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Review

Transition-Metal-Catalyzed Functionalization of Alkynes with Organoboron Reagents: New Trends, Mechanistic Insights, and Applications

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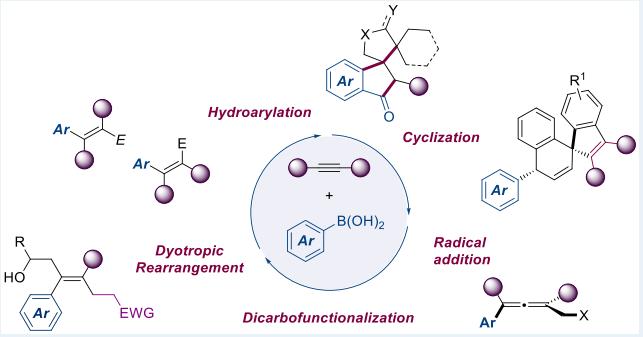
ABSTRACT: Catalytic functionalization of alkynes with organoboron reagents provides a straightforward access to stereochemically defined multisubstituted alkenes, which are structural motifs commonly found in bioactive compounds and organic materials. Recent progress has substantially broadened the scope of this field on several fronts. Strategies for regioselectivity control in the 1,2-migratory insertion across unsymmetrical internal alkynes, as well as for the direct access to products with *anti*-insertion stereochemistry, have been devised. The alkenyl-to-aryl 1,4-metal migration upon metal insertion has been recently exploited in powerful cascade sequences leading to complex polycyclic scaffolds, including the development of enantioselective processes. Elegant enantiospecific and dynamic kinetic resolution methods have been developed for accessing chiral allenes from propargylic alcohol derivatives. Mechanistic manifolds have emerged based on single-electron transfer (SET) that have provided a fresh impetus for alkyne 1,2-difunctionalization with complementary stereoselectivity to processes relying on 1,2-insertion of R−M species. Herein, we discuss the most recent advances in transition-metal-catalyzed functionalization of alkynes using organoboron reagents, categorized according to the type of mechanistic outcome. Emphasis is placed on mechanistic aspects, synthetic utility, limitations, and challenges for future research.



KEYWORDS: *alkyne functionalization, organoboron reagents, transition metal catalysis, hydroarylation, 1,2-difunctionalization, selectivity control*

1. INTRODUCTION

Transition-metal-catalyzed π-insertion processes across the triple bond of alkynes[1] allow straightforward access to stereochemically defined multifunctional olefins which are not only pivotal structural motifs found in bioactive compounds[2] and advanced materials[3] but also versatile building blocks in synthetic chemistry[4] (Figure 1). On the other hand, organic boron reagents rank among the most prevalent class of coupling partners because of their stability, ready availability, and ease of handling.[5] Merging these two fruitful chemistries has been the subject of intense research activities since the pioneering rhodium- and palladium-catalyzed hydroarylation of alkynes with boronic acids reported by Hayashi[6] and Oh,[7] respectively, at the turn of the 21st century. This continued interest has resulted in the development of many efficient approaches showing great potential for sequential inter- and intramolecular C−C bond formation in a tandem, cascade, or one-pot fashion. Several excellent reviews have already partially covered this chemistry,[1] some of them with a substantial focus on transition-metal-catalyzed alkyne hydroarylation with organoboron reagents,[8,9] including its

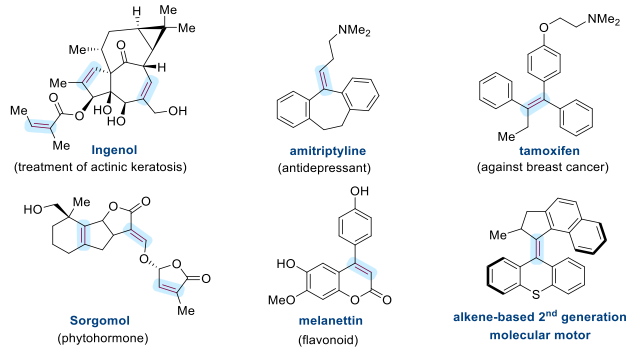


Figure 1. Examples of stereochemically defined olefins present in biologically active compounds and advanced materials.

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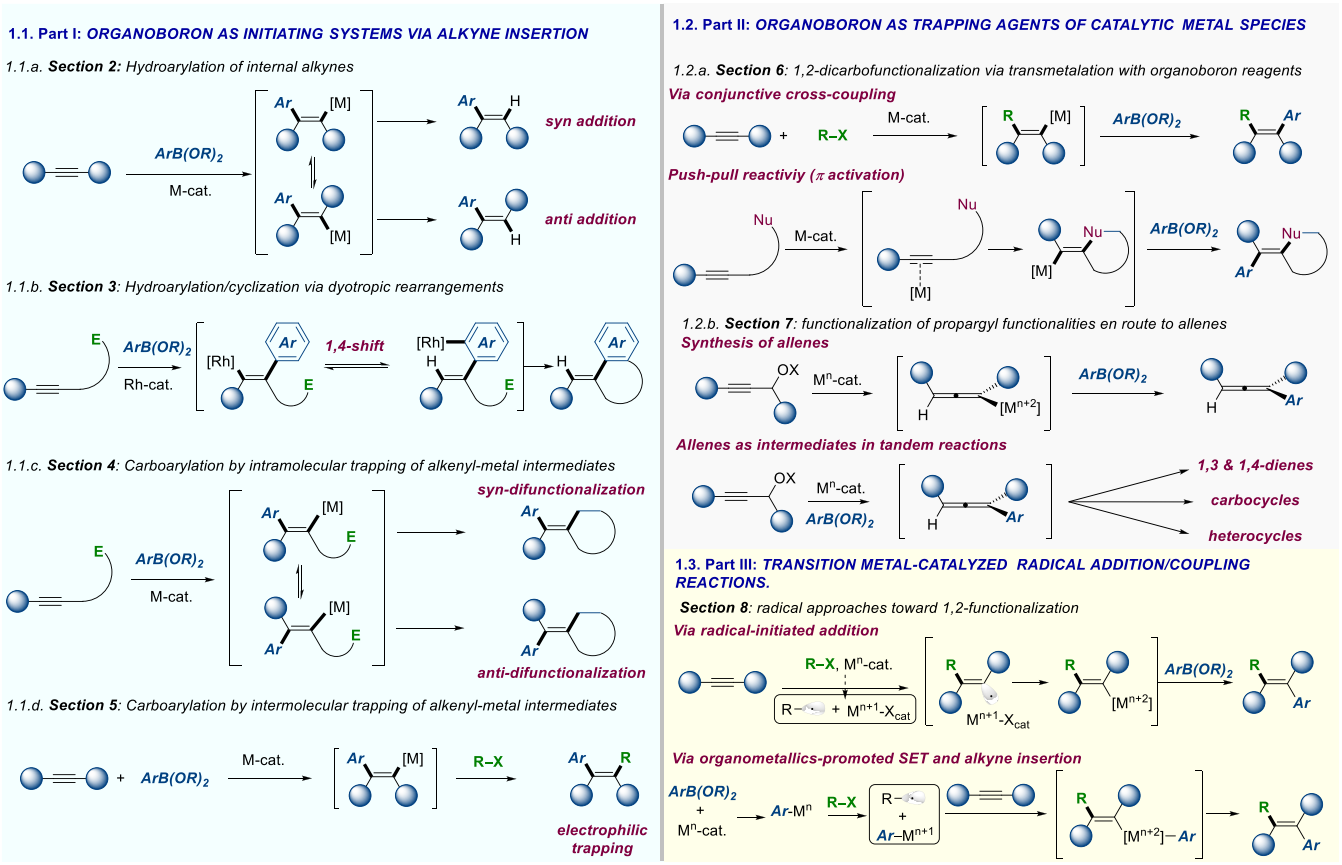
Scheme 1. General Strategies for the Catalytic Functionalization of C−C Triple Bonds with Organoboron Reagents and the Scope of the Review



application to the synthesis of heterocycles.[10] However, to the best of our knowledge, there is no previous review on transition-metal-catalyzed functionalization of alkynes with organoboron reagents, even though major advances in the past decade have substantially broadened the scope of this field on several fronts.

This Review is divided into three parts, the first two of which deal with polar reaction mechanisms, whereas the third part focuses on radical reactions. Part I is devoted to transformations in which organoboron reagents initiate the alkyne functionalization by generating catalytically competent organometallic species that undergo insertion across the C≡C triple bond (Scheme 1, 1.1). Progress on circumventing issues related to regio- and stereoselectivity is discussed in Section 2 (Scheme 1, 1.1a). This section includes new tactics for controlling regioselectivity when employing unbiased unsymmetrical internal alkynes and for selective access to *anti*-insertion products, as opposed to the conventional *syn*-stereoselectivity dictated by the *syn* addition of catalytic organometallic species across the alkyne. Section 3 deals with hydroarylation processes involving an alkenyl-to-aryl 1,4-metal migration, which have been recently exploited in powerful cyclization cascade sequences allowing the construction of complex polycyclic scaffolds (Scheme 1, 1.1b). Alkyne 1,2-difunctionalization via the intramolecular trapping of carbometalation intermediates with electrophilic species is the subject of Section 4, with special emphasis on methods enabling the access to the more challenging *anti*-cyclization products (Scheme 1, 1.1c). Finally, Section 5 focuses on intermolecular 1,2-difuntionalization combining organoboron reagents with electrophilic substrates (Scheme 1, 1.1d). The possibility of accessing both the *syn*- and *anti*-isomers from different insertion pathways has considerably expanded the chemical space available.

Part II of this Review focuses on methods where the organoboron reagent participates in the last step of the functionalization of the triple bond, generally by trapping of the *in situ* generated alkenyl-metal intermediate (Scheme 1, 1.2). Progress on either *syn*-1,2-dicarbofunctionalization via Heck−Suzuki-type cascade processes or *anti*-1,2-dicarbofunctionalization via electrophilic π-alkyne activation and subsequent outersphere nucleophilic addition followed by transmetalation with organoboron species are discussed in Section 6 (Scheme 1, 1.2a).

