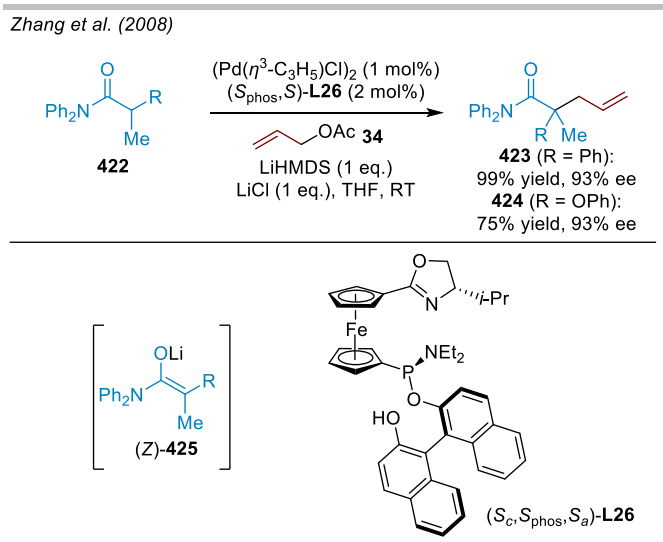
The following year, Sun *et al*. gained entry to α-iminoesters **417**, bearing an α-tetrasubstituted centre from iminoesters **415** and substituted allylic electrophiles **416** with high enantioselectivity *via* a similar iridium-catalysed AAA/2-aza-Cope rearrangement reaction sequence (Scheme 86).[123] For example, products **417a**, **417b** and **417c** were formed with 96%, 96% and 86% ee, respectively. A potential explanation for the observed stereochemical outcome is that an initial *Si*(**418**)-*Re*(π-allyliridium(III)) coupling *via* an iridium-catalysed AAA reaction occurs to give intermediate **419**. A 2-aza-Cope rearrangement of **419** then occurs through the lowest energy transition state **420**, where the R group is placed in the pseudoequatorial position, to give the observed enantiomer of product **421**.



Scheme 86. Sequential iridium-catalysed AAA/2-aza-Cope rearrangement of iminoesters.

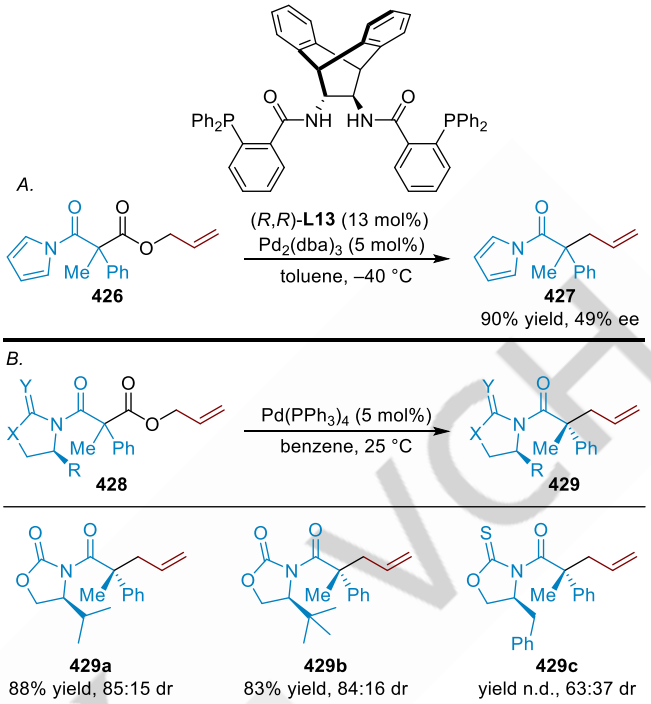
9. The AAA Reaction of Amides

Alongside 1,3-dicarbonyls, aldehydes, ketones and esters, there are a number of examples of successful AAA reactions for the synthesis of α-quaternary amide products. It is important to note, however, that all AAA reactions to afford acyclic α-quaternary amides utilise palladium catalysis. Indeed, in 2008, Zhang *et al*. reported the palladium-catalysed AAA reaction of linear enolates of amides **422** to install an α-quaternary centre in two products **423** and **424** with an excellent 93% ee in both cases (Scheme 87).[124] Given the tertiary and, thus, bulky nature of the amide substituent in **422**, deprotonation with LiHMDS is likely to result in the selective formation of *Z*-enolate (*Z*)-**425**, enabling an enantioselective allylic alkylation.



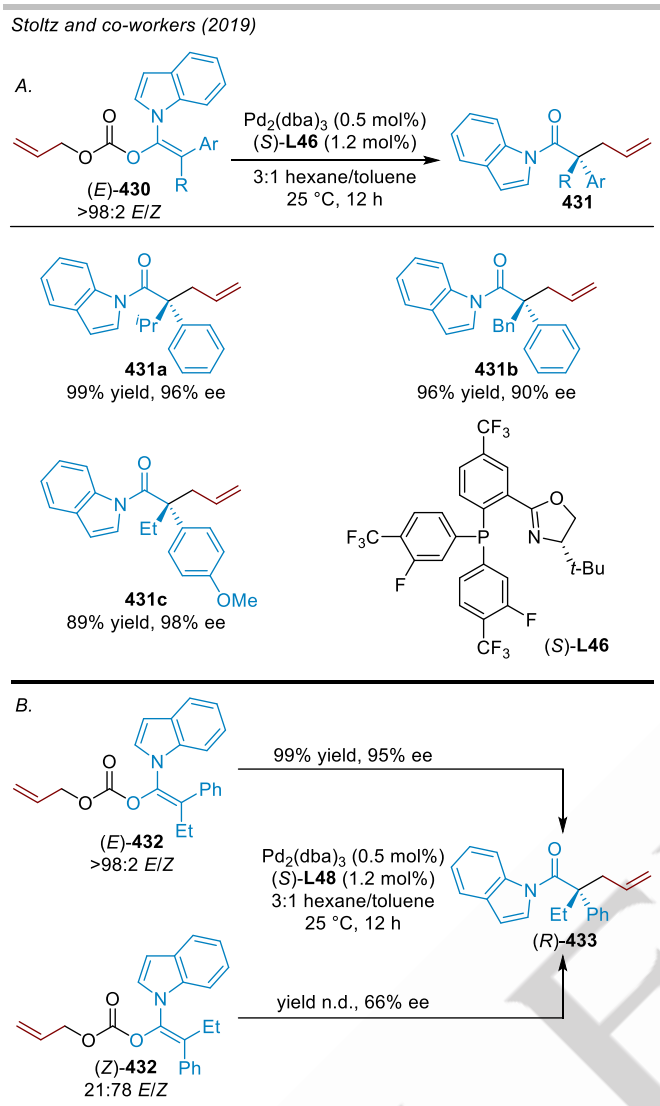
Scheme 87. The palladium-catalysed AAA of linear enolates of amides.

