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Review

Recent Advances on the Catalytic Asymmetric Allylic α-Alkylation of Carbonyl Derivatives Using Free Allylic Alcohols

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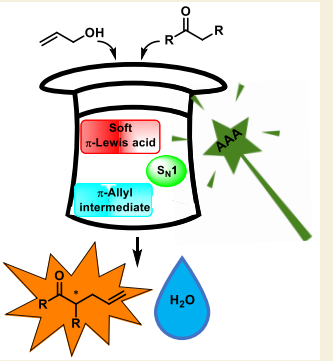
ABSTRACT: During the last years, the development of more sustainable and straightforward methodologies to minimize the generation of waste organic substances has acquired high importance within synthetic organic chemistry. Therefore, it is not surprising that many efforts are devoted to ameliorating already well-known successful methodologies, that is, the case of the asymmetric allylic allylation reaction of carbonyl compounds. The use of free alcohols as alkylating agents in this transformation represents a step forward in this sense since it minimizes waste production and the substrate manipulation. In this review, we aim to gather the most recent methodologies describing this strategy by paying special attention to the reaction mechanisms, as well as their synthetic applications.



KEYWORDS: *asymmetric catalysis, allylic alcohols, carbonyl compounds, allylic alkylation, green chemistry, organocatalysis, metal catalysis, natural products*

1. INTRODUCTION

Nowadays, public concerns about environmental issues and the need for saving resources has motivated the development of innovative approaches in organic synthesis designed to meet these demands.[1] Consequently, novel environmentally friendly and eco-conscious methods have been introduced aiming to reduce waste generation by implementing the concept of atom economy while also avoiding the use of harmful or costly substances and catalysts.

The allylic substitution reaction is a widespread methodology successfully employed in organic synthesis for the obtention of new allylic entities.[1] Among the myriad of allylation reactions described in the literature, the α-allylation of carbonyl compounds, also known as Tsuji−Trost allylation, has been extensively studied after the first reports published more than 50 years ago.[2,3]

Even more interesting is the catalytic asymmetric allylic alkylation (AAA) of carbonyl compounds (asymmetric Tsuji−Trost allylation), which generates at least a stereocenter next to the carbonyl moiety, thereby also allowing the formation of two consecutive stereocenters depending on the substrates employed.[4,5] The traditional method for this process employs alcohol derivatives as allylation agents, like allylic carbonates, acetates, phosphates, and halides, which not only generate a stoichiometric amount of waste during their preparation but also when reacting with the carbonyl nucleophile. Therefore, a more environmentally friendly and practical approach is the direct use of allylic alcohols for this transformation because they are easy to obtain, and water would be the only byproduct formed (Figure 1).[6,7]

The abovementioned benefits of using unmodified allylic alcohols in allylic substitution reactions have attracted organic chemists' interest and led to various procedures for achieving such purpose. However, the use of free allylic alcohols in these type of transformations entails two significant limitations: the

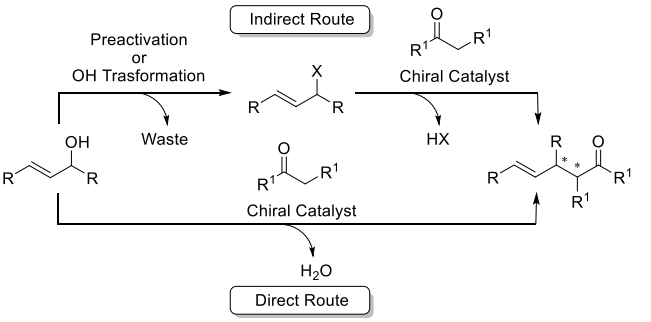


Figure 1. Alcohols in AAA.

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poor ability of the hydroxyl function as leaving group and the formation of stoichiometric amounts of water, which imposes the need for a water-tolerant catalyst.

In this regard, three main strategies based on the catalysts employed have been developed to overcome those problems (Figure 2):

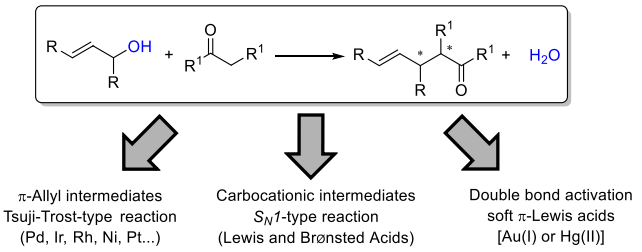


Figure 2. Activation modes of allylic alcohols.

(1) The use of transition-metal-based catalysts, such as Pd, Ir, Pt, Rh, and Ni, which implies a π-allyl intermediate as it occurs in the original Tsuji–Trost-type reaction.[5,8]
(2) The employment of Brønsted or oxophilic Lewis acids to form the corresponding carbocationic intermediate in an S_N1-type reaction.[9,10]
(3) The use of soft π-Lewis acids, such as Au(I) or Hg(II), which are able to activate the double bond and, hence, facilitate the nucleophilic attack in an S_N2'-type reaction.[11]

Last, another complex aspect of this process should also be mentioned: the asymmetric α-allylation of carbonyl compounds is not a trivial transformation since these organic entities can easily form the corresponding enol or enolate, and the background racemic reaction is often difficult to avoid. Hence, it is not surprising that there are not so many examples of asymmetric allylic alkylation of carbonyl compounds reported in which excellent results are achieved.

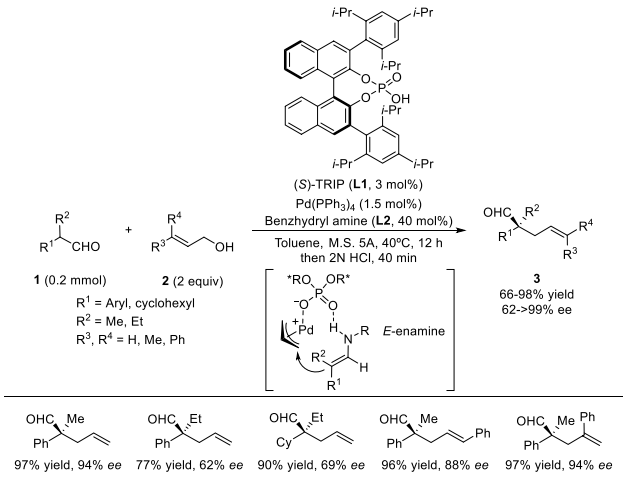
In this review, we aim to gather the most relevant recent work published since 2011 dealing exclusively with the asymmetric allylation of carbonyl compounds using free alcohols[12,13] by emphasizing the different strategies to reach the mentioned goal and paying attention to the different reaction mechanisms proposed. In addition, the application of this strategy toward the synthesis of bioactive molecules will also be briefly discussed. It is also important to note that there are some other revision articles dealing with the use of alcohols as alkylating agents in asymmetric catalysis, which somehow could cover part of the work compiled here but in a more indirect manner.[9−11,14]

2. ALDEHYDES IN THE CATALYTIC AAA USING ALCOHOLS

2.1. Using Transition Metal Catalysts through a π-Allyl Intermediate

The conventional Tsuji–Trost allylation typically demands a potent nucleophile and an allylic compound featuring an appropriate leaving group. However, numerous innovations have surfaced to tackle this challenge by combining organo- and transition metal catalysts. Expanding upon the established principle of asymmetric counteranion-directed catalysis, List's group devised a three-component catalytic system comprising $Pd(PPh_3)_4$, the chiral Brønsted acid TRIP (**L1**), and benzhydryl amine (**L2**).[15] The groundbreaking system exhibits exceptional catalytic activity and a notable degree of enantioselectivity, which enables the direct α-allylation of α-branched aldehydes with allylic alcohols. Central to this process is the crucial involvement of the *E*-enamine intermediate, which outperforms the activity of the non-selective *E*/*Z*-enol mixture (Scheme 1). The high enantioselectivity obtained in the process is proposed to arise from an asymmetric counteranion-directed catalysis (ACDC) complex that involves the amine, which engages in the formation of a configurationally defined *E*-enamine, the Pd(II) catalyst, and the chiral counteranion.

Scheme 1. Pd-Chiral Phosphoric Acid/Racemic Amine-Catalyzed Asymmetric Counteranion-Directed α-Allylation of α-Branched Aldehydes



However, an alternative Pd/enamine catalyst for directly achieving counterion-enhanced asymmetric α-allylation of branched aldehydes has been recently reported employing chiral amines, such as (1*R*,2*R*)-cyclohexane-1,2-diamine (**L4**) and achiral phosphoric acids.[16] This catalytic system has demonstrated high efficiency in the allylation of diverse α-branched aldehydes with a range of allylic alcohols. Interestingly, not only aromatic and cyclic aliphatic but also linear aliphatic aldehydes are efficiently allylated in moderate to high yield and enantioselectivity (Scheme 2). However, no reaction is observed for short-chained aliphatic aldehydes.

A stereodivergent dual-catalytic synthesis of γ,δ-unsaturated aldehydes was reported using chiral iridium and amine catalysts through the enantioselective allylation of α-substituted,[17,18] as well as linear,[19] aldehydes. As depicted in Scheme 3, for the enantioselective allylation of 2-phenylpropanal with 1-phenylprop-2-en-1-ol, all four stereoisomers of the allylated aldehyde are obtained in good yields and excellent enantio- and diastereoselectivities when combining chiral phosphoramidite **L5** and pseudoenantiomeric Cinchona-derived primary amines **L6**/**L7**. Under the optimized reaction conditions, this methodology shows good substrate scope with respect to the aldehyde component and the allylic alcohol (Scheme 3), and the competitive aldol process is not observed in any case.[17]

From the mechanistic perspective, NMR and X-ray studies have effectively characterized the key Ir complexes **A** and **B** relevant to the catalytic cycle of the Ir-catalyzed allylic substitution involving (phosphoramidite, olefin) ligands **L5**

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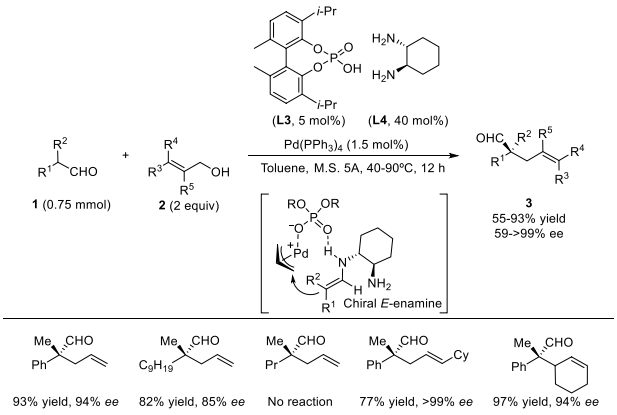
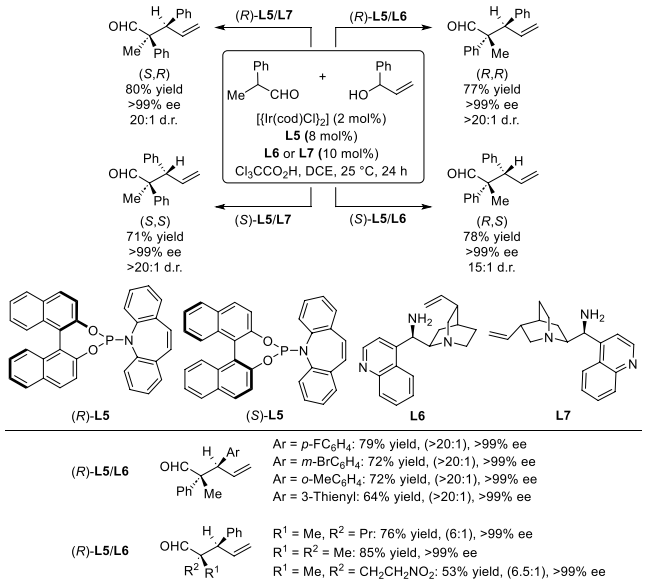
Scheme 2. Pd-Phosphoric Acid/Chiral Amine-Catalyzed Asymmetric Counteranion-Directed α-Allylation of α-Branched and Linear Aldehydes

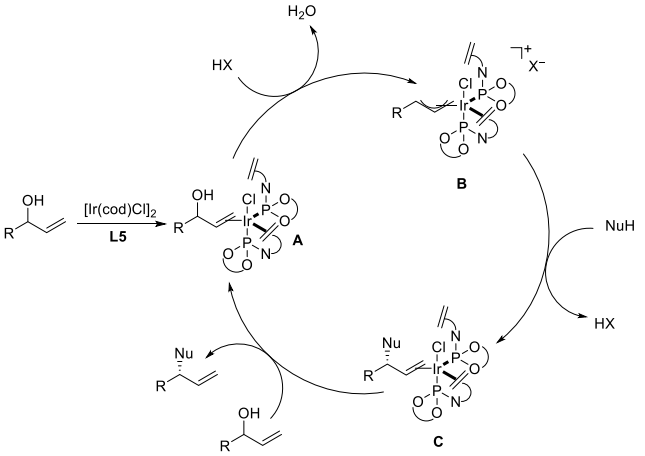


Scheme 3. Iridium-Chiral Phosphoramidite/Chiral Primary Amine Catalyzed α-Allylation of α-Branched Aldehydes



(Scheme 4).[20] The proposed mechanism involves coordination of the allylic alcohol to iridium to give the distorted trigonal bipyramidal (η^2-allylicalcohol)Ir(I) complex **A**, which undergoes acid-promoted oxidative addition to furnish (η^3-allyl)Ir-(III) complex **B**, which suffers nucleophilic attack on the allyl fragment to afford complex **C**. Final displacement of the product by the allylic alcohol completes the catalytic cycle (Scheme 4). However, the reason behind the high selectivities in the reaction stems from detailed transition-state modeling using density functional theory (B3LYP-D3). This analysis uncovered how the stereodivergence occurs by flipping the configuration of the chiral catalysts engaged in activating the reacting components. Meanwhile, the control over enantioselectivity occurs during the formation of the chiral phosphoramidite−Ir−π-allyl intermediate, while diastereoselectivity arises due to differing stabilizations in the transition states governing C−C bond formation.[21] Additionally, this investigation highlights the crucial role of the quinoline ring, thereby demonstrating its direct contribution to stabilizing the transition states that govern stereocontrol through weak π-stacking and C−H·π interactions.