Transition-metal-catalyzed coupling of propargylic alcohol derivatives with organoboronic acids for chiral allene synthesis via either the enantiospecific functionalization of chiral propargylic carbonates or the catalytic asymmetric coupling with racemic substrates is discussed in Section 7 (Scheme 1, 1.2b).

Finally, Part III addresses transition-metal-catalyzed radical addition/coupling reactions, which have opened new avenues for alkyne 1,2-difunctionalization through a new mode of reactivity based on single-electron transfer (SET), with profound implications on stereoselectivity (Scheme 1, 1.3).

Emphasis is placed on highlighting protocols showing new facets of reactivity and those circumventing challenges in selectivity control. Mechanistic aspects, synthetic utility,

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drawbacks, and challenges for future research will be discussed. Unlike most of the previous reviews that have been organized according to the nature of the metal used as the catalyst, this overview is categorized according to the type of reaction mechanism. It is our hope that it serves as a source of inspiration and stimulates further investigations leading to impactful advances in the field.

PART I: ORGANOBORON AS INITIATING SYSTEMS VIA ALKYNE INSERTION

A common feature of the methods discussed in this part (Sections 2−5) is that the organoboron reagent participates at the early stages of the functionalization process by transmetalation to a transition metal followed by 1,2-migratory insertion of the C≡C triple bond of the alkyne. Distinct terminating strategies for trapping of the resulting alkenylmetal species have been designed that offer powerful tools for the construction of stereodefined alkenes, as well as a variety of (hetero)cyclic scaffolds.

2. HYDROARYLATION OF INTERNAL ALKYNES

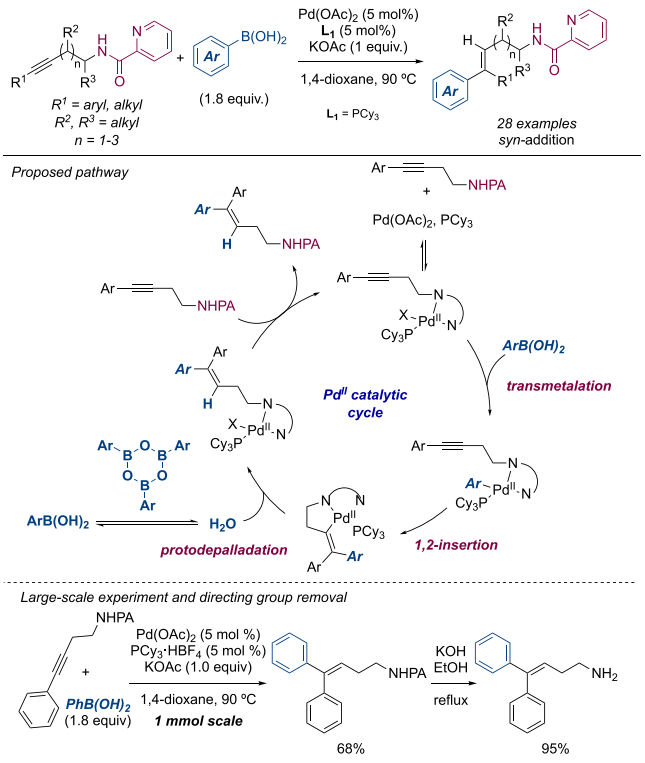
The hydroarylation of C≡C triple bonds employing organoboron compounds has been established as a direct means of generating multisubstituted stereochemically defined olefins. Since the pioneering contribution by Hayashi in 2001 employing Rh catalysis,[6] this transformation has been the subject of intense research. However, hydroarylation of unsymmetrical internal alkynes remains challenging due to the additional complication of how to control the regioselectivity. The most applied strategy for circumventing this problem is the use of electronically or sterically biased alkynes possessing a marked differentiation around the two acetylenic carbons.[1i] An alternative approach based on the use of directing groups,[1c] either removable or nonremovable, has emerged for controlling regioselectivity.

Control of the stereoselectivity is another important issue in this reaction. Because of the mechanism inherent to carbometalation of the triple bond, involving *syn*-addition of Ar−M (M = metal) species, *syn*-selectivity is typically obtained after the protodemetalation step.[12] Consequently, strategies capable of reversing this intrinsic selectivity enabling the access to the *anti*-hydroarylation products are more challenging yet highly appealing. In this section, we discuss recent advances toward efficient control of regio- and stereoselectivity in the hydroarylation of unsymmetrical internal alkynes.

2.1. *syn*-Selective Methods. In 2016, Engle and coworkers described the regioselective hydroarylation of internal alkynes using a removable 2-picolinamide directing group (PA) under Pd catalysis (Scheme 2).[13] The reaction proceeded with *syn*-stereoselectivity, and the authors demonstrated that an Ar−Pd^{II} complex is involved as catalytically active species. The electron-deficient, bidentate amide directing group was key for attaining good regiocontrol. Additionally, the precise positioning of the directing functionality with respect to the alkyne was found to be important. Poor regiocontrol was observed when the PA group was placed at the propargylic position, whereas consistently high levels of regiocontrol were achieved when it was located at further distal positions from the triple bond. The best results were obtained when the PA group was positioned at the homopropargylic position.

A mechanism based on a redox neutral Pd^{II} cycle triggered by initial complexation of the bidentate group to a cationic Pd^{II}

Scheme 2. PA-Assisted Pd^{II}-Catalyzed Hydroarylation of Unsymmetrical Internal Alkynes



species was proposed (Scheme 2). Subsequent transmetalation with the boronic acid mediated by the presence of an acetate group delivers the *N*,*N*-coordinated aryl-Pd^{II} species, which undergoes *syn*-1,2-insertion across the triple bond in a regioselective fashion. Finally, the protonolysis of the newly formed alkenyl-Pd^{II} species yields the final product. This step is believed to occur by reaction with water, which could be generated *in situ* by the self-condensation of the boronic acid to form the corresponding boroxine. This hypothesis was supported by the observation of a 40% deuterium incorporation when D_2O (1.0 equiv) was present in the reaction media.

The transformation displayed a broad substrate scope for both alkyne and boronic acid counterparts, and it was well suited for implementation on a large scale. However, alkynes bearing heteroaryl substituents with coordinating heteroatoms such as 2-thienyl and 2-pyridyl led to a decreased regioselectivity, which was ascribed to their competition for the coordination of the active Pd-species. Additionally, dialkyl-substituted alkynes showed moderate reactivity, with yields below 50% being consistently obtained for this class of substrates. Finally, removal of the directing group under basic hydrolysis gave the free homopropargyl amine with excellent yield (95%).

In 2019, Jarvo reported the hydroarylation of internal alkynes bearing a carbamate directing group at the propargylic position using Ni(COD)$_2$/trixiephos ($\mathbf{L_2}$) as the catalyst system (Scheme 3).[14] The use of PhB(OD)$_2$ as an aryl source resulted in an 88% deuterium incorporation at the resulting alkene. This observation led the authors to postulate a mechanism involving insertion of a Ni−H complex formed by reaction between a Ni^0 species by protonation with the boronic acid. Further transmetalation with the boron reagent followed by reductive elimination affords the arylated product.

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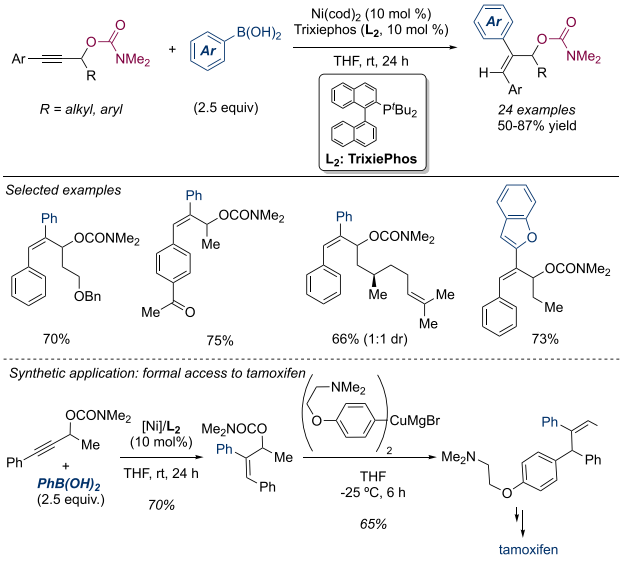
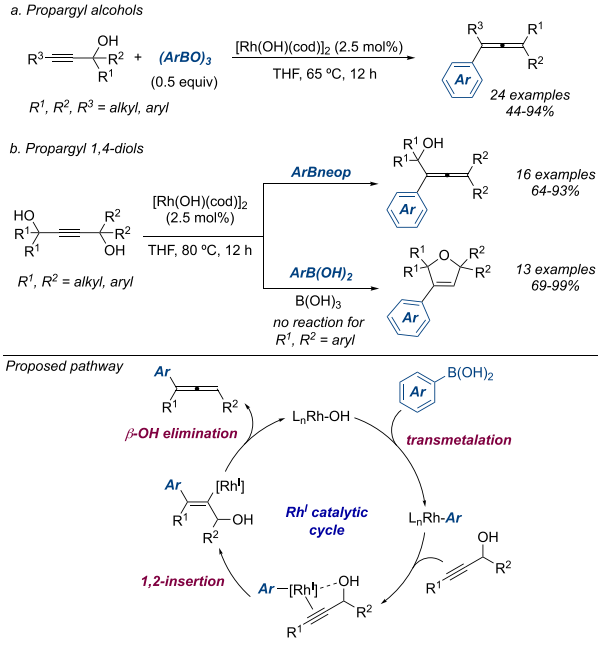
Scheme 3. Ni-Catalyzed Hydroarylation of Propargylic Carbamates



Scheme 4. Rh-Catalyzed Arylation/Dihydroxylation of *tert*-Propargylic Alcohols Leading to Allenes



However, the reaction was limited to aryl-alkynes, for which the nickel-catalyzed hydroarylation was reported to occur with the same regioselectivity in the absence of the directing group.[15] During the optimization studies, the formation of the corresponding allene product having the aryl group at the distal position with respect to the carbamate moiety was observed. This result suggests that regioselective insertion of an Ar−Ni intermediate across the alkyne and subsequent *β*-oxygen elimination might also be operative. Therefore, the presence of Ar−Ni species as active partners instead of Ni−H intermediates cannot be ruled out. The reaction showed broad substrate scope, tolerating potentially sensitive groups and heteroaromatic groups (Scheme 3). Remarkably, the practicality of this method was showcased by its application in the first step of a short synthesis of tamoxifen.

