# Catalytic Enantio- and Regioselective Addition of Nucleophiles in the Intermolecular Hydrofunctionalization of 1,3-Dienes

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ABSTRACT: Catalytic enantioselective synthesis of small-molecule building blocks with allylic stereogenic centers is an important objective in organic synthesis, but preparing this motif wherein the adjacent olefin is 1,2-disubstituted in a single step is a tremendous challenge. Late-transition-metal-catalyzed intermolecular couplings of nucleophiles and 1,3-dienes in hydrofunctionalization reactions have quickly emerged as a compelling approach to these and related compounds. In this Perspective, we illustrate how these intermolecular diene hydrofunctionalizations have provided an avenue to complex, highly desirable chemical space that is not readily accessed by other technologies. We also aim to provide some insight into the varying mechanistic pathways and nuances of these myriad reactions to help inform future reaction and catalyst design.

KEYWORDS: *diene, catalysis, hydrofunctionalization, enantioselectivity, regioselectivity*
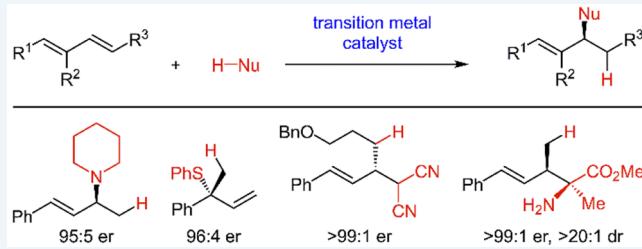
1. INTRODUCTION

Development of new catalytic methods that enable important small molecule scaffolds to be constructed from simple, cheap, and abundant precursors is a critical objective in organic synthesis. Catalysts that allow for some aspect of selectivity control—chemo-, regio-, and/or stereoselectivity—are highly sought after. The enantio- and regioselective addition of hydrogen and another element across carbon−carbon multiple bonds, broadly termed hydrofunctionalization,[1] is a particularly attractive approach for achieving these goals for several reasons. (1) Alkenes and alkynes are widely available and easily accessible. (2) The ease with which transition metal catalysts can coordinate these functional groups opens up several mechanistic avenues toward their hydrofunctionalization. (3) These hydrofunctionalizations often take place with a high degree of atom economy.[2] Within the hydrofunctionalization field, 1,3-dienes have emerged as an important substrate class because the diversity of chemical space that can be garnered is not readily accessed through other transformations. In part, this can be attributed to the variety of reaction mechanisms available in the coupling of numerous reagents with these unsaturated hydrocarbons, often proceeding through a stabilized metal−allyl intermediate. As a result, in recent years there has been a surge of reports in enantioselective hydrofunctionalizations of dienes.

Diene hydrofunctionalizations could be classified in several ways, one by the nature of the coupling partner. As shown in Scheme 1A, hydrometalation of a diene affords a metal−allyl species for addition to an electrophilic reagent, such as in reductive couplings with carbonyls[3,4] or hydrovinylation reactions with ethylene.[5] Conversely, a metal−allyl intermediate may react with a nucleophile (Nu, Scheme 1B). Formation

Scheme 1. Overview of Enantioselective Diene Hydrofunctionalizations

A. Couplings of Dienes with Electrophiles and Olefins
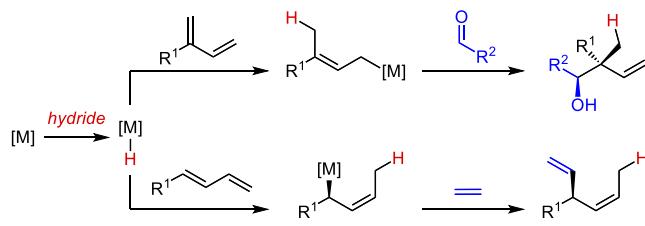
**B.** Couplings of Dienes with Nucleophiles: **This Perspective**
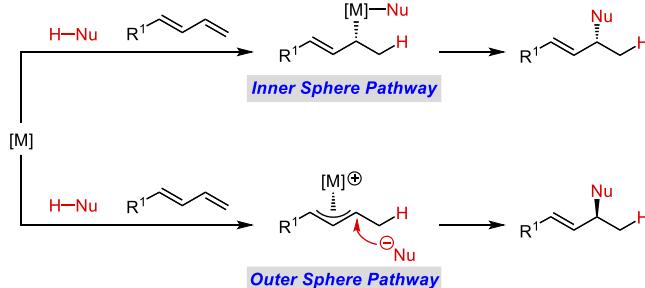
of the product may then occur via the inner-sphere reductive elimination of an η^1-allyl species (top path) or by the outer-sphere attack of the nucleophile upon an η^3-π-allyl complex (bottom path). For the nucleophile coupling mechanisms, the

Scheme 2. Diene Hydrofunctionalization versus Allylic Substitution and Allene/Alkyne Hydrofunctionalization
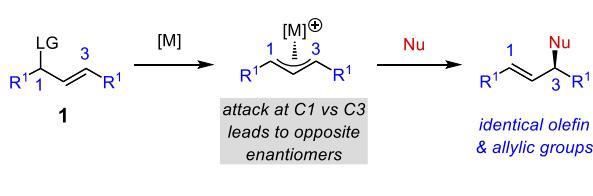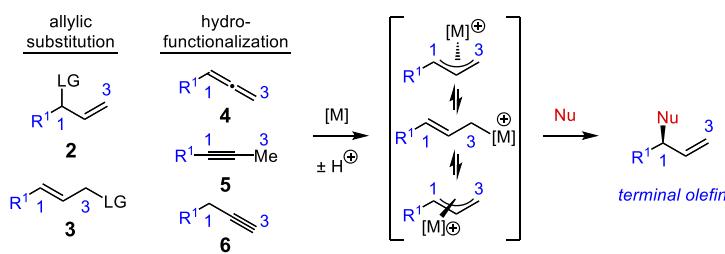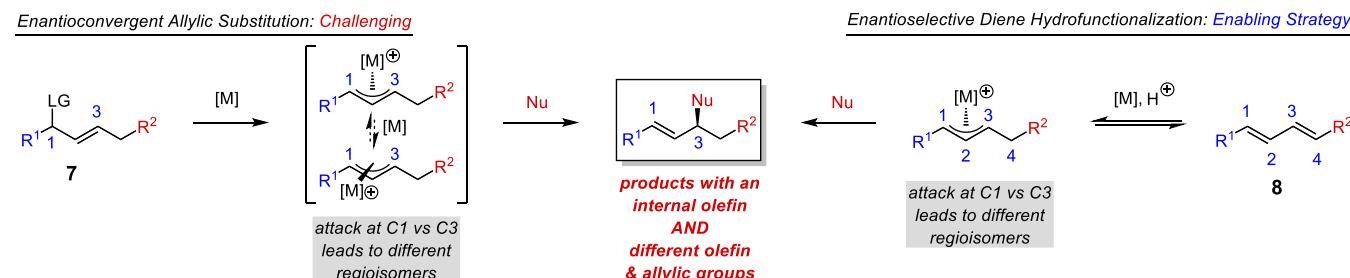
source of the hydrogen atom is typically the nucleophilic reagent itself, thus rendering a perfectly atom economical reaction. In this Perspective, we will focus on methods for the catalytic enantio- and regioselective intermolecular addition of nucleophiles in hydrofunctionalizations of 1,3-dienes, especially acyclic dienes, with a critical assessment of their practical advantages compared with competing technologies and mechanistic distinctions among different transformations. The scope will thus be restricted to reactants organic chemists commonly consider as nucleophiles (e.g., amines, thiols, cyanide, enolates, etc.), and therefore, a number of methods for diene hydroboration[6] and hydrosilylation[7] will not be discussed. Significant advances in diene difunctionalizations, the additions of two atoms neither of which is hydrogen, are not included here.[8] Similarly, nucleophilic additions to electron-poor dienes, which may be considered conjugate additions, are beyond the scope of this article.[9]

As the majority of acyclic diene−nucleophile couplings covered in this text take place via a metal−π-allyl intermediate, a comparison to well-established Tsuji−Trost allylic sub-stitutions[10] and hydrofunctionalization of allenes[11,12] and alkynes,[13] which occur by additions to the same allyl species, is warranted (Scheme 2). A number of allylic substitutions utilize substrates such as **1** that lead to symmetrical π-allyl complexes (Scheme 2A). This obviates the need for the catalyst to control regioselectivity in the coupling and provides a pathway for an enantioconvergent reaction as attack at C1 versus C3 leads to opposite product enantiomers. While enabling the discovery of new catalysts, the utility of this approach in synthesis is low since the C1 and C3 groups must be identical.

Instead, electrophiles like **2** and **3** offer a great deal of value (Scheme 2B). Branch-selective addition of the nucleophile to C1 in the resulting terminal metal−π-allyl intermediate delivers myriad desirable chiral products that bear a terminal olefin.[10d] Highly enantioselective transformations can be facilitated by the ease of the metal's equilibration between the two π-allyl faces via the η1-haptomer (metal bonded to C3 only). Monosubstituted metal−π-allyl intermediates can also be

accessed through hydrometalation of allenes[11,12] (**4**) or alkynes (**5** or **6**).[13] Largely, these hydrocarbon hydrofunctionalizations have also afforded terminal olefin-containing products.[14] However, if the goal were to prepare a molecule with an internal alkene, it would be better to do so directly as the subsequent transformation of the terminal olefin to an internal one negatively affects the overall step economy.[15] Furthermore, as the stereogenic center becomes more substituted and/or as the nucleophile and R1 group become larger, this olefin conversion will likely become more encumbered.

A reaction that proceeds through an *unsymmetrical disubstituted* metal−π-allyl intermediate allows for direct access to products that contain an allylic stereogenic center and a 1,2-disubstituted olefin (Scheme 2C). Although this type of species has been accessed in allylic substitutions from substrates such as **7**, Tsuji−Trost reactions of this type are uncommon[16] and present a number of challenges. First, attack at C1 versus C3 leads to different product regioisomers (cf., Scheme 2A). Second and as a corollary, for an enantioconvergent reaction involving **7**, a different process for facial switch of the metal−π-allyl is needed: the η3-η1-η3-isomerization mechanism shown in Scheme 2B is not viable with disubstituted π-allyl species. One pathway might involve a second equivalent of the transition metal in attacking the metal−π-allyl through an outer-sphere pathway, a documented process facilitated at high catalyst concentrations.[17,18] However, when this equilibration is not rapid, the result is either low enantioselectivity or kinetic resolution, which limits the product's theoretical yield.

