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Synthetic methodologies to access skipped dienes: a focus on the catalytic systems

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1,4-Dienes, also known as skipped dienes, are widely diffused in natural products and serve as valuable synthetic intermediates. However, their synthesis continues to pose a substantial challenge. In recent years, there has been a notable development in the field, with the emergence of highly stereoselective methodologies for the construction of the 1,4-diene moiety. This review discusses the latest advances in the synthesis of skipped dienes, with a particular emphasis on the catalytic system and reaction mechanism. Metal-mediated (Ru, Co, Rh, Ir, Ni, Pd, Cu, Au, Ca, Ti, Cr, Yb), metal-free and organocatalyzed transformations as well as synergistic/dual and metallaphotoredox-catalysed reactions, published in the last five years, are reported.

Introduction

Among the structural motifs present in biologically active compounds, including polyketides, alkaloids and polyunsaturated fatty acids, the skipped diene moiety occupies a privileged position. These compounds are also highly versatile building blocks for organic synthesis,[1,2] and are widely employed as functional intermediates in the construction of more complex structures.[3] In contrast to the stable 1,3-diene system, 1,4-diene compounds, which contain two double bonds separated by a sp^3-hybridised carbon, exhibit greater conformational flexibility and are characterised by a non-planar structure. The structural flexibility advocated for (i) stereoselective synthesis, (ii) mild conditions to avoid isomerization and (iii) stereodivergency to selectively access all the possible isomers from the same starting materials. The methodologies for obtaining 1,4-dienes have been relatively underdeveloped; however, in recent years a flowering has been observed with a rapid advancement in synthesis in this field. The majority of the syn-

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Polyssena Renzi

Polyssena Renzi completed her PhD in 2014 at the University of Rome La Sapienza (Italy) on the development of novel strategies for asymmetric synthesis and their optimization via Design of Experiment. In 2015, she joined the group of Prof. R. M. Gschwind (Regensburg University, Germany) as a post-doctoral fellow, where she dealt with mechanistic investigations of organocatalyzed reactions by means of NMR techniques. Since October 2023, she has been assistant professor at the University of Turin where she works in the field of photocatalysis and in the synthesis of molecules for BNCT applications.

Alberto Lanfranco

Dr Alberto Lanfranco graduated in chemistry in 2019 at the University of Torino, presenting a thesis on the synthesis of a biotin-functionalised carborane for BNCT/MRI applications. In 2024, he obtained a PhD degree in Chemical and Materials Sciences, working in the group of Annamaria Deagostino with a doctoral fellowship (AIRC IG). His project dealt with the synthesis of sulfamido-functionalised carboranes for inhibition of carbonic anhydrase IX and BNCT applications. He is currently a postdoc researcher in the same group, working on the synthesis of carborane-based theranostic agents for the treatment of Alzheimer's disease.

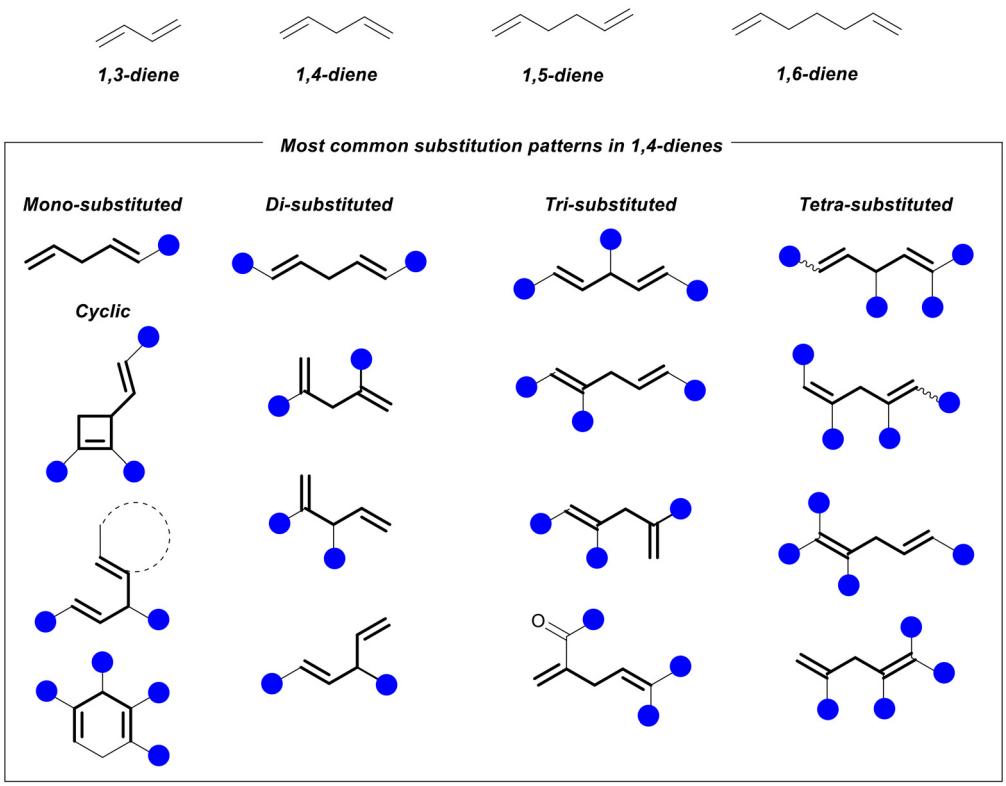


Fig. 1 Structure of dienes and summary of the most common substitution patterns in 1,4-dienes.

thetic procedures developed are characterised by a high degree of stereoselectivity, and alkynes, alkenes or dienes can be exploited as the starting materials. Fig. 1 provides a summary of the most frequent substitution patterns that can be encountered in 1,4-dienes, both in acyclic and cyclic compounds. Most simple structures are characterised by a single substituent, with the introduction of up to four different groups being possible in the 1,4-diene skeleton, thereby increasing the complexity.

This review examines the synthesis of skipped dienes over the period from 2020 to 2024. The analysis of catalysis by different metals, organic-based compounds and dual catalysis is presented as a central tool for the generation of these moieties, both in the presence and absence of light. The review is organised in the following four main sections:

(a) Metal-catalysed synthesis of skipped dienes,

(b) Metallaphotoredox-catalysed synthesis of skipped dienes,

Lucia Pazderová

Dr Lucia Pazderová is a Postdoctoral Researcher in the Department of Chemistry at the University of Turin (Italy). She received her PhD in Inorganic Chemistry from Charles University (Czechia) in 2021, following an MSc in Bioinorganic Chemistry from Palacký University Olomouc (Czechia) in 2015. The current research interest of Dr Pazderová is focused on the functionalisation of metallacarborane derivatives for synthesising antitumoral agents for boron neutron capture therapy.

Marco Rusconi

Marco Rusconi graduated in Chemistry from the University of Turin in 2023, obtaining his Master's degree with a thesis concerning a catalyst-free hydrothiolation reaction of alkenes mediated by visible light. In the same year, he started his Doctorate of National Interest in Annamaria Deagostino's group. His PhD project is dedicated to the development of synthetic methodologies for the photoinduced functionalization of carborane clusters.

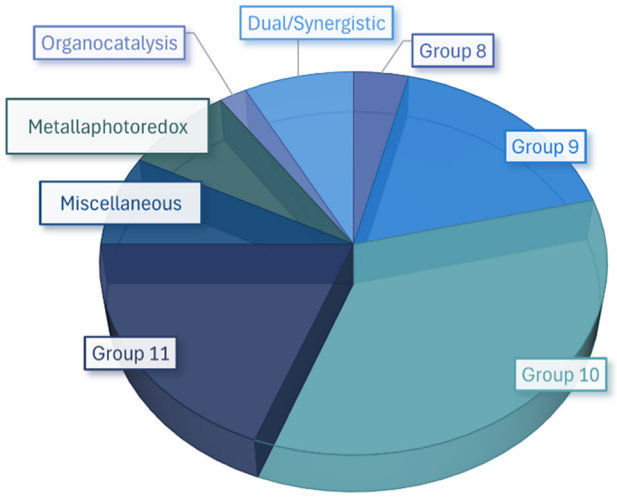


Fig. 2 Graphical overview of the last five years' publications of 1,4-diene synthesis.

(c) Metal-free transformations,
(d) Synergistic/dual catalysis.

The section on metal-catalysed transformations is further divided according to the nature of the metal centre (group 8: Ru; group 9: Co, Rh, Ir; group 10: Ni, Pd; group 11: Cu, Au; miscellaneous: Ca, Ti, Cr, Yb). Fig. 2 provides a graphical overview of the number of papers published in the last five years according to the type of catalysis exploited. It is evident that 1,4-diene synthesis is dominated by metal-catalysed transformations, particularly from metals belonging to groups 10 and 11, followed by group 9. Among the metals, catalysis by ruthenium is the least developed, with only two papers. Conversely, dual catalysis and metallaphotoredox catalysis are emergent areas.

The objective of this review is to provide a comprehensive overview of the most recent strategies for synthesising 1,4-dienes, with a particular emphasis on the catalytic system and the underlying reaction mechanism. Some examples of 1,5- and 1,6-diene synthesis were also reported. This field is expanding rapidly, with an ever-increasing number of publications. In fact, more than 40 papers have been published in the last two years, which highlights the need for an updated review.

Metal-catalysed synthesis of skipped dienes

Group 8: ruthenium (Ru)

Concerning the metal-catalysed synthesis of skipped dienes, catalysts based on ruthenium (Ru) as the active metal centre are utilised to a lesser extent. A review of the literature revealed that only two papers, exploiting a Ru-based catalyst, were published between 2020 and 2024 in which the 1,4-diene was directly employed as the starting material for a subsequent transformation, thus highlighting the wide applicability of these compounds in synthetic methodologies. The group of Trost reported a Ru-catalysed alkene–alkyne coupling reaction to synthesise unsymmetrical 3-boryl-1,4-dienes **3** (Scheme 1).[4] These compounds were not isolated but reacted *in situ* with carbonyl compounds **4** to access the 1,3-dienyl-6-oxy structural motif **5a–d**, which were further exploited as a platform for the synthesis of complex polyketides. The methodology allowed the formation of contiguous stereocenters and two new carbon–carbon bonds, and it was characterised by a high stereoselectivity.

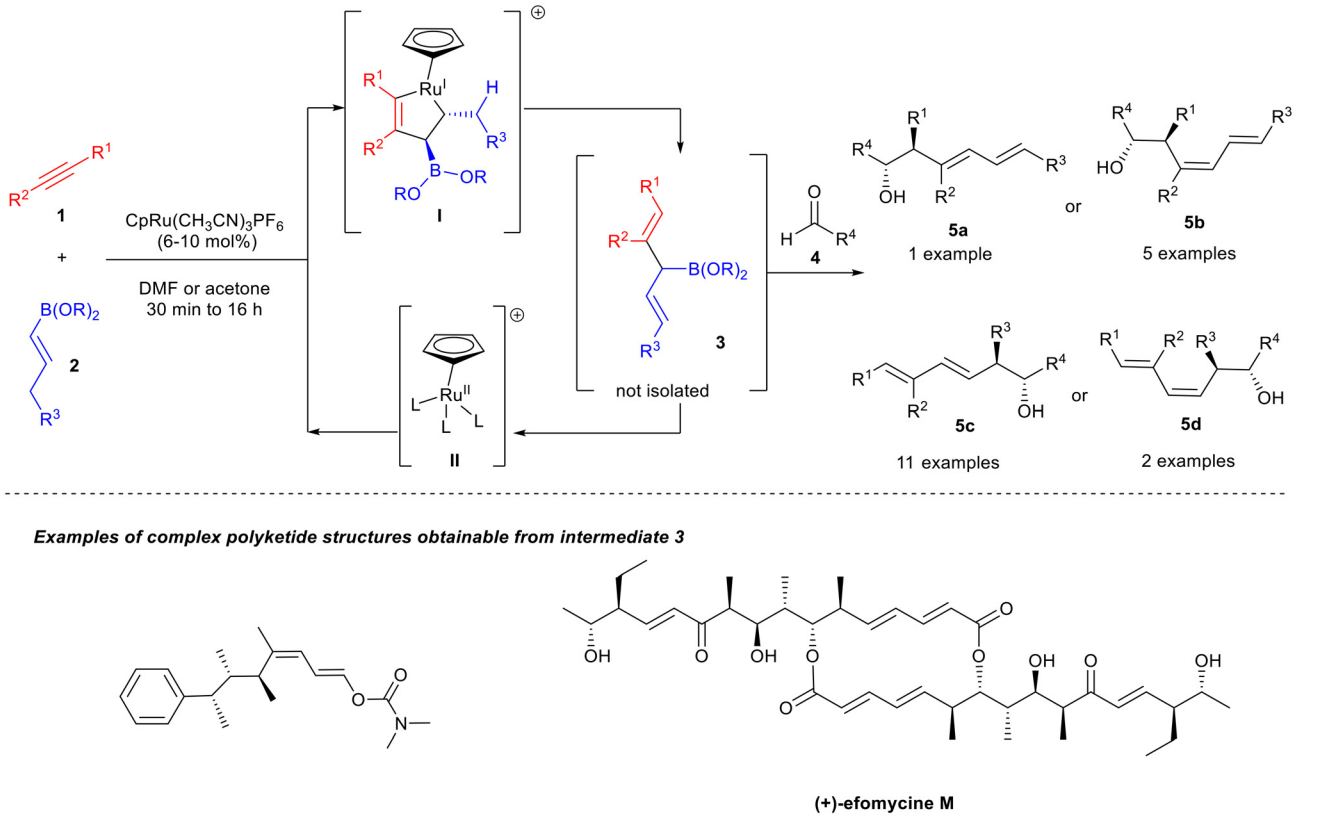
Later, in a paper published in 2022, the group of Hirano described the synthesis of borylated 1,4-dienes **8**.[5] The aforementioned compounds were obtained through a Ru(0)-promoted cross-dimerisation of borylated 1,3-diene **6** with substi-

Jacopo Scarfiello

Jacopo Scarfiello received his Master's degree in industrial chemistry from the University of Torino in 2019. His thesis consisted of synthesizing chalcones through micellar catalysis employing green surfactants in the aqueous phase. In 2022, he obtained a doctoral fellowship (PNRR) from the University of Perugia while working in Annamaria Deagostino's group under the guidance of Dr Polyssena Renzi. His PhD research involves UV-visible light-promoted chlorination reactions.

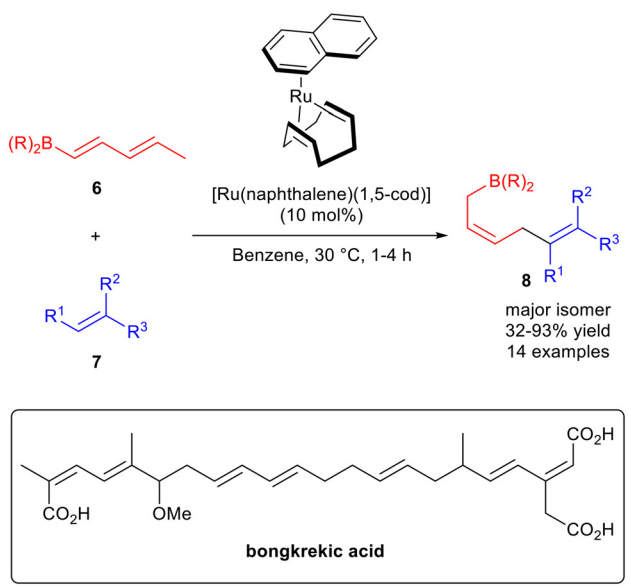
Annamaria Deagostino

Annamaria Deagostino is professor of organic chemistry at the University of Turin, where she graduated in chemistry, and after a fellowship at University of Padova, she undertook PhD studies at the University of Turin from 1994 to 1997. In 1998, she obtained a postdoctoral fellowship at the University of Caen, under the supervision of Prof. Marie-Claire Lasne, and then she returned to the University of Turin. The main interests of her research group are in the field of synthetic organic chemistry, mainly focused on organopalladium chemistry, visible light photoinduced processes and the synthesis of BNCT (boron neutron capture therapy) theranostic agents.



Scheme 1 Ru-catalysed coupling reaction to access intermediates 3-boryl-1,4-dienes **3**.

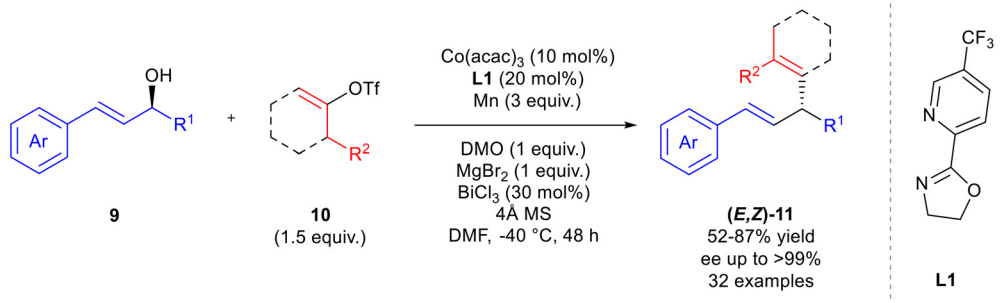
tuted alkenes 7 (Scheme 2). The reaction proceeded at 30 °C in benzene, in the presence of 10 mol% of [Ru(naphthalene)(1,5-cod)], resulting in the formation of a mixture of 1,4- and 1,5-diene products, contingent upon the substrate structure. The utility of these borylated dienes was demonstrated by their application in a variety of Suzuki–Miyaura coupling reactions, as well as in the formal synthesis of *rac*-bongkrekic acid.



Scheme 2 Ru(0)-catalysed synthesis of diborylated 1,4-dienes **8**.

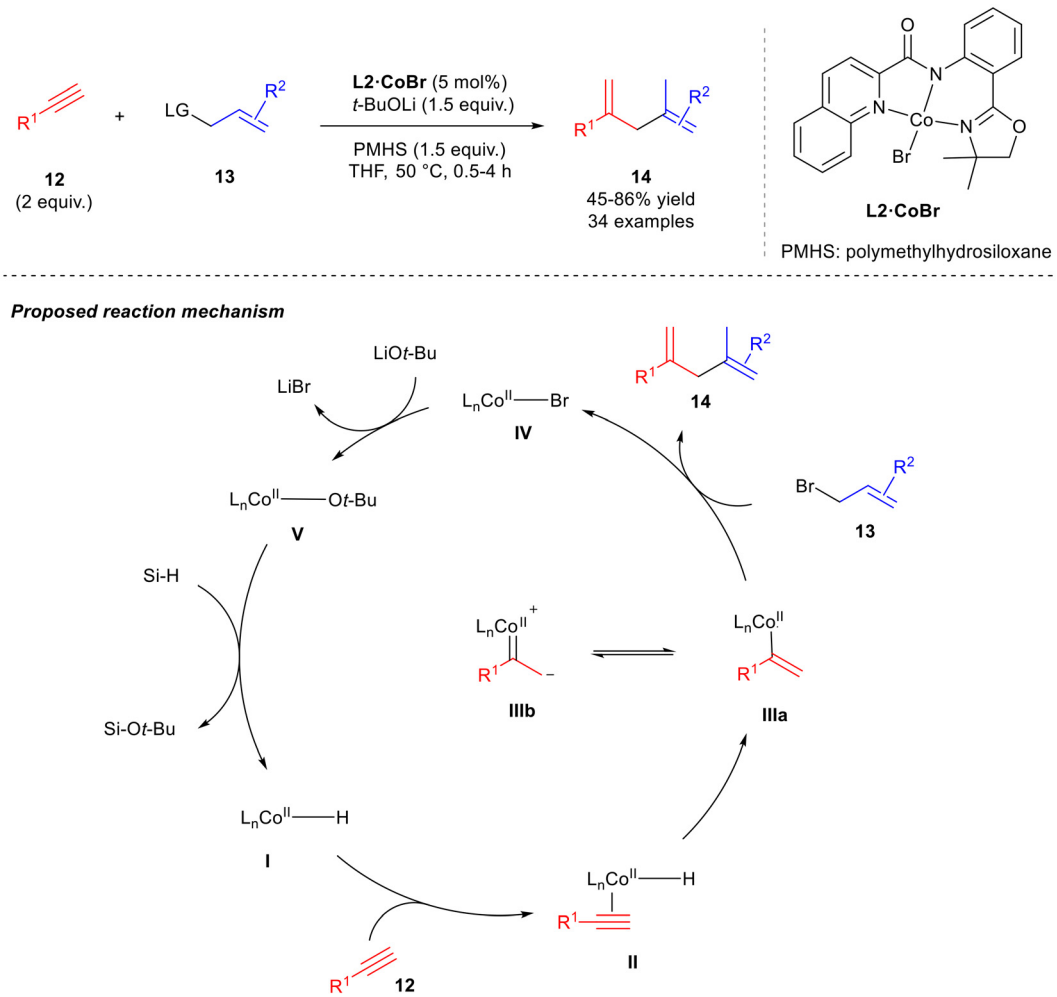
Group 9: cobalt (Co), rhodium (Rh) and iridium (Ir)

Catalysis by the metals belonging to group 9 relies on cobalt, rhodium and iridium-based catalysts. Cobalt catalysis plays an increasingly central role in cross-electrophile coupling reactions, offering a valuable alternative to other commonly employed transition metals.[6] In this field, the group of Shu recently developed an asymmetric cobalt-catalysed cross-electrophile vinylation reaction of allylic alcohols **9** with vinyl triflates **10**, (Scheme 3). The use of cobalt allowed high enantiospecificity with easily accessible enantioenriched secondary alcohols, avoiding the need for chiral ligands, to access asymmetric skipped dienes **11** with an inversion of configuration.[7] The reaction required $BiCl_3$ as a Lewis acid to activate the allylic oxalate formed *in situ* with dimethyl oxalate (DMO), and manganese (Mn) as a metal reductant to generate the active cobalt catalytic species. This protocol was applied to several allylic carbonates bearing different electronic properties on the aromatic ring, and both cyclic and acyclic vinyl triflates in moderate to very good yields and excellent enantiospecificities. Furthermore, the authors reported the functionalisation of vinyl triflates of testosterone and (+)-nootkatone, representing an efficient method for the incorporation of enantioenriched allyl alcohols into complex biologically active molecules.



Scheme 3 Cobalt-catalysed enantiospecific cross-electrophile coupling reaction of enantioenriched allyl alcohols **9** and vinyl triflates **10**.

In 2022, Lu and co-workers reported a cobalt-hydride catalysed hydroallylation reaction of terminal alkynes **12** with allylic electrophiles **13** to access Markovnikov-type skipped dienes **14** with good regioselectivity.[8] The described protocol accomplished great efficiency, as demonstrated by the high turn-over number (TON) up to 1160 and the short reaction time of 20 min of the model reaction (Scheme 4). Furthermore, this methodology was successfully scaled up to a gram-scale without any noticeable decrease in yield. Terminal alkynes **12** containing heterocycles were well tolerated, as well as conjugated enyne and silyl alkyne. The alkene scope comprised mostly aliphatic and aromatic bromides; nonetheless different allylic electrophiles such as allyl iodide and allyl phosphate could also be functionalised to the corresponding dienic product, with slightly lower yield and regioselectivity.

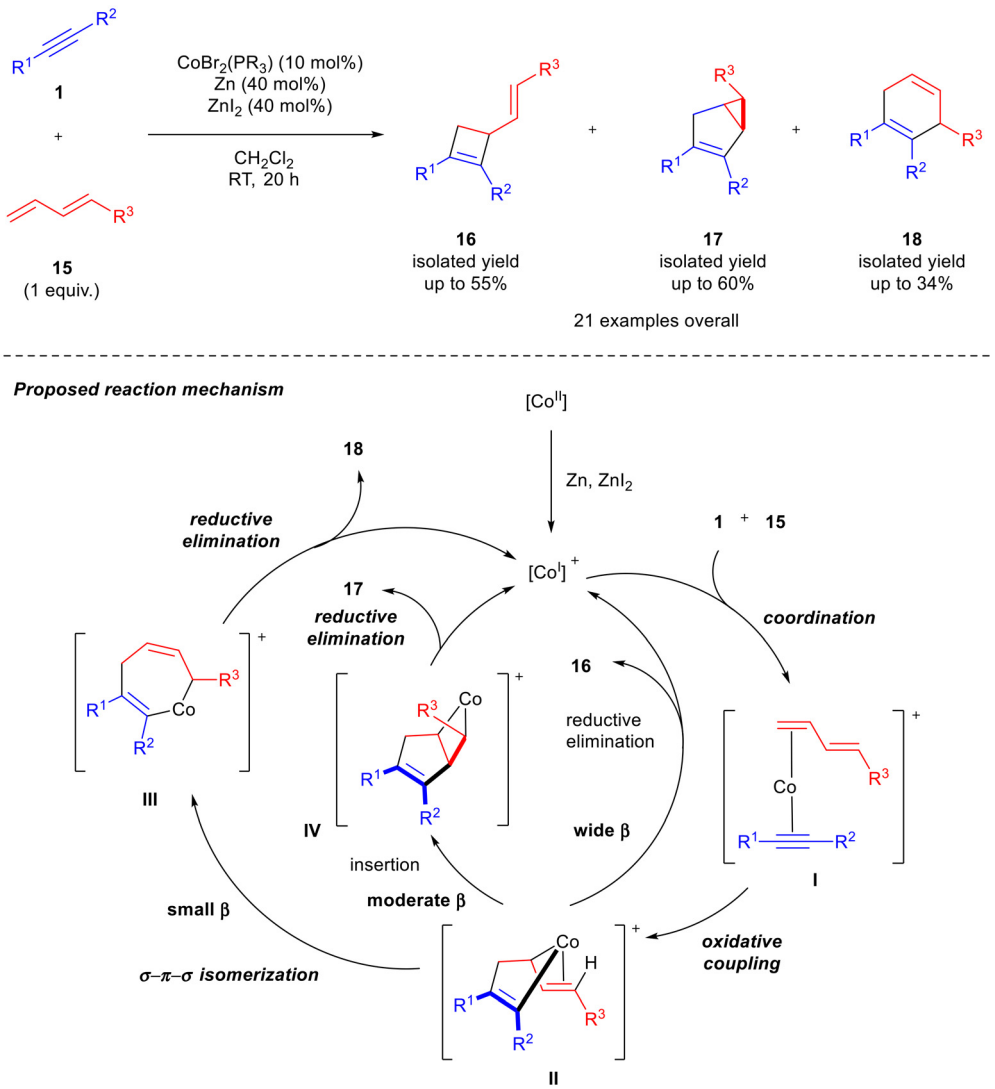


Scheme 4 Hydroallylation reaction of terminal alkynes **12** with allylic electrophiles **13**.

Based on experimental studies, the authors hypothesised that a cobalt hydride species **I** could be obtained from the reaction of the hydrosilane and Co(II) in the presence of *t*-BuOLi (Scheme 4). The coordination of the terminal alkyne **12** to **I** generates the alkynyl cobalt hydride complex **II**. Subsequently, α-selective insertion of the alkyne into the Co–H bond furnishes the alkenyl cobalt intermediate **IIIa** that quickly isomerises to the cobalt carbene zwitterion **IIIb**. Finally, an S_N2- and S_N2'-type reaction with the allylic electrophile **13** results in the formation of the skipped diene product **14.**

Recently, the group of Hirano expanded the reactivity of the apparently simple $CoBr_2$/phosphine/Zn/ZnI_2 catalytic system on internal alkynes **1** and conjugated dienes **15** to catalyse complex divergent cycloaddition reactions (Scheme 5).[9]

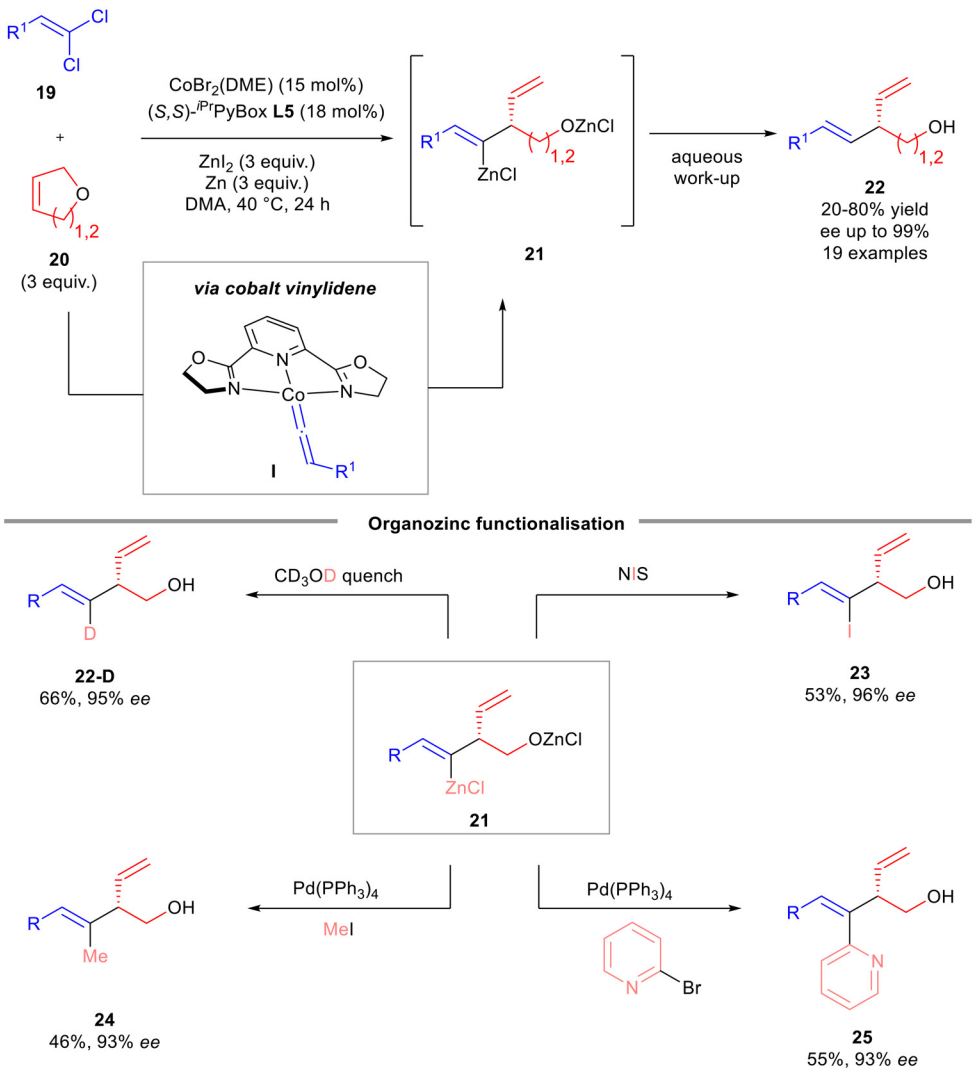
The authors observed that the bite angle of the phosphine ligand was able to significantly contribute to the chemodivergence of the reaction, providing a practical rationale for obtaining the desired cycloaddition product. Indeed, phosphines with wide bite angles such as PPh_3 (although not strictly called bite angle, the P–M–P angle with PPh_3 is wider than in most diphosphines) selectively produced 3-alkenylcyclobut-1-enes **16**, and meanwhile ligands with narrower bite angles, *i.e.* ethylenebis(diphenylphosphine) (dppe **L3**), provided cyclohexa-1,4-dienes **18.** Conversely, diphosphines like 1,3-bis(diphenylphosphino)propane (dppp **L4**) with intermediate bite angles afforded bicyclo[3.1.0]-hexenes **17** as the major product (Scheme 5). Nonetheless, it was observed that the electronic properties of the conjugated dienes could also impact the outcome of the cycloaddition reaction. Indeed, 1-aryldienes preferentially yielded the bicyclic product **17**; the electron-deficient dienes generally gave the cyclobutadienic product **16**, and meanwhile the electron-rich dienes afforded the cyclohexa-1,4-dienes **18** as the major products. According to the proposed reaction mechanism (see Scheme 5), the active catalytic species is thought to be a cationic Co(I) complex that can coordinate with the substrates to generate **I**. Next, an oxidative



Scheme 5 Divergent cobalt-catalysed cycloaddition reaction of alkynes with conjugated dienes. β: bite angle.

coupling allows the formation of the cationic cobaltacycle **II**. From the common intermediate **II**, according to the P–M–P angle, the reaction can evolve towards the different products **16–18** with different rates. A fast reductive elimination is observed with a wider P–M–P angle, leading to the [2 + 2] cycloadduct product **16**. In contrast, a narrow bite angle implies a slow reductive elimination from **II**, which instead firstly isomerises to the seven-membered cobaltacycle **III** and then produces the [2 + 4] cycloadduct product **18**. In the intermediate cases, intramolecular insertion of the alkenyl group occurs, thus yielding the bicyclic alkene **17**.