Propargylic alcohols and their positional isomers are an interesting family of compounds for catalytic *syn*-hydroarylation since the resulting allylic alcohols are structural platforms with a broad applicability.[16] For this substrate class, the formation of allenes via *β*−OH elimination from the carbometalated intermediate competes with alkyne hydroarylation. Dou and co-workers have exploited the latter pathway toward the synthesis of tetrasubstituted allenes by reaction of *tert*-propargylic alcohols with arylboroxines under rhodium catalysis (Scheme 4a).[17] This transformation was assumed to proceed through initial OH-directed carborhodation of the triple bond, leading to a transient alkenyl-rhodium species that undergoes subsequent *syn*-*β*-OH elimination. A related strategy has been reported by Mao and co-workers using Pd catalysis.[18]

When propargyl-1,4-diols were used as substrates, a divergent reactivity toward the allene or the tetrahydrofuran product was observed depending on the aryl boron source (Scheme 4b).[19] The reaction with anhydrous boronic ester provided the corresponding allenols following the typical arylation/*β*-OH elimination pathway. In contrast, when aryl boronic acids were employed under identical conditions, the allenic alcohol product further evolved through Rh-catalyzed intramolecular hydroalkoxylation to form dihydrofurans. Based on control experiments, it was hypothesized that the boric acid, generated during the arylation reaction when phenylboronic acid was used, participates in an acid−base reaction with the slightly basic hydroxorhodium catalyst leading to a cationic tetrahydroxoborato-rhodium(I) complex $[Rh(cod)]^+B(OH)_4^-$. This species could serve as the Lewis acid catalyst to promote the intramolecular hydroalkoxylation of allenic alcohols to generate dihydrofurans. Indeed, the presence of boric acid as an additive, in combination with the arylboronic acid, led to improved yields of the cyclization product.

Ma and co-workers[20] managed to prevent the *β*−OH elimination pathway in the Rh-catalyzed reaction of *tert*-propargylic alcohols with boronic acids, thereby attaining high selectivity toward the alkyne hydroarylation product (Scheme 5a). The reaction proceeds smoothly at room temperature cocatalyzed by the Rh^{III}/Ag^{I} system in the presence of NaOAc to provide the corresponding 3-arylallylic alcohol with a remarkable regioselectivity and exclusive *E*-stereocontrol. This method was also applicable to homopropargylic alcohols. It is worth noting that this Rh^{III}-catalyzed hydroarylation also performed decently with problematic secondary propargylic alcohols, which are prone to *β*−OH elimination. In this vein, the presence of the free hydroxyl unit was critical not only to ensure regioselectivity but also for achieving high reactivity, since its replacement for a −OMe group delivered poor yields (<20%). The use of NaOAc as an additive was also important for reactivity, presumably to facilitate the transmetalation step. Deuterium labeling experiments pointed to MeOH as the proton source for protodemetalation. The authors also noted the essential role of using $ArB(OH)_2$ as arylating reagents to prevent the *β*−OH elimination process.

The Xie group has recently expanded on this reactivity and devised a ligand-free manganese-catalyzed hydroarylation of *tert*-propargylic alcohols with boronic acids (Scheme 5b).[21] The reaction conditions are very user-friendly, tolerating the presence of water and an air atmosphere. Although the scope is limited to tertiary alcohols, the regioselectivity was complete, and the functional group compatibility was exceptionally high.

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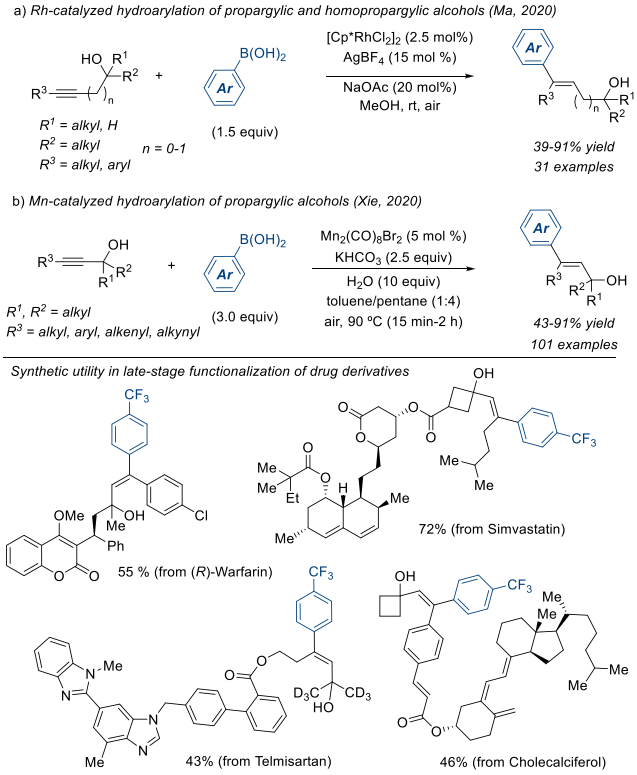
Scheme 5. Catalytic Hydroarylation of Propargylic Alcohols

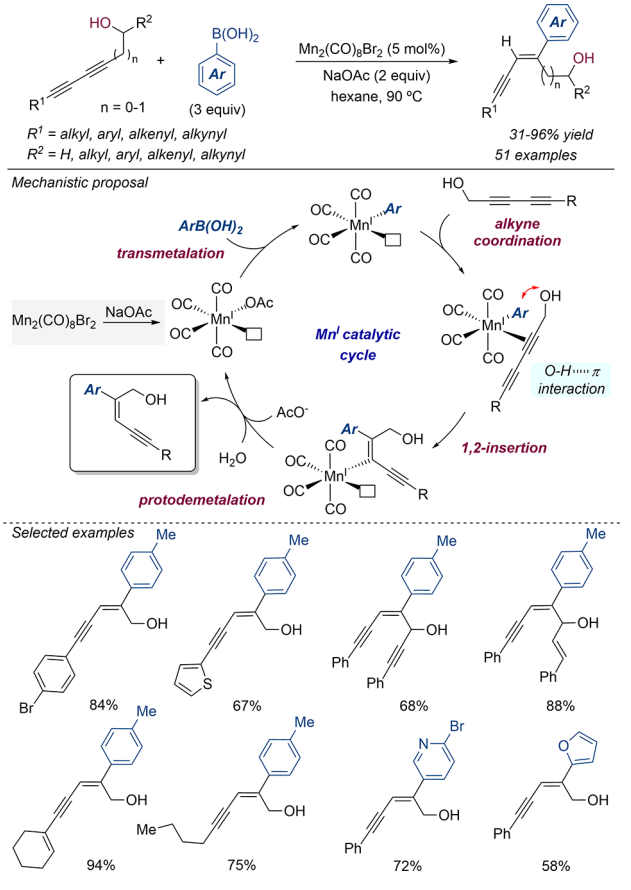


The robustness and practicality of this procedure were illustrated by late-stage functionalization of drug-type molecules and the concise synthesis of bervastatin, a hypolipidemic drug.

The same group described the regio- and stereoselective hydroarylation of 2,4-diyne propargyl alcohols with boronic acids catalyzed by $Mn_2(CO)_8Br_2$ (Scheme 6).[22] Mechanistic studies suggest that the reaction proceeds through acetate-induced dissociation of the dimeric structure $Mn_2(CO)_8Br_2$ to deliver the active Mn^I species. Transmetalation with the boronic acid would afford Ar−Mn^I species with an open coordination site for alkyne coordination, in which a OH—π interaction between the alcohol and the aryl group was identified by DFT studies. Then, a regioselective *syn*-1,2-insertion across the C≡C triple bond proximal to the hydroxyl group leads to the alkenyl-Mn^I intermediate. Finally, the hydroarylation product is delivered via protodemetalation, along with concomitant regeneration of the required Mn^I−OAc species. Although the two acetylenic carbons of the alkynes employed in this study are electronically differentiated because of the 1,3-diyne system, the presence of the OH unit seemed to be crucial for attaining regioselectivity. The substrate scope was extraordinarily varied, including internal alkynes of a diverse nature, along with a broad number of aromatic and heteroaromatic boronic acids. Remarkably, the reaction showed an excellent chemoselectivity, as no over-arylation was detected from the potential reaction with the 1,3-enyne product.