This challenge to allylic substitution creates an opportunity for diene hydrofunctionalization. 1,3-Dienes (**8**, Scheme 2C) can generate the same unsymmetrical metal−π-allyl species upon hydrometalation.[19] Facial selectivity in the hydro-metalation step or a dynamic process of hydrometalation/reversion that involves kinetic selectivity in a downstream step can lead to an enantioselective reaction. Therefore, a number of synthetically useful compounds comprised of allylic stereogenic centers and internal olefins can be prepared by diene hydrofunctionalizations that would otherwise be difficult

Scheme 3. Possible Regioisomers from Diene Hydrofunctionalization

Additional Diene Substitution Patterns
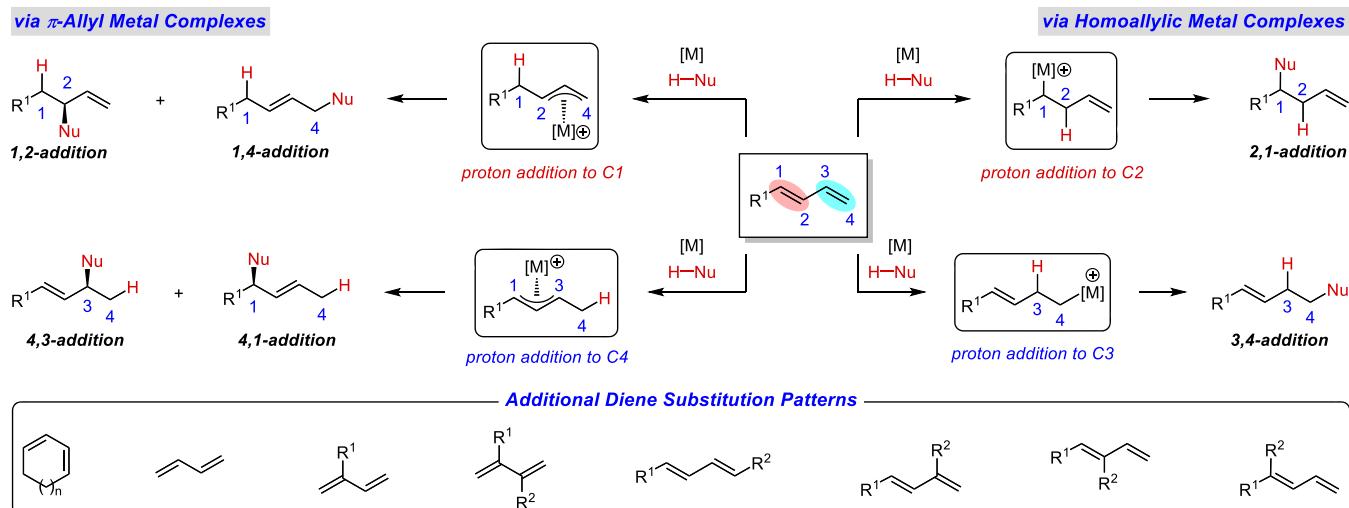
to access. Still, as discussed in the following sections, numerous selectivity challenges exist that need to be addressed by the catalysts employed.

2. CHALLENGES AND MECHANISTIC PATHWAYS

Successful late transition metal-catalyzed diene hydrofunctionalization requires several aspects of selectivity control. First, the reaction should be chemoselective: the catalyst must avoid telomerization mechanisms[20] and enable successful addition of the nucleophile substrate to the diene without any potentially nucleophilic moiety of the product reacting further (e.g., addition of a primary amine selectively leads to a secondary amine product).

Regioselectivity control is another criterion. As mentioned in Tsuji−Trost allylation (Scheme 2C), having an unsymmetrical 1,3-disubstituted π-allyl complex can lead to two regioisomers, but the situation is even more challenging in diene hydrofunctionalization. As shown in Scheme 3 for a terminal diene,[21] hydrometalation may occur at the internal olefin (C1−C2 in red) or at the terminal alkene (C3−C4 in blue). However, depending on the mechanism, either of these events could lead to different organometallic species. For example, in reaction of the terminal olefin, proton addition to C4 affords a metal−π-allyl complex, whereas proton addition to C3 delivers a homoallylic metal. While the C3 protonation, if irreversible, can lead to only one product regioisomer (3,4-addition product) the resulting unsymmetrical metal−π-allyl from proton addition to C4 could be attacked at either C1 or C3, furnishing either the 4,1- or 4,3-addition products. A similar scenario arises from reaction of the internal olefin. Since the hydrometalation may be reversible, several of these intermediates may be in equilibrium during the course of the reaction, further adding to the complexity. (Additionally, several of the products contain internal alkenes that may be formed as E/Z-mixtures.)

Thus, perhaps not surprisingly, much of the early non-enantioselective work in this field established addition of a broad range of nucleophiles to cyclohexadiene.[22] Cyclic symmetrical dienes present no regioselectivity issue: both olefins are chemically equivalent and if hydrometalation results in a π-allyl complex, that species is also symmetrical. Additionally, the aforementioned regioselectivity analysis is

for a terminal diene, but several other valuable diene classes abound, from simple butadiene, to mono- and disubstituted variants and beyond (Scheme 3). Each of these dienes possesses its own inherent reactivity trends that may influence product distribution depending on the extent of catalyst control.

Pioneering efforts by Takahashi and co-workers highlight the regio- and chemoselectivity challenges imposed by acyclic dienes (Scheme 4).[23] Although impressively suppressing

Scheme 4. Early Hydroalkylation Work Illustrates Regioselectivity Challenge with Acyclic Dienes
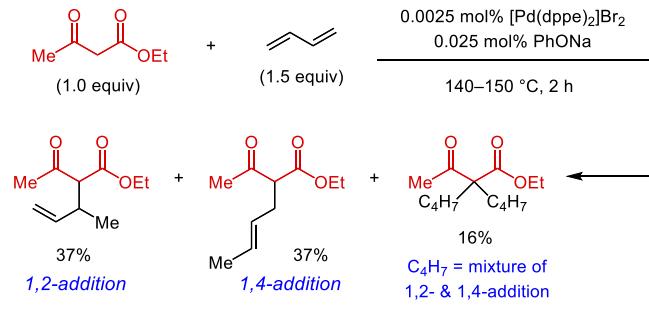
telomerization in ethyl acetoacetate addition to butadiene (hydroalkylation), the Pd-based catalyst employed affords equal quantities of 1,2- and 1,4-addition product. Furthermore, the catalyst shows only moderate chemoselectivity, promoting the addition of product to another molecule of the unhindered butadiene, resulting in 16% bis-alkylation product.

Finally, there is the challenge of enantioselectivity. For products wherein the nucleophile has added to the allylic position (those in Scheme 3 that arise from a metal−π-allyl species), ionization of the C−Nu bond could lead to product enantiomerization and eventual racemization.[24] Having a catalyst active enough to promote the forward reaction but mild enough to avoid product enantiomerization is a necessary feature.

Will the right metal−ligand combination for controlling one aspect of selectivity allow for control over all? Likely for all the possible desirable nucleophile−diene couplings, multiple classes of catalysts would be necessary, presenting numerous

opportunities for catalyst development in the course of discovery of new reactions.

One final feature of reaction mechanism to consider is the nature of the hydrometalation step, which may vary among catalysts (Scheme 5). Two inner-sphere mechanisms are

Scheme 5. Possible Hydrometalation Mechanisms
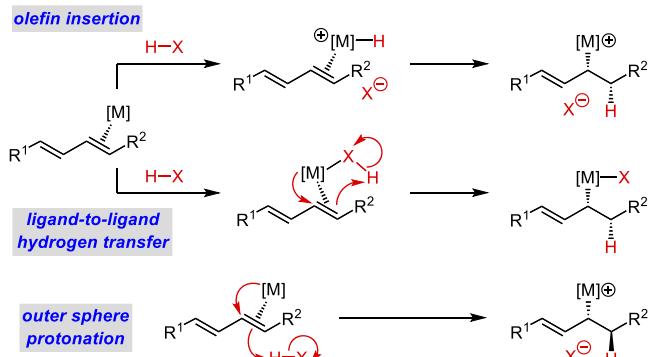
possible, delivering metal and hydrogen to the same face of the alkene. Oxidative protonation of the metal by a Brønsted acid leads to a metal−hydride that then undergoes olefin migratory insertion.[25] Alternatively, the acid may coordinate to the metal with subsequent ligand-to-ligand hydrogen transfer to the alkene.[26] Lastly, an outer-sphere protonation of a metal-bound diene is possible, resulting in metal and hydrogen on opposite alkene faces.[27,28]

In the remainder of this Perspective, we will examine the existing catalytic enantioselective intermolecular additions of nucleophiles to dienes. In these examples, we will provide a mechanistic analysis of how substrate and catalyst structure combine to affect chemo-, regio-, and enantioselectivity.

3. C−N, C−S, AND C−P BOND-FORMING REACTIONS

3.1. Hydroamination Reactions. In 2001, the Hartwig group disclosed the first examples of enantioselective diene hydrofunctionalization by demonstrating the addition of various anilines to cyclohexadiene (Scheme 6).[29] The reactions are promoted by a Pd−π-allyl catalyst modified by Trost ligand **L1**. Several anilines with various steric and electronic properties couple effectively to afford allylic amines with excellent levels of enantioselectivity.[23b,24,30] The reactions were, however, limited to anilines as aliphatic amines fail to

Scheme 6. Pd−bis(phosphine)-Catalyzed Addition of Anilines to Cyclohexadiene
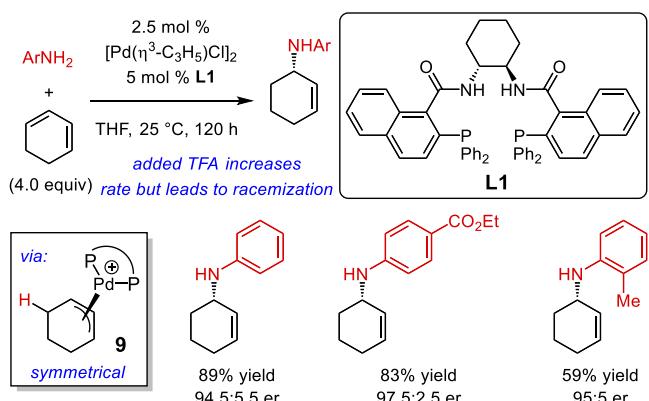
couple. Also release of the ring strain energy of cyclohexadiene seems to be an important driving force: reaction of cycloheptadiene with aniline under identical conditions leads to the respective product in only 22% yield (83:17 er).

