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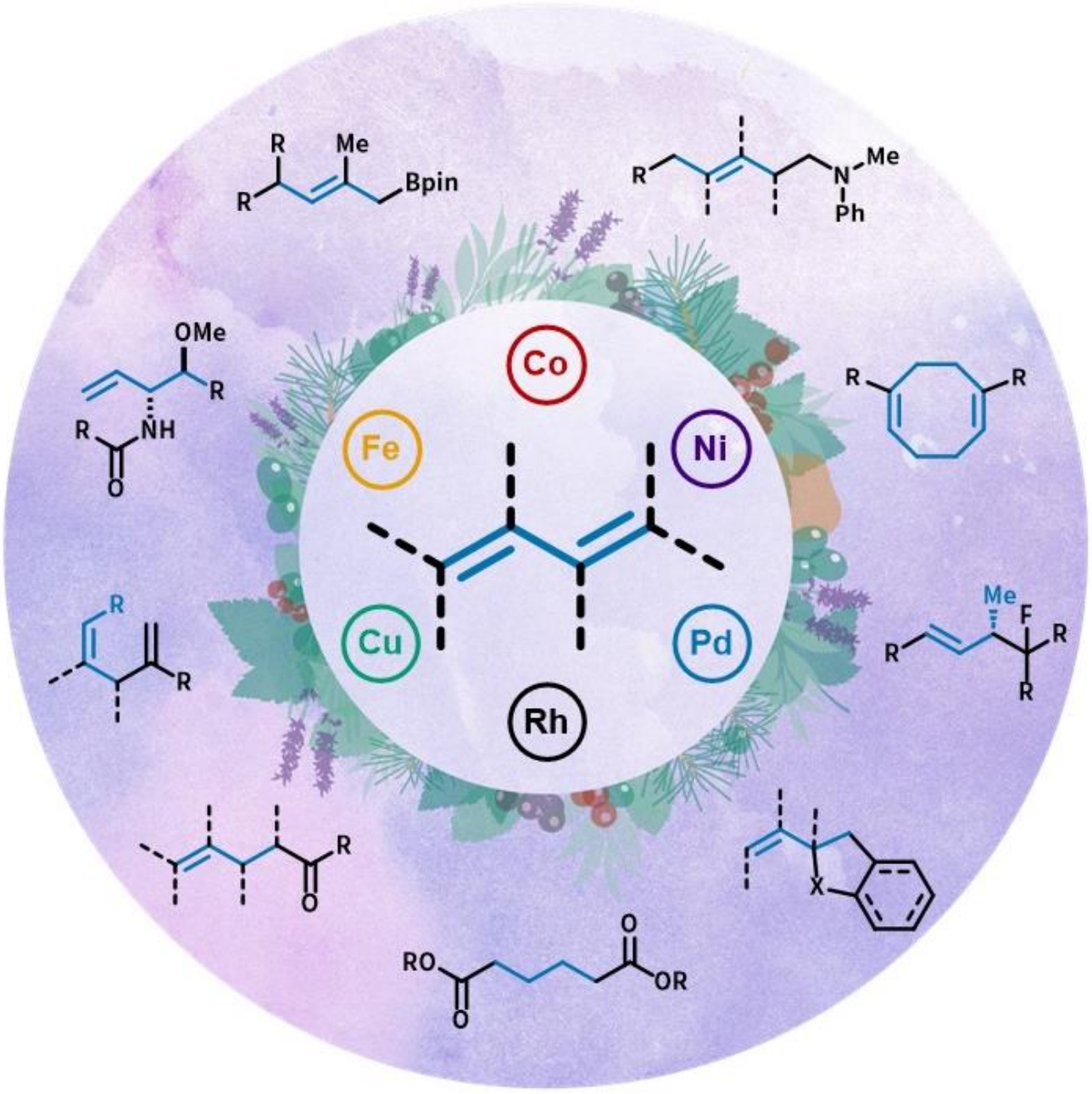
REVIEW

Dienes as Versatile Substrates for Transition Metal-Catalyzed Reactions

Amanda M. Canfield, Dasha Rodina, and Shauna M. Paradine*



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REVIEW

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Abstract:

Dienes have been of great interest to synthetic chemists as valuable substrates due to their abundance and ease of synthesis. Their unique stereoelectronic properties enable broad reactivity with a wide range of transition metals to construct molecular complexity facilitating synthesis of biologically active compounds. In addition, structural diene variation can result in substrate-controlled reactions, providing valuable mechanistic insights into reactivity and selectivity patterns. The last decade has seen a wealth of new methodologies involving diene substrates through the power of transition metal catalysis. This review summarizes recent advances and remaining opportunities for transition metal-catalyzed transformations involving dienes.

1. Introduction

Dienes are useful bifunctional building blocks for diverse applications in drug discovery and the chemical industry.[1] Conjugated 1,3-dienes (e.g., 1,3-butadiene, isoprene, and myrcene) are abundant and readily available commodity chemicals and feedstocks. Dienes are widely used for both laboratory and industry applications, with the production of valuable compounds, including polymeric materials, exceeding 10 million tons per year.[2] Selective, catalytic functionalization of dienes enables rapid preparation of highly functionalized synthetic intermediates, which can be impactful from an environmental and economical perspective. As a result, dienes are valuable reagents for the preparation of natural products and other biologically active compounds.[3]

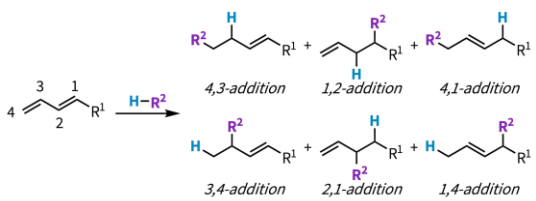

Figure 1. Potential regioselectivity outcomes for 1,3-diene addition reactions.

In addition to polymerization, dienes have long been used as substrates in cycloaddition reactions, e.g., Diels-Alder reaction, and can engage in the same traditional functionalization reactions as alkenes.[4] While methodological developments of these transformations have continued over the decades, this review will focus on recent developments using dienes as substrates in transition metal-catalyzed functionalization reactions.

Dienes are particularly versatile substrates for transition metal-catalyzed transformations. Conjugated dienes represent an attractive platform for selective functionalization reactions, as a separate π system remains in the product as a functional handle for further manipulation. Functionalization of conjugated 1,3-dienes presents selectivity challenges due to the numerous coordination and insertion modes plausible for a transition metal catalyst (Figure 1).[5] The subtle interplay of metal, ligand, additives, and substrate in catalytic transformations involving diene functionalization can lead to excellent regiocontrol over product formation, resulting in selective formation of functionalized products.[6]

Recent review articles have summarized advances in applications of 1,3-dienes in natural product synthesis; therefore, these aspects will not be discussed here.[7] In this review, we mostly focus on reports published within the last decade, where authors have demonstrated unprecedented reactivity or significantly expanded the scope of metal-catalyzed transformations involving dienes. The following text is organized to demonstrate selected approaches to diene synthesis, recent transformations of diene-monofunctionalization, diene difunctionalization, heteroannulation and cycloadditions, as well as an example of a Heck reaction.

1.1. Selected Recent Examples of Transition Metal-Catalyzed Synthesis of Dienes

A traditional approach to preparing dienes is through Wittig olefination reactions, where a diene can be generated by reaction of an aldehyde or ketone with a vinyl phosphonium ylide.[8] A significant drawback of this approach is the production of stoichiometric quantities of phosphine oxide as a byproduct. Enyne metathesis is also useful for synthesizing 1,3-dienes from alkynes and alkenes via metal carbene catalyzed reactions (Figure 2A).[9] Recent work, highlighted below, has sought to expand the toolbox of catalytic methodologies for the preparation of conjugated dienes.

In 2018, the Mazet group reported the use of two Ni(II) precatalysts for the preparation of 2-substituted 1,3-dienes by a Kumada cross-coupling between vinyl magnesium bromide and

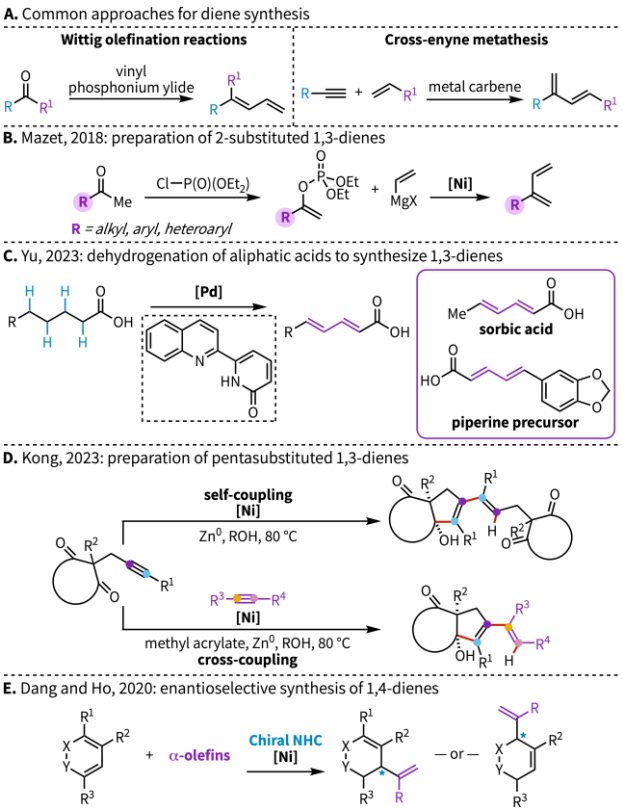

Figure 2. Selected strategies for the synthesis of dienes. (A.) Common reactions to synthesize dienes (B.) Kumada-type coupling of ketones and chlorophosphonates. (C.) C–H dehydrogenation of aliphatic acids. (D.) reductive homo- and heterocoupling of alkynes. (E.) Hydroalkenylation of cyclic dienes and α-olefins.

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vinyl phosphates (Figure 2B).[10] This reactivity is noteworthy as there are challenges associated with vinyl derivatives engaging in transition metal-catalyzed cross-coupling reactions.[11] Advantages of this methodology include operational simplicity, mild reaction conditions, low catalyst loadings, short reaction times, and scalability. This method is compatible with a broad array of functional groups and structurally complex scaffolds to enable preparation of conjugated 1,3-dienes containing various substitution patterns with high levels of stereocontrol. Additionally, a Negishi variant of the reaction (with organozinc reagents) was developed for sensitive organic functional groups, including esters and nitriles. This Ni-catalyzed Kumada vinylation approach complements existing methods to generate previously inaccessible conjugated dienes.

In 2023, the Yu group disclosed a one-step synthesis of 1,3-dienes directly from abundant, aliphatic carboxylic acids (Figure 2C). The Pd(II)-catalyzed reaction, enabled by quinoline-pyridone ligands, proceeds through a sequential dehydrogenation reaction of free aliphatic acids via β-methylene C–H activation.[12] Diversely substituted aliphatic acids could be engaged in this reaction. The synthetic utility was demonstrated by the one-step synthesis of two naturally occurring compounds, including food preservative sorbic acid and a precursor of biologically active piperine.