Scheme 4. Iridium−(Phosphoramidite, Olefin)-Catalyzed Enantioselective Allylic Substitution Mechanism



The robustness of the Ir catalytic system has been demonstrated from an off-cycle pathway involving reversible binding of molecular oxygen to Ir, which contributes to the air tolerance of the catalyst.[20] This aspect, along with the demonstrated compatibility of organocatalytic methods with aqueous media, has been used to expand the nucleophile scope of the Ir-catalyzed enantioselective allylic substitution of allyl alcohols to unstable and volatile nucleophiles usually available as aqueous solutions, such as hydrazines, methylamine, *t*-butyl hydroperoxide, *N*-hydroxylamine, α-chloroacetaldehyde, and glutaraldehyde.[22]

One challenge often encountered in the stereoselective α-functionalization of linear aldehydes is the emergence of products featuring an enolizable stereogenic center, which makes them susceptible to epimerization. Secondary amine prolinol-type Jorgensen−Hayashi organocatalyst **L8** has been successfully used as chiral enamine promoter for the Ir-catalyzed asymmetric allylation of the less sterically hindered linear aldehydes, substrates prone to participate in side reactions, such as self-condensation.[19] As depicted in Scheme 5a, in the presence of dimethylhydrogen phosphate or trichloroacetic acid as cocatalyst, a stereodivergent dual-catalyzed allylation of unfunctionalized linear aldehydes with aryl-substituted allylic alcohols has been achieved by using chiral phosphoramidite (*S*)-**L5** and Jorgensen−Hayashi chiral organocatalysts (*R*)-**L8**.

In a similar manner, phosphoramidite (*R*)-**L5** and organocatalyst (*S*)-**L8**, using dichloro- or trichloroacetic acid as cocatalysts, have been used for the allylation of protected α-amino- and α-hydroxyacetaldehydes **4**, which are substrates of special synthetic relevance since they are precursors of β,β′-disubstituted α-amino and α-hydroxy acid derivatives (Scheme 5b).

The asymmetric allylation of carbonyl derivatives is an interesting synthetic technique for the preparation of naturally occurring and other bioactive compounds. In this way, the allylation of aldehydes with a dual asymmetric catalysis has been reported in the generation of two consecutive stereocenters of an intermediate in the preparation of tetrahydrocannabinol derivatives (Scheme 6). The choice of catalysts has allowed the stereodivergent synthesis of the four possible stereoisomers with high levels of enantio- and diastereoselectivity from the same starting reagents under similar conditions. Thus, the reaction between **6** and **7** (1:3 ratio)

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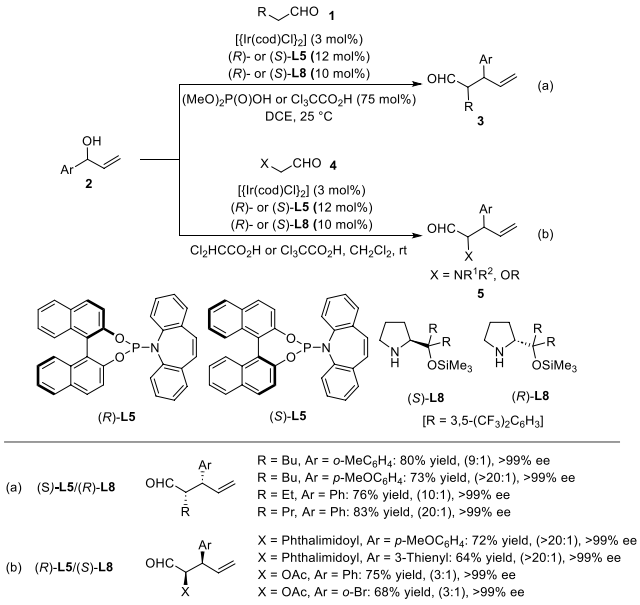
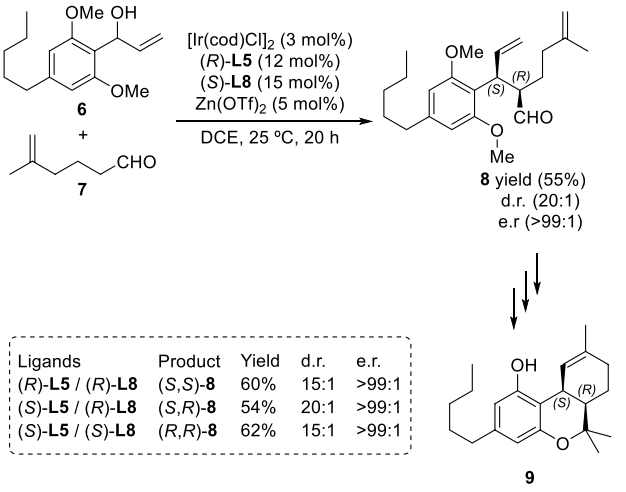
Scheme 5. Iridium−chiral Phosphoramidite/Chiral Secondary Amine-Catalyzed α-Allylation of Linear and α-Functionalized Aldehydes



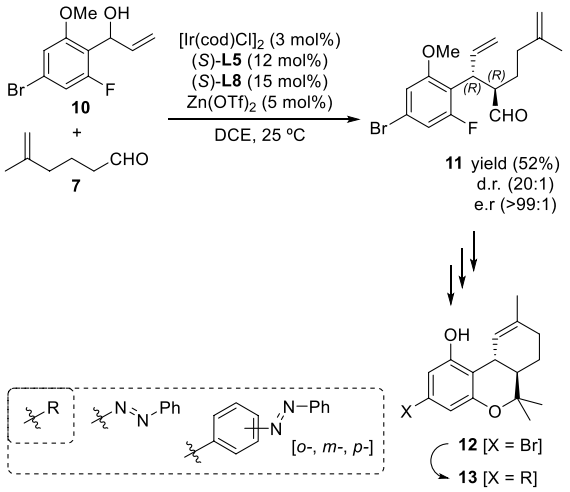
Scheme 6. Stereodivergent Synthesis of the Four Tetrahydrocannabinol 9



in the presence of iridium(I), zinc(II), and chiral ligands **L5** and **L8** constitutes the key step to control the stereochemistry of compound **8**, which has been transformed into the corresponding tetrahydrocannabinol **9** after four additional steps (Scheme 6).[23] Following the same strategy, photoswitchable *azo*-tetrahydrocannabinol derivatives **13** have been synthesized from tetrahydrocannabinol **12** following the same protocol. Thus, the allylic alcohol **10** has been transformed into the stereoisomer **11** with high selectivity, which is cyclized to **12** (Scheme 7).[24]

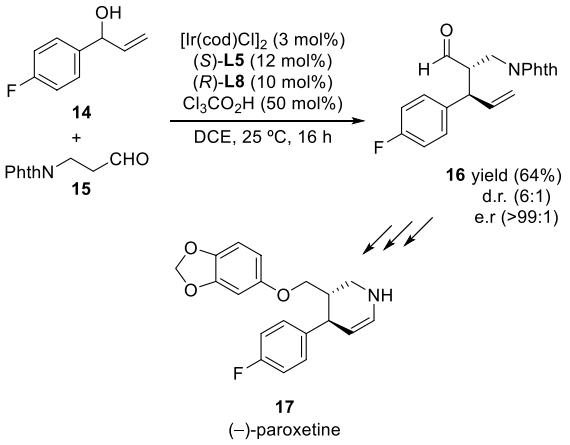
The combination of catalysts described by Carreira's group has been successfully employed in the total asymmetric synthesis of other natural compounds with bioactivity. The only difference introduced in the following cases is the use of other acidic promoters instead of Zn(II) salts, which may have an influence on the diastereoselectivity of the process. Thus, (−)-paroxetine (**17**), a selective serotonin reuptake inhibitor,

Scheme 7. Stereoselective Preparation of Compound 11 in the Synthesis of Photoswitchable *azo*-Tetrahydrocannabinol Derivatives 13



has been prepared from intermediate **16**, which is stereoselectively obtained from allylic alcohol **14** and aldehyde **15** using **L5** and **L8** in the presence of an iridium complex and trichloroacetic acid as promoter (Scheme 8).[25]

Scheme 8. Stereoselective Preparation of Compound 16 in the Total Synthesis of Paroxetine 17



The dual Ir/amine catalysis has been also employed in the reaction between a benzyl-protected 4-hydroxybutanal and two different (indolyl)allylic alcohols to yield chiral aldehydes, such as compounds **20** and **23**, with good enantio- and diastereoselectivity using trifluoroacetic acid and maleic acid, respectively, as promoters (Scheme 9).[26,27] Compound **20** has been used as a key intermediate for the synthesis of (−)-actinophyllic acid (**21**), which has potential uses for the treatment of cardiovascular diseases.[26] Similarly, the construction of the two stereogenic centers of intermediate **23** has been crucial in the total synthesis of (−)-alstoscholarine (**24**).[27]

The total synthesis of lycorane stereoisomers has been achieved employing the Carreira group's dual Ir/amine-catalyzed allylation using maleic acid as promoter. The use of 2-phthalimidoacetaldehyde (**26**) allows the introduction of a nitrogen-containing fragment in the structure with high

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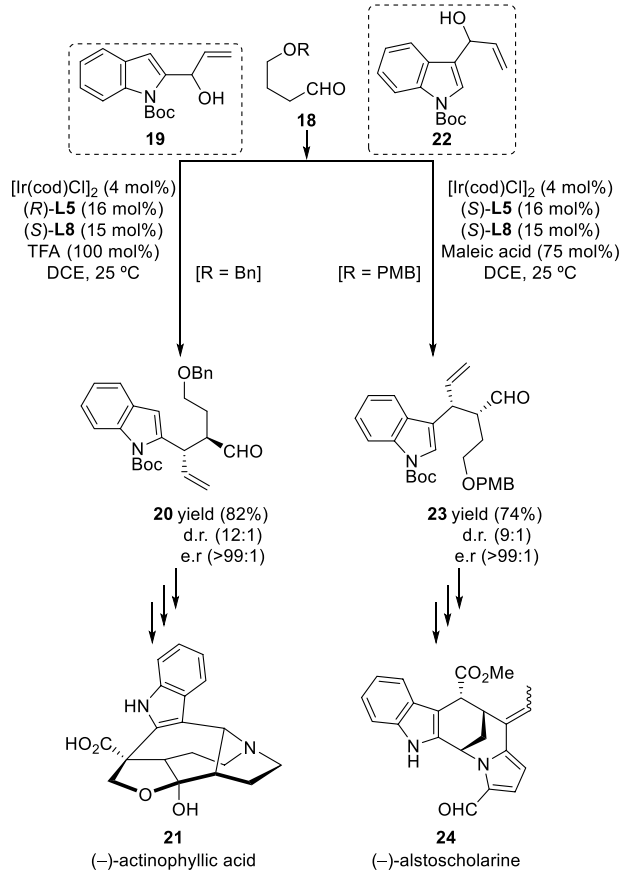
Scheme 9. Stereoselective Synthesis of Compounds 20 and 23 for the Total Synthesis of Actinophyllic Acid (21) and Alstoscholarine (24), Respectively

