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The stereo-divergent functionalization of alkynes: a comprehensive review

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Alkynes are central in crafting pharmaceuticals, agrochemicals, and materials owing to their reactivity and linear geometry. This review unveils cutting-edge advancements in the stereo-divergent functionalization of alkynes, transforming them into invaluable tools for synthesizing stereochemically defined alkenes and alkanes. The review highlights ground-breaking methodologies that achieve exceptional *E*- and *Z*-selectivity using innovative catalysts like cobalt, nickel, and palladium through hydrogenation, hydroboration, and hydrosilylation. Recent breakthroughs such as dual-catalytic systems and energy transfer catalysis enable unprecedented stereocontrol. Sustainable strategies including water as a hydrogen source and recyclable catalysts align with green chemistry principles, paving the way for eco-friendly synthesis. This synthesis of cutting-edge techniques and their applications inspire new avenues in synthetic chemistry, offering transformative tools for creating complex molecular architectures with precision and sustainability.

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Ranjay Shaw completed his master's degree in chemistry from Vinoba Bhave University, Hazaribag, India. He earned his PhD in 2021 from the University of Delhi, followed by post-doctoral research at the Indian Institute of Technology (IIT), Delhi, from 2021 to 2023. In 2023, he joined GLA University, Mathura, as an Assistant Professor. His research interests lie in organic synthesis, medicinal chemistry, and drug discovery. Dr Shaw focuses on the design and synthesis of heterocycles and carbocycles, exploring their potential therapeutic applications. His work aims to contribute to the development of novel and sustainable methodology for biologically benign organic scaffolds.

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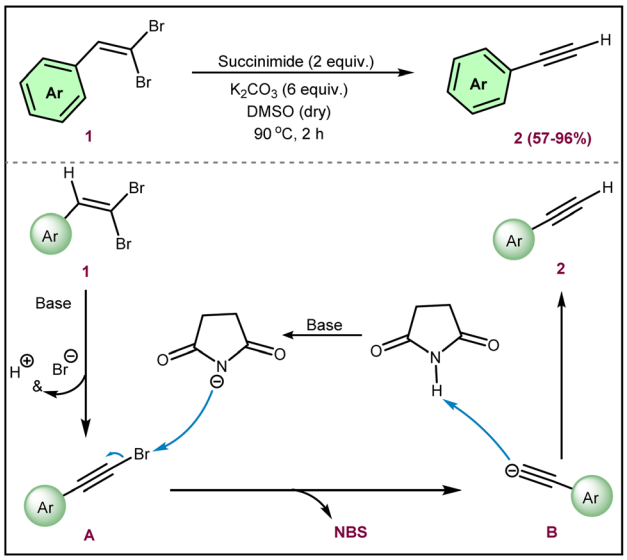
Ashmita Singh was born in New Delhi, India, in 1992. She received her BSc (2013) and MSc (2015) degrees in chemistry. In 2022, she received her PhD degree in chemistry from Guru Gobind Singh Indraprastha University, New Delhi, India, under the supervision of Professor A. K. Narula, where her research focused on the exploration of N-heterocyclic carbenes (NHCs) in the synthesis of drugs and drug-like molecules. She is a highly skilled researcher specializing in organic synthesis and synthetic chemistry with peer-reviewed research publications in esteemed international journals. Currently, she is working as a Women Scientist in a project awarded by the DST WISE PDF scheme at the University of Delhi, under the mentorship of Professor Ramendra Pratap. Through her ongoing research, she continues to contribute to advancements in catalysis and synthetic methodologies.

1. Introduction

In the realm of organic chemistry, the strategic manipulation of functional groups and the selective control of stereochemistry play pivotal roles in the synthesis of complex molecular architectures. In asymmetric synthesis, stereo-divergent functionalization represents a paradigm shift in this endeavor, emphasizing the selective manipulation of stereochemical outcomes to generate a diverse array of stereochemically distinct products. The concept of stereo-divergent functionalization emerges as a compelling strategy, offering chemists a nuanced approach in accessing a plethora of stereoisomeric products from a single starting material.[1–3] This approach to synthesis enhances the synthetic efficiency and offers insights into the underlying mechanistic intricacies governing chemical transformations. Moreover, stereo-divergent strategies pave the way for the creation of molecular libraries with enriched structural complexity and biological relevance by embracing the concept of stereochemical diversity.[4,5] Stereo-divergent routes may offer efficient approaches in obtaining various naturally occurring or biologically active enantiomers and diastereomers from the same starting material.[6–8]



Scheme 1 Dehydrohalogenation of 1,1-dibromoalkenes to alkyne.

Ismail Althagafi

Ismail Althagafi is a Professor at the Department of Chemistry, Faculty of Sciences, Umm Al-Qura University, Makkah (Saudi Arabia). He obtained his bachelor's degree from Umm Al-Qura University and his master's and PhD degrees from Cardiff University (United Kingdom). His current research interest includes physical organic chemistry, synthetic chemistry, and bio-organic chemistry. He has published more than 100 research publications in different journals.

Ramendra Pratap

Prof. Ramendra Pratap completed his master's degree from the University of Gorakhpur in 2001, and then, he moved to Central Drug Research Institute, Lucknow, Uttar Pradesh, India, for doctoral research. He worked with Dr Vishnu Ji Ram for four and a half years on ring transformation reactions of 2H-pyran-2-ones. He worked on nucleoside modification chemistry as a post-doctoral fellow at the City University of New York, USA, for two years. He received a renowned Humboldt fellowship and shifted to the University of Saarland, Germany. In Saarbrucken, he was involved in Mo-catalyzed reactions. In September 2010, he joined the Department of Chemistry, University of Delhi, India, as an Assistant Professor. Currently, he is working as a full Professor. To date, he has published more than 100 research papers in various international journals. He has also received a JSPS invitation fellowship during 2016–17. His research focuses on developing various heterocycles, carbocycles, materials, and metal-catalyzed bond formation reactions.

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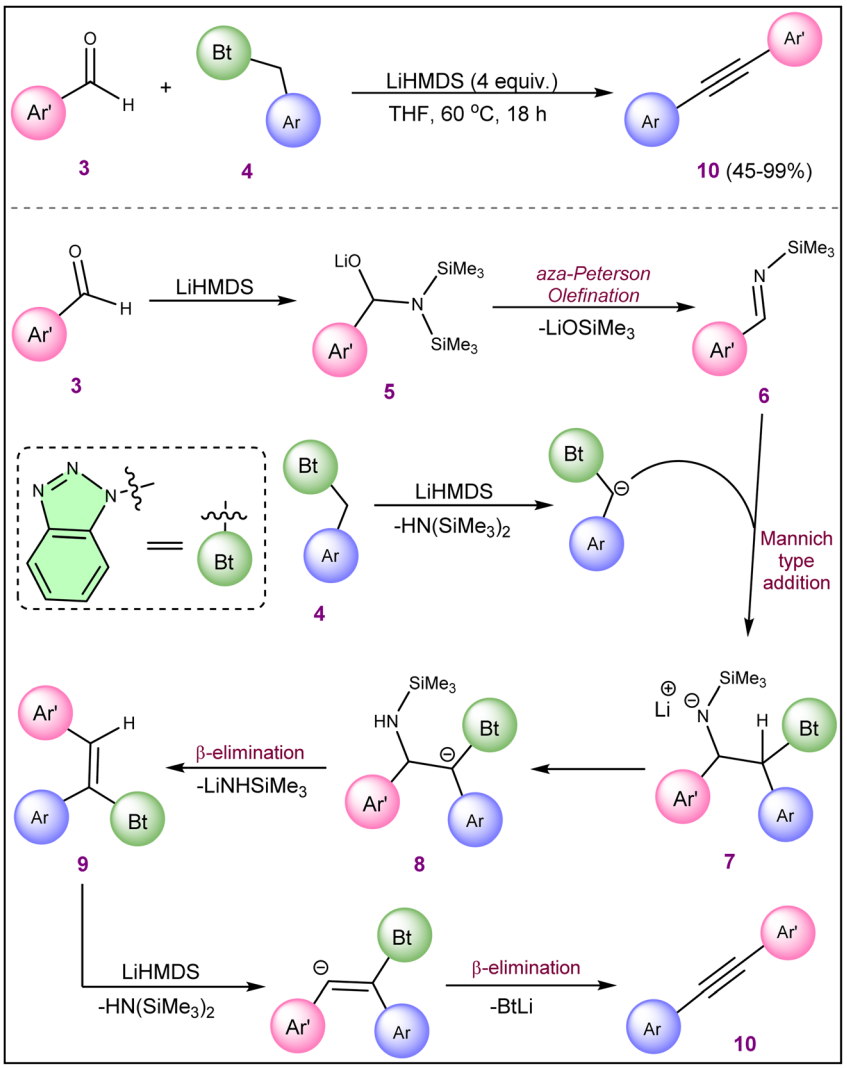
Dr Dharmendra Kumar Yadav has completed his PhD degree in Biological Science from CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow, India. He completed his post-doctoral studies at Hanyang University, Korea, and University of Delhi, India. Presently, he is working as an Assistant Professor and Principal Investigator of an NRF project (Korea Government) in the College of Pharmacy in Gachon University, Korea. He received the Young Scientist award from the Science and Engineering Research Board, New Delhi. He has worked as a Young Scientist at All India Institute of Medical Science Jodhpur, India. He has published more than 150 papers in reputed journals, 3 book chapters and a patent. He is continuing his research in atomic level molecular simulation of plasma medicine, computer-aided drug design and molecular modelling of biological networks. He is also a member of several scientific societies and academic bodies.

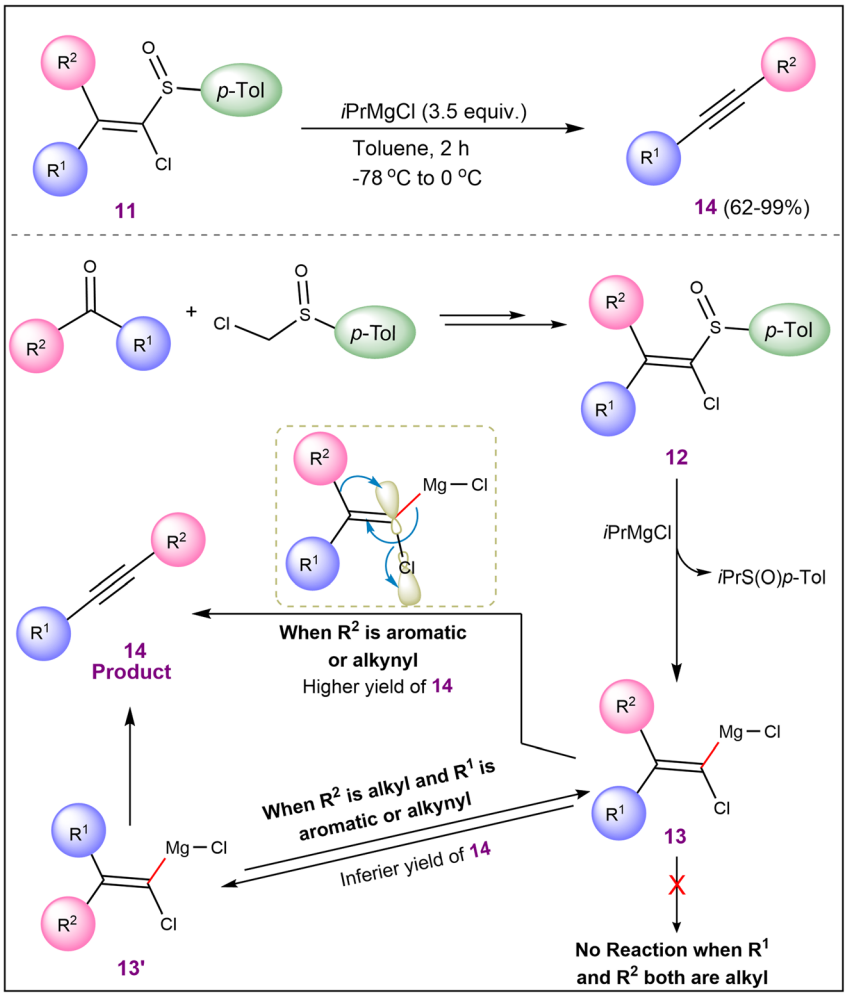


Scheme 2 Synthesis of diaryl alkyne from aryl aldehydes and 1-(aryl methyl) benzotriazoles.

Among the myriad of functional groups, alkynes have garnered significant attention owing to their inherent versatility and reactivity, making them indispensable building blocks in the construction of diverse organic compounds.[9–11] The synthetic landscape of alkynes is characterized by their unique electronic properties and distinctive linear geometry, which lend them to a wide array of transformations.[12,13] Exploiting the potential of alkynes as synthetic precursors, researchers have attempted to functionalize these compounds and achieve precise stereochemical control, thereby expanding the repertoire of available stereoisomeric motifs.[14] Recently, significant progress has been made in the stereo-divergent functionalization of alkynes, resulting in a generation of diverse *E*/*Z* alkenes or directly chiral alkanes.[15] Despite their potential in synthetic chemistry, literature reviews specifically addressing the stereo-divergent functionalization of alkynes are scarce, underscoring the necessity for a comprehensive compilation of literature on the synthesis of alkynes.

This comprehensive review delves into the recent updates on alkyne synthesis from non-alkyne sources and their stereo-divergent functionalization, examining the fundamental principles, synthetic methodologies, and transformative applications that characterize this growing field. We thoroughly investigate catalytic transformations and innovative stereochemical control strategies, elucidating the complexities and challenges inherent in this dynamic synthetic paradigm. Additionally, this review highlights the broader implications of stereo-divergent functionalization beyond synthetic chemistry, emphasizing its potential to inspire new paradigms in molecular design, drug discovery, and materials science. By elucidating the fundamental concepts and presenting exemplary case studies, we aim to stimulate further research and innovation in this rapidly evolving field, ultimately advancing chemical synthesis and molecular engineering.

In short, the study of stereo-divergent functionalization of alkynes represents a blend of creativity, precision, and scientific rigor, continuously pushing the boundaries of synthetic possibility and revealing new aspects of molecular complexity. This article guides readers through the complex realm of



Scheme 3 FBW rearrangement of magnesium alkylidene carbenoids to internal alkynes.

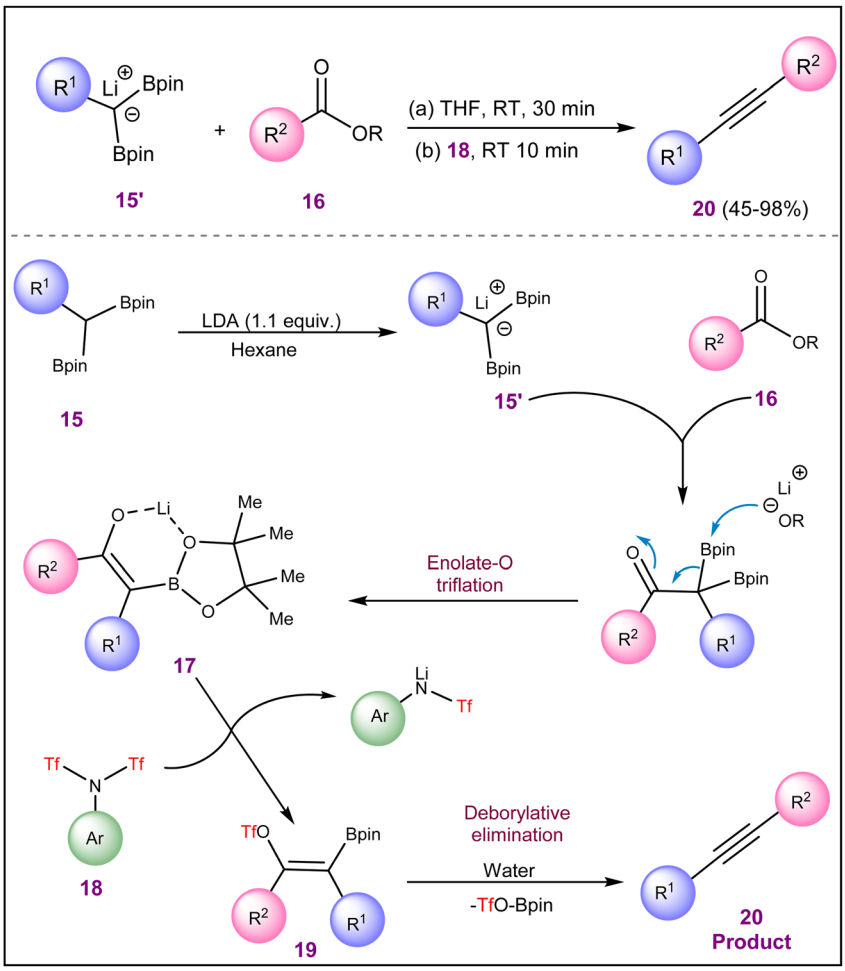
stereochemical manipulation, where innovative thinking intersects with molecular precision in advancing the future of organic synthesis.

2. Recent updates in alkyne synthesis from non-alkyne sources

Metal-catalyzed coupling of terminal alkynes is a prevalent method for synthesizing desired internal alkyne products. However, constructing C–C triple bonds from non-alkyne precursors typically involves α,β-elimination, carbene rearrangement, or fragmentation reactions. In 2020, our group published a comprehensive review on the synthesis of alkynes from non-alkyne sources.[16] Therefore, this article focuses exclusively on recent advancements in the construction of C–C triple bonds from non-alkyne sources.

Terminal alkynes can be synthesized through either a carbene pathway or β-elimination from 1,1-dibromoalkenes.[16] Some of these reactions require the use of strong and air-sensitive bases like *n*-BuLi, LDA, Grignard reagents, or inorganic bases in aqueous conditions. Recently, Rao *et al.* developed a straightforward synthetic approach for producing terminal alkynes (**2**) from 1,1-dibromoalkenes (**1**) under dry reaction conditions, utilizing succinimide and K_2CO_3 in DMSO (Scheme 1).[17] This method demonstrated wide applicability in the synthesis of a broad spectrum of aromatic alkyne (**2**). Substitution of the electron-rich aromatic ring on substrate delivered a higher yield (64–86%) of product compared to substrates with an electron-deficient aromatic ring. However polycyclic aromatic substituted 1,1-dibromoalkenes afforded corresponding terminal alkyne in 75–96%. The reaction initiates with the base-mediated dehydrobromination of substrate **1** to 1-bromoalkyne (**A**). Succinimide plays a dual role in the reaction. The *in situ* generated succinimide anion acts as a good nucleophile in DMSO, facilitating nucleophilic substitution in 1-bromoalkyne (**A**) to form the acetylide anion (**B**). Concurrently, succinimide functions as a proton donor during the reaction, protonating the anions (**B**) to yield the alkyne product (**2**).

Chen *et al.* developed a one-pot approach for the synthesis of diarylacetylene (**10**) from arylaldehydes (**3**) and 1-(arylmethyl) benzotriazoles (**4**) in the presence of LiHMDS (Scheme 2).[18] Both the electron-deficient and donating substituents on the aromatic ring of aryl aldehydes (**3**) and 1-(aryl methyl)



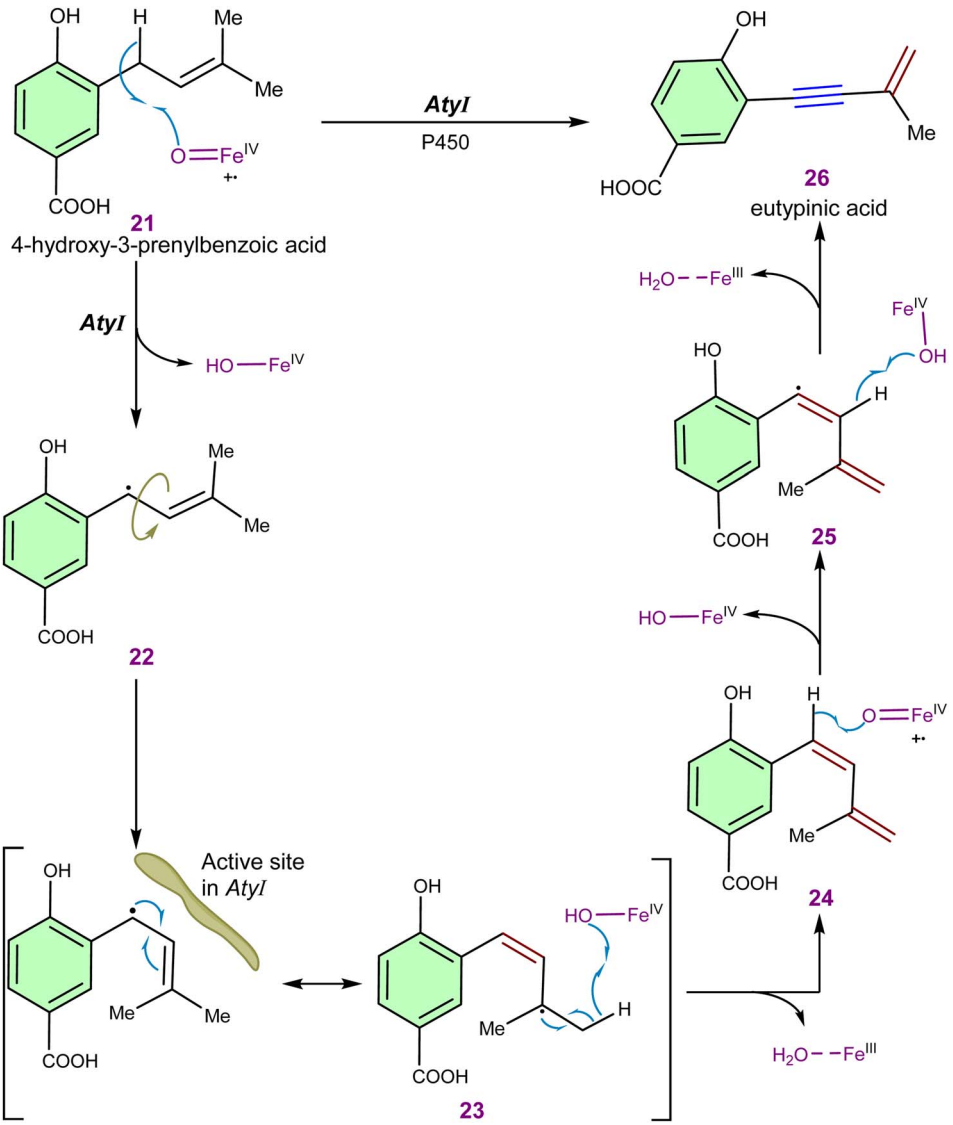
Scheme 4 Synthesis of alkynes using esters and lithiated *gem*-diborylalkanes.

benzotriazoles (**4**) were well tolerated and results in moderate to good yield (48–98%) of alkyne products (**10**) without any specific trend. However, the halide substitution at the *meta*-position of the aromatic ring of substrate **4** results in a very low yield compared to substrates with halide substitution at the *para*-position. The reaction was supposed to proceed through imine formation (**6**), followed by Mannich-type addition of benzotriazoles **4** to imine intermediate **6** and double elimination of $LiNHSiMe_3$ and benzotriazoles.

In this context, Kimura *et al.* reported a Fritsch–Buttenberg–Wiechell (FBW) rearrangement of magnesium alkylidene carbenoids (**13**) to internal alkynes (**14**) (Scheme 3).[19] Magnesium alkylidene carbenoids (**13**) are reactive intermediates produced from isopropyl magnesium chloride and 1-chlorovinyl *p*-tolyl sulfoxides. These 1-chlorovinyl *p*-tolyl sulfoxides are synthesized from carbonyl compounds and chloromethyl *p*-tolyl sulfoxide through a sulfoxide/magnesium exchange reaction. Several alkyne products (**14**) were synthesized in good to excellent yield using this method.

There is no significant difference in reactivity between the geometric isomers of 2-alkynyl-2-phenyl-substituted sulfoxide (**11**, R^1 & R^2 = aryl and alkynyl). However, 2-methyl-substituted sulfoxides (**11**, R^1 & R^2 = aryl and methyl) show reactivity differences between their isomers. The (*Z*)-sulfoxides (**11**, R^1 = aryl and R^2 = methyl) with methyl and chloro-groups *trans* to each other produce alkynes with low efficiency. As the migratory aptitude (aryl, alkynyl ≫ alkyl) matches carbanion stability trends, the FBW rearrangement of magnesium alkylidene carbenoids (**13**) appears to be an anionotropic rearrangement. The *trans* geometry of the chloro-group and the migrating substituent is crucial for a successful 1,2-rearrangement, explaining the observed reactivity differences in geometric isomers of 2-methyl-substituted sulfoxides (**11**, R^1 and R^2 = aryl and methyl, respectively).