Subsequent mechanistic work by the Hartwig group indicated the reactions proceed via Pd−π-allyl intermediate **9**, the catalyst resting state which may be formed by insertion of the diene to a coordinated Pd−H species (or alternatively Pd(0)-assisted outer-sphere protonation of the diene). Enantiodetermining and turnover-limiting addition of aniline to **9** delivers the ammonium salt of the products, which then acts as the acid source in regenerating **9**.[24,30b]

Several facets of this pioneering work merit mention. The high enantiomer ratios observed are constant throughout the reaction course, signifying that the transformations are irreversible. However, despite the high concentration of limiting reagent (1.2 M in aniline)—a common condition in hydrofunctionalization—the reactions are slow, requiring five days to achieve good product yields. The catalyst may be hampered by the chloride counterion present in solution,[31] which could coordinate reversibly to **9** thus impeding the reaction rate. The hydroaminations may be accelerated by the addition of trifluoroacetic acid although this leads to racemic products. Presumably reaction reversibility through C−N bond ionization of the product's ammonium salt is the culprit for racemization, a well-established problem in hydroamination reactions, transformations that are only slightly exoergic.[1c]

Transformations of acyclic dienes, particularly unsymmetrical ones, require more of the catalyst. Although several research groups had disclosed catalytic *regioselective* hydroaminations of terminal dienes,[30] it was not until 2017 that a regio- and enantioselective reaction was developed. Through the combination of a Rh catalyst bearing JoSPOphos ligand **L2** and triphenylacetic acid, the Dong group was able to add indoline nucleophiles to aryl-substituted dienes with Markovnikov selectivity. The allylic amine products are obtained as a single regioisomer and with high enantioselectivity (Scheme 7).[32] The carboxylic acid additive identity is critical for optimal regio- and enantiocontrol, where the confluence of steric bulk and low pK_a of triphenylacetic acid are important in this regard. A rhodium methoxide catalyst precursor versus rhodium chloride was also found to improve enantioselectivity significantly. Competitive binding of chloride to the Rh center in place of carboxylate might be responsible for this phenomenon, similar to observations made with palladium-based catalysts.

Reactions likely proceed by formation of Rh−H species from oxidative addition to the carboxylic acid and subsequent η^4 coordination to the diene to deliver complex **10**. Terminal olefin insertion to the Rh−H gives π-allyl species **11**, and indoline attack at methyl-substituted C3 affords the 4,3-addition product.

Notably, reaction efficiency and regioselectivity are unaffected by diene electronics (Scheme 7). Unfortunately, aliphatic dienes lead to lower regio- and enantioselectivity. The hydroaminations were also limited to indoline nucleophiles: both anilines and aliphatic amines fail to react.

Later that year, the Dong group also illustrated the Rh−bis(phosphine)-catalyzed anti-Markovnikov hydroamination of 2-substituted dienes (Scheme 8).[33] Although the reaction does not afford chiral products, the comparison to their previous work is instructive from a mechanistic perspective. First, both alkyl- and aryl-substituted dienes participate in the reaction

Scheme 7. Rh−bis(phosphine)-Catalyzed Markovnikov Hydroamination of Terminal Dienes

- *terminal dienes – Markovnikov addition*

82% yield
>20:1 rr, >99:1 er

68% yield
6:1 rr, 88:12 er

G = OMe: 80% yield
>20:1 rr, 98:2 er

G = Cl: 82% yield
>20:1 rr, 96:2 er

- *regioselectivity*

10   X = carboxylate   **11**   *4,3-addition*
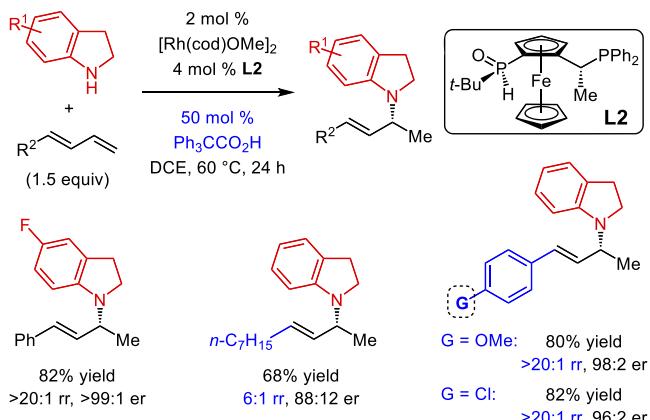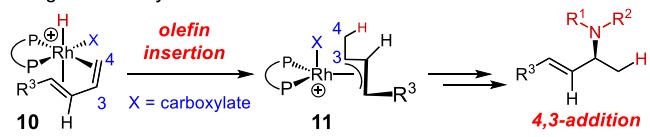
Scheme 8. Rh−bis(phosphine)-Catalyzed anti-Markovnikov Hydroamination of Acyclic Dienes

- *2-substituted dienes – anti-Markovnikov addition*

3,4-addition   1,4-addition

87% yield
>20:1 rr

G = OMe: 63% yield
11:1 rr

G = CO$_2$Et: 40% yield
5:1 rr

79% yield
>20:1 rr

- *regioselectivity*

amine addition
(major)

13   *3,4-addition*

12
X = carboxylate

reductive elimination?

olefin insertion
(minor)

14   *1,4-addition*
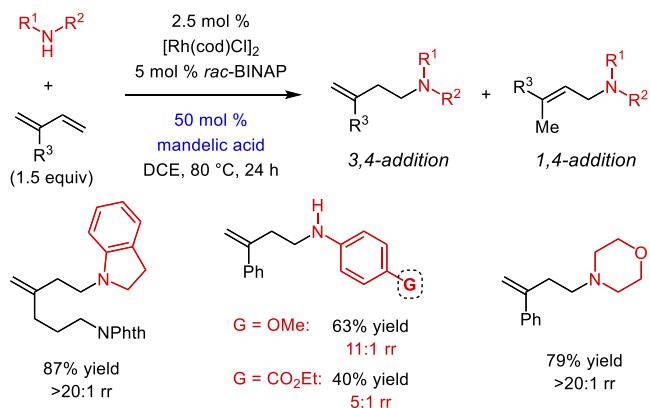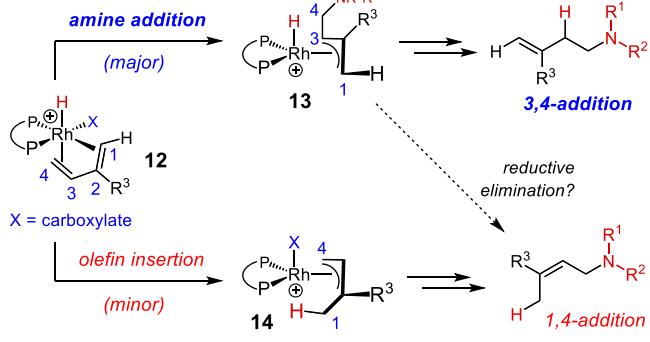
and a broader range of amines are tolerated, including indolines, anilines, and even morpholine. Second, diene identity has little to no impact on regioselectivity but several aryl amines (e.g., anilines) lead to observable quantities of 1,4-addition product. Trends point to more electron-deficient or sterically hindered nucleophiles leading to increased quantities of the minor isomer.

The large bite angle of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) is important for anti-Markovnikov selectivity in additions to 2-substituted dienes. In comparison, bis-(diphenylphosphino)methane (dppm) as the ligand delivers the Markovnikov 4,3-addition product. However, further highlighting the influence of the substrate, the optimal anti-Markovnikov-selective catalyst for 2-substituted dienes still leads to Markovnikov 4,3-addition with terminal dienes.

The authors suggest that the anti-Markovnikov selectivity arises from a path unique to Rh-catalyzed amine additions to 2-substituted dienes (Scheme 8). Oxidative protonation at Rh followed by diene coordination leads to complex **12** whereby outer-sphere attack of the amine at C4 delivers π-allyl complex **13**. Faster reductive elimination at the more substituted C3 (versus C1) then yields the major 3,4-addition product. The minor product as observed with aniline nucleophiles could arise from reductive elimination at C1 in **13**, but how the nature of the amine influences the site of reductive elimination is unclear. An alternative and perhaps more likely scenario with the less nucleophilic anilines (compared to indoline and morpholine) is that there is a competitive olefin insertion from the 1,1-disubstituted olefin of **12** to Rh−H to afford complex **14**. Amine attack at the-least hindered C4 then gives the 1,4-addition product.