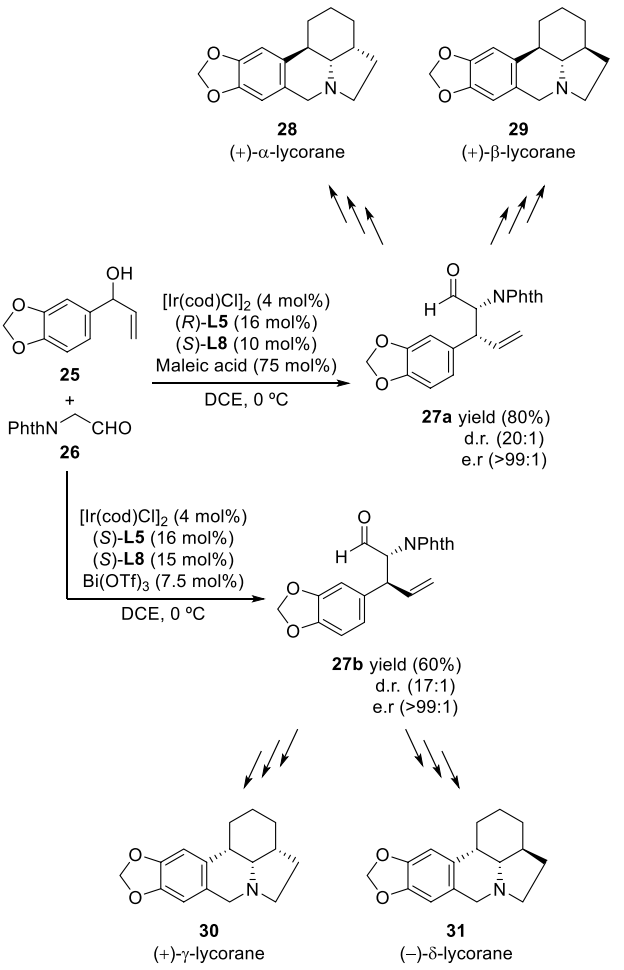


stereocontrol, which results in the synthesis of these alkaloid derivatives. Thus, the reaction of **26** with allylic alcohol **25**, under the standard conditions, provides stereoisomers **27a** and **27b** depending on the combination of Ir/**L5** and **L8** employed and the use of maleic acid or bismuth(III) triflate as promoter (Scheme 10).[28] Then, compound **27a** has been employed as an intermediate in the preparation of α-lycorane (**28**) and β-lycorane (**29**), while **27b** has been used in the synthesis of γ-lycorane (**30**) and δ-lycorane (**31**).

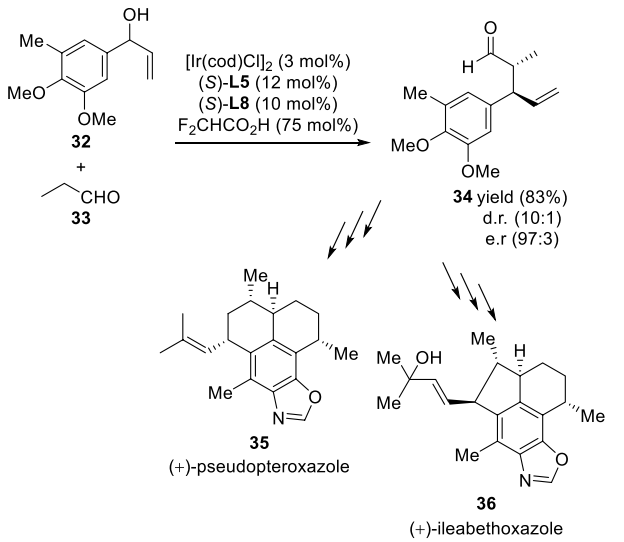
The total synthesis of the marine benzoxazole alkaloids **35** and **36**, which have shown significant antimicrobial activity for tuberculosis disease, has been achieved starting from aldehyde **34**. The chiral compound **34** has two contiguous stereocenters, which have been selectively obtained by the allylation reaction of propanal (**33**) with alcohol **32** by means of the dual-catalytic protocol employing Ir/**L5** and **L8** with difluoroacetic acid as promoter (Scheme 11).[29] The obtained isomers are the naturally occurring alkaloids, but the asymmetric dual-catalytic allylation would allow the synthesis of the other stereoisomers of intermediate **34** giving access to structural analogues of the natural product.

Stemona alkaloids, which have interesting biological activities, present polycyclic systems with different stereocenters. The tetracyclic structure **39**, which has been obtained from the pyrrole derivative **38**, has been employed in the total synthesis of bisdehydrotuberostemonine D. Compound **38** has been prepared by allylation of butanal with allylic alcohol **37** employing the Carreira group's methodology (Scheme 12).[30]

Scheme 10. Selective Synthesis of Stereoisomers 27 for the Synthesis of Four Isomers of Lycorane



Scheme 11. Selective Preparation of Chiral Compound 34 in the Total Synthesis of the Marine Benzoxazole Alkaloids 35 and 36



Because of the possibility of generating the different stereoisomers of **38** by selecting the appropriate combinations of **L5** and **L8**, bisdehydrotuberostemonine E was selectively

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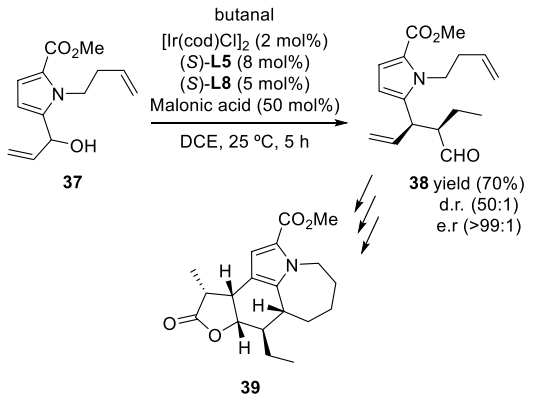
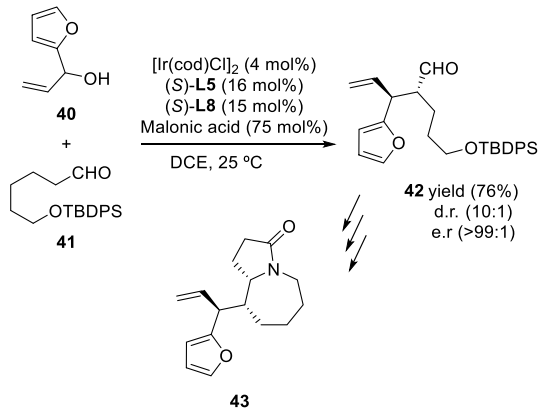
Scheme 12. Stereoselective Synthesis of Pyrrole Derivative 38 in the Preparation of Compound 39 as an Intermediate in the Synthesis of *Stemona* Alkaloids



prepared. Other *Stemona* alkaloids, such as parvistemonine and parvistemoline, can be prepared from intermediate **43**. Chiral aldehyde **42**, which is a precursor of tryciclic compound **43**, has been successfully prepared by reacting furyl vinyl carbinol **40** with the *O*-protected 6-hydroxyhexanal **41** under asymmetric dual-catalyzed allylation (Scheme 13).[31]

Scheme 13. Stereoselective Synthesis of Compound 42 as Precursor of Tricyclic Compound 43 in the Synthesis of *Stemona* Alkaloids



The iridium/amine-catalyzed strategy has resulted in an effective protocol for the allylation of aqueous solutions of acetaldehyde under biphasic conditions. The enantioenriched 3-substituted pent-4-enal **44**, formed by this methodology, can be employed in the total asymmetric synthesis of natural products. Thus, compound **44** has been transformed into compound **45**, which is an intermediate in the total synthesis of (−)-heliannuol C. Alternatively, **44** has been converted into **46**, which is a compound leading to the total synthesis of (+)-heliespirone A, (−)-heliespirone C, and (+)-heliannuol E (Figure 3).[32]

2.2. Metal-Free Strategies: Organocatalyzed AAA

The alkylation of aldehydes using allylic alcohols has also been described using an organocatalytic strategy based on the employment of a chiral amine and a boronic acid in the absence of noble metals in a S_N1-type reaction.[9,10] Concretely, the group of Hall has reported the use of the chiral pyrrolidine **L9**, a Jorgensen−Hayashi-type organocatalyst, in combination

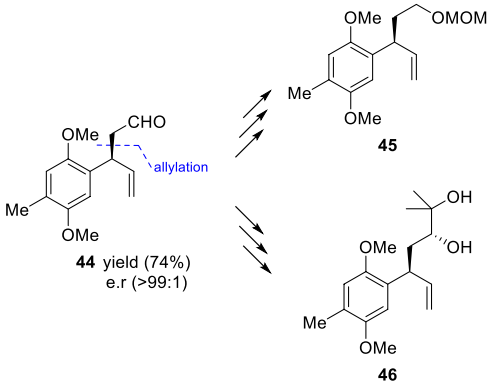
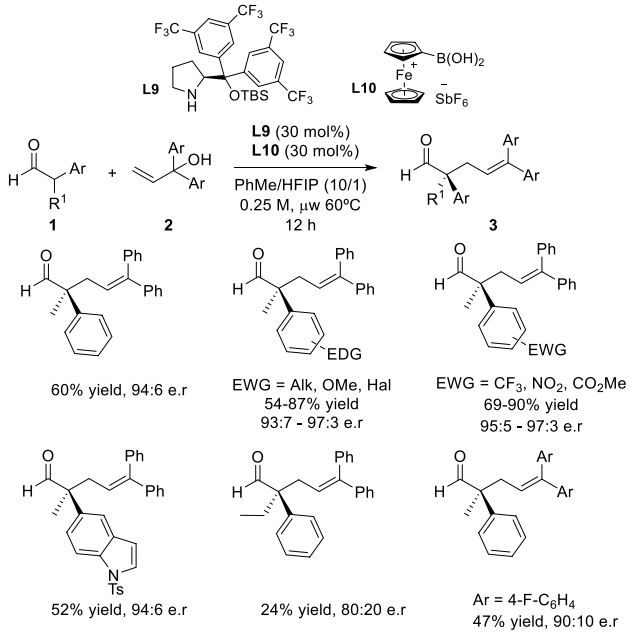


Figure 3. Intermediates lead to the total synthesis of (−)-heliannuol C, (+)-heliannuol E, (+)-heliespirone A, and (−)-heliespirone C.

with a ferrocenyl-based boronic acid **L10** as a Brønsted acid able to promote the dehydration of the allylic alcohol to render a highly stabilized carbocationic intermediate that can be trapped by the chiral enamine in an enantioselective fashion.[33] Under the optimized conditions and under microwave irradiation, the corresponding allylation products are obtained in moderate to good yields and with excellent enantioselectivities in many cases, as depicted in Scheme 14.

Scheme 14. Organocatalyzed AAA of Aldehydes Using Alcohols through a S_N1-Type Reaction Developed by Hall et al.