Sun *et al.* discovered a modular method for synthesizing alkynes **20** by reacting carboxylic esters **16** with lithiated *gem*-diborylalkanes **15′** and aryl triflimides **18** (Scheme 4).[20] The process involves forming an intermediate α-boryl lithium enolate **17**, which is then triflated using triflimide **18** to a borylated vinyl triflate intermediate **19** and subsequently quenched with water to yield the alkyne product **20**. This innovative approach allows for the efficient conversion of various aliphatic and aromatic carboxylic acid esters (**16**) into both internal and terminal alkyne products (**20**) in a short reaction period. The



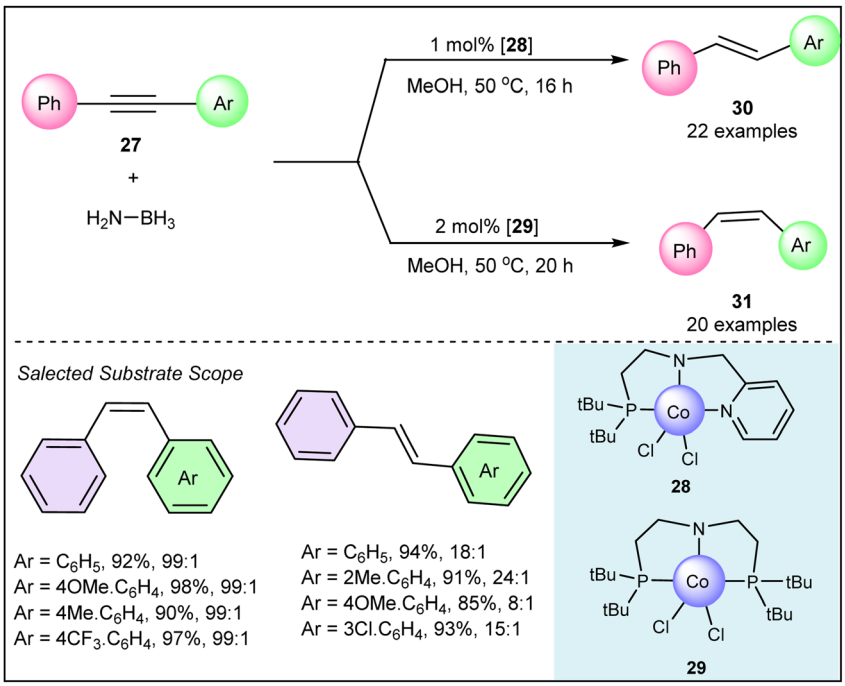
Scheme 5 P450 catalyzed dehydrogenation of 4-hydroxy-3-prenylbenzoic acid to eutypinic acid.

process accommodates a broad spectrum of functional groups, including halides, amides, amines, carbamate, –OMe, and –CF_3, positioned on both esters (**16**) and *gem*-diborylalkane (**15**) substrates. Additionally, it enables the transformation of chiral α-substituted esters into chiral propargyl compounds without causing racemization.

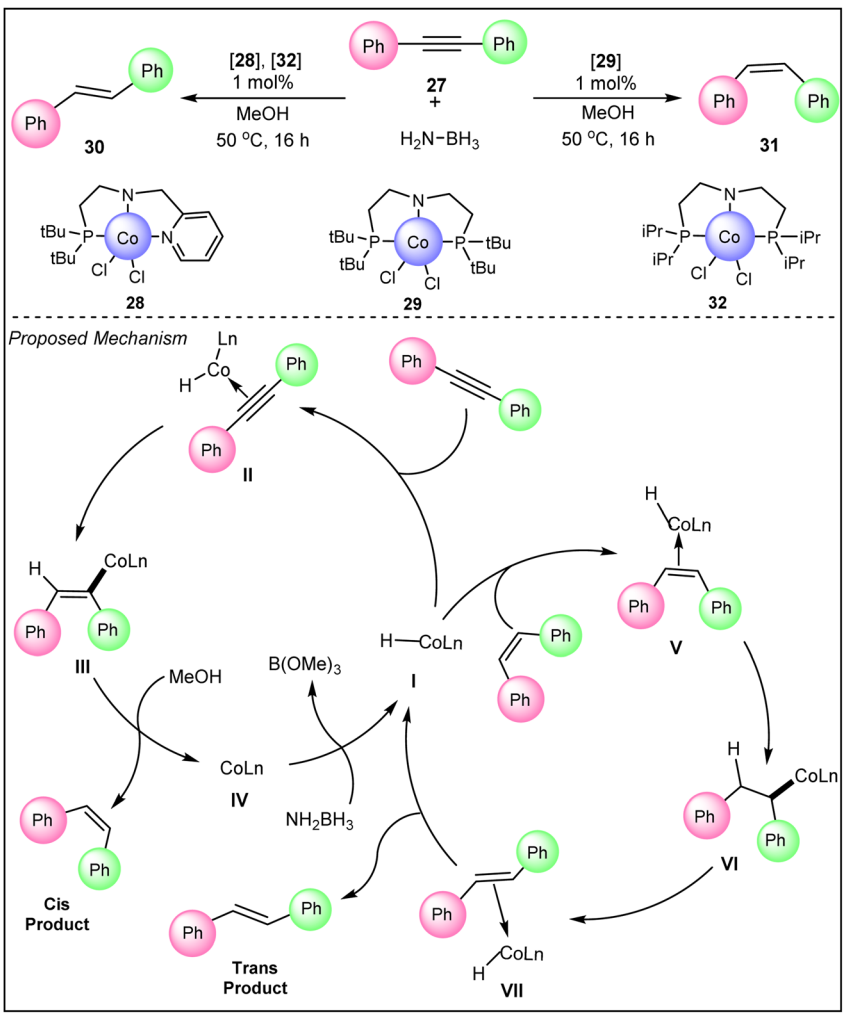
On the other hand, Chen *et al.* discovered a dual-function Cytochrome P450 monooxygenase involved in cyclohexanoid terpenoid biosynthesis that facilitates enyne formation from a prenyl chain.[21] Initially, this P450 enzyme catalyzes the dehydrogenation of the prenyl chain (**21**) to produce a *cis*-diene intermediate **24.** Subsequently, the enzyme functions as an acetylenase, forming an alkyne group, resulting in the synthesis of a 1,3-enyne (**26**). Microsome extracts from *Saccharomyces cerevisiae* expressing the *AtyI* gene were prepared and incubated with 4-hydroxy-3-prenylbenzoic acid (**21**) and NADPH, which led to the production of eutypinic acid (**26**). These findings demonstrate that *AtyI* catalyzes four-electron oxidation and is the key enzyme responsible for incorporating the enyne group. Similarly, the Gao group reported the creation of an alkyne moiety using a novel cytochrome P450 enzyme named *BisI*.[22] This enzyme exhibits versatile activity toward both C5 and C15 prenyl chains, following a similar reaction pathway demonstrated in Scheme 5.

3. Stereo-divergent functionalization of alkynes

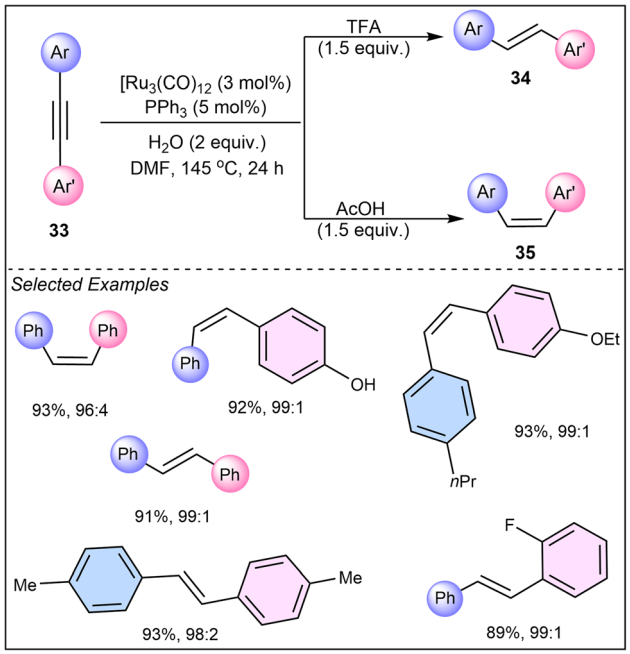
A broad spectrum of functionalized alkenes and alkanes has been synthesized through the stereo-divergent functionalization of alkynes. Among these reactions, semi-hydrogenation and hydrosilylation of alkynes are the most extensively studied. In this review, we categorize and analyze these methodologies based on the type of functionalization achieved with alkynes, providing a comprehensive understanding of the processes involved.



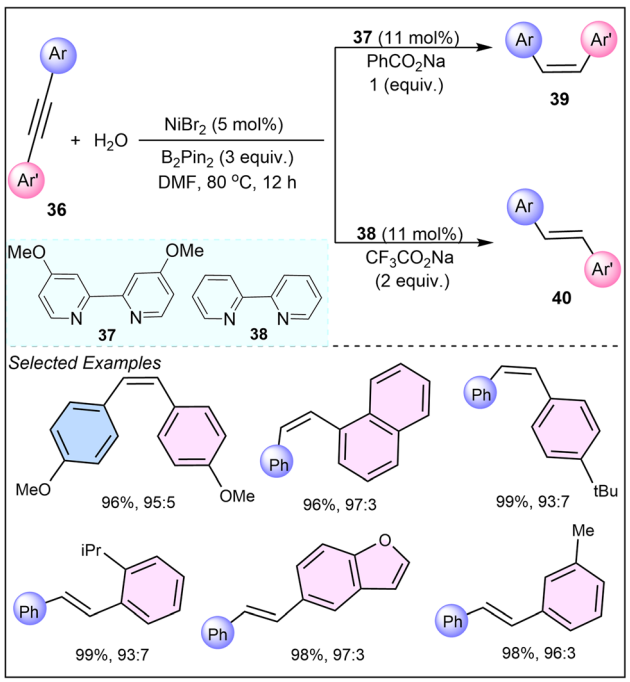
Scheme 6 Cobalt-catalyzed transfer hydrogenation of alkynes, with methanol serving as the hydrogen source.



Scheme 7 Cobalt-catalyzed semi-hydrogenation of alkynes using NNP- and PNP-type pincer ligands.



Scheme 8 Ruthenium-catalyzed semi-hydrogenation of diaryl alkynes using DMF and water as the hydrogen source.



Scheme 9 Ni-catalyzed semi-hydrogenation with water as a hydrogen source.

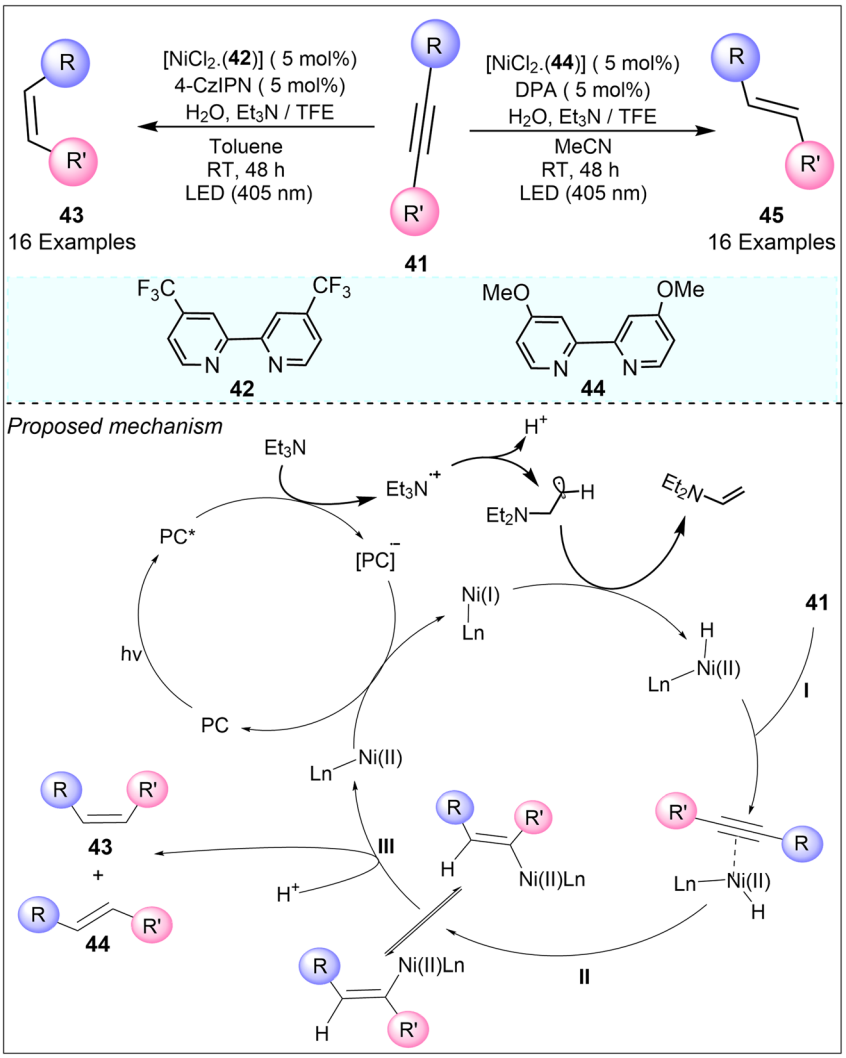
3.1 Stereo-divergent hydrogenation

Stereodivergent semi-hydrogenation of alkynes has emerged as a transformative process in modern organic chemistry, enabling the selective synthesis of *E*- or *Z*-alkenes as valuable intermediates for pharmaceuticals, agrochemicals, and other fine chemicals.[23–25] Recent advances in catalytic systems, particularly those involving transition metals such as nickel, cobalt, ruthenium, palladium, and chromium, have significantly improved our ability to control stereoselectivity under mild and environmentally friendly conditions.[26–31] Here, the authors, consolidate findings from recent studies that illustrate the latest developments and mechanistic insights in this field, providing a thorough overview of the strategies employed to achieve stereo-divergent semi-hydrogenation of alkynes.

In 2016, one of the cornerstone studies in this area focuses on cobalt-catalyzed semi-hydrogenation using NNP and PNP-type pincer ligands. In this work, Fu *et al.* reported the cobalt-catalyzed transfer hydrogenation of alkynes (**27**), with methanol serving as the hydrogen source. The system achieves effective stereocontrol through carefully designed catalysts **28** and **29** to afford the *trans*-alkene (**30**) and *cis*-alkene (**31**) products, respectively (Scheme 6).[32] Operating under mild conditions, the reaction tolerates a wide variety of functional groups and provides good yields with catalyst loadings as low as 0.2 mol%. The broad applicability of this method is demonstrated by the successful synthesis of over 50 alkenes with high chemo- and stereoselectivity. The findings highlight the potential of methanol as a sustainable hydrogen source in semi-hydrogenation reactions and demonstrate cobalt's versatility in catalytic transformations.

The underlying mechanisms of selectivity control were evaluated by combined density functional theory (DFT) calculations with experimental validation (Scheme 7).[33] They discovered that cobalt(I) hydride intermediates play a pivotal role in steering the reaction towards either *E*- or *Z*-alkenes, depending on the reaction conditions. Both pre-catalysts (**28**) and (**32**) predominantly yield the *E*-alkene (**30**) as the main product during the semi-hydrogenation of alkynes with ammonia boranes. However, the stereoselectivity of the reaction shifts when the isopropyl group in pre-catalyst (**32**) is replaced by a bulkier tertiary butyl group (**29**), favoring the formation of the *Z*-alkene (**31**). The catalytic cycle begins with the insertion of the alkyne into the Co–H bond, followed by protonation of the resulting stilbenyl cobalt(I) intermediate to produce *Z*-stilbene. Regeneration of the active cobalt catalyst occurs in the presence of ammonia borane and methanol. *Z*-stilbene undergoes further transformation, with cobalt-catalyzed β-hydride elimination leading to the final *E*-stilbene product. This alteration in stereoselectivity suggests that the steric hindrance introduced by the larger substituent plays a crucial role in controlling the product outcome, potentially influencing the transition state or intermediate stability during the catalytic cycle. The suppression of unwanted over-reduction to alkanes was achieved by controlling the methanol-mediated protonation steps, offering a robust strategy for designing more selective catalysts.

In 2011, Li and Hua presented a distinct approach in their work on ruthenium-catalyzed semi-hydrogenation of functionalized diaryl alkynes (**33**) using DMF and water as the hydrogen source, where the choice of acid (acetic acid or trifluoroacetic acid) significantly impacts the stereoselectivity, yielding either *cis*- or *trans*-stilbenes.[34] The selectivity of the reaction was controlled by the choice of additives, with trifluoroacetic acid

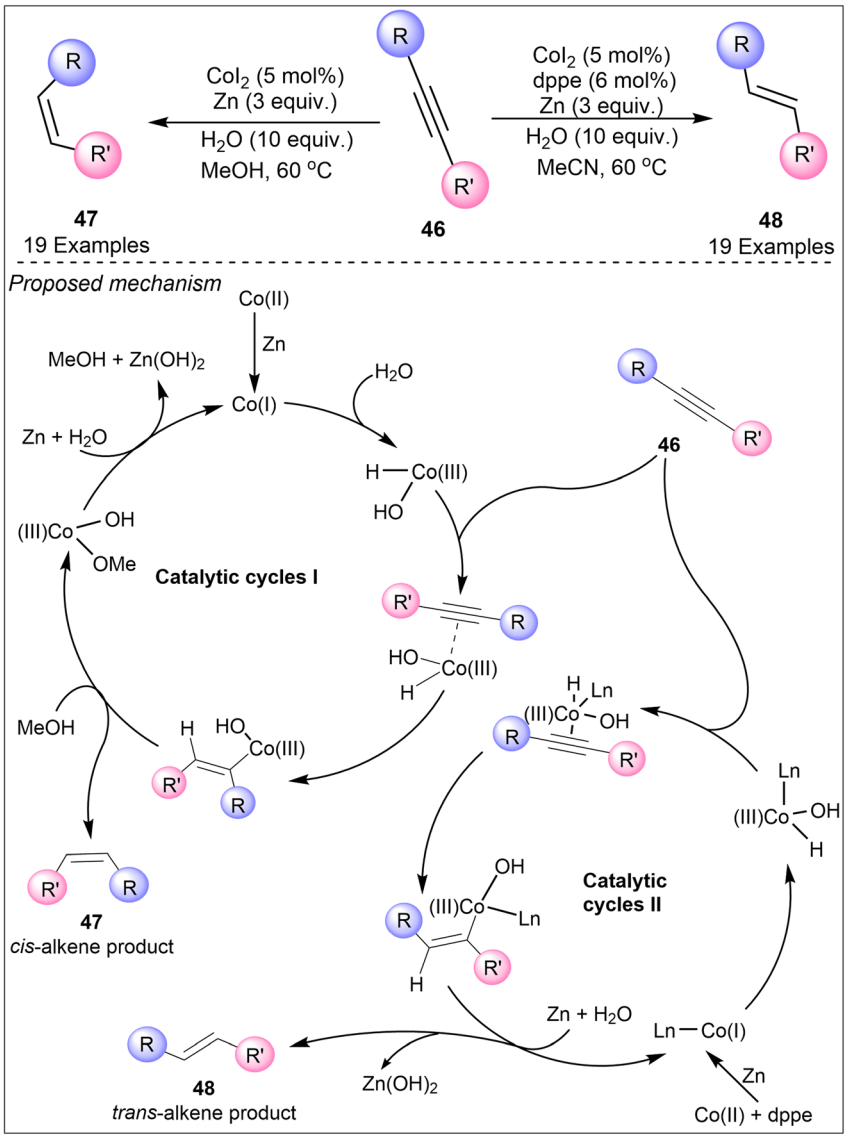


Scheme 10 Stereodivergent hydrogenation through a photoinduced nickel hydride catalysis.

(TFA) leading to the *E*-isomer (**34**) and acetic acid (HOAc) favoring the *Z*-isomer (**35**) (Scheme 8). This research underscores the importance of simple additives in fine-tuning the reaction pathway and achieving the desired product configuration, thus providing a straightforward yet powerful tool for chemists.

In 2021 Wu *et al.* presented an innovative approach involving Ni-catalyzed semi-hydrogenation of alkyne (**36**), with water as a hydrogen source (Scheme 9).[35] By carefully modulating the metal species during the early stages of the reaction, the researchers demonstrated precise control over the stereoselectivity of the resulting alkenes. Unlike many previous reactions where *E*-alkenes are generated *via* isomerization of *Z*-alkenes, this method achieves stereoselectivity through parallel catalytic pathways, forming the isomers independently. Mechanistic studies indicate that the choice of base plays a pivotal role in modulating the reaction pathways. By introducing different bases, nickel species in distinct valence states can be accessed, initiating two separate catalytic cycles that selectively lead to either the *E*- or *Z*-isomers. Ph_2CONa base selectively yields *Z*-isomer (**39**) in the presence of ligand (**37**) whereas CF_3CONa base, along with ligand (**38**), yields *E*-alkene (**40**). This strategy has been successfully applied to nearly 70 substrates, including internal and terminal alkynes, enynes, and diynes, producing semi-hydrogenated products with high yields and selectivity. This study stands out for its commitment to sustainability, highlighting the potential of using water—a green and non-toxic hydrogen donor—as a viable alternative to traditional reductants.

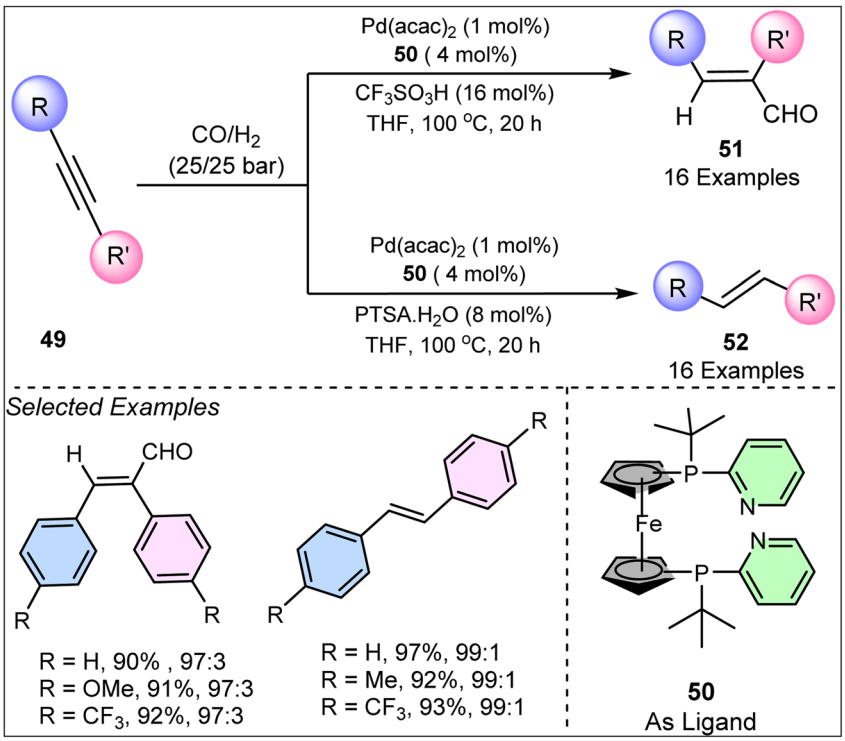
In 2023, Hu *et al.* further expanded the toolkit, exploring a photoinduced dual-catalytic system combining nickel hydride catalysis with photoredox catalysis for stereodivergent hydrogenation of alkyne **41** (Scheme 10).[36] Utilizing the dual catalytic system, the methodology offers a versatile strategy for controlling stereoselectivity between alkene products **43** and **45** with triethylamine acting as a sacrificial reductant and a source of hydrogen atoms. This system operates under mild conditions and relies on the pK_a of alcohol additives to control the stereoselectivity. This approach reduces the need for external hydrogen sources and represents a versatile, green chemistry



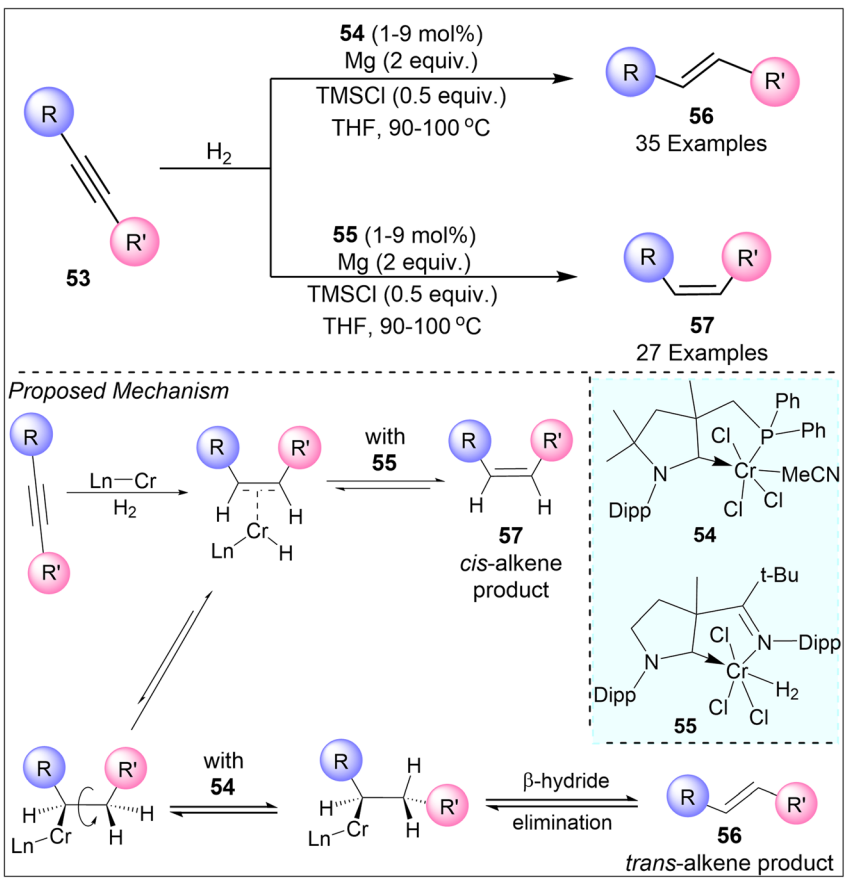
Scheme 11 Anion-controlled semi-hydrogenation through cobalt-catalysis using water/MeOH as the H-source.

method that could be scaled up for industrial applications. The mechanistic pathway involves several key steps: the photo-induced formation of a nickel hydride species followed by *syn*-hydro-nickelization of alkyne I, and subsequent alkenyl-nickel isomerization II. Unlike many traditional methods where stereoselectivity is achieved through post-reduction photoisomerization, this process controls stereochemistry at an earlier stage. The final stereoselective outcome is determined by the rate of protonolysis step III, which can be modulated by varying the pK_a of the alcohol additive used. It provides a practical, efficient means for achieving high stereoselectivity without relying on secondary photoisomerization processes.