Recently, Uyeda disclosed an asymmetric cobalt-catalysed procedure to access highly functionalised skipped dienes in an enantioselective manner through the aid of a chiral ligand **L5** in the presence of a Zn/ZnI_2 system.[10] This versatile protocol afforded acyclic organozinc compounds **21**, which could be further functionalised with an electrophile, starting from vinylidenes **19** and 2,5-dihydrofuranes **20** (Scheme 6). Deep mechanistic investigations, supported by DFT calculations, suggested a Zn-mediated generation of the cobalt vinylidene species **I** that could undergo a [2 + 2] cycloaddition pathway, followed by a ring-opening step involving a challenging ZnI_2-assisted outer-sphere β-O elimination to afford **21**. The scope of the methodology was mostly explored on the substrates **19**. In fact, 1,1-dichloroalkenes bearing electron-donating and electron-withdrawing aryl groups furnished skipped dienes **22** in moderate to good yields with excellent enantioselectivities. Furthermore, heterocycles including quinoline and benzofuran, as well as different functional groups potentially critical for transition metal-catalysed procedures, such as boronate esters and bromides, were well tolerated. The ring-opening reaction produced organozinc compounds **21** that, after aqueous work-up, were quenched to alcohols containing the skipped diene motif **22**. Nonetheless, **21** could instead be trapped with different electrophiles, accessing a broader range of functionalised 1,4-dienes. Indeed, deuterated product **22-D**



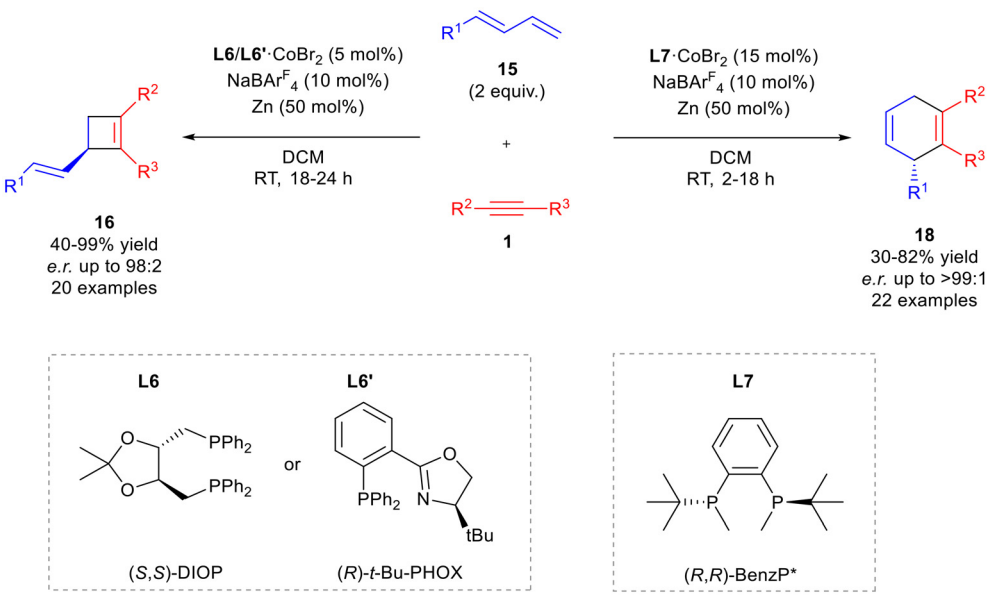
Scheme 6 Asymmetric zinc-assisted ring-opening reaction of unstrained heterocycles using cobalt vinylidenes **I**.

was obtained with 82% deuteration by quenching the crude reaction with CD_3OD. Otherwise, functionalisation with NIS (*N*-iodosuccinimide) furnished the iodinated C2 skipped diene **23** with 53% yield and excellent enantioselectivity. Finally, Negishi reaction conditions could be employed to obtain the cross-coupling products with methyl iodide and 2-bromopyridine (products **24** and **25**, 46% and 55% yield, respectively).

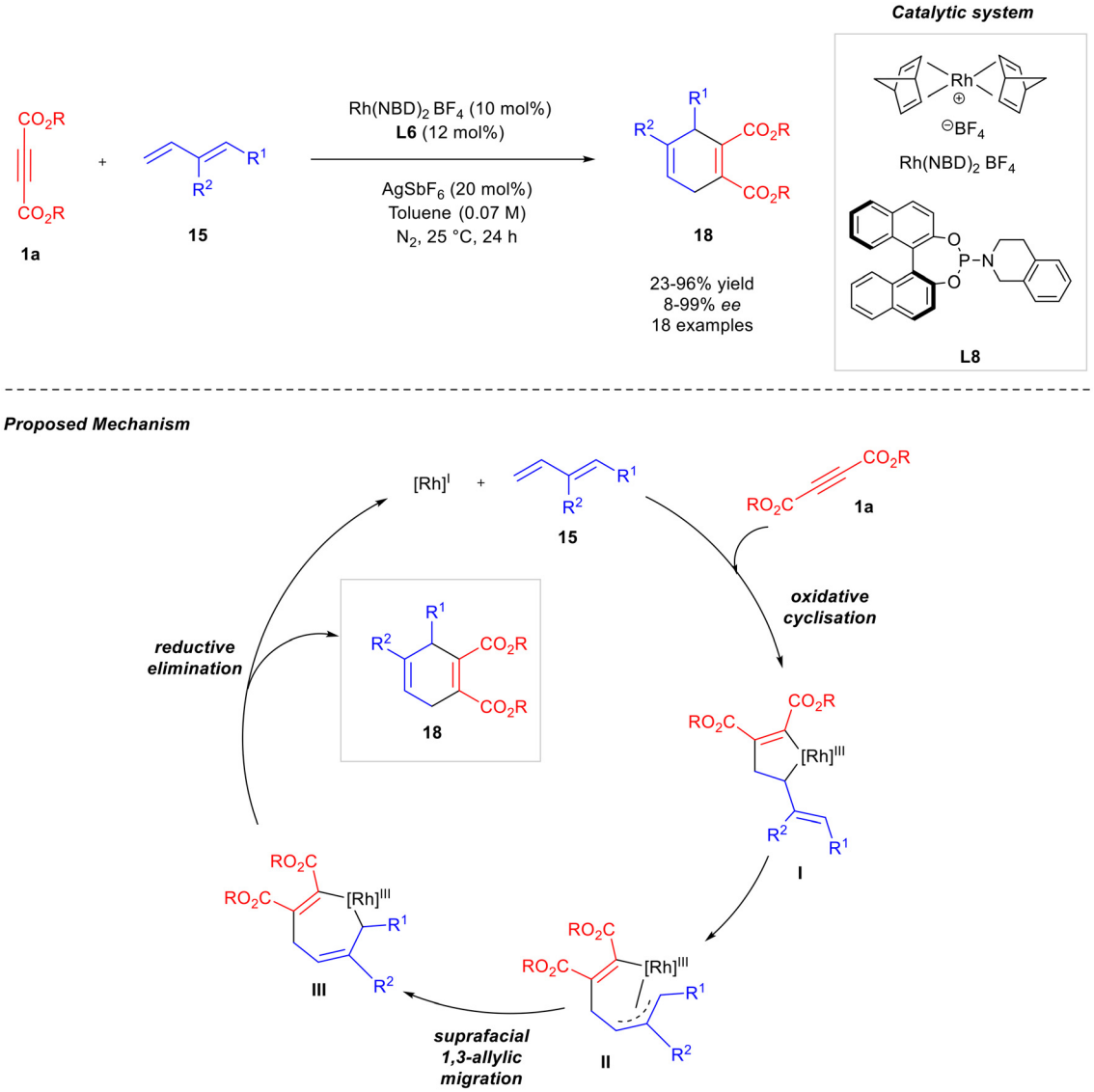
In 2023, the group of RajanBabu reported a chemodivergent asymmetric cycloaddition reaction between alkynes **1** and 1,3 dienes **15** to furnish skipped dienes employing a chiral ligand/cobalt catalytic system in the presence of zinc as the metal reductant and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate ($NaBAr^F_4$) as the activator.[11] Notably, starting from the same set of substrates, this protocol accomplished an enantioselective cobalt-catalysed [4 + 2] or [2 + 2] cycloaddition reaction to produce 1,4-cyclohexadienes **18** or cyclobutenes **16**, respectively (Scheme 7). Control experiments demonstrated that the active catalytic species is a cationic Co(I) complex, although no mechanistic studies were reported to rationalise the observed ligand-dependent chemodivergence. Nonetheless, the authors noted that chiral and achiral biphosphines with relatively narrow bite angles (<93°), such as (*R*,*R*)-BenzP* **L7**, were the most effective for the synthesis of 1,4-cyclohexadienes **18**. Meanwhile, the cobalt complexes with (*S*,*S*)-DIOP **L6** or (*R*)-*t*-Bu-PHOX **L6′** ligand could be employed to selectively furnish cyclobutenes **16** containing the skipped diene unit.

Rhodium is a highly versatile transition metal catalyst widely used in organic synthesis due to its exceptional ability to assist various bond-forming reactions with high efficiency and selectivity. Its catalytic properties enable key transformations such as hydrogenation, hydroformylation, C–H activation, and cycloaddition reactions.[12] In this regard, exploiting rhodium's versatility in promoting cycloadditions, Zheng and colleagues developed a method to obtain carbonyl-substituted cyclohexa-1,4-dienes **18** with up to 96% yield and >99% enantiomeric excess.[13] This transformation was based on an asymmetric intermolecular [4 + 2] cycloaddition of 1,3-dienes **15** with acetylenedicarboxylates **1a**, catalysed by rhodium(I)-chiral phosphoramide complex. In the optimised reaction conditions, $Rh(NBD)_2BF_4$ was employed as the catalyst in the presence of ligand **L8** and the additive $AgSbF_6$ in toluene at room temperature (Scheme 8).

The best results were achieved with R = Me, R^1 = *n*-pentyl, R^2 = H. Generally, the yields decreased with more hindered substituents. The reactivity was, also, compromised in the presence of low boiling 1,3-dienes. Good tolerance was observed toward different masked alcohols, protected amines, esters and phenyl groups. Moreover, in cases of low reactivity, the reaction temperature was increased up to 110 °C, adding 1,2-dichloroethane as a co-solvent. A plausible mechanism is shown in Scheme 8. The pre-formed rhodium(I) complex coordinates with the acetylenedicarboxylates **1a** and the 1,3-diene **15** forming the rhodacyclopentene species **I** after an oxidative cyclisation. The subsequent suprafacial 1,3-allylic migration generates the heptadiene intermediate **III**, through the metal-mediated η^3-complex **II**. Finally, a reductive elimination allows the cycloaddition product **18** to be obtained, along with the regeneration of the rhodium(I) complex. 1,5-Dienes could be obtained through allyl–allyl cross coupling between allylic electrophiles and allylmetal reagents.[14] Moreover, *gem*-difluorinated cyclopropane emerged as fluoroallyl surrogates to access fluoroallylic skeletons in presence of nucleophiles through transition-metal catalysed C–C bond activation.[15] Interestingly, rhodium-based catalysts promote fluoroallylation of arenes *via* the aryl C–H fluoroallylation of olefins starting from *gem*-difluorinated cyclopropanes.[16] Exploiting this potentiality, by fine-tuning the rhodium precursor and the ligand, the group of Xia reported a regio-switchable rhodium-catalysed methodology



Scheme 7 Cobalt-catalysed chemodivergent and enantioselective cycloaddition reactions between conjugated alkenes **15** and alkynes **1**.

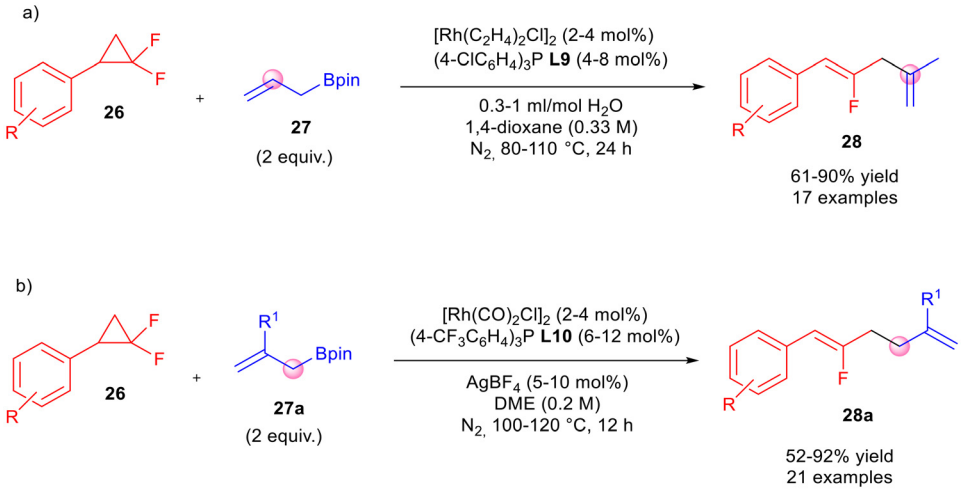


Scheme 8 Catalytic asymmetric [4 + 2] cycloaddition of 1,3-dienes **15** with acetylenecarboxylates **1a**.

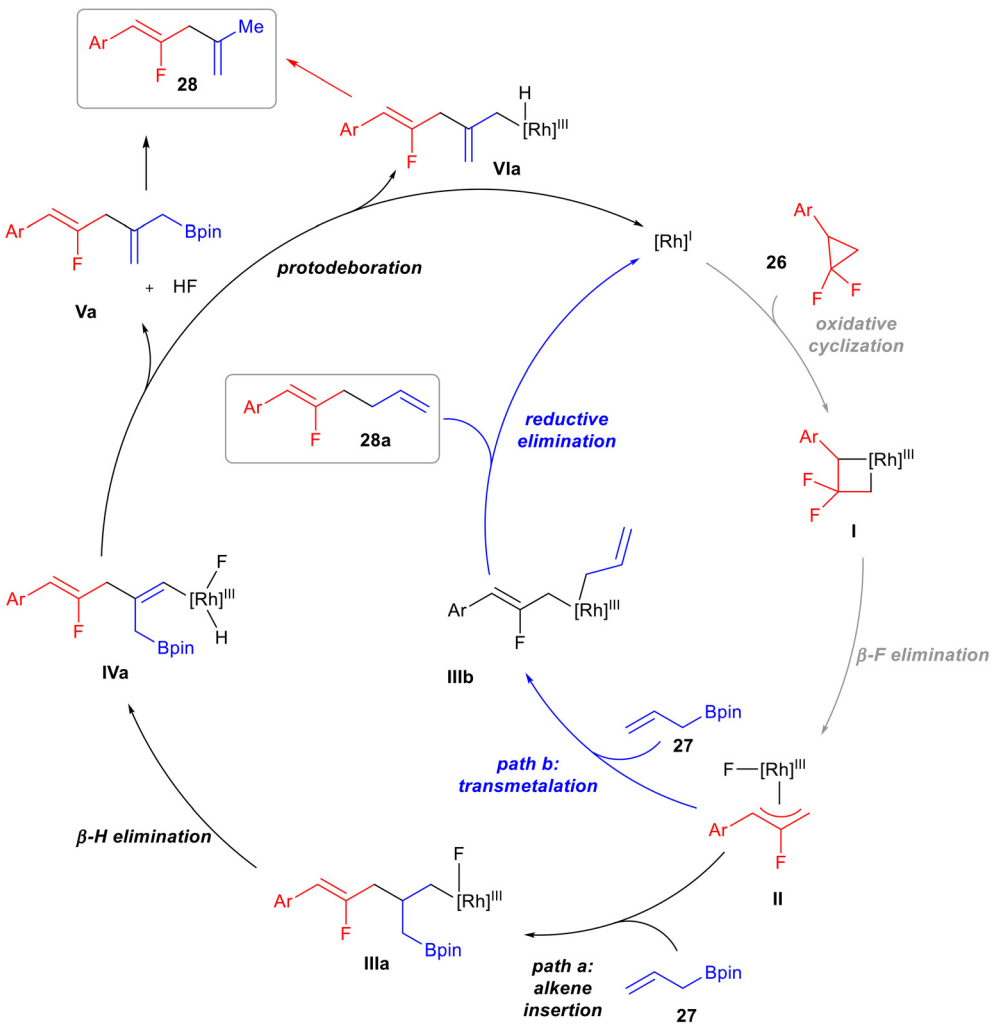
to obtain fluorinated 1,*n*-dienes (*n* = 3, 4, 5) from *gem*-difluorinated cyclopropanes **26** and allyl-Bpin **27**.[17] As shown in Scheme 9, fluorinated 1,4-dienes **28** were selectively obtained employing $[Rh(C_2H_4)_2Cl]_2$ in the presence of phosphine $(4\text{-}ClC_6H_4)_3P$ **L9** using water as an additive, in dioxane at 110 °C for 24 hours. In order to obtain fluorinated 1,5-dienes **28a** both the rhodium catalyst and the ligand were changed to $[Rh(CO)_2Cl]_2$ and $(4\text{-}CF_3C_6H_4)_3P$ **L10**, respectively. Moreover, $AgBF_4$ replaced water as the additive with dimethoxyethane (DME) serving as the solvent at 120 °C for 12 hours (Scheme 9b).

Several *gem*-difluorinated cyclopropanes **26** were tested bearing both electron-donating, electron and di-substituted aryl moieties. The scope was also extended to different allyl-Bpin **27a** bearing phenyl and benzyl groups in the R^1 position.

The proposed reaction mechanism, illustrated in Scheme 10, involves the oxidative addition of the *gem*-difluorinated cyclopropanes **26** to the rhodium(I) complex as the first step, to give the four-membered rhodacycle **I**. Then, the β-F elimination gives the key allyl-Rh(III) complex **II**. At this stage, there are two possible pathways for the formation of intermediate **II**. In path a, allyl-Bpin **27** inserts into the rhodium complex **II** to afford intermediate **IIIa**, followed by β-H elimination to obtain the dienyl-Bpin-bound rhodium complex **IVa**. The dissociation of the rhodium complex **IVa** gives dienyl-Bpin **Va** and F–Rh(III)–H. The reductive elimination of F–Rh(III)–H would regenerate the rhodium catalyst releasing one molecule of HF. Fluorinated 1,4-diene **28** can be formed by either protodeboronation of dienyl-Bpin **Va** or through a sequence of intramolecular transmetallation and reductive elimination *via* intermediate **VIa**. Concerning the path b, the allyl-Rh(III) complex **II** undergoes transmetallation with allyl-Bpin **27a** to obtain the di-allyl rhodium complex **IIIb**. The following allyl–allyl reductive elimination allows the fluorinated 1,5-diene **28a** to be formed.

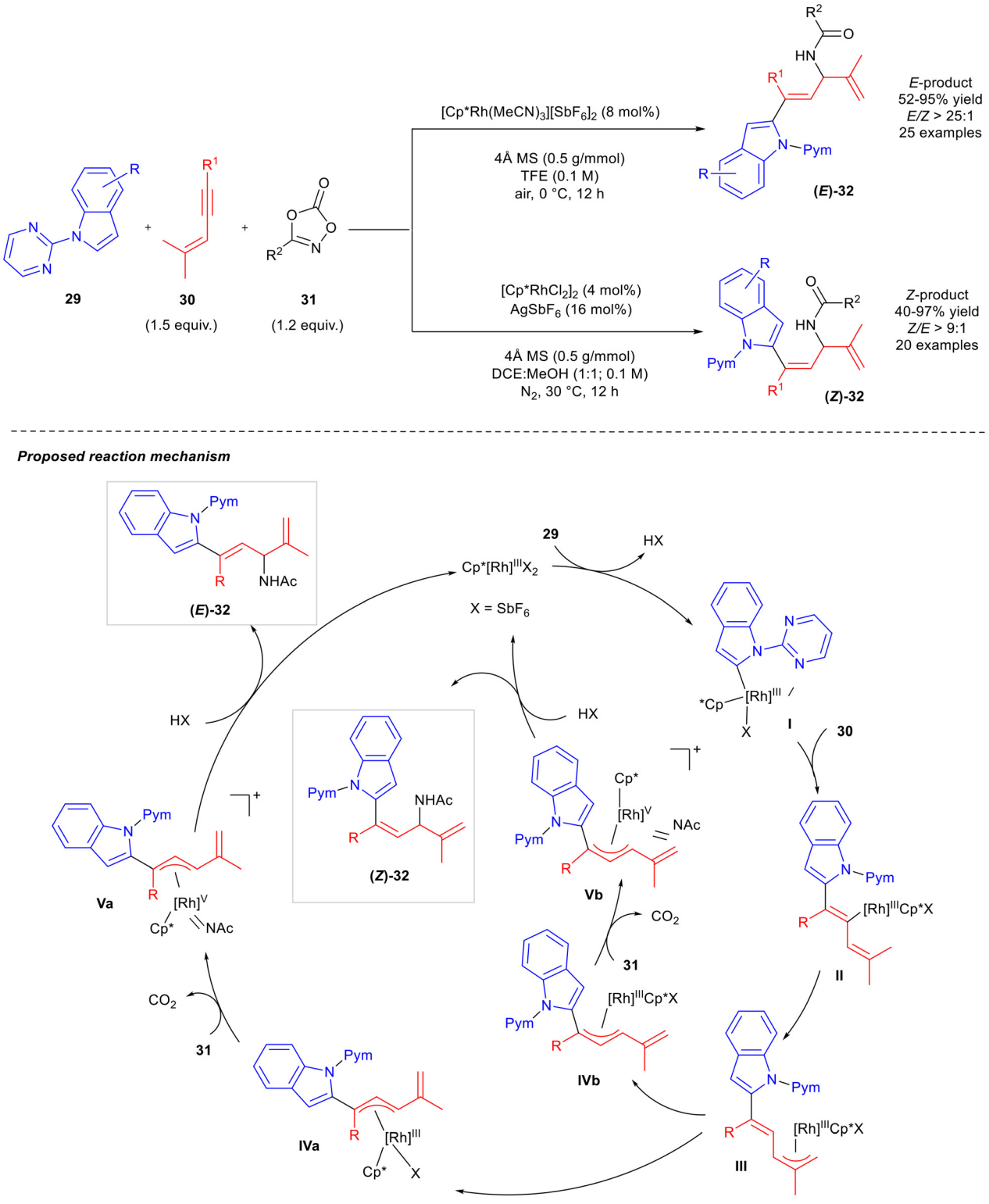


Scheme 9 Catalytic regioselective synthesis of fluorinated 1,4-dienes **28** and fluorinated 1,5-dienes **28a**.



Scheme 10 Mechanistic proposal for the synthesis of fluorinated 1,4-dienes **28** and fluorinated 1,5-dienes **28a**.

To obtain 1,4-dienes from 1,3-enynes, a [3 + 3] oxidative annulation strategy leveraging 1,4-rhodium(III) migration is essential.[18] Since rhodium catalysis promotes three-component carboamination reactions,[19] an interesting multicomponent approach, where *N*-pyrimidylindoles **29**, 1,3-enynes **30** and dioxazolones **31** were reacted to afford 1,4-dienes **32**, was developed by Li and colleagues (Scheme 11).[20] The process was characterised by high *E*/*Z* selectivity and regioselectivity and

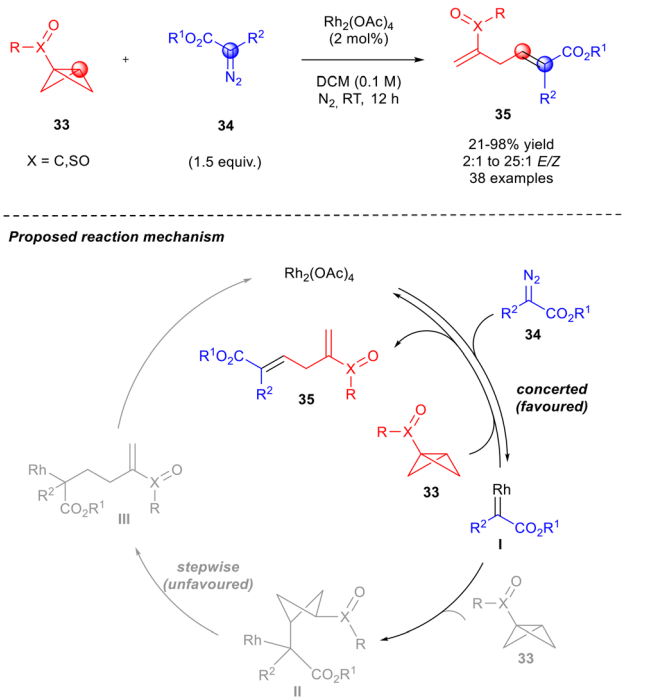


Scheme 11 Regioselective catalytic three-component carboamination and mechanistic proposal.

the carboamination was promoted by a Rh(III) complex. The *E* isomer product was, selectively, formed in the presence of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ and 4 Å molecular sieves in 2,2,2-trifluoroethanol (TFE) at 0 °C for 12 hours without exclusion of air or moisture. On the other hand, the *Z* isomer was formed employing $[Cp^*RhCl_2]_2$ with $AgSbF_6$ and 4 Å molecular sieves in a 1 : 1 mixture of DCE : MeOH at 30 °C for 12 hours under N_2. For both the regioisomers, *N*-pyrimidinylindoles **29** bearing electron-donating, electron-withdrawing, *n*-hexyl, benzyl, phenyl and halogen groups in different positions of the aromatic ring were tested with successful results. 1,3-Enynes **30** bearing i-propyl and bulkier groups such as ethylbenzyl, i-pentyl, *n*-pentyl were well tolerated in both reactions. Acetyl-, *n*-hexyl-, benzyl- and phenyl-substituted dioxazolones **31** all afforded high yields and selectivity. A plausible catalytic cycle is outlined in Scheme 11. First, C–H activation of indole **29** allows the formation of the five-membered rhodacycle **I** with the catalyst. Subsequently, the coordination of the 1,3-enyne **30** and regioselective migratory insertion of Rh–C(aryl) delivers the rhodium alkenyl intermediate **II**, which evolves to the π-allyl rhodium(III) species **III**. Allyl-to-allyl rearrangement generates intermediates **IVa** and **IVb**, where the stereochemistry of the allyl ligand is largely dictated by the steric hindrance between the rhodium complex, the indole ring and the R group in the 1,3-enyne. Then, the dioxazolone **31** ligation followed by decarboxylation forms the reactive Rh(V) allyl nitrene species **Va** and **Vb**. Finally, the C–N reductive elimination and protodemetalation releases the product in a specific configuration, closing the catalytic cycle.

Pioneeringly, merging metal–carbene and strain-release chemistry, the group of Hari developed a novel regio- and stereoselective rhodium-catalysed strain-enabled protocol (Scheme 12),[21] where skipped dienes **35** were obtained from bicyclo[1.1.0]butanes (BCBs) **33**. BCBs are nucleophiles, able to react with electrophilic metal–carbene species generated by diazocompounds **33** in the presence of $Rh_2(OAc)_4$. The reaction was conducted without additives in dichloromethane at room temperature for 12 hours.