The Kong group developed a stereoselective synthesis of pentasubstituted conjugated dienes via Ni-catalyzed reductive self- and cross-coupling of two unsymmetrical internal alkynes (Figure 2D).[13] They used a hemilabile directing group strategy to control the regioselectivity for rapid access to highly substituted 1,3-dienes with diverse functional groups in good yields with high enantioselectivity. This protocol features high efficiency and atom economy, without the use of stereodefined coupling partners (e.g., vinyl halide or vinyl organometallic), which are required for traditional cross-coupling reactions.

The Dang and Ho groups developed a method for the synthesis of 1,4-dienes by cross-hydroalkenylation of cyclic 1,3-dienes and hetero-substituted terminal olefins (Figure 2E).[14] A chiral [NHC-Ni(allyl)]BAr^F catalyst provided efficient access to enantioenriched 1,4-dienes, which are synthetically valuable building blocks in asymmetric synthesis.[15] It was suggested that the structurally flexible chiral, C_2-symmetric NHC-Ni catalyst design is vital for accessing a wide range of 1,4-dienes with high enantioselectivity and regiocontrol performed under mild conditions. Additionally, this study provided insight on how to control the 1,3-allylic shift on cyclic dienes to construct sterically hindered endocyclic chiral allylic structures.

Dasha Rodina received her B.A. in Chemistry and Sociology and Anthropology from Lake Forest College in 2018. She is currently pursuing her Ph.D. under the supervision of Dr. Paradine at the University of Rochester. Her research focuses on using unconventional ligands for controlling regioselectivity in Pd-catalyzed heteroannulation reactions.

Amanda Canfield received her B.S. in Pharmaceutical Chemistry from St. John Fisher University in Rochester, New York, in 2019. She is currently pursuing her Ph.D. under the supervision of Dr. Paradine at the University of Rochester. Her research focuses on methodology development using transition metal-catalysis to access ubiquitous heterocyclic motifs.

Shauna Paradine received her B.A. in Chemistry with Honors from Albion College in Albion, Michigan, in 2008. She then conducted Ph.D. studies with M. Christina White at University of Illinois Urbana-Champaign, followed by a postdoctoral fellowship with Eric Jacobsen at Harvard University. In 2018, Shauna started her independent career at the University of Rochester. Her group's research focuses on the development of useful synthetic methods through the discovery of novel strategies in transition metal catalysis.

2. Hydrofunctionalization

2.1 Hydroalkylation

In 2021, the RajanBabu group reported regio- and enantioselective hydroacylation reactions of dienes to synthesize stereochemically defined, *β*-functionalized ketones **3** with an additional latent functionality (Figure 3A).[16] Three classes of dienes, 2- or 4-monosubstituted and 2,4-disubstituted 1,3-dienes, could be engaged in the reaction. The reaction was proposed to undergo a Co(I)/Co(III) redox cycle initiated by a cationic Co(I) intermediate. The authors identified optimized reaction conditions for each class of dienes. Bulky, electron-rich phosphines performed best for 1,2-selective hydroacylation, with (*R,R*)-^{i}Pr-DUPHOS **L1** or (*S,S*)-Ph-BPE **L2** identified as the best ligands to obtain the desired enantiomer. The applicability of this transformation was demonstrated by a two-step, gram scale

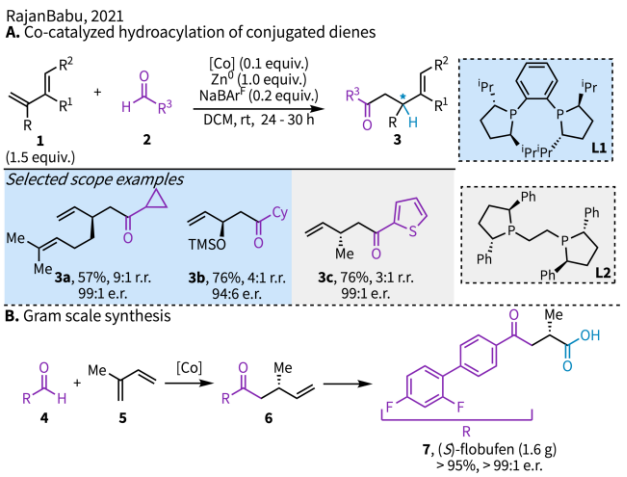

Figure 3. Regio- and enantioselective hydroacylation of 1,3-dienes with selected scope examples. (A.) Reaction scheme and selected substrate scope. (B.) Gram-scale synthesis of NSAID flobufen.

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synthesis of anti-inflammatory agent (*S*)-flobufen **7** with >95% yield and excellent enantioselectivity (Figure 3B).

An interesting example of fluorination came from the Yu group in 2022.[17] Here, they reported a highly enantio- and regioselective hydromonofluoro(methyl)alkylation of 1,3-dienes under redox-neutral nickel catalysis (Figure 4). Key features of this method include a broad substrate scope, impressive enantio- and regioselectivity, commendable functional group tolerance, and the potential for diverse product derivatizations. Phenyl dienes bearing terminal alkyl olefin and *p*-aldehyde functionality reacted smoothly to yield substrates **10a** and **10b**, respectively, with high yield and e.r. Alkyl 1,3-dienes resulted in lower yields under the reaction conditions (e.g., **10c**, 67%), albeit with high enantioselectivity. The primary limitation of this transformation is the requirement for terminal, unbranched dienes and highly acidic carbon nucleophiles (1,3-dicarbonyl and 1,3-disulfonyl).

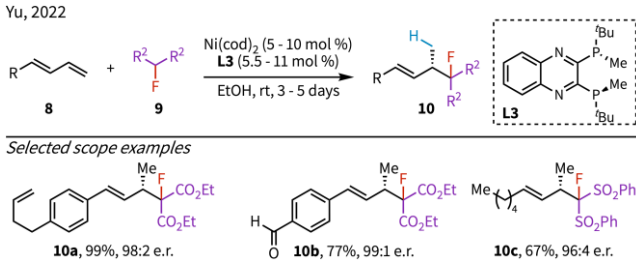

Figure 4. General reaction scheme and selected scope of hydromonofluoro-methylation of dienes.

In 2022, the Huang and Ye groups realized an enantioselective C2–H alkylation of pyridines with 1,3-dienes.[18] In this report, a chiral secondary phosphine oxide-ligated Ni–Al bimetallic catalyst was used to prevent undesired coordination of pyridine to the metal, which could inhibit coordination of the chiral ligand. Previous transition metal-catalyzed methods required C2-blocked pyridines which resulted in limited product complexity.[19] The authors envisioned that the Al Lewis acid would coordinate to pyridine, the ligand linker between Ni and Al would promote preferential activation of the proximate C2–H bond by Ni, and inserting the Ni–H species into 1,3-dienes would generate a more stable allylic intermediate to deliver the branched product. The 1,3-diene scope consisted of aryl dienes bearing electron-donating groups, such as alkyl (**13a**), alkenyl (**13b**), and amino groups (**13c**). Aryl dienes with electron-withdrawing *para*-fluoride (**13d**) and carboxamide (**13e**) groups were also effective diene substrates (Figure 5). A diene substrate bearing a furan was also

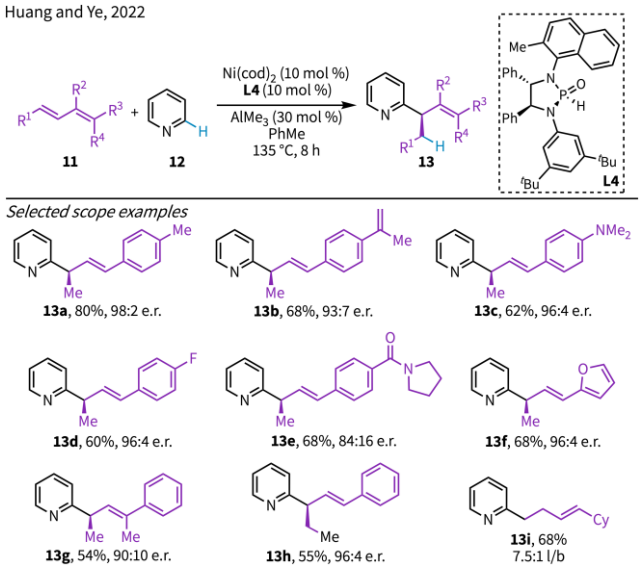

Figure 5. Enantioselective C2–H alkylation of pyridines with 1,3-dienes.

a suitable substrate, providing product **13f** in 68% yield. In addition to monosubstituted dienes, disubstituted 1,3-dienes were also compatible (**13g** and **13h**). This methodology was limited to aryl-containing 1,3-dienes to favor branched selectivity, as replacing the aryl group with an alkyl group or H afforded the linear isomer as the major product (**13i**).

Hydroalkylation of 1,3-dienes via transition metal catalysis is a valuable and atom-economical approach for the construction of substituted allylic compounds.[20] In 2018, Xiao and Zhou developed a highly regioselective Ni-catalyzed hydroalkylation between 1,3-dienes and simple ketones.[21] Selective addition of carbon nucleophiles such as enols/enolates with 1,3-dienes is an efficient method for coupling two simple components via C–C bond formation.[22] This report enables the coupling of dienes with unstabilized carbon nucleophiles, which has remained a synthetic challenge.[23] For these coupling reactions, the active catalyst species is typically a metal hydride, which reacts with a diene to generate an electrophilic Ni–π-allyl intermediate that then reacts with the carbon nucleophile. The 1,2-addition was mediated by a Ni-hydride catalyst with DTBM-SegPhos as ligand and potassium *tert*-butoxide as the base.

The 1,3-diene scope was examined by reaction of acetophenone with a variety of dienes (Figure 6A). Aryl dienes afforded the 1,2-addition products in moderate to good yield and excellent regioselectivity (>99:1). A 2-furyl diene provided the desired product **16a** in 68% yield. Alkyl 1,3-dienes were also compatible and resulted in moderate product yields. Product **16c** highlights the chemoselectivity of this reaction, as the isolated C=C double bond was preserved. The limitations for this chemistry are the long reactions times and the diene scope consisting of only monosubstituted dienes. It was noted that the olefin geometry of the diene had minimal impact on yield, regioselectivity, or enantioselectivity. The (*E*)-olefin product was exclusively observed when a ~2:1 mixture of *E*- and *Z*-phenylbutadienes were subjected to the optimized reaction conditions. This reaction can also be rendered enantioselective with chiral ligand (*R*)- or (*S*)-DTBM-HO-BIPHEP, **L5**, affording enantioenriched γ,δ-unsaturated ketones bearing a β-stereocenter. The enantioenriched product contained an olefin functional handle for further modification and was subjected to oxidative cleavage for the enantioselective synthesis of bioactive (*R*)-flobufen (**20**), a nonsteroidal anti-inflammatory drug (Figure 6B).