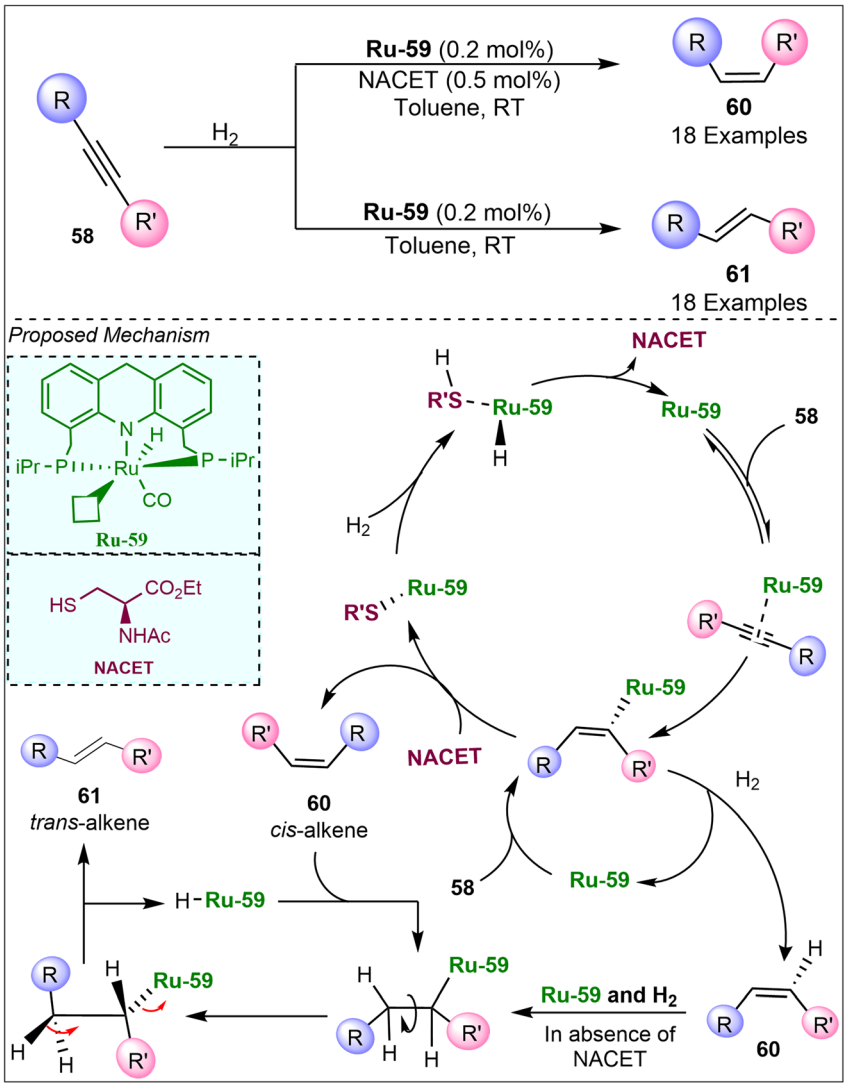
Another notable study on anion-controlled semi-hydrogenation features a cobalt-catalyzed method using water/methanol as the hydrogen source. In 2019, Li *et al.* demonstrated how varying the solvent or including bidentate phosphine ligand dppe can steer the reaction towards either *E*- or *Z*-alkenes (Scheme 11).[37] In the presence of CoI_2 catalyst, reductant zinc, water, and methanol, the internal alkyne substrates (**46**) were converted into *Z*-alkenes (**47**). The addition of the dppe ligand in this reaction leads to stereoselective formation of *E*-alkenes (**48**). The developed methodology was applicable to an array of internal alkynes. This method showcases the potential of using inexpensive and readily available base metals in achieving sustainable and selective hydrogenation reactions. The plausible mechanism for the formation of both isomers was supported by different catalytic cycles. Cobalt catalyst was first reduced by Zn, which then coordinates with water to form a complex. This complex binds with the alkyne substrate which becomes protonated by methanol and leads to the formation of *Z*-alkene (**47**) (catalytic cycle I). The formation of *E*-alkene (**48**) follows another pathway (catalytic cycle II) as it includes the dppe ligand. In this, the cobalt catalyst gets reduced by Zn after combining with ligand dppe. The generated catalyst further



Scheme 12 Palladium catalyzed stereodivergent semi-hydrogenation.



Scheme 13 Chromium-catalyzed *E*- and *Z*-selective olefin synthesis through alkyne hydrogenation.

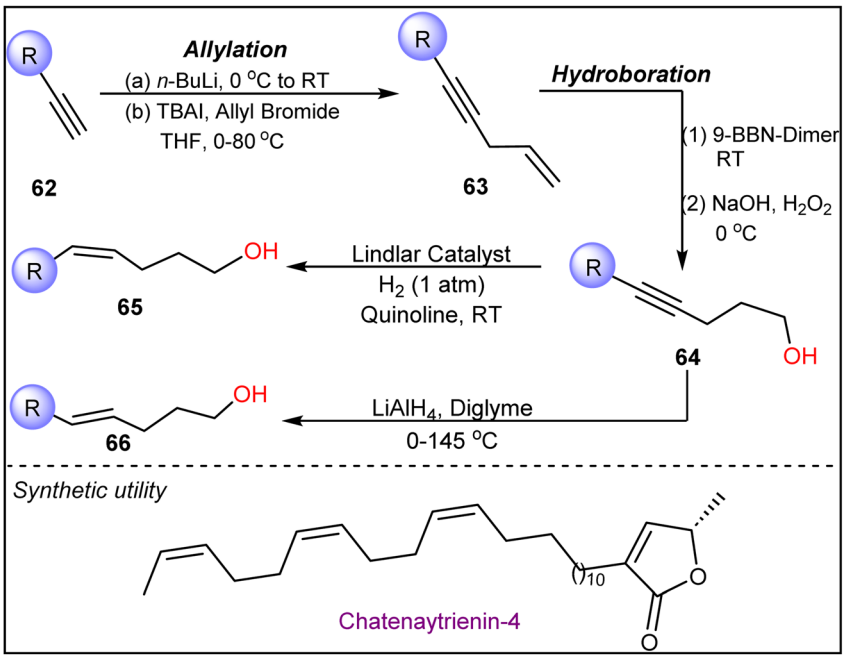


Scheme 14 Ruthenium catalyzed *E*- and *Z*-selective hydrogenation using catalytic thiol as a reversible inhibitor.

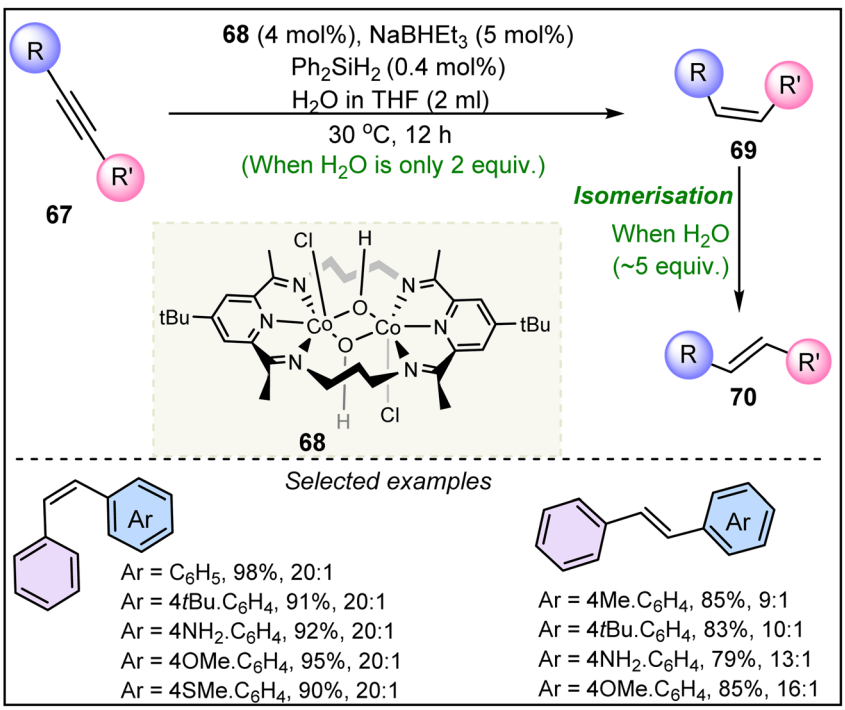
binds with the alkyne moiety and water molecules followed by the migratory insertion. To circumvent the steric repulsion caused by bulky dppe ligand, the resultant product was formed with the *anti*-selective stereoisomer **48**.

The field of stereodivergent semi-hydrogenation also benefits from innovations in palladium catalysis, where the interplay of ligands and acidic co-catalysts can direct the reaction toward either hydroformylation or semi-hydrogenation. In 2020, Liu *et al.* highlighted how specific ligand environments and co-catalyst choices can substantially influence reaction outcomes, allowing for a high degree of control over product formation.[38] This study introduces a palladium-catalyzed system designed for the chemo-divergent functionalization of alkynes **49** using syngas (Scheme 12). The key to this selectivity is an advanced ligand, **50**, featuring a 2-pyridyl substituent that acts as an internal base. Depending on the reaction conditions, this system allows for either hydroformylation or semi-hydrogenation of a broad range of alkynes with high chemo- and stereoselectivity. The reaction in the presence of CF_3SO_3H demonstrated *syn*-hydroformylation of substrate **49** to afford the alkene products **51**. Meanwhile, PTSA·H_2O shows simple anti-semi-hydrogenation of **49** to result in *E*-alkenes (**52**) as products. Mechanistic investigations, including density functional theory (DFT) calculations, kinetic studies, and control experiments, revealed that the strength and concentration of acidic cocatalysts are critical factors in determining chemoselectivity. The DFT analysis showed that ligand **50** plays a dual role: it facilitates heterolytic hydrogen activation, similar to frustrated Lewis pair (FLP) systems, during the hydrogenolysis step in hydroformylation, while simultaneously preventing CO coordination under strong acidic conditions to promote semi-hydrogenation. This work provides new strategies for palladium-catalyzed transformations and opens up avenues for further catalyst development.

Chromium catalysts have also proven effective in stereodivergent hydrogenation, particularly those employing cyclic (alkyl)(amino)carbene ligands. In, 2023 Ling *et al.* presented a chromium-catalyzed system for *E*- and *Z*-selective olefin

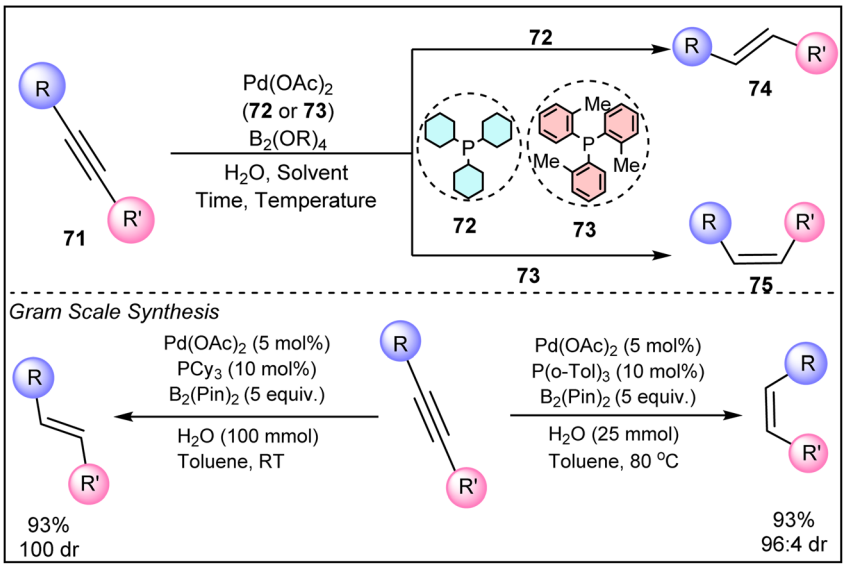


Scheme 15 Iterative and stereodivergent approach for synthesizing unbranched polyenes from polyynes.

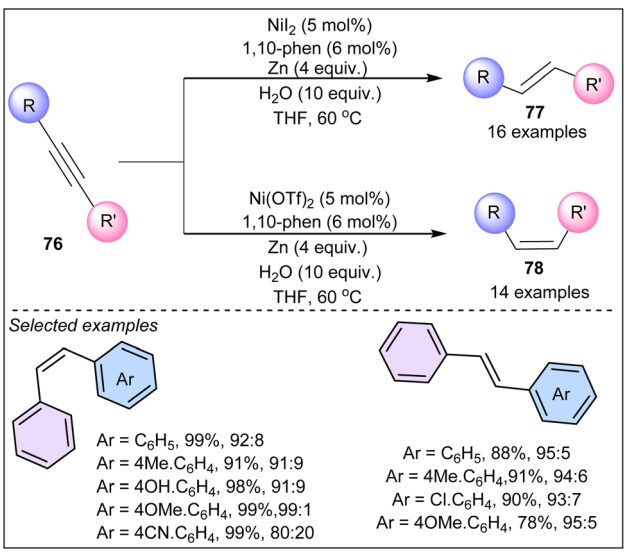


Scheme 16 Bis-pyridyl diamine (PDI) di-Co(III) complex catalyzed semi-hydrogenation of alkynes.

synthesis through hydrogenation of alkyne (**53**) that demonstrates the critical role of carbene ligands design in determining reaction selectivity (Scheme 13).[39] Using a cyclic (alkyl)(amino) carbene ligand with a phosphine anchor **54**, the hydrogenation proceeds *via* a *trans* addition, yielding *E*-olefins (**56**) with high selectivity. In contrast, switching to a carbene ligand containing an imino anchor **55** enables the stereoselective formation of predominantly *Z*-isomers (**57**). This ligand-driven stereo inversion strategy allows for selective control over *E* and *Z* geometry using a single metal catalyst, overcoming the typical requirement of employing different metals for each isomer. Their work contributes valuable insights into the mechanistic pathways



Scheme 17 Palladium-catalyzed system for *Z*/*E* stereodivergent olefin synthesis from alkynes.



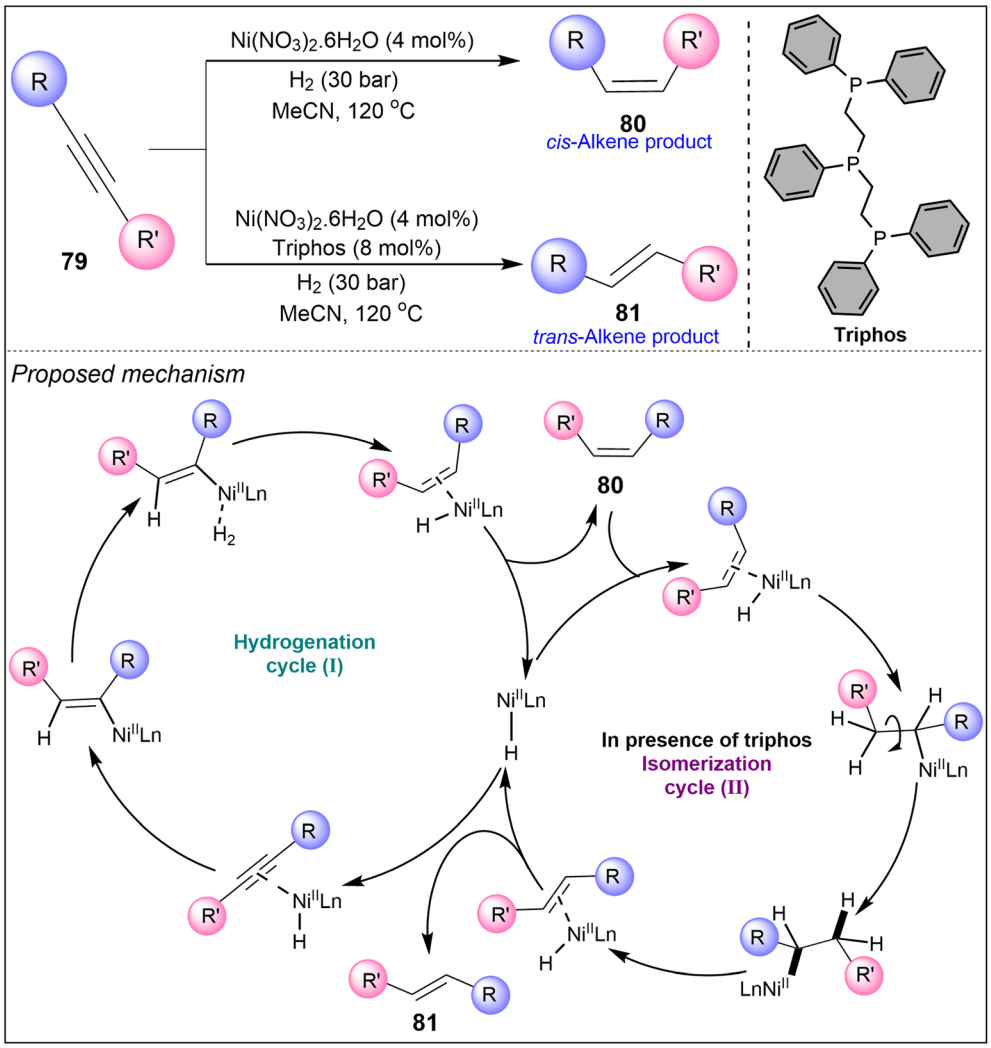
Scheme 18 Nickel-catalyzed ligand guided stereoselective hydrogenation.

involved in metal-catalyzed hydrogenation, laying the groundwork for future advancements in catalyst design.

An intriguing study on reversible catalyst inhibition using ruthenium introduces a novel strategy to switch between *E*- and *Z*-selectivity in the hydrogenation of alkyne **58**. In 2022, Luo *et al.* showed that a catalytic thiol can act as a reversible inhibitor, allowing for fine-tuning of the product configuration of a ruthenium (Ru-59) catalyzed semi-hydrogenation process by simply adjusting the inhibitor's concentration (Scheme 14).[40] Mechanistic investigations revealed that the *Z*-alkene (**60**) serves as an intermediate in the formation of the *E*-alkene (**61**). The addition of a catalytic amount of bidentate thiol (NACET) effectively blocks the *Z*/*E* isomerization step by forming stable ruthenium-thiol(ate) complexes, while still permitting the primary hydrogenation to proceed. As a result, the absence or presence of the catalytic thiol dictates the stereoselectivity of the reaction: the reaction proceeds to the *E*-alkene **61** without the thiol, while the process halts at the *Z*-alkene **60** intermediate with the thiol present. This innovative approach offers a new dimension of control in stereodivergent hydrogenation chemistry.

An iterative and stereodivergent approach for synthesizing unbranched polyenes and polyynes was explored in the early study by Adrian and Stark in 2016, offering a method to achieve complete stereocontrol in the formation of both *E*- and *Z*-olefins from terminal alkynes **62** (Scheme 15).[41] The process involves a series of high-yielding C–C bond couplings, followed by stereospecific alkyne reductions. The synthetic cycle includes a C-3 chain extension to **63** *via* allylation, followed by chemoselective hydroboration to **64** and reduction of the alkyne. The geometric control of the double bonds is achieved through stereoselective alkyne reduction, using Lindlar hydrogenation for *Z*-alkenes **65** and aluminium hydride reduction for *E*-alkenes **66**. Notably, the total synthesis of membranacin (*Annonaceous* acetogenin) precursor chatenaytrienin-4 was achieved without the need for protecting groups, showcasing the methodology's efficiency. Furthermore, this approach has significant implications for the synthesis of complex natural products, highlighting its versatility and practicality in organic synthesis.

In 2021, Chen *et al.* demonstrated the catalytic efficiency of a bis-pyridyl diamine (PDI) di-Co(III) complex **68** for the semi-hydrogenation of alkynes **67** (Scheme 16).[42] The system employs Ph_2SiH_2 and H_2O as hydride sources and is able to switch stereoselectivity between *E*- and *Z*-alkenes by modulating the water concentration. This stereodivergent system was highly tolerant to various functional groups, making it a robust and versatile tool for alkyne reduction. The ability to fine-tune the reaction conditions to achieve the desired stereochemistry



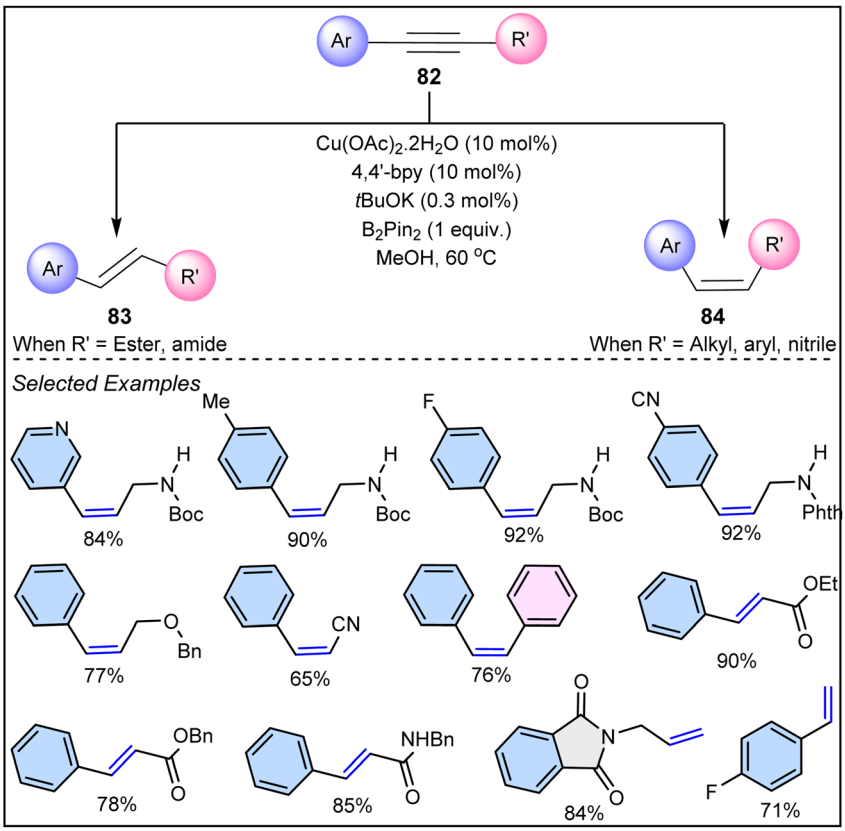
Scheme 19 Ni(II)-catalyzed hydrogenation of alkynes to *E*- and *Z*-alkenes.

marks a significant advancement in stereoselective alkyne transformations. In the presence of about 2 equivalents of H_2O, the reaction affords the *Z*-alkene product (**69**), whereas 5 equivalents of H_2O lead to the isomerized product, *E*-alkene (**70**).