To investigate the reaction potential, a series of diazocompounds **34** were tested. The electron-withdrawing and electron-donating groups on the aryl moiety, as well as the biphenyl, naphthalene, and thiophene groups as R^2, were well tolerated. The use of different diazo esters, including those with alkyl, allyl, and trichloroethyl groups, resulted in favourable outcomes. Only ethyl diazoacetate, *t*-butyl diazoacetate, and diazomalonate exhibited poor yields and stereoselectivities (21–31% yield, *E*/*Z* = 2 : 1). It is worthy of mention that diazo compounds derived from biological molecules, including menthol, borneol, and cholesterol, participated in this reaction, with yields ranging from 85 to 95% and *E*/*Z* ratios exceeding 20 : 1. As far as the BCBs **37** are concerned, esters bearing i-propyl, *t*-butyl, and vinyl cyclohexyl groups yielded the desired skipped diene. Furthermore, BCB amides substituted on the nitrogen with phenyl, electron-poor aryls, and benzyl groups also reacted well. Based on DFT and experimental studies, a concerted mechanism was proposed by the authors, where the

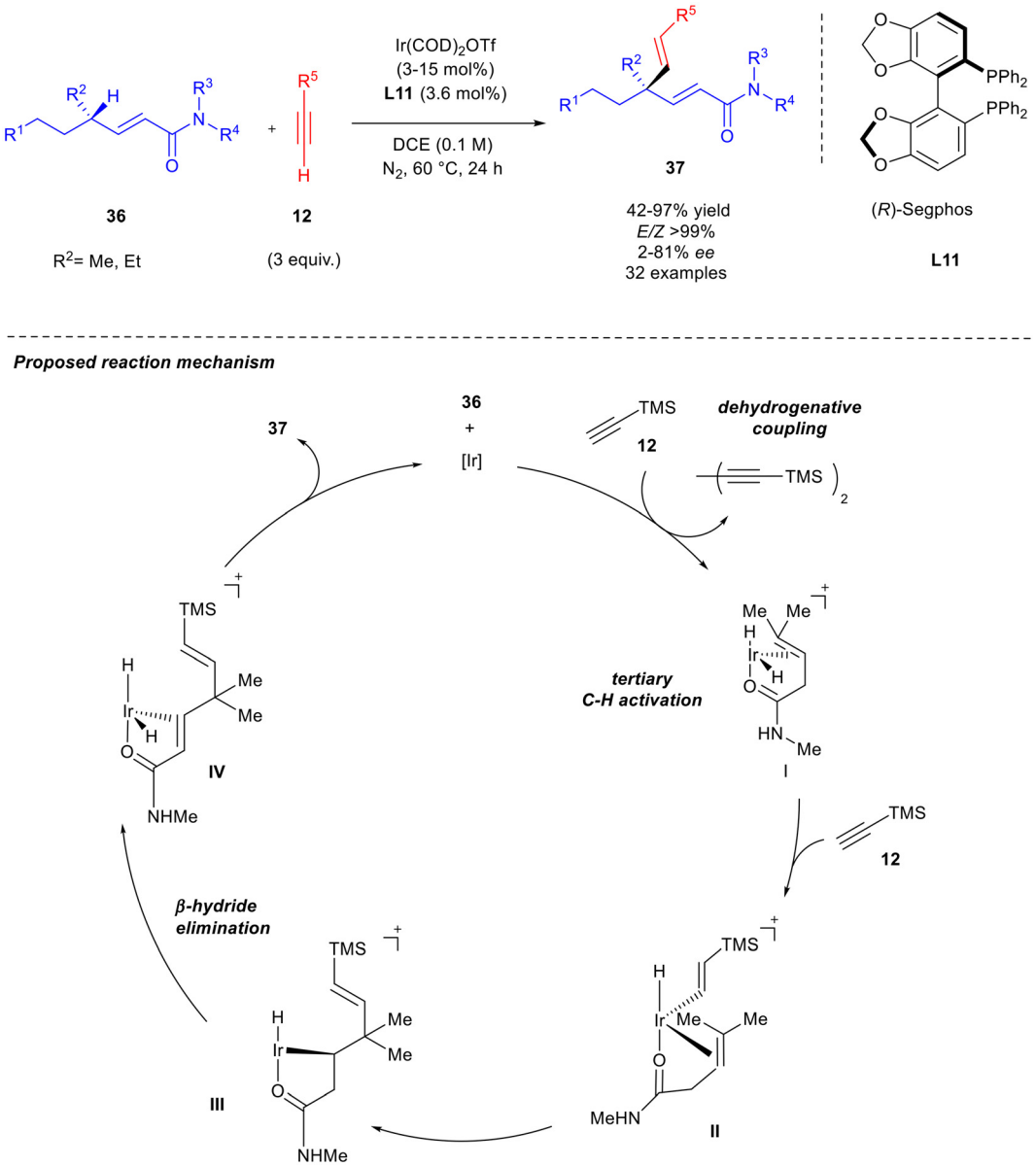


Scheme 12 Regio- and stereo-selective catalytic synthesis of 1,4-dienes **35** through strain release and concerted mechanism.

Rh(II) catalyst forms the metallocarbene species **I** by reacting with the diazo compound, upon loss of N_2. Since it was not possible to optimise computationally intermediates **II** and **III**, it was supposed that the concerted mechanism should proceed through a less energetic transition structure able to facilitate the formation of the *trans* product **35** (Scheme 12).

In an attempt to extend the reactivity to non-acceptor metal carbenes, the group of Echavarren deeply investigated the reactivity of 1,3-dienes in [4 + 3] cycloadditions, catalysed either by Rh or Au.[22] As far as the rhodium catalysis is concerned, 7-vinyl-1,3,5-cycloheptatrienes were investigated as model substrates in the [4 + 3] cycloaddition with 1,3-dienes *via* a retro-Buchner reaction in the presence of Rh_2TFA_4 [rhodium(II) trifluoroacetate dimer] at 40 °C, using 1,2-dichloroethane (DCE) as the solvent. A library of cycloheptadienes was successfully synthesised in modest to excellent yield with this methodology, showing a high functional group tolerance. A detailed mechanism was proposed by both DFT calculations and kinetic experiments, starting from the rhodium(II)-catalysed retro-Buchner reaction followed by a Cope rearrangement of the cyclopropane scaffold.

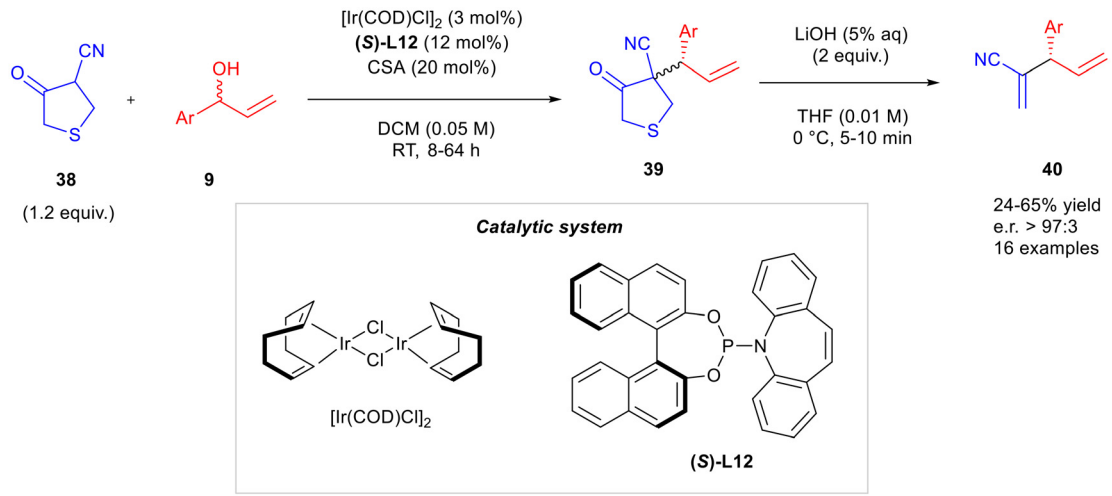
Among group 9 metals, also iridium-based catalysts have been exploited for the stereo- and enantio-selective synthesis of skipped dienes.[23] In 2022, the group of Li reported an unprecedented enantioselective Ir-catalysed *E*-selective addition of α,β-unsaturated amides **36** to terminal alkynes **12** to form 1,4-dienes **37** with a quaternary carbon center at the C-3 position (Scheme 13).[24] The best catalytic system was composed of $Ir(COD)_2Otf$ and the ligand (*R*)-Segphos **L11**, in dichloroethane (DCE) at 60 °C for 24 hours.



Scheme 13 Regio- and stereo-selective Ir-catalysed addition of a tertiary allylic C–H bond of α,β-unsaturated amides **36** to alkynes **12**.

Secondary and tertiary amides were tolerated, although the latter required an increased amount of catalyst. Substrates containing ether, aryl halide, phenol, and thiophene as the R^3/R^4 were well tolerated. Moreover, the formation of skipped dienes was observed when the amides possessed aryl, alkyl, cyclohexyl, cyclopentyl, and alkene groups in the R^1 position. In the case of substrates containing two alkenes, the reaction exhibited chemoselectivity. Additionally, silyl-substituted terminal alkynes underwent regioselective addition, and a higher catalyst loading was required for alkyl- and aryl-substituted terminal alkynes. Computational studies and control experiments helped to clarify the reaction mechanism, which is shown in Scheme 13. First, the alkyne–alkyne coupling allows the formation of the iridium dihydride intermediate **I** able to coordinate the amide **36.** A migratory insertion of the alkyne **12** into the iridium hydride generates the corresponding vinyl iridium complex **II.** Then, the alkene forms an iridium–carbon bond to generate intermediate **III.** Finally, β-hydride elimination occurs to form the 1,4-diene iridium complex **IV,** releasing the desired skipped diene **37** and regenerating the iridium dihydride complex.

A methodology to synthesise 1,4-dienes bearing a nitrile group without employing volatile, carcinogenic, flammable and prone to polymerisation acrylonitriles was developed by Roy and Mukherjee (Scheme 14).[25] Their strategy involved an enantioselective formal α-allylation of acrylonitriles using 4-cyano-3-oxotetrahydrothiophenes (c-THTs) **38** as an easy-to-handle surrogate of acrylonitriles. The first step consisted of a

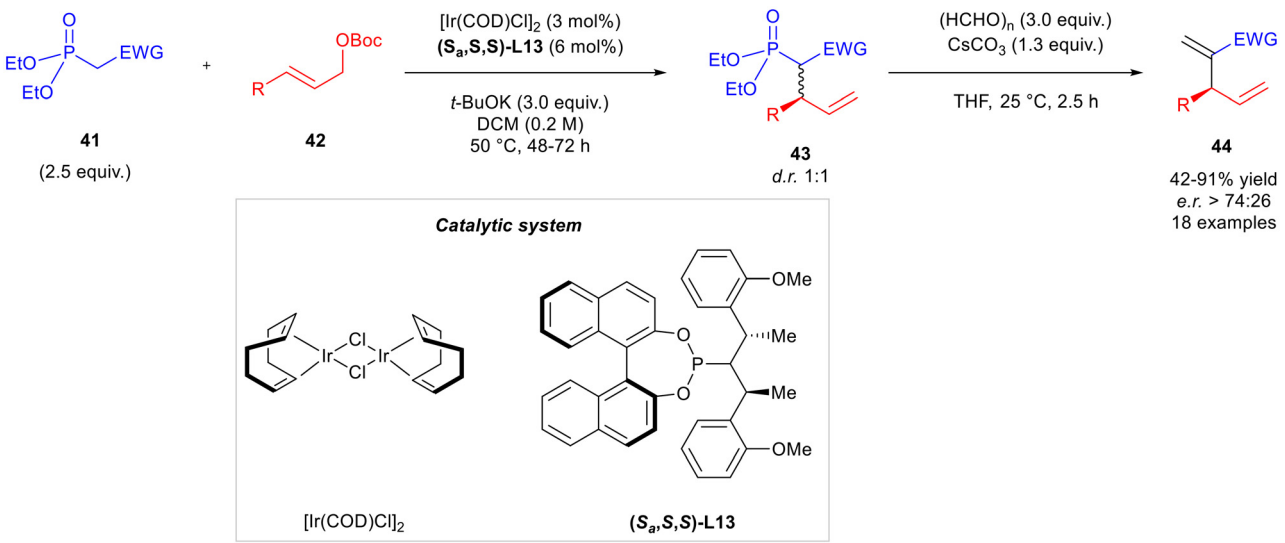


Scheme 14 Two-step enantioselective iridium-catalysed synthesis of cyano skipped dienes **40**.

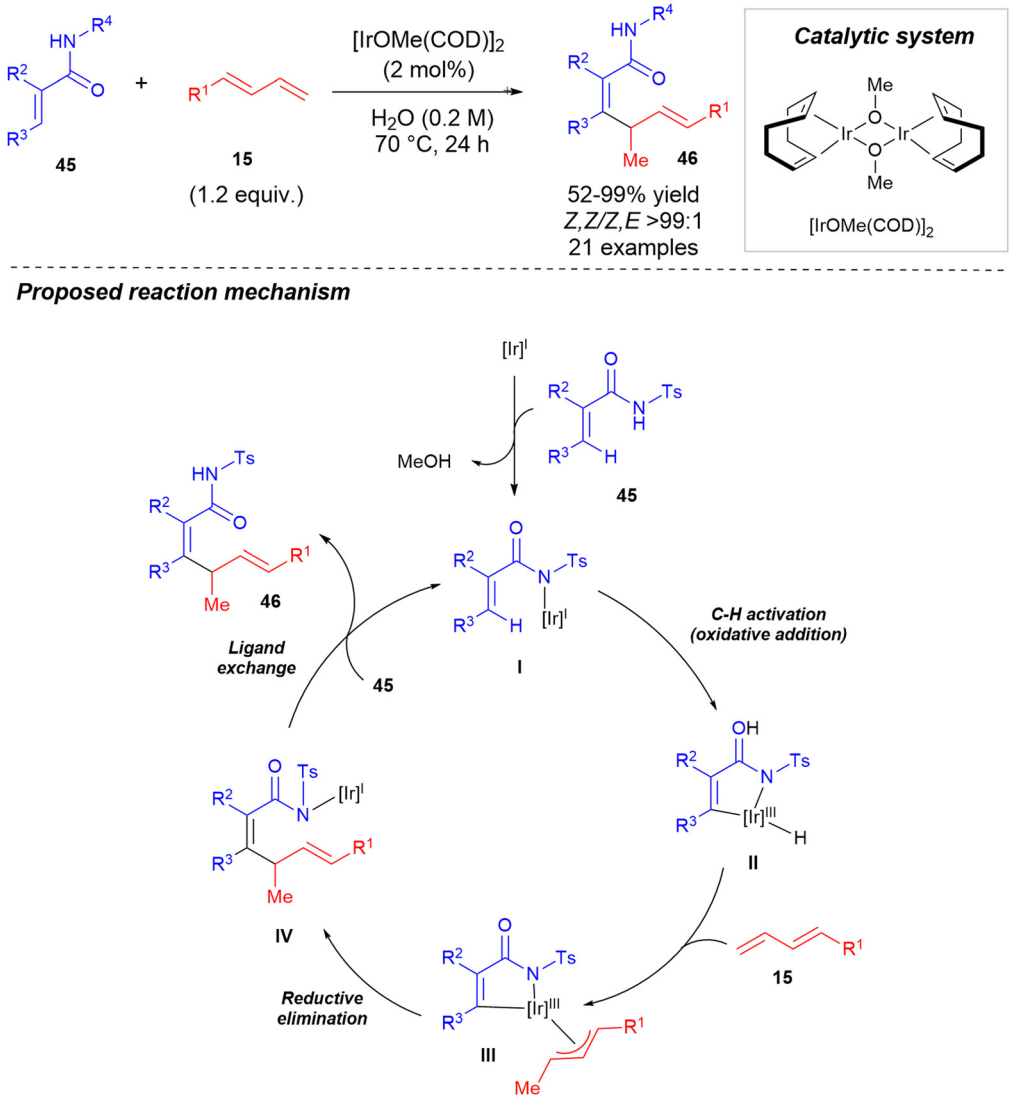
selective alkylation of racemic allyl alcohols **9** on c-THTs **38**, catalysed by $[Ir(COD)Cl]_2$ in the presence of the ligand (*S*)-**L12** and the additive camphor sulfonic acid (CSA) in dichloromethane at room temperature, for up to 64 hours. The final skipped diene **40** was obtained in the second step where the intermediate **39** underwent a retro-Dieckmann/retro-Michael reaction after treatment with an aqueous solution of LiOH in THF at 0 °C.

Several branched allylic alcohols **9** were considered to investigate the scope of the reaction. Both electron-donating and electron-withdrawing groups on the aryl ring were well tolerated. Unfortunately, alkyl, alkenyl, and highly electron-rich aryl-substitution remained unreactive. More recently, the same research group reported an iridium-catalysed allylic alkylation on phosphonates followed by a Horner–Wadsworth–Emmons olefination, to form skipped dienes bearing electron-withdrawing groups (Scheme 15).[26] Diethyl ethylphosphonates **41** were firstly reacted with allylic *tert*-butyl carbonates **42** employing $[Ir(COD)Cl]_2$ as the catalyst, (S_a,*S*,*S*)-**L13** as the ligand and *t*-BuOK as the base in dichloromethane at 50 °C for up to 72 hours. Then, product **43** was reacted with paraformaldehyde in the presence of Cs_2CO_3 in THF at 25 °C for 2.5 hours to form the skipped diene **44**. In the reaction scope, cinnamyl carbonates **42** bearing electron-withdrawing and electron-donating groups on the aryl ring generally presented high yields and enantioselectivities. Also, naphthyls and heterocycles were well tolerated. On the other hand, aliphatic substituents were not suitable because of a lack of regioselectivity. Furthermore, phosphonates **41** bearing electron-deficient moieties such as ketones, nitrile and several esters were suitable as the starting materials.

Another strategy to synthesise skipped dienes through iridium-catalysed olefinic C–H allylation and alkenylation in



Scheme 15 Two-step enantioselective iridium-catalysed synthesis of 1,4-dienes **44**.



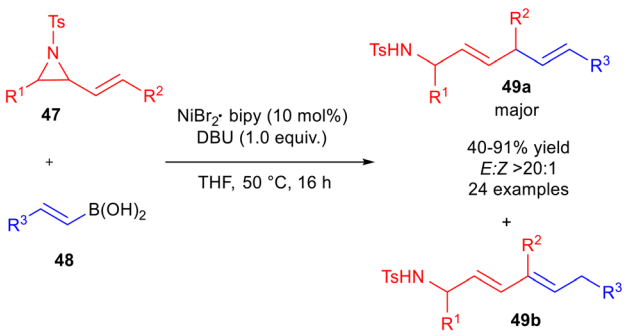
Scheme 16 Regioselective iridium-catalysed synthesis of 1,4-dienes **46**.

water was developed by Zhang and colleagues (Scheme 16).[27] In this protocol, acrylamides **45** and 1,3-butadienes **15** were reacted in water in the presence of $[IrOMe(COD)]_2$ at 70 °C for 24 hours. Several 1-aryl-1,3-butadienes **15** were exploited, demonstrating that halogens and methoxy groups on the aryl and anthranyl ring were well tolerated. Several aromatic *N*-Ts acrylamides, bearing electron-donating and -withdrawing groups and different *N*-substituted acrylamides, such as methanesulphonyl, were efficiently converted to the final product. The catalytic cycle proposal is illustrated in Scheme 16. First, the methoxoiridium catalyst reacts with the *N*-Ts acrylamide **45** to form amidoiridium species **I** through a ligand exchange. The following oxidative addition of the olefinic C–H bond gives the hydroiridium species **II** which reacts with 1,3-diene **15** to generate the π-allyliridium species **III** by a branch selective alkene insertion. Irreversible reductive elimination forms the amidoiridium species **IV** followed by a ligand exchange that allows the formation of the 1,4-diene **46** and the regeneration of the catalytic active amidoiridium species **I**.

Group 10: nickel (Ni) and palladium (Pd)

Catalysis by group 10 metals relies on nickel- and palladium-based catalysts. The nickel-catalysed approach has emerged as a significant advancement in synthetic chemistry, distinguished by its cost-effectiveness, operational simplicity, and compatibility with a variety of functional groups. As a readily available and affordable transition metal, nickel facilitates efficient catalysis also in reactions involving skipped dienes.[28,29]

In 2023, Gao and co-workers introduced a novel method for synthesising skipped aminodienes **49** using a nickel-catalysed ring-opening and cross-coupling reaction with vinylaziridines **47** and multifunctional organoboronic acids **48** (Scheme 17).[30] Optimised reaction conditions include $NiBr_2$·bipy as the cata-



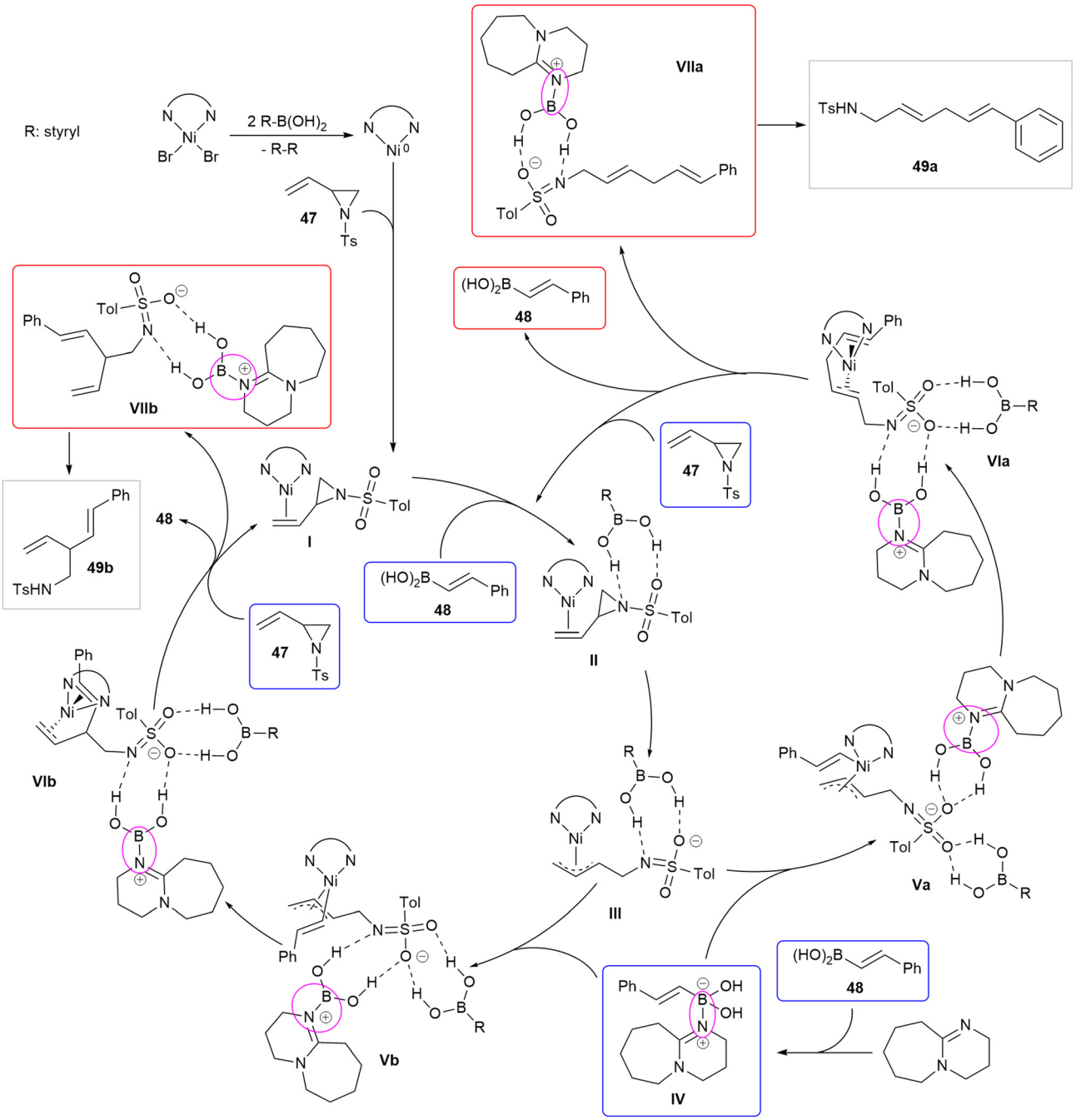
Scheme 17 Nickel-catalysed ring-opening/cross-coupling reaction.

lyst, and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as the base in THF as the solvent, at 50 °C for 16 hours. These conditions provided the highest yield (91%) and excellent regioselectivity of the skipped aminodiene product **49**. The reaction exhibited first-order kinetics with respect to the nickel catalyst, indicating its crucial role in facilitating the process. In contrast, it displays zero-order kinetics regarding the vinylaziridine substrate **47**, meaning that the substrate's concentration does not significantly affect the reaction rate once it has begun.

The proposed mechanism (Scheme 18) begins with a sequential transmetalation and reductive elimination involving styrylboronic acid, which converts Ni(II) species into the active Ni(0) species, leading to the formation of intermediate **I** through coordination with substrate **47**. When DBU is employed, it facilitates the formation of the η^3-allyl nickel intermediate **III** from the intermediate **II** by promoting the ring-opening of vinylaziridines **47** through hydrogen bonding with styrylboronic acid **48**. Concurrently, the complex **IV** is formed from **48** and DBU *via* N–B bond coordination. The presence of complex **IV** enhances the transmetalation between styrylboronic acid and **III**, resulting in intermediates **Va** and **Vb**. These intermediates, undergoing reductive elimination, yield linear intermediate **VIa** and branched intermediate **VIb**. This process releases one molecule of **48** and Ni(0) for further reactions, producing intermediates **VIIa** and **VIIb**, which subsequently undergo protonation to form products **49a** and **49b**.[30] DBU enhances the reaction by stabilising the lower-energy intermediate **II** through hydrogen bonding, facilitating the formation of **III**. DFT calculations showed that the transition state with *trans*-styrene and bulky allyl is more favourable than the *cis*-configuration. By lowering transition state energies during transmetalation, DBU promoted the production of linear-selective products and contributed to regioselectivity, making it essential for optimising the reaction.[30]

Liu and co-workers reported a nickel-catalyzed method for the regioselective allylic alkenylation of allylic alcohols **9** with alkenyl boronates **50**, enabling efficient synthesis of 1,4-dienes **51** in excellent yields (up to 97%) under mild conditions (50 °C in acetonitrile) (Scheme 19).[28] The reaction employs Ni $(cod)_2$ (5 mol%) and a monodentate phosphine ligand (10 mol%), operating without the need for a base or alcohol activator. This streamlined system offers high efficiency, broad substrate compatibility, and excellent regioselectivity. Ligand selection played a critical role in optimizing reaction outcomes. Monodentate ligands proved significantly more effective than bidentate ones, which gave lower yields and poor selectivity. Among those tested, PBu_3 delivered the highest regioselectivity (linear : branched ratio of 26 : 1), while PPh_2Cy showed a favorable balance of steric and electronic properties. Two optimized conditions were established: *t*-Bu_3P **L14** for aryl alkenyl boronates and PPh_2Cy **L15** for alkyl variants and selected alcohols. In both cases, regioselectivity remained excellent, with linear products strongly favored (ratios >50 : 1), and the stereochemistry of the diene products was exclusively *E*-configured. Compared with other transition metal systems—such as palladium, iridium, or copper—the nickel-catalyzed approach excels in atom economy, mildness, and selectivity. It avoids the need for pre-activated electrophiles or strong additives and works efficiently with both aryl- and alkyl-substituted allylic alcohols and a wide range of alkenyl boronates, making it a highly practical and selective method for constructing linear 1,4-dienes.

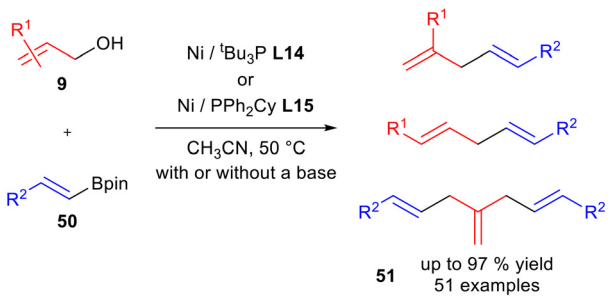
In 2023, Xi and co-workers presented an innovative method for the direct hydroallylation of terminal alkynes **12** with allylic alcohols **9**, utilising a nickel catalyst and promoted by carbon dioxide (Scheme 20).[31] This method is notable for its straightforward and efficient approach to the synthesis of valuable compounds under mild conditions, achieving excellent Markovnikov selectivity for both alkyl- and aryl-substituted terminal alkynes. The reaction occurred through three catalytic cycles (see Scheme 20). The proposed mechanism of catalytic cycle A includes the activation of allylic alcohol 9 and the generation of Ni(I) intermediate in three steps. The activation of the allylic alcohol 9 by CO_2 allows the formation of the allyl hydrocarbonate **I**, which is a more reactive species compared with the original alcohol. The second step is the oxidative addition of Ni(0) with the allyl hydrocarbonate. This process results in the formation of an η^1-allylnickel(II) intermediate **II** bearing a Ni–C bond. Next, a ligand exchange with lithium acetate (AcOLi) replaces a ligand on the nickel centre, generating intermediate **III** and $LiHCO_3$. This latter is a key species that is involved in the subsequent catalytic cycle. Then the vinylzinc species **IV**, generated in the catalytic cycle C, reacts with the Ni (II) intermediate **III** leading to the formation of intermediate **V**, which contains a Ni–C bond and is essentially the final product in a semi-reduced form. To obtain the final 1,4-diene product **52**, intermediate **V** undergoes reductive elimination, which entails the cleavage of the Ni–C bond and the release of the desired diene. In catalytic cycle B, formic acid was formed through the activation of $LiHCO_3$. The $LiHCO_3$ generated in catalytic cycle A interacts with the Ni catalyst, resulting in the release of formic acid (HCOOH) and the regeneration of the active Ni catalyst ($Ni(0)L_2$). In catalytic cycle C, the Ni(0) catalyst undergoes oxidative addition with the newly generated HCOOH, forming a hydride complex **VIII**. Then, the terminal alkyne **12** inserts into the Ni–H bond of intermediate **VIII**, resulting in the formation of a new Ni–C bond and creating



Scheme 18 Mechanism proposal for the nickel-catalysed ring-opening/cross-coupling reaction.