To further demonstrate the applicability of this methodology, a gram-scale experiment was performed using 2-(3,4-dichlorophenyl)propanal as substrate. After the allylation protocol and further elaboration of the resulting product **47**, the alcohol **48** bearing an all-carbon quaternary stereocenter was obtained in an 89% yield with high enantiomeric ratio. Alcohol **48** is an intermediate in the synthesis of peptidomimetic biologically active NK1/NK3 receptor antagonist **49** (Scheme 15).[33]

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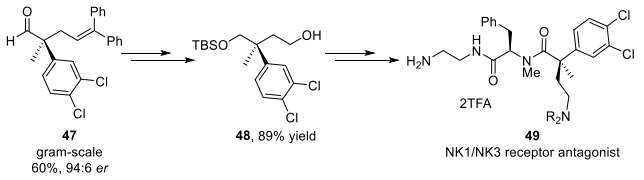
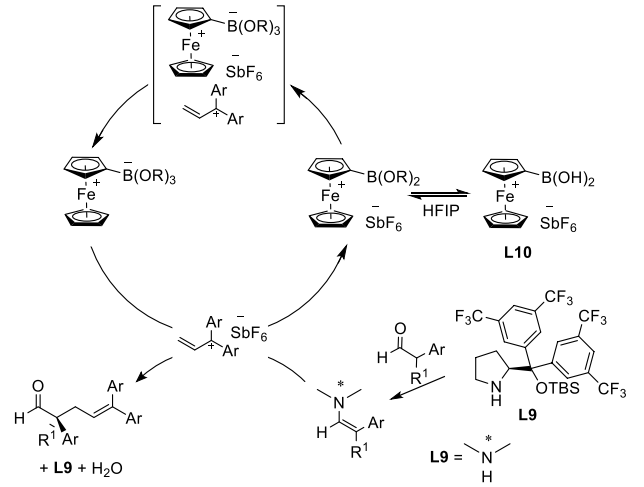
Scheme 15. NK1/NK3 Receptor Antagonist 49 Synthesis Using Organocatalyzed AAA of Aldehydes with Allylic Alcohols



Concerning the reaction mechanism, the authors propose a cooperative activation of both the aldehyde and the allylic alcohol where the presence of hexafluoroisopropanol (HFIP) seems to be beneficial for the reaction. Thus, whereas organocatalyst **L9** would lead to the formation of a chiral enamine, the boronic acid **L10** is responsible for the formation of the carbocationic intermediate, according to the cycle depicted (Scheme 16).[33]

Scheme 16. Mechanism Proposed by Hall and Coworkers for the Organocatalyzed AAA of Aldehydes with Free Alcohols



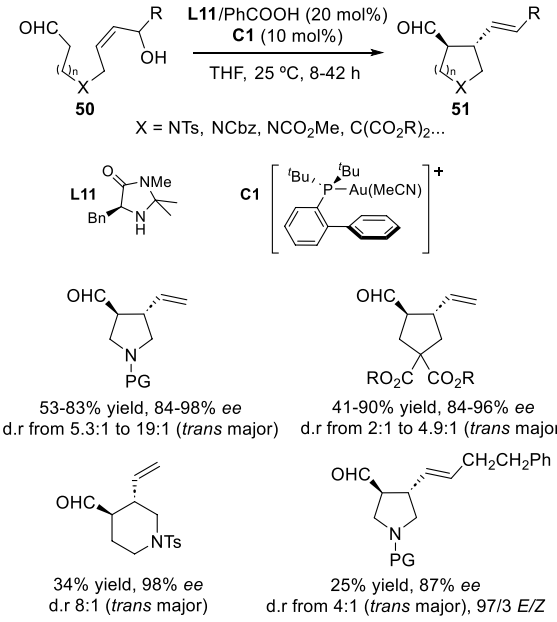
2.3. Using Soft π-Lewis Acids

Some years ago, the use of soft π-Lewis acids, mainly cationic gold complexes, for the activation of alkenes and other substrates containing π-bonds received much attention.[34] In this regard, allylic alcohols have been a class of substrates, among others, upon which these Au catalysts have been applied in order to perform the allylic substitution reaction.

This strategy was employed by Bandini, Cozzi, and co-workers in combination with enamine organocatalysis for the intramolecular asymmetric α-allylic alkylation of aldehydes with free alcohols. Thus, the synthesis of *trans*-formylpyrrolidines and piperidines, as well as formylcyclopentanes, in good to excellent yields and usually high enantio- and diastereoselectivities has been accomplished using McMillan imidazolidinone-type organocatalyst **L11** and cationic gold(I) complex **C1** (Scheme 17).[35]

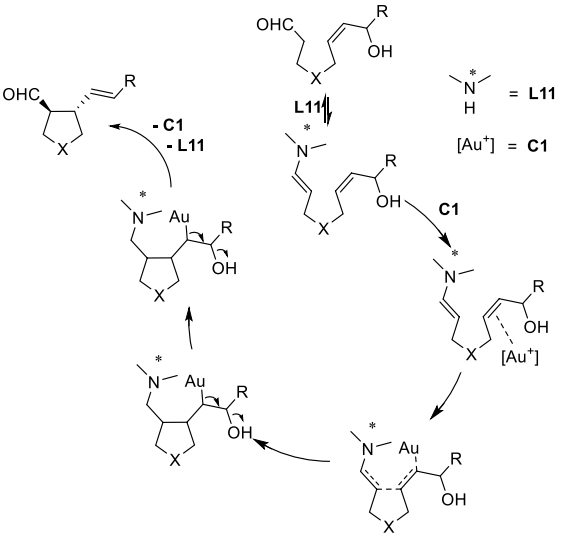
Concerning the reaction mechanism, the authors propose that after the enamine formation a gold-assisted electrophilic activation of a double bond takes place. Onto the activated alkene, the enamine attack occurs to render the carboauration of the olefinic moiety in an *anti-* fashion. Finally, an *anti-β-*

Scheme 17. Gold−Enamine Catalyzed Intramolecular AAA of Hydroxy Aldehydes Developed by Cozzi and Bandini et al.



elimination occurs giving rise to the corresponding product once the chiral amine is also released (Scheme 18).[35]

Scheme 18. Mechanism Proposed for the Gold−Enamine-Catalyzed Intramolecular AAA of Hydroxy Aldehydes 50



3. KETONES AND DERIVATIVES IN THE CATALYTIC AAA USING ALCOHOLS

3.1. Using Transition Metal Catalysts through a π-Allyl Intermediate

An enantioselective *C*-allylation between allylic alcohols **2** and Meldrum's and tetronic acids (**52** and **53**, respectively, including their 5- and 3-methyl-substituted analogues) was developed by Kitamura et al. in 2011 (Scheme 19).[36] The reaction, which involves the use of the chiral bidentate sp^2-N ligand [(*S*)-**L12**] in combination with $[RuCp(CH_3CN)_3]PF_6$ and *p*-TsOH, proceeds with high reactivity and selectivity.

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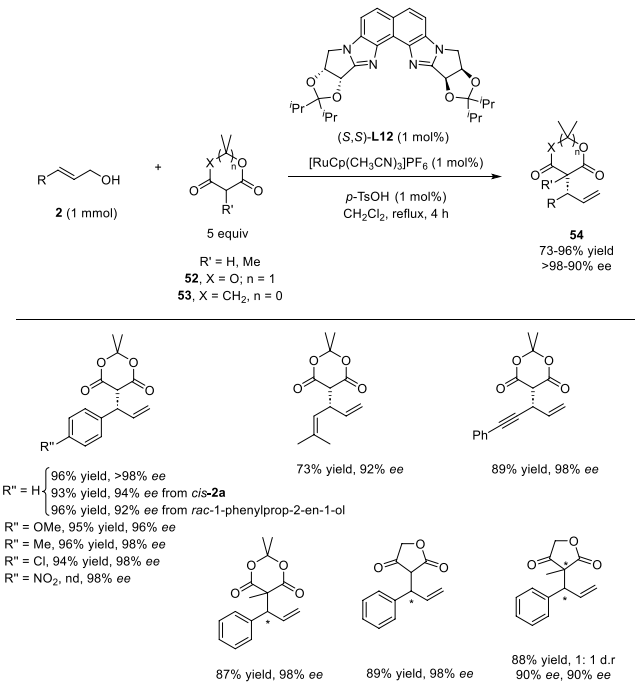
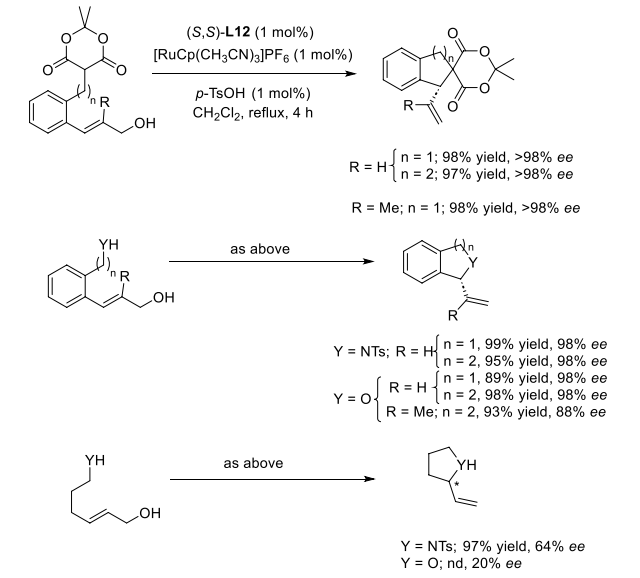
Scheme 19. Intermolecular *C*-Allylation Reaction Developed by Kitamura et al.



Various allylic alcohols **2** having an sp^2- or sp-hybridized carbon at C(3) can be used both in inter- (Scheme 19) and intramolecular (Scheme 20) allylation reactions. It is worth noting that saturated R substituents or 3,3-disubstituted alcohols **2** lead to no detectable intermolecular *C*-allylation and that the reaction does not occur when dimethyl malonate is used as nucleophile instead of the Meldrum's (**52**) or tetronic (**53**) acids.

The predominant formation of the (*S*)-branched product from both *E* and *Z*-**2a** (R″ = Ph) implies that *π*−*σ*−*π* interconversion should be faster than the intermolecular nucleophilic attack on a *π*-allyl intermediate. This hypothesis is also supported by the high level of asymmetric induction in the dynamic kinetic resolution (DKR) of racemic 1-phenyl-prop-2-en-1-ol.

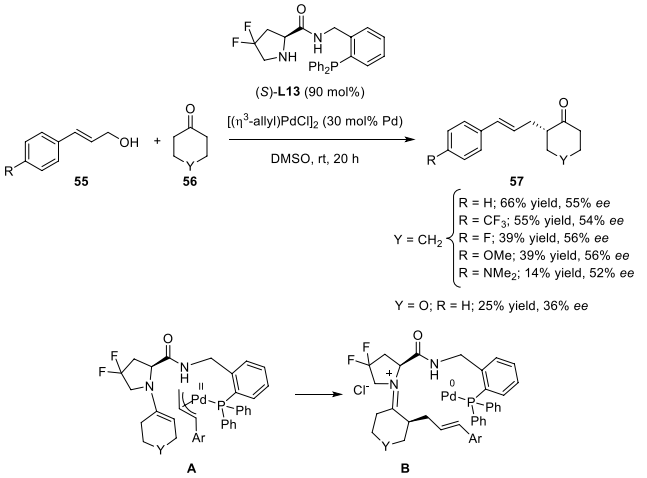
Scheme 20. Intramolecular *C*-, *O*- and *N*-Allylations Reaction Developed by Kitamura et al.



The scope of the reaction includes intramolecular *C*-, *O*-, and *N*-allylations (Scheme 20), thereby allowing the highly enantioselective construction of five- and six-membered cycloalkanes and *N*- and *O*-heterocycles, all of which are versatile key intermediates for a wide range of biologically active natural products.

In 2012, Shibasaki developed the first example of a direct asymmetric *α*-allylation of cyclic ketones with simple allylic alcohols using a novel tethered complex that provides cooperative Pd/phosphine activation and enamine activation (Scheme 21).[37] The reaction proceeds with moderate yields (14−66%) and enantioselectivities (36−56% ee), and high loading of Pd and ligand **L13** are required. The scope of the reaction is limited to *para*-substituted aromatic alcohols **55** and cyclohexanone and dihydro-2*H*-pyran-4(3*H*)-one as cyclic ketones (**56**). Three equivalents of ligand (*S*)-**L13** to Pd are required for efficient conversion, which the authors attribute to the fact that the active Pd complex is a Pd/(*S*)-**L13** complex in a ratio of 1:2 or 1:3 and/or attribute to the reluctant hydrolysis of the proposed iminium intermediate **B**.

Scheme 21. Asymmetric *α*-Allylation of Cyclic Ketones with Simple Allylic Alcohols Developed by Shibasaki et al.



In 2013, Gong et al. reported the combined use of a palladium complex with the chiral phosphoramidite ligand (*R*)-**L14** and the chiral phosphoric acid (*R*)-**L15** that enables a highly enantioselective allylic alkylation of pyrazol-5-ones with allylic alcohols (Scheme 22).[38] The methodology is compatible with a diverse scope of functional groups in both the allylic alcohol and the pyrazol-5-one **58**, which furnishes multiple functionalized heterocyclic products in high yields with excellent enantioselectivities (see examples in Scheme 22). Chiral pyrazol-5-one-derived compounds appear prevalently in several nonsteroidal anti-inflammatory drugs, such as Analgin, nifenazone, and Feprazone.