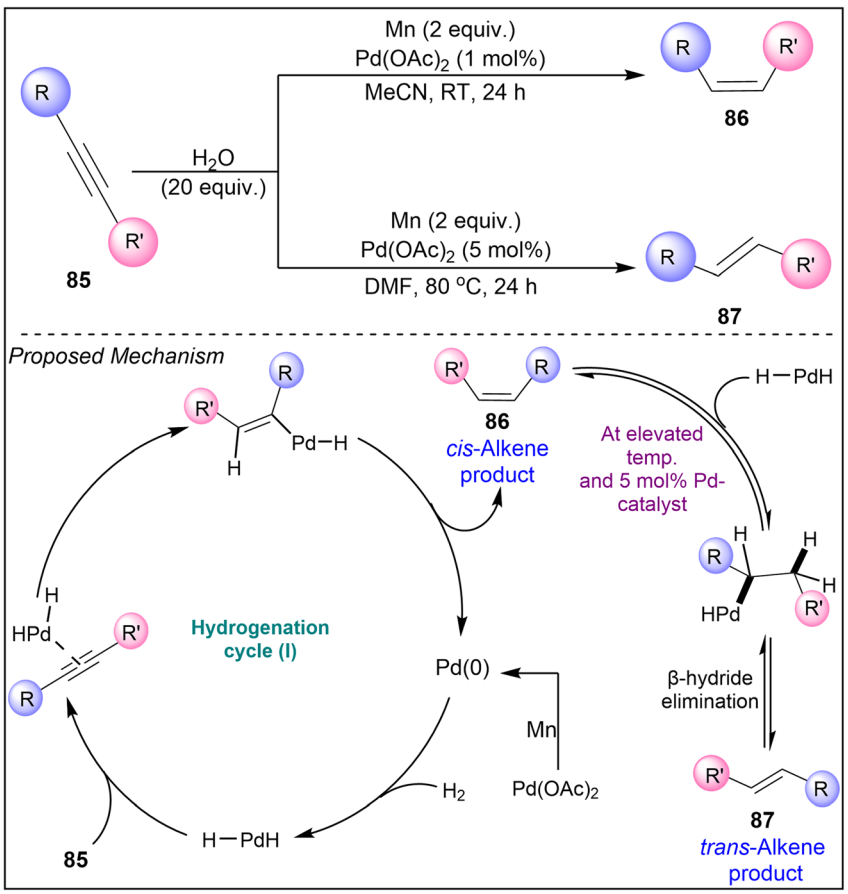
In 2018, Rao and Prabhu successfully detailed a palladium-catalyzed system for *Z*/*E* stereodivergent olefin synthesis from alkyne (**71**). The process utilizes H_2O as the hydrogen source, with diboron compounds as mediators (Scheme 17).[43] The choice of ligands, such as PCy_3 (**72**) for *E*-olefins (**74**) and P(*o*-Tol)$_3$ (**73**) for *Z*-olefins (**75**), plays a crucial role in governing the reaction's stereoselectivity. Additionally, deuterium oxide (D_2O) can be used in place of water to produce deuterated alkenes, broadening the utility of this method. Their method demonstrates excellent scalability, enabling the production of stereo-defined olefins in high yields.

In 2021, Li *et al.* published a ligand-guided stereoselective semi-hydrogenation of alkynes (**76**), focusing on how different ligands direct the formation of *Z*- or *E*-olefins. The process utilizes cost-effective and stable nickel(II)-salts, with water serving as a sustainable hydrogen source and zinc powder as a reductant (Scheme 18).[44] Remarkably, the stereoselectivity—whether producing *trans*-alkenes (**77**) or *cis*-alkenes (**78**)—is dictated by the specific anion in the nickel salt. This approach was particularly effective for internal alkynes, demonstrating high yields across various substrates, including those with sensitive functional groups such as carbonyls. The role of ligand design in controlling stereochemistry is a significant aspect of this work, providing insights for future applications in catalytic hydrogenation.

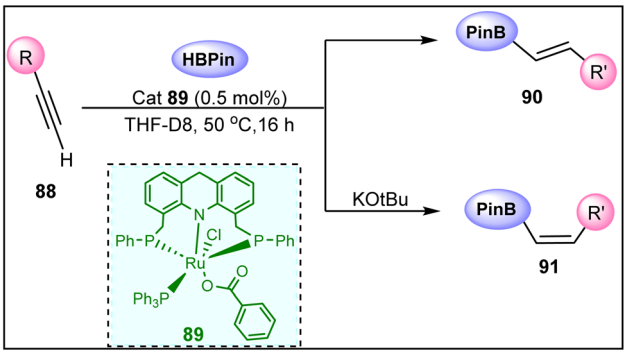
In 2019, Murugesan *et al.* developed yet another methodology using Ni(II)-catalyzed hydrogenation of alkynes **79** to *E*- and *Z*-alkenes. The study outlines a two-step process, where *Z*-alkenes **80** initially form, followed by isomerization to *E*-alkenes **81** (Scheme 19).[45] $Ni(NO_3)_2 \cdot 6H_2O$ used as a catalyst precursor forms active nanoparticles that exhibit excellent selectivity for *Z*-isomer **80** (*Z*/*E* > 99 : 1). By incorporating multidentate ligands such as triphos or tetraphos, the system becomes *E*-selective for alkene **81** (*E*/*Z* > 99 : 1). Mechanistic insights suggest that the catalyst favouring *Z*-alkene formation operates *via*



Scheme 20 $Cu(OAc)_2$ and nitrogen-based ligand catalyzed semi-hydrogenation of alkynes.



Scheme 21 Pd-assisted semi-hydrogenation utilizing water as the hydrogen source and Mn as an electron donor.

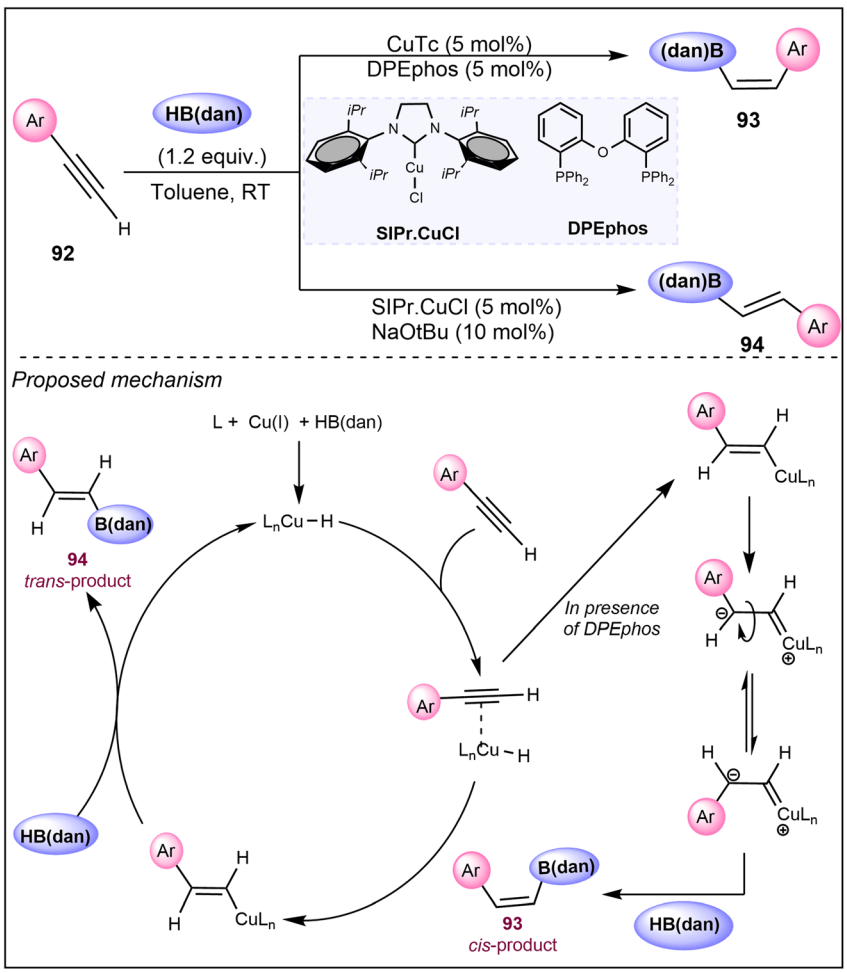


Scheme 22 Ruthenium-catalyzed system that enables the hydroboration of alkynes.

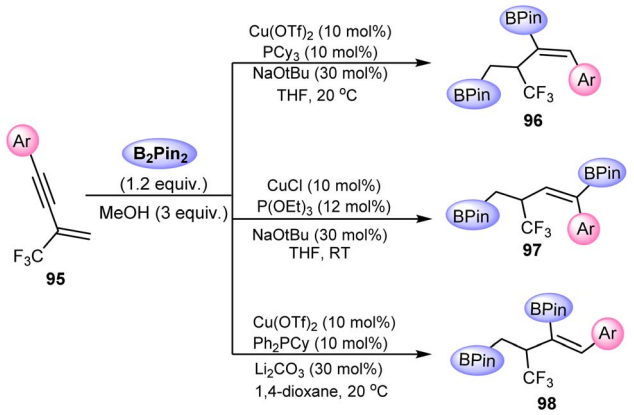
a heterogeneous pathway, while the *E*-selective catalyst follows a homogeneous process. In the latter case, alkyne **79** is initially reduced to *Z*-alkene **80** (Scheme 19, cycle I), which subsequently undergoes isomerization to form *E*-alkene **81** (Scheme 19, cycle II). Their findings offer a deeper understanding of nickel–hydride complexes and their role in chemoselective hydrogenation. This technique was successfully applied to over 40 substrates and scaled up for multigram synthesis, showcasing its versatility and practicality for larger-scale applications. Their work contributed valuable knowledge to the field of nickel catalysis, enhancing the development of new catalytic systems for stereoselective alkyne transformations.

Additionally, Huang *et al.* reported a novel methodology for *Z*-selective semi-hydrogenation of alkynes **82**, employing $Cu(OAc)_2$ and nitrogen-based ligands like 4,4′-bipyridine (Scheme 20).[46] The method is highly effective, offering high yields and stereoselectivity across a broad range of substrates, whether with internal or external alkynes. The optimization of reaction conditions and expanded substrate scope highlight the utility of this approach in producing *Z*-alkenes **84** with high precision. However, *E*-isomers **83** were formed predominately in place of *Z*-isomers when substrates of internal alkynes bearing carboxylate or amide functionality were taken. This work underscores the importance of copper catalysis in achieving stereoselectivity in semi-hydrogenation reactions.

In 2019, Zhao *et al.* reported a Pd-assisted semi-hydrogenation of alkynes **85** utilizing water as a hydrogen source and Mn as an electron donor (Scheme 21).[47] The developed process was effective against a wider range of alkynes, selectively yielding *E*- or *Z*-alkenes in good yield. Initially, *Z*-alkenes **86** were formed under the developed reaction condition, which could isomerize



Scheme 23 Copper-catalyzed *E*-/*Z*-selective hydroboration of terminal and internal alkynes using HB(dan).

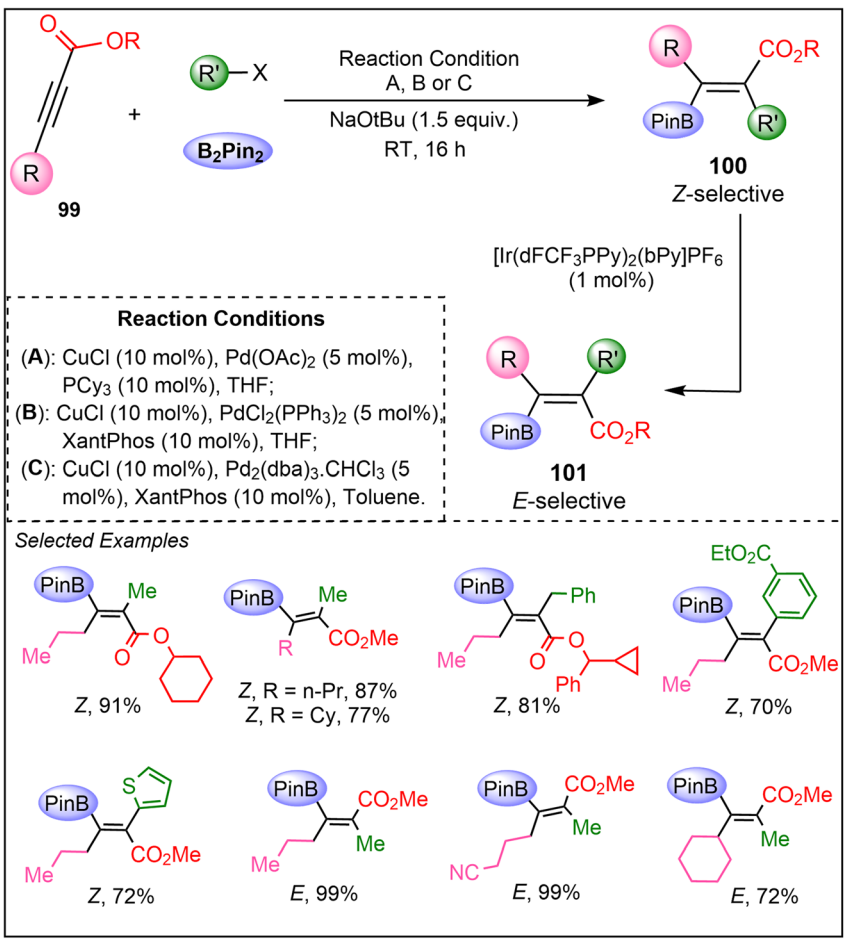


Scheme 24 Copper-catalyzed stereoselective diborylation of CF_3-containing 1,3-enynes.

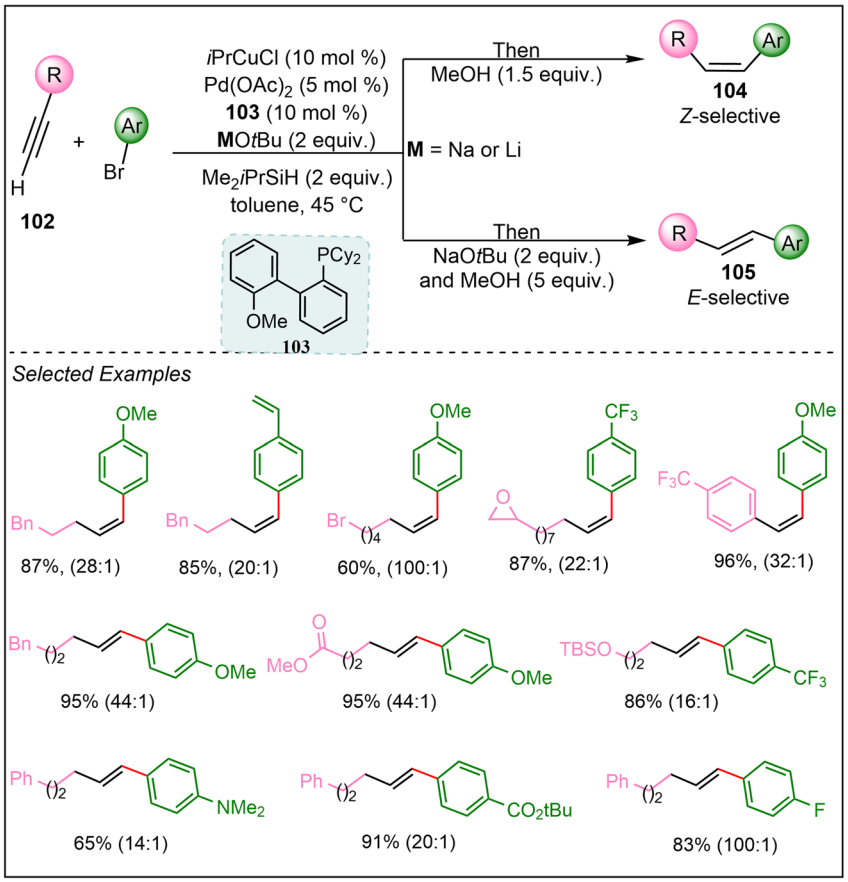
to *E*-alkenes **87** at elevated temperatures. In the proposed mechanistic insight, the Pd(0) catalyst plays a pivotal role to form palladium hydrides, engaging in an intricate interaction with water, enhanced by manganese (Mn). This dynamic process leads to the formation of molecular hydrogen through reductive elimination from the palladium. Once the palladium hydrides are generated, they eagerly combine with an alkyne, which leads to a migratory insertion. Further, the reductive elimination step releases *cis*-alkene **86**, while regenerating the versatile Pd(0) catalyst. At elevated temperatures, *cis*-alkene may continue to react with palladium hydride and could undergo β-hydride elimination, transforming it into *trans*-alkene **87**.

3.2 Stereo-divergent boration

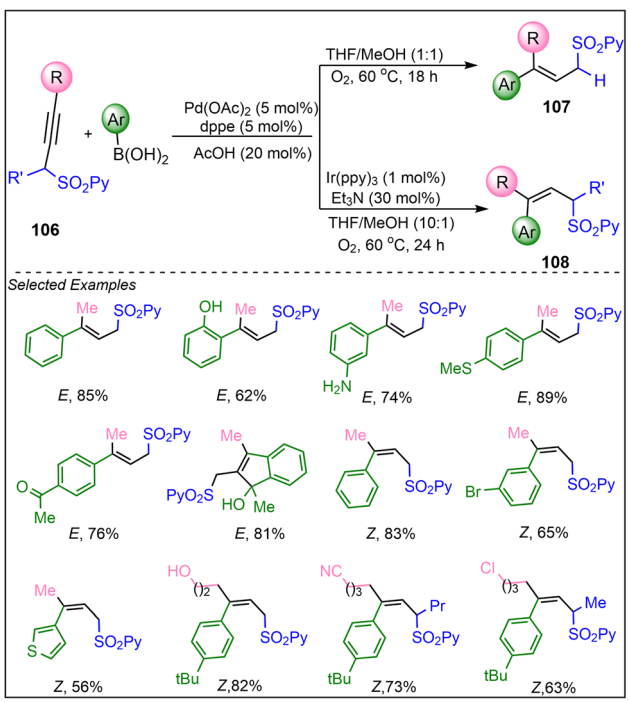
Tetrasubstituted olefins are important structural motifs in many organic compounds and play a crucial role as intermediates in synthetic chemistry.[48–50] The alkyne's hydroboration reaction is fundamental in synthetic chemistry, crucial for the construction of alkenyl boron substrates, which serve as key intermediates in synthesizing a diverse range of valuable chemicals. These compounds play a critical role in distinct sectors, particularly in pharmaceuticals and advanced materials.[51–56] However, the development of versatile methods to achieve stereodivergent access to both *E*- and *Z*-isomers from a single precursor remains a significant challenge.[57,58] The development of stereodivergent hydroboration reactions has significantly transformed this domain, enabling the selective production of both *Z*- and *E*-alkenyl boron isomers from a single alkyne precursor. This ability to control stereochemistry



Scheme 25 Iterative dual metal (Cu, Ir) catalyzed stereoselective hydroboration of alkynes.



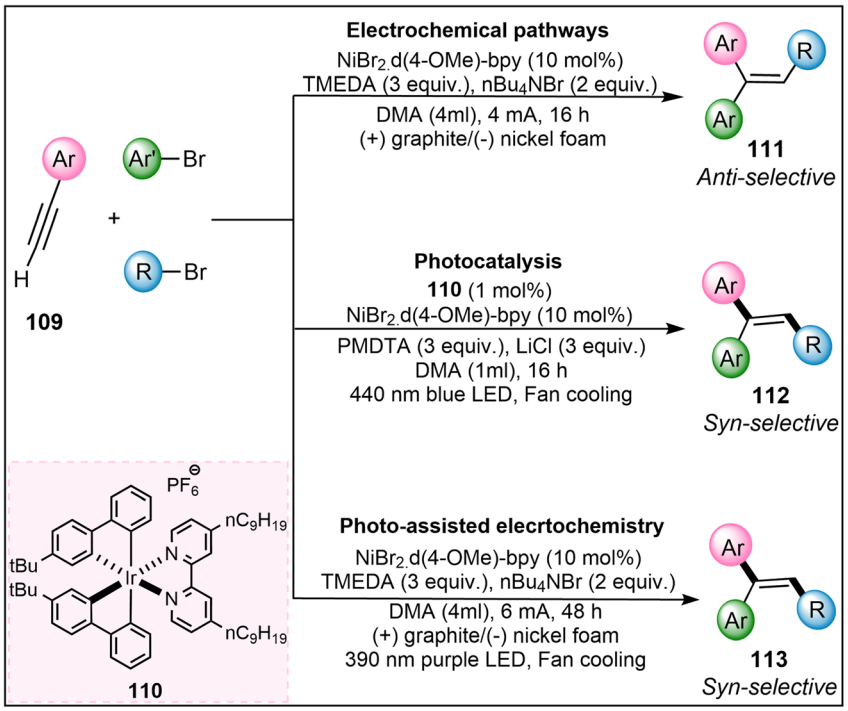
Scheme 26 Diastereodivergent hydroarylation of terminal alkynes *via* palladium and copper co-catalysis.



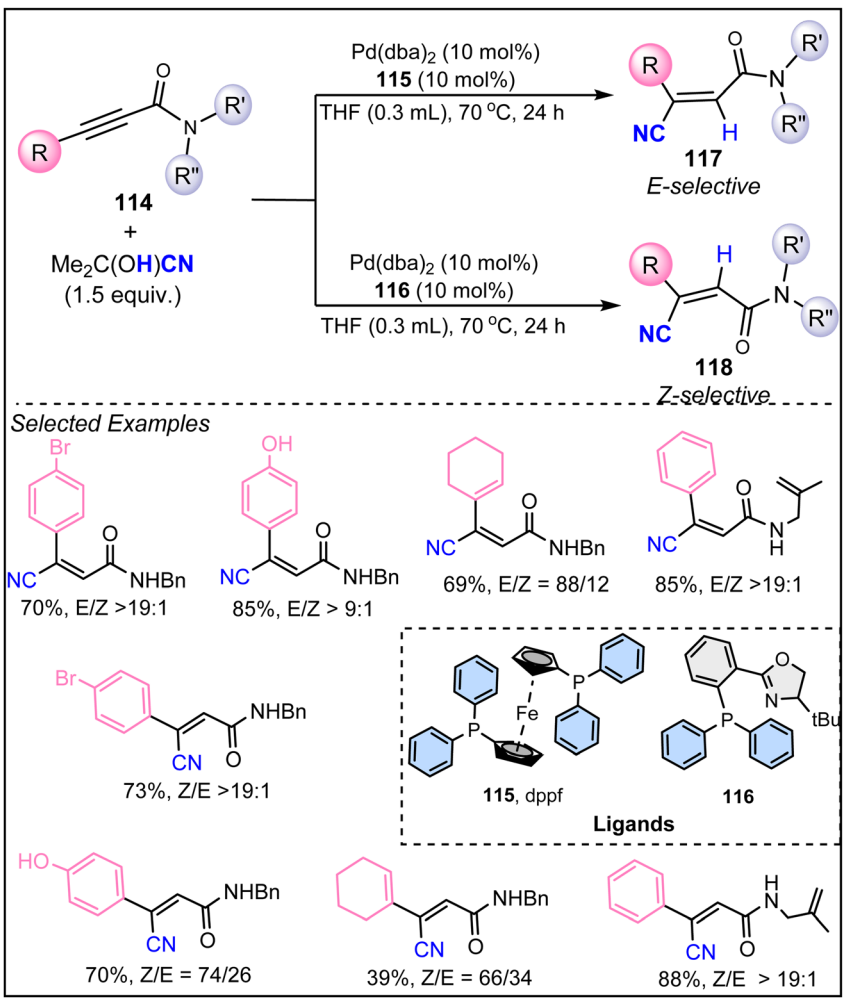
Scheme 27 Photocatalytic approach for regio- and stereocontrol hydroarylation of dialkyl alkynes.

expands the practical applications of hydroboration reactions and facilitates the design and production of complex substrates with highly specific stereochemical arrangements.[59,60] Recent advancements in stereodivergent hydroboration of alkynes have been significantly propelled by several key publications, each contributing a deeper understanding of this critical reaction.