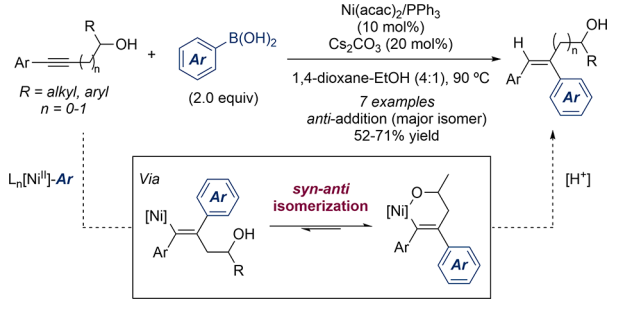
2.2. *anti*-Selective Methods. An important limitation often encountered in hydroarylation of internal alkynes with organoboron reagents is the inability to access the *anti*-hydroarylated product in a selective manner. Although the *anti*-addition of arenes to both internal and terminal alkynes is well-known to occur with electron-rich arenes in the presence

Scheme 6. Mn^I-Catalyzed Hydroarylation of Unsymmetrical 1,3-Diyne Alcohols



of π-Lewis acidic catalysts via a Friedel−Crafts type mechanism, this reaction is not suitable for electron-poor or neutral aryl reagents, which limits its synthetic utility.[23] Although some rare examples have been reported,[11n,24] general methods capable of accessing *anti*-selectivity in a rational and predictable manner have not been described until recently. A seminal contribution came from the team of Reddy in the context of hydroarylation of alkynes under Ni catalysis (Scheme 7).[25] The reaction was broadly applicable for a wide variety of propargylic and homopropargylic alcohols. However, unlike the previously discussed studies, the regioselectivity in this case was not controlled by the hydroxyl group; instead, it seemed to be governed by the electronic effect of the aryl group attached at the alkyne. The *anti*-addition selectivity observed for internal alkynes was ascribed

Scheme 7. *anti*-Selective Ni-Catalyzed Hydroarylation of Aryl-Alkyl Internal Alkynes



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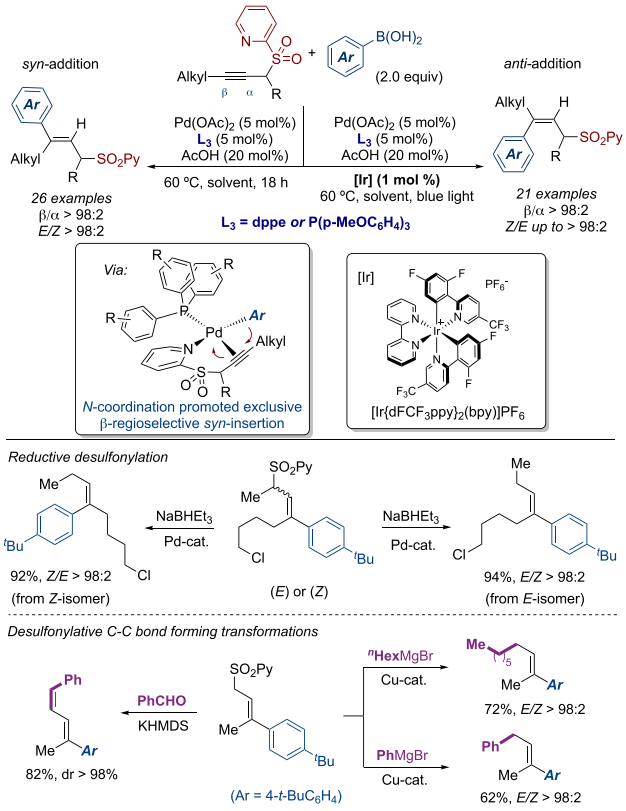
to an *in situ* *syn*-to-*anti* isomerization of the intermediate alkenyl-Ni^{II} species.[26] Such isomerization is favored by intramolecularly induced chelation of the propargyl OH group to the metal, which shifts the equilibrium toward the thermodynamically more stable *anti*-intermediate prior to the protodemetalation step.[27]

Unlike the above method based on thermodynamic control, the Carretero research team devised an alternative strategy for reversing the stereoselectivity of the Pd-catalyzed hydroarylation of unsymmetrical dialkyl alkynes with boronic acids (Scheme 8).[28] A stereodivergent approach was designed that

Scheme 8. Stereodivergent Hydroarylation of Unsymmetrical Dialkyl Alkynes by Pd/Ir Tandem Orthogonal Catalysis (Dppe = (1,2-Diphenylphosphino)ethane)



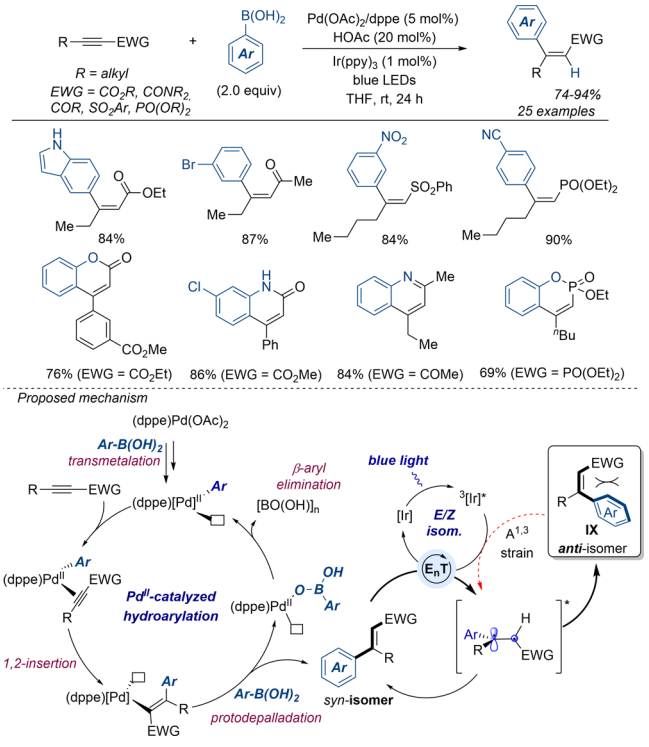
enables the access to unconventional *anti*-addition products by merging, in a tandem fashion, an initial thermodynamically favored an *E*-selective Pd-catalyzed *syn*-hydroarylation with arylboronic acids, with a kinetically controlled Ir-photocatalyzed $E \rightarrow Z$ photoisomerization (see the mechanistic discussion below).[29]

The presence of the 2-pyridyl sulfonyl (SO_2Py) directing group at the propargylic position enabled excellent levels of β-regiocontrol and *syn*-stereoselectivity via a redox-neutral Pd-catalytic cycle. The use of monodentate, electron-rich phosphines in combination with $Pd(OAc)_2$ catalyst was crucial, whereas the use of bidentate ligands delivered poor regioselectivities caused by the lack of available coordination sites around the palladium center. The open coordination site is necessary for binding of the pyridyl group before the 1,2-insertion event, thereby orienting the aryl group in a way that favors the β-insertion. Different alkyl chains were tolerated at both sides of the triple bond, and a range of aryl- and heteroaryl groups were easily installed under the optimized conditions.

Competition experiments with the analogue phenyl sulfonyl group and DFT calculations supported the important role of the 2-pyridyl unit in facilitating the insertion step. A practical feature of the SO_2Py directing group is its facile removal under reductive conditions (e.g., with $NaBHEt_3$ under Pd catalysis), delivering the formal hydroarylation products from unbiased dialkyl-alkynes in a stereoretentive way. This synthetically flexible directing group is also amenable to desulfonylative C−C bond forming transformations such as Julia−Kocienski olefination or Cu-catalyzed cross-coupling with Grignard reagents.

Exploiting the compatibility between both Pd- and Ir-catalytic cycles, Carretero's group has recently expanded this reactivity to the *anti*-arylation of internal alkynes activated with electron-deficient substituents (Scheme 9).[30] The reaction

Scheme 9. *anti*-Hydroarylation of Activated Internal Alkynes Merging Pd and Energy Transfer Catalysis



rendered the corresponding formal *anti*-arylation product for a diverse array of both electron-poor and electron-rich aryl boronic acids. A variety of electron-withdrawing alkyne substituents were amenable to the reaction, including esters, amides, ketones, aldehydes, sulfones, and phosphonates. Importantly, the use of boronic acids bearing OH or NH_2 functionalities at the *ortho* position triggered a cascade process that provided access to heterocyclic products (coumarins, quinolones, quinolines, and phosphacoumarins).

Several literature precedents on Pd-catalyzed hydroarylation with boronic acid postulated as the initial step the insertion across the alkyne of a Pd—H species, generated *in situ* by oxidative addition of AcOH to a Pd^0 catalyst.[7,11g] The resulting alkenyl-Pd intermediate was proposed to engage in transmetalation with the boronic acid, followed by reductive elimination. However, various pieces of evidence against this

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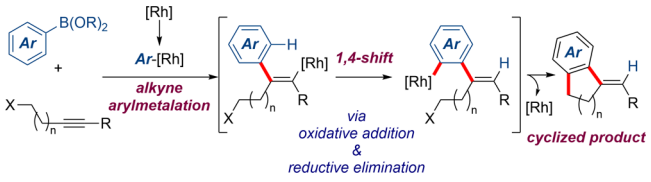
mechanism were obtained from deuterium labeling, intramolecular trapping, KIE analysis, and inhibition test experiments. These studies support the addition of Ar—Pd^{II} species to the alkyne instead of the previously postulated Pd—H species. Therefore, a new mechanistic hypothesis for this reaction was formulated, characterized by a first transmetalation of the Pd^{II}—OAc catalyst with the boronic acid, which renders the active Pd^{II}—Ar species (Scheme 9). Regio- and stereoselective insertion across the alkyne leads to an alkenyl-Pd^{II} intermediate which undergoes protodemetalation to yield the final trisubstituted alkene. Deuteration studies suggested that the protodemetalation step occurs by reaction of the alkenyl-Pd with the O—H bond of the boronic acid, yielding a key Pd^{II}—OB(OH)Ar species which regenerates the active Pd^{II}—Ar species via β-aryl elimination.[31] The access to the *Z*-isomer takes place via the known energy transfer sensitization of the *E*-alkene with an Ir photocatalyst under blue light irradiation.[29] Thus, in a parallel cycle, the Ir photocatalyst exposed to blue light irradiation is excited toward a triplet excited state (^{3}Ir*) and made available for interaction with the hydroarylation product via an energy transfer process. Subsequent relaxation of the resulting excited state of the alkene toward the ground state would generate either the *syn*- or *anti*-isomer. However, the *anti*-isomer is much less available for interaction with the photocatalyst because of the deconjugation between the EWG (or the aryl unit) and the C═C double bond caused by the 1,3-allylic strain, which raises up the triplet state of the alkene. In this scenario, the *anti*-isomer accumulates in the photostationary state.