Shortly after the Dong laboratory published the enantiose-lective addition of indolines to terminal dienes, our group disclosed the first examples of aliphatic amine couplings with dienes.[34] Several secondary amines add with high regio- and enantioselectivity to terminal dienes (Scheme 9); however, less-nucleophilic primary amines and anilines are inferior partners. We found that whereas Pd catalysts with bis-(phosphine) ligands are poorly enantioselective, Pd−PHOX (PHOX: phosphinooxazoline) catalysts bearing a BF$_4$ counter-ion deliver the 4,3-addition products with exceptional

Scheme 9. Pd−PHOX-Catalyzed Alkyl Amine Addition to Terminal Dienes

4,3-addition

65% yield
>20:1 rr, 95:5 er

G = OMe: 86% yield
>20:1 rr, 96:4 er

G = CF$_3$: 78% yield
6:1 rr, 95.5:4.5 er

84% yield
17:1 rr
95:5 er

77% yield
>20:1 rr
94.5:5.5 er

- *regioselectivity*

major path

15   *4,3-addition*

minor path

16   *1,4-addition*
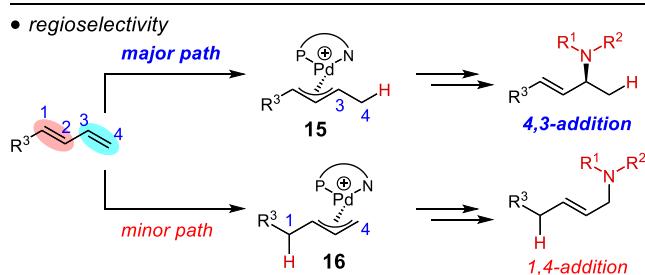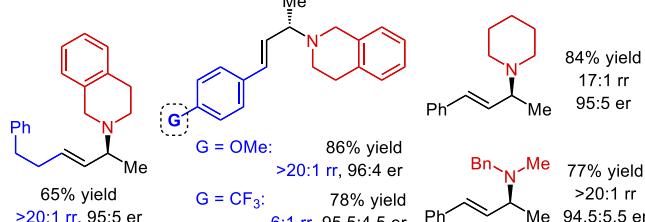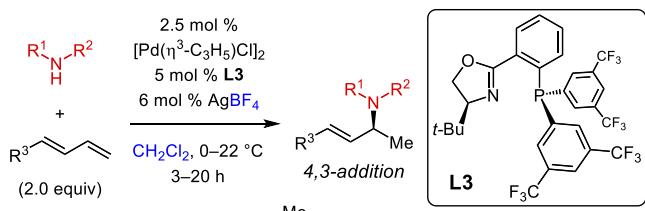
enantiocontrol. Having chloride still present from the palladium precatalyst results in significantly lower enantioselectivity levels.

A key parameter in controlling regioselectivity was the discovery of the electron-deficient bis(trifluoromethyl)aryl-containing phosphine ligand **L3**. Whereas the parent diphenylphosphino-based ligand generates significant quantities of achiral 1,4-addition product, **L3** leads to ≥12:1 regiomeric ratio (rr) in most cases with some noteworthy exceptions. Alkyl-substituted dienes generate the desired chiral amine exclusively, but even with the optimal ligand, the regioselectivity of aryl diene couplings is strongly dependent upon diene electronics. Electron-rich dienes lead to more 4,3-addition; the regiomeric ratio tracks precisely with the Hammett $\sigma+$ parameter ($\rho = -0.75$ at 0 °C). These data might be explained by partitioning of outer-sphere protonation of a Pd(0)-bound diene at C4 and C1 according to the size of the orbital coefficients at these positions to generate the two Pd−π-allyl species **15** and **16**. Deuterium labeling experiments with **L3** indicate that diene coordination to Pd(0) is irreversible and that introduction of the deuterium largely determines the distribution of **15** and **16** for electron-poor dienes and does so exclusively for phenylbutadiene. Perhaps the more electron-deficient phosphine of **L3** leads to a greater disparity of orbital coefficients at C1/C4 of the Pd-bound diene.

It is also notable how the nature of the amine can affect regioselectivity, if only slightly, as a result of its ammonium salt acting as the Brønsted acid in the diene protonation event.[23b] Cyclic amines generate various amounts of achiral 1,4-addition product; contrastingly, acyclic secondary amines lead exclusively to the chiral 4,3-addition product.

Two other facets of these transformations warrant attention. (1) The majority of transformations show constant enantiopurity of products over the course of the reaction, illustrating that they are irreversible under the reaction conditions. The exceptions are transformations of more sterically hindered amines: acyclic secondary amines where both substituents are larger than a methyl group (e.g., diethylamine) show diminishing enantiomeric ratio (er) as the reaction progresses. (2) The electron-poor ligand **L3**, beyond improving regioselectivity, additionally provides the benefit of a large rate acceleration in the hydroamination.

Our group has further extended the utility of Pd−PHOX catalysts in the hydroamination of 1,4-disubstituted dienes.[35] Prior to our hydroamination work (Scheme 10), only two other reports of catalytic enantioselective intermolecular addition of nucleophiles with this diene class had been disclosed: a single example from the Hayashi group in hydroalkynylation (section 4.1) and indole additions (hydroarylation) from the Meek laboratory (section 4.2). These internal dienes provide a greater challenge for any catalyst due to the increased steric hindrance from both olefins being disubstituted.

In our hydroamination studies with internal dienes, the electron-poor **L3** again proved best. Due in part to the increased steric demand of the internal diene, but moreover to a higher propensity toward reaction reversibility in these transformations, several other reaction variables had to be altered from the previous terminal diene hydroaminations. (1) Superstoichiometric quantities of Et₃N are needed to shuttle proton away from the product and toward the Pd(0)-coordinated diene, preventing ionization of the allylic

Scheme 10. Pd−PHOX-Catalyzed Hydroaminations of 1,4-Disubstituted Dienes
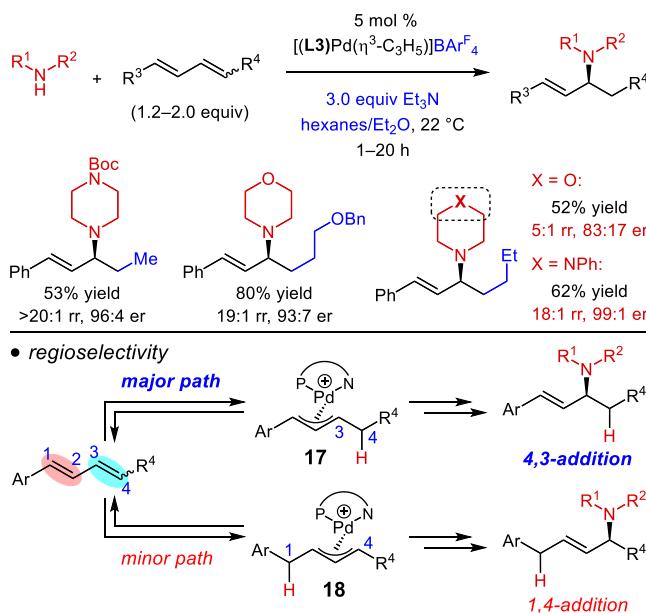
ammonium C−N bond and helping drive the reaction forward. Reaction efficiency is low with all amines investigated in the absence of this additive; enantioselectivity is also depressed. (2) The noncoordinating counterion BArF₄ in place of BF₄ is necessary. Not only does this potentially increase the ability of Pd to coordinate the diene (a step which deuterium labeling studies revealed to be reversible), but this also generates a different counterion to the triethylammonium Brønsted acid, which likely effects the kinetics of proton transfer.[31] (3) The use of a more nonpolar solvent compared to CH₂Cl₂ proved critical in achieving an enantioselective reaction: hexanes/Et₂O mixture was best, affording products in high enantiopurity compared to racemates in CH₂Cl₂. The less-polar solvent likely retards both the forward and reverse reaction but may also change the rate of proton shuttling versus C−N bond ionization in preserving product enantiopurity.

The nonpolar solvent may have an additional effect. In a number of transformations we have investigated, the data indicate that Pd−PHOX catalysts, particularly those with a BArF₄ counterion, undergo more rapid catalyst decomposition in more polar solvents. In the internal diene hydroaminations, reactions plateau in terms of yield, which experiments revealed to be well below an equilibrium value, yet the products continue to undergo enantiomerization. These data suggest that a catalyst decomposition product is capable of causing product enantiomerization without promoting the hydroamination reaction. The identity of this species has not yet been determined.

In the hydroaminations shown in Scheme 10, a stereochemical mixture of the dienes was employed. The E,Z-diene proved more reactive but both isomers converge to the same product enantiomer. With a phenyl group at R³, several alkyl groups are tolerated at R⁴, and a number of secondary amines add effectively to these dienes. Regio- and enantioselectivities are broadly excellent, although the nature of the amine and diene undergoing coupling can have a profound effect (compare the morpholine and N-phenylpiperazine results in Scheme 10).

Interestingly, the electronic nature of the arene at R^3 has no effect on the regioselectivity (cf., reactions of terminal dienes, Scheme 9). Deuterium labeling studies illustrate that with internal dienes, protonation at C4 and C1 to generate Pd−π-allyl isomers **17** and **18**, respectively, occurs indiscriminately, yet π-allyl **17**, which delivers the 4,3-addition product, is attacked significantly faster. Both π-allyl isomers **17** and **18** are 1,3-disubstituted but only attack upon π-allyl **17** preserves conjugation of the alkene with the aromatic ring. Comparatively, in terminal diene hydrometalation (Scheme 9), isomer **16**, which is analogous to **18**, similarly lacks conjugation with the aromatic ring but is monosubstituted, thereby increasing the rate of nucleophilic attack at the terminal position of the π-allyl.

A recent advance in diene hydroamination was reported by the Mazet group. 2-Aryl-substituted dienes undergo Ni−bis(phosphine)-catalyzed Markovnikov addition of primary alkyl amines (Scheme 11).[36] In the reaction, BenzP* (**L4**) offers the best regio- and enantioselectivity of the ligands investigated.