The Zhou group further explored different alkyl carbon nucleophiles to expand the utility of hydroalkylation reactions with 1,3-dienes, reporting a Ni-catalyzed hydroalkylation and hydroalkenylation of dienes with hydrazones.[24] Reaction

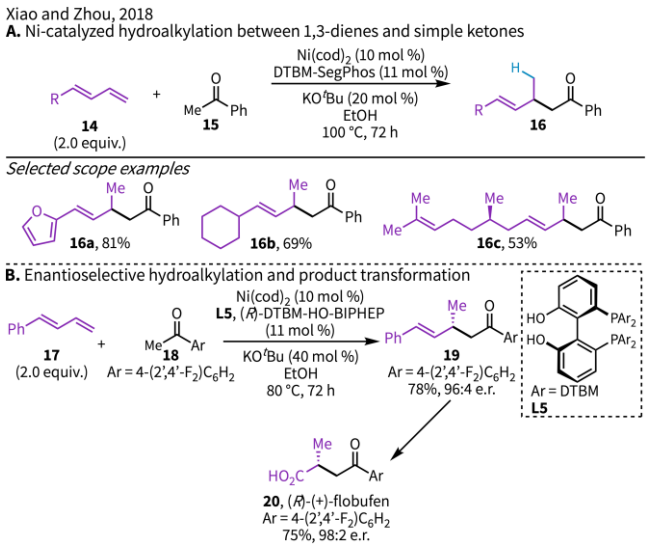

Figure 6. Hydroalkylation of 1,3-dienes with simple ketones. (A.) Selected substrate scope. (B.) Enantioselective hydroalkylation.

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optimization found electron-deficient ligand, tris[4-(trifluoromethyl)phenyl]phosphine, and the base LiO^{t}Bu crucial for achieving the desired 1,2-hydroalkylation in high yield and regioselectivity. The 1,3-diene scope displayed good functional group compatibility (Figure 7A). For example, terminal thienyl diene **23a** reacted smoothly to afford the corresponding hydroalkylation product. Notably, internal aromatic dienes were suitable substrates (**23b**), as well as aliphatic dienes when the diphosphine ligand DPPPe was used (**23c**).

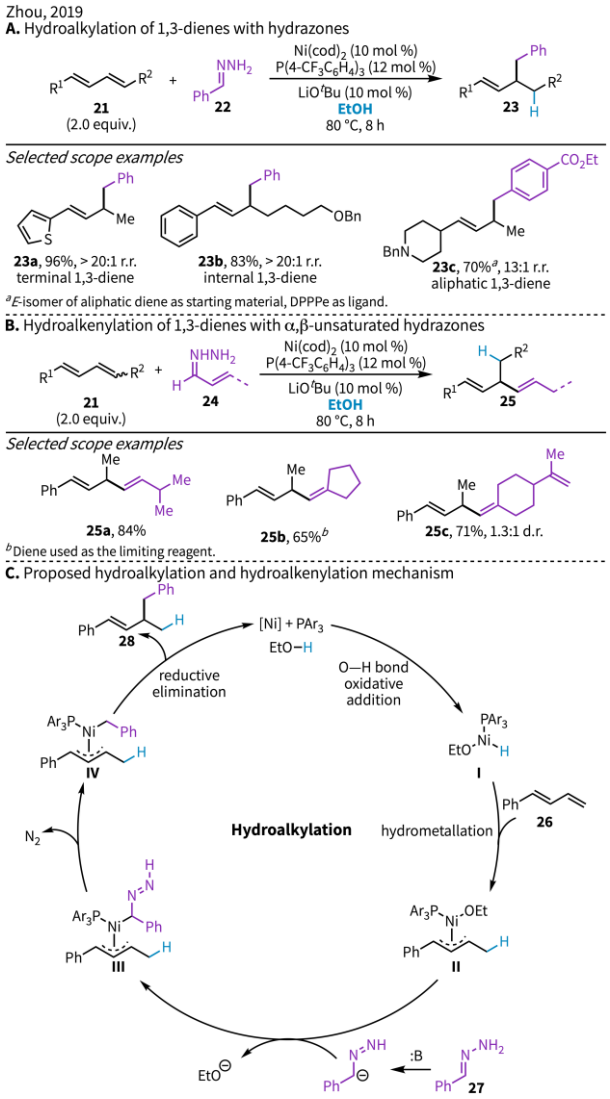

Figure 7. Ni-catalyzed hydroalkylation and hydroalkenylation of 1,3-dienes. (A.) Selected hydroalkylation substrate scope. (B.) Selected hydroalkenylation substrate scope. (C.) Proposed catalytic cycle.

A protocol for hydroalkenylation of dienes with α,β-unsaturated hydrazones provided a new synthetic route to 1,4-skipped dienes. This method avoids preparation of stoichiometric alkenylmetal reagents required for the typical synthesis of 1,4-dienes by transition metal-catalyzed allylic substitution reactions and operates under mild conditions. Variously substituted 1,4-dienes were synthesized by reactions of 1,3-dienes with hydrazones (Figure 7B). Acyclic and cyclic enal-hydrazones were amenable (**25a-b**). Natural-product-derived perillaldehyde was employed to give 1,4-diene product **25c**. A plausible mechanism for the hydroalkylation reaction is shown in Figure 7C. Initial oxidative addition of EtOH and Ni(0) forms Ni–H intermediate **I**, which adds to diene **26** to generate a π-allyl-nickel intermediate **II**. Intermediate **III**, which resulted from a ligand exchange reaction between **II** and the diazene anion generated from hydrazone **27**, undergoes expulsion of nitrogen and proton transfer in the presence of base in the protic medium to form intermediate **IV**. Reductive elimination of **IV** affords hydroalkylation product **28** and regenerates the Ni(0) catalyst. Similar steps are proposed for hydroalkenylation.

The Chirik group reported a selective intermolecular [1,4]-hydrovinylation of conjugated dienes with unactivated α-olefins enabled by α-diimine iron complexes (Figure 8).[25] This efficient approach afforded skipped diene products with exclusive [1,4]-selectivity and overcame chemo-, regio-, and stereoselectivity challenges observed for previous hydrovinylation reactions of 1,3-dienes. This iron-catalyzed method was highly stereoselective, as only the (*Z*)-isomers were observed for **31a-f**, with no evidence of alkene isomerization (Figure 8A). Dienes bearing substitution at the C2 position exclusively, such as isoprene and myrcene, underwent C–C bond formation at the C1 terminus and formed the branched regioisomers (**31b-d**). C–C bond formation was still observed at C1 with additional substitution (**31e**), although branched selectivity slightly decreased. The authors used bench-stable iron(II) halide precatalyst (^{Mes}DI)FeBr$_2$ directly with the addition of magnesium butadiene (Mg(C$_4$H$_6$)·2THF) as an in situ reductant, and Et$_2$O was added to improve solubility of the iron(II) halide and reductant, to selectively synthesize hydrovinylation product **34** on a multigram scale (Figure 8B). The authors conducted deuterium-labeling experiments and kinetic analysis to elucidate a mechanistic pathway involving oxidative cyclization of an alkene with the diene complex to generate an iron metallacycle.

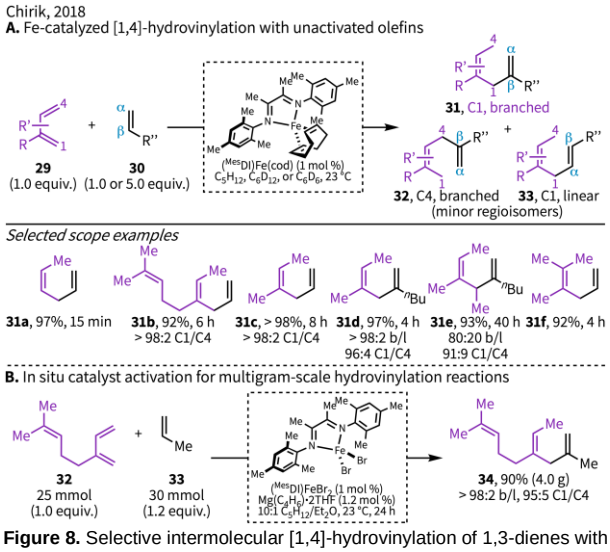

Figure 8. Selective intermolecular [1,4]-hydrovinylation of 1,3-dienes with unactivated α-olefins. (A.) Selected substrate scope. (B.) Multigram synthesis via in situ catalyst activation.

2.2 Hydroalkoxylation

Hydroalkoxylation offers a compelling and direct route to generate allyl ethers. While this transformation has been realized using allenes and alkynes, employing readily available 1,3-dienes presents challenges, most notably racemization and isomerization. Recently, the Dong and Yang groups reported a regio- and enantioselective hydrofunctionalization of 1,3-dienes using a Ni-DuPhos catalytic system, enabling the synthesis of enantioenriched allylic ethers from alcohols (Figure 9).[26] Reaction time analysis revealed a decrease in enantioselectivity over extended reaction time periods. However, control over the reversibility of C–O bond formation was achieved by conducting the reaction in a solvent free environment. The method showed good reactivity with phenyl butadiene derivatives. Additionally, dienes bearing heterocyclic substituents such as furans (**37a**) gave excellent product yields and enantioselectivity. Alkyl 1,3-dienes were lower yielding, with only 31% of **37b** isolated (88:12 e.r.) (Figure 9A). Branching along the 1,3-diene was tolerated but

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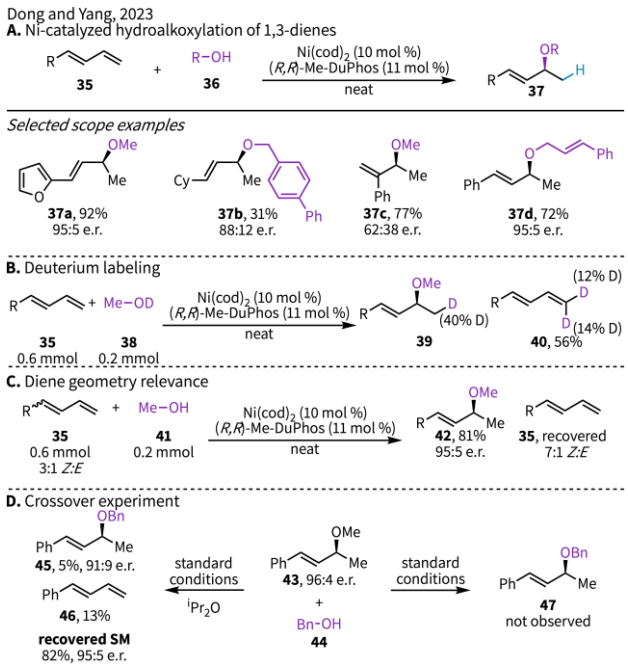

Figure 9. Selective hydroalkoxylation of 1,3-dienes scope examples and selected mechanistic experiments. (A.) Selected substrate scope. (B.) Isotopic labeling studies. (C.) Effect of diene geometry. (D.) Crossover experiments.

with poor enantioselectivity (**37c**, 62:38 e.r.). The alcohol substrate could also be varied, with cinnamyl alcohol affording allyl ether product **37d** in 72% yield and with excellent enantioselectivity.