In 2014, Tunge and co-workers attempted the palladium-catalysed DAAA reaction of β-amide allyl ester **426** (A, Scheme 88).[125] Following a ligand screen, ANDEN phenyl Trost ligand (*R*,*R*)-**L13** afforded **427** in 90% yield and 49% ee. The low enantioselectivity was attributed to the poor control of enolate geometry upon decarboxylation. In light of the moderate enantioselectivity in the palladium-catalysed DAAA reaction of **427**, the authors attempted the analogous diastereoselective reaction using chiral β-imido allyl esters **428** in the presence of an achiral palladium catalyst, where the auxiliary in **429** could potentially be subsequently removed, resulting in enantioenriched products (B, Scheme 88). In practice, moderate diastereoselectivities were observed, with **429a** and **429b** formed with 85:15 and 84:16 dr, respectively. Utilising the oxazolidinethione auxiliary gave **429c** with a lower 63:37 dr. Whilst these results show the compatibility of chiral auxiliaries in the palladium-catalysed decarboxylative allylic alkylation reaction, the moderate levels of diastereoselectivity, poor atom economy and the additional synthetic steps associated with the attachment and cleavage of the chiral auxiliary makes the case for future investigations to improve the enantioselective catalytic variant of the reaction.



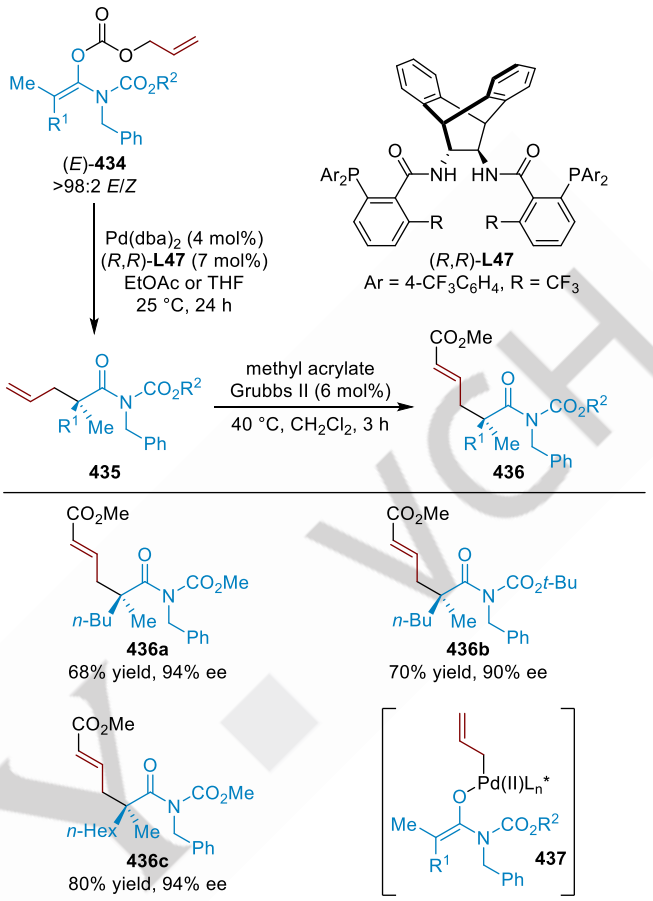
Scheme 88. The palladium-catalysed diastereoselective allylic alkylation of chiral β-imido allyl esters.

To overcome the challenges associated with uncontrolled enolisation of pyrrolyl β-amide allyl esters **426** (*vide supra*, A, Scheme 88), the Stoltz group developed the palladium-catalysed DAAA reaction of *N*-acyl indole-derived *E*-allyl enol carbonate substrates (*E*)-**430**, using ligand (*S*)-**L46**, to access structurally similar α-quaternary indolyl amides **431** (A, Scheme 89).[126] Given the geometrically pure nature of *E*-allyl enol carbonates (*E*)-**430**, the authors observed high levels of enantioselectivity throughout, forming **431a-c** with ≥90% ee. The analogous palladium-catalysed DAAA reaction of both *E*-enol carbonate (*E*)-**432** and *Z*-enol carbonate (*Z*)-**432** was also carried out, which gave the same major enantiomer of product (*R*)-**433** for both (*E*)-**432** (95% ee) and (*Z*)-**432** (66% ee) (B, Scheme 89). This observation provided evidence for a dynamic kinetic resolution of palladium amide enolates that is similar to that previously observed for enolates of aryl ketones (*vide supra*, Scheme 50); however, in this case, either the *E*/*Z* isomerisation of palladium enolate intermediates is slower, or the difference in the rate of allylic alkylation of *E*- and *Z*-enolate intermediates may be less pronounced.