High-resolution mass spectrometry (HRMS) analysis of a reaction mixture of the palladium complex with **2-l** and (*S*)-**L15** shows that two molecules of (*S*)-**L14** are favorably coordinated to palladium. Authors propose that the chiral phosphoric acid facilitates the formation of a *π*-allyl−Pd

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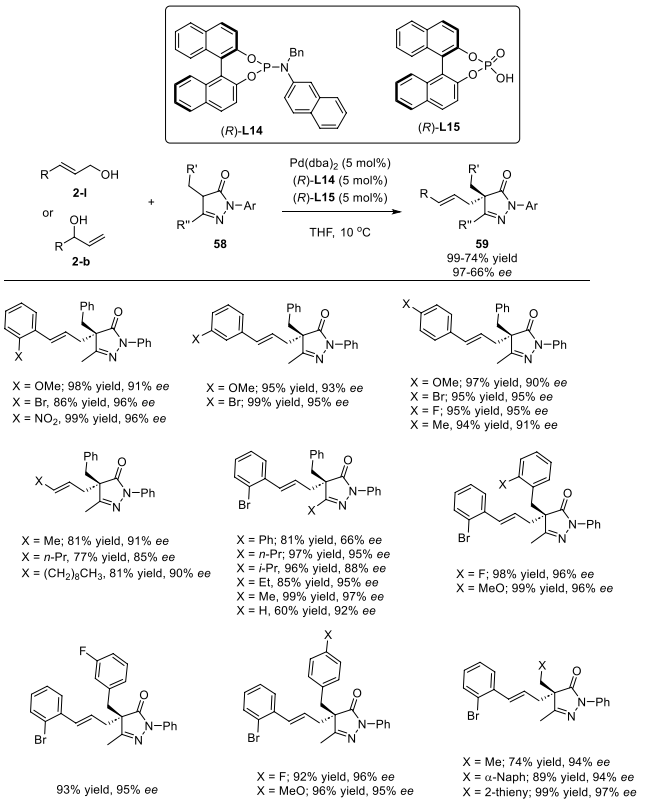
Scheme 22. AAA of Pyrazol-5-ones with Allylic Alcohols Developed by Gong et al.



complex by activation of the C−O bond and that the AAA reaction proceeds via intermediate **I** (Figure 4) in which the

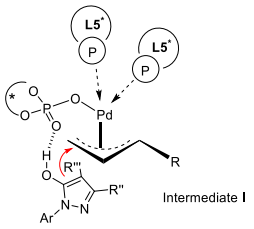
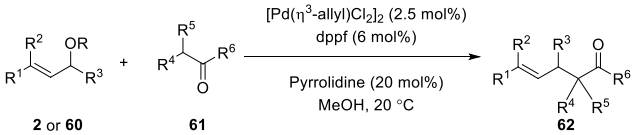


Figure 4. Intermediate proposed in the AAA of pyrazol-5-ones with allylic alcohols developed by Gong et al.

chiral phosphate counteranion has a hydrogen-bonding interaction with the nucleophile **58**. In intermediate **I**, the chiral palladium complex and chiral phosphate counteranion work cooperatively to activate the substrates and control the stereochemistry, thereby affording the products with high enantioselectivity.

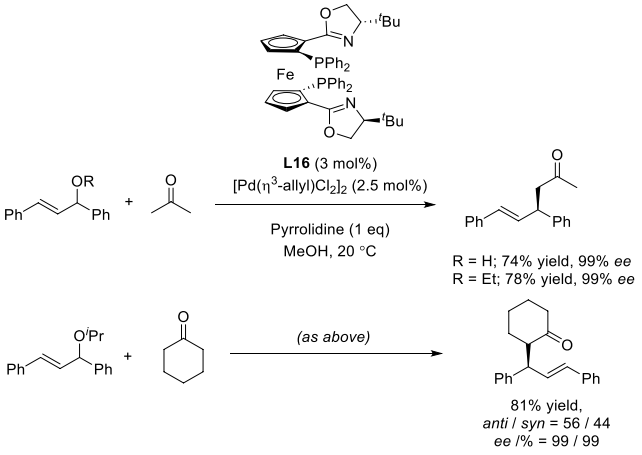
In 2014, while reporting the direct use of allylic alcohols[39] or allylic alkyl ethers[40] in the nonenantioselective Pd-catalyzed allylic alkylations of simple ketones/aldehydes (Scheme 23), Zhang et al. also showed that the Pd-catalyzed asymmetric allylic alkylation of acetone and cyclohexanone can be carried out with high yield and excellent enantioselectivity in the presence of the chiral ferrocene-based phosphinooxazoline ligand **L16** (Scheme 24). Both enantioselective and nonenantioselective reactions take place under mild conditions by using pyrrolidine as cocatalyst and methanol as a hydrogen-bonding solvent. Computational studies suggest that methanol

Scheme 23. Nonenantioselective Pd-Catalyzed Allylic Alkylation of Simple Ketones/Aldehydes Developed by Zhang et al.



2; R = H (22 examples; 54-98% yield)
60; R = Me, Et, ^{i}Pr, Cy, Bn, Ph (33 examples, 35-99% yield)

Scheme 24. Enantioselective Pd-Catalyzed Allylic Alkylation of Simple Ketones Developed by Zhang et al.



plays a crucial role in the formation of the π-allylpalladium complex by lowering the activation barrier and stabilizing the hydroxide leaving group.

Xia and Jiang et al. also reported in 2014 a Brønsted acid-accelerated Pd-catalyzed asymmetric allylic alkylation of azlactones with simple allylic alcohols under mild reaction conditions using a commercially available ligand **L17** and benzoic acid (Scheme 25).[41] The benzoic acid accelerates the reaction by activating the alcohol by hydrogen bonding to expel the hydroxy group, followed by insertion of a Pd(0) catalyst for the generation of the key π-allyl-Pd intermediate.[15,38] The reaction is compatible with a wide range of azlactones (**63**) and functionalized linear and branched allylic alcohols. The fact that branched allylic alcohols afford exclusively linear allylated products in similar yields and enantioselectivities compared with the liner analogues reveals that the reaction might require a cationic π-allylpalladium(II) intermediate to facilitate acquiring a linear product regioselectively.[42] The method provides a direct and readily scalable approach for the synthesis of all-carbon quaternary allylic amino acid derivatives in excellent yields with good enantioselectivities.

In 2015, Luo et al. reported an efficient synergistic dual-catalytic system composed of the chiral primary−tertiary diamine **L18a** and allylpalladium(II) chloride dimer to promote the direct asymmetric allylic alkylation (AAA) of β-ketocarbonyl compounds **65** with simple allylic alcohols (Scheme 26).[43] The reaction features the enantioselective construction of quaternary stereocenters with challenging acyclic aliphatic ketones, such as β-ketocarbonyl compounds and 1,3-diketones, where the transition-metal-catalyzed AAA reaction is often hampered because of the steric and electronic similarities of the two keto moieties. Both diamines **L18a** and

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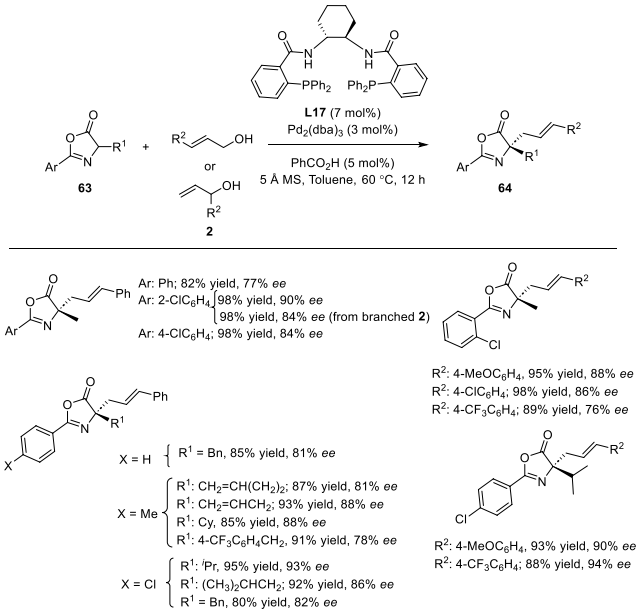
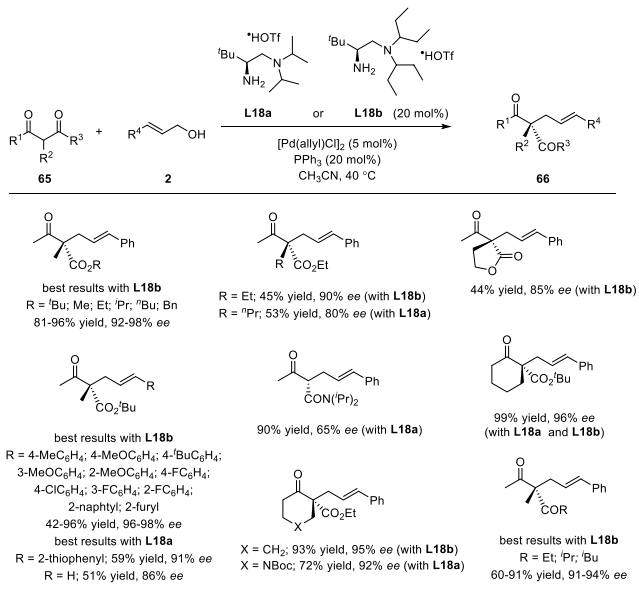
Scheme 25. Enantioselective Brønsted Acid-Accelerated Pd-Catalyzed Asymmetric Allylic Alkylation of Azlactones with Allylic Alcohols Developed by Xia and Jiang et al.



Scheme 26. AAA under Synergistic Dual Catalysis Developed by Luo et al.



L18b provide comparable results in most cases with, in general, slightly higher enantioselectivities for **L18b**. Diamine **L18a** often allows higher yields at the expense of a small drop in enantioselectivity and it also provides better results for bulky α-substituted 1,3-dicarbonyl compounds and for allylic alcohols, such as (*E*)-3-(thiophen-2-yl)prop-2-en-1-ol and the aliphatic prop-2-en-1-ol. Secondary allylic alcohols, such as 2-cyclohexen-1-ol and 4-phenyl-2-butenol, show very low reactivity, probably as a result of their inertness toward the formation of an π-allyl intermediate.

The authors propose a *Si*-facial attack of the π-allylpalladium complex on the enamine intermediate, on the basis of the observed (*S*)-stereoinduction of the products (Figure 5). Thus, steric effects play a key role in channeling the attack of the π-

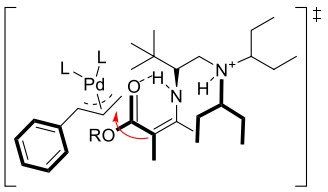
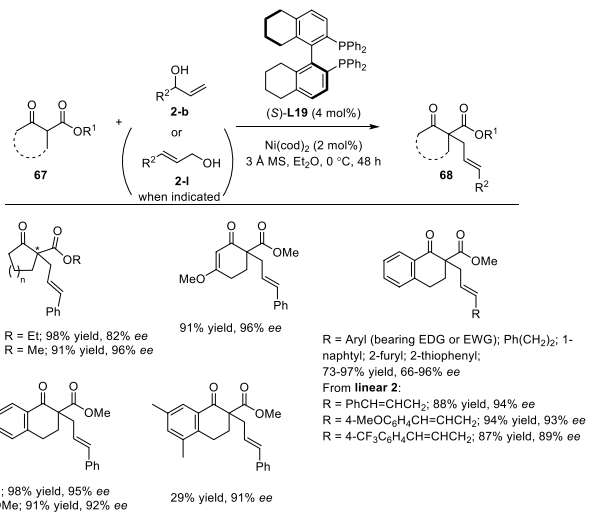


Figure 5. (*S*)-Selective sterically favored transition state proposed by Luo et al.

allylpalladium species for which a notable H-bonding site is lacking. The observed effect of bulky substituents on the tertiary amino moiety is clearly in support of this steric model (Scheme 26). Besides serving as a steric directing group, the protonated tertiary amine also participates in intramolecular H-bonding, as previously verified,[44] and results in a restricted conformation, which is also beneficial for stereoselectivity.

The same year, Mashima et al. reported the asymmetric allylic alkylation of β-ketoesters with allylic alcohols catalyzed by [Ni(cod)$_2$]/(*S*)-H$_8$−BINAP (**L19**) as an excellent synthetic protocol for constructing quaternary chiral centers at the α-position of cyclic β-ketoesters (Scheme 27).[45] The reaction

Scheme 27. AAA of β-Ketoesters with Allylic Alcohols Catalyzed by [Ni(cod)$_2$]/(*S*)-H$_8$−BINAP Developed by Mashima et al.



proceeds in high yield and with high enantioselectivity using a wide range of functionalized β-ketoesters **67** and branched (**2-b**) and linear (**2-l**) allylic alcohols without any additional activators. The fact that branched alcohols provide linear products suggests that the reaction proceeds via a π-allyl nickel intermediate.[46] A drop in enantioselectivity is observed when increasing the bulkiness of the R^1 group in the β-ketoesters **67**; the methyl and ethyl ester derivatives are the ones that provide better results. Noncyclic β-ketoesters undergo allylic allylation but in low enantioselectivity. The scope for aromatic allylic alcohols is wide and it includes heteroaromatic systems; only when the R group in the allylic alcohol is an alkyl group is the enantiomeric excess moderate.