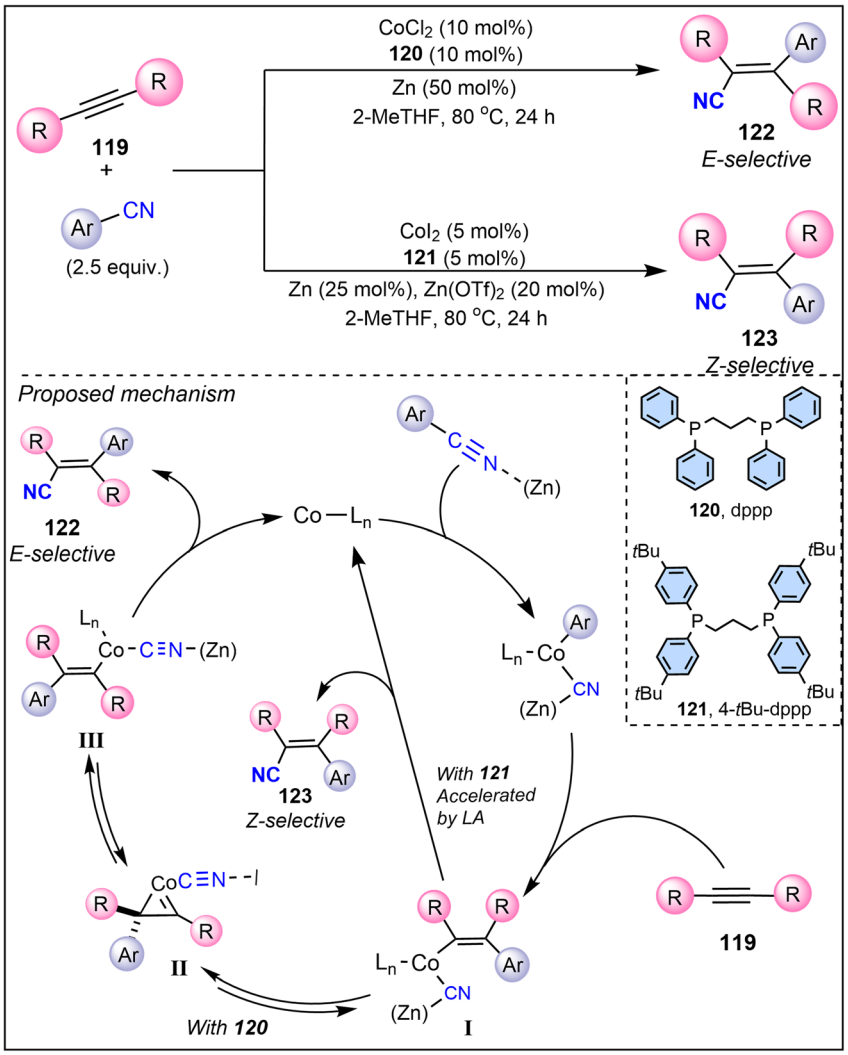
In this context, Lu (2012) reported a ruthenium-catalyzed system that enables hydroboration of alkynes (**88**) with excellent control over stereoselectivity (Scheme 22).[61] This method utilizes ruthenium acriphos complexes, which were systematically synthesized and evaluated for their catalytic properties. The key finding was the ability to selectively produce *E*- or *Z*-stereoisomers by modifying the ligands and reaction conditions. The potential for catalyzing stereodivergent hydroboration reactions using different activation methods with various Ru catalysts was explored. Complex **89** was highly effective in catalyzing the stereodivergent hydroboration of terminal alkynes **88**, selectively yielding *E*- or *Z*-configured products based on the activation approach. When treated with pinacolborane, complex **89** facilitates efficient hydroboration reactions, predominantly forming *E*-vinyl boranes **90**. However, the system switched to favour *Z*-selectivity **91** when activated with potassium *tert*-butoxide (KO*t*Bu). The developed ruthenium-based catalytic system shows a high degree of stereocontrol under mild reaction conditions and demonstrates compatibility with a variety of terminal alkynes carrying diverse



Scheme 28 Nickel-catalyzed arylalkylation of alkynes for the stereodivergent synthesis of trisubstituted olefins.



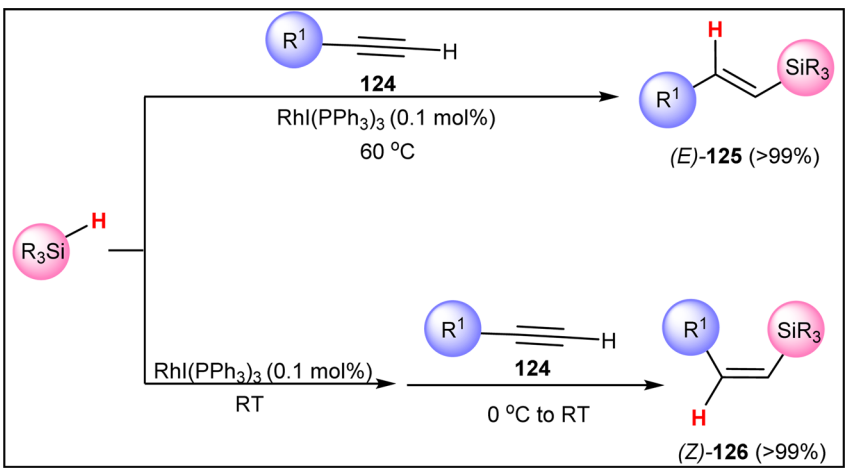
Scheme 29 Palladium-catalyzed stereodivergent hydrocyanation of alkynes.



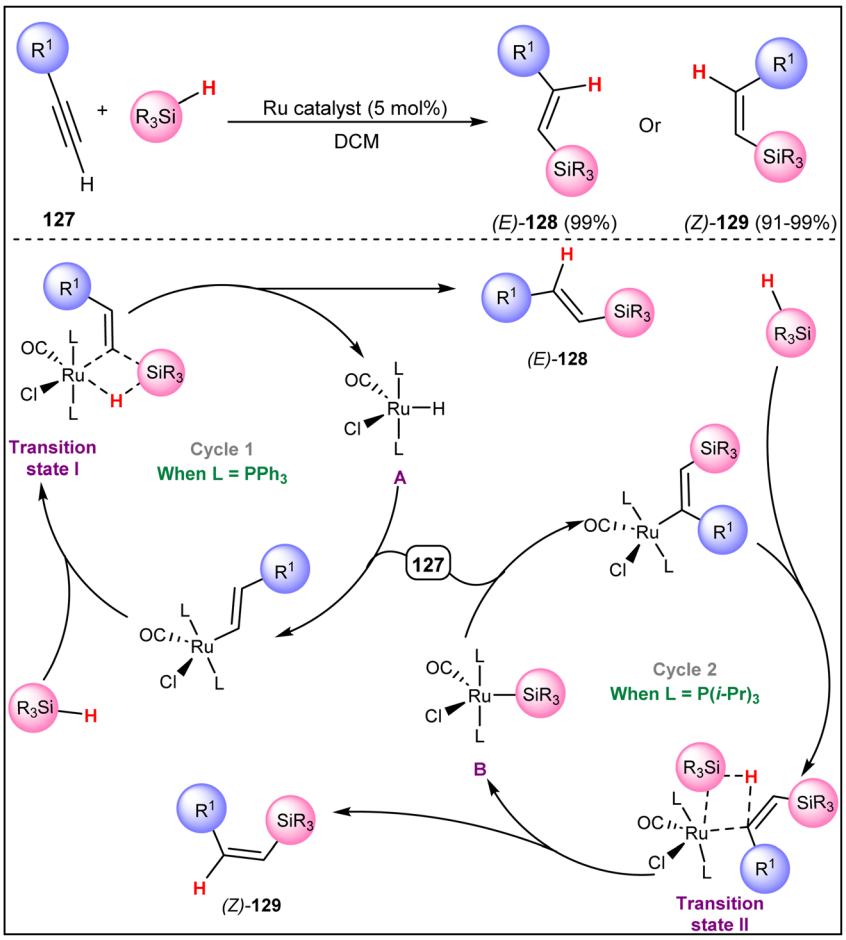
Scheme 30 Cobalt-catalyzed system for the arylcyanation of alkynes.

functional groups. The findings underscore the versatility of Ru-complex **89** in enabling efficient, stereodivergent hydroboration reactions by simply adjusting the activation method.

In another study, Jang *et al.* in 2016 contributed a versatile copper-catalyzed hydroboration method using 1,8-naphthalenediaminatoborane HB(dan) that is applicable to various



Scheme 31 Hydrosilylation of terminal alkynes using $RhI(PPh_3)_3$ catalyst for *Z*- and *E*-alkenylsilanes.

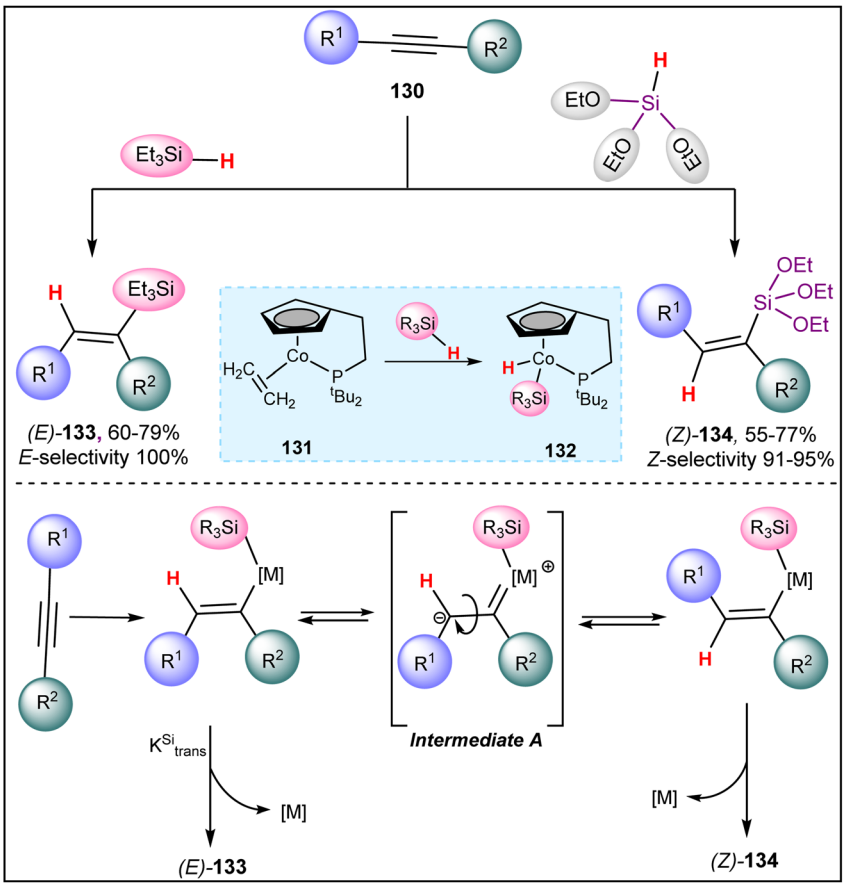


Scheme 32 Stereodivergent hydrosilylation of terminal alkynes utilizing $RuHCl(CO)(PPh_3)_3$ as the catalyst.

terminal and internal alkynes **92**, achieving high *E*/*Z* selectivity through meticulous optimization of ligands and solvents (Scheme 23).[62] In their process, Cu catalyst along with ligand DPEphos (bis[(2-diphenylphosphino)phenyl]ether) exclusively yields *Z*-stereoselective alkenyl borons **93**. On the other hand, employing an NHC–Cu complex SIPr–CuCl as a catalyst predominantly leads to *E*-hydroboration products **94** under mild conditions. The provided mechanistic details suggest that *in situ* generated copper–hydride intermediates are crucial for stereocontrol. The *Z*-selectivity was explained by HB(dan) favoring an intermediate conformation in which the phenyl group is positioned *cis* to the Cu center. This alignment minimizes steric clashes between the incoming dan group and the phenyl group during the σ-bond metathesis step. On the contrary, the bulky NHC–Cu complex discourages this specific intermediate orientation due to steric hindrance, leading to an *E*-stereochemical outcome **94**.

Another noticeable contribution was made by Kuang *et al.* in 2020, where a copper-catalyzed diborylation of CF_3-containing 1,3-enynes was developed (**95**), offering a novel approach for the selective formation of stereochemically defined alkenylboronates (Scheme 24).[63] This copper-catalyzed strategy utilizes the distinct reactivity of CF_3-enynes (**95**) to facilitate the regio- and stereoselective addition of boron. Cu catalyst in the presence of the ligand PCy_3, base sodium-*tert*-butoxide, methanol, and THF solvent at 20 °C selectively yields *Z*-isomeric product 1,3-diborylation (**96**). Meanwhile, 1,4-diboryl *Z*-selective product (**97**) is obtained if the ligand is interchanged with $P(OEt)_3$. Ligand Ph_2PCy along with base lithium carbonate and solvent 1,4-dioxane was used for the *E*-selective product (**98**). The study demonstrates that *E*- and *Z*-isomers could be produced with high selectivity by varying the ligands, bases, and solvents. This copper-catalyzed system enables diborylation without defluorination, expanding the substrate scope to include multi-borylated products. The method is significant for drug discovery and materials science, where trifluoromethylated compounds are highly sought after due to their unique electronic properties. Mechanistic insights into this process were obtained through deuterium labelling and quantum-chemical calculations, which revealed that the *Z*-selective hydroboration proceeds *via trans*-addition of the boron reagent.

In 2023, Corpas *et al.* introduced a groundbreaking iterative dual-metal and energy transfer catalysis approach, allowing for the precise stereochemical control of hydroboration across a broad range of alkynes (Scheme 25).[64] The methodology is effective for the synthesis of stereoisomers of tetrasubstituted β-



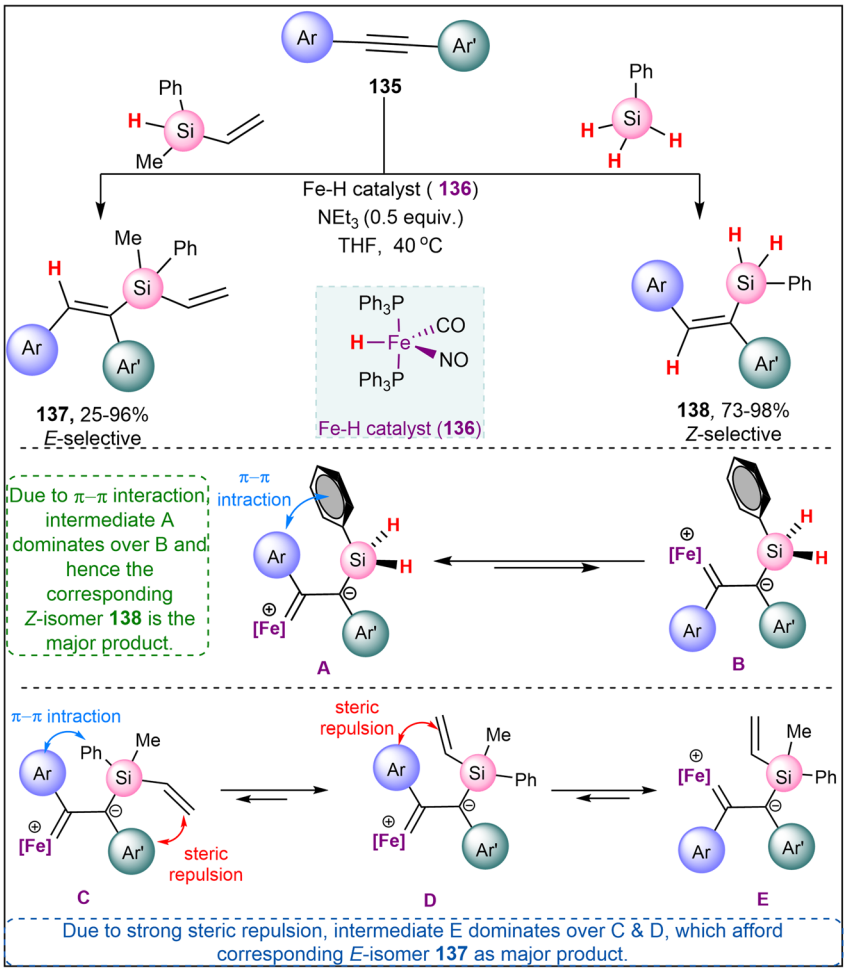
Scheme 33 Cobalt(I) catalyzed silane source-dependent stereoselective hydrosilylation of internal alkynes.

boryl acrylates from internal alkynoates **99** with excellent stereocontrol. Mechanistic insights into these reactions were gained through advanced techniques, including quantum-chemical calculations, quenching experiments, and transient absorption spectroscopy. These studies shed light on the intricate details of both the carboboration and photoisomerization processes, offering a deeper understanding of how stereoselectivity is controlled in this system. The process involves a two-step reaction sequence: first, a *syn*-carboboration reaction of **99** using B_2Pin_2 and an electrophile produce a *Z*-alkene product **100**, followed by its *E*-selective photoisomerization to product **101**. The challenge of overcoming the inherent reluctance of electron-deficient internal alkynes to undergo catalytic carboboration was addressed through the cooperative action of copper and palladium catalysis. Additionally, an iridium complex was employed as an effective sensitizer to facilitate the photoisomerization of the sterically hindered alkenes (**100**). Hence, this work offers a novel dual-metal system that combines iridium and nickel catalysts, with mechanistic studies revealing the importance of energy transfer in achieving stereodivergence.

3.3 Stereo-divergent arylation

Recent advancements in the arylation of alkynes have been propelled by innovative research that explores new catalytic strategies, expands substrate scope, and provides deeper mechanistic insights.[65–68] Trisubstituted alkenes serve as important synthetic intermediates in organic chemistry, with extensive uses in the production of pharmaceuticals, materials, and fine chemicals.[69–72] One of the most efficient methods for synthesizing these compounds is through multicomponent reactions (MCRs). These reactions enable the one-pot difunctionalization of alkynes, where two chemical bonds are formed across a triple bond in a single step. This approach is direct and useful for creating valuable trisubstituted alkenes, offering a simplified and effective route to complex molecule synthesis by minimizing reaction steps and increasing overall efficiency.[73–75]

In this context, Armstrong *et al.* (2018) made a significant contribution by developing a novel approach for achieving diastereodivergent hydroarylation of terminal alkynes (**102**) using a tandem catalysis system *via* palladium and copper co-catalysis (Scheme 26).[76] The method allows for selective formation of either *E*- or *Z*-isomers of aryl alkenes from the same starting materials **102** by adjusting the stoichiometry of an alcohol additive. This control over stereoselectivity provides access to both isomers with high precision, demonstrating broad functional group tolerance, including compatibility with esters, nitriles, halides, and other functionalities. *Z*-selective hydroarylation to product **104** was accomplished *via* a tandem

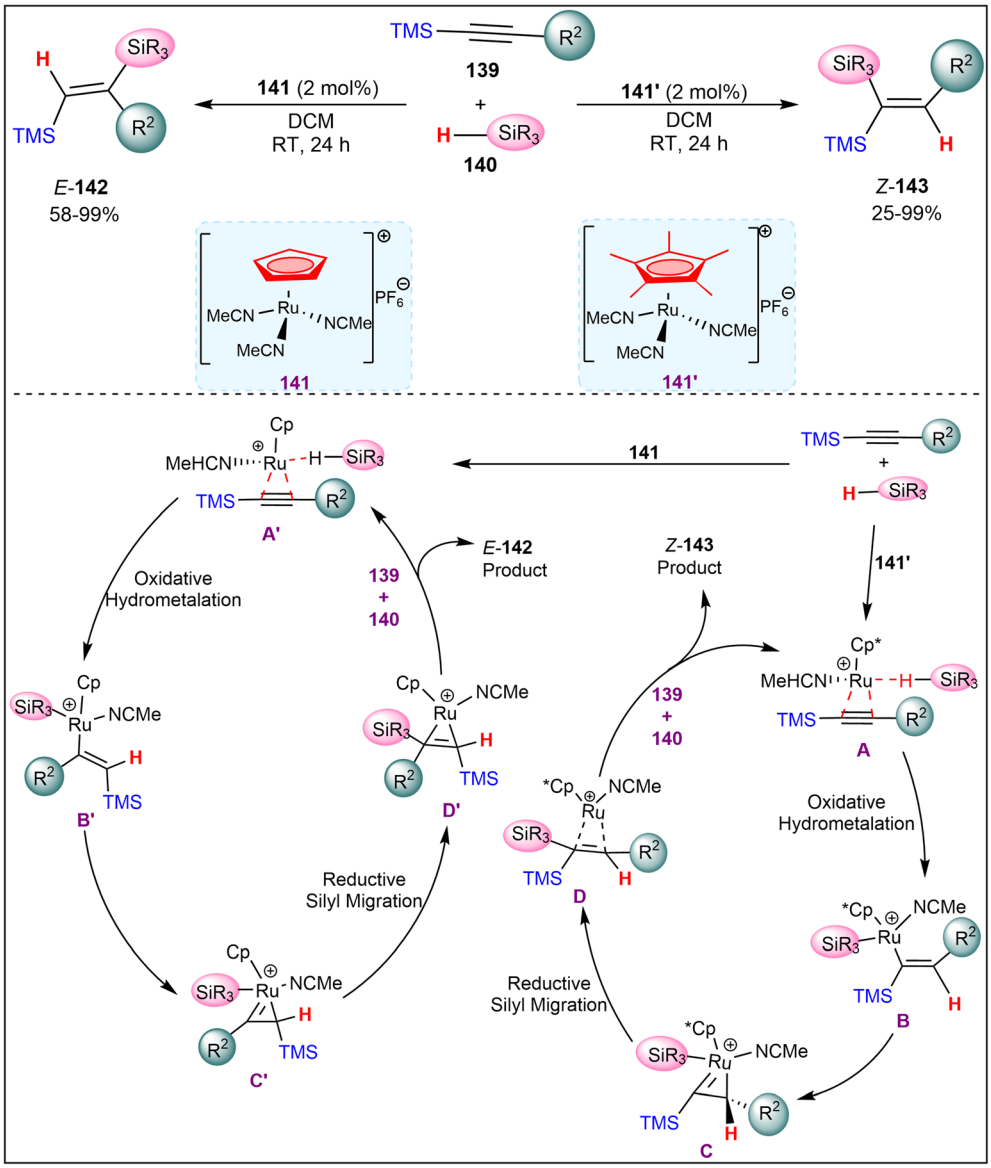


Scheme 34 Iron nitrosyl hydride complex catalyzed stereodivergent hydrosilylation of diaryl alkynes.

Sonogashira coupling followed by a catalytic semireduction, whereas *E*-selective hydroarylation product **105** was achieved through an additional catalytic isomerization step of the *Z*-alkene in the presence of an excess of MeOH in strong alkaline medium.

In 2019, Corpas *et al.* further advanced the field by introducing a dual catalytic system that synergistically combines Pd-catalysis with photocatalysis to achieve regio- and stereocontrol in hydroarylation reactions of unsymmetrical dialkyl alkynes (**106**) with arylboronic acids, enabling precise access to either the *E*- or *Z*-isomer of trisubstituted alkynes (Scheme 27).[77] The novelty of this approach lies in the integration of photocatalysis, which enables energy transfer processes that influence the regioselectivity and stereoselectivity of the products. This work introduces a regioselective and stereodivergent catalytic hydroarylation of unsymmetrical dialkyl alkynes **106** with arylboronic acids, enabling precise access to either the *E* or *Z* isomer of trisubstituted alkenes. The *E*-selective product **107** was achieved through a *syn*-carbopalladation mechanism involving an Ar–Pd species, followed by protodepalladation. The regioselectivity is tightly controlled by a 2-pyridyl sulfonyl (SO_2Py) directing group, which ensures accurate positional selectivity during the reaction. The reaction utilizes a Pd/Ir tandem catalytic approach to obtain the *Z*-isomer **108**. This involves a hydroarylation step followed by an *E*-to-*Z* photoisomerization, enabling access to the complementary stereochemistry with precision. This versatility allows for the selective formation of stereo-defined olefins and dienes, providing an efficient approach to controlling the stereochemistry in olefin synthesis. The methodology was demonstrated to be versatile, accommodating a wide range of alkynes and aryl halides with various functional groups.

Zhu *et al.* in 2022 contributed to the field by developing a nickel-catalyzed multicomponent reductive cascade cross-coupling reaction for the arylalkylation of alkynes that integrates electrochemistry and photocatalysis for the stereodivergent synthesis of trisubstituted olefins (Scheme 28).[78] This method allows for the selective synthesis of *E*- or *Z*-isomers of trisubstituted alkenes by switching between electrochemical and photocatalytic conditions. When the reaction was conducted electrochemically using nickel catalysis, the *E*-isomer of the trisubstituted alkene (**111**) was formed exclusively. In contrast, the iridium and nickel-catalyzed photocatalytic transformation under 440 nm blue light results in the *Z*-



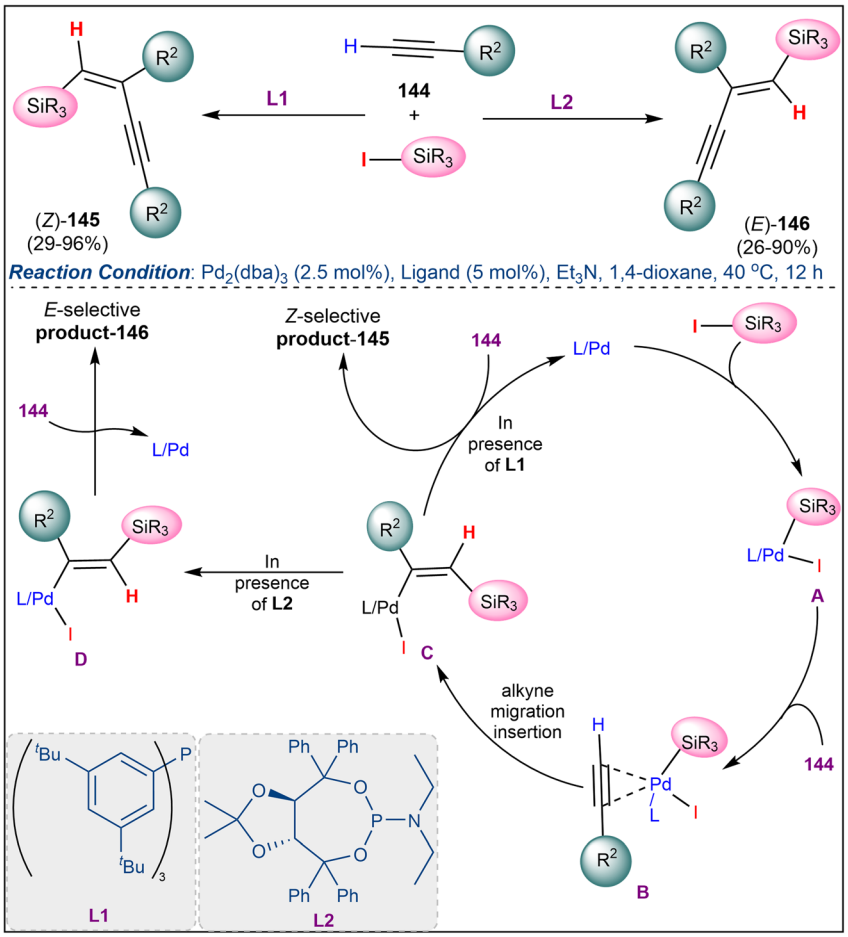
Scheme 35 [cp*Ru(MeCN)$_3$]PF$_6$ catalyzed ligand-controlled regio- and stereodivergent hydrosilylation.

selective product (**112**). Similarly, employing a combination of nickel-catalyzed photocatalysis and electrocatalysis also enables the selective formation of *Z*-isomeric product (**113**) with high stereocontrol. The study revealed the complementary roles of Ir-catalyst (**110**) single-electron transfer (SET) and energy transfer (ET) in controlling stereochemistry, with a broad substrate scope that includes a variety of alkynes (**109**), along with aryl halides and alkyl bromides. The novelty of this approach lies in its ability to combine electrochemistry with photocatalysis to achieve complex transformations with high stereoselectivity.