Deuterium labelling studies were conducted to elucidate the reaction mechanism. The authors proposed that the hydrogen transfer proceeds via a ligand-to-ligand pathway. The recovered diene exhibited deuterium incorporation at its terminal end, indicating the reversibility of the hydrogen transfer step (Figure 9B). Although the *Z* diene did not impact yields or selectivity, it did prolong the reaction time. Moreover, the isolated diene remained predominantly in the *Z* isomer, suggesting that isomerization occurs at a rate slower than the alcohol addition (Figure 9C). Finally, a crossover experiment was conducted to illustrate the impact of the solvent on the reversibility of the C–O bond formation step. Under the solvent-free reaction conditions, there was no formation of benzyl ether product **47**. The addition of diisopropyl ether as a solvent resulted in observation of **45** and 13% yield of recovered phenyl butadiene **46**. The remaining mass consisted of unreacted starting material (Figure 9D).

2.3 Hydroamination

Transition metal-catalyzed amination reactions of double bonds efficiently transform simple starting materials into valuable nitrogen-functionalized compounds.[27] In the past, intermolecular variants of these reactions have suffered from poor regio-, diastereo-, and enantiocontrol.[28] In 2017, the Dong group developed a catalytic and regioselective intermolecular hydroamination of 1,3-dienes.[29] This was the first report of intermolecular coupling between amines and 1,3-dienes to generate homoallylic amines with *anti*-Markovnikov selectivity. Intermolecular hydroamination of 1,3-dienes was previously limited to 1,3-addition or 1,4-addition due to a stabilized metal–π-allyl intermediate.[30] However, the Dong lab found that catalyst choice could control the regioselectivity of intermolecular hydroamination. A combination of a Rh catalyst, *rac*-BINAP (**L6**), and mandelic acid transformed conjugated dienes via 1,2-*anti*-Markovnikov addition of indoline for the synthesis of homoallylic amines **50**. Highlights of the diene scope include a sterically demanding, *ortho*-methyl substituted aryl ring that afforded the desired homoallylic amine **50a** in 60% yield, and the compatibility of aliphatic dienes (**50b** and **50c**) with the reaction conditions (Figure 10A). Dienes bearing an ether (**50d**) and a phthalimide functional group (**50e**) reacted smoothly. Sterically hindered 1,2-disubstituted dienes were also competent substrates (**50f**).

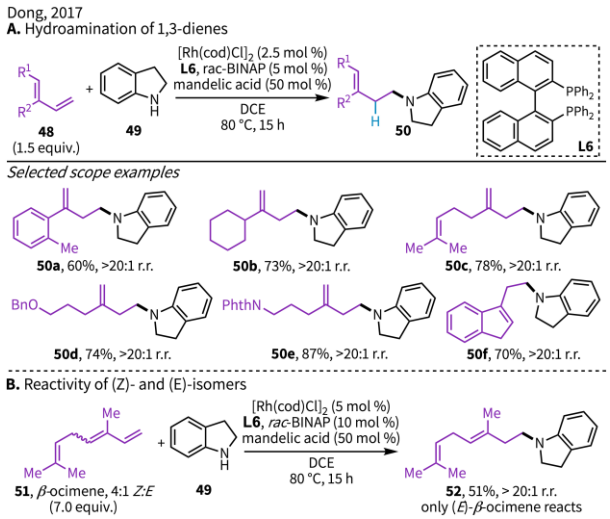

Figure 10. *Anti*-Markovnikov hydroamination of 1,3-dienes to generate homoallylic amines. (A.) Selected diene scope. (B.) Effect of diene geometry.

When a mixture of (*Z*)- and (*E*)-β-ocimene isomers **51** was subjected to the amination reaction conditions, only (*E*)-β-ocimene reacted to generate the homoallylic amine (**52**) in 51% yield, while the (*Z*)-isomer remained unreacted (Figure 10B). The exclusive reactivity of (*E*)-β-ocimene to form the hydroamination product suggests that the 1,3-diene coordinates to the catalyst in an *s-cis* conformation. The authors hypothesized that the anti-Markovnikov selectivity results from key interactions between the catalyst structure and the orientation of the alkene, where the favorable generation of the Rh-π-allyl intermediate occurs with the less sterically hindered E-isomer.

In 2019, the Mazet group disclosed an enantioselective Ni-catalyzed hydroamination of 1,3-dienes using primary and secondary amines.[28] This serves as the first reported enantioselective synthesis of secondary amines via intermolecular hydroamination between branched dienes and unactivated, primary aliphatic amines. Previous challenges overcome by this methodology include detrimental exchange processes and requirement for modified amine transfer reagents.[27],[31] The catalytic combination of $Ni(cod)_2$ and (*R,R*)-BenzP* (**L7**) achieved the desired 3,4-hydroamination to construct allylic amines. 2-aryl-substituted dienes with various functional groups and heteroaryl substituents reacted with high

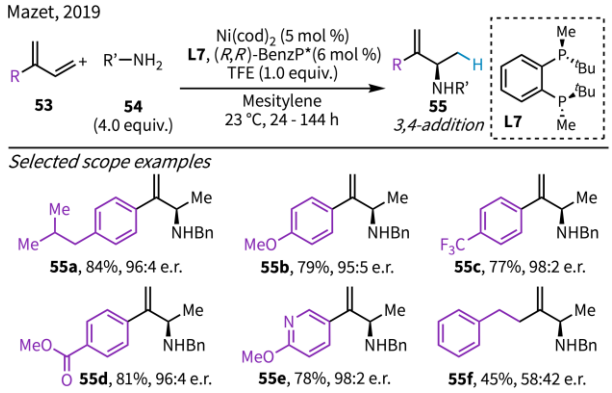

Figure 11. Ni-catalyzed hydroamination of 2-substituted 1,3-dienes.

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regio- and enantioselectivity, while yield, regio-, and enantioselectivity suffered with aliphatic dienes (Figure 11).

In addition, these reactions sometimes required upward of 144 hours to proceed to completion, with 48 hours being the shortest reaction time for the reported dienes. Both primary and secondary alkylamines are competent nucleophiles under the reaction conditions. Mechanistic studies suggested that a Ni–π-allyl complex is the catalytic resting state, and the rate-determining step is an outer-sphere nucleophilic addition of H-bonded amine aggregates.

The Rovis group established a mild method for hydroaminoalkylation of conjugated dienes using a photoredox and Co co-catalytic system.[32] This report entails the coupling of photoredox-generated α-amino radicals with dienes to access homoallylic amines from simple, commercially available precursors. Optimized conditions involved a unified cobalt and photoredox catalytic system, a diphosphine ligand (dppp), and CsOPiv as the base. The fluorinated catalyst **PC** led to higher yields and increased catalyst longevity. Examples from the diene coupling partner scope are highlighted in Figure 12A.

Simple dienes, such as butadiene, were reactive under the optimized reaction conditions, albeit with low stereoselectivity (**58a**). Electron-poor dienes (**58c**) were compatible, while electron-rich dienes were poor yielding. Functionally diverse linear dienes, including myrcene (**58b**), piperine (**58d**), and pseudoionone (**58e**), were engaged under the optimized reaction conditions. Notably, when pseudoionone was used as substrate, the resulting product contained a quaternary stereocenter.

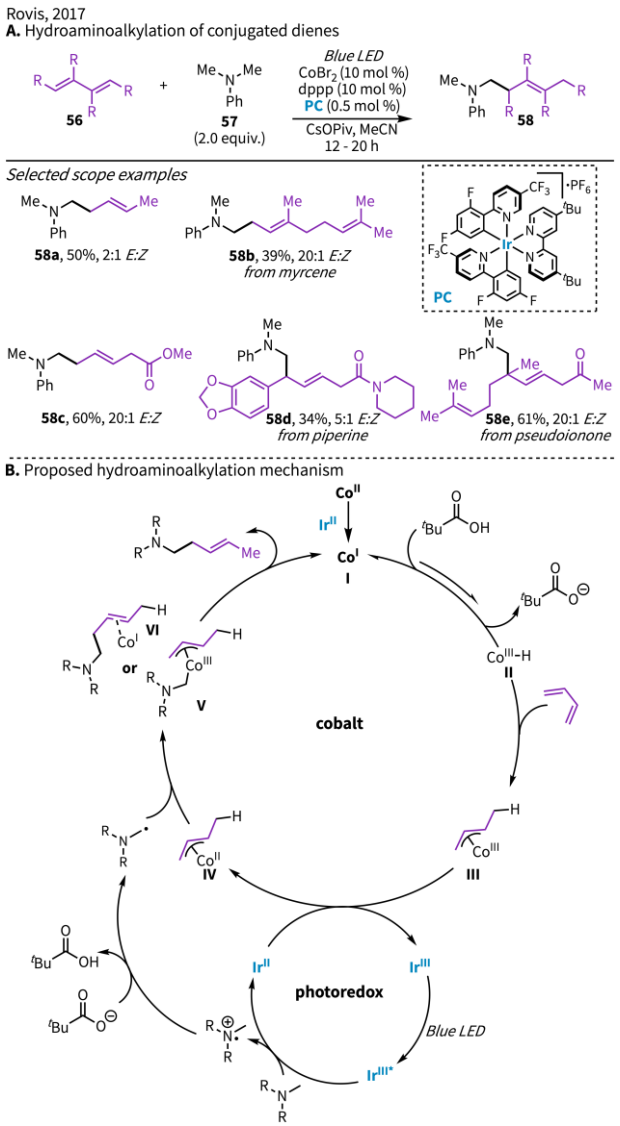

Figure 12. Hydroaminoalkylation of dienes to generate homoallylic amines. (A.) Selected diene scope. (B.) Proposed catalytic cycle.

The proposed mechanism is shown in Figure 12B. The Co(I) species **I** formed in situ by reduction of the Co(II) salt in the presence of the photocatalyst reacts with an equivalent of carboxylic acid to generate species **II**, a transient Co(III) hydride species. CV experiments support migratory insertion of the diene into the Co–H bond to form a Co(III)–π-allyl species **III**, which can be reduced by the photocatalyst to generate a Co(II)–allyl species **IV**. An α-amino alkyl radical can be generated through deprotonation of the oxidized tertiary amine, where the radical can add to the Co center, **V**, which undergoes reductive elimination to generate the homoallylic amine and Co(I), completing the catalytic cycle. The authors also proposed an alternative pathway where the radical may add to the allyl ligand directly, **VI**, affording the product and a Co(I) species. This reactivity allows for coupling of π-rich functionalities with photoredox-generated radical intermediates.

2.4 Hydroboration

Transition metal-catalyzed hydroboration of 1,3-dienes represents a fruitful strategy to access functionalized, and potentially enantioenriched, structural motifs.[33] Highly substituted 1,3-dienes can undergo metal-catalyzed hydroboration reactions to provide valuable organoboron intermediates that can be readily transformed into valuable functional groups like alcohols, making them versatile building blocks in synthetic organic chemistry and catalysis.

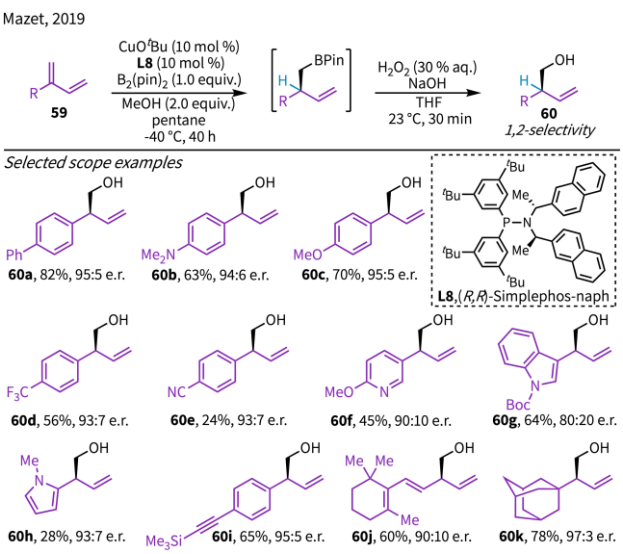

Figure 13. Sequential hydroboration/oxidation of 2-substituted 1,3-dienes.