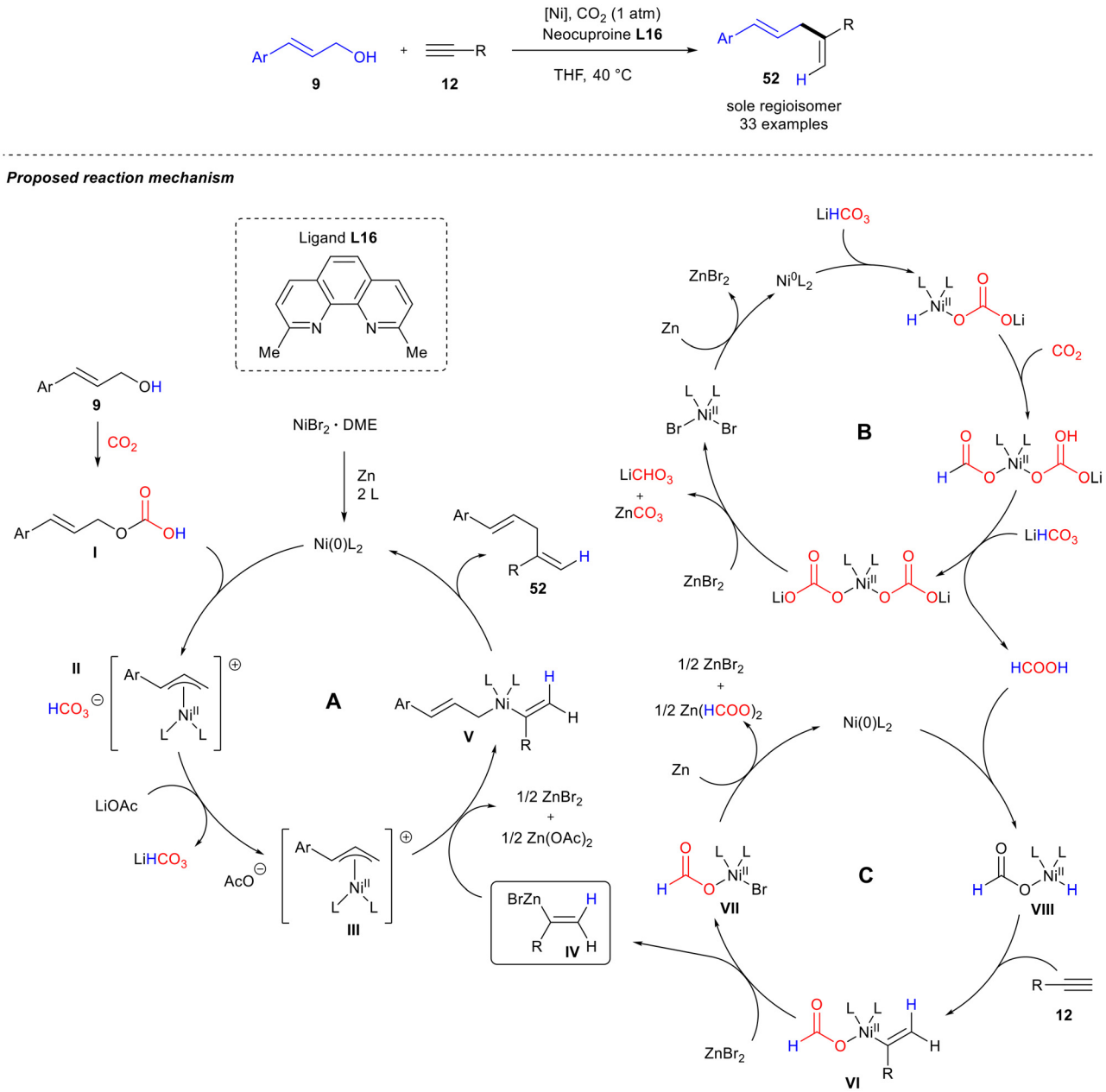
the alkenyl–nickel intermediate **VI**. This step is the key for the regioselectivity of the reaction, favouring the Markovnikov addition. The last step included transmetalation of the alkenyl–nickel intermediate **VI** with $ZnBr_2$, producing the vinylzinc species **IV** and regenerating the Ni (0) catalyst (NiL_2), which is ready to begin the cycle again. The presented method was scalable, allowing for gram-scale reactions that yielded significant amounts of 1,4-dienes **52**, highlighting its practical utility in synthetic organic chemistry.[31]

A nickel-catalysed allylmethylation of alkynes **1** using allylic alcohols **9** and trimethylaluminum was described in 2020 by Li and co-workers. This reaction was highly stereoselective and produced tetrasubstituted alkenes **53** with good yields (Scheme 21).[29] The combination of $Ni(cod)_2$ and PPh_3 as the catalyst, along with 1.5 equivalents of allylic alcohol **9** and $AlMe_3$, in toluene at 60 °C, yielded the highest amount of the desired product while reducing unwanted side reactions. The proposed mechanism (Scheme 21) for the nickel-catalysed allylative dicarbofunctionalisation of alkynes involves the rapid

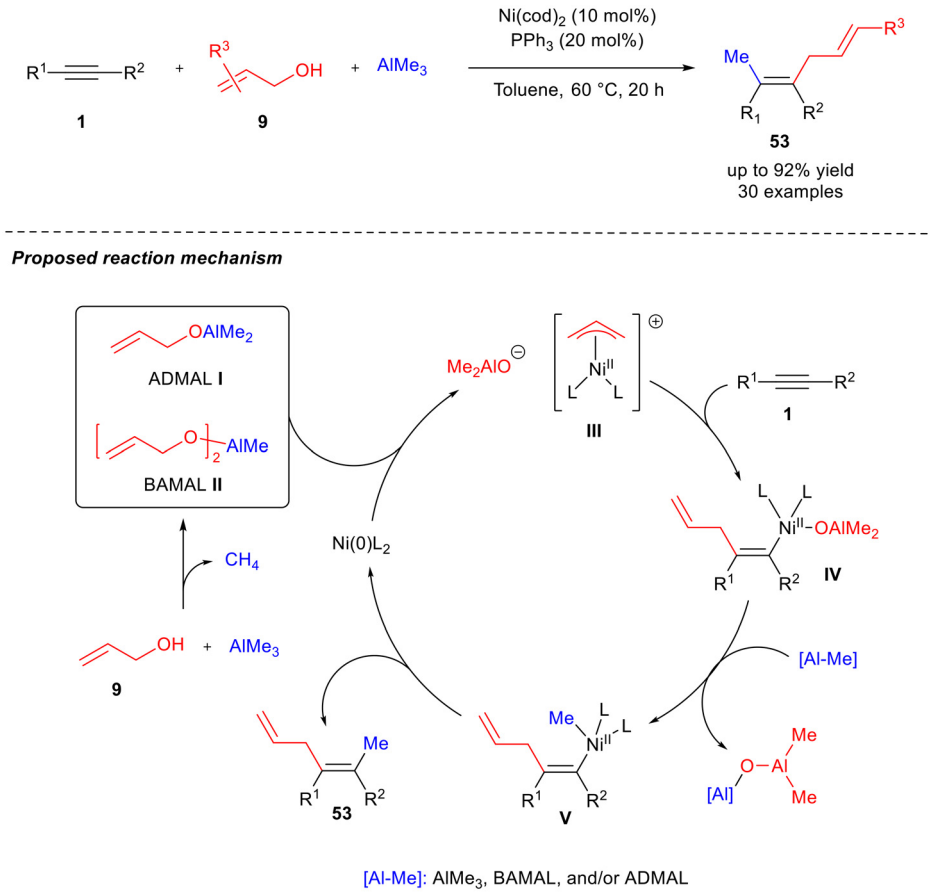


Scheme 19 Nickel-catalysed coupling of allylic alcohol derivatives with alkenyl boronates.

reaction of trimethylaluminum ($AlMe_3$) with the allylic alcohol **9**, leading to the formation of alkoxyaluminum species such as allyloxydimethylaluminum **I** (ADMAL) and/or bis(allyloxy) methylaluminum **II** (BAMAL). The alkoxyaluminum species **I** coordinates to the nickel catalyst, and then an allylnickelation takes place, *i.e.* the allyl group from the alkoxyaluminum species is transferred to the nickel catalyst, forming an allylnickel species **III**. This species then undergoes a carbonickelation reaction with the alkyne **1**, forming the vinylnickel species **IV**. In the following step, the methyl group is transferred to the vinylnickel species from the trimethylaluminum or a newly



Scheme 20 Nickel-catalysed hydroallylation of alkynes **12** with allylic alcohols **9**.

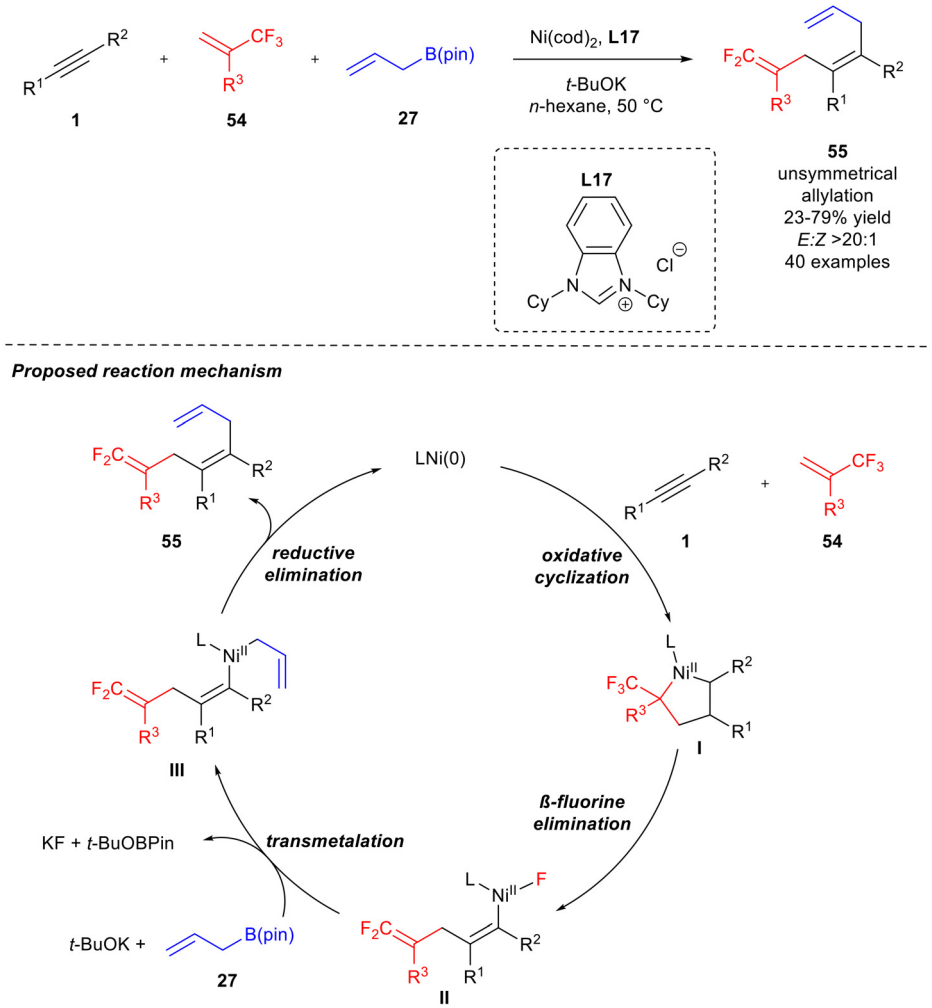


Scheme 21 Nickel-catalysed dicarbofunctionalisation of alkynes **1**.

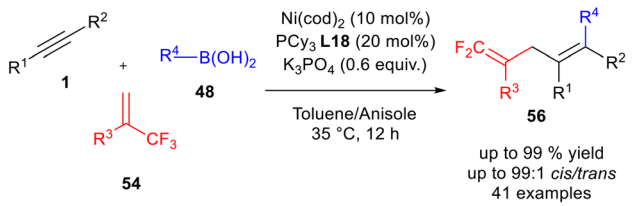
generated alkoxyaluminum species **I**/**II** (ADMAL or BAMAL), affording a skipped diene complex **V**. The last step is a reductive elimination in which the skipped diene product **53** is released, regenerating the active nickel catalyst for further reaction cycles. The key advantage of the described method is the use of easily accessible and affordable reagents, making it a practical and cost-effective approach for the synthesis of the skipped dienes and trienes.

An innovative technique for the unsymmetrical bis-allylation of alkynes, crucial for constructing complex molecular architectures in organic synthesis, was recently introduced by Ji and co-workers (Scheme 22).[32] The authors utilised a nickel catalyst, specifically a robust Ni(0)/NHC (N-heterocyclic carbene) system, to facilitate this reaction under mild conditions. This method allowed for the effective use of both electrophilic trifluoromethyl alkenes **54** and nucleophilic allylboronates **27**, resulting in the formation of valuable skipped triene **55** products with high regio- and stereoselectivity. The optimised reaction conditions consisted of alkyne **1**, α-trifluoromethyl alkene **54**, and allylboronates **27** reacted with 5 mol% $Ni(cod)_2$, 5 mol% NHC ligand **L17**, and 1.5 equivalents of *t*-BuOK in *n*-hexane at 50 °C for 24 hours. The authors addressed challenges in unsymmetrical bis-allylation, which has been underexplored compared with symmetrical methods. They emphasised the importance of the selectivity due to potential complications from multiple reactive species. The mechanism (Scheme 22) begins with the oxidative cyclometallation of an alkyne **1** and α-trifluoromethyl styrene **54**, creating a crucial nickel metallacycle intermediate **I**. This intermediate enables the selective *syn*-addition of the alkyne to the electrophile, ensuring desired regioselectivity. Following this, a β-fluorine elimination step occurs, releasing a fluorine atom from the trifluoromethyl group and generating a new σ-complex **II** which undergoes transmetalation with allylboronate **27**, introducing the allyl group into the intermediate **III** and affording the skipped triene **55** by reductive elimination. The authors noted that the regioselectivity remained consistent despite potential competitive pathways due to the steric hindrance of the tertiary C–Ni bond, which makes certain interactions less favourable. Furthermore, the method demonstrated a wide functional group tolerance, making it versatile for various synthetic applications.[32]

Chen and co-workers developed an efficient nickel-catalyzed strategy for the synthesis of *gem*-difluorinated 1,4-dienes **56** through a three-component coupling of trifluoromethyl alkenes **54**, internal alkynes **1**, and organoboronic acids **48** under mild conditions (Scheme 23).[33] This protocol exhibited excellent chemo-, regio-, and stereoselectivity, providing access



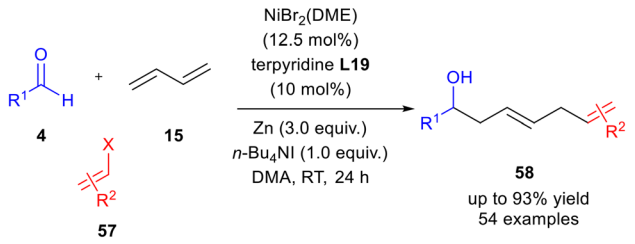
Scheme 22 Nickel-catalysed difluorinative bis-allylation of alkynes **1** and proposed reaction mechanism.



Scheme 23 Nickel-catalysed defluorinative three-component coupling reaction.

to structurally diverse fluorinated dienes that are otherwise difficult to obtain using traditional methods. The optimized reaction conditions involved a 1.8 : 1 : 1.5 ratio of alkyne, α-trifluoromethyl alkene, and organoboronic acid, respectively, in a 9 : 1 toluene : anisole solvent mixture. The catalytic system comprised $Ni(cod)_2$ (10 mol%) and PCy_3 **L18** (20 mol%), with K_3PO_4 (0.6 equivalents) as the base. The reaction was performed at 35 °C for 12 hours. These mild conditions proved broadly effective, addressing limitations of earlier methods that required more complex reagents or showed narrow scope. High yields and excellent *cis*/*trans* selectivity were achieved, even on a gram scale. The success of the reaction hinged on the $Ni(cod)_2/PCy_3$ catalytic system; replacing either component or altering the base or solvent significantly reduced reactivity and selectivity. Mechanistic studies revealed a key nickelacyclopropane intermediate, supporting a pathway involving oxidative cyclization, alkyne insertion, β-fluorine elimination, transmetalation, and reductive elimination. This sequence highlights the central role of ligand and metal in enabling selective C–F bond activation and C–C bond formation.

The same research group presented a nickel-catalysed reductive three-component coupling of aldehydes **4**, 1,3-butadiene **15**, and alkenyl triflates or bromides **57** to access skipped dienes **58** (Scheme 24).[34] The method accommodates a broad range of functional groups and heterocycles, and is scalable, underscoring its synthetic and industrial utility. The optimal system uses $NiBr_2$(DME), 2,2′:6′,2″-terpyridine ligand **L19**, zinc powder, and *n*-Bu_4NI in dimethylacetamide (DMA) at room temperature, using compound **15** as a 2 M solution in

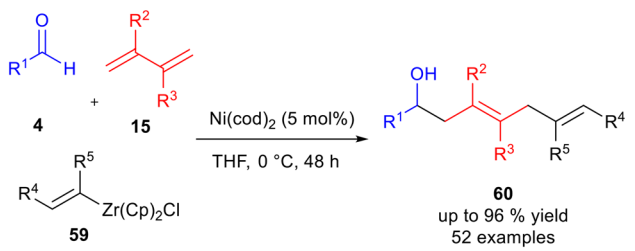


Scheme 24 Nickel-catalysed reductive carboalkenylation of 1,3-butadiene **15**.

THF. Ligand screening revealed the unique efficiency of **L19**, while bidentate or electron-rich terpyridines were ineffective. The iodide additive likely aids electron transfer from the zinc to the nickel. Mechanistically, the Ni(II) precatalyst is reduced to Ni(0), which undergoes oxidative addition to the alkenyl electrophile (Ni(II)) and is further reduced to Ni(I). Insertion of butadiene **15** forms an allyl-Ni(I) species that adds to the aldehyde, completing the cycle through reductive workup.

The resulting skipped dienes can be further transformed into polyenes, epoxides, ketones, azides, and triazoles. Limitations include poor regioselectivity with isoprene and lower yields with electron-deficient aldehydes. This study demonstrates the importance of fine-tuned catalyst systems for achieving efficient multicomponent couplings.[34]

A similar protocol employing aldehydes **4**, 1,3-butadiene **15**, and alkenylzirconium reagents **59** was recently developed for the efficient synthesis of skipped dienes **60** (Scheme 25).[35] This method provides notable advantages, including high regio- and stereoselectivity under ligand- and additive-free conditions. Alkenylzirconium reagents uniquely enabled the desired three-component coupling, in contrast to ineffective alkenylaluminum and alkenylboron reagents. Optimal conditions were established at 0 °C for 48 hours to maximize yields and chemoselectivities. The reaction likely proceeds *via* an electrophilic allylnickel(II) intermediate formed by oxidative cyclometalation, subsequently coupling with the alkenylzirconium reagent to form the skipped diene while avoiding premature aldehyde reactions. The substrate scope was broad, including various electron-rich, electron-poor, *ortho*-substituted arylaldehydes, and heterocyclic aldehydes. The skipped dienes **60** obtained featured diverse functional groups suitable for further synthetic transformations into derivatives such as

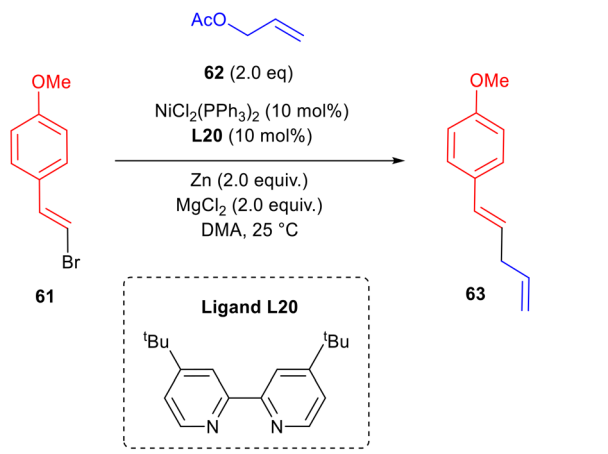


Scheme 25 Nickel-catalysed carboalkenylation of 1,3-dienes **15**.

1,3,6-trienes and conjugated dienes. The reaction's practicality and scalability were demonstrated *via* one-pot procedures and scale-up experiments, underscoring its potential for industrial applications and further exploration of multi-component nickel-catalyzed reactions.

Xie and co-workers reported a highly efficient nickel-catalyzed cross-electrophile allylation of vinyl bromides **65**, providing a powerful strategy for the construction of 1,4-dienes **63** under mild conditions (Scheme 26).[36] This transformation employs readily available allylic acetates **62** and diverse (*E*)-alkenyl bromides, with Zn as a terminal reductant and $MgCl_2$ as an additive. Optimal performance was achieved using $NiCl_2(PPh_3)_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine **L20** in DMA, affording products in up to 85% isolated yield. The methodology demonstrated broad functional group tolerance, accommodating electron-rich, electron-deficient, and sterically hindered substrates, including bioactive and structurally complex compounds. The approach was successfully applied to the site-selective modification of β-elemene, a natural anti-tumour agent, enabling the introduction of various vinyl substituents at the allylic position. Several of these modified analogs showed significantly improved anti-proliferative activity, underscoring the synthetic and medicinal value of the transformation.

Mechanistic investigations support a Ni(0)/Ni(I)/Ni(III) catalytic cycle. Radical scavengers such as TEMPO and BHT did not suppress the reaction, while oxygen inhibited product formation, suggesting that radical pathways are unlikely and that air-sensitive nickel intermediates are involved. The proposed mechanism begins with oxidative addition of the allylic acetate to Ni(0), generating a (π-allyl)Ni(II) intermediate, which is reduced by Zn to Ni(I). Subsequent oxidative addition of the vinyl halide **61** forms a Ni(III) species that undergoes reductive elimination to afford the product. The choice of ligand was crucial, with **L20** outperforming others, likely due to its ability to stabilize key nickel species. The selectivity of Ni for this transformation was highlighted by the failure of Co, Cu, or Fe,



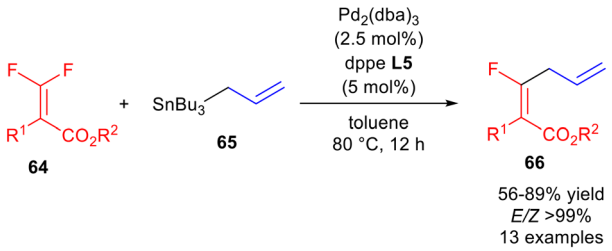
Scheme 26 Nickel-catalysed cross-electrophile allylation of vinyl bromides **61**; optimised reaction conditions.

reinforcing its unique suitability in this cross-electrophile coupling strategy. Preliminary attempts at asymmetric induction using a chiral pybox ligand resulted in only 24% ee, suggesting opportunities for further development in enantioselective variants.[36]

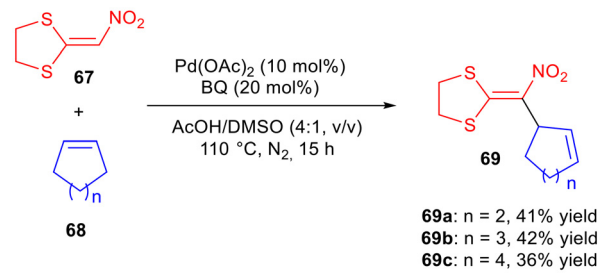
The majority of the palladium-catalysed strategies exploited to prepare skipped dienes, here reported, concern the allylation or vinylation of suitable substrates, among them alkynes, alkenes and arylhydrazones.[37–42]

As far as strategies involving alkenes are concerned, a Stille cross-coupling was used by Tsui and co-workers to obtain fluorinated 1,4-dienes **66** starting from *gem*-difluorotetrasubstituted vinyl esters **64** and allylstannanes **65** *via* a C–F bond activation in a stereoselective manner. $Pd_2(dba)_3$ and dppe **L5** were demonstrated to be the best catalytic system (Scheme 27).[43] The reactions were carried out in toluene at 80 °C. Several allylating reagents were tested, among them boron and silyl derivatives, although stannanes **65** gave best results, allowing 13 functionalised 1,4-dienes **66** in good to excellent yields to be recovered. The reaction was applied to benzyl, aryl-substituted vinyl esters containing both electron-withdrawing and -donating groups.

Un-activated cycloalkenes **68**, and α-nitro ketene dithioacetals **67** were the starting materials for the synthesis of polyfunctionalised-1,4-dienes **69** in a palladium-catalysed cross-dehydrogenative-coupling (Scheme 28).[44] The pre-functionalisation of the substrates was not necessary. $Pd(OAc)_2$ in the presence of benzoquinone (BQ) was the catalyst which showed the best efficiency, although only three skipped dienes **69a–c** were obtained in moderate yields.



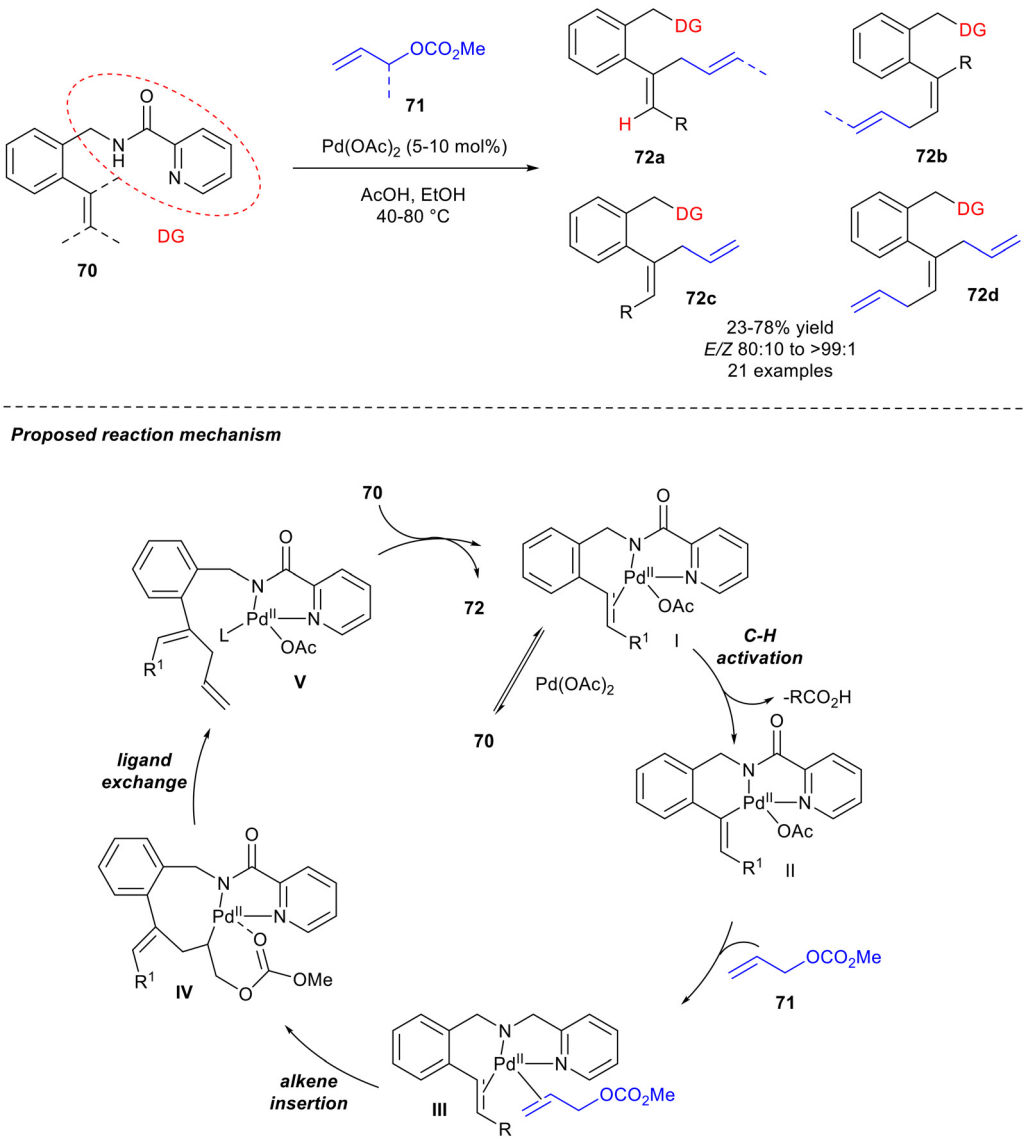
Scheme 27 C–F activation of difluoroalkenes **64** to prepare fluorinated 1,4-dienes **65**.



Scheme 28 Pd-catalysed cross-dehydrogenative-coupling to obtain 1,4 dienes **69**.

Very recently, the α- and β-C–H allylation of *E*- and *Z*-styrenes **70**, in order to obtain multifunctionalised 1,4-dienes and 1,4,7-trienes with excellent diastereoselectivities, was reported by the research group of Zhang (Scheme 29).[45] The process was enabled by the chelation-assistance of pyridine-2-carboxamide (DG), using allyl carbonates **71** as the reagents and $Pd(OAc)_2$/AcOH as the catalytic system in ethanol. A wide scope was described, both in α- and β-allylation, in moderate to excellent yields, and both *E*- and *Z*-arylalkenes were used to obtain 21 skipped dienes **72** (Scheme 29). *meta*- and *para*-substituents such as F, OMe, CF_3, and Me successfully reacted in addition to long alkyl chain derivatives. In one case, the reaction was demonstrated to be scalable. Moreover, the reaction showed good to excellent diastereoselectivities in the α-allylations. The proposed mechanism, described in Scheme 29, involves the coordination between the substrate **70** and palladium to give a π-olefin–palladium complex **I**, which affords a six-membered palladacycle **II** by a reversible α-C–H activation. Ligand exchange by allyl carbonate **71** coordination and alkene insertion take place to produce an eight-membered palladacycle **IV**, followed by ligand exchange with the formation of intermediate **V**. The cycle is ended by a β-oxygen elimination to produce aryl 1,4-diene **72**.

The direct allylation of alkynes[46,47] is an efficient and straightforward method for the preparation of skipped dienes, so many examples of this strategy have been reported in last years and are here described. Chen and co-workers reported the synthesis of spirocyclo-containing skipped dienes **75** with an all-carbon tetrasubstituted alkene by reacting aryl phenol-tethered alkynes **73** with allyl iodides **74a**, in the presence of a Pd catalyst by a cascade allylative di-carbofunctionalisation (Scheme 30).[48] A dearomative *C*-allylation instead of *O*-allylation of aryl phenols was the key of the process. $PdCl_2(PhCN)_2$ was revealed to be the best catalyst in the presence of *t*-BuOLi at 70 °C in 1,2-dichloroethane (DCE). Both the base and Pd catalyst were essential to the success of the reaction. A wide scope was presented, both in alkynes **73** and aryl iodides **74a**, and 54 skipped dienes **75** were successfully recovered in moderate to high yields. Arylacetylenes with electron-donating and electron-withdrawing groups were tolerated, and examples with alkyl substituents were reported. As far as the allylating agent is concerned, iodides were the most efficient, both linear and branched. The reaction is scalable to 2 mmol. The authors proposed a mechanism in which, following a classical Tsuji–Trost reaction, a π-allyl palladium intermediate **I** is formed and coordinates to the alkene moiety of **74a** to afford intermediate **II**. Subsequently, the activated triple bond is attacked by the phenol with the assistance of a base to furnish intermediate **III**. Finally, product **75** and Pd(0) are released by reductive elimination. Recently, starting from results reported by the same research group on the palladium-catalysed regioselective hydroallylations of alkynes with allylborons,[49] an exhaustive computational study was published. A unified mechanism called "Lewis-acid–base-interaction promoted deprotonation/3,3-rearrangement" was proposed.[50]

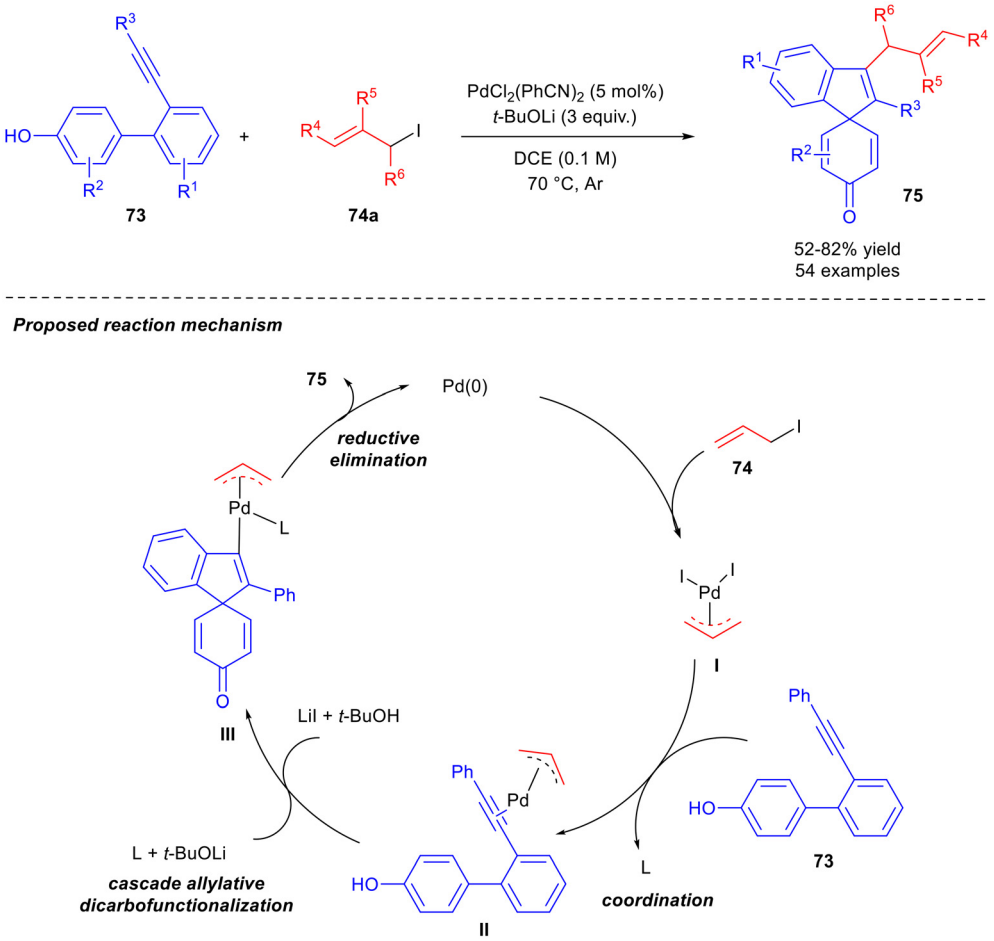


Scheme 29 Chelation-assisted α and β C–H allylation of aryl alkenes **70**.