3.4 Stereo-divergent cyanation

Hydrocyanation of alkynes is a vital transformation in organic chemistry, enabling the construction of nitrile-containing compounds, which are highly valuable synthetic intermediates in pharmaceuticals, agrochemicals, and materials science.[79–82] The nitrile functional group is versatile, serving as a precursor to amines, amides, carboxylic acids, and other key functional groups.[83–85] Moreover, the ability to control the stereochemistry of the resulting alkenes is crucial because the configuration of alkenes (*E* or *Z*) can significantly influence the biological and physical properties of target molecules.[86,87] Hence, developing efficient and stereoselective methodologies for the hydrocyanation of alkynes has always been an area of significant interest. With recent advancements, there is a growing emphasis on sustainable and cost-effective synthetic catalytic systems that use earth-abundant metals. Here, we focus on the stereodivergent hydrocyanation of alkynes, exploring the unique methodologies developed for *E*- and *Z*-alkene synthesis.

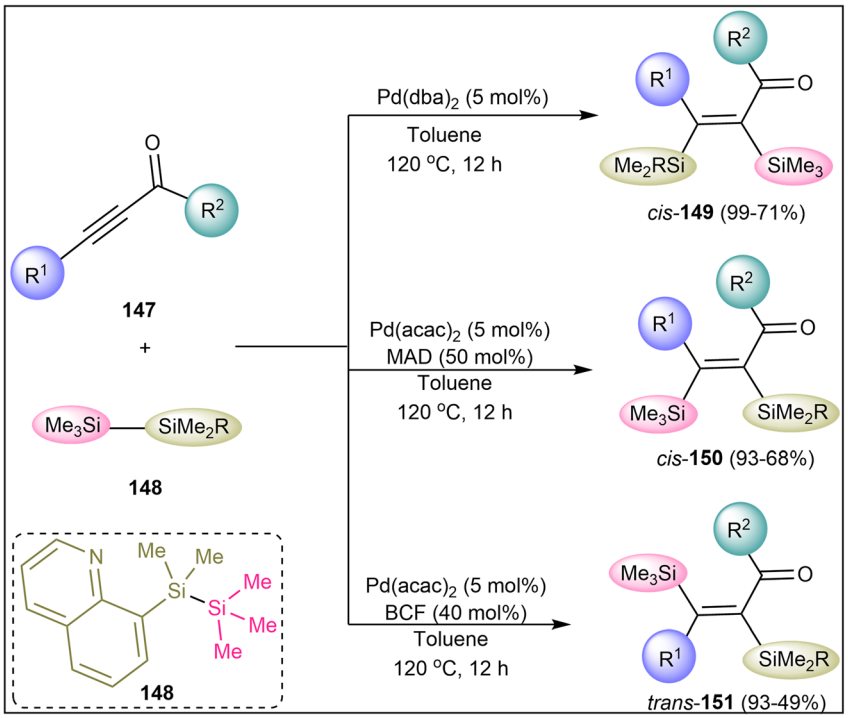
In this context, Long *et al.* (2023) presented a detailed study on the palladium-catalyzed stereodivergent hydrocyanation of alkynes (**114**) to selectively produce *E*- and *Z*-acrylonitriles.[88]



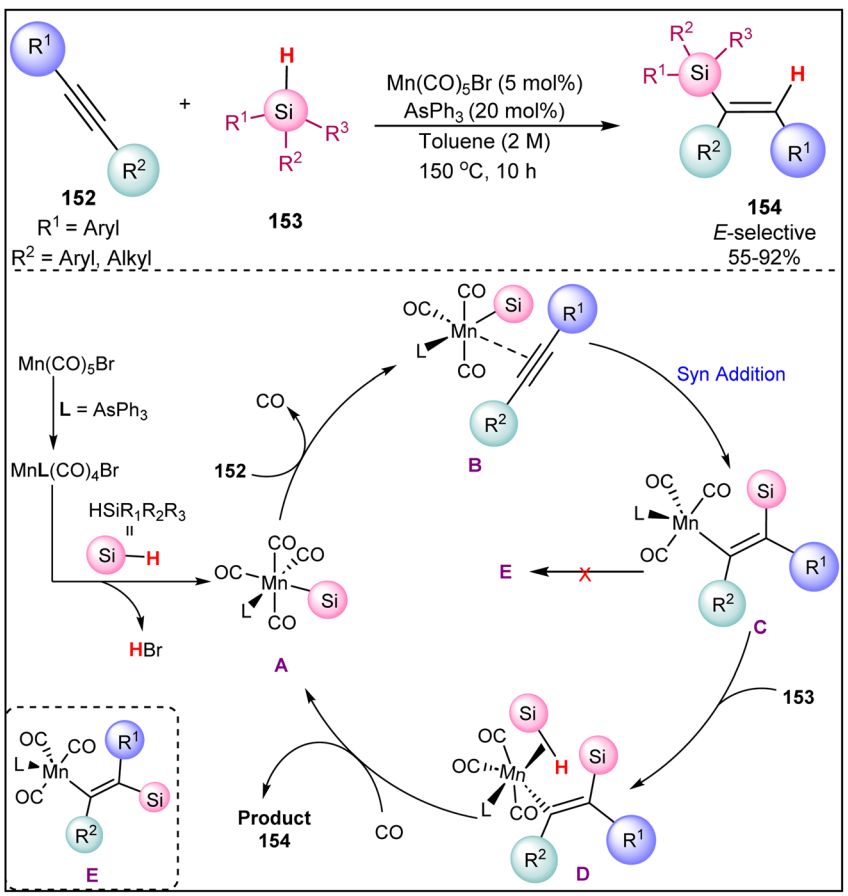
Scheme 36 Ligand-dependent Pd-catalyzed stereodivergent synthesis of *E*- and *Z*-enynes using silyl iodides.

Palladium-based systems have long been favoured for their high catalytic activity and versatility in functionalizing alkynes (Scheme 29).[88] In this methodology, ligand selection was key to controlling the stereochemistry of the product, where the monodentate ligands **115** direct the formation of *E*-isomeric product **117**. In contrast, the alkene **117** system facilitates cyclometallation with Pd-catalyst in the presence of bidentate ligands **116**, which allows for the isomerization of **117** to *Z*-isomeric product **118**. One of the standout features of their method is its wide substrate compatibility. The study demonstrates that various functionalized propiolamides, including primary, secondary, and tertiary amides, undergo hydrocyanation with high stereoselectivity. This versatility is crucial for practical applications in organic synthesis where functional group tolerance is often a limiting factor. Additionally, the methodology's scalability is demonstrated through large-scale reactions, which are essential for industrial applications. Mechanistic investigations using density functional theory (DFT) calculations reveal that the palladium-catalyzed system operates through a well-defined pathway involving activation of the alkyne, followed by selective hydrogenation and isomerization steps. Their method is noteworthy for its use of water as a hydrogen source, aligning with green chemistry principles.

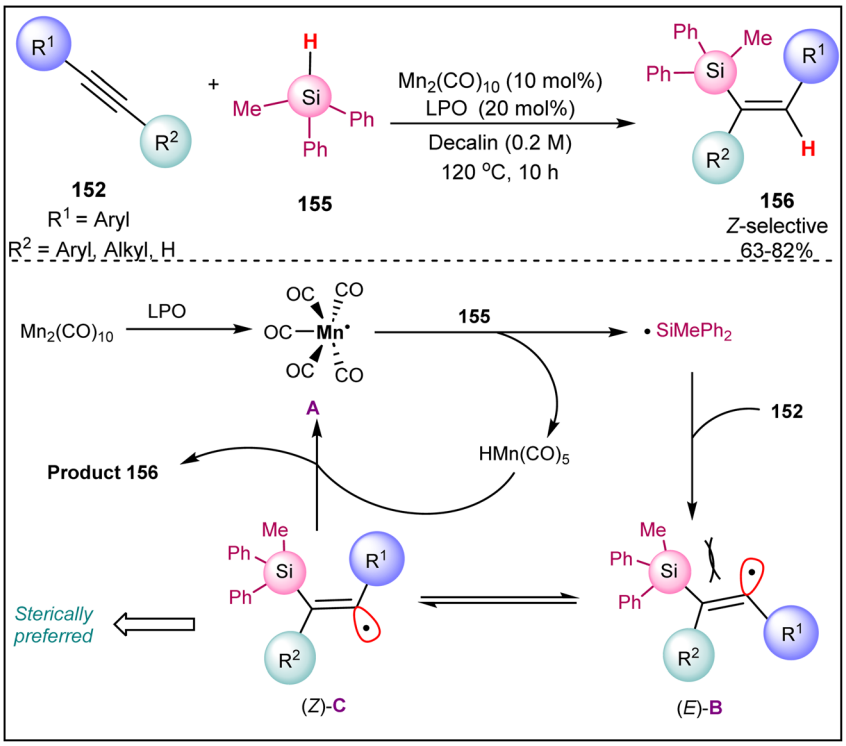
Meanwhile, Wang *et al.* (2022) introduced a cobalt-catalyzed system for the arylcyanation of alkynes, marking an important shift toward the use of earth-abundant and less toxic metals.[89] Cobalt is a relatively inexpensive and sustainable alternative to precious metals that exhibits remarkable potential in the stereoselective transformation of alkynes into *E*- and *Z*-alkenes (Scheme 30).[89] Their system is unique in its ability to switch between *cis* and *trans* selectivity by adding Lewis acid cocatalysts, such as $Zn(OTf)_2$. The study highlights the use of a cobalt(II) catalyst with a 4-*t*Bu-dppp (**121**) ligand system in the presence of $Zn(OTf)_2$ that offers high efficiency and excellent *Z*-selectivity of product **123**. Mechanistic studies suggest that the cobalt catalyst with ligand **120** proceeds *via* metallacyclopropene intermediates **II**, which enable facile isomerization of intermediate **I** to **III** and control over the stereochemical outcome of product **122**. Its compatibility with a variety of functional groups, along with its scalability to multigram synthesis, positions it as a practical and efficient methodology for stereoselective alkyne functionalization. The cobalt-catalyzed process tolerates various aryl nitriles and cyanides, demonstrating its broad applicability across diverse substrates. One of the main advantages of this approach is the ease of catalyst handling and its cost-effectiveness.



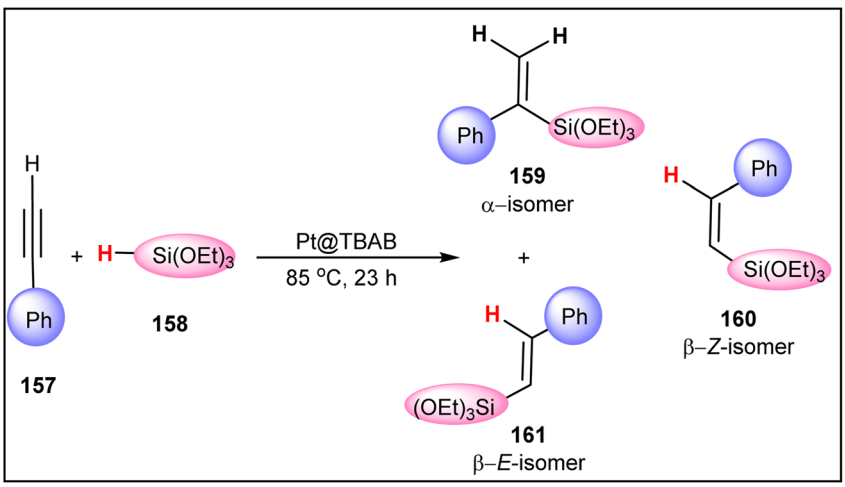
Scheme 37 Pd and Lewis acid catalyzed regio- and stereodivergent bis silylation of alkynoates.



Scheme 38 Mn-catalyzed stereodivergent *E*-hydrosilylation of internal alkynes using a wide variety of silanes.



Scheme 39 Mn-catalyzed stereodivergent *Z*-hydrosilylation of internal alkynes using a wide variety of silanes.

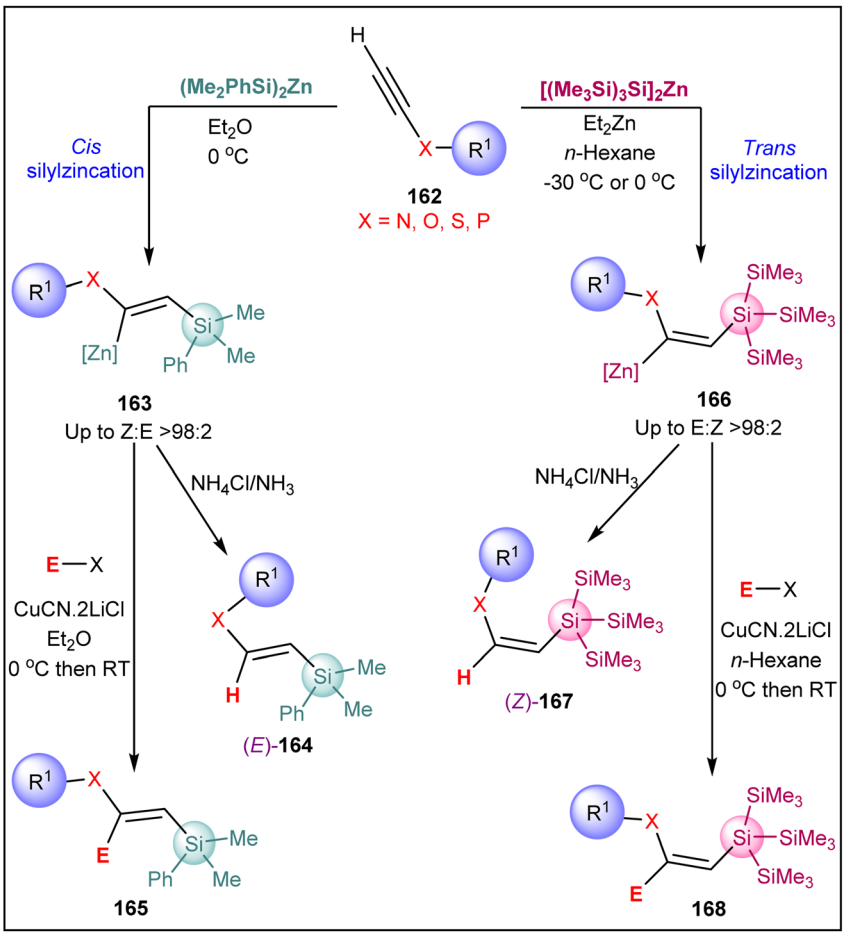


Scheme 40 Onium salt (OS) stabilized metal nanocatalysts in supercritical CO_2 for the *E*/*Z* hydrosilylation of alkynes.

3.5 Stereo-divergent silylation

Vinylsilanes are versatile reagents in synthetic chemistry due to their low toxicity and high stability, facilitating applications in material and medicinal chemistry.[90–93] They serve as multi-functional precursor or intermediates in various organic transformations including Hiyama–Denmark coupling[94,95] and Tamao–Fleming oxidation.[96,97] Hydrosilylation of alkyne is one of the most efficient methods for the synthesis of vinylsilanes.[98] Herein, only stereodivergent hydrosilylation approaches were summarized in this section.

Mori *et al.* demonstrated the hydrosilylation of terminal alkynes (**124**) using $RhI(PPh_3)_3$ as a catalyst, revealing that *Z*- and *E*-alkenylsilanes can be produced in a stereodivergent way by altering the reaction conditions and the sequence in which the reagents are added (Scheme 31).[99] *Z*-Alkenylsilanes **126** were produced with a high yield (99%) and excellent stereoselectivity (99 : 1) by adding an alkyne **124** to a pretreated mixture of organosilane and rhodium catalyst at room temperature for 2 hours. In contrast, conducting the reaction with a mixture of an organosilane, an alkyne **124**, and the catalyst at 60 °C results in *E*-products **125**, also with a 99% yield and 99% selectivity.



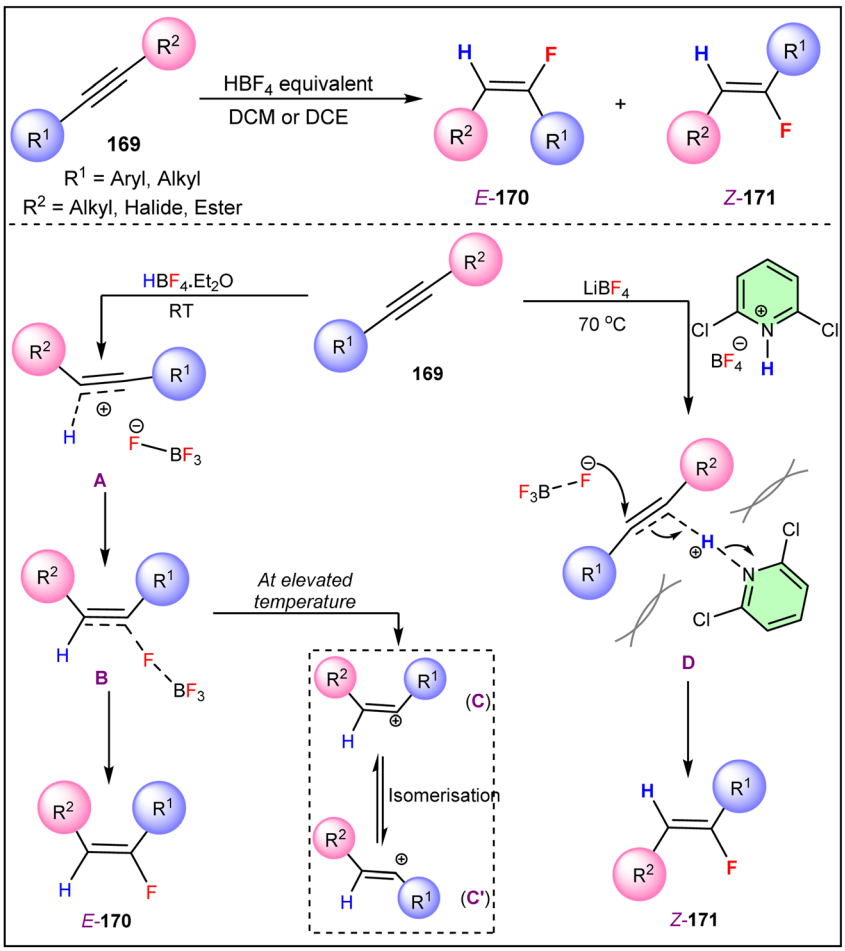
Scheme 41 *E*-/*Z*-Selective silylzincation of α-heteroatom-substituted terminal alkynes using organo-zinc.

Meanwhile, the corresponding rhodium chloride catalyst shows relatively lower reactivity, which could be enhanced by the addition of 5% of NaI in the reaction medium.[100]

In a similar study, the Ozawa group reported a ruthenium catalyst-dependent stereodivergent hydrosilylation of terminal alkynes **127** using various organosilanes (Scheme 32).[101] Utilizing $RuHCl(CO)(PPh_3)_3$ (**A**) as the catalyst resulted in the formation of *E*-selective vinylsilanes **128** with over 99% selectivity and excellent yield. In contrast, $Ru(SiMe_2Ph)Cl(CO)(i\text{-}Pr_3)_2$ (**B**) as the catalyst produces *Z*-selective vinylsilanes **129** with 91–99% selectivity. The catalytic pathway for synthesizing *E*-selective **128** involves alkyne insertion into catalyst **A**, generating an alkenyl ruthenium complex, followed by insertion of organosilanes through a four-membered transition state (I) to yield **128**. The synthesis of *Z*-selective **129** follows a similar reaction pathway with catalyst **B**, proceeding through a transition state (II).

Later on, Yong *et al.* reported a cobalt(I) catalyzed silane source-dependent stereoselective hydrosilylation of internal alkynes **130** (Scheme 33).[102] When an internal alkyne **130** reacts with triethylsilane in the presence of a hemilabile phosphane-tethered cobalt(I) catalyst **131**, *E*-alkenyl silane **133** is formed *via* *syn*-addition. A key step in this hydrosilylation process is the oxidation of silane at the vacant coordination sites of the cobalt complex. Interestingly, triethoxysilane instead of triethylsilane reverses the regioselectivity of the reaction, predominantly forming *anti*-adducts *Z*-alkenyl silane **134**. For unsymmetrical internal alkynes, the yields and regioselectivity of hydrosilylation products are moderate, but *syn*-hydrosilylation product **133** is exclusively observed in all cases. This indicates that the process is not sterically controlled. Although the reaction mechanism has not been extensively studied, it is speculated to involve *syn*-hydrosilylation, followed by isomerization through intermediate **A**.[103]

In this context, the Plietker group introduced an iron nitrosyl hydride complex **136** catalyzed stereodivergent hydrosilylation of diaryl alkynes **135** (Scheme 34).[104] The stereoselectivity of the process is controlled by employing different silane reagents, and a variety of alkynes **135** are converted into their respective *E*- or *Z*-configured vinylsilanes in excellent yields. The iron nitrosyl hydride complex $FeH(CO)(NO)(PPh_3)_2$ (**136**) was prepared from protonation of iron tricarbonyl nitrosyl anion $[Fe(CO)_3(NO)^-]$ with trifluoroacetic acid in the presence of an excess of triphenylphosphine in ether.[105] Hydrosilylation of diaryl alkyne **135** using $PhSiH_3$ in the presence of 1 mol% of the Fe-hydride catalyst **136** and 0.5 equivalents of NEt_3 in THF at 40 °C afford *Z*-isomer (*trans*) of vinyl silane product **138** through a formal *trans*-addition of the Si–H bond across the C–C triple bond.



Scheme 42 Metal-free hydrofluorination of alkyne using protic tetrafluoroborate salts as tunable hydrofluorinating reagents.

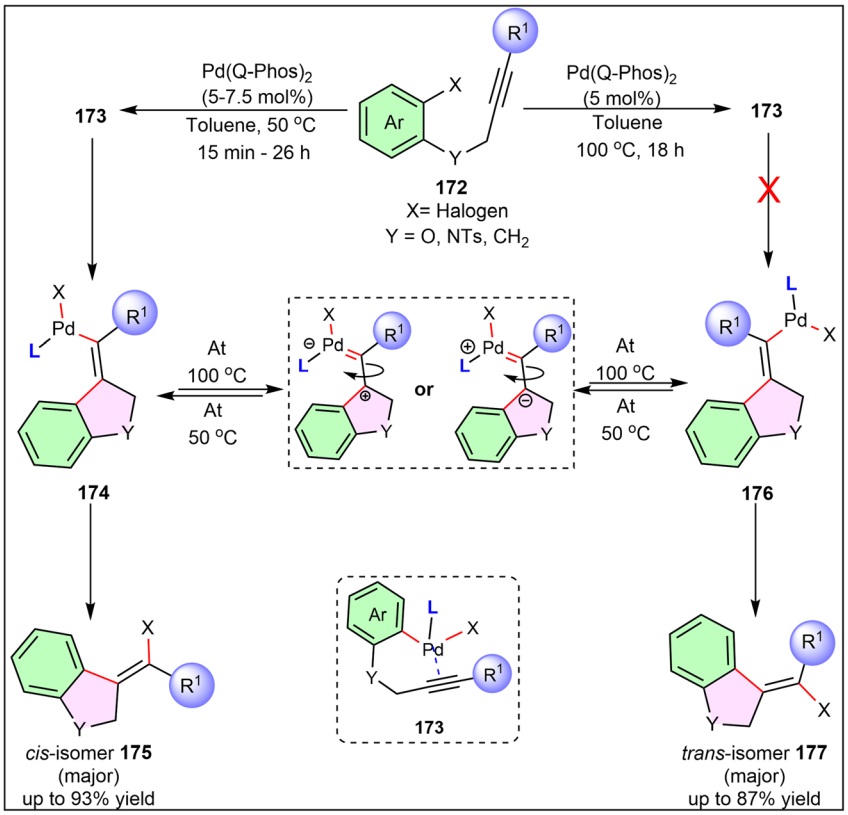
Instead of $PhSiH_3$, the application of sterically hindered $PhMe(CH_2{=}CH)SiH$ as the silane reagent inverses the stereoselectivity of the reaction and *E*-isomer (*cis*) of vinyl silane **137** is formed as a product.