Scheme 11. Ni−BenzP*-Catalyzed Addition of Alkyl Amines to 2-Aryl-Substituted Dienes
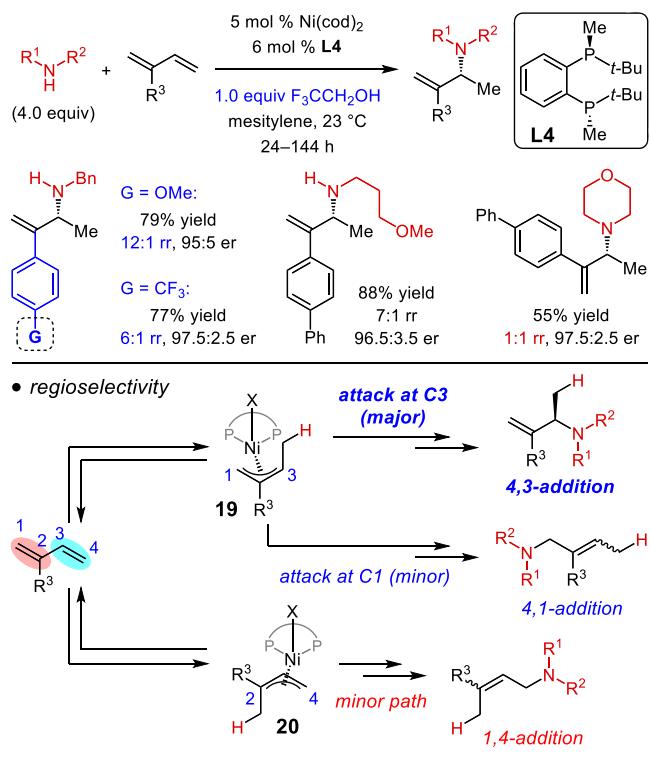
Deuterium labeling studies show that hydrogen addition to the diene occurs equally between C4 and C1 en route to Ni−π-allyl species **19** and **20**, but that attack at C3 of **19** occurs most rapidly to deliver the 4,3-addition product. The authors attribute the faster attack at C3 compared to C1 (4,1-addition) to the greater steric repulsion of the more-substituted C3 with the Ni center, which increases its electrophilicity. Although kinetically accessible, the concentration of **20** is presumably low compared with **19** thereby reducing the rate of attack (1,4-addition).

Primary amines couple with good regioselectivity and high enantioselectivity with an aryl group at R^3. Electron-rich dienes lead to more of the 4,3-addition product (Scheme 11) but

reactions are slower. With an alkyl group at R^3, hydroamination occurs but without regio- or enantiocontrol. Reactions of secondary amines proceed readily and with high enantioselectivity but regioselectivity is poorer. Chemoselectivity with the primary amine nucleophiles is high: coupling of the secondary amine products with another equivalent of the diene was not observed, perhaps partially controlled by stoichiometry (4.0 equiv amine) but likely also by the added steric hindrance of the products. It was proposed that the active nucleophile in the outer-sphere attack upon the Ni−π-allyl is an aggregate of the amine and trifluoroethanol (TFE), an additive required for reaction to take place (the likely initial H source). The amount of nucleophile could be lowered to 2.0 equiv if Et₃N were added, which the authors propose changes the nature of the aggregate.

In total, the enantioselective intermolecular diene hydroaminations that have been developed utilize a number of Pd-, Rh-, and Ni-based catalysts that enable the addition of anilines, indolines, and primary and secondary aliphatic amines to dienes with several different substitution patterns. Mechanistic nuances vary considerably depending on the catalyst and reagents but all enantioselective couplings are proposed to proceed via outer-sphere addition of the amine to a metal−π-allyl intermediate.

3.2. Hydrothiolation Reactions. In 2018, the Dong group published the first examples of enantioselective hydrothiolation of 1,3-dienes.[37,38] The greater acidity of thiols compared to amines (cf., Schemes 7 and 8) leads to distinct differences in reaction condition requirements and mechanism. For example, hydroamination with a Rh-based catalyst requires addition of a carboxylic acid in order to form a Rh−hydride, whereas in hydrothiolation the thiol itself may form the hydride by oxidative addition at the metal, identified as the turnover-limiting step of the catalytic hydrothiolation cycle. Another notable difference is that hydroamination proceeds by outer-sphere nucleophilic attack of the amine upon a Rh−π-allyl intermediate. Contrastingly, the C−S bond is formed by reductive elimination since the thiolate remains coordinated to rhodium after oxidative addition of the thiol.

One of the most notable features of this method is its capacity to facilitate couplings with dienes of several substitution patterns through the judicious choice of the appropriate ligand (Scheme 12). For cyclic dienes (i.e., 1,3-cyclohexadiene), the authors found that a BINAP-based ligand (**L5**) was unique in forming the allylic sulfide product selectively. Other bis(phosphine) ligands resulted in mixtures containing homoallylic sulfides. Unsymmetrical acyclic dienes, which have the capacity to form many regioisomers, could also be engaged in this transformation. While 1-substituted 1,3-dienes worked best with a BINAP ligand to deliver 1,2-hydrothiolation products (not shown), 2-substituted dienes required a switch to a JosiPhos-type ligand (**L6**). Within this class of substrate, electron-deficient aryl groups at the 2-position result in much higher regioselectivities than electron-rich substituents (range of 7:1−20:1 rr), with the regioisomers arising from Rh−H insertion at the 1,1-disubstituted olefin (major) versus the terminal olefin. The site of hydride insertion has been shown to be an irreversible step (*vide infra*). Butadiene, a feedstock chemical produced on a million metric ton scale annually, can also be converted into enantioenriched allylic sulfides by switching to a GarPhos-type ligand **L7**; impressively, exclusive 1,2-hydrothiolation is observed.

Scheme 12. Ligand Dependence on Diene Class for Rh−bis(phosphine)-Catalyzed Hydrothiolation[39]

Scheme 13. Counterion Control of Regioselectivity in Rh−bis(phosphine)-Catalyzed Hydrothiolation

- *Markovnikov selectivity via η^4 diene coordination*

- *anti-Markovnikov selectivity via η^2 diene coordination*
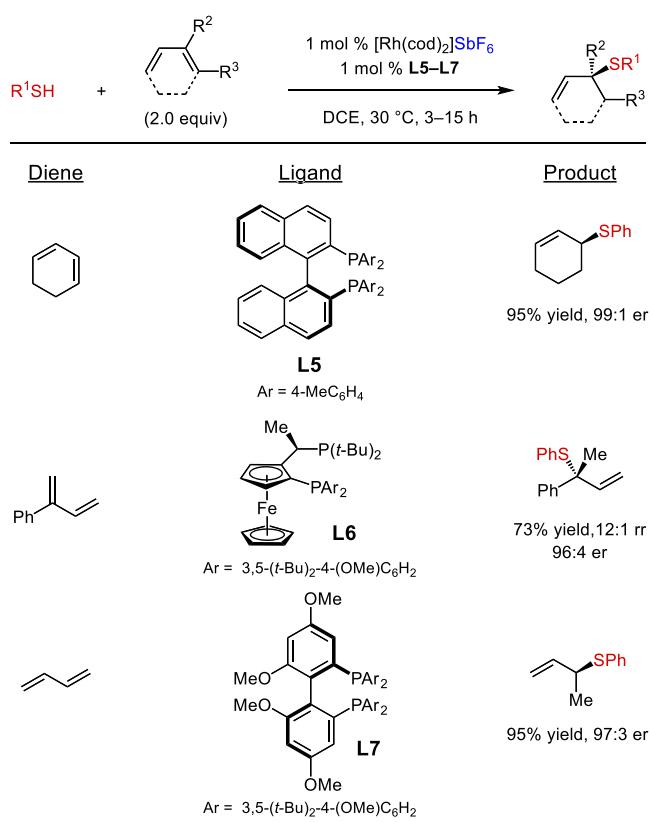
With 2-substituted dienes, deuterium labeling studies (PhSD, 80% D) result in scrambling of the label among several carbons within the product (obtained as a single regioisomer). However, the lack of deuterium incorporation in the recovered diene demonstrates that olefin coordination is irreversible. Subsequent experiments revealed that the origin of deuterium scrambling in the product occurs after product formation through a pathway that lies outside the catalytic cycle. Thus, regioselectivity is largely determined by the site of initial hydride insertion.

In addition to 1,2-selective Markovnikov hydrothiolation of 1,3-dienes, the Dong lab has also reported a protocol for anti-Markovnikov 3,4-hydrothiolation of 2-substituted dienes (Scheme 13).[40] Though reminiscent of their earlier anti-Markovnikov hydroamination work (Scheme 8), the origin of regioselectivity is different. Whereas hydroamination is proposed to occur by outer-sphere nucleophilic addition of an amine to the least hindered olefin of a Rh−η^4-diene species, the hydrothiolation occurs by an exclusively inner-sphere pathway involving rhodium oxidative addition to the thiol. The authors discovered that the counterion to the Rh-based catalyst plays a significant role in hydrothiolation regioselectivity. Noncoordinating counterions such as SbF$_6$ result in Markovnikov product (1,2-addition). The authors propose that a noncoordinating counterion leaves an additional coordination site open at Rh, enabling η^4-diene complex **21** to form. Insertion of the more substituted olefin to Rh−H produces allyl intermediate **22**, and subsequent reductive elimination at the more substituted C2 results in the observed 1,2-Markovnikov selectivity. Contrastingly, coordinating counterions such as Cl result in anti-Markovnikov 3,4-addition (typically >20:1 rr although somewhat affected by diene
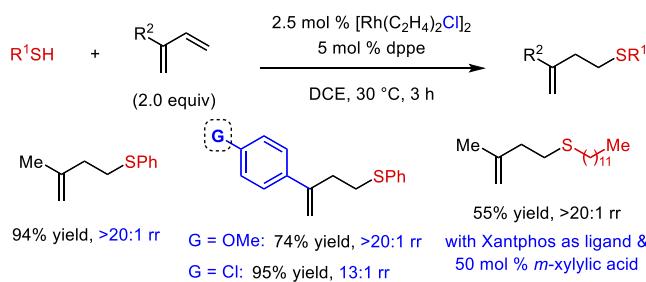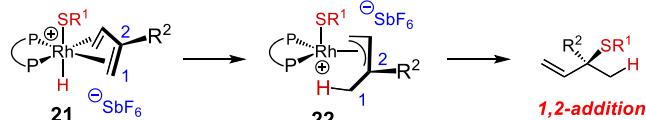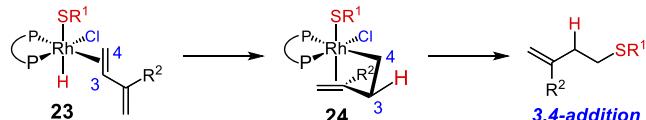
electronics; see Scheme 13). With a chloride occupying a coordination site, the diene is limited to η^2-coordination of the terminal olefin (species **23**). Migratory insertion to (dppe)-Rh−H favors the least hindered Rh−alkyl species (**24**), and reductive elimination delivers the 3,4-addition product (dppe: bis-(diphenylphosphino)ethane).