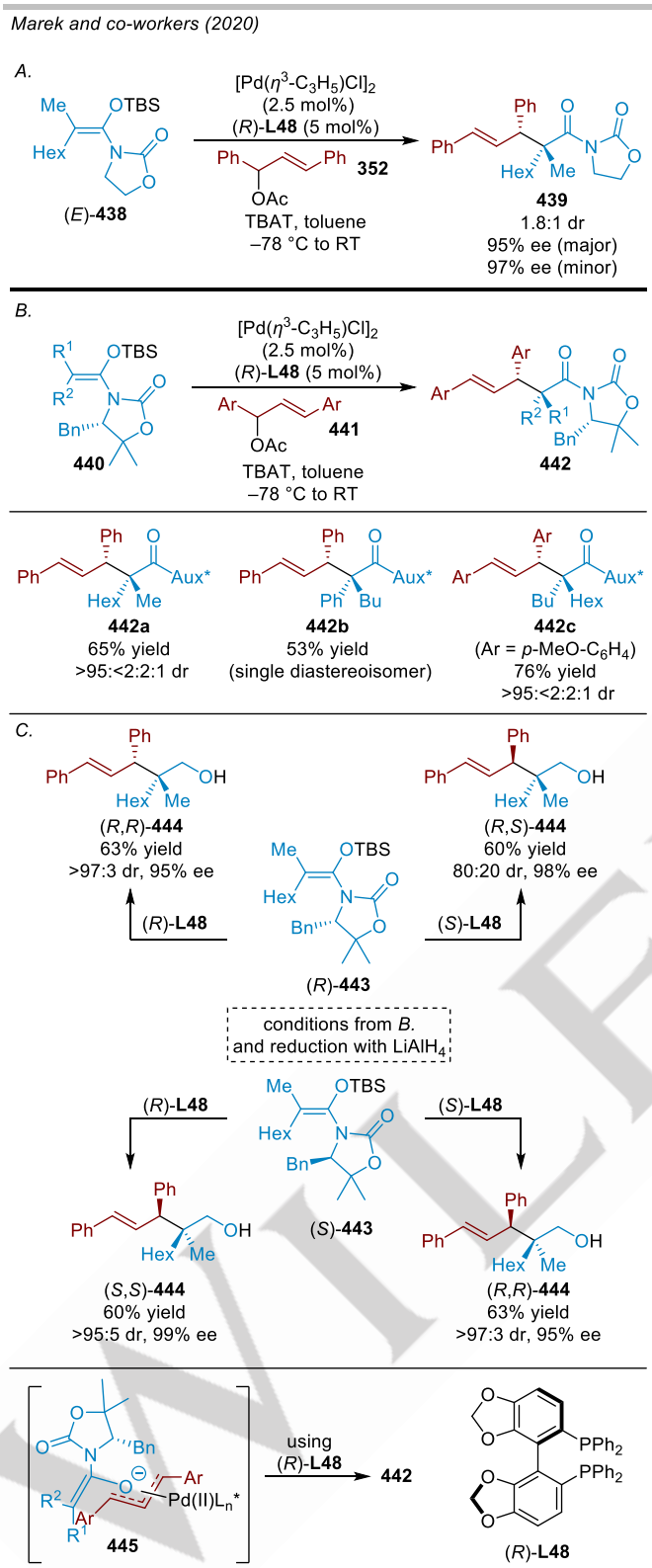
Scheme 89. The palladium-catalysed DAAA reaction of *N*-acyl indole-derived allyl enol carbonates.

In 2017, Marek and co-workers developed a strategy to generate a range of *N*-substituted *E*-enol carbonates (*E*)-**434** with high levels of stereoselectivity (>98:2 *E*/*Z* ratio) (Scheme 90).[127] With *E*-enol carbonate substrates (*E*)-**434** in hand, the palladium-catalysed DAAA reaction was performed using modified ANDEN Trost ligand (*R*,*R*)-**L47**. The reaction gave rise to α-quaternary imides **435**, which, following a cross-metathesis with methyl acrylate, paved the way to imides **436a-c** with good to excellent enantioselectivity (76-94% ee). Given the geometrically pure nature of *E*-allyl enol carbonates (*E*)-**434**, geometrically pure palladium enolate (*E*)-**437** is expected to form upon decarboxylation.



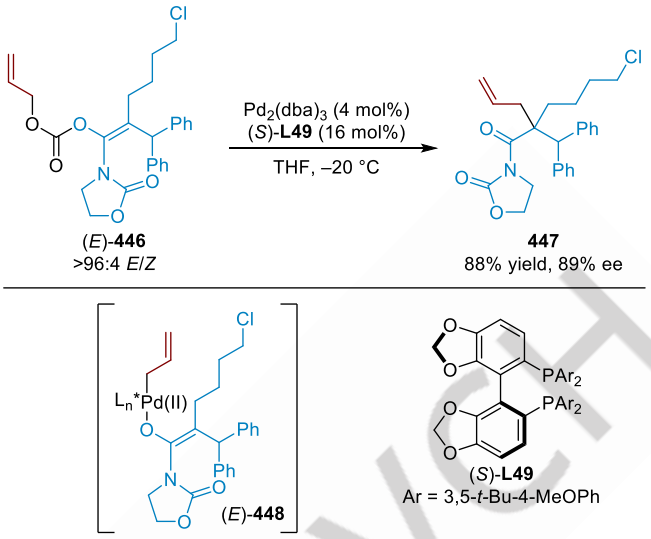
Scheme 90. The palladium-catalysed DAAA reaction of *N*-substituted *E*-enol carbonates.

By utilising *E*-silyl enol ethers (*E*)-**438** in place of *E*-allyl enol carbonates (*E*)-**434**, Marek showed that the palladium-catalysed AAA reaction of oxazolidinone (*E*)-**438** with substituted allylic electrophile **352** gave almost no diastereoselectivity in the formation of **439** (1.8:1 dr), albeit with excellent enantioselectivity for the two diastereoisomers (95% and 97% ee, respectively) (A, Scheme 91).[128] Therefore, the authors developed the palladium-catalysed diastereoselective allylic alkylation of geometrically and enantiomerically pure silyl enol ethers **440** with allylic electrophiles **441** in the presence of chiral ligand (*R*)-**L48** for palladium (B, Scheme 91). Specifically, **442a** was formed with >95:<2:2:1 dr of the four possible diastereoisomers, showing a marked improvement when compared with the analogous AAA reaction of achiral silyl enol ether (*E*)-**438** (1.8:1 dr). By varying the substituents R^1 and R^2 in silyl enol ether **440**, as well as the aryl group of allylic electrophile **441**, product **442b** was formed as a single diastereoisomer and **442c** with >95:<2:2:1 dr. The authors also showed that each of the four possible diastereoisomers of **444** was accessible with high levels of diastereo- and enantioselectivity where the chirality of the auxiliary controls the absolute configuration of the α-stereogenic centre and the choice of ligand **L48** for palladium controls the configuration of the β-stereogenic centre. It can be envisioned that the reaction proceeds *via* a Zimmerman-Traxler six-membered transition state **445**, in which the benzyl substituent of the auxiliary faces away, and the dipoles of the auxiliary and the enolate oppose.