3. HYDROARYLATION/CYCLIZATION VIA DYOTROPIC REARRANGEMENTS

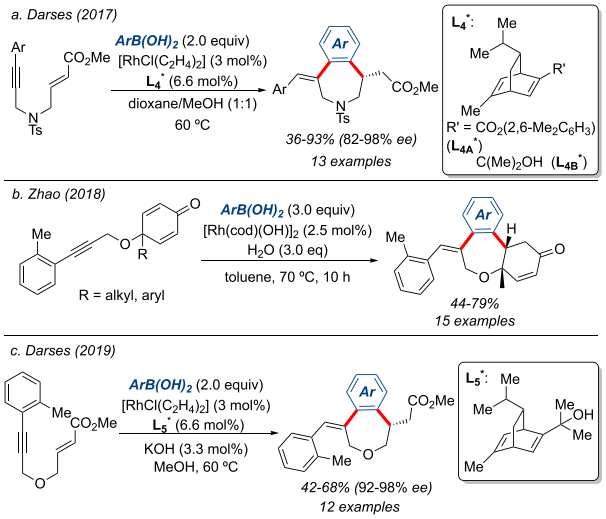
Since the first example on Rh-catalyzed addition of boronic acids to alkynes,[6] several methods relying on the ability of alkenyl-rhodium species to promote an intramolecular 1,4-migration[32] to the corresponding aryl-rhodium intermediate have been disclosed.[33] This 1,4-shift offers the opportunity to employ arylboron reagents with a free C−H bond at the *ortho* position as 1,2-dimetallate synthons (Scheme 10).

Scheme 10. Cascade Arylative Cyclization Triggered by Arylmetalation/1,4-Rhodium Migration



In this domain, Darses and co-workers[34] described the catalytic asymmetric synthesis of 3-benzazepines in a cascade sequence involving a first aryl-rhodation of the triple bond followed by 1,4-rearragement and a final intramolecular 1,4-addition of the resulting aryl-rhodium species to a pendant unsaturated ester using the chiral diene ligand $\mathbf{L_4}$* (Scheme 11a). The success of the method relies on the electronic bias exerted by the aryl substitution at the C≡C triple bond, which ensures a regioselective *syn*-insertion of the aryl-rhodium species. In contrast, when the substituent is an alkyl group, the regioselectivity of the insertion is reversed, and the formation of a 5-membered heterocycle is favored[35] rather than the 1,4-migration.[36] Later on, Zhao extended this strategy to the

Scheme 11. Construction of 7-Membered Rings from Aryl-Alkynes by Aryl-Rhodation/1,4-Metal Migration



synthesis of oxepine derivatives by using cyclohexadienone-tethered *o*-tolyl-substituted alkynes (Scheme 11b).[37] The asymmetric version of Zhao's reaction was developed by Darses using O-tethered 1,6-enynes as substrates and a chiral diene ligand $\mathbf{L_5}$* (Scheme 11c).[38] Interestingly, in both cases, the presence of an *ortho*-tolyl group attached to the alkyne moiety was required for good regioselective control, which ensured that the concomitant Rh-1,4-shift for the cascade process took place.

This 1,4-migration of rhodium has also been used as a key step in cascade processes leading to 6-membered carbocycles through a terminating intramolecular 1,2-addition to a carbonyl group. Lam and co-workers described a ligand-free Rh-catalyzed arylation/cyclization of internal propynyl malonates and arylboronic acids for the synthesis of 1-tetralones (Scheme 12a).[39] Although the presence of an aryl substituent at the alkyne was a structural requirement for regioselectivity control, a wide range of aryl substituents were tolerated. This reaction is amenable to desymmetrization by reaction of the aryl-rhodium intermediate with an ester function, thus generating the ketone functionality with the concomitant formation of a valuable quaternary stereocenter. However, attempts to develop an asymmetric version using chiral phosphine ligand $\mathbf{L_6}$* resulted in modest enantioselectivity (76% ee), along with the formation of side-products (regioisomers/protodemetalation). Darses and co-workers described a more efficient catalytic asymmetric synthesis of 1-tetralones utilizing a C1-symmetric chiral diene having a very bulky anthracen-9-yl substituent (up to 96% ee).[40] In this case, an aromatic substituent at the alkyne bearing at least a trifluoromethyl group at the *ortho* position was needed for attaining high regiocontrol in the insertion, with the 2,4-bis(trifluoromethyl)phenyl group providing the best results.

The Lam group later extended this asymmetric desymmetrization to 1,3-diketones, leading to tetralol structures (Scheme 12b).[41,42] The combination of $[RhCl(C_2H_4)_2]_2$ with the chiral biphosphine ligand (*S*)-DTBM-SEGPHOS $\mathbf{L_7}$* provided the corresponding cyclized products with moderate to high yields and typically excellent levels of asymmetric induction (typically >95% ee). A variant of this Rh-catalyzed reaction has been reported by Darses employing chiral diene ligands.[43] Although the corresponding 1-tetralol products were produced with

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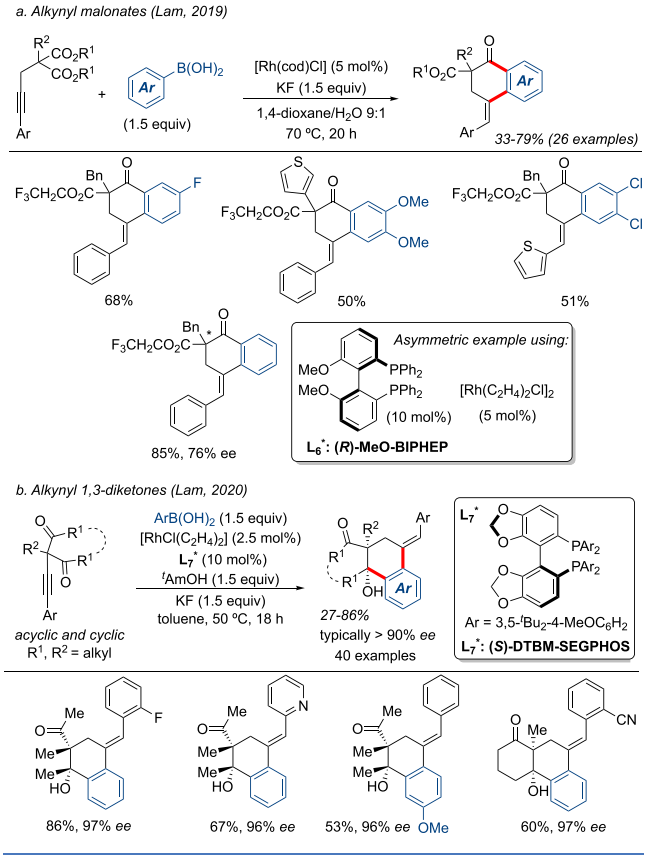
Scheme 12. Cascade Arylative Cyclization Triggered by Arylmetalation/1,4-Rhodium Migration

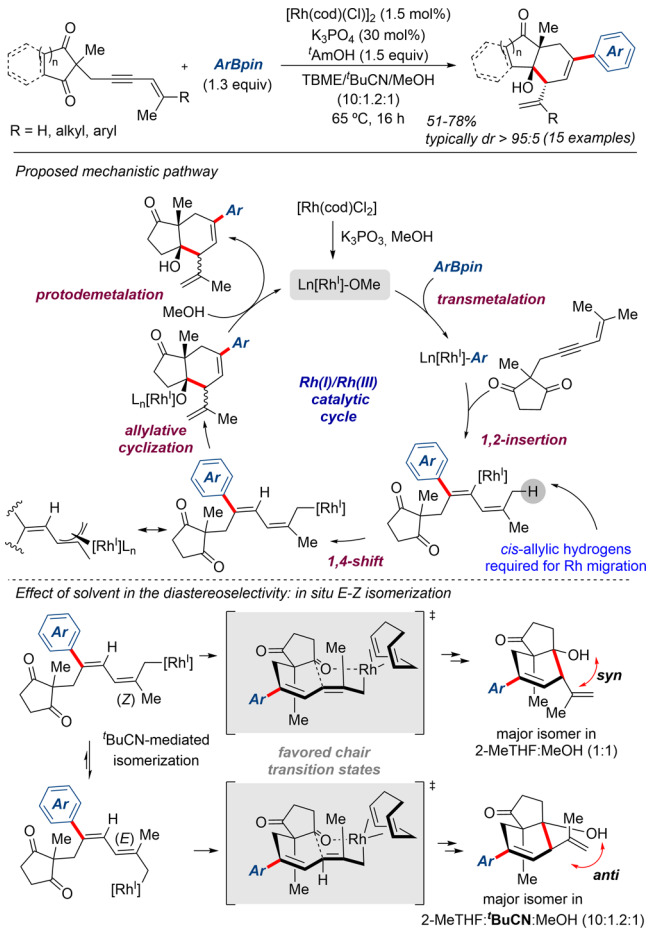


consistently high yields and enantiomeric excesses, the aryl group attached to the alkyne functionality was restricted to 2-trifluoromethylphenyl. Matsuda and co-workers have adapted this method to the synthesis of naphthyl derivatives by dehydration of the resulting alcohol obtained after the intramolecular aryl-rhodium ketone insertion.[44]

In 2017, Lam and co-workers reported the Rh-catalyzed arylative intramolecular allylation of cyclic 1,3-diketones bearing a tethered 1,3-enyne fragment by reaction with aryl Bpin-boronates (Scheme 13).[45] The aryl-metalation of the C≡C triple bond proceeded in a chemoselective fashion in the presence of the conjugated alkene. In this case, an allylic 1,4-shift of the metal is preferred over the 1,4-migration to the aryl group. Interestingly, a reversed diastereoselectivity was observed when switching the solvent from THF/MeOH (10:1) to TBME/MeCN/MeOH (10:1.2:1). It was suggested that allylation occurs through cyclic six-membered transition states (Scheme 13). In the absence of a nitrile-containing solvent in the reaction medium, the (*Z*)-allyl-rhodium species, formed upon 1,4-rhodium(I) migration, cyclizes through a chairlike arrangement to give the *syn*-configured product as the major isomer. However, when a coordinating nitrile-based solvent is present, the rate of cyclization could be decreased, allowing the (*Z*)- to (*E*)-isomerization of the allyl-rhodium intermediate, whose cyclization through a similar chairlike TS provides the *anti*-configuration product.