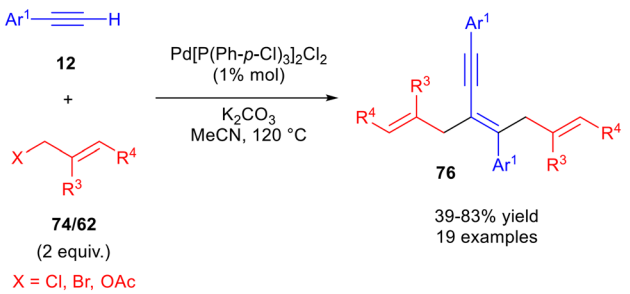
Terminal alkynes **12** and allyl halides **74**/**62** were exploited by Qin and collaborators to afford skipped trienes **76** in a stereoselective manner by a palladium-catalysed cascade synthesis (Scheme 31).[51] Thanks to the possibility of a C–H activation, the use of toxic and unstable organometallic reagents was avoided, although high temperatures were required (120 °C). The best catalyst was shown to be {Pd[P(Ph-*p*-Cl)$_3$]$_2$Cl$_2$}, that was used in the presence of K_2CO_3 as the base, in CH_3CN. Several allylating agents such as allyl bromide **74b**, chloride **74c** and acetate **62** were successfully tested, affording the suitable skipped trienes **76**.

Both electron-rich and electron-deficient aryl terminal alkynes **12**, in the *meta*- and *para*-positions, were appropriate substrates for generating the multicomponent coupling products in moderate to excellent yields, whereas the substituents at the *ortho*-position were less efficient. Also, heteroaryl derivatives were demonstrated to be good starting materials. Preliminary mechanistic studies indicated that both a Sonogashira reaction as the intermediate step, and a radical pathway should be involved, and the allylic dimeric {[Pd(allyl)Cl]$_2$} could be the active catalyst.

Since allylpalladium species can be produced either by 1,2- or 1,3-dienes, results on the use of these reagents have been recently reported.[52–55] An interesting multicomponent approach, where allenamides **77**, alkynes **12** and aryl (alkyl) silylboronic pinacol esters **78**, in the absence of the phosphine ligand, afforded skipped 1,4-dienes **79** decorated with one boryl and two silyl functionalities was described (Scheme 32).[56] A very broad scope was presented both in allenyl amides **77** and alkynes **12**. Notably, allyl acetates were tolerated under the reaction conditions. Many successful examples of natural complex molecules were reported, such as



Scheme 30 Cascade allylative dicarbofunctionalisation to obtain skipped dienes **75** and mechanism proposal.

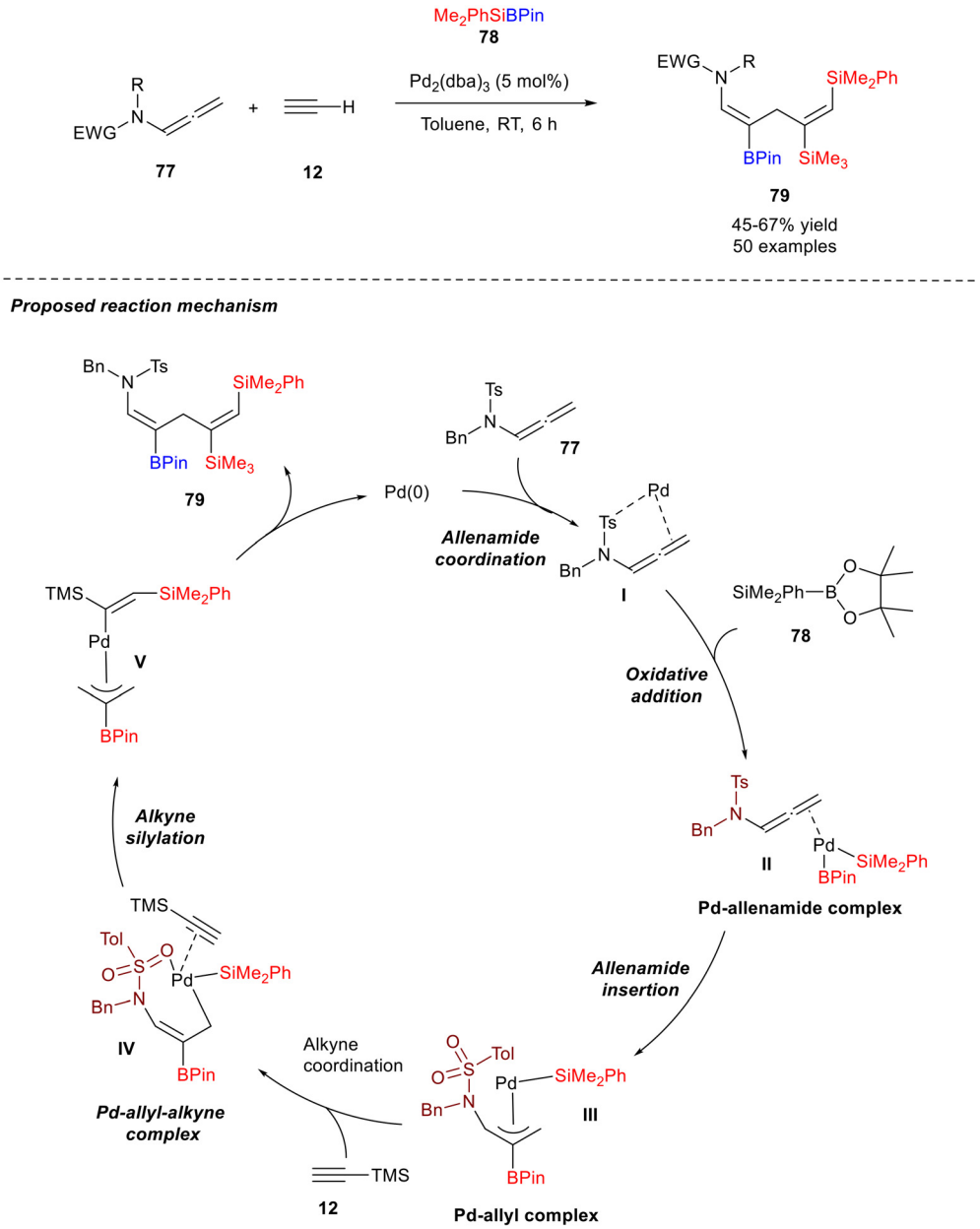


Scheme 31 Cascade process to afford skipped dienes **76** from terminal alkynes **12**.

estrone, vitamin E or gibberellic acid. The protocol was examined for allenamides **77** bearing different chelating groups on the N atom. Substrates with different sulphonyl-based directing groups, both aryl and alkyl sulphonamides, participated in this reaction with slight variations in the standard conditions.

As shown in Scheme 32, a mechanism, based on DFT and experimental studies, was proposed by the authors in which the allenylamide Pd complex **I** is obtained by the oxidative addition of $PhMe_2SiBpin$ **78**, followed by the coordination of Pd to the allenamide (**II**). The insertion of the allenamide **77** allows the Pd-allyl complex **III** to be obtained. Alkyne coordination to **III** leads to Pd-allyl–alkyne complex **IV**, with the chelation of the SO_2 group with Pd in η^1 coordination mode. Finally, product **79** is obtained by the insertion of the $PhMe_2Si$ into the alkyne producing the complex **V**, followed by the reductive elimination which regenerates the Pd(0) species.

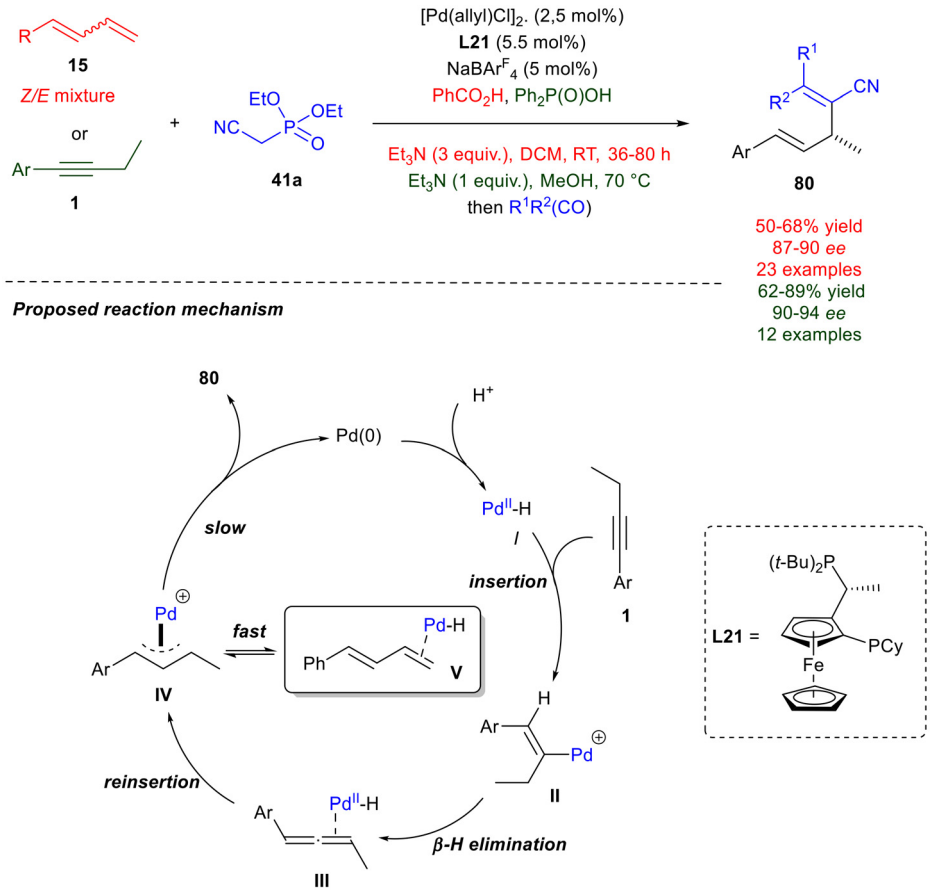
In 2023, the research group of He reported the stereodivergent asymmetric formal hydroalkenylation of 1,3-dienes **15** to produce all the four stereoisomers of 1,4-diene **80** bearing a stereocenter, with a total control of the *Z*/*E* geometry of the olefins (Scheme 33).[57] A series of Josiphos-type chiral ligands were evaluated, and the most efficient is represented in Scheme 33. The geometry of internal olefin in the diene substrates did not affect the reaction, presumably due to the facile isomerisation of (*Z*)-**15** into (*E*)-**1**, so *Z*/*E* mixtures of **15** were directly used as the substrates. A broad scope was presented, several functional groups with different steric hindrance and electronic characters being suitable for this strategy to afford di-, tri- and tetrasubstituted dienes **80**. Interestingly, similar reaction conditions, and the same chiral ligand **L21**, were suc-



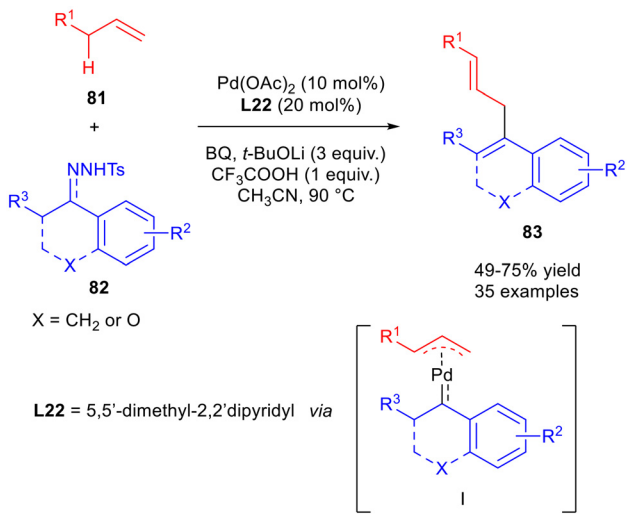
Scheme 32 Pd-catalysed reaction of allenamides **77**, alkynes **12** and silylboron pinacol esters **78**.

cessfully applied to alkynes **1** too. In this case, following the author's hypothesis, the alkyne **1** undergoes hydrocarbonation *via* the formation of conjugated diene intermediate **V**, instead of the more conventional hydrofunctionalisation which involves the allene species **III**. Alkyne **1** is first converted into the allene **III**, which quickly produces the stable η^3-Pd species **IV** *via* irreversible hydrometallation.

N-Tosylhydrazone's role in Pd(0) cross-couplings is well established, especially thanks to the pioneering work of Barluenga, Valdés and Wang.[58–60] Examples of dienes obtained *via* Pd(0) catalysed reactions of *N*-tosylhydrazones have been recently developed. In 2023, a palladium-catalysed oxidative allylation of *N*-tosylhydrazones **82** to produce skipped 1,4-dienes **83** was reported (Scheme 34).[61] The protocol demonstrated a high site selectivity, allowing the 1,4-dienes, containing a trisubstituted alkene, in a regio- and stereoselective manner to be obtained. The scope was studied both on allylarenes **81** and tosylhydrazones **82**, both mono- and bicyclic, affording 1,4-dienes **83** in moderate to good yields. Whereas in the case of the alkenes, electron-rich substituents showed better efficiency, electron-withdrawing substituents on the *N*-tosylhydrazones aromatic ring gave the higher yields. Preliminary mechanistic studies hypothesised the π-allylpalladium carbenoid species **I** as the active intermediate



Scheme 33 Asymmetric hydroalkenylation of 1,3-dienes **15** and alkynes **1**.

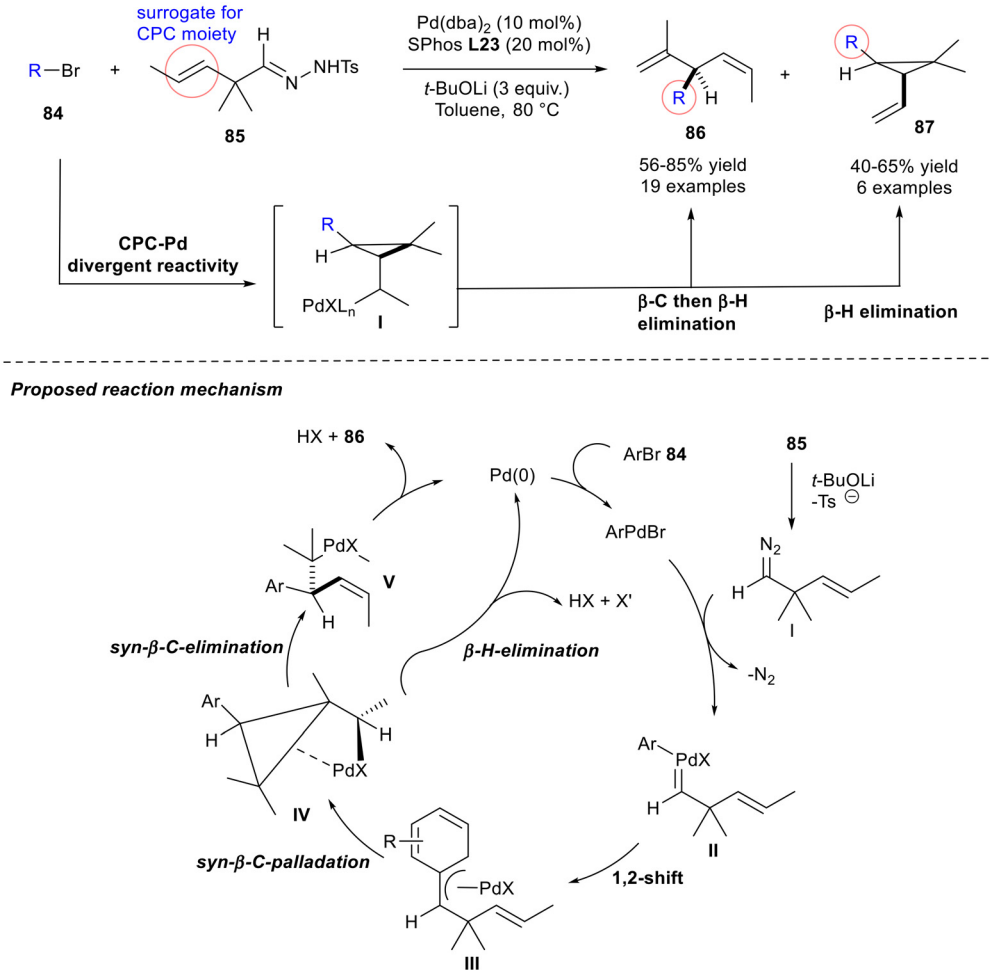


Scheme 34 Oxidative allylation to afford skipped dienes **83**.

which, upon carbene migratory insertion, delivers the alkyl palladium intermediate, producing the 1,4-diene **83** after β-H elimination.

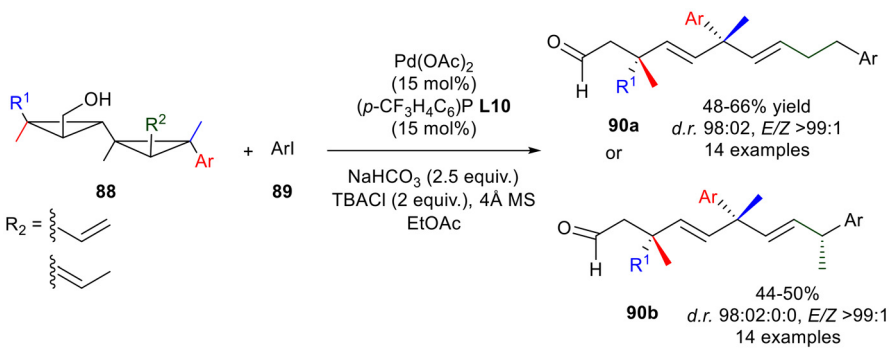
In 2022, a divergent protocol for *Z*-selective synthesis of 3-aryl-1,4-dienes **86** and *gem*-dialkylvinylcyclopropanes **87** from 2,2-dialkyl-3-(*E*)-alkenyl *N*-tosylhydrazones **85** under Pd-catalysis in an enantioselective manner was reported (Scheme 35).[62] The dialkylbiaryl phosphine ligand SPhos **L23** was the optimal ligand. In this case, α,α-disubstituted tosylhydrazones **85** played the role of cyclopropylcarbinyl (CPC) equivalents to produce skipped dienes. Moreover, the palladium catalysis assured a greater structural diversity of products **86** due to the wide availability of the aryl halides **84**. This resulted in a controlled divergent reactivity which allowed skipped dienes **86** and cyclopropane derivatives **87** to be obtained, inaccessible by traditional vinylation methods, exploiting the palladium complex **I** described in Scheme 35. A tentative mechanism was illustrated, where oxidative addition of Pd(0) to an aryl bromide **84** would afford an aryl Pd(II) species, which would then react with intermediate **I** formed *in situ* producing Pd-carbene **II**. A subsequent 1,2-aryl migration affords Pd complex **III** that is subjected to a *syn*-carbopalladation resulting in the alkyl palladium intermediate **IV**. The latter is supposed to undergo a sequence of β-alkyl and β-hydride eliminations to generate **86**. Alternatively, direct β-hydride elimination from **IV** could lead to vinylcyclopropane products **87**.

The last example of this paragraph concerns a very peculiar strategy, reported by Marek's research group, which allows skipped dienes **90**, including two congested quaternary carbons, to be obtained, exploiting the double carbometala-



Scheme 35 *Z*-Selective synthesis of 3-aryl-1,4-dienes **86** and *gem*-dialkylvinylcyclopropanes **87** from 2,2-dialkyl-3-(*E*)-alkenyl *N*-tosylhydrazones **85**.

tion of cyclopropenes (Scheme 36).[63] Since the synthesis of the reagents alkenyl-[1,1]-bicyclopropyl methanol derivative **88** is quite challenging, the authors firstly optimised a protocol for the synthesis of the single diastereomers, based on the Cu catalysis starting from cyclopropenyl ester. Following a Heck strategy, the regioisomer **88a**, containing a hydroxymethylene function and an allylic group on each cyclopropene ring, was reacted with aryl iodide **89** to provide the corresponding skipped dienes **90** with excellent diastereoselectivity for the creation of the two distant quaternary carbon stereocenters. In order to add a stereocenter to the 1,4 dienes, the regioisomer (*E*)-propenyl[1,1]-bicyclopropyl methanol **88b** was produced by



Scheme 36 Synthesis of skipped dienes with two congested quaternary carbons.

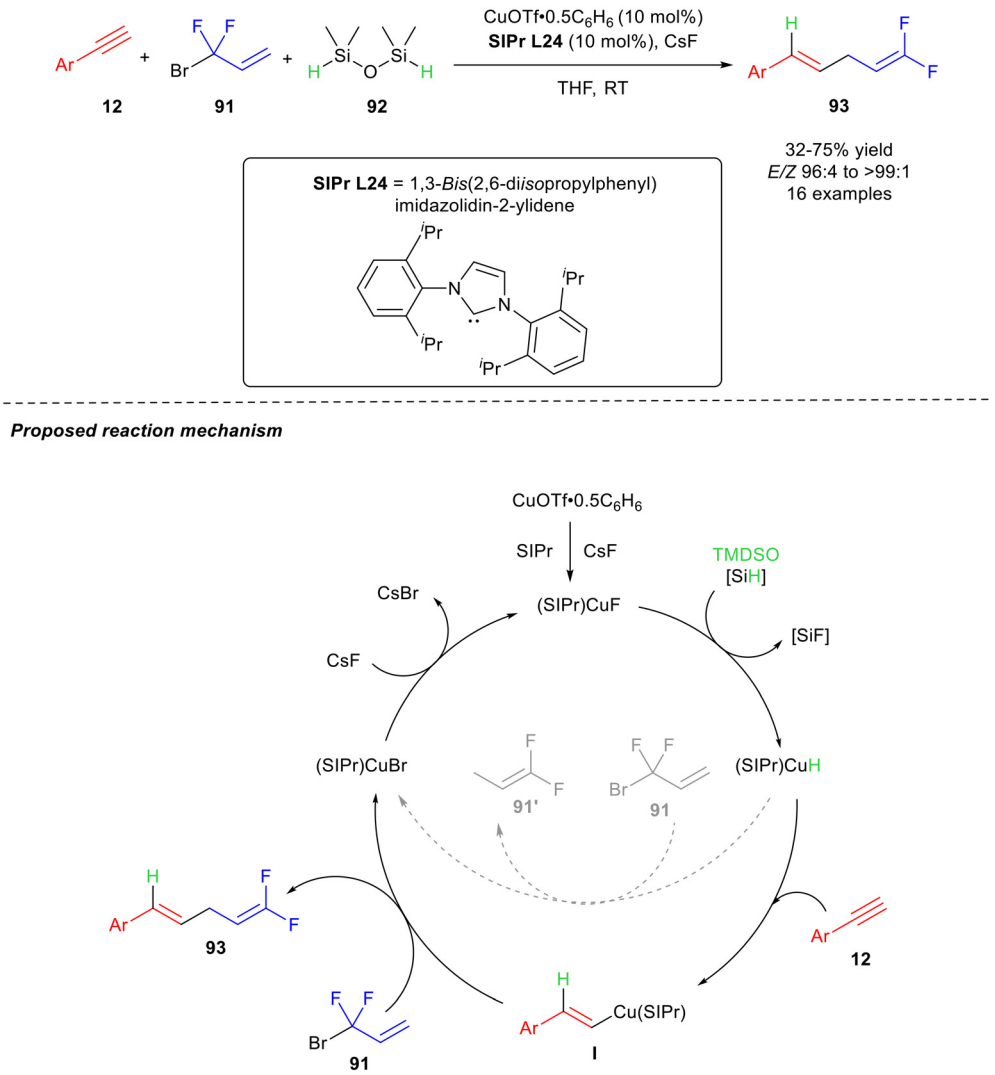
Ru-catalysed isomerisation of **88a**. In the same reaction conditions, dienes which contain three distant stereocenters **90b**, including two quaternary carbons, were recovered in moderate yields (47–50%) as a single (*E*,*E*)-isomer (>99 : 1) and excellent diastereomeric ratio (dr 92 : 08 : 0 : 0).

Group 11: copper (Cu) and gold (Au)

The synthesis of skipped dienes through metals belonging to group 11 is based on the usage of catalysts containing copper or gold as the active metal centre. The copper-catalysed synthesis of skipped dienes is usually carried out on alkynes as the substrates, exploiting the ability of copper to coordinate the triple bond.

In 2020, Qing *et al.* published a copper-catalysed hydrodifluoroallylation of terminal alkynes in a regio- and stereo-selective manner (Scheme 37).[64] The importance of the fluoroalkyl moiety has grown, especially in pharmaceuticals and agrochemicals.[65,66] The authors performed the reaction on ethynylbenzenes **12** and 3-bromo-3,3-difluoropropene (BDFP) **91**, using CuOTf·0.5C_6H_6 as the catalyst, SIPr **L24** as the ligand, 1,1,3,3-tetramethyldisiloxane (TMDSO) **92** as the hydride source, CsF as the base and THF as the solvent at room temperature. Difluoroallylated (*E*)-alkenes **93** were obtained with total *anti*-Markovnikov regioselectivity. The substrate scope was then investigated by varying the substituents on the (hetero) aromatic ring. A wide variety of functional groups was tolerated, both electron-donating and electron-withdrawing, despite these latter leading to lower yields and traces of the *Z*-isomers. A reaction mechanism was proposed, starting from the generation of (SIPr)CuF species, which reacts with TMDSO, *i.e.* the hydride donor, yielding (SIPr)CuH. The *syn*-addition of this latter to the alkyne **12** affords the alkenyl intermediate **I** in a stereoselective fashion. Finally, **I** undergoes a regioselective difluoroallylation with **91** to give the desired skipped diene **93**, thus regenerating the (SIPr)CuF species. A competing pathway (in grey) has also been proposed, leading to lower yield especially in the case of the electron-withdrawing group and internal alkynes.

In 2022, the group of Fañanás-Mastral employed allylic *gem*-dichlorides **94** as the partner in the copper-catalysed allylbora-



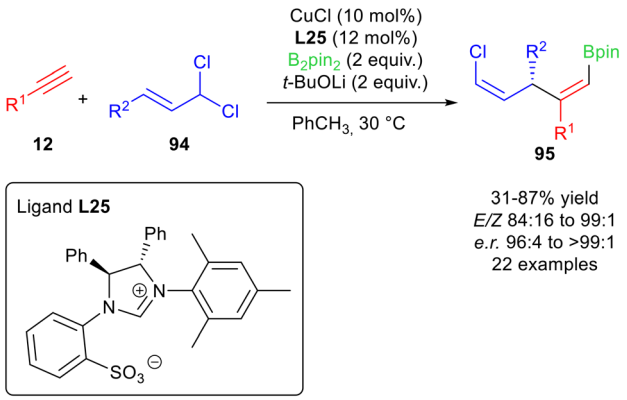
Scheme 37 Copper-catalysed hydrodifluoroallylation of alkynes **12** and plausible mechanism.

tion reaction of alkynes **12**, in an enantio- and diastereo-selective manner thanks to a chiral ligand **L25**, *i.e.* Hoveyda's sulphonate-bearing N-heterocyclic carbenes, using B_2pin_2 as the borylating agent, *t*-BuOLi as the base, in toluene as the solvent (Scheme 38).[67] Skipped (*E*,*Z*)-dienes **95** were obtained in modest to high yields and with excellent regio-, enantio- and diastereo-selectivity thanks to this methodology.

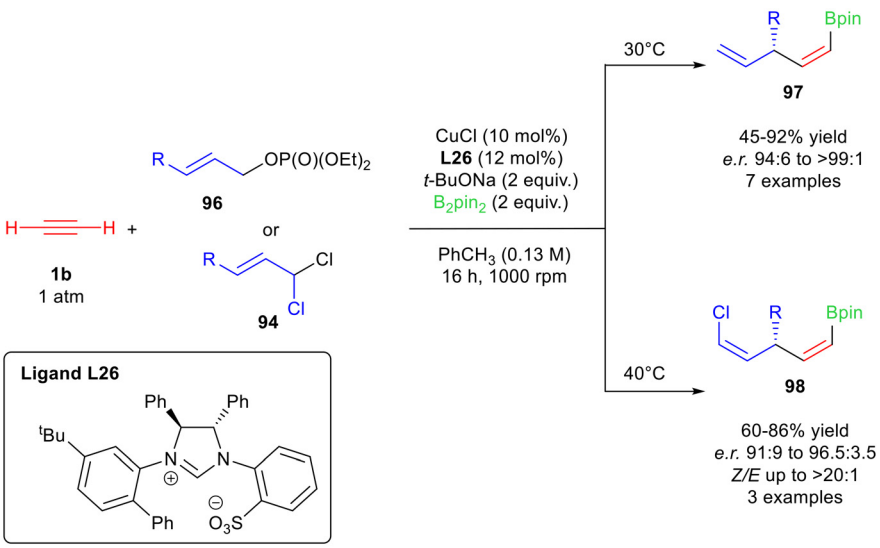
The substrate scope was investigated on both the alkyne **12** and the allyl dichloride **94**, leading to a wide tolerance of many functional groups. Only in some cases, *i.e.* in the presence of electron-withdrawing groups on the alkyne **12**, was the reaction slower or was a slight decrease in the selectivity observed. The authors did not report the mechanism of the reaction; however a detailed rationalisation of the origin of the selectivity was achieved thanks to DFT calculations, and in particular all the possible transition states were deeply studied and compared. Very recently, the same research group applied this methodology to the enantioselective allylboration of acetylene **1b**.[68] The optimised conditions concerned the use of CuCl as the catalyst and the bulky N-heterocyclic carbene **L26**, substituted with a phenyl and a *tert*-butyl groups, as the ligand, *t*-BuONa as the base and B_2pin_2 as the borylating agent (Scheme 39). These conditions afforded either the skipped dienes **97**, if allylic phosphates **96** were used as the partner, or chlorinated skipped dienes **98**, when allylic *gem*-dichlorides **94** were employed. Chemo-, regio- and diastereo-selectivities were excellent in both cases, in the presence of methyl, (hetero)aryl and cyclohexyl substituents.