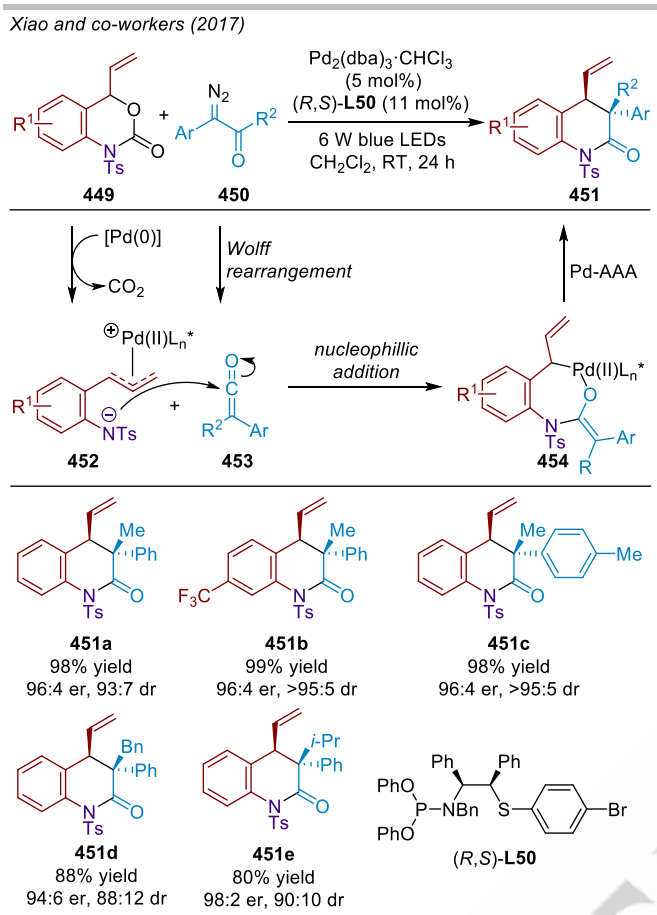
Scheme 91. The palladium-catalysed diastereoselective allylic alkylation of silyl enol ethers of amides.

More recently, Xiao *et al.* developed a stereoselective synthetic route to *E*-enol carbonate (*E*)-**446** (*E*/*Z* ratio of >96:4) (Scheme 92).[129] The palladium-catalysed DAAA reaction of (*E*)-**446** using ligand (*S*)-**L49** then afforded α-quaternary amide **447** in 88% yield and 89% ee, presumably *via* *E*-enolate (*E*)-**448** formed after decarboxylation.



Scheme 92. The palladium-catalysed DAAA reaction of an amide-derived enol carbonate.

As a means of enhancing the structural diversity attainable by AAA reactions, Xiao and co-workers developed an intercepted palladium-catalysed DAAA reaction of cyclic carbamates **449** in the presence of diazocarbonyls **450** (Scheme 93).[130] In this context, sulfonamide anion **452** was generated following oxidative addition of palladium(0) and decarboxylation. Simultaneously, ketene **453** was generated from diazo carbonyl **450** photochemically. The nucleophilic addition of sulfonamide anion **452** to ketene **453** then gave intermediate **454**, which possesses both the σ-allylpalladium(II) electrophilic component and the *N*-tosyl protected amide enolate nucleophilic component. Finally, intramolecular allylic alkylation, using ligand (*R*,*S*)-**L50** for palladium, gave rise to α-quaternary β-tertiary lactam **451**. In this process, high stereoselectivity was observed for a number of products, including **451a-e**, which were formed with 84:16 to >95:5 dr and 94:6 to 98:2 er. It was suggested that the enolate geometry of intermediate **454** primarily existed with the larger aryl group *Z* to the oxyanion of the enolate in order to minimise allylic strain with the bulky sulfonamide. As previously discussed, Xiao and co-workers extended the scope of this reaction towards ω-lactones *via* the AAA of ester enolates by replacing *N*-tosyl protected carbamates **449** with cyclic carbonates **273** (*vide supra*, Scheme 55).



Scheme 93. The intercepted palladium-catalysed DAAA reaction of cyclic carbamates.

10. Summary and Outlook

To enable the construction of highly congested stereogenic centres, the catalytic asymmetric allylic alkylation (AAA) reaction process has traditionally centred around the functionalisation of cyclic prochiral nucleophiles, primarily enolates, that benefit from the fixed nature of the alkene geometry. In contrast, the AAA reaction of acyclic enolates is substantially more challenging, where an extra layer of complexity in achieving a stereoselective alkylation is introduced due to the presence of *E*/*Z* geometrical isomers of the nucleophile. Despite this obstacle, the number of AAA reactions that enable access to acyclic quaternary and tetrasubstituted centres with high levels of stereoselectivity is rapidly growing.

To achieve stereocontrol in the allylic alkylation of acyclic prochiral enolates, stereoselective enolisation prior to alkylation has been found to be essential in most cases. Towards this end, a number of strategies that enable stereocontrolled enolisation have been successfully adopted, predominantly by means of a judicious choice of substrate. The simplest scenario involves the use of pre-functionalised, geometrically pure precursors to acyclic enolates, such as allyl enol carbonates, as they specifically result in the formation of geometrically pure enolate intermediates. Nevertheless, unenolised carbonyl compounds have also been shown to undergo successful AAA reactions provided that they are either predisposed to form just one enolate selectively for steric or electronic reasons, or they give rise to a chelated and, thus, cyclic enolate intermediate. Alternatively, the AAA reaction of enamine intermediates as specific enol equivalents has been found to be highly selective due to the more stereoselective nature of enamine formation as compared to enolisation. Furthermore, the AAA reaction has even been successfully extended to acyclic prochiral nucleophiles beyond enolates, e.g., in the umpolung functionalisation of imines, so long as the geometry of the nucleophilic intermediate is also adequately controlled.

Remarkably, several observations have been made wherein unselective enolisation can still result in a highly stereoselective allylic alkylation. In these examples, a dynamic kinetic resolution of enolates was found to operate, enabling the stereoselective alkylation of sterically unbiased carbonyl compounds. However, this process is not yet well-understood and has been shown to steer the AAA reaction of only a handful of substrates. The future development of AAA processes driven by the dynamic kinetic resolution of enolates of carbonyl compounds that are traditionally difficult to enolise selectively would substantially widen the scope of acyclic stereofunctionalised building blocks accessible by the reaction.