Later on, Ding *et al.* reported ruthenium-catalyzed ligand-controlled regio- and stereodivergent hydrosilylation of internal silyl alkynes **139** to generate vinyl silanes (Scheme 35).[106] The reaction of 1-trimethylsilyl-1-hexyne with triethoxysilane **140** in the presence of a catalytic amount of $[cp^*Ru(MeCN)_3]PF_6$ (**141′**) in DCM affords vinyl disilanes **143** in quantitative yield with exclusive α *anti* addition of silane ($\alpha/\beta > 50:1$, $Z/E > 50:1$) in 24 hours. Remarkably, substituting the cp* ligand with cp in the catalyst **141** completely alters the stereo- and regioselectivity of the reaction, resulting in a β *syn*-addition product **142** with a quantitative yield ($\beta/\alpha > 50:1$, $E/Z > 50:1$). Notably, this study was one of the few examples of Ru-catalyzed *syn*-selective alkyne hydrosilylations.[107]

A wide range of silyl alkynes **139** with different functional groups including esters, mesylates, acetals, and protected alcohols and amines are well tolerated in the mild reaction condition; however, aryl-substituted alkynes are unreactive in the reaction condition. Changing the silyl group on the alkyne substrates does not affect the selectivity and yield of the β *syn*-addition product **142**. The bulky silyl group on the alkyne substrates does not affect the selectivity of the α *anti*-addition product **143** but significantly reduces the yield. Similarly, the alkoxysilane and chlorosilanes efficiently participate in the hydrosilylation process, but electron-rich trialkyl silanes are unreactive.

Two different catalytic cycles were proposed for the formation of α-*anti* and β-*syn* products. In both cases, the reaction starts with the co-ordination of alkyne and silane on the ruthenium catalyst (**A** and **A′**), which further undergoes oxidative hydrometalation to form the planar σ-vinyl intermediate (**B** and **B′**). An electronic rotation in the σ-vinyl intermediate leads to the formation of metallacyclopropene-like intermediate (**C** and **C′**). The preferred rotation causes the β-substituent to position itself opposite to the Cp (or Cp*) to minimize steric hindrance, thereby determining the stereoselectivity of the reaction. Subsequently, the reductive silyl migration from intermediate **C** or **C′** to the carbene center leads to the formation of intermediate **D** or **D′**, respectively, which produces the final product through reductive elimination in the presence of precursor **139** and **140**.

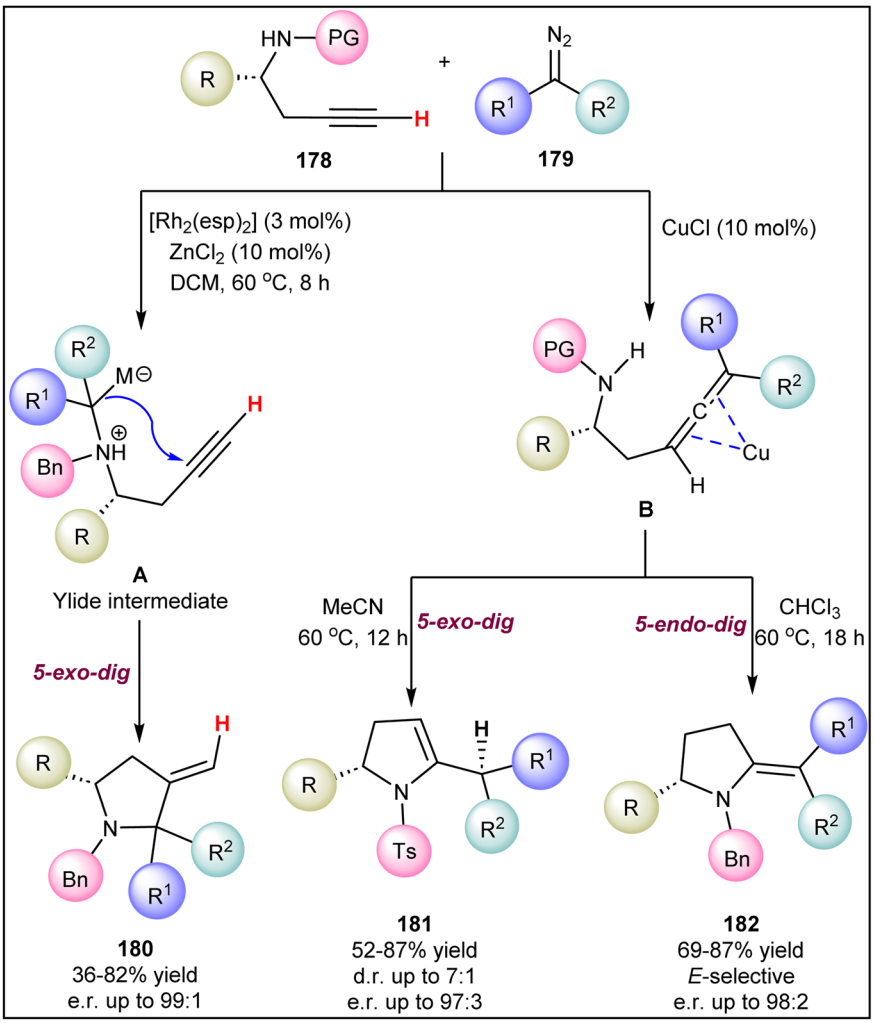
Similarly, a ligand-dependent palladium-catalyzed stereodivergent approach was reported for the synthesis of *E*- and *Z*-



Scheme 43 Pd-catalyzed intramolecular alkyne carbohalogenation for the stereodivergent addition of aromatic halide across alkyne to yield vinylic halides.

enynes from terminal alkyne **144** and silyl iodides (Scheme 36).[108] Upon optimizing several ligands, tris(3,5-di-*tert*-butylphenyl)phosphane (**L1**) as a ligand in the reaction condition afford *Z*-conjugated enynes **145** (29–96%) with excellent stereoselectivity up to $Z:E > 19:1$. Meanwhile, the presence of α,α,α′,α′-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol (TADDOL) derived phosphoramidite ligand (**L2**) delivers *E*-conjugated enyne product **146** in good yield (26–90%) and selectivity ($E:Z > 19:1$). A broad variety of aryl-substituted alkynes (**144**) with different electronic properties are successfully tolerated under the reaction conditions; however, alkyl alkynes did not exhibit reactivity. Similarly, various silylated enynes, both *E*- and *Z*-selective, could be produced in high yields using different iodosilanes. Even sterically hindered triethylsilyl iodide was reactive, although it yielded a lower product amount. The catalytic cycle of the process starts with the oxidative addition of silyl iodide to Pd-catalyst to generate silylpalladium iodide (**A**), which reacts with alkyne **144** to yield vinylpalladium species **C** through intermediate **B**. In the presence of triaryl phosphine ligands **L1**, vinylpalladium **C** undergoes subsequent coupling with another alkyne **144** to afford the *Z*-selective enynes **145**. In contrast, phosphoramidites **L2** that are less electron-rich may cause isomerization of vinylpalladium **C** to the intermediate **D**, which then leads to the formation of *E*-enynes **146**.

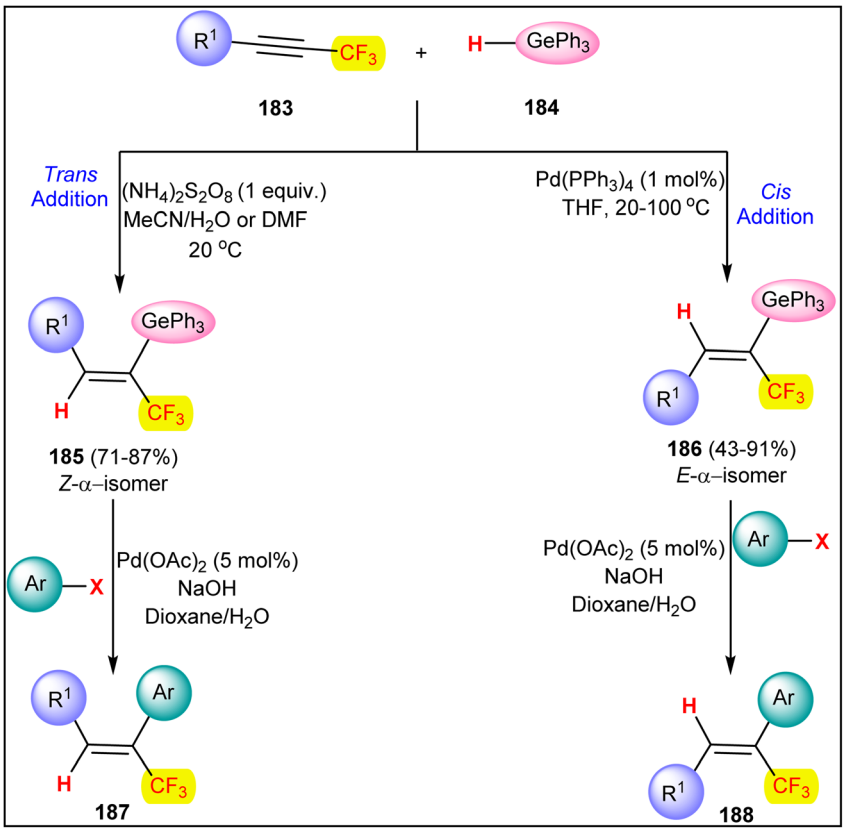
Recently, Zhao *et al.* described regio- and stereodivergent bis silylation reactions of alkynoates **147** using disilane reagents, catalyzed by palladium and Lewis acids (Scheme 37).[109] An air-stable disilane reagent, 8-(2-substituted-1,1,2,2-tetramethyldisilanyl)quinoline (TMDQ; **148**) was synthesised, which plays a crucial role in controlling selectivity within this catalytic system, enabling the divergent synthesis of 1,2-bissilyl alkenes **149–151**. The reaction of alkynoates **147** with an asymmetrical disilane **148** in the presence of a catalytic amount of $Pd(dba)_2$ (5 mol%) in toluene at 120 °C yields the *cis*-product **149** with over 97% selectivity. Switching the catalytic system to $Pd(acac)_2$ and using 50 mol% of methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD) as an additive reverses the reactivity of the silane reagent with alkyne **147**, leading to the formation of *cis*-product **150** in excellent yield and with greater than 97% selectivity. Meanwhile, the *trans*-product **151** was obtained when the reaction was conducted using a catalytic system of $Pd(acac)_2$ and 40 mol% of tris(pentafluorophenyl)borane (BCF). Increasing the BCF concentration improves selectivity but reduces the overall yield of **151**. A wide variety of alkyl and aryl-substituted alkynoates **147** were efficiently converted into corresponding alkenyl silicon derivatives. In the TMS group, silicon is more positively charged than the silicon connected at the C8 position of quinoline of **148**, and the α-carbon in alkynoates **147** is more electronegative than the β-carbon. This difference creates a thermodynamic driving force that facilitates the migration of TMS to the α-carbon of the C–C triple bond of **147**. The alkyne migration insertion step has the highest activation energy (16.7 kcal mol^{-1}) in the reaction pathway, making



Scheme 44 Catalyst-controlled stereodivergent synthesis of five-membered *N*-heterocycles *via* the tandem annulation of amino alkynes with diazo compounds.

it the rate-limiting step and it determines the regioselectivity of the reaction. Adding MAD as an additive completely reverses the regioselectivity of this *cis*-bis-silylation. MAD acts as a bulky coordinating group, altering regioselectivity by making electronically favoured migratory insertion more difficult due to steric effects. The introduction of BCF changes the reaction mechanism, making reductive elimination the rate-determining step, which leads to *E*-selectivity in the final product **151**.

Yang and Wang envisioned the manganese-catalyzed stereodivergent hydrosilylation of internal alkynes using a wide variety of silanes.[110] The reaction of alkyne **152** with different silane **153** in the presence of the catalytic amount of mononuclear $MnBr(CO)_5$ and arsenic ligand, $AsPh_3$ in toluene at 150 °C affords the *E*-selective vinyl silane product **154** (Scheme 38). The reaction starts with the formation of Mn–Si complex **A** from Mn-catalyst, ligand, and silane. Complex **A** produces intermediate **C** through CO alkyne exchange followed by *syn*-addition of the Mn–Si bond to alkyne **152**. The interaction of complex **C** with silane **153** followed by σ-bond metathesis *via* intermediate **D** leads to the formation of product **154** and Mn–Si complex **A**. A diverse array of mono-, di-, and tri-substituted silanes with both electron-donating and withdrawing properties are well tolerated in the reaction condition and result in *E*-configured products **154** in high yields with good to excellent stereoselectivity. Similarly, various aryl and alkyl-substituted alkynes are effectively utilized in this protocol. Surprisingly, the stereoselectivity was reversed in the reaction of alkyne **152** and silane **155** using the dinuclear manganese catalyst $Mn_2(CO)_{10}$ along with dilauroyl peroxide (LPO), resulting in the formation of the *Z*-isomeric vinyl silane product **156** (Scheme 39). Unlike *E*-selective hydrosilylation, this *Z*-selective hydrosilylation protocol is also effective with various terminal aryl alkynes, including those with sensitive halogens. This reaction proceeds through a radical mechanism and initiates from LPO-initiated homolysis of $Mn_2(CO)_{10}$ to an Mn-radical complex **A**. Silane readily reacts with Mn-complex **A** to produce $HMn(CO)_5$ and silyl radical. The silyl radical forms an adduct with alkyne to produce *E*-alkenyl radicals **B**, which isomerize to sterically preferred *Z*-alkenyl radicals **C**.[111] Finally, the hydrogenolysis of **C** with



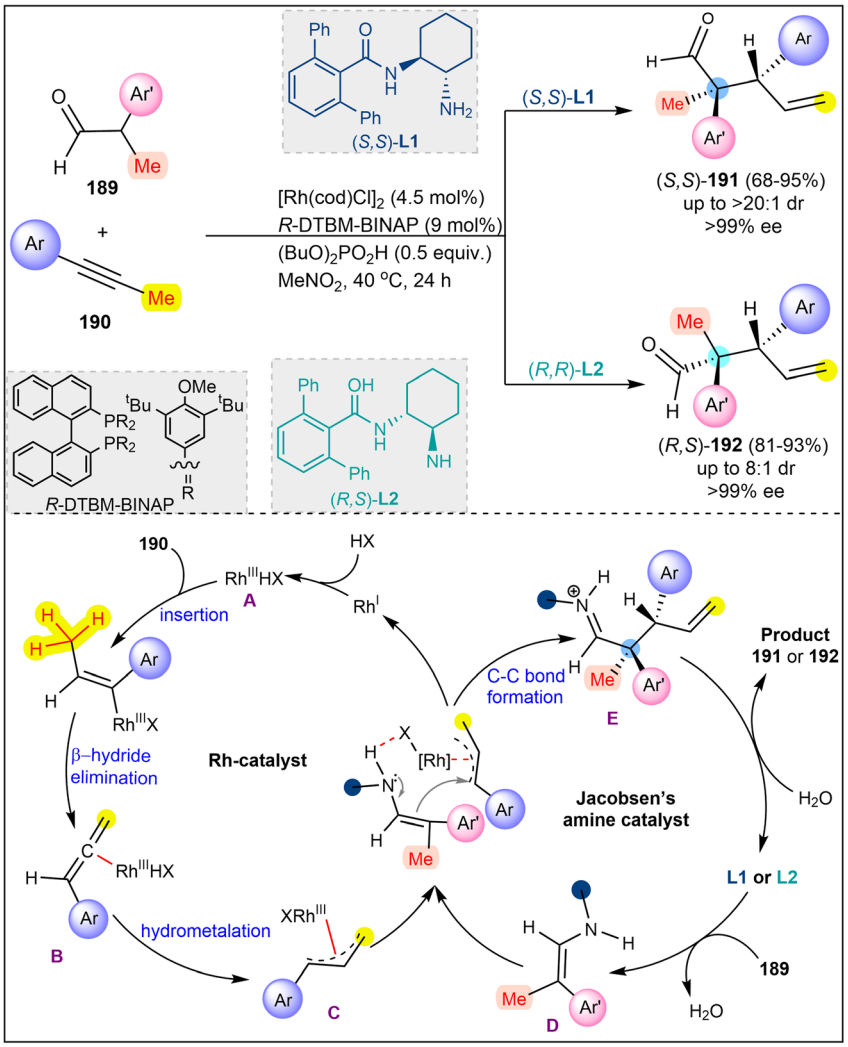
Scheme 45 Stereoselectivity tunable hydrogermylation reaction for the synthesis of α-CF_3-vinylgermanes.

$HMn(CO)_5$ yields the desired product **156** and regenerates the radical Mn-complex **A**.

However, this proposed organometallic catalytic cycle does not fully explain why the *Z*-isomer is not formed with $Mn(CO)_5Br$. Li's computational study on Mn-catalyzed hydrosilylation provides additional insight into the mechanism, attributing the lack of *Z*-isomer formation to the large steric hindrance and high energy barrier of isomerization from Mn-complex **C** to **E** in Scheme 38.[112] In both mononuclear $Mn(CO)_5Br$ and binuclear $Mn_2(CO)_{10}$-catalyzed cycles, the rate-determining step is the addition process of the substituted alkyne.

The Aymonier group synthesized onium salt (OS) stabilized metal nanocatalysts (M(0)NCs) in supercritical CO_2 ($scCO_2$) and employed them in stereodivergent hydrosilylation of alkynes **157** with triethoxysilane **158** (Scheme 40).[113] Hydrosilylation reactions can be catalyzed by various metals such as Pt, Ir, Rh, and Ru, with Pt(0)NCs the most effective. After optimizing these metals with three different OS stabilizers [cetyltrimethylammonium bromide (CTAB), tetrabutylammonium bromide (TBAB) and calcium bis(trifluoromethanesulfonimide) ($CTANTf_2$)], Pt@TBAB exhibits quantitative conversion of alkyne to corresponding vinylsilane (**159–161**) with up to 71% selectivity of β-*E* isomer **161**. Although the selectivity of the product was less than the previously reported homogeneous ruthenium-catalyzed reaction, this is one of the milestone observations in the field of hydrosilylation through heterogeneous catalysis. Also, a significant loss in β-*E*-selectivity was observed with increasing concentration of NC from 100 ppm to 10 000 ppm.

To advance hydrosilylation, Fopp *et al.* described a catalyst-free *cis*- and *trans*-selective silylzincation of various α-heteroatom-substituted terminal alkynes **162** using $(Me_2PhSi)_2Zn$ and $[(Me_3Si)_3Si]_2Zn$, respectively (Scheme 41).[114,115] Both reagents exhibit highly regio- and stereoselective addition across the C–C triple bond of alkynes **162** substituted with nitrogen, sulfur, oxygen, and phosphorus, exclusively yielding β-silyl isomers. The reaction of **162** with $(Me_2PhSi)_2Zn$ in ether at 0 °C leads to the formation of *Z*-2-(silyl)vinyl zinc isomer **163**. Quenching of this organozinc intermediate **163** with NH_4Cl/NH_3 produces α-heteroatom-substituted vinyl silanes **164** in moderate to good yields with excellent stereoselectivity. A copper-mediate electrophilic substitution of zinc in **163** proceeds efficiently with complete retention of the geometry across the double bond and further extends the scope of the reaction to product **165**. On the other hand, the reaction of **162** with $[(Me_3Si)_3Si]_2Zn$ in *n*-hexane at lower temperature leads to the formation of *E*-2-(silyl)vinyl zinc isomer **166**, which shows similar reactivity with electrophiles with retention of geometry. The *syn*-addition of $(Me_2PhSi)_2Zn$ to the triple bond through a polar mechanism was supposed for the formation of **163**.[116] Meanwhile, a radical-chain mechanism was supposed for the reversal of stereoselectivity in **166** with $[(Me_3Si)_3Si]_2Zn$.[117]



Scheme 46 Chiral Jacobsen's amine-dependent stereodivergent synthesis of α-β-chiral homoallylic ketones and through Rh-hydride catalyzed coupling of α-branched aldehydes with alkynes.

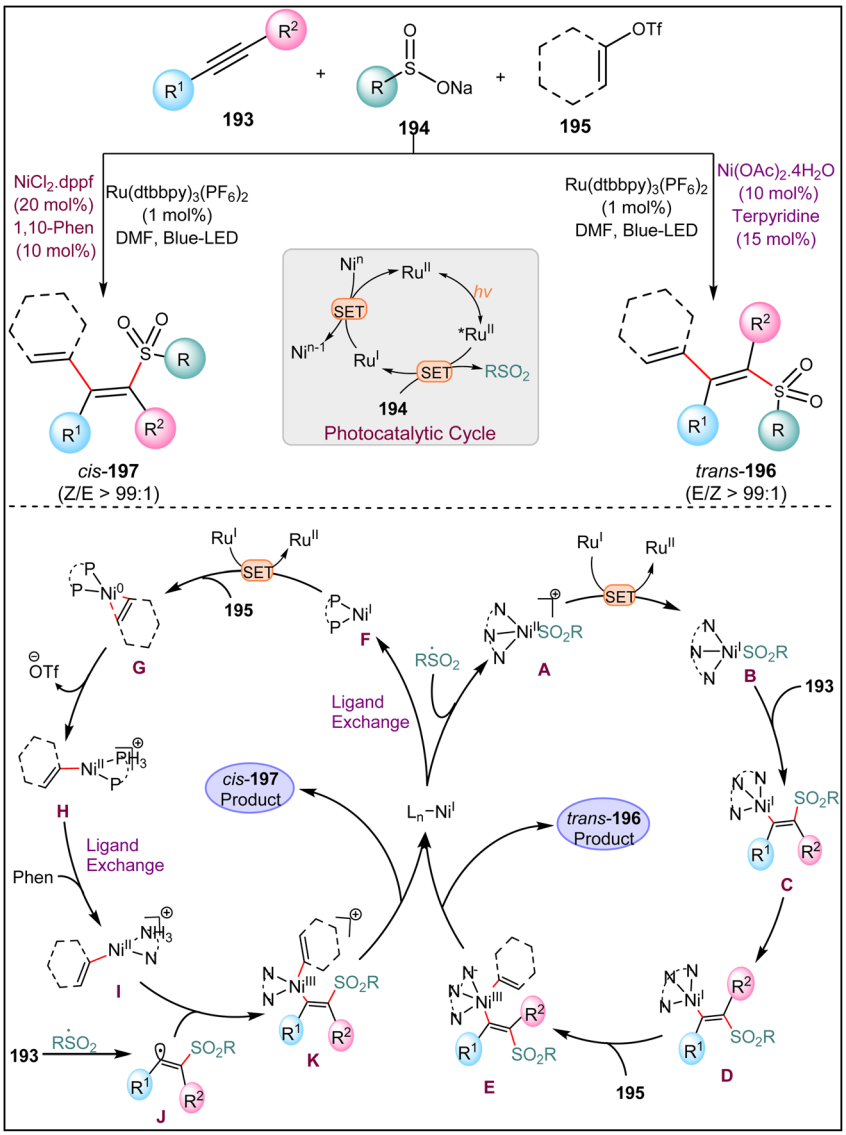
3.6 Stereo-divergent fluorination

Fluoroalkene are isosteres of peptide amide bonds and have become increasingly prevalent as structural and mechanistic probes in biological[118,119] and chemical studies.[120,121] These analogs are valuable because they can mimic the electronic and geometric properties of peptide bonds while offering enhanced stability and unique interactions. Given the importance of fluoroalkenes, significant efforts have been made to develop efficient regio- and stereoselective syntheses of these compounds.[122–124] In particular, stereodivergent hydrofluorination allows for precise control over the synthesis of specific fluoroalkene isomers with desired configurations.

In this context, Guo *et al.* reported a metal-free hydrofluorination of alkyne **169** using protic tetrafluoroborate salts as tunable hydrofluorinating reagents to control the regio- and stereoselectivity of the reaction (Scheme 42).[125] A wide variety of internal alkyne **169** were treated with different tetrafluoroborate salts in DCM or DCE. The reported conditions are compatible with a wide range of functional groups and successfully employed for the late-stage functionalization of drug derivatives and for synthesizing fluorinated drug analogues. The reaction of alkyne **169** with $HBF_4 \cdot Et_2O$ results in the *E*-isomer of fluoroalkenes **170** as a major product through intermediate **A** and **B**, whereas 2,6-dichloropyridinium tetrafluoroborate as tetrafluoroborate salt along with $LiBF_4$ afforded the *Z*-isomer of fluoroalkenes **171**. The presence of $LiBF_4$ as an additive enhances the concentration of tetrafluoroborate anion, promotes the *anti*-attack of fluoride on intermediate **D**, suppresses the formation of this side product, and further enhances the yield of *Z*-alkene product **171**. At elevated temperatures, *in situ* generated BF_3 leads to fluoride elimination from **B** to produce the vinyl cation **C**, which undergoes isomerization to **C′** and reduces the selectivity of the final product **170**.