A highly chemo-, regio-, and enantioselective Cu-catalyzed 1,2-hydroboration of 1,3-dienes was developed by the Mazet group using a chiral phosphanamine ligand (**L8**).[33] This methodology enabled the selective functionalization of 2-substituted 1,3-dienes, which are underexplored scaffolds relative to linear 1,3-dienes.[34] This is a challenging feat in terms of regioselectivity, given that up to six different regioisomers can be generated from exclusive monofunctionalization. With Simplephos (**L8**) as the chiral ligand, this reaction provided rapid access to enantioenriched, homoallylic boronates/alcohols. 2-aryl and 2-heteroaryl 1,3-dienes, in addition to sterically demanding 2-alkyl 1,3-dienes, are among the highlights of the substrate scope (Figure 13).

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Products resulted solely from 1,2- and 4,3-hydroboration for most substrates, which was followed by oxidation to afford homoallylic alcohol **60**. Conjugated 1,3-dienes bearing aromatic substitution of varying electronic properties afforded products in moderate to good yields, with good to excellent regioselectivity and good enantioselectivity. Functional groups such as amino (**60b**), methoxy (**60c**), and trifluoromethyl (**60d**) were tolerated. However, a homoallylic alcohol containing a *p*-CN substituent was isolated in 24% yield (**60e**). Reduced yields were also reported for heteroaromatic-containing 1,3-dienes (**60f**-**60h**). Additionally, the reaction demonstrated excellent chemoselectivity in the presence of alkyne substitution (**60i**). Skipped dienes derived from parent dendralenic 1,3-dienes were also compatible and the 1,2-hydroboration product was obtained as a single regioisomer (**60j**). Conjugated 2-alkyl-1,3-dienes were also employed, and it was found that sterically demanding tertiary alkyl substituents (**60k**) were necessary for good yields, chemoselectivity, and enantioselectivity. When primary and secondary alkyl dienes were used, 4,3-borylation was favored.

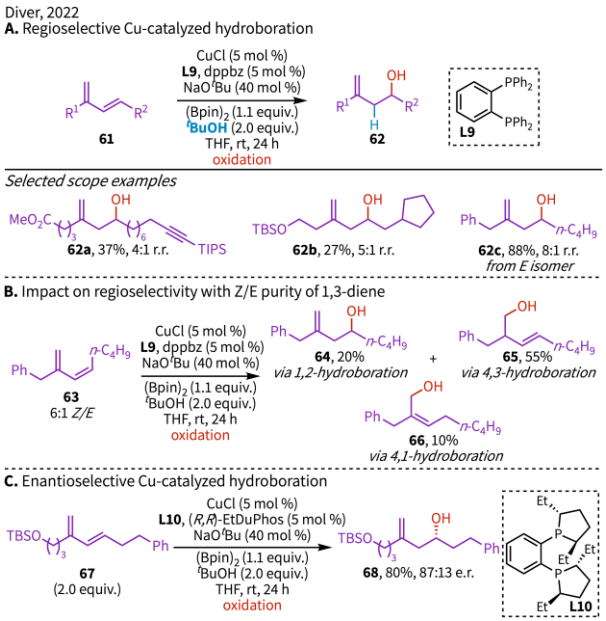

Figure 14. Cu-catalyzed hydroboration of 1,3-disubstituted-1,3-dienes. (A.) Selected diene scope. (B.) Impact of diene geometry on regioselectivity. (C.) Enantioselective hydroboration.

Inspired by Mazet's work, the Diver group disclosed a regio- and enantioselective, Cu-catalyzed hydroboration of 1,3-disubstituted-1,3-dienes generated from catalytic enyne metathesis.[6] The racemic variant of the reaction proceeded with high regioselectivity using chelating diphosphine ligand, 1,2-bis(diphenylphosphino)benzene (**L9**, dppbz). A two-step protocol of Cu-catalyzed hydroboration followed by oxidation afforded homoallylic alcohols, with substituents at both the 1- and 3-positions tested (Figure 14A). The major regioisomer resulted from 1,2-hydroboration and the only other regioisomer observed was from 4,3-addition. The chemoselectivity of Cu–Bpin addition for the 1,3-diene moiety was demonstrated through compatibility with a terminal alkyne **62a**; Cu and ligand loadings were increased to 20 mol% for this substrate. A diene substrate that contained branching in the sidechain was poorly reactive under the reaction conditions.

The reactivity and regioselectivity of *E*- and *Z*-isomeric dienes was investigated. *E*-1-butyl-3-benzyl-1,3-butadiene afforded the desired product in 88% yield and a 9:1 mixture of regioisomers. The *Z* isomer underwent full conversion under the reaction conditions but the regioselectivity was altered to favor 4,3-hydroboration (**65**) (Figure 14B). When *E*/*Z* mixtures of dienes were used, diminished regioselectivity was observed. Given that 1,2-addition generates a stereocenter, the authors rendered the reaction enantioselective using chiral diphosphine ligand (*R,R*)-EtDuPhos (**L10**) (Figure 14C). Seven substituted 1,3-dienes afforded enantioselectivities ranging from 83:17-94:6 e.r.. Overall, the diene scope lacked functional group diversity – for example, no heterocycles or nitrogen substitution were shown. Synthetic utility of the regioselective hydroboration was demonstrated by product functionalization and a photoredox cross-coupling.

3. Difunctionalization

Difunctionalization reactions, particularly of dienes, are valuable in synthetic chemistry for simultaneously introducing two functional groups into a molecule in a single step,[35] streamlining the construction of complex structures from simple precursors. This approach, which leads to the versatile synthesis of diverse, multifunctional compounds,[36] can enable the efficient preparation of pharmaceuticals, agrochemicals, and advanced materials, enabling precise molecular control and fostering significant advances in the generation of complex, functionalized molecules.

3.1 Silylation

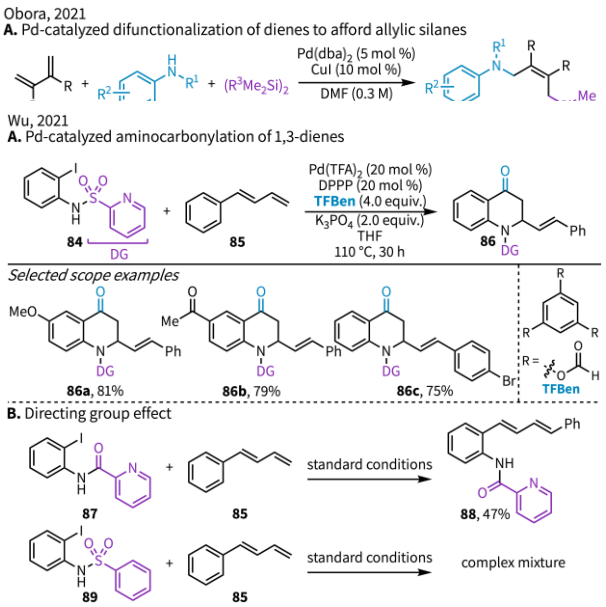

Figure 18. 1,2-amino carbonylation of 1,3-dienes. (A.) Selected scope examples. (B.) Mechanistic investigations into the role of directing group.

The Obora group reported a highly regioselective and stereoselective difunctionalization reaction of 1,3-dienes with amines and disilane to form C–N and C–Si bonds via a one-step Pd/Cu/O_2 co-catalytic system.[37] Under the optimized conditions various amines, dienes, and disilanes were engaged in the 1,4-aminosilylation reaction (Figure 15A). The highest yielding substrate was diphenylamine derivative **72a** at 92% with high Z selectivity. Another halogenated amine, *o*-chloro-*N*-methylaniline, reacted with good yield but lower selectivity (**72b**). Reactivity with simple butadiene was significantly lower than with 2,3-dimethyl-1,3-butadiene, yielding only 51% of desired **72c** *E*-isomer as major product. Despite the somewhat limited scope of diene and disilane substrates, the developed synthetic methodology was scaled up to 100 grams, maintaining high yield and selectivity with model substrates. To elucidate reaction mechanism, authors subjected four plausible intermediates to their reaction conditions (Figure 15B). Diene **73**, the intermediate formed from oxidative amination between 1,3-butadiene and N-methylaniline, reacted with hexamethyldisilane to yield 20% of desired product. Intermediates **74**, **75**, and **76** did not react when subjected to standard reaction conditions. The experimental results suggested

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that difunctionalization reaction occurs via oxidative amination which is followed by silylation.

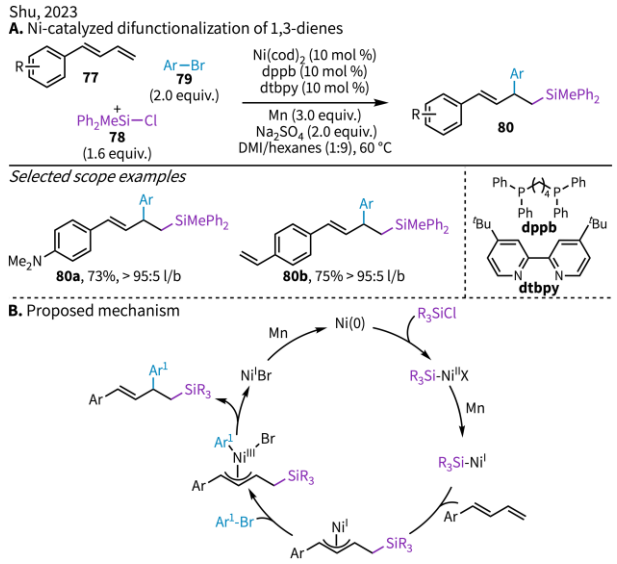

Figure 16. Ni-catalyzed silylation reaction of 1,3-dienes with chlorosilanes and aryl bromides. (A.) Selected scope examples. (B.) Proposed mechanistic pathway.

In 2023, the Shu group reported a Ni-catalyzed three-component, cross-electrophile coupling of dienes and chlorosilanes with aryl bromides.[38] The reaction afforded 1,2-linear-silylated products, regioselectivity that is different from that obtained from conventional methods via H(C)–π-allylmetal species as intermediates.[39] The unconventional regioselectivity is proposed to be from reaction of diene with R_3Si–Cl prior to coupling with aryl bromide. This work demonstrated that nonradical three-component cross-electrophile coupling of unsaturated bonds is possible and extended the scope of this chemistry from C–C coupling to C–Si coupling. The method displayed good functional group tolerance within the substrate scope; for example, electron-donating substrate **80a** gave 73% yield with excellent selectivity (Figure 16A). Interestingly, a diene substrate bearing a distal alkene afforded the desired product **80b** with high chemoselectivity. The major limitation of the scope is the lack of reactivity with aliphatic dienes. Based on control experiments, the authors proposed that the 1,3-diene initially reacts with R_3SiCl, followed by coupling with the aryl bromide (Figure 16B). Manganese acts as a reductant and promotes the migratory insertion process.