The abovementioned selectivities were corroborated by DFT calculations of the transition state energies. Moreover, the utility of this methodology was highlighted with several late-stage functionalisations and through the stereodivergent enantioselective total synthesis of (+)-Nyasol and (+)-Hinokiresinol, as well as the enantioselective formal synthesis of (+)-Phorbasin C and other relevant chiral compounds. A Cu(I)/NHC catalytic system was also employed by the group of Teichert in the H_2-mediated C–C coupling of internal alkynes **1** and allyl chlorides **74c** to access skipped dienes **99** (Scheme 40).[69] The first set of reactions was carried out on aryl-substituted internal alkynes **1** and (*E*)-1-chlorohex-2-ene, *i.e.* R^3 = *n*-Pr and R^4 = H, using [SIMesCuCl] as the catalytic system, and H_2 as the hydride source, in 1,4-dioxane which allowed *t*-BuONa to be soluble, thus favouring the heterolytic H–H bond cleavage (Scheme 40). A variety of functional groups, both electron-withdrawing and electron-donating, were well tolerated, giving the products **99** in modest to good yields and excellent regioselectivity concerning the hydrocupration reaction. Moreover, the presence of reactive groups, such as tosylate, acetate and chloride, did not affect the reaction outcome.

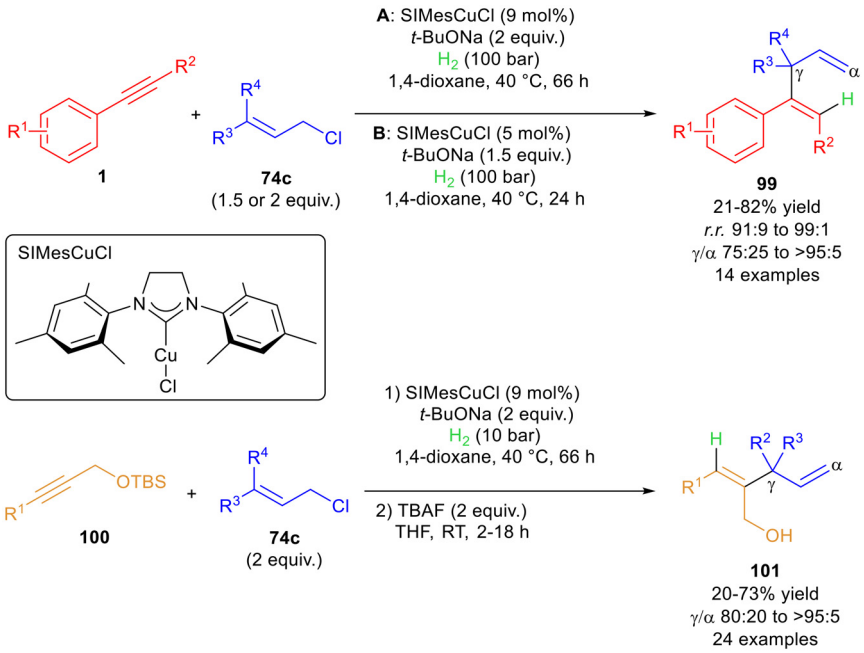
Propargylic silyl ethers **100** showed a similar reactivity in the abovementioned conditions (Scheme 40). The H_2 pressure could be lowered to 10 bar with these substrates and, delightfully, 1,4-dienes **101** bearing an allylic alcohol portion could be



Scheme 38 Enantioselective copper-catalysed allylboration of alkynes **12**.

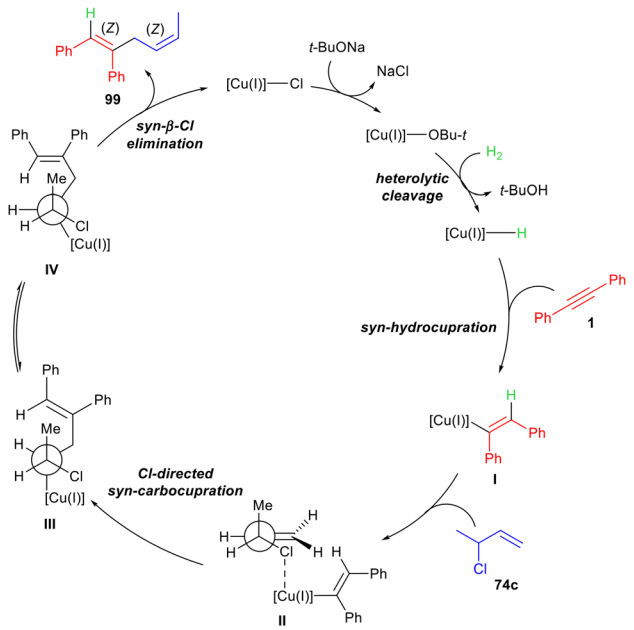


Scheme 39 Copper-catalysed enantioselective allylboration of acetylene **1b**.



Scheme 40 H_2-mediated copper-catalysed C–C coupling reactions to access skipped dienes **99** and **101**.

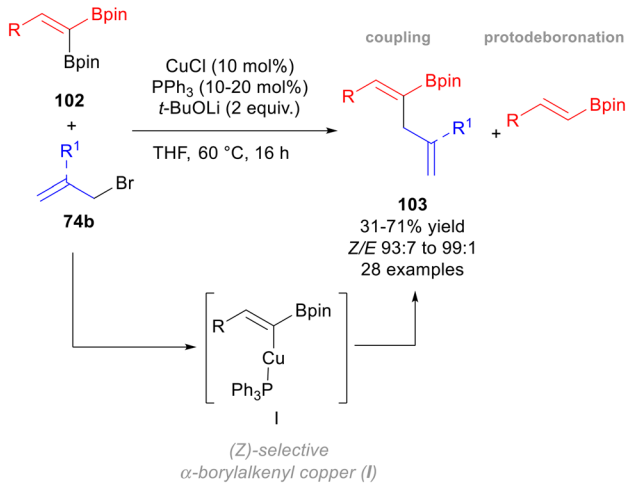
obtained after the deprotection of the silyl ether. The substrate scope was even wider in this case, tolerating bulky substituents and heterocycles. Noteworthy, benzyl ethers were not cleaved under H_2 conditions, whereas halogen-substituted aryls did not undergo protodehalogenation. A plausible mechanism was elucidated upon kinetic isotopic effect (KIE) studies and control experiments (Scheme 41). CuCl is first activated by *t*-BuONa to generate the active species *t*-BuOCu, which favours the heterolytic H_2 cleavage, thus forming the Cu–H hydride species. The *syn*-hydrocupration reaction with alkyne **1** affords vinyl copper adduct **I**, which in turn reacts with allyl chloride **74c**. While hypothesising this mechanism, the authors considered the methyl group as the sterically most demanding substituent, which blocks one hemisphere from the attack of **I**, thus favouring the formation of adduct **II**. (*Z*,*Z*)-1,4-Diene **99** originates from a chlorine-directed *syn*-carbocupration to access **III**, which is in equilibrium with the **IV** species. This latter undergoes *syn*-β-Cl-elimination yielding the desired diene **99**, thus restoring CuCl.



Scheme 41 Plausible reaction mechanism for the Cu(I)-catalysed C–C coupling.

In 2022, Fernández and co-workers reported a Cu(I)-catalysed allylic coupling of 1,1-diborylalkenes **102** and allyl bromides **74b** to afford (*Z*)-skipped dienes **103** using PPh_3, *t*-BuOLi as the base and THF as the solvent at 60 °C (Scheme 42).[70] This methodology allowed the selective activation of the more hindered Bpin group on **102**, leading to a (*Z*)-α-borylalkenyl copper(I) complex **I**, which behaves as α-borylalkyl copper(I) systems in nucleophilic substitutions, thus generating the desired (*Z*)-diene **103**.

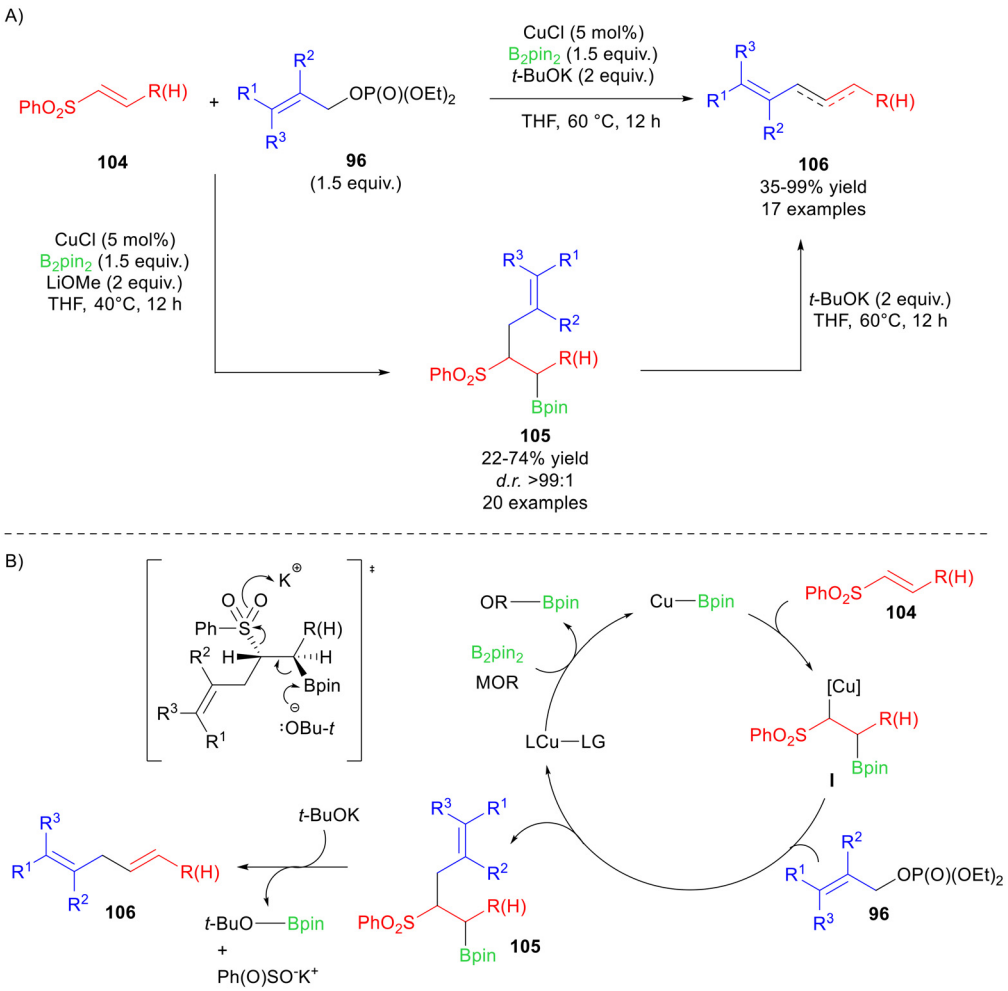
The optimised conditions were set up to minimise the protodeboronation side reaction; however an increase in the steric hindrance on **102** increased the formation of the protodeboronation by-product. On the other hand, aromatic rings substituted with both electron-donating and electron-withdrawing groups on **102** afforded the (*Z*)-dienes **103** in modest to good isolated yields, pointing out that lower yields could be obtained because of the instability of the C(sp^2)–Bpin moiety during the purification. A deep insight into the mechanism was finally reported by means of DFT calculations and free-



Scheme 42 Copper-catalysed reaction of 1,1-diborylalkenes **102** and allyl bromides **74b**.

energy profiles, whereas some control experiments were performed to justify the hypothesis of a S_N2' pathway. More recently, Yun *et al.* developed a diastereoselective borylative allylation of α,β-unsaturated sulfones **104**, tuning the reactivity depending on the strength of the base.[71] In fact, the use of MeOLi at 40 °C afforded *syn*-3,4-boroallylated sulfones **105** starting from alkenyl sulfones **104** and allylic phosphate **96**, in the presence of CuCl as the catalyst (Scheme 43). On the other hand, the skipped dienes **106** can be selectively obtained by using *t*-BuOK, *i.e.* a stronger base, at 60 °C. The authors proposed that **106** can also be formed from **105** upon a deborylation–desulfonylation process, in the presence of *t*-BuOK, as also shown in the catalytic cycle (Scheme 43A).

The substrate scope was investigated by coupling either terminal vinyl sulfones **104** with differently substituted allyl phosphates **96**, *i.e.* R = H and R^1, R^2, R^3 = H, alkyl, aryl, benzyl, naphthyl, or internal vinyl sulfones **104** with simple allyl phosphates **96**, *i.e.* R = alkyl, aryl, benzyl and R^1, R^2, R^3 = H or phenyl. In all cases, modest to good yields of **105** were observed, with a slight decrease in reactivity when bulkier sub-

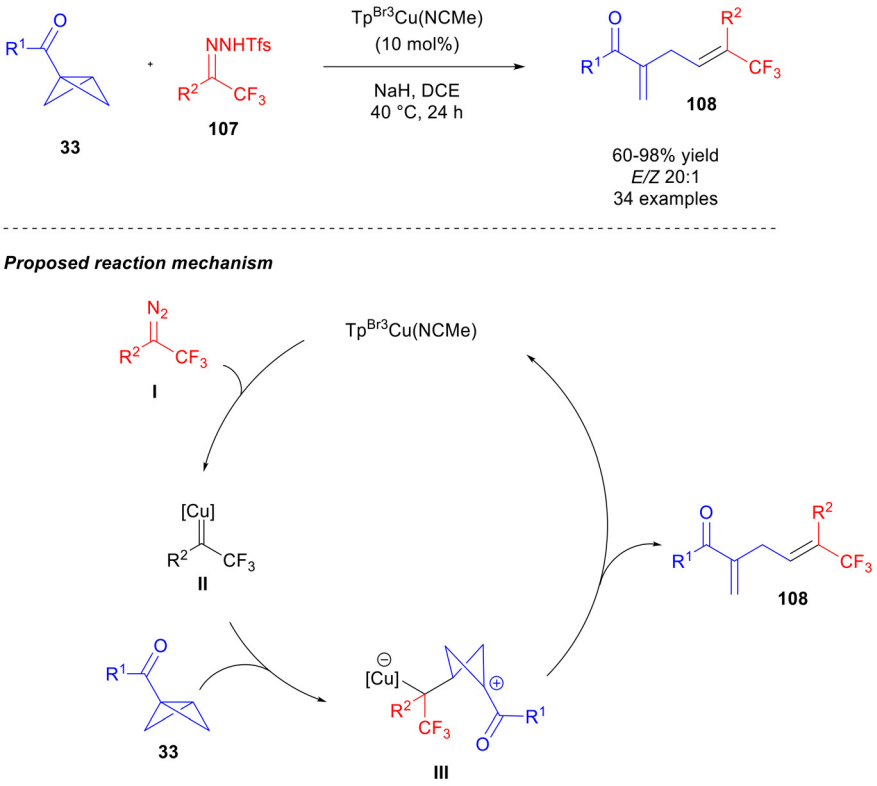


Scheme 43 (A) Copper-catalysed reaction of alkenyl sulfones **105** with allyl phosphates **96** to access skipped dienes **106**. (B) Plausible catalytic cycle for the chemical transformation.

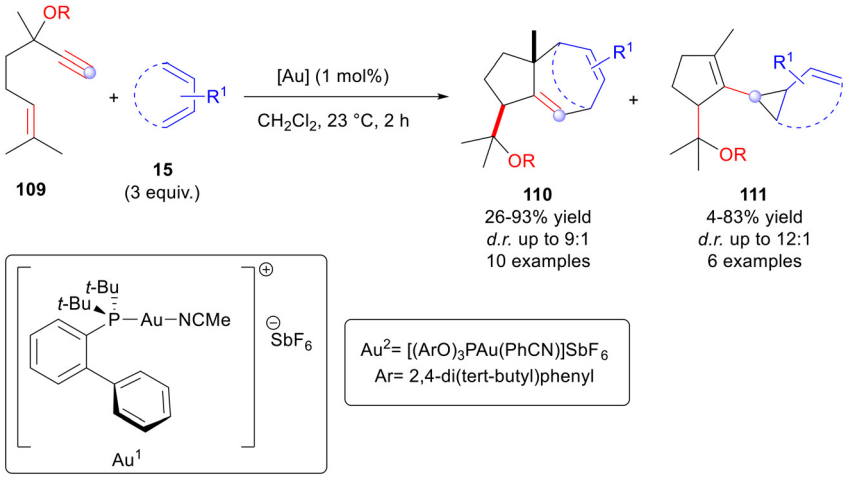
stituents were employed. Skipped dienes **106** were smoothly obtained with un-substituted vinyl sulfones **104** and linear allyl phosphates **96**, whereas branched allyl phosphates **96** ended up in the formation of 1,3-dienes due to isomerisation under basic conditions. Despite this fact, aryl-substituted vinyl sulfones **104** gave the skipped dienes **106** in moderate to good yield, if coupled with un-branched allyl phosphates. The deborylation/desulfonylation process on **105** allowed to extend the scope of the dienes **106**. The catalytic cycle is shown in Scheme 43B, starting from the formation of the Cu–Bpin species, which reacts with the double bond of **104** affording the active catalytic species **I**. The subsequent reaction with **96** gives compound **105** that converts into the skipped diene **106** upon treatment with *t*-BuOK, *via* *anti*-elimination of both the boryl and the phenylsulfonyl groups.

Drawing inspiration from the research of the group of Hari on the coupling of BCBs **37** with α-diazoesters **34** in the presence of a ruthenium catalyst (see Scheme 12),[20] Zhang and colleagues developed a novel methodology to obtain skipped dienes from BCBs (Scheme 44).[72] The unstable diazo compound, which was exploited as the carbene precursor, was substituted with the safer and easier to handle triftosylhydrazone **107**. In this case, the cross-coupling reaction was mediated by the copper-based catalyst, $Tp^{Br3}Cu(NCMe)$, in DCE at 40 °C in the presence of an excess of NaH for 24 h. As regards the triftosylhydrazone scope, both aryl- and vinyl-substituted trifluoromethyl triftosylhydrazones were well tolerated, as well as heteroaryl rings (benzofuran, thiophene and benzothiophene). In the context of the BCB core, the utilisation of ketones, biphenyl, ester, and amide substituents was found to be effective, exhibiting no discernible influence on the *E*/*Z* selectivity, which remained at a consistent 20/1 ratio across all instances. Control experiments and DFT calculations were utilised to elucidate the reaction mechanism, excluding a concerted pathway differently from Hari because of the impossibility of locating possible transition states. The catalytic cycle starts with the generation of the copper carbene **II** from the catalyst and the triftosylhydrazone **107**. Subsequently, the BCB **33** can attack carbene **II** to generate the ylide intermediate **III**. The latter undergoing ring opening allowed the formation of the skipped diene **108** and the regeneration of the copper catalyst. The transition state of **III**, formed from the *E* isomer, was found to be lower in energy than in the case of the *Z*-isomer, thus providing a rational explanation for the observed stereoselectivity.

Gold catalysis is a valuable strategy for the synthesis of both cyclic and acyclic skipped dienes, commonly *via* the formation of gold carbene intermediates. The synthesis of 7-membered carbocycles is usually accomplished by ring expansion,[73] ring-closing metathesis,[74,75] cross-coupling[76] or cycloaddition strategies.[77,78] In particular, 1,4-cycloheptadienes can be obtained *via* a cyclopropanation/Cope rearrangement sequence, starting from a diazo compound.[79] However, this methodology is limited to the acceptor metal carbenes. The group of Echavarren extended the reactivity to non-acceptor



Scheme 44 Copper-catalysed cross-coupling reaction of BCBs **33** with triftosylhydrazone **107**.



Scheme 45 Gold-catalysed [2 + 1] and [4 + 3] cycloadditions of alkoxyenynes **109**.

metal carbenes investigating both Rh or Au catalysis (see the paragraph on Rh catalysis).[22] The gold(I)-catalysed [4 + 3] cycloadditions were investigated on 5-alkoxy-1,6-enynes **109** as the substrates in a cycloisomerisation/migration/cycloaddition cascade sequence (Scheme 45).[22] The gold(I) catalyst played a crucial role in governing the selectivity towards either the cycloheptadiene **110** or the cyclopropane **111**. Catalysts [Au^1] and [Au^2] were chosen upon reaction optimisation, thus leading to modest to complete selectivities and modest to good yields.

Furthermore, this transformation was subjected to a deep mechanistic investigation, starting from an enyne cycloisomerisation cascade, *i.e.* a 5-*exo*-dig cyclisation followed by a 1,5-migration of the OR group. Then, the reaction with 1,3-diene **15** can generate either **110** or **111** *via* a [2 + 1] or a [4 + 3] cycloaddition, respectively, according to the energy barriers of the transition states. In 2021, López *et al.* reported the gold-catalysed reaction of vinyl-diazo compounds **112** with vinylsilanes **113**, exploiting the β-silicon effect, thus stabilising an adjacent carbocation, to access skipped dienes **114** (Scheme 46).[80] Upon optimisation, JohnPhos AuCl was chosen as the best catalytic system, using sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate as a halide scavenger.

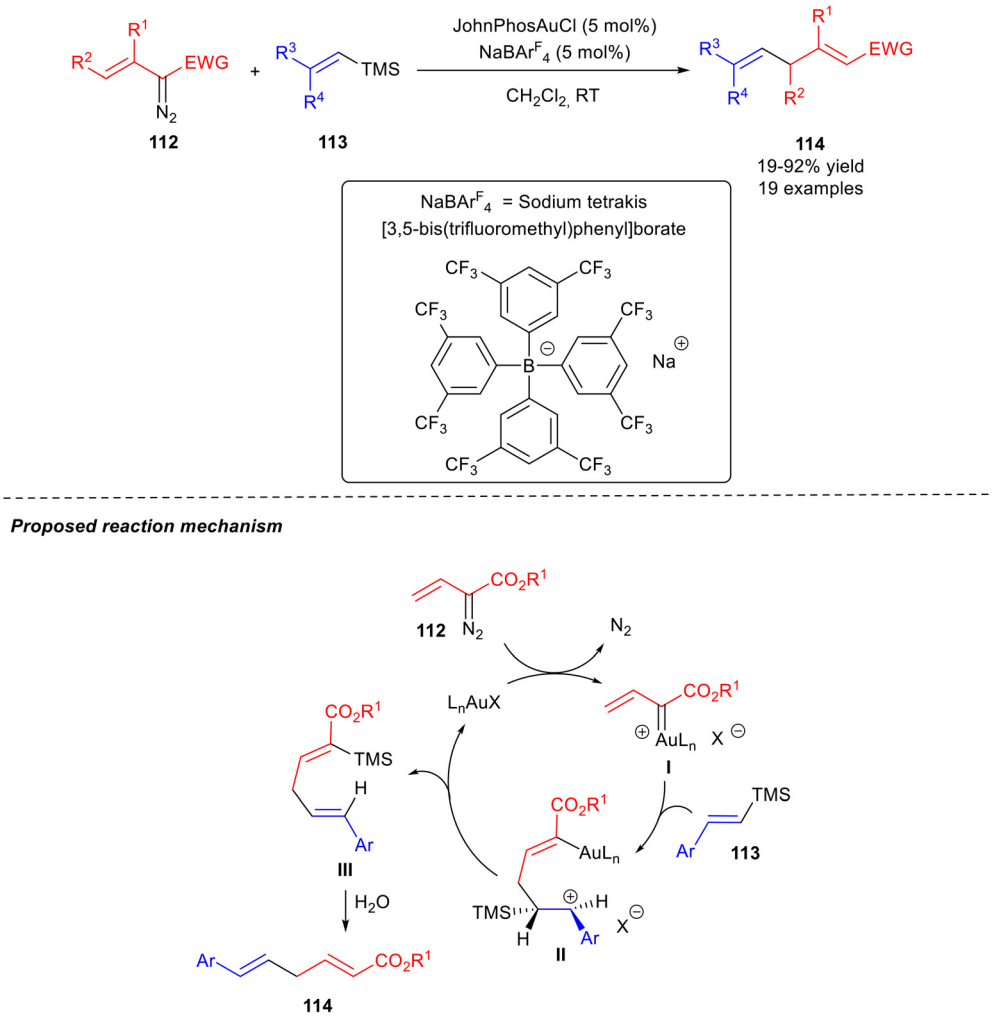
As far as the vinylsilane **113** is concerned, only aromatic substituents bearing both electron-withdrawing and electron-donating groups were investigated, giving the desired product **114** in good to excellent yields. The electron-withdrawing groups on the diazo compound **112** were mainly alkyl/benzyl esters but also ketones were tested, affording dienes in good yields. The authors proposed the mechanism illustrated in Scheme 46, starting from the decomposition of the diazo compound **112** which affords the gold carbene intermediate **I** upon loss of N_2. Then, the vinylsilane **113** attacks **I** giving a carbocation **II**, stabilised by both π-conjugation from the adjacent phenyl group and hyperconjugation from the TMS group at the β-position. An intramolecular 1,4-migration of this latter yields a diene intermediate **III**, which in the presence of water traces affords the final skipped diene product **114**.

More recently, Shin and co-workers published a gold-catalysed sulfonium-Claisen rearrangement on cinnamyl thioethers **115** and *tert*-butyl propiolates **116** to access skipped dienes **118** in an enantioselective fashion (Scheme 47).[81] The authors pointed out the novelty of this methodology since usually cinnamyl substituents do not effectively undergo this kind of rearrangement. In fact, the sulfonium intermediate **I** can break down into allyl cation **II** in the presence of cinnamyl groups, *i.e.* R = Ar^2, leading to the formation of **119** and **120** as by-products (Scheme 47).

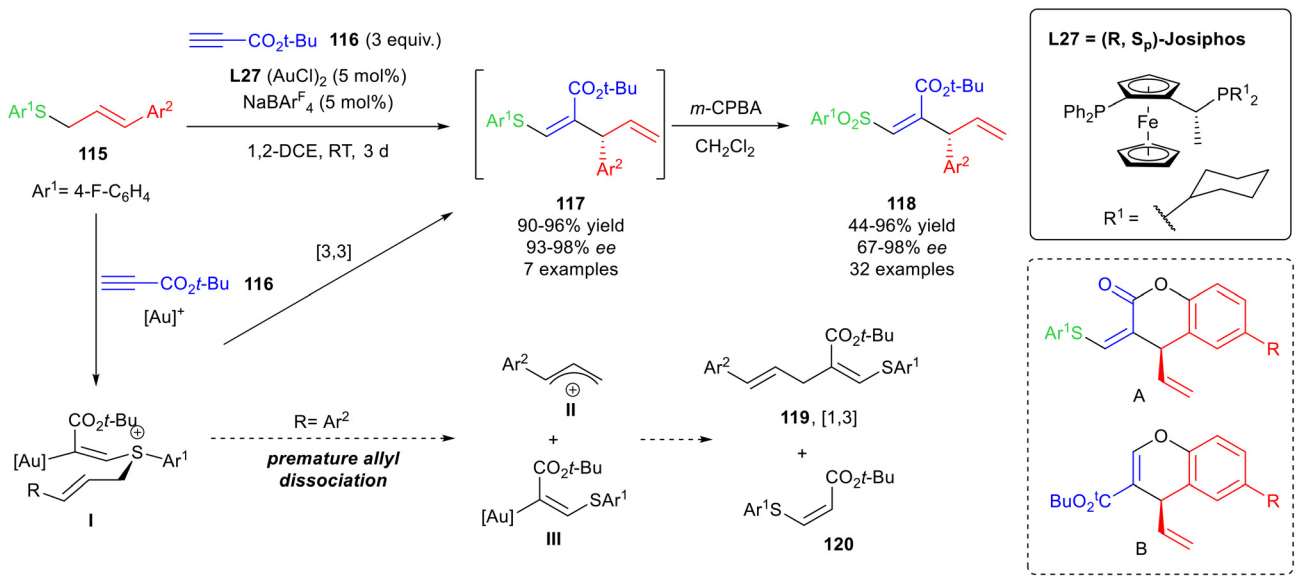
Upon optimisation, (R,S_p)-Josiphos **L27** was found to be the best ligand which gave the highest yield, thus limiting the formation of by-products. As far as the scope is concerned, only Ar^2 was studied, and in particular mono-, di- and tri-substituted aromatic rings were investigated. Both electron-withdrawing and electron-donating groups on the *para*- and *ortho*-positions were well tolerated, giving the product in high yields and enantioselectivities, as well as halogens and alkoxy groups. Notably, the former can be then exploited to further functionalise the scaffold *via* cross-coupling reactions. On the other hand, the authors focused their attention on *o*-acetoxy derivatives, proposing a facile route to 2-chromanones **A** and 4*H*-chromenes **B**, with complete retention of the optical purity (Scheme 47). Finally, a late-stage functionalisation was done to further confirm the wide applicability of this methodology.