Acyclic monoketones were also suitable substrates for this transformation, albeit with low stereoselectivities. Attempts to develop an enantioselective version of the reaction using chiral phosphine ligands resulted in no reactivity, whereas chiral diene ligands led to only modest results. However, the use of a

Scheme 13. Alkenyl-to-Allyl 1,4-Rh Migration in the Arylative Cyclization of 1,3-Enynes with Ketones



chiral sulfinamide-alkene ligand provided high enantioselectivity (around 90% ee), albeit a slightly lower diastereoselectivity. The intermolecular version of this reaction has also been successfully developed, leading to the formation of chiral bis(homoallyl)amines.[46]

An intriguing feature of the 1,4-shift as an elementary step in a catalytic cycle is the ability of the ligand to trigger this reactivity mode. A salient example of this ligand modulation has been recently reported by Dou and co-workers[47] in the context of Rh-catalyzed synthesis of 1,1-disubstituted indenes from propargyl alcohols and arylboronic acids (Scheme 14). This reaction is another important transformation involving the Rh-dyotropic rearrangement, in which the 1,4-shift is preferred over of the typically observed *β*—OH elimination[17−19] or hydroarylation pathways,[20−22] as previously discussed in Section 2. The use of DPEPhos $\mathbf{L_8}$ as a ligand was key for success which, in combination with [Rh(OH)(cod)]$_2$, is able to promote a sequential aryl-rhodation of the C≡C triple bond, followed by 1,4-rhodium migration to a previously existing aryl group in the substrate. This rhodium species further evolves via an intramolecular Heck-type cyclization with concomitant *β*—OH elimination (Scheme 14). DFT calculations suggest that the DPEPhos ligand imposes a unique conformation that lowers the energy of the intermediate leading to the dyotropic rearrangement. The authors pointed out the oxygen atom present in the ligand as a crucial element of stabilization, which makes possible the formation of a transient tetracoordinated square-planar 16e Rh^{I}

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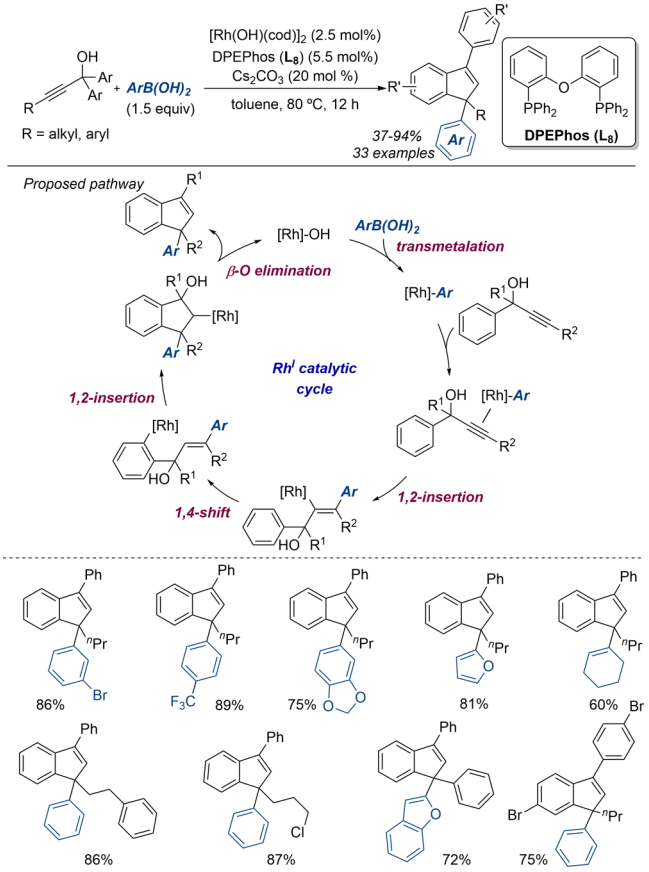
Scheme 14. Synthesis of Indenes from Propargyl Alcohols via Aryl-Rhodation/1,4-Rh Shift/β-*O*-Elimination



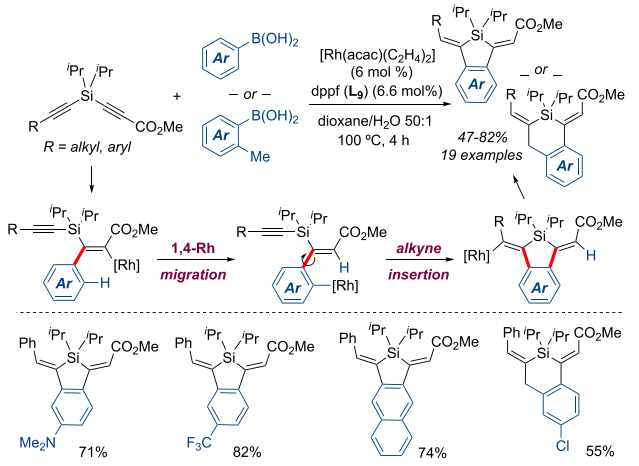
species via the formation of a Rh—O bond, not possible with other bidentate ligands such as dppe or dppbz ((1,2-diphenylphosphino)benzene).

Finally, Shintani has developed a method for the synthesis of silicon-bridged 1,2-dialkenylbenzenes by reaction of dialkynylsilanes possessing an electron-withdrawing group with arylboronic acids under rhodium catalysis in combination with dppf (L_9) as a ligand.[48] The reaction proceeds via a first chemo- and regioselective aryl-rhodation of the alkynoate unit, followed by 1,4-rhodium migration and final 1,2-insertion into a pendant alkynyl silicon group, thus leading to the final 5-membered silacycle which undergoes protodemetalation (Scheme 15). Importantly, when a methyl group is located at the *ortho* position of the boronic acid, a 1,5-shift is preferred over the 1,4-migration. This reactivity mode allows the access to 6-membered silacycles.

4. CARBOARYLATION BY INTRAMOLECULAR TRAPPING OF ALKENYL-METAL INTERMEDIATES

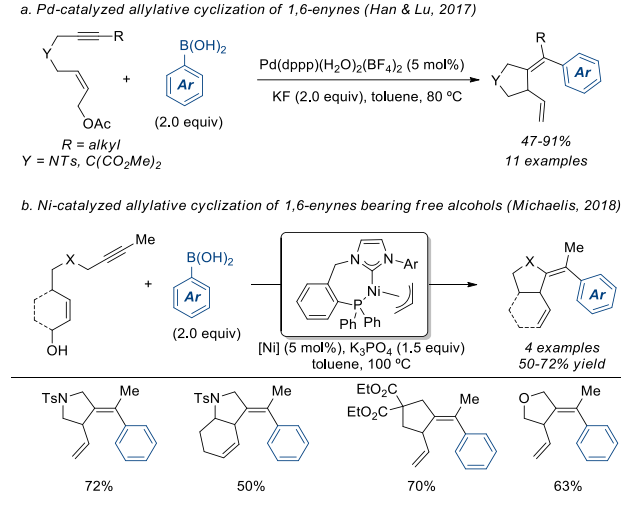
4.1. *syn*-Selective Functionalization. In this section, different strategies that harness the carbometalation across the triple bond to initiate cascade C−C bond forming reactions are discussed. One of the simplest as well as highly efficient and useful types of cyclizations involves the intramolecular trapping of the alkenyl-metal intermediate generated after alkyne carbometalation. This strategy, which necessitates the use of alkynes containing pendant reactive electrophilic moieties, has been widely applied to the synthesis of carbo- and heterocycles.[49] Particularly reactive functional groups for this

Scheme 15. Rh-Catalyzed Synthesis of Silicon-Bridged 1,2-Dialkenylbenzenes from Dialkynyl Silanes via 1,4-Rh Migration (Dppf (L_9) = 1,1′-Ferrocenediyl-bis(diphenylphosphine))



electrophilic trapping are alkynes and allenes,[50] Michael-type acceptors,[51] carbonyl groups,[52] allylic systems,[53] and isocyanates.[54] The redox neutral cationic Pd^{II}-catalyzed allylative cyclization of 1,6-enynes, reported by Han, Lu, and co-workers, is a recent example of this chemistry (Scheme 16a).[55] The

Scheme 16. Alkyne Carbometalation-Initiated Arylative Cyclization of Tethered Allylic Systems



reaction was proposed to proceed by initial carbopalladation of the alkyne followed by intramolecular alkene insertion from the resulting alkenyl-Pd intermediate. Then, an alkylpalladium species is formed which undergoes β-acetoxy elimination, rather than β-hydride elimination, likely due to easy coordination of the carbonyl oxygen of the acetoxy group to the cationic Pd^{II} center. Along similar lines, Michaelis has reported a related arylative cyclization employing allylic alcohols as a trapping element catalyzed by nickel(0) complexes of bidentate N-heterocyclic carbene/phosphine ligands (Scheme 16b).[56] The bidentate nature of the ligand was found to extend catalyst lifetime and enable high yields of the corresponding cross-coupling products with as little as 1.25 mol % nickel catalyst.