3.2 Carbonylation and Carboxylation

Transition metal-catalyzed carbonylation transforms unsaturated C–C bonds and nucleophiles like amines or alcohols into high-value products using inexpensive, broadly available CO.[40],[41] The Beller group demonstrated the highly selective, Pd-catalyzed polycarbonylation of 1,3-butadiene through ligand design; they found pyridyl-substituted bidentate phosphine **L11** (HeMaRaphos) to be optimal.[42] Through this method, they were

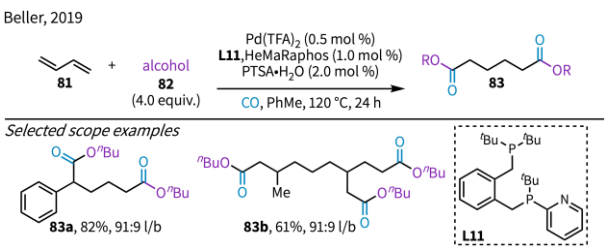

Figure 17. Pd-catalyzed carbonylation of 1,3-dienes.

able to overcome longstanding challenges of isomerization, hydroalkoxylation, and monocarbonylation to access selective di-**83a** and tri-esters **83b** from polyenes (Figure 17).

In 2021, the Wu group reported a 1,2-aminocarbonylation of 1,3-dienes with (*N*-SO_2Py)-2-iodoanilines, with N-SO_2Py as directing group, and benzene-1,3,5-triyl triformate (TFBen) as a benign CO source to yield 2,3-dihydroquinolin-4(1H)-ones.[43] Iodoanilines bearing both electron-rich **86a** and electron-deficient **86b** substituents para to nitrogen were effective, as well as conjugated linear dienes. Aryl bromides were tolerated under the reaction conditions (**86c**) (Figure 18A). Aliphatic and branched dienes are not tolerated in this methodology. Control experiments elucidated key aspects of the reaction mechanism and the role of the directing group. Unprotected, methyl, or *N*-Boc protected 2-iodoaniline did not yield desired product. *N*-picolinyl-2-iodoaniline **87** was converted to the corresponding Heck product **88**, suggesting the importance of the pyridinyl nitrogen in the sulfuryl unit on the directing group (Figure 18B). Additionally, the post-CO insertion catalytic intermediate was isolated and characterized; the crystal structure showed coordination between Pd and N of the directing group.

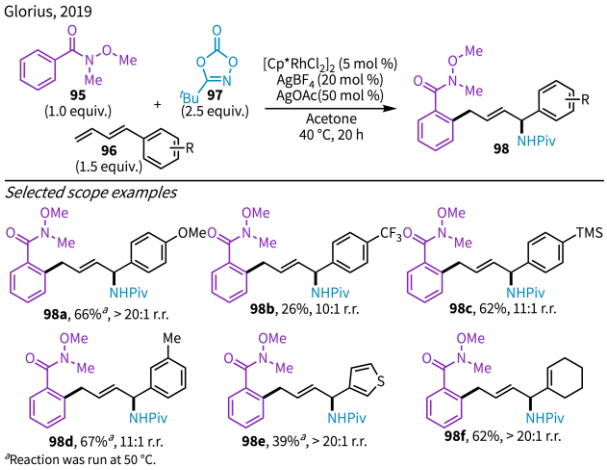

Figure 21. 1,4-carboamination of conjugated dienes.

The Martin group reported a catalytic, site-selective carboxylative difunctionalization of 1,3-dienes under atmospheric pressure to access a variety of adipic acids.[44] Using $NiBr_4(TBA)_2$, phenanthroline ligand **L12**, and Mn as a reductant they generated the desired product in good yields and with excellent regioselectivity. The scope of methodology is broad, tolerating electronically diverse and sterically demanding substituents, in addition to aliphatic and functionalized substrates (Figure 19). The authors highlighted the utility of the transformation by obtaining carboxylic acids from butadiene, isoprene, and piperylene, compounds that are generated in bulk as byproducts of steam cracking in the production of ethylene.[45] The authors gathered mechanistic information by isolating the Ni π-allyl intermediate prior the addition of second CO_2 to the substrate, and found that reaction with cyclohexadiene affords primarily trans-substituted product; based on these results they

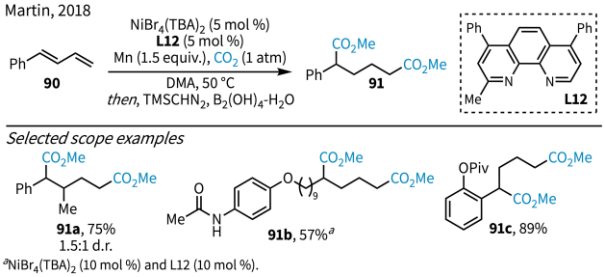

Figure 19. Ni-catalyzed dicarboxylation of 1,3-dienes using CO_2.

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hypothesize that the reaction occurs through formal backside addition of the second CO_2.

3.3 Amination

Aminofunctionalization reactions of alkenes are effective for building molecular complexity by incorporating nitrogen functionality into organic molecules through rapid installation of C–C and C–N bonds across simple precursors.[46] Wang and colleagues introduced an innovative one-step method to generate medicinally relevant β-fluoroalkylamines through the 1,2-aminofluorination of alkenes.[47] The authors realized a three-component aminofluorination across a variety of alkenes and 1,3-dienes via a copper-catalyzed electrophilic amination approach, using *O*-benzoylhydroxylamines as the alkylamine source and $Et_3N{\cdot}3HF$ as the nucleophilic agent (Figure 20). While initially designed for isolated alkenes, they expanded the methodology to 1,3-dienes, addressing the selectivity challenges introduced by an additional alkene. A 4-bromophenyl-substituted diene afforded product **94a** in 48% yield, while a linear aliphatic diene **94b** exhibited moderate yield, with a preference for the 1,2-product (7:1 r.r.). Notably, isoprene reactions highlighted the affinity for aminofluorination of the branched alkene **94c**, giving 45% yield at a 10:1 regioselectivity (Figure 20A). This approach boasts impressive regioselectivity and broad functional group tolerance, offering efficient access to a wide range of β-fluorinated, electron-rich alkylamines. The team further showcased the synthetic utility by modifying derivatives of recognized drugs, like ibuprofen and fenofibrate, under their standard reaction conditions. Their proposed reaction mechanism, depicted in Figure 20B, was informed by radical scavenger experiments and a radical clock reaction. The process commences with a copper-driven N–O cleavage, producing intermediate **I**, which, after alkene electrophilic amination, forms a stable radical **II**. This radical then undergoes copper-facilitated fluorination. Throughout this mechanism, $Et_3N{\cdot}3HF$ serves a dual purpose: aiding the formation of the aminyl radical cation **I** as an acid source and promoting the fluorination stage as a nucleophilic fluoride.

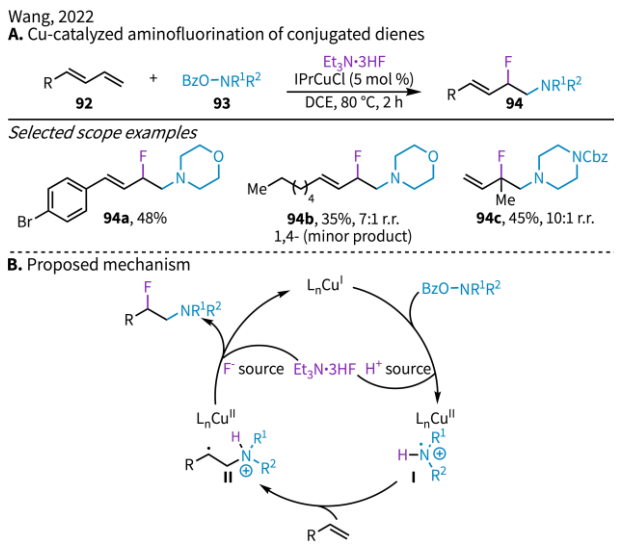

Figure 20. Three-component aminofluorination of 1,3-dienes. (A.) Selected diene scope. (B.) Proposed mechanism.

The Glorius group reported a general method for regio- and stereoselective 1,4-carboamination of conjugated dienes.[48] The intermolecular 1,4-carboamination involves the reaction of Weinreb amide **95**, conjugated diene **96**, and *tert*-butyl dioxazolone **97**, with $[Cp^*RhCl_2]_2$ as the catalyst to afford protected primary amine product **98** (Figure 21).The authors proposed that the carboamination of dienes is enabled by Cp^*Rh^{III} C–H activation, and mechanistic insights supported an intermediate Rh^{III}–allyl species coupled with the electrophilic amination reagent. Overall, the 1,3-diene scope primarily consisted of aromatic substrates that proceeded with moderate yields and good to high regioselectivity. Methoxy (**98a**) and trimethylsilyl (**98c**) functional groups were well tolerated, while trifluoromethyl substituent (**98b**) resulted in lower yield. Only para substitution on 1-phenylbutadienes was reported, with one example of a *meta*-methyl substitution (**98d**). A single example of a heterocyclic diene included a thiophene-containing diene (**98e**). In addition, an aliphatic diene was used, which afforded product in 62% yield (**98f**).

Another modular three-component transformation was developed in 2021 by the Rovis group, which involved a cationic heptamethylindenyl Rh(III)-catalyzed oxyamination of 1,3-dienes.[49] This diastereoselective 3,4-aminooxygenation rapidly converted olefins into vicinal amino alcohols. Advances from this work include exclusive internal oxidation, as well as high diastereoselectivity and regioselectivity for the internal olefin. The authors proposed that selective aminooxygenation resulted from activation of 1,3-dienes with Lewis acidic Rh(III) complexes to

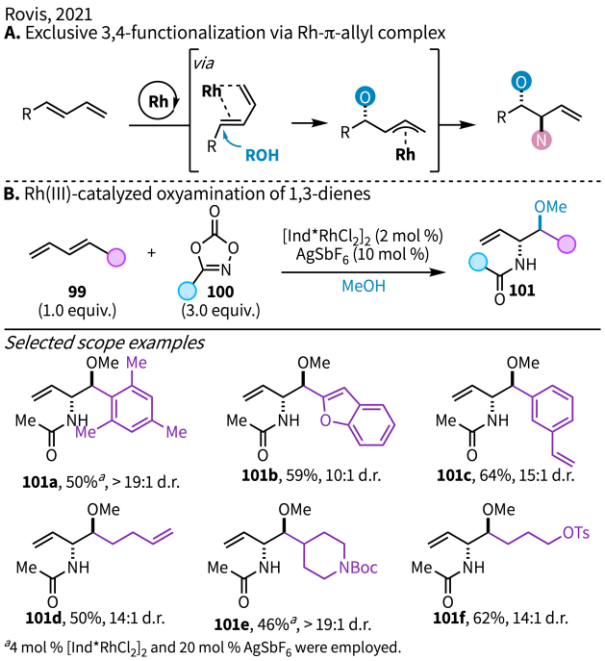

Figure 22. 3,4-selective aminooxygenation of 1,3-dienes. (A.) Site-selective functionalization via formation of π-allyl intermediates. (B.) Selected substrate scope.

access a π-allyl Rh/Ir intermediate (Figure 22A). Addition of the nucleophile at the 4-position could promote the formation of a terminal Rh(III)–π-allyl complex to afford sole oxidation of the internal double bond.