The authors propose that the mechanism of this reaction involves a π-allylcation intermediate (Scheme 28). Initially, allylic alcohol is oxidatively added to a Ni^0/diphosphine complex derived from [Ni(cod)$_2$] and **L19** to generate

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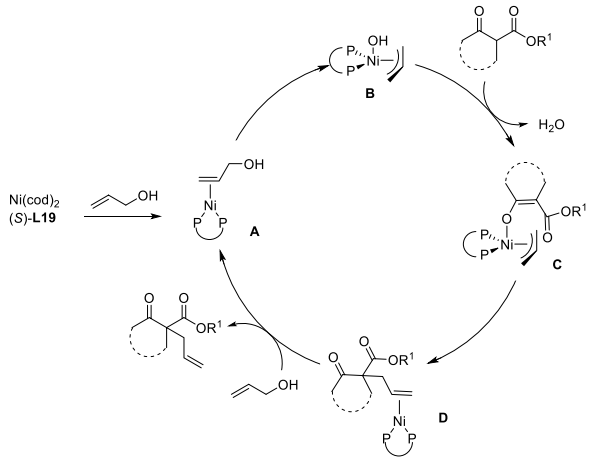
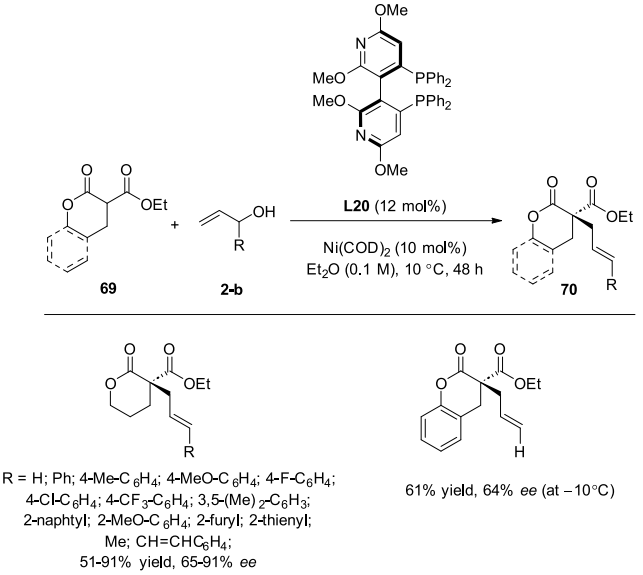
Scheme 28. Proposed Mechanism for the Ni-Catalyzed AAA Reaction of Allylic Alcohols Developed by Mashima et al.



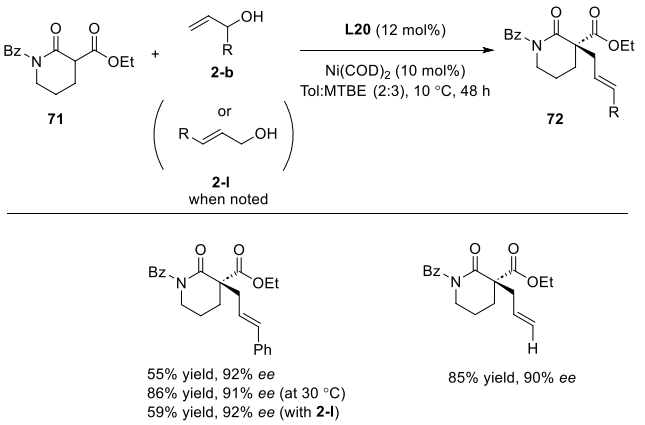
hydroxo π-allyl Ni^{II} complex **B**. The hydroxo ligand abstracts the α proton of the β-ketoester,[46] thus generating complex **C**. It is not clear whether the resulting enolate ligates to Ni^{II} or not. Finally, the nucleophilic attack of the enolate affords the product and regenerates the Ni^0/diphosphine intermediate. The lack of a requirement for an activator of β-ketoesters could be attributed to the generation of the hydroxo π-allyl Ni^{II} complex abstracting the α proton of β-ketoesters because other transition metal systems normally generate cationic π-allyl metal complexes with the concomitant formation of water by oxidative addition of allyl alcohols.

In 2018, Stoltz et al. reported the first nickel-catalyzed enantioselective allylic alkylation of α-ester lactones **69** and lactams **71** with free unactivated allylic alcohols to deliver products bearing an all-carbon quaternary stereocenter (Schemes 29 and 30).[47] The reaction utilizes the commercially available chiral bisphosphine ligand **L20** and proceeds in moderate to good yields with high levels of enantioselectivity

Scheme 29. Nickel-Catalyzed Enantioselective Allylic Alkylation of α-Ester Lactones with Free Unactivated Allylic Alcohols Developed by Stoltz et al.



Scheme 30. Nickel-Catalyzed Enantioselective Allylic Alkylation of α-Ester Lactams with Free Unactivated Allylic Alcohols Developed by Stoltz et al.



(up to 90% ee) on lactone and lactam nucleophiles under slightly different reaction conditions. The corresponding α-ethyl esters (for both lactones and lactams) provide higher yield and enantioselectivity in the reaction than the α-methyl esters; so, only these examples have been compiled here. The alcohol scope for lactone nucleophiles **69** (Scheme 29) consists mainly of (hetero)aromatic allylic alcohols, with one example of an aliphatic and another example of an alkenyl derivative. In general, electrophiles containing electron-rich aryl substituents provide the corresponding products in higher yields than their electron-deficient counterparts, and *para*- and *meta*-substituted aryl rings exhibit higher reactivity compared with the *ortho*-substituted aryl ring.

While only branched allylic alcohols **2-b** were explored for the AAA of lactones, a linear allylic alcohol **2-l** was also included in the electrophiles scope with the benzyl-protected α-ester lactam **71**, which provided an almost identical result compared with the corresponding branched alcohol **2-b**, thereby indicating that a nickel π-allyl is likely an intermediate in the catalytic cycle (Scheme 30).[45] The utility of this method is further highlighted via a number of synthetically useful product transformations/derivatizations for the construction of small chiral building blocks with multiple functional handles.

Also, in 2018, You et al. reported a highly regio- and enantioselective rhodium-catalyzed allylic alkylation of 1,3-diketones with secondary racemic allylic alcohols (Scheme 31).[48] In the presence of Rh, phosphoramidite ligand **L5** and catalytic TFA to activate the alcohol, chiral-branched α-allylated 1,3-diketones **66** can be obtained in good to excellent yields and enantioselectivities with excellent regioselectivities (b/l > 19/1) in all cases. Both aryl- and aliphatic-substituted allyl alcohols with a wide range of functional groups are suitable substrates with excellent reaction outcomes. In general, aromatic substrates with electron-withdrawing groups require prolonged reaction times compared with those with electrodonating substituents. It is worth noting the good tolerance with Cl, Br, and I groups, which are known to undergo diverse Pd-mediated transformations, under this Rh catalytic system. 1,3-Diketones **65** with both aliphatic and aromatic R^1 substituents are tolerated, although the enantioselectivity of the reaction drops for bulky substrates (R^1 = ^{t}Bu). α-Branched 1,3-diketones (with a methyl, ethyl, or chlorine substituent) also provide good results with longer reaction times (48 h). Aliphatic allylic alcohols, known as challenging

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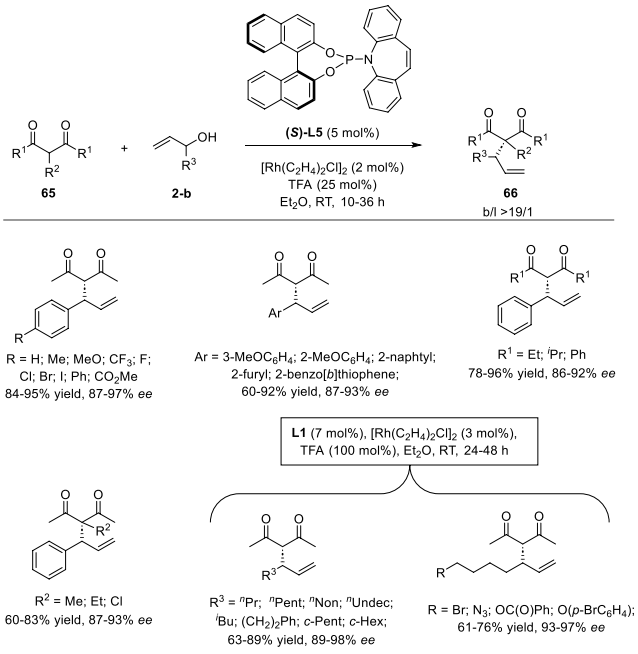
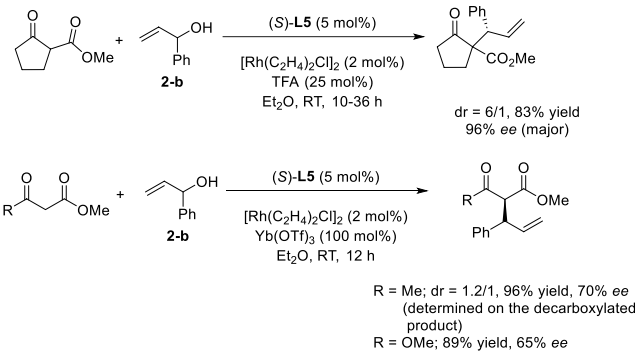
Scheme 31. Rhodium-Catalyzed Allylic Alkylation of 1,3-Diketones with Secondary Racemic Allylic Alcohols Developed by You et al.



substrates in allylic substitution reactions catalyzed by other metals,[49−51] provide their corresponding alkylation products in high to excellent selectivities and good yields under slightly modified reaction conditions. The scope of aliphatic alcohols includes generally labile functional groups, such as Br, N_3, benzoyl, and ether.

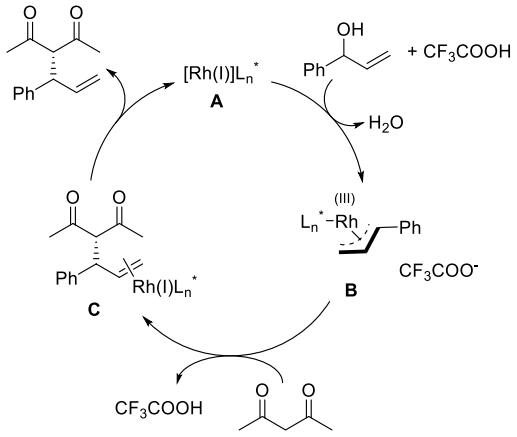
In addition to 1,3-diketones **65**, β-ketoesters are also suitable substrates for this methodology, although acyclic β-ketoesters only react when 1 equiv of $Yb(OTf)_3$ is used instead of TFA and provide the corresponding product in opposite configuration as the standard conditions (Scheme 32).

Scheme 32. Rhodium-Catalyzed Allylic Alkylation of β-Ketoester with Secondary Racemic Allylic Alcohols Developed by You et al.



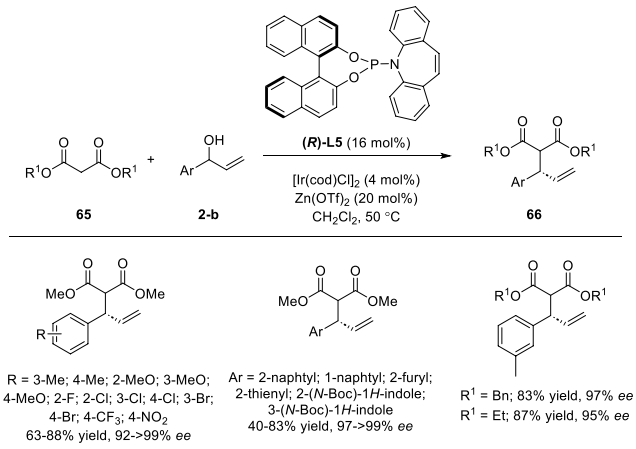
Mechanistic studies prove that for the product formation, an overall dynamic kinetic resolution process of the racemic allylic alcohols takes place. On the basis of the experimental observations, the authors propose a plausible mechanism (Scheme 33) involving (η^3-allyl)rhodium(III) species **B** produced by oxidative addition of the allylic alcohol into the rhodium(I) initial species **A**.