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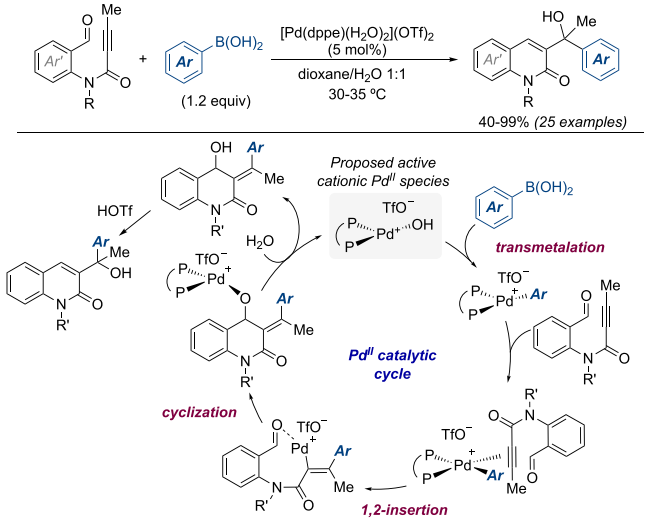
This strategy also provides access to heterocyclic structures. In 2015, Lu and co-workers described the synthesis of N-containing heterocycles via a sequential Pd-catalyzed aryl-metalation of alkynyl amides and subsequent intramolecular cyclization by insertion to a pendant aldehyde (Scheme 17).[57]

Scheme 17. Pd-Catalyzed Arylation of Alkynyl Amides and Cyclization via Aldehyde Insertion

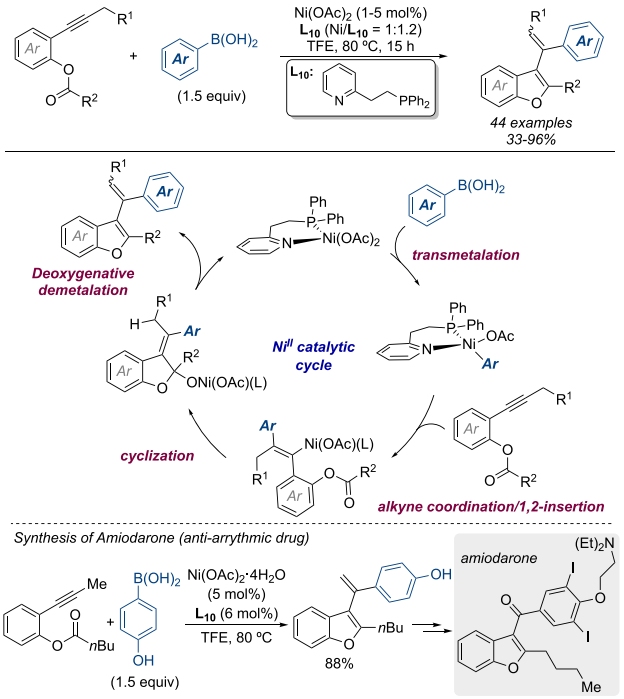


The resulting alcohol further evolves via 1,3-OH migration, a step that is believed to be promoted by catalytic amounts of HOTf liberated by the hydrolysis of the cationic triflate palladium precatalyst.[58] This cascade process allows for the preparation of highly useful six-membered lactams under very mild conditions.

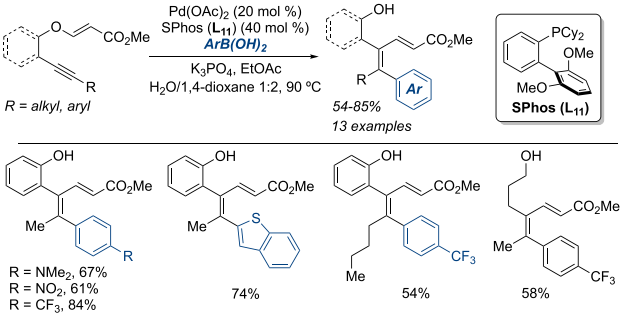
Following this approach, Maiti, Cho, and co-workers have reported the synthesis of multisubstituted benzofurans via a Ni-catalyzed alkyne aryl-metalation of alkyne-tethered phenolic esters followed by intramolecular attack to the ester group employing a phosphinopyridine ligand $\mathbf{L_{10}}$ (Scheme 18).[59] This arylative cyclization/isomerization was applied to the late-stage functionalization of natural products and bioactive compounds with excellent selectivity and reactivity. Additionally, this methodology was used as a key step in a short-step-synthesis of amiodarone, an antiarrhytmic drug. A catalytic cycle was proposed in which carbometalation of the alkyne with Ar−Ni^{II} species, resulting from transmetalation with the boronic acid, generates a nucleophilic alkenyl-Ni^{II} species which then undergoes an intramolecular attack to the phenol ester. Subsequent dehydration yields the benzofuran skeleton.

Fürstner and co-workers have described a conceptually novel Pd-catalyzed enyne cycloisomerization/Suzuki cross-coupling cascade reaction that provides 1,3-dienes comprising a stereodefined tetrasubstituted alkene (Scheme 19).[60] This method relies on the use of strategically designed alkynes bearing a Michael acceptor moiety attached to an oxygen atom at the β-position. The cascade process results in the net formation of two new C−C bonds while a C−O bond in the substrate backbone is broken. Although the mechanism remains unclear, the reaction can proceed either via enyne cycloisomerization followed by a reductive C−C bond forming step with cleavage of the C−O bond in its backbone or through a stepwise mechanism involving *syn*-aryl-palladation of the alkyne followed by insertion of the alkenyl-

Scheme 18. Ni-Catalyzed Synthesis of Benzofuranes via Carbometalation and Intramolecular Trapping with an Ester Function



Scheme 19. Pd-Catalyzed Cascade Reaction Merging Enyne Cycloisomerization and Suzuki Cross-Coupling



Pd^{II} bond and final β-O elimination. Different aryl and an alkenyl boronic acids reacted in high yields, whereas alkylboronic acids failed to react. The reaction must be stopped immediately once full conversion is reached to avoid the oxa-Michael attack of the resulting OH group to the newly formed unsaturated ester. The use of boronic acids, rather than the popular pinacol boronates, is mandatory in this transformation.

Nitrogen-substituted alkynes, commonly named "ynamides", represent one of the most versatile classes of alkynes and have emerged as appealing candidates for catalytic functionalization.[61] Because of the two electronically well-differentiated acetylenic carbons, achieving regio- and stereoselective difunctionalization appears to be relatively straightforward.[62] However, umpolung difunctionalization where electrophiles and nucleophiles are incorporated at the α- and β-positions, respectively, remains a significant challenge. This issue has been recently addressed by Qian, Ye, and co-workers following a strategy based on *syn*-carbometalation/cyclization of imine-ynamides with arylboronic acids under Cu catalysis (Scheme

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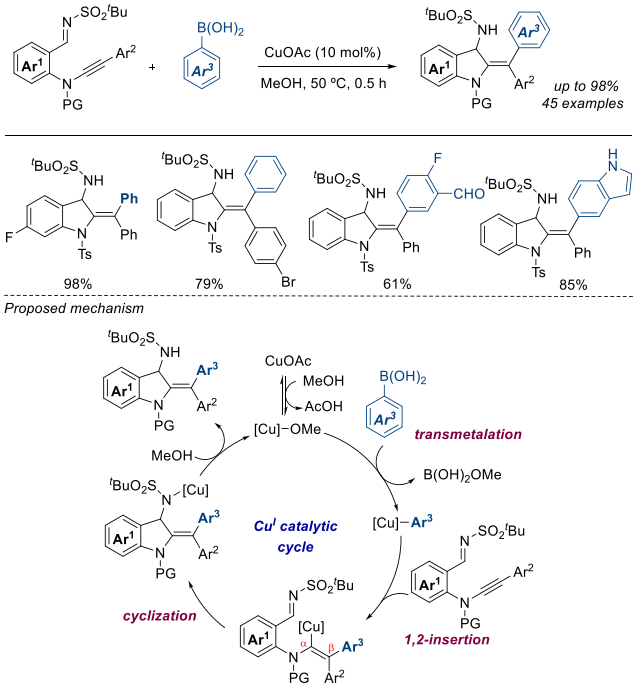
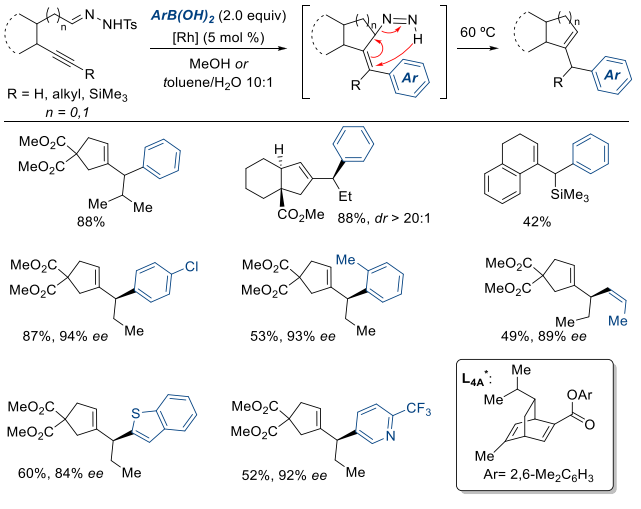
20).[63] This method provides a practical access to 2,3-disubstituted indolines in moderate to excellent yields.