3.7 Miscellaneous

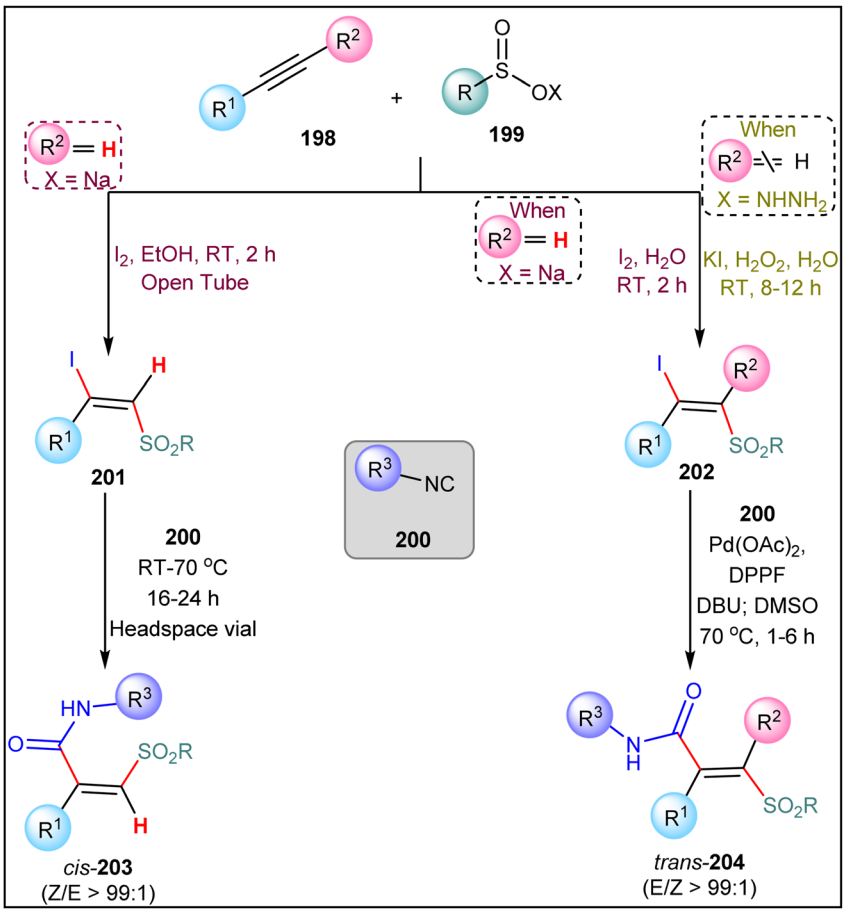
Halogenated alkenes play a crucial role in various scientific fields, notably in pharmaceuticals, agrochemicals, and



Scheme 47 Ligand-controlled stereodivergent functionalization of terminal alkynes using sodium sulfinates and vinyl triflates.

chemical industries.[126] They serve as key starting materials for metal-mediated cross-coupling reactions,[127] which are widely utilized in scientific research for small molecule synthesis and in the industrial production of numerous compounds. In this context, Lauten's group realized a Pd-catalyzed intramolecular alkyne carbohalogenation for stereodivergent addition of aromatic halide across alkyne to prepare vinylic halides.[128] 1-Halo-2-((prop-2-yn-1-yl)oxy)benzene type substrates **172** undergo intramolecular carbohalogenation in the presence of $Pd(Q\text{-}Phos)_2$ catalyst in toluene at 50 °C to produce *cis*-3-(halomethylene)-2,3-dihydrobenzofurans **175** (Scheme 43). Raising the reaction temperature to 100 °C did not significantly affect the product yield, but it completely reversed the stereoselectivity, resulting in the *trans*-isomer **177**. *In situ* NMR studies indicate that the thermodynamic *trans*-product **177** primarily forms through the isomerization of the intermediate **174** rather than directly from the substrate **172**. To better understand the mechanism of olefin isomerization, isomerically pure *cis*-isomers **175** were re-exposed to standard reaction conditions at 100 °C, leading to their conversion into the *trans*-isomer **177**. Similarly, *trans*-isomer **177** was converted to *cis*-isomer **175** when treated at 50 °C. The reaction effectively tolerates electron-withdrawing and electron-donating substituents on the aryl bromide substrate **172**.

Similarly, Liu *et al.* reported a catalyst-controlled stereodivergent synthesis of five-membered *N*-heterocycles (**180–182**) *via* tandem annulation of amino alkynes **178** with diazo compounds **179** (Scheme 44).[129] The rhodium-catalyzed method involves carbenoid insertion into the N–H bond to generate ylide intermediate **A**, followed by Conia-ene 5-*exo-dig* cyclization, resulting in 3-methylene pyrrolidines **180**. In contrast, the copper-catalyzed reaction begins with the cross-coupling of an alkyne **178** with diazo compounds **179**, producing allenoate intermediates **B** that may undergo either 5-*exo-dig* or 5-*endo-dig*

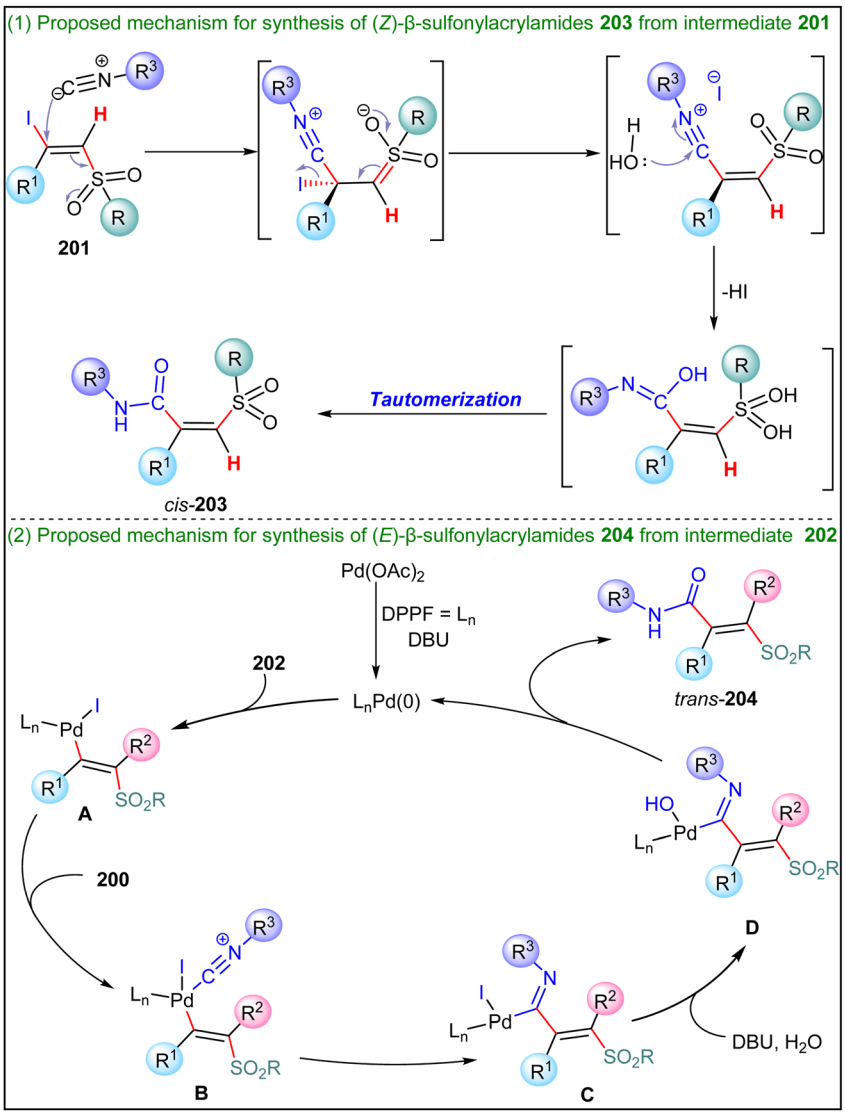


Scheme 48 Stereodivergent difunctionalization of terminal and internal alkynes using various sulfinates and isocyanides to synthesize *Z*- and *E*-β-sulfonylacrylamides.

intramolecular hydroamination, yielding the respective cycloaddition products **181** and **182**. When this copper-catalyzed transformation was carried out with *N*-tosyl amino alkynes in acetonitrile, it led to the formation of dihydropyrroles **181** *via* 5-*exo-dig* cyclization. However, using sterically hindered *N*-benzyl amino alkynes in chloroform produces *E*-selective pyrrolidines **182**. Generally, the chiral propargyls **178** substrates containing either electron-rich or electron-deficient aryl or alkyl substituents adjacent to the *N*-atom gave the corresponding products in moderate to high yields and with good stereoselectivity.

Like halogenated alkene, CF_3-alkenes are excellent precursors in various organic transformations and are of great importance in pharmaceutical, agricultural, and materials science.[130,131] Hydrometallation of α-CF_3-alkynes is one of the most efficient approaches for producing trifluoromethylated alkene precursors.[132] In this context a stereoselectivity tunable hydrogermylation reaction was developed for the synthesis of α-CF_3-vinylgermanes **185** and **186**, which could be further utilized as precursors in cross-coupling reactions (Scheme 45).[133,134] Hydrogermylation of aryl and alkyl α-CF_3-alkynes **183** with organogermanium hydrides **184** selectively produces *Z*-isomer of α-CF_3-vinylgermane **185** in 71–87% isolated yield in the presence of a radical initiator peroxydisulfate. Radical initiator $(NH_4)_2S_2O_8$ efficiently oxidizes organogermanium species **184** to the corresponding organogermyl radical, which leads to the *trans*-addition of radicals and forms *Z*-selective vinylgermanes **185**. Meanwhile, exploration of $Pd(PPh_3)_4$-catalyzed hydrogermylation shows a regio- and stereoselective *cis*-addition of reagent **184** to α-CF_3-alkyne substrate **183** to form *E*-isomer of α-CF_3-vinylgermane **186** in moderate to good yield (43–91%). The synthesized vinylgermanes were further investigated in Pd-catalyzed coupling reactions with aryl halides to expand the scope of the reaction and prepare α-CF_3-styrenes **187** and **188**.

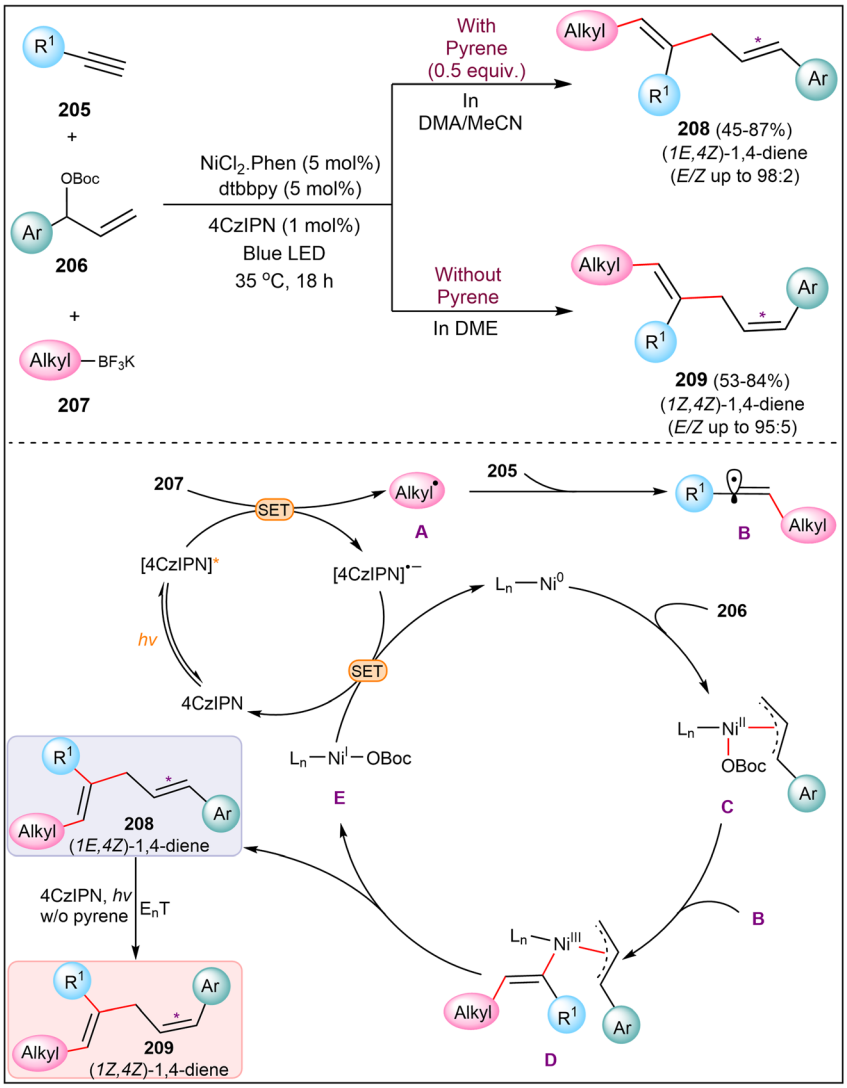
Homoallylic ketones, also known as γ,δ-unsaturated ketones are widely employed in the synthesis of heterocycles, natural products, electronic optical organic materials, peptidomimetics, and much more.[135] Cruz and Dong demonstrated a chiral Jacobsen's amine (**L1** and **L2**) dependent stereodivergent synthesis of α-β-chiral homoallylic ketones **191** and **192** through Rh-hydride catalyzed coupling of α-branched aldehydes **189** with alkynes **190** (Scheme 46).[136] Electron-rich aromatic aldehydes (**189**) show good performance under the reaction conditions, while the electronic properties of the substituents on alkynes **190** did not significantly affect the reactivity. The reaction achieved excellent diastereoselectivity and reactivity (68–95%, up to >20 : 1 dr and >99% ee) for the



Scheme 49 Stereodivergent difunctionalisation of alkyne to (1): *Z*-sulfonylacrylamides and (2): *E*-sulfonylacrylamides.

anti-diastereomer product (*S*,*S*)-**191** when the chiral organocatalyst amine (*S*,*S*)-**L1** was used along with a Rh-(*R*)-DTBM-BINAP catalyst. By switching to the ligand (*R*,*S*)-**L2**, the diastereoselectivity was reversed, allowing for the formation of the *syn*-diastereomer (*R*,*S*)-**192** (81–93%, up to 8 : 1 dr and >99% ee). A detailed computational study on the mechanism of the coupling of aldehydes and alkynes catalyzed synergistically by rhodium and amine revealed the reaction pathway.[137] Rh-hydride species **A** was generated *in situ* from $[Rh(cod)Cl]_2$ and phosphoric acid. The Rh-hydride reacts with alkyne and generates a Rh-π-allyl complex **C** *via* the formation of allene intermediate **B**. At the same time, the amine organocatalyst generates an enamine **D** with aldehyde substrate **189**. The regioselective C–C bond formation between Rh-π-allyl complex **C** and enamine **D** (at the more substituted carbon of complex) forms the intermediate **E** which undergoes hydrolysis to result in the desired homoallylic ketones **191** and **192**. The diastereoselectivity was determined by the *syn*- or *anti*-configuration of intermediate **C** and **D** during C–C bond formation, which was influenced by the steric hindrance created by the chiral Jacobsen's amine (**L1** and **L2**) and the chiral Rh-(*R*)-DTBM-BINAP catalyst.

Vinyl sulfone serves as a versatile building block in organic transformations and is also a core structural component in many drug candidates and bioactive compounds.[138] It has been recognized as a substitute for α,β-unsaturated carbonyl groups, readily participating in 1,4-addition and cycloaddition reactions.[139,140] In this context, Long *et al.* demonstrated a ligand-controlled stereodivergent difunctionalization of terminal alkynes **193** using sodium sulfinates **194** and vinyl triflates **193** (Scheme 47).[141] This approach employs dual photoredox and nickel catalysis to efficiently produce synthetically valuable *cis*- and *trans*-sulfonyl-1,3-dienes in moderate to good yield. The reaction of alkyne substrate **193** with **194** and **195** in the presence of a catalytic amount of $Ru(dtbbpy)_3(PF_6)_2$ and $Ni(OAc)_2 \cdot 4H_2O$, along with terpyridine as the ligand, results in an *anti*-



Scheme 50 Metallaphotoredox approach for the stereodivergent carboallylation of terminal alkynes with allylic carbonates and alkyl trifluoroborates.

addition process, producing highly *E*-selective 1,3-dienes **196** (*E*/*Z* > 99 : 1) as a product. In contrast, when 1,10-phenanthroline was used as the ligand with the $NiCl_2$·dppf catalyst, the reaction favoured *syn*-addition, yielding *Z*-selective 1,3-dienes **197** (*Z*/*E* > 99 : 1). Aromatic and aliphatic alkynes **193** and sulfinates **194** serve as suitable substrates for both reactions. The reaction conditions are compatible with a broad range of functional groups in sulfinates **194** and alkynes **193**, including halides and esters. Additionally, cyclic vinyl triflates **195** provide good yields of 1,3-dienes (**196** and **197**), while acyclic vinyl triflates result in lower diene yields, albeit with excellent selectivity.

Upon light excitation, the photoexcited $*Ru(dtbbpy)_3^{2+}$ ($E^{*ox}_{1/2}$ = +0.81 V *vs.* SCE) interacts with **194** (E^{red} ≈ +0.45 V *vs.* SCE in CH_3CN), releasing a sulfonyl radical and generating Ru(I). When terpyridine is used as the ligand, the sulfonyl radical is trapped by Ni(I) to form Ni(II)–SO_2R (**A**), which is further reduced by Ru(I) to produce Ni(I)–SO_2R complex (**B**). The alkyne **193** coordination to intermediate **B** and successive regioselective migratory insertion yields the *cis*-alkenyl-Ni(I) species **C**, which undergoes *anti*/*syn*-isomerization (activation energy = 25.1 kcal mol^{-1}), leading to the intermediate *trans*-alkenyl-Ni(I) (**D**). The oxidative addition of **D** with vinyl triflate **195** *via* an SN-Ar type mechanism forms *trans*-Ni(III) (**E**), which produces *anti*-addition dienes **196** through reductive elimination.

On the other hand, dppf-ligated Ni(I) (**F**) is a relatively more electron-rich and sterically less hindered catalytic system, generating a Ni(0) species (**G**) through single-electron transfer (SET) reduction by Ru(I) species, which binds with vinyl triflate **195**, and undergoes S_N-Ar type oxidative addition to form the dppf-ligated alkenyl-Ni(II) intermediate **H**. A subsequent ligand exchange with 1,10-phenanthroline produces phenanthroline-ligated alkenyl-Ni(II) complex **I**. Simultaneously, the sulfonyl radical adds to alkyne **193**, forming vinyl radical **J**, which is captured by complex **I**, resulting in the more stable *cis*-Ni(III) species **K**. Reductive elimination of Ni(III) complex **K** produces

the *syn*-selective product **197** and regenerates Ni(I)-species, which undergoes ligand exchange with dppf to reform the catalyst **F**. Finally, $Ru(dtbbpy)_3^+$, ($E_{1/2}^{II/I} = -1.45$ V *vs.* SCE), reduce (dppf)Ni(I) **F** or (terpy)Ni(II) **A**, [$E_{1/2}^{(N^{II}/Ni^0)} = -1.2$ V *vs.* SCE in DMF] regenerating the ground-state $Ru(dtbbpy)_3^{2+}$ and completing the catalytic cycles.

Concurrently, the Srivastava group reported stereodivergent difunctionalizations of terminal and internal alkynes **198** using various sulfinates **199** and isocyanides **200** to synthesize *Z*- and *E*-β-sulfonylacrylamides **203** and **204** (Scheme 48).[142] The *Z*-β-sulfonylacrylamides **203** can be synthesized in a one-pot process by sequentially adding sulfonates **199** and isocyanides **200** to terminal alkynes **198** in ethanol. In contrast, a two-step approach is used to produce *E*-sulfonylacrylamides **204**, which involves the preparation of *E*-β-iodovinylsulfones **202** from sulfinates **199** and terminal or internal alkynes **198** in water, followed by a palladium-catalyzed isocyanide (**200**) addition reaction.

Both reactions proceed smoothly with aliphatic isocyanides (**200**), but aromatic isocyanides are unsuitable. Appreciatively, both electron-rich and electron-poor acetylenes (**198**) with aromatic or aliphatic substitution react smoothly, providing the corresponding sulfonylacrylamides **203** and **204** products in good to excellent yields. Similarly, both aromatic and aliphatic sulfonates **199** afford the products **203** and **204**, but the yields are slightly lower with aliphatic sulfinates. A reaction mechanism is proposed for the metal-free addition of isocyanide to the *in situ*-generated *E*-intermediate **201**, leading to the formation of *Z*-β-sulfonylacrylamide **203** through a Michael-type addition–elimination sequence. It is presumed that *Z*-selectivity is preferred due to the charge stabilization after Michael-type addition (Scheme 49(1)). The formation of *E*-β-sulfonylacrylamide **204** occurs through Pd-catalyzed isocyanide addition to *E*-intermediate **202** (Scheme 49(2)). This reaction initiates with the generation of Pd(0) species from $Pd(OAc)_2$ and DPPF in the presence of DBU, which undergoes oxidative addition with **202** to generate organopalladium complex **A**, followed by coordinates with isocyanide **200** to form complex **B**. Subsequent migratory insertion of isocyanide gives rise to complex **C**, which takes a water molecule to furnish complex **D** and undergoes successive reductive elimination and then tautomerization to afford *E*-β-sulfonylacrylamide **204**.

In the realm of alkyne functionalization, Qin *et al.* introduced a metallaphotoredox approach for stereodivergent three-component carboallylation of terminal alkynes **205** with allylic carbonates **206** and alkyl trifluoroborates **207** (Scheme 50).[143] The reaction of terminal alkyne **205**, allylic carbonate **206**, and *tert*-butyl trifluoroborate **207** in the presence of a catalytic amount of $Ni(phen)Cl_2$, 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy) as the ligand, 4CzIPN as the photocatalyst, and pyrene as an additive was carried out in a DMAc/MeCN solvent mixture under blue LED irradiation ($\lambda_{max} = 467$ nm) at 35 °C, yielding the desired (*E*,*Z*)-1,4-diene product **208** with an 84% yield and high stereoselectivity (*E*/*Z* = 92 : 8). Interestingly, the stereoisomer (*Z*,*Z*)-1,4-diene **209** was obtained with a 79% yield and an opposite stereoselectivity (*E*/*Z* = 16 : 84) when the reaction was conducted without pyrene in the DME solvent.

This redox-neutral dual catalytic method employs commercially available organic photocatalyst 4CzIPN and nickel catalysts to initiate a radical addition/alkenyl–allyl coupling sequence, providing a straightforward route to functionalized 1,4-dienes **208** and **209** with high chemo-, regio-, and stereoselectivity. The process begins with the single-electron oxidation of alkyl trifluoroborate ($E_{1/2}^{red} = +1.26$ V *vs.* SCE) by photoexcited [4CzIPN]* ($E_{1/2} = +1.35$ V *vs.* SCE), generating an alkyl radical **A**, which then adds to an alkyne **205** to form alkenyl radical **B**. The catalytic cycle continues with the oxidative addition of allylic ester **206** to a Ni^0 catalyst, forming allylnickel intermediate **C**. This intermediate captures alkenyl radical **B** to generate a *trans*-(alkenyl)(allyl)Ni^{III}-species **D**, which yields the (*E*,*Z*)-skipped diene product **208** and Ni^I-species **E** upon reductive elimination. A final single-electron transfer between the reducing photocatalyst and Ni^I-species **E** regenerates the ground-state photocatalyst and Ni^0 catalyst, closing both catalytic cycles. The (*E*,*Z*)-skipped diene **208** remains stable in the presence of pyrene but undergoes photoinduced *4CzIPN-enabled *E*-to-*Z* isomerization to form **209** in the absence of pyrene, providing modular access to both *trans*- and *cis*-1,4-dienes.

4. Conclusion

The collective research presented in this review reflects significant progress in the field of stereodivergent semi-hydrogenation of alkynes. By leveraging different metals, ligand architectures, and sustainable hydrogen sources, researchers have developed a diverse array of catalytic systems capable of achieving high levels of stereoselectivity. The emphasis on green chemistry principles, such as the use of water as a hydrogen source and the avoidance of toxic reagents, further underscores the drive toward more sustainable chemical processes. Moving forward, the field is poised to benefit from continued exploration into catalyst stability, reaction scalability, and expanded substrate scope, which will undoubtedly lead to new discoveries and applications in selective alkyne hydrogenation.

This comprehensive overview provides a solid foundation for understanding the current state of research in stereodivergent semi-hydrogenation, highlighting the challenges and opportunities. By integrating innovative mechanistic insights with environmentally conscious methodologies, the field will continue to evolve, driving future breakthroughs in selective alkene synthesis for pharmaceuticals, materials science, and beyond.

Data availability

The datasets generated during the current study are compilations of publicly available literature.

Conflicts of interest

There are no conflics of interest to declare.

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