Scheme 33. Mechanism Proposed for the Rh-Catalyzed Allylic Alkylation of 1,3-Diketones Developed by You et al.



In 2019, Yang et al. reported the Ir-catalyzed enantioselective allylic alkylation of branched racemic allylic alcohols with malonates by using the phosphoramidite ligand (*R*)-**5**.[52] The scope of the reaction includes methyl, ethyl, and benzyl malonates and a wide range of aromatic and heteroaromatic alcohols (Scheme 34), and all of them provide moderate to good yields and excellent enantioselectivities. Aliphatic allylic alcohols provide, however, very low yield in the reaction.

Scheme 34. Ir-Catalyzed Enantioselective Allylic Alkylation of Branched Racemic Allylic Alcohols with Malonates Developed by Yang et al.



Ethyl nitroacetate is also a suitable nucleophile for this Ir-phosphoramidite catalytic system. The corresponding AAA reaction takes place in good yields and excellent enantioselectivities, albeit with poor diastereocontrol (dr 1.3:1, Figure 6). In the case of using acetylacetone as nucleophile, lower enantioselectivity is observed, especially compared with the previous Rh-catalyzed system reported by You et al.[48]

In 2021, Yang, Tian, and Deng et al. reported the asymmetric allylation/ring expansion reaction of 2-(1-hydroxyallyl)phenols **73** and cyclobutanone carboxamides **74**, enabled by sequential iridium/zinc/bifunctional squaramide catalysis, to furnish 8-membered benzo[*b*]oxocines **77** in high diastereoselectivities and excellent enantioselectivities (Scheme 35).[53] First, the cascade allylation/hemiketalization reactions occur to deliver key hemiketals **76** via dual Ir/Zn catalysis in

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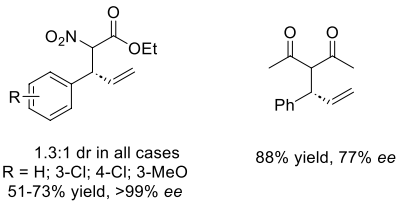
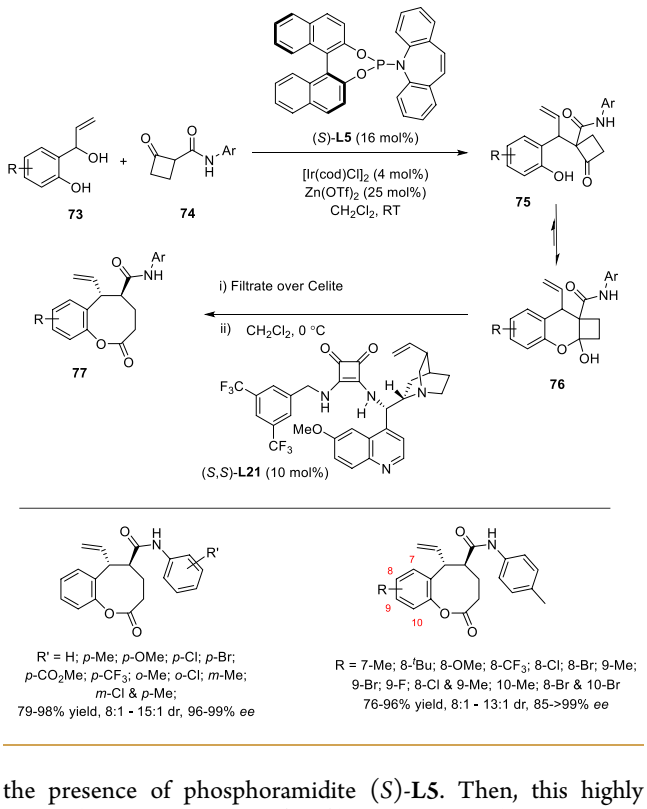


Figure 6. Products of AAA of ethyl nitroacetate and acetylacetone under the reaction conditions are shown in Scheme 33.

Scheme 35. Asymmetric Allylation/Ring Expansion Reaction of Phenols 73 and Cyclobutanone Carboxamides 74, Enabled by Sequential Iridium/Zinc/Bifunctional Squaramide Catalysis Developed by Yang, Tian, and Deng et al.



the presence of phosphoramidite (*S*)-**L5**. Then, this highly strained intermediate **76**, after filtration over Celite to remove the metals that poison (*S*,*S*)-**L21** and lower the diastereoselectivity of the reaction, is activated by the chiral bifunctional squaramide (*S*,*S*)-**L21** catalyst to produce benzo[*b*]oxocine products **77** through a fragmentation process. Mechanistic investigations supported by density functional theory calculations reveal that the enantioselectivity is controlled by the chiral iridium catalyst, while the diastereoselectivity is controlled by the chiral bifunctional squaramide catalyst.

The ester- or tertiary-amide-substituted cyclobutanone performs poorly in this transformation, thereby indicating that the secondary amide activating group is indispensable. The phenolic hydroxyl group on the allylic alcohol partner **77** also plays a key role for excellent diastereocontrol in the allylation step. The plausible mechanism proposed for this transformation involves, at first, the coordination of the *in situ* generated iridium catalyst to the allylic alcohol **77**, which undergoes oxidative addition to produce the π-allyliridium intermediate **AA** (Figure 7) with the assistance of the Lewis acid $Zn(OTf)_2$. The acidity of the α-proton for the

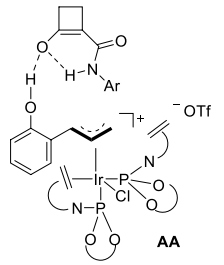
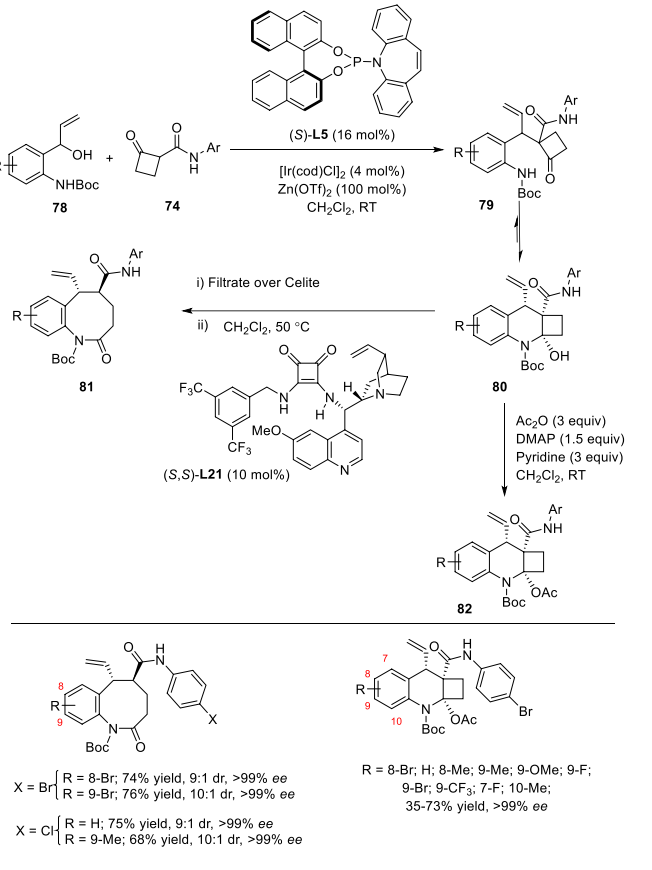


Figure 7. AA intermediated proposed by Yang, Tian, and Deng et al. in their AAA/ring expansion reaction of 2-(1-hydroxyallyl)phenols and cyclobutanone carboxamides to explain the formation of **77**.

cyclobutanone carboxamide **74** is believed to be enhanced via the intramolecular hydrogen bond between the acidic N−H proton and the ketone carbonyl group, so the corresponding enolate is believed to participate in the proposed intermediate **AA**.

The methodology can also be applied to hydroxyallylanilines **78** (Scheme 36) for the construction of cyclobuta[*b*]quinolines **80** and **82** and benzo[*b*]azocines **81**. These aniline allylic alcohols **78** require higher amounts of $Zn(OT)_2$ (1 equiv) during the AAA step and higher catalyst loading [(*S*,*S*)-**L21**, 20 mol %] and temperature (50 °C) during the fragmentation step compared with the hydroxyallylphenol counterparts (**73**) but a wide range of products with potential biologically activity

Scheme 36. Asymmetric Allylation/Ring Expansion Reaction of Hydroxyallylanilines 78 and Cyclobutanone Carboxamides 74 Enabled by Sequential Iridium/Zinc/Bifunctional Squaramide Catalysis Developed by Yang, Tian, and Deng et al.



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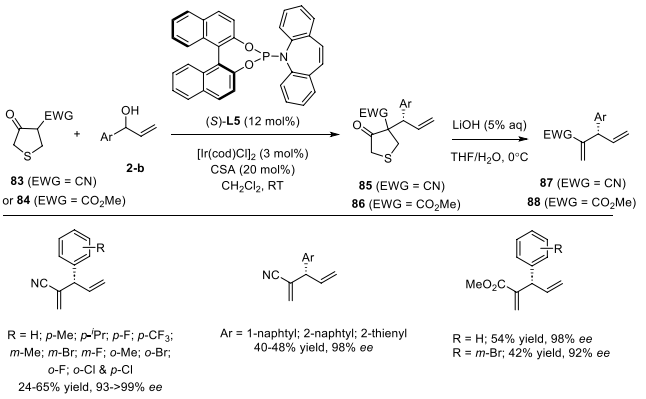
and bearing different substituents that can be accessed in good yields (35−76%) and excellent enantioselectivities (>99% ee) with high diastereoselectivities (9:1−10:1 dr) in the case of the benzo[*b*]azocines **75**.

In 2023, Mukherjee et al. reported a highly enantioselective α-allylic alkylation of 4-cyano-3-oxotetrahydrothiophene (**83**, a safe and easy-to-handle surrogate of acrylonitrile) and 4-carbomethoxy-3-oxotetrahydrothiophene (**84**, a surrogate of methyl acrylate) using branched racemic allylic alcohols in the presence of Ir(I) and the phosphoramidite (*S*)-**L5** with camphor sulfonic acid (CSA) as promoter (Scheme 37).[54]

Scheme 37. Enantioselective α-Allylic Alkylation of 4-Cyano-3-oxotetrahydrothiophene and 4-Carbomethoxy-3-oxotetrahydrothiophene Developed by Mukherjee et al.



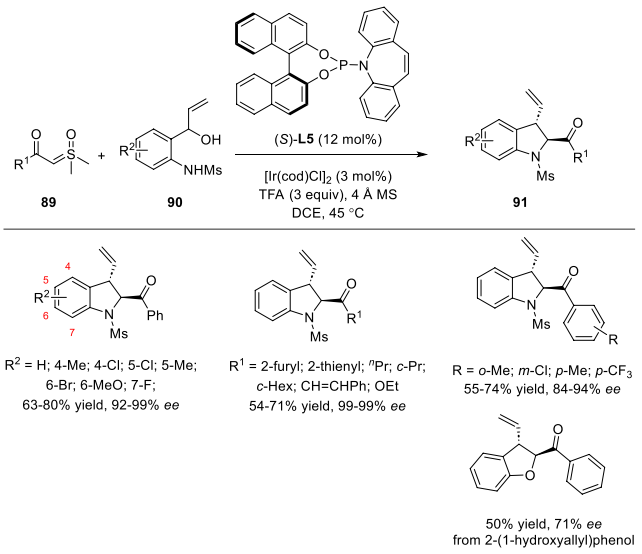
The AAA reaction is followed by a retro-Dieckmann/retro-Michael fragmentation to produce α-allylic acrylates **87** and acroleins **88** (Scheme 37) in moderate yields and good enantioselectivities.

In the same year, Sun et al. reported the iridium-catalyzed diastereo- and enantioselective [4 + 1] cycloaddition reaction of a wide range of substituted hydroxyallyl anilines with aromatic and aliphatic sulfoxonium ylides **89** (Scheme 38).[55] The reaction is a straightforward way to synthesize highly substituted 3-vinyl indolines **91** containing two stereogenic centers in moderate to good yields with good diastereoselectivities (>19:1 dr in all cases) and excellent enantioselectivities. On the basis of experimental results, the reaction is believed to proceed via an AAA process that furnishes intermediate **C** from the π-allyliridium species **B**, followed by an intramolecular *N*-nucleophilic substitution that provides intermediate **D** and dimethyl sulfoxide. (Scheme 39).