3.3. Hydrophosphinylation Reactions. Reported methods for the construction of C−P bonds by transition metal-catalyzed hydrofunctionalization are rare when compared with other related C−heteroatom bond-forming reactions. In the case of enantioselective diene hydrofunctionalization there is only a single report. In 2018, the Dong group published enantioselective addition of phosphine oxides to conjugated dienes (Scheme 14).[41,42] Unlike hydroamination and hydrothiolation, Rh-based catalysts proved ineffective in this transformation; however, with a Pd catalyst derived from JosiPhos ligand **L8** the reaction proceeds in up to 91% yield and 97.5:2.5 er often with >20:1 selectivity for the 4,3-hydrophosphinylation product. The minor regioisomer observed in some cases is the 1,4-addition product analogous to Pd-catalyzed hydroamination of dienes (Scheme 9).

Regardless of steric or electronic effects, 1-aryl-substituted dienes ubiquitously provide the desired 4,3-addition products as single regioisomers and in good enantioselectivity (88:12−96:4 er). A 1-aryl-2-alkyl substituted diene required switching the ligand to DTBM-SegPhos (**L9**) (DTBM: 3,5-di(tert-butyl)-4 methoxy) to achieve good selectivity. Likewise, this same ligand was needed for a 1-alkyl-substituted diene, although the product was obtained in only 35% yield and 3:1 rr. As the authors note, these observations further underscore the importance of matching the catalyst to the diene substitution pattern.

The diphenylphosphinic acid additive was found to accelerate the reaction. In its absence, the authors report a significant induction period, but ultimately similar yields can be achieved with prolonged reaction times. The role of acid is

Scheme 14. Pd−bis(phosphine)-Catalyzed Enantioselective Hydrophosphinylation
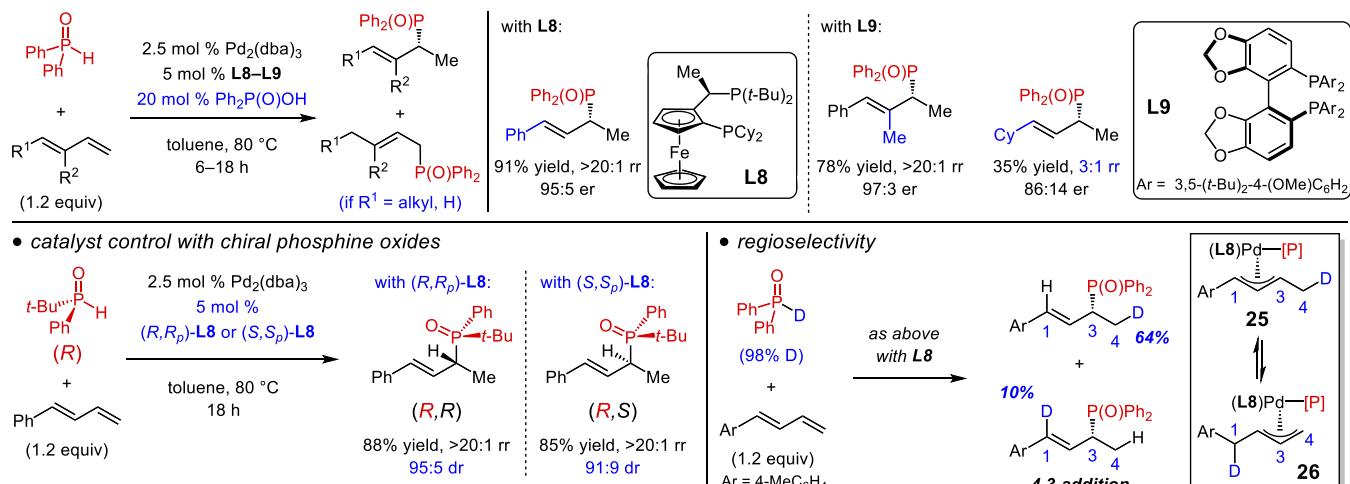
therefore likely to facilitate the formation of a Pd−hydride through oxidative protonation of Pd(0).

In this work, the Dong laboratory also demonstrated that if the starting phosphine oxide contained a stereogenic phosphorus atom, the chiral catalyst could exert control over the newly formed stereogenic carbon of the product. Stereochemistry at phosphorus is preserved, enabling a diastereodivergent approach to these compounds.

Several important mechanistic insights were also disclosed. Deuterated phosphine oxide affords the desired product with 10% D-incorporation at the 1-position and 60% at the 4-position despite the fact that the product is formed exclusively as the 4,3-addition product. This result suggests that hydrometalation is reversible. Thus, the two Pd−π-allyl isomers **25** and **26** are both formed and in equilibrium, but selective and turnover-limiting reductive elimination from **25** forms the observed regioisomer, presumably due to olefin conjugation with the aryl group within the product. This may explain the poorer regioselectivity with 1-alkyl-substituted dienes.

4. C−C BOND-FORMING REACTIONS

4.1. C−C(sp) Bond-Forming Hydrocyanation and Hydroalkynylation.
In 2006, RajanBabu and co-workers demonstrated the first examples of enantioselective hydrocyanation of dienes (Scheme 15).[43,44] Under the Ni−phosphinite-catalyzed conditions, dienes of several substitution

patterns couple with HCN with moderate enantiocontrol. Phosphinite ligands (**L10−L11**) derived from (D)-glucose were critical to achieving reactivity at low temperature, enabling higher er of products to be attained. Prior nonenantioselective diene hydrocyanation utilized phosphite ligands, which required higher temperatures and resulted in product racemates.[44d]

Mechanistic evidence from nonenantioselective hydrocyanation suggests that this reaction proceeds through an inner-sphere pathway of diene hydrometalation and cyanide reductive elimination from Ni. For example, Bäckvall and co-workers demonstrated that DCN addition to 1,3-cyclo-hexadiene occurs in a syn-selective manner.[44c] Most products in Scheme 15 arise from a Ni−π-allyl intermediate, affording allylic cyanides. However, a 1,1-dialkyl-substituted diene leads to 2,1-addition and a homoallylic cyanide, which could be explained by rapid and reversible hydrometalation followed by selective reductive elimination at the most substituted position.

Two groups have reported the addition of terminal alkynes to dienes.[45] In 2010, the Suginome laboratory disclosed an enantioselective Ni-catalyzed process utilizing a taddol-derived phosphoramidite ligand (**L12**).[46] The desired products could be obtained in up to 68% yield and 96.5:3.5 er (Scheme 16, top). The reaction proceeds by insertion of Ni(0) into the alkyne C−H bond, hydrometalation of the diene to form a

Scheme 15. Ni−bis(phosphinite)-Catalyzed Hydrocyanation


Scheme 16. Hydroalkynylation Reactions
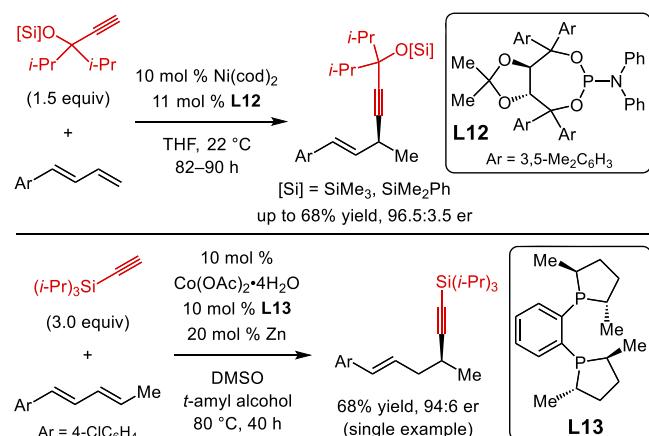
Ni−π-allyl complex, and reductive elimination that preserves olefin conjugation to the arene in the product (substrates limited to aryl dienes). The transformation is sensitive to a number of reaction parameters due to the complicating factor of alkyne dimerization via insertion of a second alkyne molecule to the Ni−H rather than the diene. In addition to achieving the best enantioselectivity, a bulky ligand was found to suppress alkyne dimerization. Additionally, a large substituent on the alkyne and a *trans*- as opposed to *cis*-1,3-diene were needed to promote diene hydrofunctionalization. To a certain extent, alkyne dimerization could be mitigated by slow addition of alkyne (over 82−90 h); however, even under optimized reaction conditions approximately 50/50 mixtures of diene addition and alkyne dimerization are obtained.

The Hayashi group has disclosed a single example of anti-Markovnikov hydroalkynylation of dienes with a Co−bis-(phosphine) catalyst (Scheme 16, bottom).[47] This Co(I)-catalyzed process is facilitated by Me-DuPhos **L13** and initiates by Co(OAc) σ-bond metathesis with the alkyne C−H bond to form a Co−acetylide. Thus, unlike Suginome's Ni-catalyzed reaction, there is no metal−hydride involved and so diene insertion to the Co−acetylide occurs to generate a Co−π-allyl intermediate, which can then undergo protodemetalation by reaction with another molecule of alkyne (or potentially the AcOH formed as byproduct in catalyst initiation). Alkyne oligomerization is again a complicating feature, requiring a large silyl group on the alkyne.

4.2. C−C(sp²) Bond-Forming Hydroarylation Reactions.

A handful of diene hydroarylation examples, utilizing aryl nucleophiles, have emerged over the last several years.[48] The first class of reactions adds the arene and hydrogen from two separate reagents by employing aryl boronic esters or acids and an alcohol as the hydrogen source.