Although palladium and iridium catalysts are most commonly utilised in AAA processes, there have been a growing number of reports of highly enantioselective AAA reactions of acyclic nucleophiles using non-rare-earth metal catalysts, such as those based on nickel and copper. For example, the AAA reaction of enamines with substituted allylic nickel electrophiles has been shown to undergo successful alkylation with high levels of enantioselectivity and with a regioselectivity pattern that is similar to that of palladium-catalysed AAA reactions, where addition at the less substituted position of the allylic electrophile is favoured due to steric effects. Similarly, copper enolates have also been demonstrated to undergo highly stereoselective alkylation with simple S_N2 or Michael acceptor electrophiles. In addition, the use of non-metal catalysts, such as phase-transfer and organocatalytic approaches, are also becoming increasingly efficient. As such, the development of AAA reactions using greener and more sustainable catalysts should open up new avenues to more cost effective and renewable methodologies for the assembly of stereofunctionalised molecular architecture.

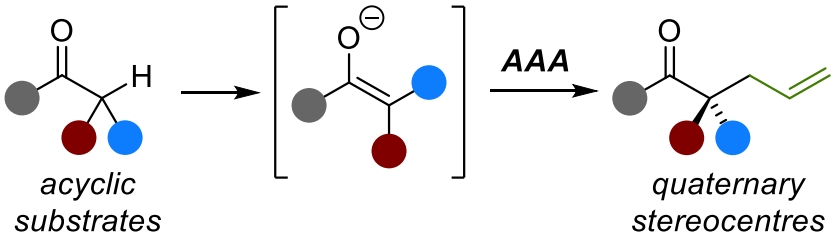
Keywords: enolates • asymmetric allylic alkylation • acyclic stereocontrol • quaternary centers • stereoselectivity

[1] F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752-6756.
[2] a) D. G. Brown and J. Boström, *J. Med. Chem.* **2016**, *59*, 4443-4458; b) S. D. Roughley and A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451-3479.
[3] a) T. J. Ritchie and S. J. F. Macdonald, *Drug Discov. Today.* **2009**, *14*, 1011-1020; b) Y. Liu, S.-J. Han, W.-B. Liu and B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740-751.
[4] I. P. Silvestri and P. J. J. Colbon, *ACS Med. Chem. Lett.* **2021**, *12*, 1220-1229.
[5] a) T. T. Talele, *J. Med. Chem.* **2020**, *63*, 13291-13315; b) P. Arya, R. Joseph, Z. Gan and B. Rakic, *Chem Biol* **2005**, *12*, 163-180.
[6] a) J. P. Das and I. Marek, *Chem. Commun.* **2011**, *47*, 4593-4623; b) T. Ling and F. Rivas, *Tetrahedron* **2016**, *72*, 6729-6777; c) K. W. Quasdorf and L. E. Overman, *Nature* **2014**, *516*, 181-191.
[7] a) A. Heumann and M. Réglier, *Tetrahedron* **1995**, *51*, 975-1015; b) L. Milhau and P. J. Guiry in *Palladium-Catalyzed Enantioselective Allylic Substitution*, (Ed. U. Kazmaier), Springer Berlin Heidelberg, Berlin, Heidelberg, **2012**, pp. 95-153; c) O. Pàmies, J. Margalef, S.

Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J.-E. Bäckvall, A. Pfaltz, M. A. Pericàs and M. Diéguez, *Chem. Rev.* **2021**, *121*, 4373-4505; d) J. Le Bras and J. Muzart, *Eur. J. Org. Chem.* **2016**, *2016*, 2565-2593.
[8] a) P. Tosatti, A. Nelson and S. P. Marsden, *Org. Biomol. Chem.* **2012**, *10*, 3147-3163; b) L. Süsse and B. M. Stoltz, *Chem. Rev.* **2021**, *121*, 4084-4099.
[9] a) B. M. Trost, J. Xu and T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357; b) B. P. Pritchett and B. M. Stoltz, *Nat. Prod. Rep.* **2018**, *35*, 559-574; c) B. M. Trost, *Chem. Pharm. Bull.* **2002**, *50*, 1-14; d) R. Cano, A. Zakarian and G. P. McGlacken, *Angew. Chem. Int. Ed.* **2017**, *56*, 9278-9290; e) Z. Lu and S. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258-297; f) F. Richard, P. Clark, A. Hannam, T. Keenan, A. Jean and S. Arseniyadis, *Chem. Soc. Rev.* **2024**, *Advance Article*, DOI: 10.1039/d3cs00856h.
[10] a) T. B. Wright and P. A. Evans, *Chem. Rev.* **2021**, *121*, 9196-9242; b) S. Vera, A. Landa, A. Mielgo, I. Ganboa, M. Oiarbide and V. Soloshonok, *Molecules* **2023**, *28*, 2694; c) G. Wu, J.-R. Wu, Y. Huang and Y.-W. Yang, *Chem. Asian J.* **2021**, *16*, 1864-1877; d) J. James, M. Jackson and P. J. Guiry, *Adv. Synth. Catal.* **2019**, *361*, 3016-3049; e) J. Feng, M. Holmes and M. J. Krische, *Chem. Rev.* **2017**, *117*, 12564-12580.
[11] B. W. H. Turnbull and P. A. Evans, *J. Am. Chem. Soc.* **2015**, *137*, 6156-6159.
[12] A. Sripada and C. Wolf, *J. Org. Chem.* **2022**, *87*, 11880-11887.
[13] T. Fujita, T. Yamamoto, Y. Morita, H. Chen, Y. Shimizu and M. Kanai, *J. Am. Chem. Soc.* **2018**, *140*, 5899-5903.
[14] M. Sawamura, Y. Nakayama, W.-M. Tang and Y. Ito, *J. Org. Chem.* **1996**, *61*, 9090-9096.
[15] K. Ohmatsu, M. Ito, T. Kunieda and T. Ooi, *Nat. Chem.* **2012**, *4*, 473-477.
[16] R. T. Davison, P. D. Parker, X. Hou, C. P. Chung, S. A. Augustine and V. M. Dong, *Angew. Chem. Int. Ed.* **2021**, *60*, 4599-4603.
[17] P. Koschker and B. Breit, *Acc. Chem. Res.* **2016**, *49*, 1524-1536.
[18] B. M. Trost, J. E. Schultz and Y. Bai, *Angew. Chem. Int. Ed.* **2019**, *58*, 11820-11825.
[19] T. Hayashi, K. Kanehira, T. Hagihara and M. Kumada, *J. Org. Chem.* **1988**, *53*, 113-120.
[20] M. Sawamura, H. Nagata, H. Sakamoto and Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 2586-2592.
[21] R. Kuwano and Y. Ito, *J. Am. Chem. Soc.* **1999**, *121*, 3236-3237.
[22] R. Kuwano, K.-i. Uchida and Y. Ito, *Org. Lett.* **2003**, *5*, 2177-2179.
[23] M. Nascimento de Oliveira, J. Fournier, S. Arseniyadis and J. Cossy, *Org. Lett.* **2017**, *19*, 14-17.
[24] S. A. Asad, J. Ulicki, M. Shevyrev, N. Uddin, E. Alberch and M. M. Hossain, *Eur. J. Org. Chem.* **2014**, *2014*, 5695-5699.
[25] E. Alberch, C. Brook, S. A. Asad, M. Shevyrev, J. S. Ulicki and M. M. Hossain, *Synlett* **2015**, *26*, 388-392.
[26] N. Uddin, M. Rahaman, E. Alberch, S. A. Asad and M. Mahmun Hossain, *Tetrahedron Lett.* **2018**, *59*, 3401-3404.
[27] J. Han, L. Hoteite and J. P. A. Harrity, *Chem. Eur. J.* **2022**, *28*, e202201595.
[28] a) C. P. Butts, E. Filali, G. C. Lloyd-Jones, P.-O. Norrby, D. A. Sale and Y. Schramm, *J. Am. Chem. Soc.* **2009**, *131*, 9945-9957; b) S. Aubert, T. Katsina and S. Arseniyadis, *Org. Lett.* **2019**, *21*, 2231-2235; c) J. James and P. J. Guiry, *ACS Catal.* **2017**, *7*, 1397-1402.
[29] P. Trillo and A. Baeza, *Adv. Synth. Catal.* **2017**, *359*, 1735-1741.
[30] W.-B. Liu, C. M. Reeves and B. M. Stoltz, *J. Am. Chem. Soc.* **2013**, *135*, 17298-17301.
[31] Q. Cheng, H.-F. Tu, C. Zheng, J.-P. Qu, G. Helmchen and S.-L. You, *Chem. Rev.* **2019**, *119*, 1855-1969.
[32] L. Ding, H. Song, C. Zheng and S.-L. You, *J. Am. Chem. Soc.* **2022**, *144*, 4770-4775.
[33] L.-H. Chen, Y.-T. Ma, F. Yang, X.-Y. Huang, S.-W. Chen, K. Ji and Z.-S. Chen, *Adv. Synth. Catal.* **2019**, *361*, 1307-1312.
[34] H. Wang, Y. Xu, F. Zhang, Y. Liu and X. Feng, *Angew. Chem. Int. Ed.* **2022**, *61*, e202115715.