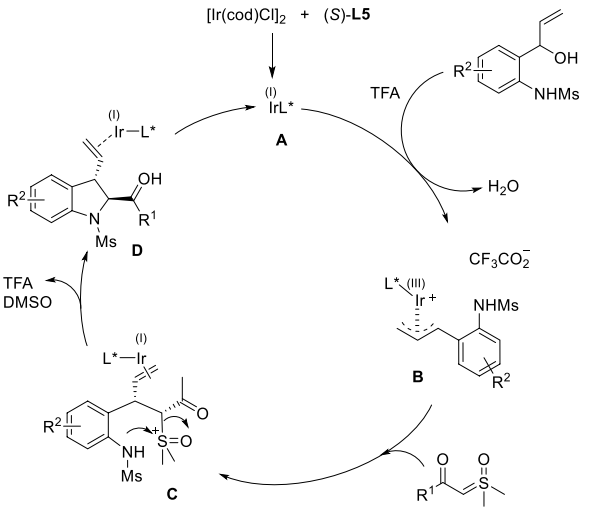
3.2. Metal-Free Strategies: Organocatalyzed AAA

The allylation of 1,3-dicarbonyl compounds can also be performed using a fully organocatalyzed strategy. The first work, and the one that reached the best results so far, was disclosed by the group of Gong in 2014.[56] In the article, the authors described the use of BINOL-derived chiral phosphoric acids as a chiral organocatalyst playing a dual role (Scheme 40). Accordingly, the acidic proton of the chiral phosphoric acid can protonate the hydroxyl group, which leads to the formation of a highly stabilized carbocation and renders the corresponding chiral ion pair with the conjugated phosphate. In addition, this base can also act as a Lewis base to activate the dicarbonyl compound and promote the organocatalytic asymmetric allylic alkylation.

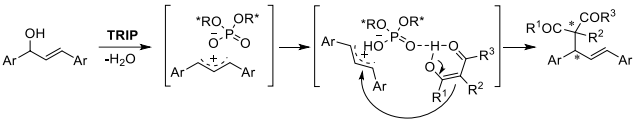
Scheme 38. Iridium-Catalyzed Diastereo- and Enantioselective [4 + 1] Cycloaddition Reaction of Substituted Hydroxyallyl Anilines with Aromatic and Aliphatic Sulfoxonium Ylides Developed by Sun et al.



Scheme 39. Mechanism Proposed for the Iridium-Catalyzed Diastereo- and Enantioselective [4 + 1] Cycloaddition Reaction of Substituted Hydroxyallyl Anilines with Aromatic and Aliphatic Sulfoxonium Ylides Developed by Sun et al.



Scheme 40. Chiral Phosphoric Acids as Organocatalysts in AAA Working Hypothesis Model



With this strategy, the use of (*S*)-TRIP (**L1**) as chiral phosphoric acid under optimized reaction conditions provides the best results in terms of both yield and enantiomeric excess. In general, the yields and enantioselectivities are high when different 1,3-diketones are employed in combination with electron-rich 1,3-diarylpropenols as allylating agents (Scheme

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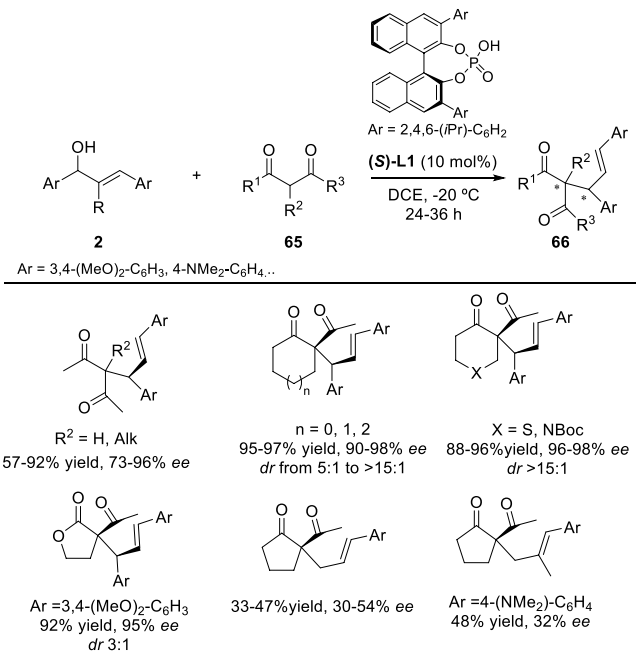
41). It is also remarkable that good diastereomeric ratios are normally achieved when two consecutive stereocenters are

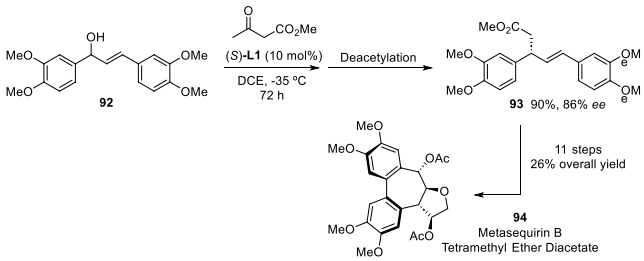
Scheme 41. Chiral Phosphoric Acid-Organocatalyzed AAA of 1,3-Dicarbonyl Compounds with Free Alcohols Developed by Gong et al.



formed. The enantioselectivities and yields are lower when other allylic substrates, such as electron-rich cinnamyl alcohols, are used.[56]

Finally, it is worth mentioning that the protocol described was implemented in the synthesis of a natural product metasequirin B (**94**) derivative in an 11-step sequence with a 26% overall yield (Scheme 42).[56]

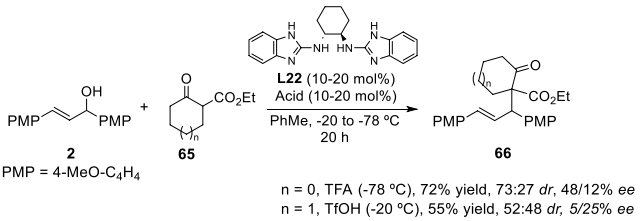
Scheme 42. Metasequirin B Synthesis Using Organocatalyzed AAA Developed by Gong and Coworkers



In the same year, the group of Baeza reported the use of a chiral bis(2-aminobenzimidazole) (**L22**) in combination with a strong Brønsted acid, such as TFA or TfOH, as a bifunctional organocatalyst for the allylation of cyclic 1,3-ketoesters. Although the work is mainly focused on the alkylation of such dicarbonyl compounds with electron-rich diarylmethanols, the strategy developed was also implemented to electron-rich 1,3-diarylpropenols. The corresponding allylation products were obtained with good yields but with modest to poor enantio- and diastereoselectivities (Scheme 43).[57]

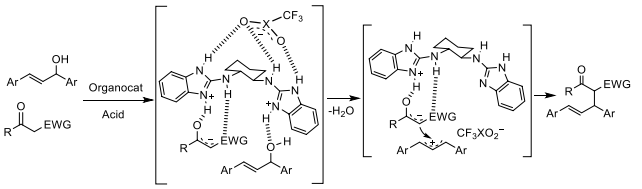
The mechanism therein proposed implies a bifunctional role of the protonated bis(2-aminobenzimidazole) **L22** derived

Scheme 43. Bis(2-aminobenzoimidazole)-Organocatalyzed AAA Developed by Baeza et al.



from 1,2-cyclohexanediamine. Thus, the protonated arm can promote dehydration of the allylic alcohol, whereas the other benzimidazole arm can act as a base and activate the corresponding enolate of the 1,3-dicarbonyl compound through an H-bond interaction (Scheme 44).

Scheme 44. Bis(2-aminobenzimidazole)-Organocatalyzed AAA Proposed Mechanism



3.3. Using Transition Metal Catalysts through a S_N1-Type Reaction

Some years later, Baeza et al. were able to perform the aforementioned reaction with better results. The key to success was the employment of a metal-catalyzed strategy. Thus, different 1,3-ketoesters, cyclic and acyclic, can be successfully allylated with electron-rich allylic alcohols employing a 10 mol % (*S,S*)-*t*BuBOX (**L23**)-Cu(OTf)$_2$ catalytic system. The outcome of the reaction is highly substrate-dependent but in general good yields, along with moderate to high enantioselectivities and modest diastereoselectivities for the products containing two all-carbon consecutive stereocenters (Scheme 45).[58]

The authors propose a reaction mechanism where the catalytic system formed by mixing Cu(OTf)$_2$ and the chiral BOX ligand (*S,S*-**L23**) not only could activate the dicarbonyl compound through the formation of an enolate within a chiral environment but also liberate a catalytic amount of TfOH responsible for the dehydration of the allylic alcohol, as depicted in Scheme 46.[58]

4. SUMMARY AND OUTLOOK

With this review article, we aimed to describe the different strategies in the asymmetric allylic substitution of carbonyl compounds using free alcohols as allylating agents that have been developed in the last years. Throughout the article, the different activation modes employed for such reaction, the scope and limitations, and the mechanisms and synthetic applications of the methodologies developed have been described.

Nowadays, as happens in other classical reactions, one of the main goals of synthetic chemistry is to focus on the amelioration of the sustainability of the whole process. This includes a minor substrate manipulation, hence generating a lower possible amount of waste without detriment to the

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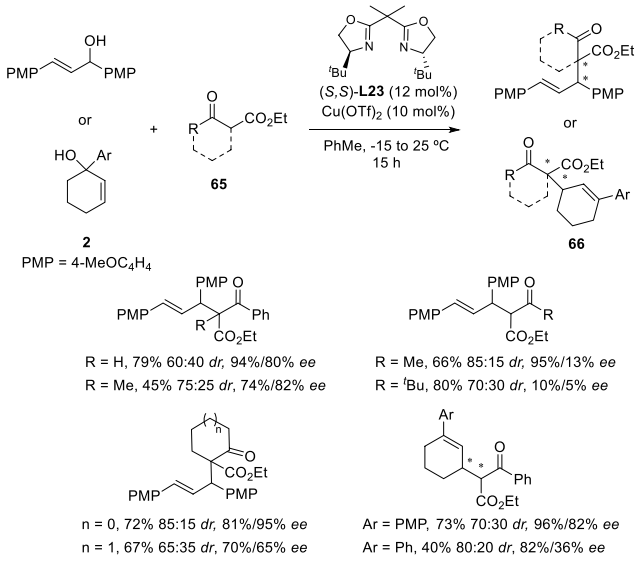
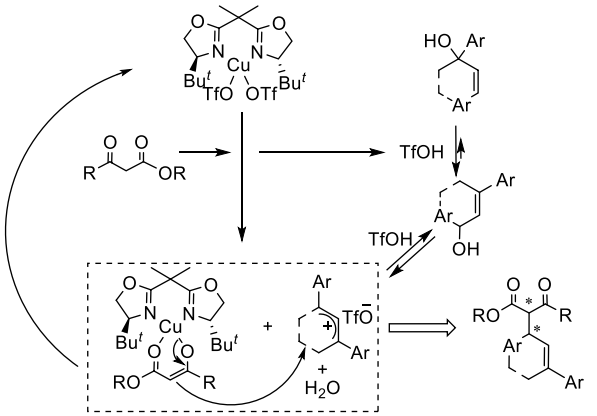
Scheme 45. (*S,S*)-*t*BuBOX L23-Cu(OTf)$_2$-Catalyzed AAA of 1,3-Dicarbonyl Compounds Using Free Alcohols Developed by Baeza et al.



Scheme 46. Mechanism Proposed for the *t*BuBOX-Cu(OTf)$_2$-Catalyzed AAA through a S$_N$1-Type Reaction



result. In this sense, the use of alcohols as allylating reagents in the asymmetric allylic substitution of carbonyl compounds falls into this category.

However, despite the great achievement that represents the use of free alcohols in AAA, there are still issues that can be improved in this transformation. For example, as disclosed in this revision, the best results in terms of both enantio- and diastereoselectivity, as well as substrate scope diversity, still require the use of catalytic systems based on precious noble transition metals (mainly Pd or Ir).

Conversely, although some breakthroughs have been described so far, the results achieved with the use of new chiral catalysts based on other earth-abundant metals and/or in the absence of any metal (organocatalysts) in this transformation are still far from satisfactory. For this reason, future investigations need to be focused on the development of these kinds of catalysts to make them able to accomplish similar levels of efficiency with those traditionally employed, and special efforts need to be put toward broadening the scope of alcohols used as allylating agents.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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