Sigman and co-workers have illustrated a reductive coupling strategy in hydroarylation.[49] Although their approach was largely applied to reactions of styrenes, they demonstrated a single example of aryl boronic ester addition to phenyl-butadiene (Scheme 17, top): the Pd−Box-catalyzed reaction (Box: bis(oxazoline)) delivers the product in 28% yield and 72.5:27.5 er. The Pd(II)-initiated cycle affords Pd−H by hydride transfer from isopropanol with concomitant formation of acetone. Diene insertion to Pd−H, transmetalation of the
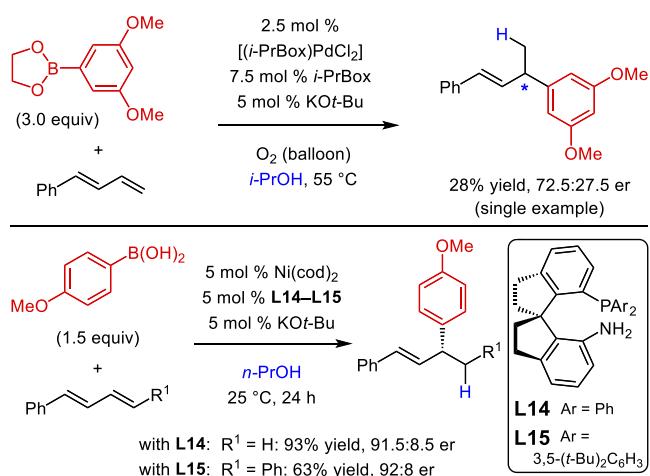
boronic ester and reductive elimination then deliver the product and a Pd(0) species. The palladium is reoxidized by the O₂ atmosphere to complete the catalytic cycle.[48b,50] Although so far limited in its study, this avenue for enantioselective addition of nucleophiles to dienes presents a unique mechanism that should be considered for future exploration.

Recently, a report from the Zhou group has also illustrated enantioselective additions of aryl boronic acids to dienes, including one example of an internal diene, utilizing Ni-based catalysts bearing spiro-aminophosphine ligands **L14** and **L15** (Scheme 17, bottom).[51] In this instance, Ni(0) insertion to the alcohol O−H bond furnishes the nickel−hydride for the diene insertion and the nickel−alkoxide for boronic acid trans-metalation in a related but distinct process to the one reported by the Sigman group.

In 2017, the Meek group reported the enantioselective addition of N-heteroarenes to 1,3-dienes (Scheme 18).[52]

## Scheme 18. Rh−CDC-Catalyzed Indole Additions
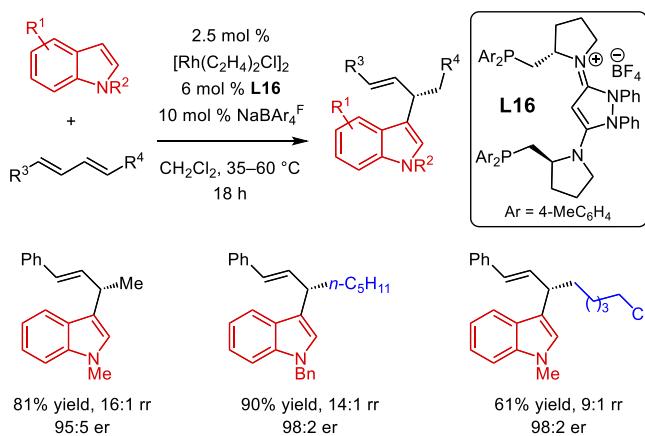
Indole nucleophiles proved to be the best and delivered the desired 4,3-hydroarylation products in up to 98:2 er and >20:1 rr. The reactions are facilitated by a Rh catalyst derived from a new class of chiral carbodicarbene (CDC) pincer ligands (**L16**). CDC ligands are an emerging class of highly electron-rich carbon(0) donor ligands that show utility in several transition metal-catalyzed hydrofunctionalizations.[30d,48d] The utility of this class of ligand is further underscored by the fact that Rh catalysts derived from traditional bis(phosphine) ligands were inactive in this transformation. The NaBAr$^F_4$ additive is crucial in forming the highly electrophilic dicationic Rh(III)−π-allyl, which has been characterized by X-ray and NMR spectroscopy and shown to be catalytically competent for outer-sphere indole attack. In addition to exploring terminal diene partners, the Meek group carried out the first systematic study of nucleophilic additions to 1,4-disubstituted (internal) dienes. These significantly more challenging substrates require slightly elevated temperatures (50−60 °C as opposed to 35 °C with terminal dienes) but generally lead to higher product er than terminal dienes.

Upon reaction with a phenylbutadiene, a C3-deuterated indole starting material delivers the product with 67% deuterium incorporation at the methyl group (C4 of the diene). Furthermore, approximately 36% D-incorporation at the C4 terminus is also observed in the recovered diene, indicating that both Rh−hydride insertion and diene

Scheme 17. Hydroarylation Reactions with Aryl Boronic Esters/Acids

coordination are rapid and reversible. It should be noted that deuterium is detected exclusively at the C4 position in both the product and recovered diene, illustrating that hydrometalation occurs only at the least-hindered olefin.

4.3. C−C(sp³) Bond-Forming Hydroalkylation Reactions with Enolates.

The addition of $C(sp^3)$ nucleophiles to dienes (hydroalkylation) dates back to the early 1970s with the work of Takahashi (see Scheme 4), but it was not until 2004 that the Hartwig laboratory developed an enantioselective version with JosiPhos ligand **L17** (Scheme 19).[53] Although only two examples are provided, these represent the first instances of enantioselective addition of carbon-based nucleophiles to dienes.

Scheme 19. First Examples of Enantioselective Enolate Additions to Dienes
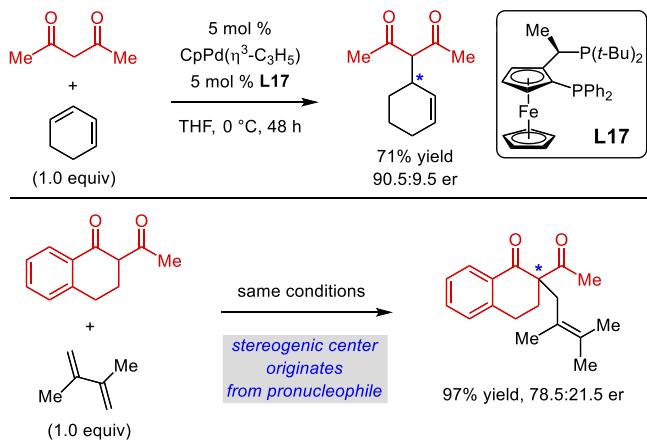
In the first example, acetylacetone adds to 1,3-cyclohexadiene, which, as mentioned in sections 2 and 3.1, obviates regioselectivity concerns. Since acetylacetone is symmetrical, the only stereogenic center formed arises from the diene, and the product is generated in 90.5:9.5 er. In the second example, an acetyltetralone couples with 2,3-dimethylbutadiene in a 1,4-hydroalkylation, delivering a product with a quaternary stereogenic center (78.5:21.5 er) arising from the nucleophile. These two transformations highlight an important aspect of hydroalkylation reactions: stereochemistry in the products can result from either the nucleophile, the diene, or both. The ability of a catalyst or catalysts to set two contiguous stereogenic centers in a single C−C bond-forming reaction is a powerful means of quickly building molecular complexity that has only recently been exploited in hydrofunctionalization (vide infra).[13d,54] Additionally, the pronucleophiles utilized by the Hartwig group—β-diketones—are what we term "activated". They contain a proton of sufficient Brønsted acidity to form the stabilized enolate nucleophile easily without strong base.

In 2018, our group reported the first highly enantioselective examples of acyclic diene hydroalkylation using Pd catalysts derived from PHOX ligands **L3** (see section 3.1) and **L18** (Scheme 20).[55] Several activated pronucleophiles add to terminal aryl-substituted dienes with the Pd(**L3**) catalyst, selectively affording the 4,3-addition product (>20:1 rr) regardless of diene electronics, a significant difference from diene hydroamination (cf., Scheme 9). Without deuterium labeling data, this difference cannot be definitively explained. It might be due to an inherent preference for carbon-based

Scheme 20. Pd−PHOX-Catalyzed Addition of Activated Pronucleophiles to Terminal Dienes
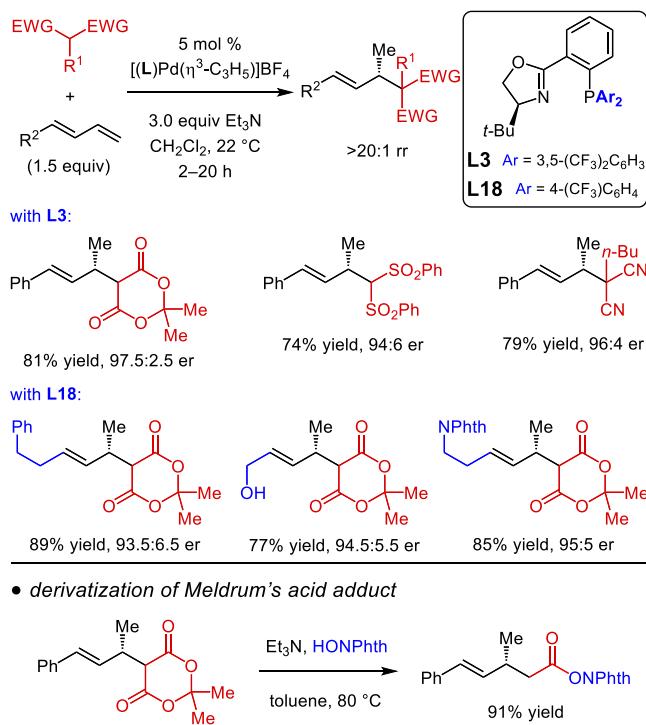

nucleophiles to add selectively to a Pd−π-allyl intermediate that results in olefin conjugation to the arene (Curtin−Hammett situation described in Scheme 10) or it may be that Et₃N·HBF₄, the propagating Brønsted acid in these hydroalkylations, exclusively protonates C4 of the Pd-coordinated diene.

Alkyl-substituted terminal dienes also undergo regio- and enantioselective alkylation but require the Pd(**L18**) catalyst to proceed efficiently (>70% yield in 6 h). Contrastingly, the **L3**-derived catalyst furnishes the same products in <50% yield after 20 h. Although aryl-substituted dienes lead to inferior enantioselectivities with **L18** compared to **L3**, the er is roughly the same with both ligands for alkyl-substituted dienes.

Pronucleophiles with a range of pK_as, from 7.3 (Meldrum's acid DMSO value) to 14.2 (acetylacetone DMSO value) can be successfully coupled. Dimethyl malonate ($pK_a = 15.9$ in DMSO) failed to add to phenylbutadiene under the conditions shown in Scheme 20, but we subsequently discovered that a Pd(**L3**) catalyst with a BAr$^F_4$ counterion in place of BF₄ leads to effective coupling, notably generating a different Brønsted acid: Et₃N·HBAr$^F_4$. Several of the many connected equilibria as well as their kinetics may be affected by this switch. Chiral pronucleophiles, which deliver products with an additional stereogenic center at the carbonyl α-position, do so without stereocontrol at this α-center.