Miscellaneous: calcium (Ca), chromium (Cr), titanium (Ti) and ytterbium (Yb)

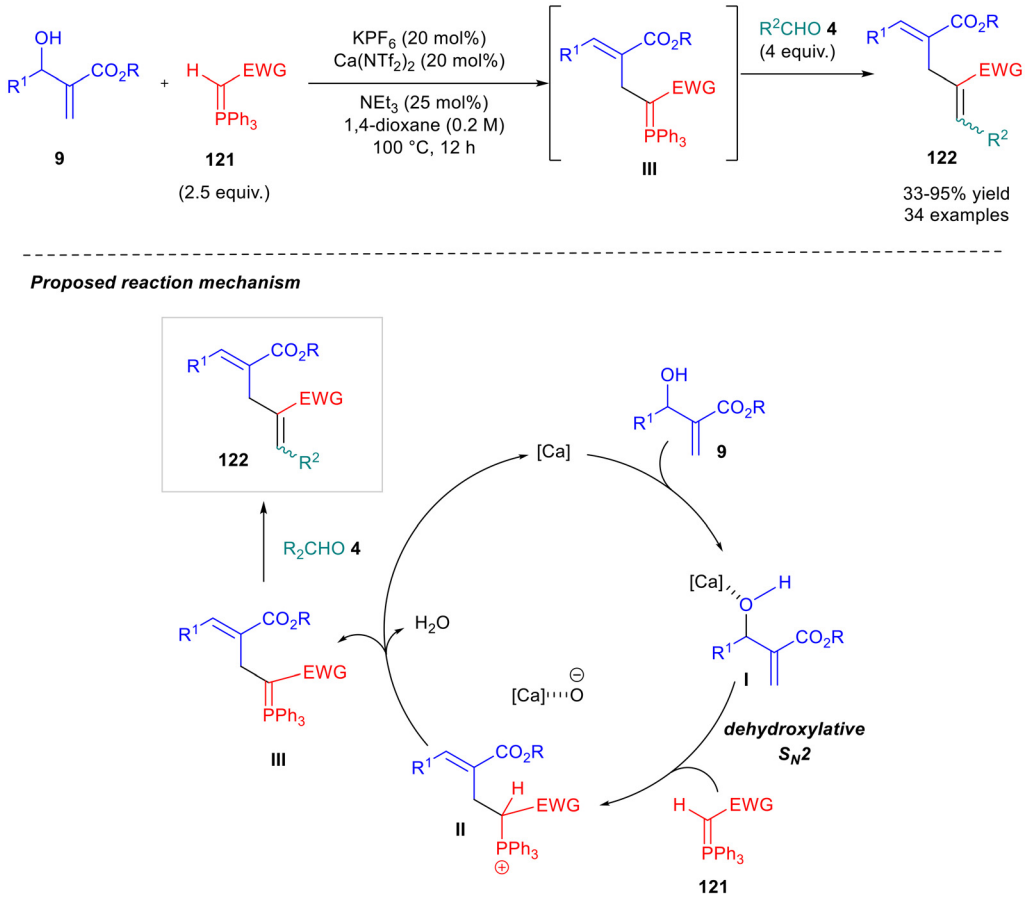
This section deals with the synthesis of skipped dienes by methodologies based on the use of metals, for which only one example each is known in the literature in the period analysed, in particular, calcium, chromium, titanium and ytterbium. In 2023, Li *et al.* presented a calcium-promoted synthesis of 1,4-dienes through the activation of the C–OH bond of Morita–



Scheme 46 Gold-catalysed reaction of vinyldiazo compounds **112** with vinylsilanes **113**.



Scheme 47 Gold(I)-catalysed sulfonium-Claisen rearrangement of cinnamyl thioethers and *tert*-butyl propiolates.

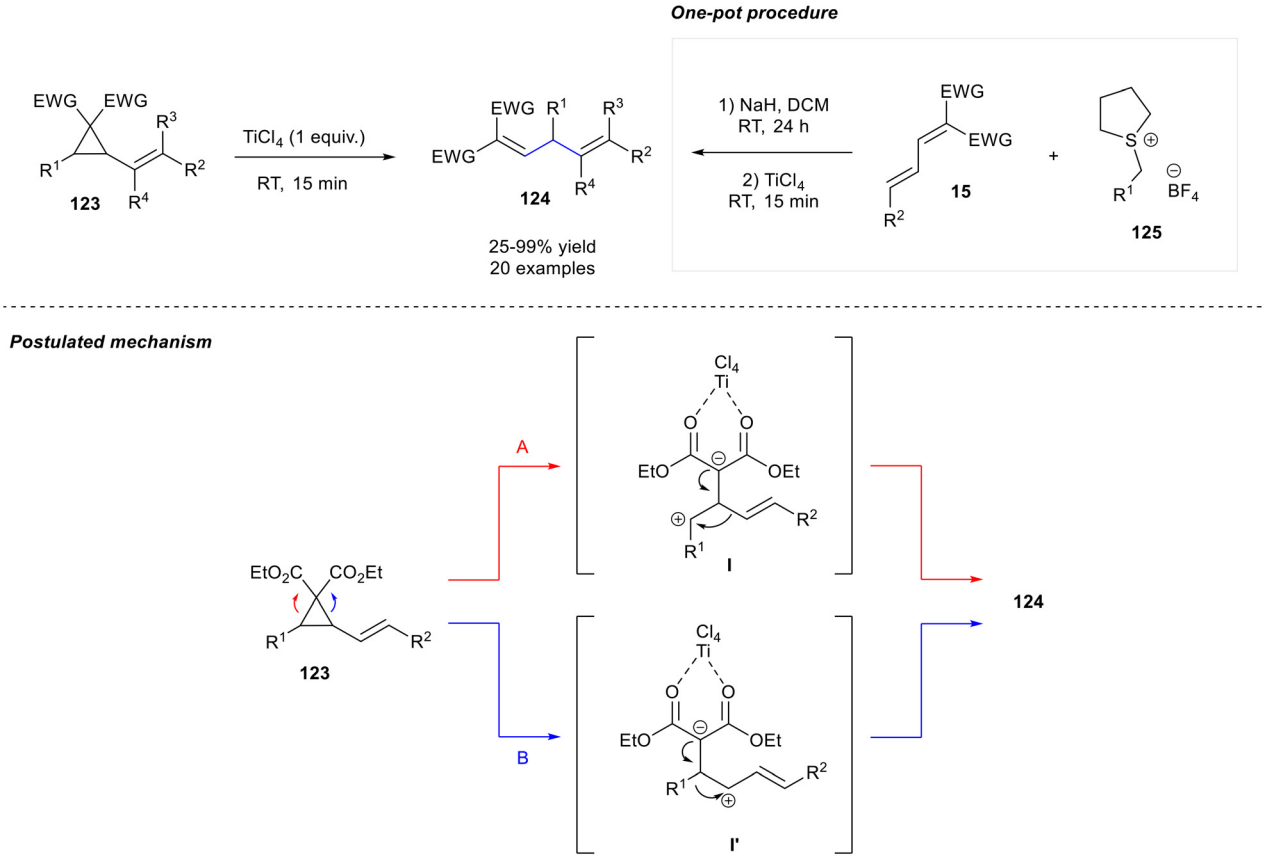


Scheme 48 One-pot calcium-catalysed dehydrative allylation and Wittig reaction.

Baylis–Hillman alcohol (Scheme 48).[82] The catalytic system, composed of $Ca(NTf_2)_2$, KPF_6 and NEt_3, was able to facilitate the C–OH bond cleavage of activated allylic alcohols **9** promoting the dehydrative allylation of stabilised P-ylides **121** in dioxane at 100 °C for 12 hours. Skipped dienes **122** were obtained through a one-pot Wittig reaction.

Several aryl substituted compounds **9** with both electro-withdrawing and -donating groups on the aromatic ring were tested, and demonstrated to be suitable to obtain the final product. Also, cycloalkyl, alkyl, phenyl, fused ring, heteroaromatic and pyridine groups were tolerated. As far as P-ylides **121** are concerned, ethyl and benzyl esters were suitable substituents. Aryl aldehydes bearing electron-withdrawing groups performed with a low stereoselectivity for trisubstituted 1,4-dienes. The proposed mechanism, illustrated in Scheme 48, involves the initial interaction between calcium and the hydroxyl group of **9**, enabling Ca–OH activation with the formation of complex **I**. Subsequently, the S_N2 substitution of the P-ylides **121** occurs generating intermediate **II**. It follows a dehydration process delivering the desired P-ylide **III** with the regeneration of the catalyst. Finally, the allylic P-ylide reacts with the aldehyde **4** to generate the final 1,4-diene **122**.

In 2019, the group of Robiette reported the rearrangement of substituted 1,1-dicarbonylester vinylcyclopropane **123** into skipped dienes **124** in the presence of sub-stoichiometric amounts of $TiCl_4$ in DCM as the solvent (Scheme 49).[83] An in-depth experimental and computational study revealed that the reaction mechanism leading to the skipped dienes **124** involves the cleavage of the three-membered ring followed by a 1,2-migration.[83,84] Two possible 1,3-zwitterion intermediates **I**/**I′** can be formed either *via* ring-opening on the benzylic or on the styryl side. In the first case, the 1,2-migration is in charge of the styryl group (intermediate **I**), and in the other case the phenyl group is migrating (intermediate **I′**). The deuteration experiment confirmed the phenyl group migration while the computational study proved that the 1,2-migration is a reversible process allowing, for prolonged reaction times, the cyclisation of the zwitterionic intermediate to a stable cyclopentene, thus revealing the skipped diene to be the kinetic product in this transformation. As far as the scope of the reaction is concerned, different R groups were tolerated in the vinylcyclopropane **123**, in particular alkyl and aromatic groups. Only electron-rich aromatic groups were not tolerated, leading to the isolation of the sole cyclopentene because of the stabilisation of the zwitterion by conjugation. Suitable migrating groups R^1 were aromatic ring-bearing electronic-rich substituents and fluorine atoms in the *para*-position, or a 2-furyl

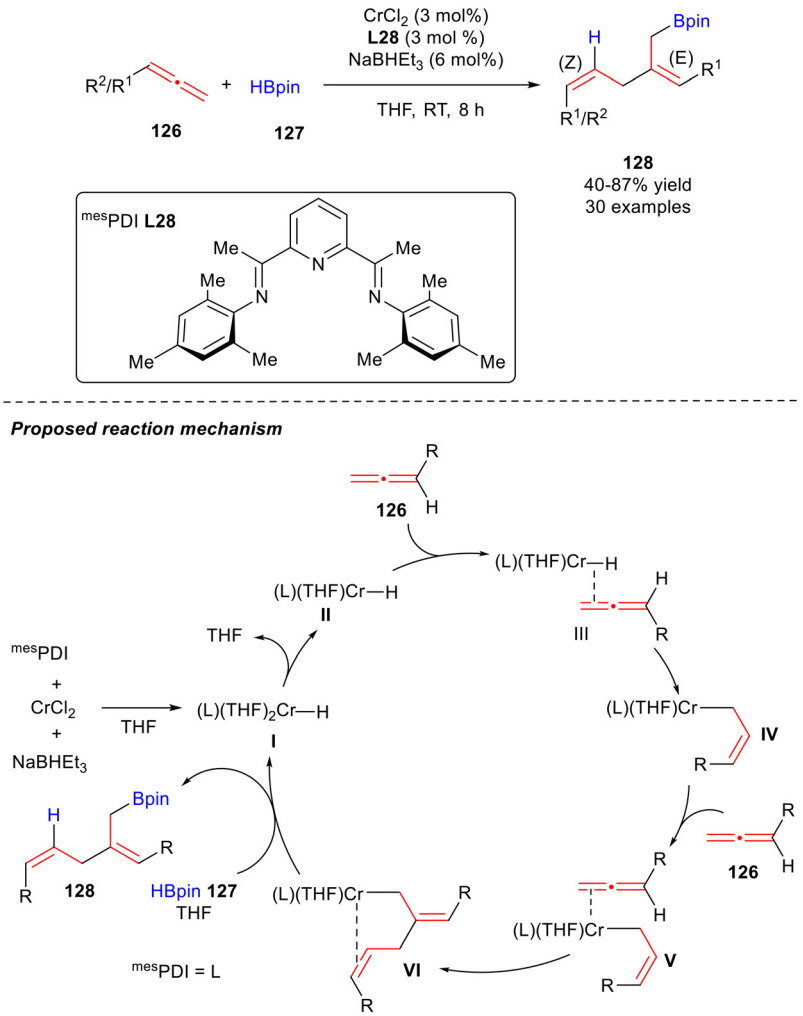


Scheme 49 $TiCl_4$-mediated rearrangement of 1,1-dicarbonylester vinylcyclopropane **123** into skipped dienes **124**.

group. Electron-poor and alkyl groups did not deliver the desired skipped diene. A one-pot procedure was also reported for this transformation employing 1,3-dienes **15** and sulfonium salts **125** as the starting materials.

Chromium-based catalysts found applications in several reactions that involve unsaturated hydrocarbons.[85–88] However, a functional methodology related to the chromium-catalysed hydroboration reaction of unsaturated hydrocarbons was still missing. In 2021, Zhao and Ge reported a chromium-catalysed dimerisation/hydroboration of allenes to obtain borylated skipped (*E*/*Z*)-dienes **128** with high chemo-, regio- and stereoselectivities (Scheme 50).[89] The reactions were performed on a series of functionalised allenes **126**, treated with HBpin **127** in the presence of $CrCl_2$, ^{mes}PDI **L28**, *i.e.* a pyridine-2,6-diimine ligand, and $NaBHEt_3$ as the activator, at room temperature and using THF as the solvent. The robustness of this methodology was emphasised by the high functional group tolerance. Indeed, moieties such as (silyl)ethers, halogens, acetals, tosylates and terminal alkynes were well tolerated, giving the desired products in modest to good yields, whereas the presence of carbonyl groups did not allow the transformation. The authors also reported examples of the cross-dimerisation/hydroboration reactions, by using two differently substituted allenes **126**, and of different late-stage functionalisation of borylated skipped dienes **128**. A plausible catalytic cycle was proposed based on EPR analyses, control experiments and kinetic studies (Scheme 50). $CrCl_2$ undergoes activation in the presence of $NaBHEt_3$, ^{mes}PDI **L28** and THF as the solvent, affording the active species (L)$(THF)_2$Cr–H **I**. An electronically unsaturated Cr(I) hydride **II** species is then formed upon the loss of a THF molecule. Allene **126** is coordinated to **II** giving **III**, which converts into the allylchromium species **IV** by migratory insertion. A second molecule of allene **126** coordinates to **IV**, forming a new C–C bond in another allylchromium intermediate **VI**. This latter reacts with HBpin **127** in THF to yield the desired skipped diene **128**, regenerating the active Cr(I) hydride **I**.

In 2021, Gogoi *et al.* developed the Yb(III)-catalysed *syn*-thioallylation of ynamides **129** to give tetrasubstituted thioamino-skipped dienes **131** (Scheme 51).[90] The reaction was carried out starting from *N*-oxazolidinone-protected ynamides **129** and allyl substituted sulfides **130** in the presence of a catalytic amount of $Yb(OTf)_3$ in 1,2-dichloroethane as the solvent at 80 °C for 8 hours. The presence of the oxazolidinone carbonyl moiety was essential for the reactivity due to the stabilisation of the vinyl-ytterbium intermediate **II** thanks to the possible coordination with the putative sulfonium species (Scheme 51, bottom). The scope of the reaction for the

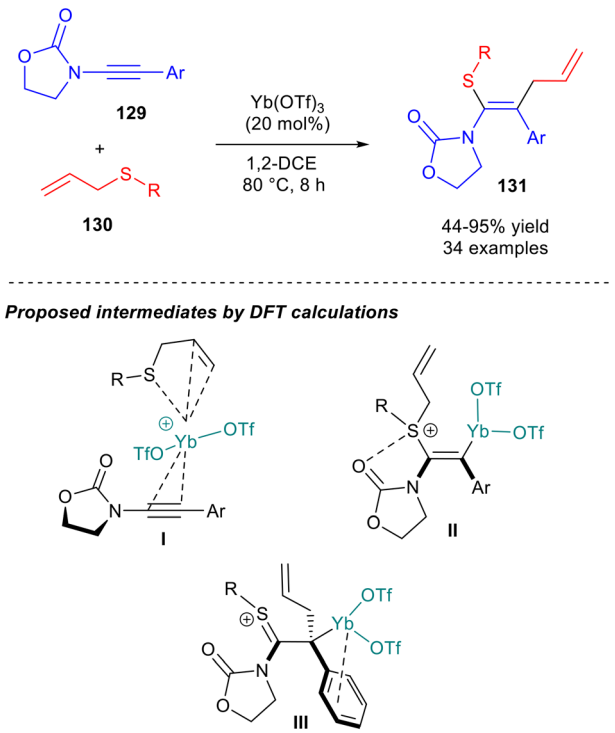


Scheme 50 Chromium-catalysed dimerisation/hydroboration of allenes **126** to access skipped dienes **128**.

ynamide **129** was limited to compounds bearing the oxazolidinone moiety and an aryl substituent in the alkyne terminus. In fact, no reaction was observed with the alkyl terminus, while complex mixtures were formed with *N*-sulfonyl protected ynamides. The range of allylsulfides **130** was quite broad, tolerating both electron-rich and halogen substituents when the R group is an aryl ring. This latter can also be disubstituted with electron-rich groups or two chlorine atoms. The corresponding skipped dienes **131** were successfully prepared with alkyl–allyl sulfides. The reaction mechanism was elucidated by DFT calculations, which identified $Yb(OTf)^{2+}$ as the active species capable of coordinating to the starting materials to give **I**. The subsequent *syn*-insertion of the alkyne **129** into the S–Yb bond yields the stabilised intermediate **II**. The latter, which undergoes a suprafacial [3,3]-sigmatropic shift, promotes the migration of the allyl group from the sulfonium to the C=C bond, yielding intermediate **III**. DFT calculations were corroborated by an experimental study using crossover and competition experiments which demonstrated the intramolecular allyl migration.

Metallaphotoredox-catalysed synthesis of skipped dienes

Recently, visible-light mediated metallaphotoredox catalysis has been recognised as a powerful tool to access complex moieties under mild conditions, exploiting the combination of the exceptional efficiency of the C–C bond formation of transition metal catalysis with the innovative activation modes of light-promoted processes.[91] In this context, Chu and co-workers reported a photoinduced stereodivergent reductive coupling reaction between vinyl triflates **10** and allylic carbonates **42** (Scheme 52) to selectively afford skipped dienes **132** both in the *E*- and *Z*-configuration from the same set of substrates.[92] Through an elegant fine-tuned matching of the triplet energies of the employed photocatalysts, this cross-electrophile coupling furnished *E*-configured skipped dienes with a Ru-based photocatalyst, while the opposite stereoisomer was obtained with a Ir-based photocatalyst, both with excellent stereoselectivity. Indeed, the contra-thermodynamic $E \rightarrow Z$ alkene

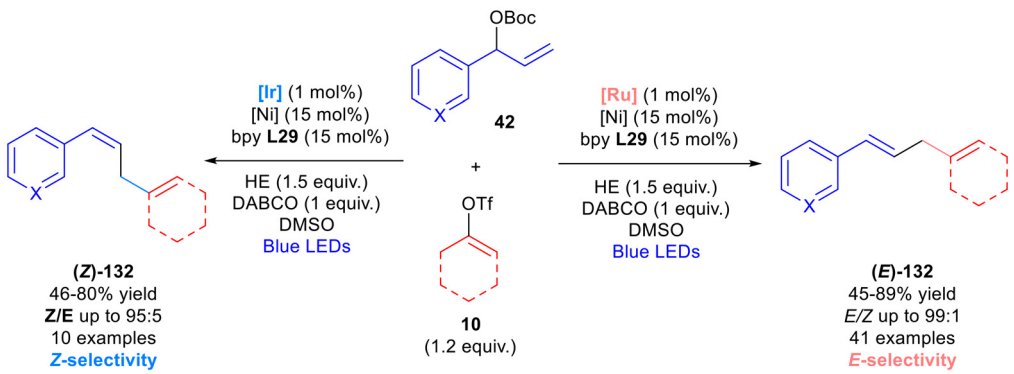


Scheme 51 Yb(III)-catalysed *syn*-thioallylation of ynamides **129**.

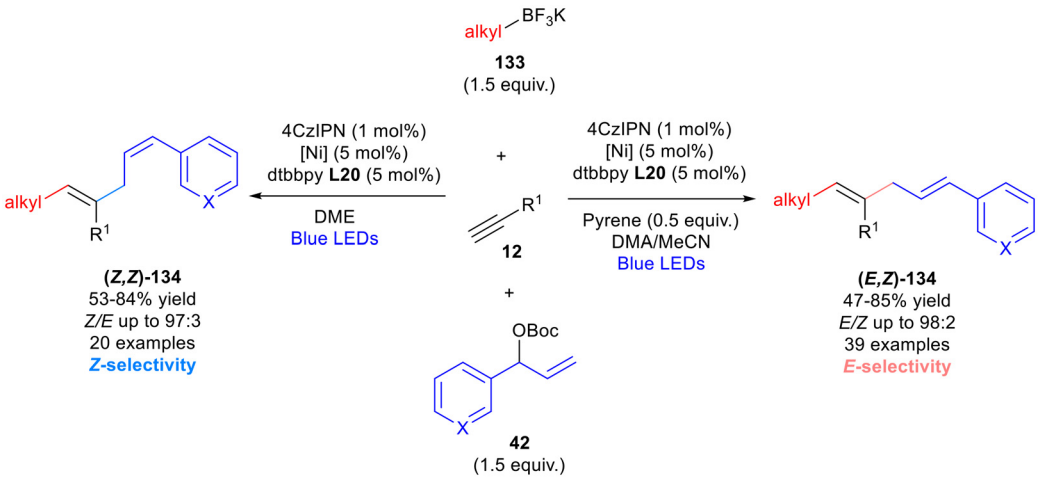
isomerisation through a photoinduced energy transfer process was feasible with $[Ir(ppy)_2(dtbbpy)]^+$, which possess a sufficiently high triplet state energy, as opposed to $[Ru(bpy)_3]^{2+}$. The vast application of this dual photoredox/nickel catalysis was demonstrated by its broad scope, comprising both electron-withdrawing and -donating substituents on the aromatic platform of the allylic partner, as well as both cyclic and acyclic vinyl triflates. Furthermore, specifically for the case of *Z*-configured skipped dienes **132**, the authors noted an appreciable decrease in *Z*/*E* stereoselectivity in the functionalisation of allylic carbonates **42** with free *ortho* positions.

In 2023, Chu's group developed another metallaphotoredox procedure for the stereodivergent synthesis of *E*- and *Z*-configured skipped dienes **134** (Scheme 53). This three-component reaction involved a 1,2-carboallylation of terminal alkynes **12** with allylic carbonates **42** and alkyl tetrafluoroborates **133**, employing a nickel catalyst and commercially available 4CzIPN as the photocatalyst to selectively furnish either (*Z*,*Z*)-1,4-dienes or, with the aid of pyrene, (*E*,*Z*)-1,4-dienes.[93] The protocol displayed great generality, as demonstrated by the functionalisation of several allylic carbonates **42** bearing useful synthetic handles such as nitrile, ester, carboxylic acid, bromide and others in good to excellent yields, with no significant effect on reaction efficiency from both the electron-withdrawing and -donating groups. A wide range of terminal alkynes with different electronic properties and steric hindrance was well tolerated by the reported methodology, although the less reactive internal alkynes were unsuitable due to competitive self-coupling of the allylic carbonates or cross-coupling of the latter with alkyl tetrafluoroborates **133**.

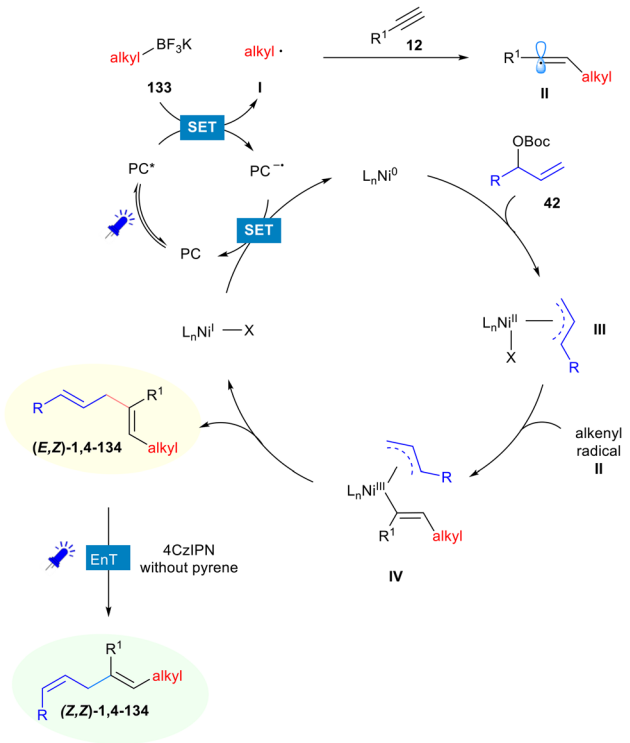
A deep mechanistic investigation was performed by the authors to study the reaction mechanism of the metallaphotoredox-catalysed carboallylation reported in Scheme 53. As demonstrated by Stern–Volmer fluorescence quenching experiments, photoexcited 4CzIPN* is involved in a single-electron oxidation of the alkyl tetrafluoroborate **133** (Scheme 54). This event generates the corresponding alkyl radical **I**, identified by trapping the *t*-Bu$^\bullet$ radical from *t*-$BuBF_3K$ with the radical scavenger TEMPO, which then could add to the terminal alkyne **12** to produce the alkenyl radical intermediate **II**. The nickel catalytic cycle starts with Ni(0), which could undergo an oxidative addition with the allylic carbonate **42** to afford the π-allyl Ni(II) species **III**. The previously generated alkenyl radical **II** could be captured by **III** to form *trans*-(alkenyl)(allyl)Ni(III) **IV**. A subsequent reductive elimination generates the (*E*,*Z*)-1,4-diene **134** as the final reaction product in the presence of pyrene and a Ni(I) complex that, through a final single electron transfer, closes both catalytic cycles, regenerating 4CzIPN to its electronic ground state and Ni(0). In the absence of pyrene that acts as a triplet energy modulator, electronically excited 4CzIPN* is able to quench itself through a photoinduced energy transfer process with **(*E*,*Z*)-1,4-134**, producing the thermodynamically disfavoured alkene **(*Z*,*Z*)-1,4-134**.



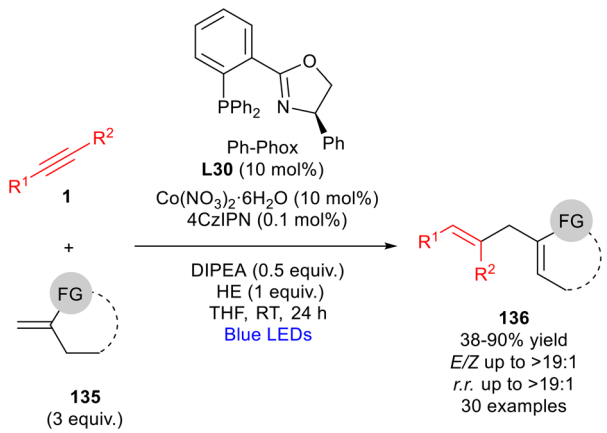
Scheme 52 Stereodivergent cross-electrophile coupling reaction of vinyl triflates **10** and allylic carbonates **42**; [Ir]: $Ir(ppy)_2(dtbbpy)(PF_6)_2$; [Ru]: $[Ru(bpy)_3](PF_6)_2$; [Ni]: $Ni(OAc)_4{\cdot}4H_2O$; bpy L29: 2,2′-bipyridine; HE: Hantzsch ester.



Scheme 53 Three-component stereodivergent 1,2-carboallylation of alkynes **12** with allyl carbonates **42** and alkyl tetrafluoroborates **133**. [Ni]: $NiCl_2$·Phen.



Scheme 54 Mechanism of the carboallylation reaction reported in Scheme 53. PC: photocatalyst (4CzIPN).



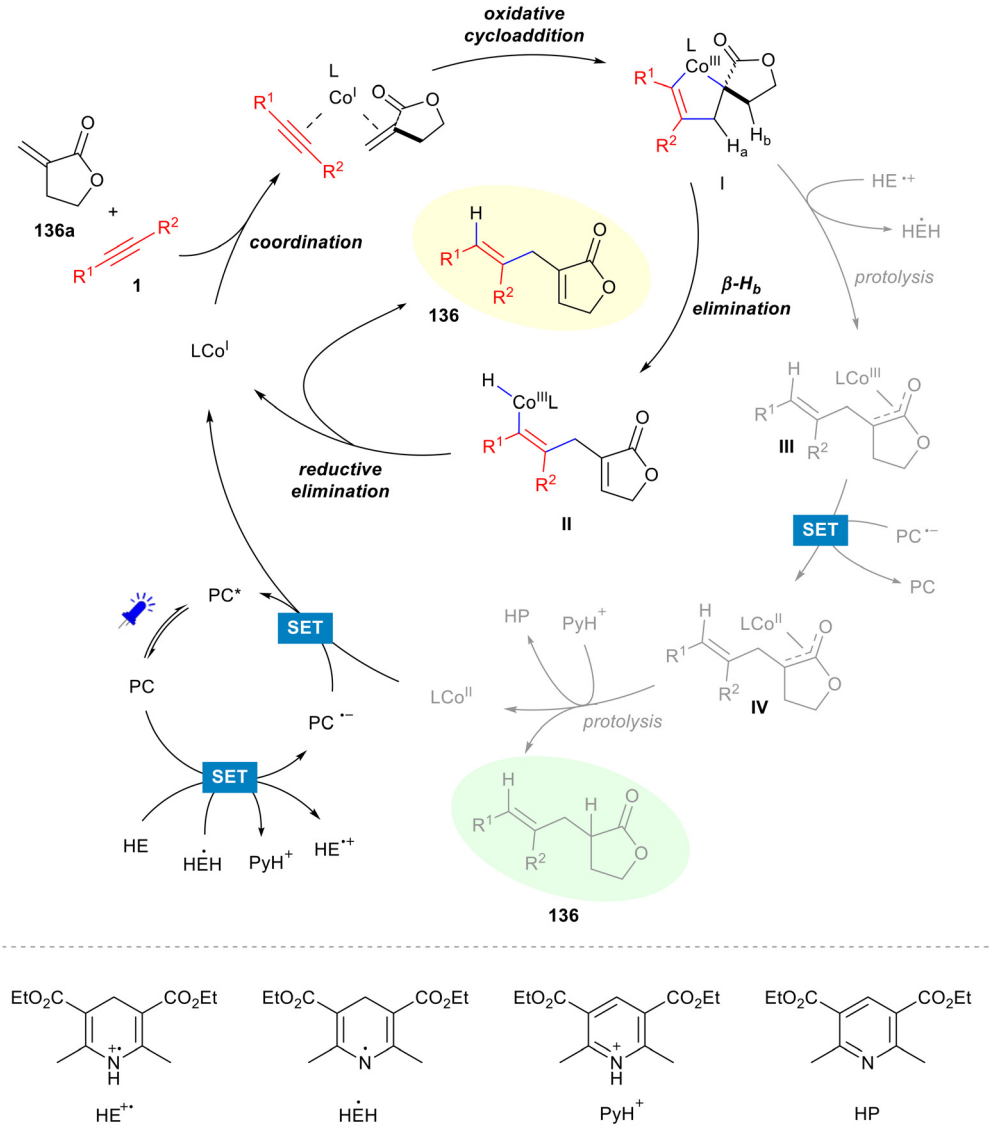
Scheme 55 Ligand-controlled dual cobalt/4CzIPN cross-coupling reaction of alkynes **1** with alkenes **135**.