4-Aryl-1,3-butadienes containing various functional groups and substitution patterns were compatible under the optimized reaction conditions. Overall, aryl butadiene substrates proceeded with good yields (50-73%) and high selectivity (>13:1 d.r.). A slight increase in catalyst loading was required in the case of a sterically demanding diene (**101a**). Heteroarenes (**101b**) were tolerated. Substrate 4-(3-vinylphenyl)-1,3-butadiene resulted in 64% yield and no oxidation of the vinyl group was observed (**101c**). The regioselectivity of this protocol was further highlighted when an alkyl-substituted diene containing two terminal olefins was exclusively oxidized in the internal position (**101d**). A (Boc)-protected piperidinyl group (**101e**) and sensitive primary tosylate (**101f**) were also compatible (Figure 22B). The oxygenated motif could also be diversified with common alcohol solvents, such as ethanol and allyl alcohols.

3.4 Carboboration

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Recent advances in catalytic methods for converting unsaturated hydrocarbons into chiral, enantioenriched molecules underscore the significance of carboboration of olefins, a process offering an atom-efficient strategy for the synthesis of functionalized compounds.[50] In 2017, the Brown group reported a Pd/Cu-cooperative catalysis methodology for the regiodivergent arylboration of dienes.[51] This has been achieved regioselectively through catalyst control, design of the substrate, and modification of reaction conditions. The mechanism elucidated in this paper involves initial addition of a Cu–BPin complex across the diene followed by Pd-catalyzed cross-coupling with an aryl halide or pseudohalide. Sterically and electronically modified 1-phenylbutadienes were used with no significant loss of yield or regioselectivity (Figure 23A).

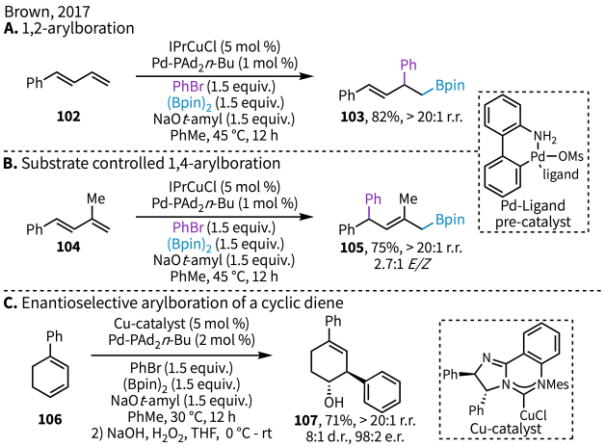

Figure 23. Regiodivergent arylboration of 1,3-dienes. (A.) Selective 1,2-arylboration. (B.) Selective 1,4-arylboration. (C.) Enantioselective arylboration.

The authors subjected a 1,3-substituted diene **104** to the reaction conditions and observed exclusive formation of the 1,4-arylboration product **105** (Figure 23B). This regiodivergent arylboration is hypothesized to be substrate controlled, as 1,2-arylboration would involve formation of a quaternary carbon. In addition, the arylboration reaction was rendered enantioselective. The enantioselective reaction relied on cyclic diene substrates to achieve high levels of enantio- and diastereoselectivity (Figure 23C). When acyclic dienes were used as substrates, no enantioselectivity was observed.

4. Heteroannulation and cycloaddition

Heteroannulation is a convergent approach for the synthesis of aza-and oxa-heterocycles, which are a privileged structural motifs in drug discovery, owing to their ubiquity in compounds derived from plant, animal, and marine organisms, which exhibit a wide range of biological activities.[52] The first reports of this transformation date to 1980s where Dieck and Larock independently reported a convergent approach to heterocycle synthesis through the coupling of dienes with ambiphilic reagents (e.g., iodoanilines).[53] Recently, there has been considerable interest in developing heteroannulation methodologies, with important advances in both reactivity and enantioselectivity.

In 2022, the Paradine group published two reports of heteroannulation reactions between ambiphiles and 1,3-dienes to generate diverse libraries of indolines and dihydrobenzofurans using urea pro-ligands as a novel platform.[54] The findings highlight the efficacy of ureates in Pd-mediated reactions of tosyl-anilines and conjugated dienes by accommodating a functionally and structurally diverse substrate scope, good scalability, and low (down to 1.5 mol %) catalyst loading (Figure 24A). Mechanistic investigations revealed a preferential binding of ureate to Pd(II) through the nonsubstituted nitrogen, an uncommon binding mode for transition metal–urea complexes.

The second report extended this urea-enabled heteroannulation methodology to 2-bromophenols (Figure 24B). In contrast to their prior report on indoline synthesis, trisubstituted ureas were as effective as monosubstituted ureas; ultimately, a trisubstituted urea (**L14**) was identified as the optimal ligand. A diverse range of dienes could be engaged in the reaction, including those bearing heterocyclic substituents **113a**, sterically hindered dienes **113b**, and even unprotected alcohols **113c** (Figure 24B). Notably, a pyridinol-based ambiphile reacted

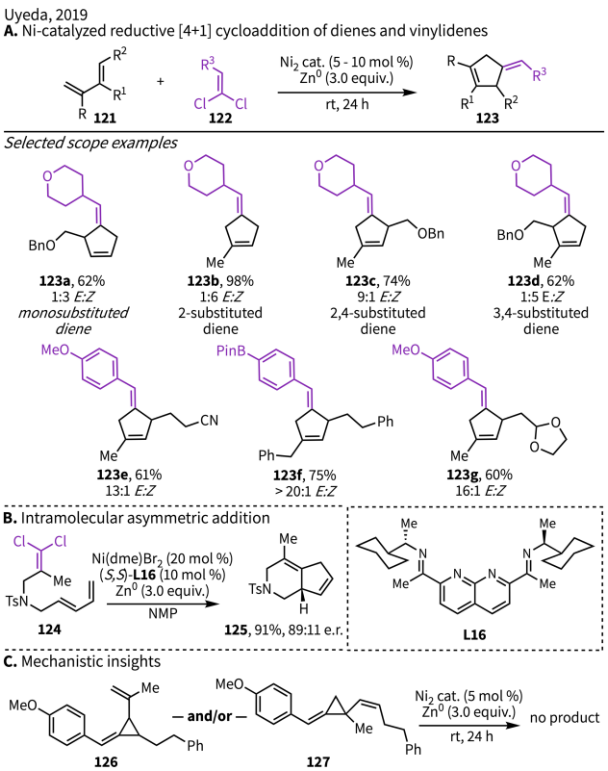

Figure 26. Catalytic [4 + 1]-cycloaddition of dienes and vinyldienes. (A.) Selected diene scope. (B.) Enantioselective, intramolecular cycloaddition. (C.) Mechanistic studies.

smoothly to afford product **113d** in 65% yield.

The Zhang and Zhang groups recently reported an enantioselective Pd-catalyzed heteroannulation reaction of o-bromophenols with various 1,3-dienes, allowing access to enantioenriched, substituted 2,3-dihydrobenzofurans (Figure 25).[55] This reaction displays excellent regio- and enantioselectivity, along with a high tolerance for diverse functional groups. 3-substituted dienes were competent, but lower yielding (35%, **116a**). Notably, a bromine-bearing diene demonstrated impressive reactivity, achieving an 81% yield of **116b** with high enantioselectivity. The epimer of the chiral ligand led to product **116c** with equivalent and opposite enantioinduction. Moreover, both branched **116d-e** and cyclic dienes **116f** were competent, affording product in modest to good yields (Figure 25A). The authors demonstrated the synthetic utility of this transformation by synthesizing natural product (–)-tremetone **120** with 68% yield and 97:3 e.r. (Figure 25B).

Cycloaddition reactions are a direct way to access cycloalkanes commonly present in natural products. While it is relatively easy to generate six-membered rings through Diels-Alder reactions, generating five-membered carbocycles through cycloadditions has a more limited scope. In 2017, the Uyeda group reported a dinickel catalyst that promotes the [2 + 1]-cycloaddition of vinylidenes and alkenes, yielding methylenecyclopropane products. 1,1-Dichloroalkenes, readily prepared from aldehydes or ketones, act as vinylidene

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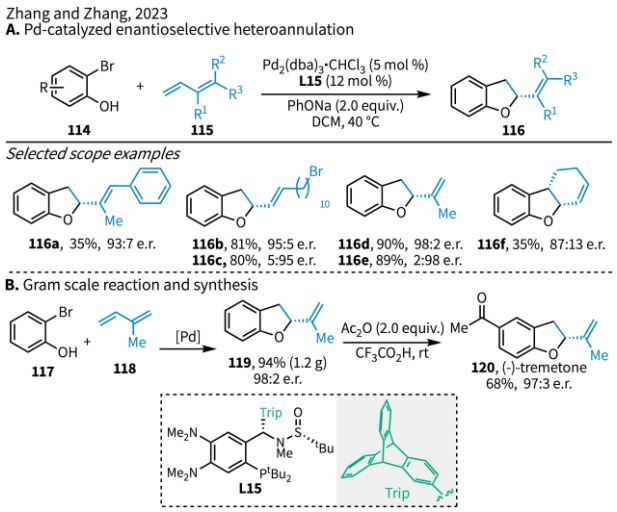

Figure 25. Pd-catalyzed asymmetric heteroannulation between 2-bromophenol and 1,3-dienes. (A.) Selected diene scope. (B.) Gram scale reaction and application to synthesis of tremetone.

precursors.[56] Studies with stereochemically-labeled alkenes suggested a stepwise mechanism for cyclopropane formation, possibly involving a metallacycle formed from Ni_2(C=CHR) species addition to the alkene, followed by C–C reductive elimination to form the three-membered ring.

In 2019, Zhou and Uyeda extended this strategy to 1,3-dienes, offering an alternative to the pericyclic [4 + 1]-cycloaddition pathway.[57] In this method, the C_1 partner is a vinylidene equivalent produced through the reductive activation of a 1,1-dichloroalkene with stoichiometric zinc (Figure 26). With optimization and control studies, the authors demonstrated the need for a dinuclear catalyst since no desired product was formed with mononucleating ligands. The methodology accommodates diverse functionality in the dichloroalkene substrate. The diene scope was investigated to probe the effect of varying substitution patterns on product yield and stereoselectivity. Both *E*/*Z* selectivity and yield is affected by the branching along diene (Figure 26A); the best selectivity was observed with 2,4-substituted dienes. Cyclopentane products bearing cyanide **123e**, Bpin **123f**, and dioxolane **123g** functional groups could be readily prepared under the reaction conditions. The cycloaddition could also be performed intramolecularly; in addition, the intramolecular reaction was enantioselective when chiral ligand **L16** was used, affording product **125** with a 91% yield and 89:11 e.r. (Figure 26B).