[35] H. Zhou, L. Zhang, C. Xu and S. Luo, *Angew. Chem. Int. Ed.* **2015**, *54*, 12645-12648.
[36] H. Zhou, Y. Wang, L. Zhang, M. Cai and S. Luo, *J. Am. Chem. Soc.* **2017**, *139*, 3631-3634.
[37] M. Yoshida, *J. Org. Chem.* **2017**, *82*, 12821-12826.
[38] Y.-N. Xu, M.-Z. Zhu and S.-K. Tian, *J. Org. Chem.* **2019**, *84*, 14936-14942.
[39] Y. Wang, J. Chai, C. You, J. Zhang, X. Mi, L. Zhang and S. Luo, *J. Am. Chem. Soc.* **2020**, *142*, 3184-3195.
[40] T. Hashimoto, K. Sasaki, K. Fukumoto, Y. Murase, N. Abe, T. Ooi and K. Maruoka, *Chem. Asian J.* **2010**, *5*, 562-570.
[41] M. W. Ha, S. Choi, S. Kim, J. Y. Lee, J. K. Lee, J. Lee, S. Hong and H.-g. Park, *RSC Adv.* **2016**, *6*, 77427-77430.
[42] D. Kim, M. W. Ha, S. Hong, C. Park, B. Kim, J. Yang and H.-g. Park, *J. Org. Chem.* **2017**, *82*, 4936-4943.
[43] B. M. Trost, J. Xu and M. Reichle, *J. Am. Chem. Soc.* **2007**, *129*, 282-283.
[44] T. B. Wright and P. A. Evans, *J. Am. Chem. Soc.* **2016**, *138*, 15303-15306.
[45] S. Mukherjee and B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336-11337.
[46] G. Jiang and B. List, *Angew. Chem. Int. Ed.* **2011**, *50*, 9471-9474.
[47] Á. M. Pálvölgyi, J. Smith, M. Schnürch and K. Bica-Schröder, *J. Org. Chem.* **2021**, *86*, 850-860.
[48] M. Yoshida, T. Terumine, E. Masaki and S. Hara, *J. Org. Chem.* **2013**, *78*, 10853-10859.
[49] M. Yoshida, E. Masaki, T. Terumine and S. Hara, *Synthesis* **2014**, *46*, 1367-1373.
[50] P.-S. Wang, H.-C. Lin, Y.-J. Zhai, Z.-Y. Han and L.-Z. Gong, *Angew. Chem. Int. Ed.* **2014**, *53*, 12218-12221.
[51] Y.-L. Su, L.-L. Li, X.-L. Zhou, Z.-Y. Dai, P.-S. Wang and L.-Z. Gong, *Org. Lett.* **2018**, *20*, 2403-2406.
[52] K. Zhang, C. Carmo, L. Deiana, E. S. Grape, A. K. Inge and A. Córdova, *Chem. Eur. J.* **2023**, *29*, e202301725.
[53] W.-Q. Zhang and H.-C. Shen, *ACS Catal.* **2021**, *11*, 11849-11854.
[54] S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, *Science* **2013**, *340*, 1065-1068.
[55] M.-M. Zhang, Y.-N. Wang, B.-C. Wang, X.-W. Chen, L.-Q. Lu and W.-J. Xiao, *Nat. Commun.* **2019**, *10*, 2716.
[56] F. A. Cruz and V. M. Dong, *J. Am. Chem. Soc.* **2017**, *139*, 1029-1032.
[57] A. Ballesteros, P. Morán-Poladura and J. M. González, *Chem. Commun.* **2016**, *52*, 2905-2908.
[58] a) M. P. Brochu, S. P. Brown and D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108-4109; b) M. Marigo, D. Fielenbach, A. Braunton, A. Kjærsgaard and K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3703-3706.
[59] J. Fernández-Casado, R. Nelson, J. L. Mascareñas and F. López, *Chem. Commun.* **2016**, *52*, 2909-2912.
[60] L. D. M. Nicholls and H. Wennemers, *Chem. Eur. J.* **2021**, *27*, 17559-17564.
[61] R. Blieck, S. Lemouzy, A. van der Lee, M. Taillefer and F. Monnier, *Org. Lett.* **2021**, *23*, 9199-9203.
[62] S. Huang, F.-F. Tong, D.-C. Bai, G.-P. Zhang, Y.-J. Jiang, B. Zhang, X. Leng, Y.-L. Guo, X.-L. Wan, X. Zhang, C.-H. Ding and X.-L. Hou, *Nat. Commun.* **2021**, *12*, 6551.
[63] S. Huang, G.-P. Zhang, Y.-J. Jiang, F.-L. Yu, C.-H. Ding and X.-L. Hou, *Chem. Commun.* **2022**, *58*, 3513-3516.
[64] Y. Ito, M. Sawamura, M. Matsuoka, Y. Matsumoto and T. Hayashi, *Tetrahedron Lett.* **1987**, *28*, 4849-4852.
[65] A. Nowicki, A. Mortreux and F. Agbossou-Niedercorn, *Tetrahedron Lett.* **2005**, *46*, 1617-1621.
[66] Q. Bao, T.-J. Sun, Y.-P. Zhang, Z.-H. Wang, Y. You, Z.-Z. Ge, M.-Q. Zhou, J.-Q. Zhao and W.-C. Yuan, *Org. Chem. Front.* **2023**.
[67] R. Kuwano, R. Nishio and Y. Ito, *Org. Lett.* **1999**, *1*, 837-839.
[68] Y. Huang, Q.-S. Zhang, P. Fang, T.-G. Chen, J. Zhu and X.-L. Hou, *Chem. Commun.* **2014**, *50*, 6751-6753.
[69] R. Kuwano, N. Ishida and M. Murakami, *Chem. Commun.* **2005**, 3951-3952.
[70] a) J. M. Curto and M. C. Kozlowski, *J. Org. Chem.* **2014**, *79*, 5359-5364; b) J. M. Curto, J. S. Dickstein, S. Berritt and M. C. Kozlowski, *Org. Lett.* **2014**, *16*, 1948-1951.
[71] B. M. Trost, J. E. Schultz, T. Chang and M. R. Maduabum, *J. Am. Chem. Soc.* **2019**, *141*, 9521-9526.