The Meldrum's acid adducts can be readily derivatized to simpler carbonyl containing compounds. Treatment of these adducts with an appropriate nucleophile, such as N-hydroxyphthalimide, in the presence of Et₃N delivers good yields of γ,δ-unsaturated carbonyls with β-stereogenic centers, useful building blocks for downstream synthesis.

Our group has also shown that internal dienes are competent reaction partners for hydroalkylation with activated pronucleophiles (Scheme 21).[56] As with Pd(**L3**)-catalyzed hydroamination of this diene class (Scheme 10), the

Scheme 21. Addition of Activated Pronucleophiles to Internal Dienes with Pd−PHOX Catalysts

Scheme 22. Ni−bis(phosphine)-Catalyzed Additions of Ketone-Derived Enolates
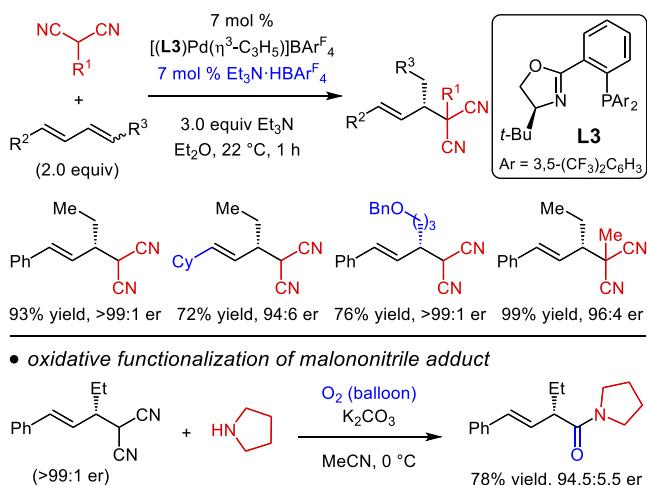
hydroalkylations require a relatively nonpolar solvent and for the catalyst to bear a BAr$^F_4$ counterion. The noncoordinating counterion likely (1) allows the catalyst to engage the more hindered diene better, (2) increases the electrophilicity of the Pd−π-allyl intermediates,[31] and (3) as the counterion to the Brønsted acid, perhaps more readily protonates a Pd(0)− internal diene complex. It was also discovered that addition of 7 mol % Et$_3$N·HBAr$^F_4$ as an additive was needed to promote the reaction.[57]

In most cases, the dienes were utilized as E/Z mixtures. Studies illustrated that the (E,Z)-diene was more reactive but both led to the same major enantiomer with equal selectivity. With both diene stereoisomers, the diene recovered from the reaction was ≥10:1 E,E:E,Z. Together these data illustrate that (1) diene coordination to Pd(L3) and formation of Pd−π-allyl intermediates are rapid and reversible and (2) multiple Pd−π-allyl species are in rapid equilibrium with one reacting faster to afford the product (Curtin−Hammett kinetics).

Malononitrile nucleophiles were found to be the most effective in this reaction. Most other C-pronucleophiles examined either fail to react or deliver near equimolar ratios of regioisomers (4,3- and 1,4-addition). Meldrum's acid, one of the most successful nucleophiles with terminal dienes, is unreactive with internal dienes. This reactivity difference is likely predominantly due to sterics, since malononitrile is one of the smallest partners and 1,4-disubstituted dienes result in more sterically congested products. Nonetheless, malononitrile is a particularly useful C-pronucleophile because it serves as a masked acyl anion equivalent.[58] Under oxidative conditions, malononitrile adducts can be converted into carbonyl containing compounds such as amides or esters with minimal erosion of er. The result, as highlighted in Scheme 21, is a product composed of a β,γ-unsaturated carbonyl with an α-stereogenic center, challenging motifs to prepare.

In a recent development by the Zhou group, enolates derived from simple ketones were found to add enantioselectively to terminal dienes using a Ni catalyst formed from a 2,2′-bis(diphenylphosphino)-1,1′-biphenyl (BIPHEP) ligand (L19 or L20, Scheme 22).[59] In our previous work, we were limited to the use of C-pronucleophiles with an upper pK$_a$ limit of 15.9, whereas the ketones utilized by Zhou and co-workers have a pK$_a$ greater than 20. Thus, this work greatly expands the scope of hydroalkylation. The desired 4,3-hydroalkylation
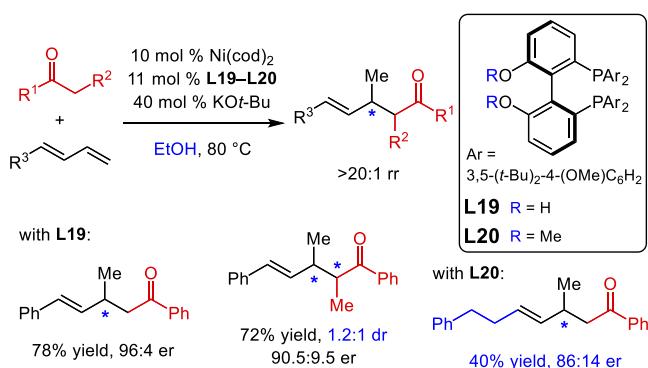
products were formed exclusively (>20:1 rr) in up to 97:3 er; however, other ligands and bases result in formation of 1,4-hydroalkylation as well as 4,3-hydroalkoxylation from the ethanol solvent. The reaction is compatible with both aryl- and alkyl-substituted dienes but the latter suffer from diminished yields and enantioselectivities. Methyl ketones lead to products with a single stereogenic center at the β-position, but much like in our own work with activated pronucleophiles, ketone-derived nucleophiles that generate an additional α-stereogenic center in the products do so without stereocontrol (ca. 1:1 diastereomeric ratio (dr)). It is unclear whether the poor dr is due to lack of selectivity in the enolate stereochemistry, lack of facial selectivity in the enolate addition, post-reaction epimerization, or some combination thereof.

Much like in their hydroarylation work (Scheme 17) the alcohol solvent is the proposed source for the hydrogen incorporated into the diene. The authors suggest two possible mechanisms for hydrometalation: (1) oxidative addition into the O−H bond by Ni(0) to form a Ni−H followed by migratory insertion of the terminal olefin or (2) ligand-to-ligand hydrogen transfer from a Ni(0) species coordinated to both the diene and EtOH (see Scheme 5). While further experiments would be necessary to distinguish between these two pathways, there is good evidence for ligand-to-ligand hydrogen transfer mechanisms in other Ni-catalyzed reactions.[26]

Deuterium labeling experiments using EtOD reveal exhaustive deuteration of the products' methyl group and carbonyl α-position and exclusively at C4 of the recovered diene. These data indicate that hydrometalation occurs only at the terminal olefin and is fast and reversible with respect to nucleophilic attack. The authors additionally propose that C−C bond formation occurs through an inner-sphere pathway which is in line with the harder nucleophiles derived from simple ketones.[60]

As mentioned earlier, hydroalkylation reactions have the capacity to form products with vicinal stereogenic centers, one derived from the diene and one from the nucleophile. A recent dual catalyst strategy disclosed by the Zi group has enabled stereocontrol at both centers (Scheme 23).[61] Their Pd−JosiPhos/Cu−PHOX approach mirrors recent developments in allylic substitution.[62] The Pd(L21) catalyst hydrometalates a diene to form Pd−π-allyl 27. Meanwhile, an amino ester Schiff base, not of appropriate acidity itself to enable appreciable deprotonation by Et$_3$N, reacts with the Cu(L22) catalyst. This Lewis acid activation allows for deprotonation by the weak base, generating Cu−azomethine ylide 28 and simultaneously

Scheme 23. Dual Cu and Pd Catalyst Strategy for the Stereodivergent Addition of Amino Ester Schiff Bases

mixtures of regioisomers. More recently we have seen how mechanistic insights can lead to creative catalyst developments that help solve difficult regioselectivity problems or even completely change the regioselectivity profile of a reaction. Furthermore, there are a large number of different possible substitution patterns for dienes including position and type of substituent (i.e., alkyl vs aryl substituents) that have not been examined and create additional opportunities for catalyst development. Thus, the future of this field will likely involve evolutions in discovery of new catalysts that allow for new regioisomers to be accessed from previously investigated diene classes and for methods to be developed with unexplored dienes. Investigating key mechanistic questions, including the hydrometalation step, will likely facilitate these advances.

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Notes
The authors declare no competing financial interest.

providing the Brønsted acid for the diene hydrometalation. Enolate stereochemistry is imparted by the chelate. Facial control of both reaction partners is achieved independently, and perhaps synergistically, by the two catalysts, furnishing products with both high enantio- and diastereoselectivity. Both terminal and internal dienes participate in the reaction, but the latter class leads to lower yields.

Furthermore, as shown in Scheme 23, because the facial selectivity of each component is controlled with a separate chiral catalyst, exchanging the enantiomer of one of the two catalysts results in a different diastereomer of the product formed. All four possible stereoisomers are thus accessible. Incredibly, ligand exchange between the two metal centers is not detrimental.

5. CONCLUSIONS AND OUTLOOK

Recent years have witnessed a swell in the number of reports for regio- and enantioselective nucleophile additions to 1,3-dienes. The prospects that arise from this strategy are complementary to existing enantioselective methods, including Tsuji−Trost allylation and hydrofunctionalizations of allenes, alkynes, and simple olefins. A major appeal of the current approach is the variety of nucleophiles, most of which are commercially available or easily prepared, which can be used to generate new C−C or C−heteroatom bonds enantioselectively in a highly atom economical way. Future work will likely expand the scope even further, particularly in the areas of P- and C(sp²)-type nucleophiles, which are still largely underexplored. An area that has been investigated in allene hydrofunctionalization but is surprisingly lacking for dienes is addition of oxygen-based nucleophiles. To our knowledge, highly enantioselective intermolecular hydroalkoxylation of dienes has yet to be achieved.[63,64]

Regioselectivity is often a major challenge in this field, but it is also an area of great opportunity. Initial reports on nucleophile additions to dienes often generated complex

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