In the same year, He and Xia described a divergent synthesis of skipped dienes **136** and trisubstituted alkenes **138** from the same set of substrates.[94] Their highly regio- and stereoselective protocol employed dual cobalt/photoredox catalysis, with a remarkably low catalyst loading (0.1 mol%) of the photocatalyst 4CzIPN (Scheme 55). Stereodefined skipped dienes **136** were obtained as the ene-type coupling product of alkynes **1** with functionalised alkenes **135** using a hemilabile P,N-ligand such as Ph-Phox **L30**. Meanwhile, trisubstituted alkenes were produced by simply changing the ligand to a strong bidentate one such as Xantphos **L31**. The authors mainly focused on the cross-coupling reaction of Tulipalin A **136a** as the alkene partner, a useful synthon considered to be a cyclic analogue of methyl methacrylate (MMA) due to its *exo*-methylene group at the α-position of the lactone moiety. Concerning the chemoselective generation of skipped dienes, Tulipalin A was employed to install the 1,4-diene motif on a broad scope of terminal and internal alkynes, although no reaction was observed in the case of propargylic moieties. Furthermore, one example of an alkyne derived from a natural steroid was successfully converted under the Ph-Phox-controlled conditions, demonstrating the applicability to late-stage functionalisation. Under the same reaction conditions, the authors also explored the generality of the alkene partners, reporting four examples with moderate yields (44–46%). Interestingly, only activated alkenes such as acrylate and acrylonitrile were suitable coupling partners.

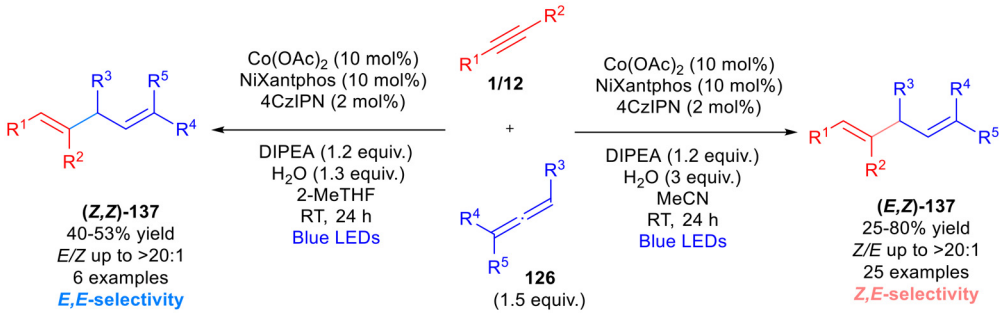
The authors proposed a reaction mechanism (Scheme 56) in which photoexcited 4CzIPN* could initiate a single-electron oxidation of Hantzsch ester (HE) generating $HE^{\bullet-}$ and $4CzIPN^{\bullet-}$. Subsequently, the latter could reduce the Co(II) complex to Co(I), regenerating the photocatalyst.

Next, the substrates are coordinated to the Co(I) species, followed by an oxidative addition that generates the spirocyclic cobaltacyclopentene **I**, the common intermediate of this chemodivergent protocol. The presence of the hemilabile ligand Ph-Phox **L30** favours an exocyclic β-H_b elimination, more competitive than the β-H_a elimination not being in a *syn* coplanar arrangement. Consequentially, the alkenyl Co(III)–H species **II** is generated and, through a reductive elimination the skipped diene **136** is produced, while regenerating the Co(I) complex. Otherwise, the strong bidentate ligand Xantphos **L31** could dictate the progress of the reaction toward the protolysis of **I** by $HE^{\bullet-}$, affording the Co(III)-enolate **III**, which through subsequent single-electron transfer by $4CzIPN^{\bullet-}$ and protolysis could afford the trisubstituted alkene as the alternative reaction product.

Recently, Li, Gu and Xia developed an elegant stereodivergent protocol for the synthesis of (*Z*,*Z*)- and (*E*,*Z*)-configured skipped dienes obtained through the synergistic catalysis of cobalt and 4CzIPN (Scheme 57). This reaction between alkynes **1** and allenes **126** efficiently used DIPEA and water as the hydrogen source instead of the Hantzsch ester, commonly employed for such purpose.[95] Under otherwise identical conditions, by changing the solvent from MeCN to 2-MeTHF, the reaction furnished (*E*,*Z*)- and (*Z*,*Z*)-1,4-dienes **137**, respectively. Thorough mechanistic investigation supported by DFT calculations allowed the authors to hypothesise that the origin of the solvent-controlled



Scheme 56 Mechanism of the cross-coupling reaction reported in Scheme 55. PC: photocatalyst (4CzIPN); HE: Hantzsch ester.

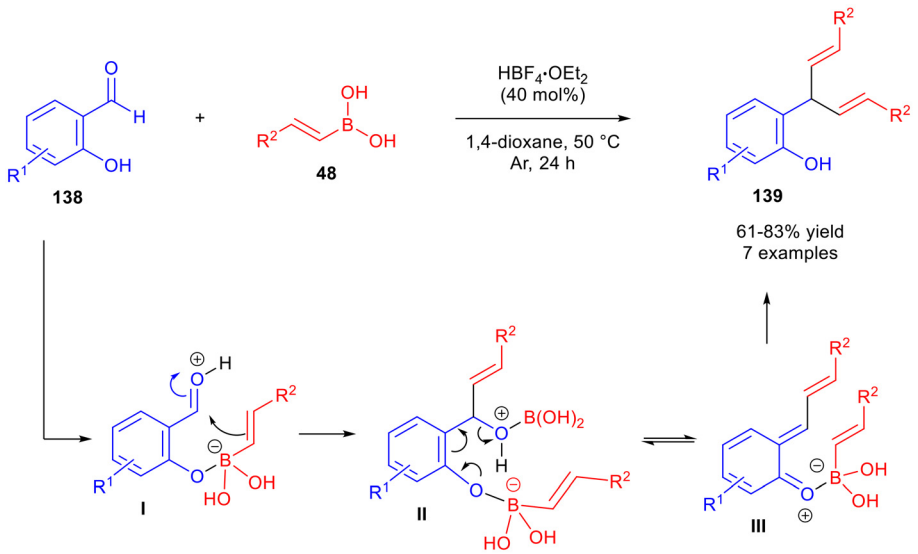


Scheme 57 Solvent-controlled stereoselective synthesis of skipped dienes **137** from alkynes and allenes with synergistic cobalt/4CzIPN catalysis.

stereoselectivity lay in the modulation of the triplet energy state of electronically excited 4CzIPN, involved in the photo-induced energy transfer process that triggered the $E \rightarrow Z$ alkene isomerisation. Indeed, the triplet energy levels of 4CzIPN* and the (*E*,*Z*)-1,4-diene **137** were better matched in MeCN as opposed to in THF, allowing the isomerisation to the (*Z*,*Z*)-configured product **137** to occur only in the former. The described reaction tolerated several active groups on the alkyne partner, such as hydroxyl and ester, and was successfully applied to both internal **1** and terminal alkynes **12**. However, terminal aryl alkynes were not suitable substrates for this reductive coupling strategy. Finally, the authors observed a noticeable effect of the substituents of the allenic platform on the reaction efficiency, specifically with ester groups. Indeed, allenoates bearing small ester groups (methyl, ethyl) afforded the products in low yields in the MeCN conditions, differently from bulkier ester groups (isopropyl, benzyl). Furthermore, functionalised allenes containing Ts and Ac groups in place of CO_2R could not be employed for this reaction, suggesting that the ester moiety might coordinate with cobalt.

Metal-free transformations

Among the published methodologies, only one metal-free transformation was reported for the synthesis of skipped dienes. In 2020, Harris *et al.* described a metal-free dialkenylation of salicylaldehydes **138** with alkenyl boronic acids **48**, which was mediated by the Brønsted acid $HBF_4{\cdot}OEt_2$ (Scheme 58).[96] The reaction was conducted in the presence of 2.8 equivalents of boronic acids **48**, 40 mol% of the acid, in dioxane at 50 °C. The skipped dienes products **139** were found to be sensitive compounds. As highlighted by the authors, this may impact the yield in instances of complete conversion of the starting materials. The scope was extended to include unsubstituted and di-substituted salicylaldehydes **138** bearing electron-donating and halogen groups at the 3 and 5 positions, which yielded the corresponding dienes in yields ranging from 61 to 83%. Moreover, tolylvinyl boronic acid, as well as phenylvinyl and 1*H*-indene-2-boronic acids, were tested within the scope of this study, forming dienes **139** in comparable yields. It is worth noting that the formation of 2*H*-chromenes was observed when 6-halosalicylaldehydes were employed as the



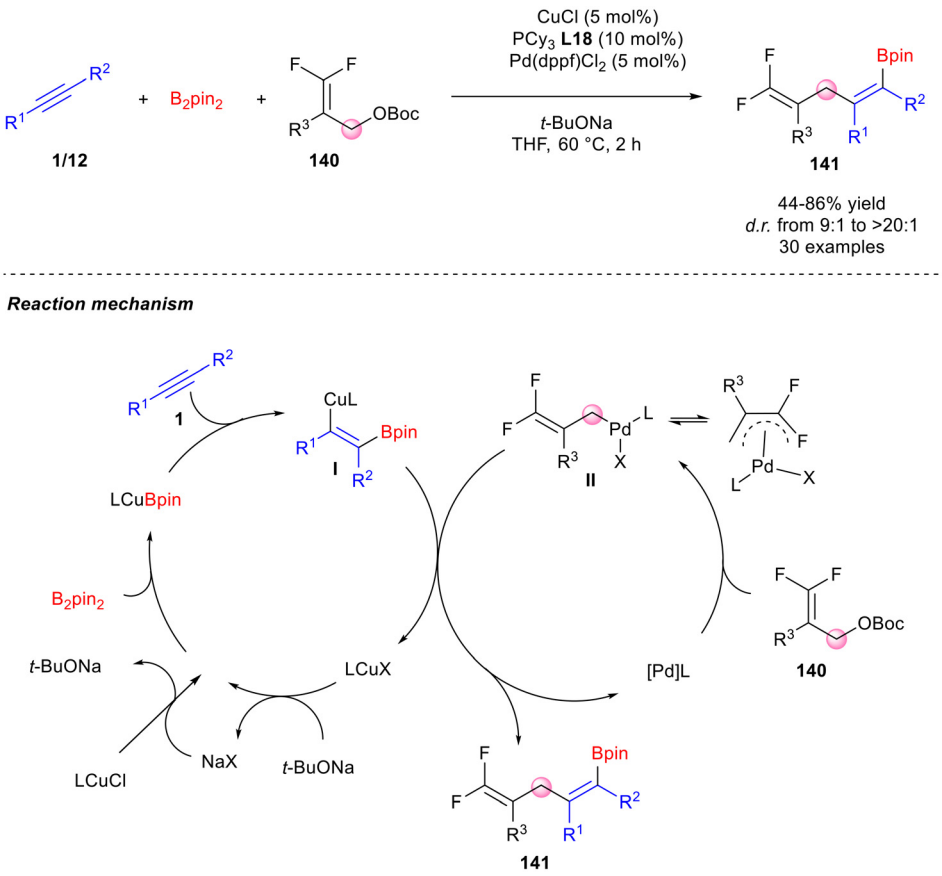
Scheme 58 Metal-free synthesis of skipped dienes **139** from salicylaldehydes **138** with alkenyl boronic acids **48**.

substrate. As illustrated in Scheme 58, the authors proposed the following mechanism: the acid is employed to activate the aldehyde, enabling its coordination with the boronic acid to form **I**. The subsequent Petasis-like transfer of the vinyl group from the borate to the carbonyl moiety yields intermediate **II**. The diene is formed in the last step by an 1,4-addition of **II**.

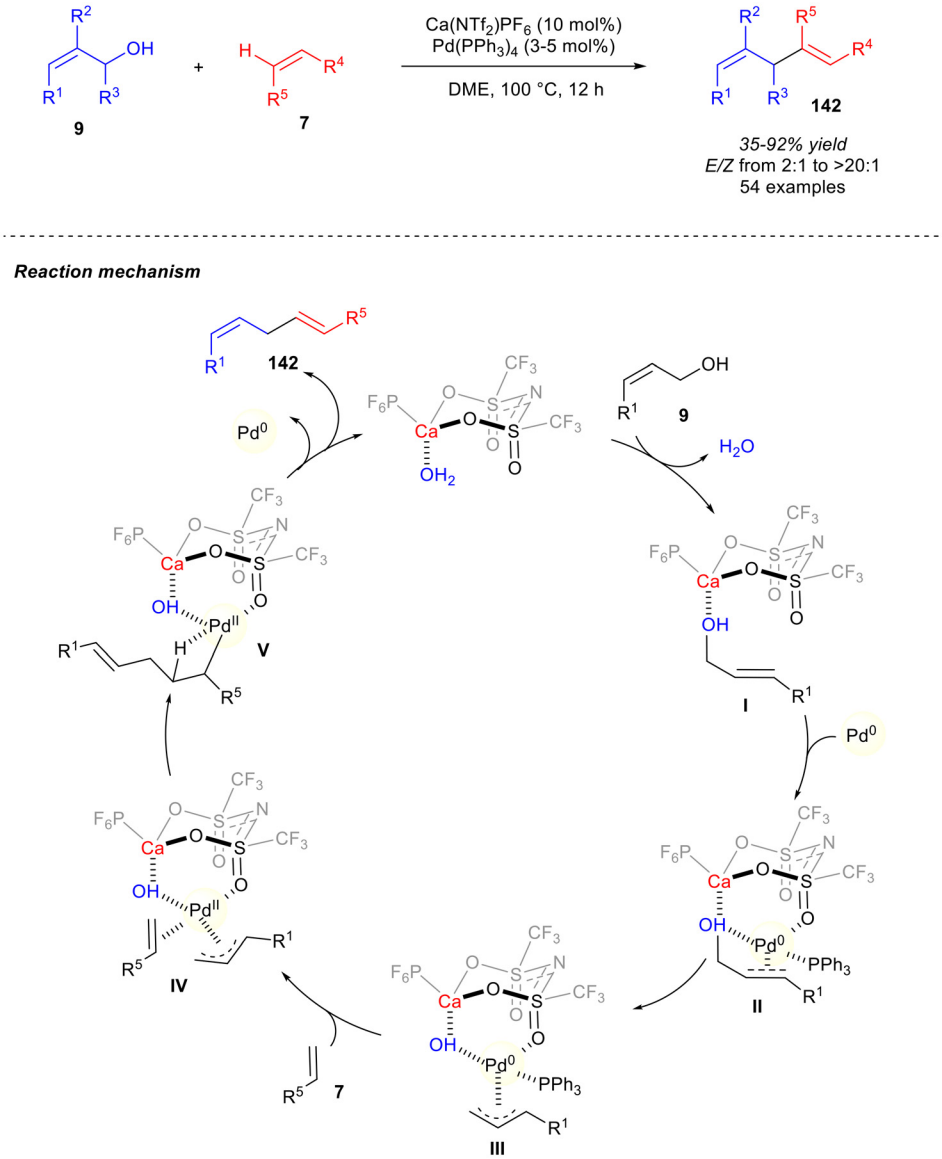
Synergistic/dual catalysis

Synergistic catalysis represents a robust strategy for the formation of new bonds, wherein two catalysts and two catalytic cycles operate in concert.[97] Additionally, the synthesis of skipped dienes has been enhanced by this approach. In 2020, Zhuo and colleagues developed a novel approach to accessing boron and fluorine-containing molecules (Scheme 59).[98] A dual catalytic system composed of CuCl/PCy_3 and $Pd(dppf)Cl_2$ was employed to obtain skipped *gem*-difluorodienes **141** through a regioselective boryldifluoroallylation of alkynes **1**/**12** with 3,3-difluorosubstituted allylic esters **140** and B_2pin_2 in the presence of *t*-BuONa, in THF at 60 °C. Regarding the scope of the transformation, both internal and terminal alkynes were suitable substrates, with lower yields observed for cyclic derivatives. The reaction exhibited high regioselectivity towards the alkyne moiety when the starting material presented both a terminal alkene and alkyne functionality, and functional groups such as amide, ether, and alkyl halide were well tolerated. The addition of electron-donating and electron-withdrawing groups, as well as halogens and heterocycles, to the allylic electrophiles proceeded smoothly, affording the diene **141** in yields ranging from good to high. The process was also proved to be scalable, and the diene **141** was subjected to a variety of transformations, demonstrating the utility of the boryldifluoroallylation reaction. A plausible mechanism was also proposed (Scheme 59, bottom). The catalytic cycle starts with the stereo- and regio-selective borylcupration of the alkyne with the complex formed between the copper-based catalyst and B_2pin_2, resulting in the generation of the borylalkenylcopper intermediate **I**. In the second catalytic cycle, palladium is exploited to activate the 3,3-difluorosubstituted allylic esters **140** *via* an oxidative addition into the Pd(0) complex. The interaction between the two intermediates **I** and **II** permits the formation of the product **141** and the regeneration of both catalysts. The regioselectivity of this step is controlled by the palladium catalyst.

The synthesis of linear 1,4-dienes can be achieved through the dehydrative allylation of alkenyl sp^2 C–H bonds, as outlined by the research group of Xie in 2021 (Scheme 60).[99] A dual cooperative catalytic system, composed of commercially available $Ca(NTf_2)PF_6$ and $Pd(PPh_3)_4$, was employed in con-



Scheme 59 Synthesis of skipped *gem*-difluorodienes **117** though dual copper and palladium catalysis.



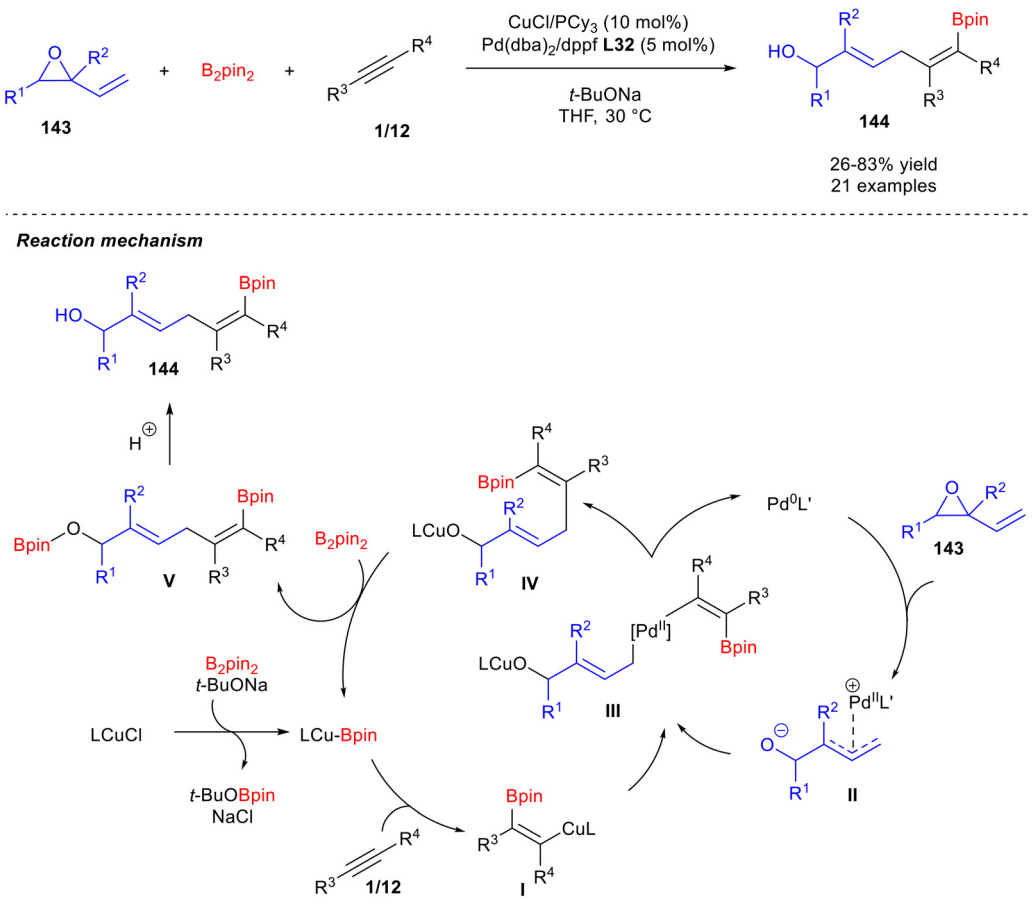
Scheme 60 Allylation of alkenyl sp^2 C–H bonds by a dual catalytic system.

junction with feedstock starting materials, including acrylates **7** and allylic alcohols **9**. The reaction exhibited sensitivity to temperature, with reduced yields observed at temperatures below 100 °C. The use of $Ca(NTf_2)PF_6$ was crucial in facilitating the cleavage of the C–OH bond. A total of 50 products was obtained, exhibiting yields ranging from low to high, using primary, secondary, and tertiary allylic alcohols. Furthermore, Morita–Baylis–Hillman alcohols were subjected to the dehydrative allylation reaction, wherein the position and electronic properties of the substituents on the aromatic ring did not affect the yields. In contrast, the stereoselectivity was influenced by the electronic properties, and a lower *E*/*Z* ratio was observed in the presence of electron-withdrawing groups. The reaction was found to be suitable for use with a variety of acrylates and alkenes, including styrenes and derivatives of biologically active compounds (estradiol, cholesterol, galactopyranose). The formation of a complex in 1 : 1 stoichiometry between $Ca(NTf_2)PF_6$ and the alcohol was detected by applying the method of continuous variation and DOSY experiments. The results of deuteration and kinetic isotopic effect experiments demonstrated that the alkenyl sp^2 C–H bond cleavage was not the rate-determining step. Consequently, a proposed mechanism was formulated based on these findings (Scheme 60 bottom). The C–OH bond is activated by the interaction with $Ca(NTf_2)PF_6$ (**I**). Once the allylic alcohol has been activated, the oxidative addition of palladium enables the formation of intermediate **II**. The coordination of the oxygen atom to calcium and its interaction with palladium initiates the OH elimination, which results in the formation of intermediate **III**. This latter intermediate then coordinates the

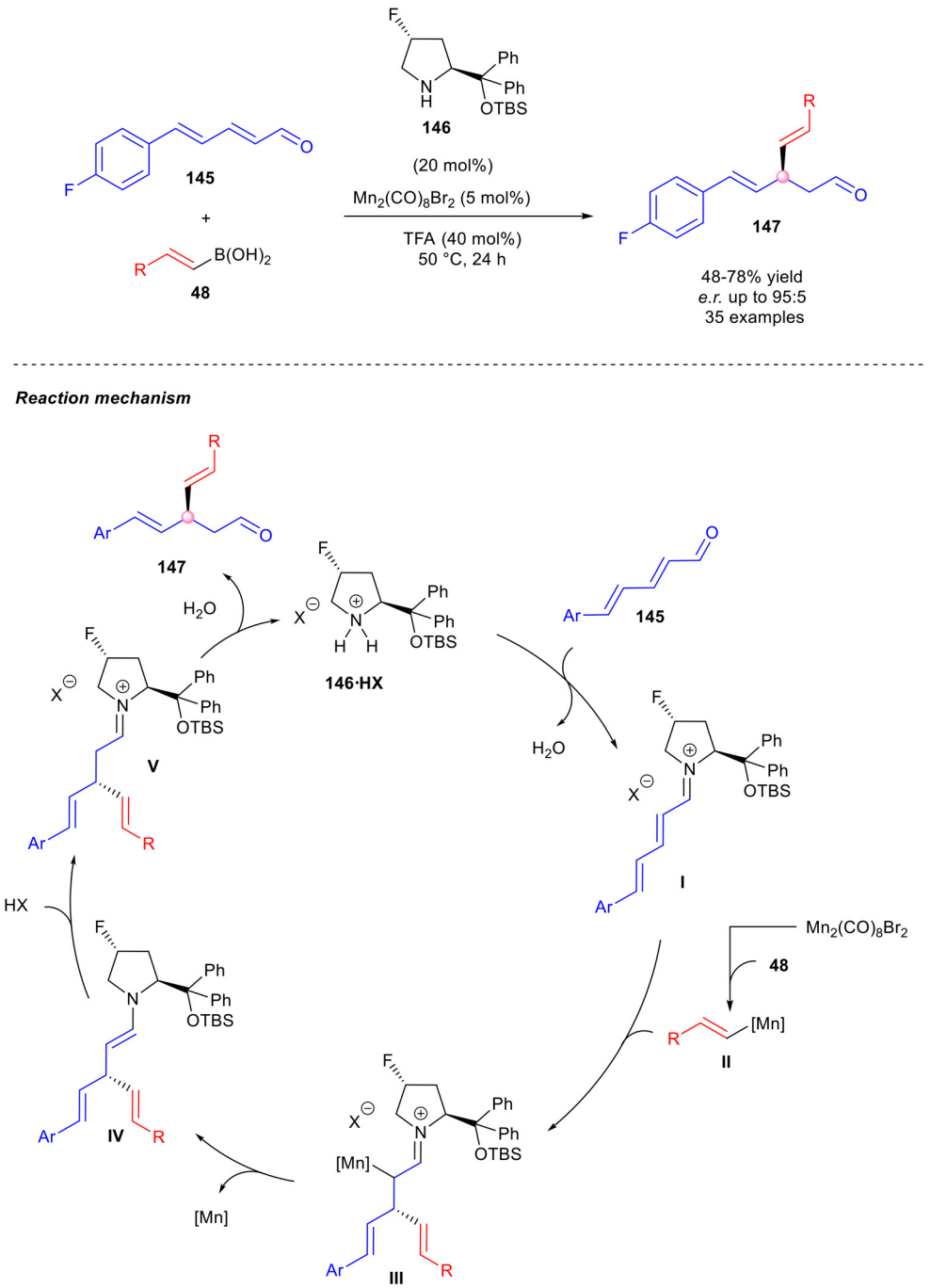
alkene, leading to the generation of intermediate **IV**. The 1,4-diene product **142** is obtained from **IV** after a Heck-like process.

Bifunctional skipped dienes **144** bearing an allylic alcohol and an alkenylboronate moiety can be obtained from a three-component coupling between a substituted vinyl epoxide **143**, a B_2pin_2 molecule, and alkynes **1/12** (Scheme 61).[100] As described by the group of Fañanás-Mastral, a dual synergistic catalytic system composed of a copper and a palladium-based catalyst should be employed to observe the diene formation. A catalytic amount of *t*-BuONa was added to the reaction mixture in THF to increase the efficiency of the reaction. Furthermore, the authors observed that the addition of the vinyl epoxide **143** at a slow rate was essential to achieve higher yields. The use of different alkynes, including internal aryl alkyl alkynes and 1,2-diarylalkynes, as well as trimethylsilylacetylene, proved to be effective substrates, while the use of 1-hexyne or phenylacetylene did not result in the desired product formation. 1,2-Disubstituted vinyl epoxides gave yields ranging from moderate to good, albeit at temperatures exceeding 30 °C. Furthermore, the protocol was extended to cyclic vinyl carbonates. The reaction was found to be regioselective, with no addition of B_2pin_2 to the vinyl epoxide observed. Indeed, the LCu–Bpin complex has been shown to add in a regio- and stereoselective manner to the alkyne **1/12**, thereby generating the β-borylalkenylcopper(I) intermediate **I**. Concurrently, the oxidative addition of epoxide **143** to the Pd(0) complex facilitates the formation of η^3-allylpalladium complex **II**. Subsequent transmetallation of organometallic intermediates **I** and **II** allows the generation of **III**, which, following a reductive elimination pathway, permits the regeneration of the Pd(0) catalyst and the formation of the copper alkoxide **IV**. The latter is reactive enough to undergo σ-bond metathesis with B_2pin_2, regenerating the active LCu–Bpin complex and releasing intermediate **V**, the protonation of which permits the formation of diene **144**.

In 2024, the group of Han and Xie developed an enantioselective synthesis of skipped dienes **147** by the synergistic activity of a chiral pyrrolidine **146** and a Mn(I)-catalyst (Scheme 62).[101] In the optimised reaction conditions, the 2,4-dienals **145** were coupled with the boronic acids **48** in the presence of 20 mol% of the aminocatalyst **146** and 5 mol% of $Mn_2(CO)_8Br_2$ in TFA at 50 °C. The structure of the aminocatalyst was modified with the objective of enhancing the enantioselectivity. This was achieved by incorporating a fluorine atom in a *trans* arrangement with respect to the bulky silyl ether group, which improved the reactivity of the chiral iminium ion intermediate. The synthesis of skipped 1,4-dienals **147** was



Scheme 61 Cu/Pd-catalysed allylboration of alkynes with B_2pin_2 and vinyl epoxides **143**.



Scheme 62 Synthesis of skipped dienes **147** from 2,4-dienals **145** and boronic acid **48** by synergistic aminocatalysis.

achieved with exclusive regioselectivity and good stereoselectivity using a range of 2,4-dienals **145**, including heteroarenes and both electron-withdrawing and electron-donating groups on the different positions of the phenyl ring, with yields ranging from 49 to 78%. Furthermore, polyfluoroarenes were included in the scope, given their biological importance. Furthermore, alkenyl boronic acids with diverse substitutions, including aromatic rings, heteroarenes, and alkyl groups, were also tested. Some of the final products **147** were, also, subjected to downstream transformations, and the synthesis of (−)-blepharocalyxin D was also undertaken. According to the proposed reaction mechanism (see Scheme 62 bottom), the aminocatalyst **146** reacts with the dienal **145** to form an iminium ion **I**. The presence of TFA facilitates this process by lowering the LUMO energy. Concurrently, the boronic acid **48** undergoes a metallation process with $Mn_2(CO)_8Br_2$, resulting in the formation of intermediate **II**. This is achieved through a selective migratory insertion of the C–C bond of **48** into the C–

Mg bond of **I**, with the insertion side being influenced by the steric bulk of the catalyst. The final three steps entail the demetallation and isomerisation of intermediate **III**, resulting in the formation of enamine **IV**. The subsequent hydrolysis of **V** leads to the release of the diene product **147** and the regeneration of the catalysts.

Summary and outlook

This review presents a comprehensive overview of the latest developments in synthetic methodologies for accessing skipped dienes in the past five years. Since metal-mediated protocols play a major role in the synthesis of skipped dienes, the contribution of the different metal catalysts, classified by chemical group, is here covered. The combination of unsaturated starting materials with a metal-based catalyst, as well as metal-free transformations and synergistic catalysis, with and without light mediation, has been employed to produce 1,4-dienes with excellent regio- and stereo-selectivities. Despite copper- and palladium-promoted processes still being exploited in most of the papers, the role of group 9 elements, cobalt, rhodium and iridium, is clearly emerging, together with nickel. In many reported examples, a careful tuning of the catalytic system, by choosing the proper ligand, solvent, temperature and the presence of an additive, proved to be a crucial factor in enabling a regio-switchable approach and a rapid access to a specific stereoisomer of the diene product. Moreover, novel approaches focused on mild reaction conditions, the use of visible light photoredox protocols, and also metal free processes for the selective preparation of 1,4-dienes will, surely, increase in the next years.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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