To elucidate the mechanism and ascertain whether it follows a direct [4+1] pathway or a [2+1] cycloaddition followed by a 1,3-rearrangement, vinylcyclopropanes **126** and **127** were tested under the reaction conditions. No rearrangement was observed to afford the desired product (Figure 26C). Based on these experiments and DFT calculations, a direct [4+1] cycloaddition was determined to be the more likely pathway.

In 2019, the Chirik group reported the regioselective [4+4]-cyclodimerization and intermolecular cross-[4+4]-cycloaddition of 1,3-dienes enabled by single-component iron precatalysts.[58] These methods provide an atom-economical approach for the modular and convergent synthesis of eight-membered rings from readily available and commodity starting materials. The authors observed remarkable chemo-, regio-, and diastereoselectivity for the iron-catalyzed [4+4]-cycloaddition of substituted dienes to afford disubstituted cyclooctadienes and demonstrated its application on a hectogram scale (>100 g). Mechanistic studies support a mechanism in which stereoselective oxidative cyclization of two dienes from the resting state complex is followed by a stereospecific allyl-isomerization/ C–C bond forming reductive elimination sequence.

Previous mechanistic work by the Chirik group provided evidence for the intermediacy of metallacycles in C–C bond forming reactions catalyzed by α-diimine iron complexes,[25] which led them to investigate bidentate redox-active ligands. Ancillary ligands on iron led to high regio- and diastereocontrol for the [4+4]-cycloaddition of unactivated dienes without the need for directing groups or electronically activating substituents. The scope of the [4+4]-cycloaddition was evaluated with varied 4- and 2-substituted 1,3-dienes using 1-5 mol% of (^{Mes}DI)Fe(COD), (^{iPr}PI)Fe(COD), or (^{Me}PI)Fe(COD). 4-substituted diene substrates

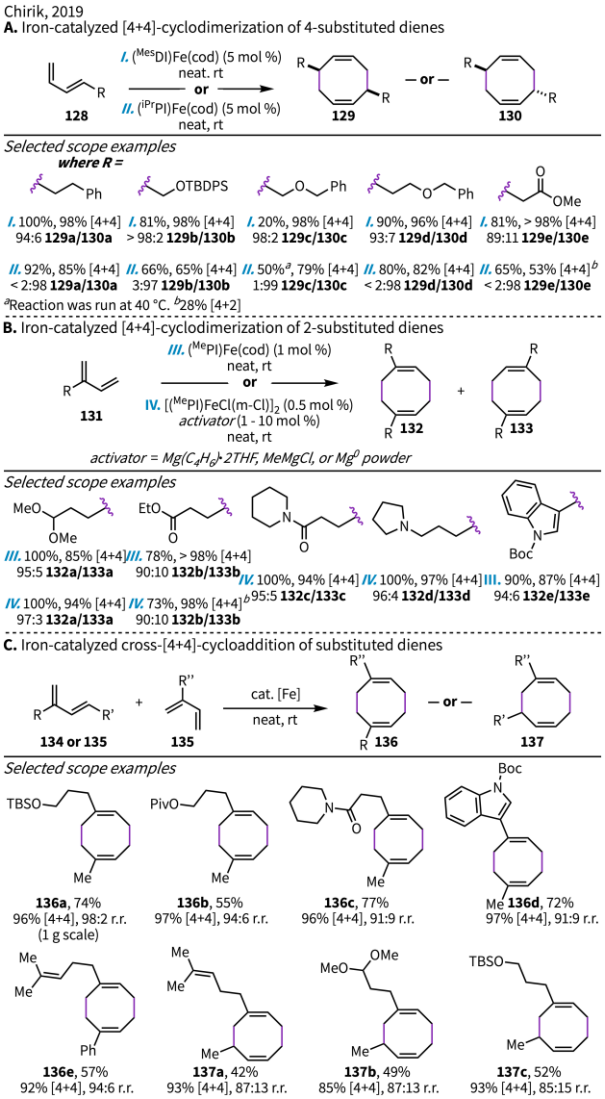

Figure 27. 3,4-selective amino oxygenation of 1,3-dienes. (A.) Stereodivergent cyclodimerization reaction. (B.) Selected scope of cyclodimerization of 2-substituted dienes. (C.) Cross-cycloaddition reaction.

afforded the cyclooctadiene product with high regioselectivity, and catalyst control allowed access to either *Z*- or *E*-stereoisomers. Dienes bearing ester (**129e**, **130e**, **132b**), acetal (**132a**), amide (**132c**), amine (**132d**), and heteroarene (**132e**) functionality were competent (Figure 27A-B). Protecting groups (e.g., benzyl ethers **129c-d**, **130c-d**, silyl ethers **129b** and **130b**) were used for sensitive functional groups, as this method was incompatible with residual water and other protic functionalities. This method was limited to monosubstituted dienes; disubstituted dienes resulted in poor substrate conversion or exclusive formation of linear adducts. The authors also explored the cross-[4+4]-cycloaddition of 4-substituted dienes with 2-substituted dienes using precatalyst (^{Mes}Di)Fe(COD) to afford unsymmetric disubstituted

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cyclooctadienes in high yield, chemo-, and regioselectivity (Figure 27C, **136a**-**136e**, **137a**-**c**).

5. Miscellaneous

In 2023, the Chen group presented a nickel-catalyzed, regioselective Mizoroki-Heck reaction involving 1,3-dienes.[59] By fine-tuning the ligand and additives, they selectively obtained both linear and branched products (Figure 28). Under their linear-selective conditions, electron-rich dienes displayed excellent performance (Figure 28A), while electron-poor dienes exhibited diminished stereoselectivity (**141a**). Branching in the reacting alkene led to diminished reactivity, resulting in only 18% yield of the desired product **141c**. The branched reactivity demonstrated greater resilience toward steric hindrance, and o-substituted triflates reacted smoothly (**142a**). Furthermore, alkyl dienes participated in the reaction with excellent selectivity, albeit with a reduced yield of 47% (**142b**). Notably, steric bulk on the diene was readily accommodated in branched reactivity **142c** as compared to the linear counterpart.

Their mechanistic hypothesis was based on previous studies and experimental data. For the linear Heck reaction, the catalyst precursor, Ni(dppe)Cl_2, undergoes reduction to form the active Ni^0 species **I** in situ, facilitated by Mn^0 and Et_3N. Complex **II** forms from the oxidative addition of iodoarene to **I**. A subsequent migratory insertion between complex **II** and 1,3-diene results in allyl-Ni complex **III**. The linear Heck product **141d** and the Ni^{II} species, **IV**, are produced from β-hydride elimination. Ni^0 catalyst **I** is regenerated with the assistance of Mn^0 and Net_3. For the branched Heck reaction, when promoted by the Ipr ligand, the process commences with the formation of the cationic Ni^{II} species, **II′**, from an oxidative addition of aryl triflate to **I**. A subsequent chelation between the cationic Ni^{II} species **II′** and anionic organoborate results in the Ni^{II} complex **V′**. This is followed by a migratory insertion of diene into the Ni–Ar bond of **V′**, to yield the alkyl-Ni^{II} species, **III′**. Notably, the steric hindrance posed by the bulky Ipr ligand restricts the formation of isomer **III**. Branched product and Ni^{II} species **IV′** are produced by β-H elimination from complex **III′**. Lastly, with the intervention of base, a reductive elimination from the allyl-Ni^{II} species **IV′** revives the Ni^0 catalyst **I**.

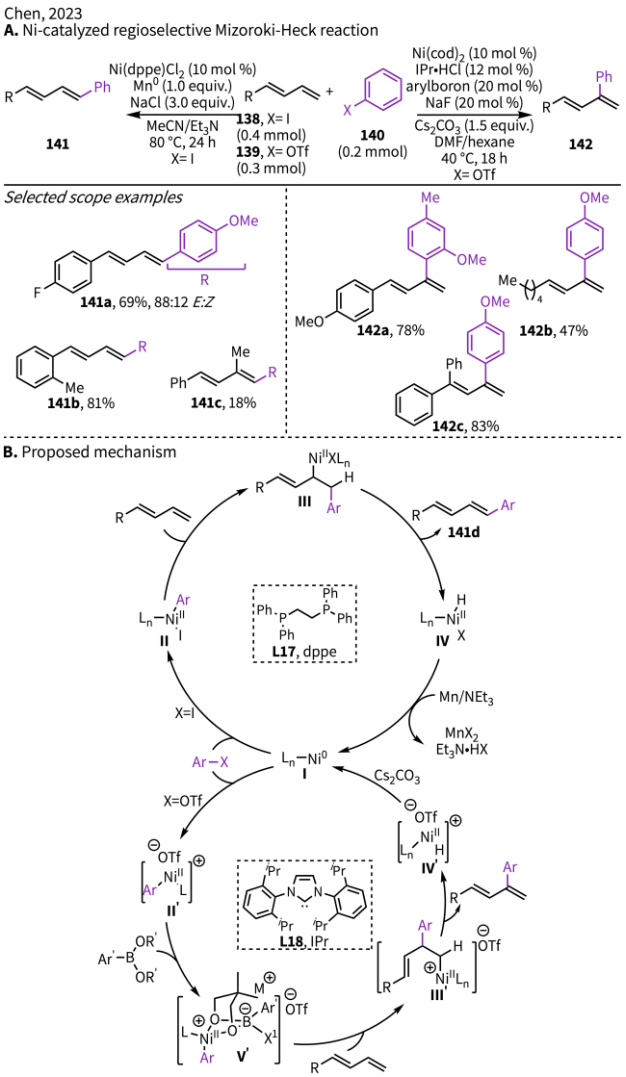

Figure 28. Nickel catalyzed regioselective Mizoroki-Heck reaction with 1,3-dienes selected scope and proposed mechanism.

6. Summary and Outlook

Over the last decade, conjugated dienes have garnered significant interest from organic chemists due to their commercial availability and ease of synthesis, making them valuable substrates for diverse catalytic functionalization reactions. This review highlighted numerous transformations that represent first-of-their-kind methodologies, underlining the versatility of dienes in demonstrating novel reactivity patterns with transition metals. Despite the groundbreaking nature of these transformations, common limitations include the typical use of phenyl butadiene and its linear aromatic derivatives, which often lack substitution along the π–system. In addition, the ability to exert catalytic, ligand-based regiocontrol in diene functionalization reactions remains a largely unsolved problem. However, the diverse reactivity and functionalization strategies presented in these transformations are noteworthy. Establishing these methodologies sets a foundation for future reaction development, where the methods can be extended to more challenging and less reactive substrates. Such exploration will further unveil the full synthetic potential of transition metal-catalyzed transformations.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: dienes • transition metal catalysis • synthetic methods • olefin functionalization

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REVIEW

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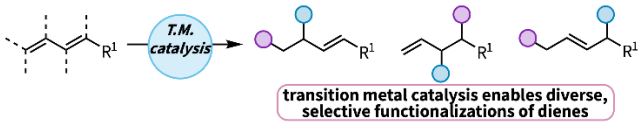

Dienes are valued for their abundance, ease of preparation, and unique properties, as they play a crucial role in synthesizing complex, bioactive molecules. This review focuses on the past decade's advances and challenges in transition metal-catalyzed reaction involving diene substrates, emphasizing their versatility and the emergence of novel reactivity patterns.

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