[72] M. Nakamura, A. Hajra, K. Endo and E. Nakamura, *Angew. Chem. Int. Ed.* **2005**, *44*, 7248-7251.
[73] É. Bélanger, K. Cantin, O. Messe, M. Tremblay and J.-F. Paquin, *J. Am. Chem. Soc.* **2007**, *129*, 1034-1035.
[74] É. Bélanger, C. Houzé, N. Guimond, K. Cantin and J.-F. Paquin, *Chem. Commun.* **2008**, 3251-3253.
[75] W. Wang, H. Shen, X.-L. Wan, Q.-Y. Chen and Y. Guo, *J. Org. Chem.* **2014**, *79*, 6347-6353.
[76] W.-F. Lian, C.-C. Wang, H.-P. Kang, H.-L. Li, J. Feng, S. Liu and Z.-W. Zhang, *Tetrahedron Lett.* **2017**, *58*, 1399-1402.
[77] H. Kondo, M. Maeno, K. Sasaki, M. Guo, M. Hashimoto, M. Shiro and N. Shibata, *Org. Lett.* **2018**, *20*, 7044-7048.
[78] E. J. Alexy, H. Zhang and B. M. Stoltz, *J. Am. Chem. Soc.* **2018**, *140*, 10109-10112.
[79] R. Lavernhe, E. J. Alexy, H. Zhang and B. M. Stoltz, *Org. Lett.* **2020**, *22*, 4272-4275.
[80] R. Lavernhe, E. J. Alexy, H. Zhang and B. M. Stoltz, *Adv. Synth. Catal.* **2020**, *362*, 344-347.
[81] G. Laidlaw and V. Franckevičius, *Org. Lett.* **2022**, *24*, 400-405.
[82] E. Bowen, G. Laidlaw, B. C. Atkinson, T. A. McArdle-Ismaguilov and V. Franckevičius, *J. Org. Chem.* **2022**, *87*, 10256-10276.
[83] R. Shintani, M. Murakami and T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 12356-12357.
[84] R. Shintani, S. Park, F. Shirozu, M. Murakami and T. Hayashi, *J. Am. Chem. Soc.* **2008**, *130*, 16174-16175.
[85] Y. Wei, S. Liu, M.-M. Li, Y. Li, Y. Lan, L.-Q. Lu and W.-J. Xiao, *J. Am. Chem. Soc.* **2019**, *141*, 133-137.
[86] J. Chen, X. Zhao and W. Dan, *J. Org. Chem.* **2017**, *82*, 10693-10698.
[87] A. G. Doyle and E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2007**, *46*, 3701-3705.
[88] B. M. Trost, J. R. Miller and C. M. Hoffman, Jr., *J. Am. Chem. Soc.* **2011**, *133*, 8165-8167.
[89] J. Zhang, B. Lu, Z. Ge, L. Wang and X. Wang, *Org. Lett.* **2022**, *24*, 8423-8428.
[90] M. Sawamura, M. Sudoh and Y. Ito, *J. Am. Chem. Soc.* **1996**, *118*, 3309-3310.
[91] A. Nowicki, A. Mortreux and F. Agbossou-Niedercorn, *Tetrahedron: Asymmetry* **2005**, *16*, 1295-1298.
[92] X. Jiang, W. Chen and J. F. Hartwig, *Angew. Chem. Int. Ed.* **2016**, *55*, 5819-5823.
[93] Z.-T. He, X. Jiang and J. F. Hartwig, *J. Am. Chem. Soc.* **2019**, *141*, 13066-13073.
[94] X.-J. Liu, S. Jin, W.-Y. Zhang, Q.-Q. Liu, C. Zheng and S.-L. You, *Angew. Chem. Int. Ed.* **2020**, *59*, 2039-2043.
[95] X. Yan, Z. Li, L. Fan, J. Li and G. Liu, *Chem. Asian J.* **2023**, *18*, e202300160.
[96] J. Wang, F. He and X. Yang, *Nat. Commun.* **2021**, *12*, 6700.
[97] S.-L. You, X.-L. Hou, L.-X. Dai, B.-X. Cao and J. Sun, *Chem. Commun.* **2000**, 1933-1934.
[98] Y. N. Belokon, D. Bhave, D. D'Addario, E. Groaz, M. North and V. Tagliazucca, *Tetrahedron* **2004**, *60*, 1849-1861.
[99] H.-L. Teng, F.-L. Luo, H.-Y. Tao and C.-J. Wang, *Org. Lett.* **2011**, *13*, 5600-5603.
[100] Z.-C. Liu, Z.-Q. Wang, X. Zhang and L. Yin, *Nat. Commun.* **2023**, *14*, 2187.
[101] L. Wei, S.-M. Xu, Q. Zhu, C. Che and C.-J. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 12312-12316.
[102] H.-M. Wu, Z. Zhang, L. Wei, X.-Q. Dong and C.-J. Wang, *Chem. Commun.* **2021**, *57*, 6538-6541.
[103] X. Huo, R. He, J. Fu, J. Zhang, G. Yang and W. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 9819-9822.
[104] R. He, X. Huo, L. Zhao, F. Wang, L. Jiang, J. Liao and W. Zhang, *J. Am. Chem. Soc.* **2020**, *142*, 8097-8103.
[105] Y. Luo, Y. Ma, G. Li, X. Huo and W. Zhang, *Angew. Chem. Int. Ed.* **2023**, *62*, e202313838.
[106] L. Zhao, G. Li, R. He, P. Liu, F. Wang, X. Huo, M. Zhao and W. Zhang, *Org. Biomol. Chem.* **2021**, *19*, 1955-1959.
[107] Q. Zhang, H. Yu, L. Shen, T. Tang, D. Dong, W. Chai and W. Zi, *J. Am. Chem. Soc.* **2019**, *141*, 14554-14559.
[108] B. Li, Q. Zhang, W. Zi and Y. Dang, *ACS Catal.* **2023**, *13*, 14476-14491.
[109] X. Huo, J. Zhang, J. Fu, R. He and W. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 2080-2084.
[110] L. Wei, Q. Zhu, S.-M. Xu, X. Chang and C.-J. Wang, *J. Am. Chem. Soc.* **2018**, *140*, 1508-1513.
[111] H.-M. Wu, Z. Zhang, F. Xiao, L. Wei, X.-Q. Dong and C.-J. Wang, *Org. Lett.* **2020**, *22*, 4852-4857.
[112] Y. Peng, X. Huo, Y. Luo, L. Wu and W. Zhang, *Angew. Chem. Int. Ed.* **2021**, *60*, 24941-24949.
[113] L. Xiao, L. Wei and C.-J. Wang, *Angew. Chem. Int. Ed.* **2021**, *60*, 24930-24940.
[114] L. Xiao, X. Chang, H. Xu, Q. Xiong, Y. Dang and C.-J. Wang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202212948.
[115] L. Chen, M.-J. Luo, F. Zhu, W. Wen and Q.-X. Guo, *J. Am. Chem. Soc.* **2019**, *141*, 5159-5163.
[116] Q. Li, Y. Liu and C. Li, *Chem. Eur. J.* **2023**, *29*, e202301348.
[117] Q. Zhou, Z.-W. Yin, Z.-L. Wu, T. Cai, W. Wen, Y.-M. Huang and Q.-X. Guo, *Org. Lett.* **2023**, *25*, 5790-5794.
[118] J.-H. Liu, Q. Zhou, Y. Lin, Z.-L. Wu, T. Cai, W. Wen, Y.-M. Huang and Q.-X. Guo, *ACS Catal.* **2023**, *13*, 6013-6022.
[119] P. Ji, J. Li, Y. Tao, M. Li, W. Ling, J. Chen and B. Zhao, *ACS Catal.* **2023**, *13*, 9150-9157.
[120] P. Chen, Z. Yue, J. Zhang, X. Lv, L. Wang and J. Zhang, *Angew. Chem. Int. Ed.* **2016**, *55*, 13316-13320.
[121] P. Chen and J. Zhang, *Org. Lett.* **2017**, *19*, 6550-6553.
[122] Y. Wang, L.-F. Deng, X. Zhang and D. Niu, *Org. Lett.* **2019**, *21*, 6951-6956.
[123] X.-S. Sun, X.-H. Wang, H.-Y. Tao, L. Wei and C.-J. Wang, *Chem. Sci.* **2020**, *11*, 10984-10990.
[124] K. Zhang, Q. Peng, X.-L. Hou and Y.-D. Wu, *Angew. Chem. Int. Ed.* **2008**, *47*, 1741-1744.
[125] Y. Ariyarathna and J. A. Tunge, *Org. Biomol. Chem.* **2014**, *12*, 8386-8389.
[126] E. J. Alexy, T. J. Fulton, H. Zhang and Brian M. Stoltz, *Chem. Sci.* **2019**, *10*, 5996-6000.
[127] P. Starkov, J. T. Moore, D. C. Duquette, B. M. Stoltz and I. Marek, *J. Am. Chem. Soc.* **2017**, *139*, 9615-9620.
[128] J. Huang and I. Marek, *Eur. J. Org. Chem.* **2020**, *2020*, 3133-3137.
[129] Y. Xiao, L. Tang, T.-T. Xu, J.-Y.-H. Sheng, Z. Zhou, L. Yue, G. Wang, M. Oestreich and J.-J. Feng, *Chem. Sci.* **2023**, *14*, 5608-5618.
[130] M.-M. Li, Y. Wei, J. Liu, H.-W. Chen, L.-Q. Lu and W.-J. Xiao, *J. Am. Chem. Soc.* **2017**, *139*, 14707-14713.

Entry for the Table of Contents



This review describes the catalytic asymmetric allylic alkylation (AAA) of acyclic prochiral nucleophiles, namely enolates, as a means of accessing congested quaternary and tetrasubstituted stereogenic centres. In particular, strategies for the stereocontrolled access to acyclic enolate nucleophiles, as well as the impact of enolate geometry on the stereochemical outcome of allylic alkylation, are highlighted.

Institute and/or researcher Twitter usernames: @DrVil1983