Scheme 20. Cu-Catalyzed Umpolung Functionalization of Imine-Ynamides by Domino *syn*-Carbometalation/Cyclization



This addition−cyclization transformation can be coupled with subsequent cascade processes in which the acceptor enables further structural elaboration. For example, the Lee group devised a protocol for cycloalkene synthesis based on the merger of rhodium-catalyzed addition−cyclization of alkynes containing *N*-sulfonyl hydrazone acceptors with a pericyclic allylic diazene rearrangement (Scheme 21).[64] The reaction proceeded via a Rh-catalyzed insertion of a boronic acid into a triple bond, followed by intramolecular alkenyl

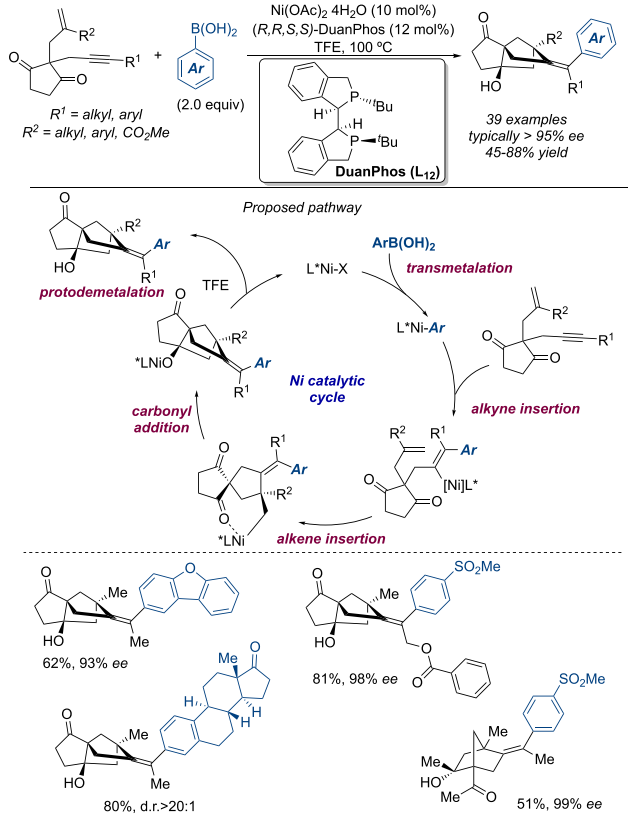
Scheme 21. Rh-Catalyzed Addition−Cyclization−Rearrangement of Alkynylhydrazones Leading to Cycloalkenes



addition to the C═N bond at 0 °C to form an allylic hydrazide. Upon conversion to an allylic diazene, a facile retro-ene reaction (heating up to 60 °C) takes place that brings about a rearrangement of the alkene from *exo* to *endo* positions. The reaction can also be rendered asymmetric by using chiral diene ligands such as $\mathbf{L_{4A}}$*, whereby the chirality of the newly formed C—N stereocenter is transferred to an allylic C—H center via suprafacial bond formation. High-asymmetric inductions were achieved, allowing the incorporation of different aromatic groups, heterocyclic structures, and even alkenyl boronic acids.

Concomitant with the burgeoning number of methodologies based on this approach has been an increase in the degree of complexity generated in terms of chemical functionality, structure, and stereoselectivity. These aspects were elegantly exemplified by the Kong group in their Ni-catalyzed asymmetric domino cyclization of enynones enabling the formation of three consecutive C—C bonds along with the construction of three quaternary stereocenters.[65] The catalytic cycle starts with transmetalation of the arylboronic acid with a suitable nickel catalyst to yield an active Ar−Ni^{II} species. Then, this intermediate promotes the aryl-nickelation of the C≡C triple bond in a regio- and *syn*-stereoselective fashion, triggering a subsequent cascade reaction involving a second insertion to an alkene via a Heck-type reaction. Final cyclization of the resulting σ-alkylnickel species by addition to the ketone moiety and subsequent protodemetalation regenerates the catalytically active nickel species and delivers the final cyclized product (Scheme 22). The use of trifluoroethanol was suggested to be important as an activating agent to facilitate the involvement of the pendant alkene

Scheme 22. Ni-Catalyzed Asymmetric Domino Cyclization of Enynones toward Bridged Tricyclo[5.2.1.$0^{1,5}$]decanes



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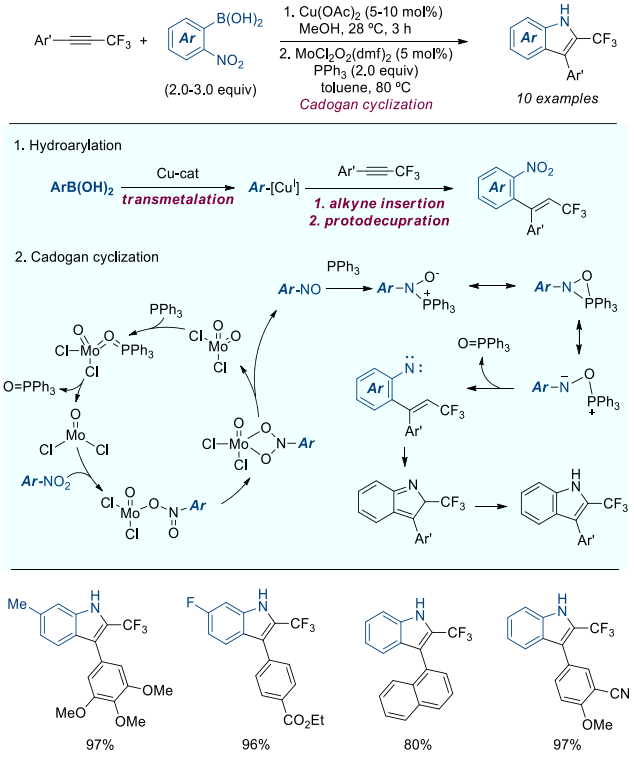
moiety in the cascade process. The use of MeOH, DMF, and MeCN led to bicyclic products, whose formation can be ascribed to the catalyst not engaging with the alkene unit. While typical chiral bidentate phosphine ligands provided low levels of reactivity and enantioselectivity, the phospholane-based DuanPhos $\mathbf{L_{12}}$*, featuring a conformationally rigid *P*-stereogenic center, was highly effective. The reaction yielded bridged tricyclo[5.2.1.$0^{1,5}$]decanes, a structural platform widely found in many biologically active molecules.[66] The existence of two carbonyl groups in the starting material was found to be crucial for the process, with monocarbonyl-substituted substrates providing low yields. The products were rapidly derivatized to increase the molecular functionality. Additionally, this process could be used in late-stage functionalization of complex structural cores, highlighting its wide functional group compatibility.

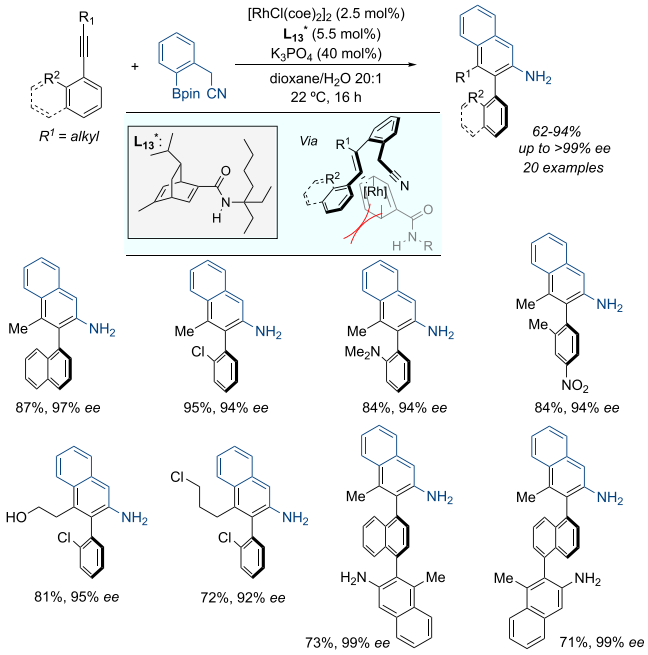
A complementary approach en route to cyclic scaffolds relies on the use of bifunctional aryl boronic acids bearing an electrophilic group at the *ortho* position which, upon regioselective carbometalation of the alkyne, undergoes subsequent facile nucleophilic addition by the resulting alkenyl-metal intermediate. This strategy has been successfully applied to the synthesis of indole derivatives, which are privileged *N*-heterocyclic cores in terms of biological activity.[67] A recent contribution from Yamamoto describes a two-step process initiated by a Cu-catalyzed hydroarylation of aryl trifluoromethyl alkynes with *ortho*-nitroaryl boronic acids, which is followed by a reductive Cadogan reductive cyclization[68] promoted by PPh_3 in the presence of catalytic quantities of $MoCl_2O_2(dmf)_2$ (Scheme 23).[69] This reaction provides 3-aryl-2-(trifluoromethyl)indoles in good yields.

Scheme 23. Cu-Catalyzed Hydroarylation and Subsequent Cadogan Cyclization toward 3-Aryl-2-(trifluoromethyl)indoles



Hayashi recently demonstrated that the judicious selection of strategically functionalized alkynes and boron reagents, along with a chiral catalyst, can result in the asymmetric synthesis of axially chiral biaryls.[70] In particular, the Rh-catalyzed reaction of internal 1-aryl alkynes with 2-(cyanomethyl)arylboronates in the presence of chiral diene ligands such as $\mathbf{L_{13}}$* renders an asymmetric benzannulation yielding axially chiral 2-aminobiaryls typically with greater than 90% ee (Scheme 24). The reaction proceeds via conventional

Scheme 24. Rh-Catalyzed Benzannulation of 1-Arylalkynes with 2-(Cyanomethyl)phenylboronates: Access to Axial Chirality



carbometalation of the alkyne, upon transmetalation of the boronate with the catalyst, and further insertion into the nitrile functionality of the resulting alkenylboron species. Finally, hydrolysis of the intermediate imino-rhodium species and aromatization deliver the aminoaryl moiety. This transformation is amenable to a wide range of substrates, opening the access to different chiral biaryls, including 1,4- and 1,5-bis(biaryl) containing products. A model for the origin of enantioselection was postulated where a steric repulsion between the bulky amido group of the ligand and the aryl moiety of the 1-naphthyl substituent at the alkyne may be responsible for the observed asymmetric induction.

ortho-Substituted and electron-poor boronic acids have proven to be an excellent coupling partner in (3 + 2) annulation with alkynes toward the construction of indene derivatives.[71] A recent enantioselective version providing access to chiral 1-aminoindenes has been reported by Hsieh, Cheng, and co-workers using Co catalysis in combination with the chiral ligand $\mathbf{L_{14}}$* ((*R*)-Ph-PHOX, Scheme 25a).[72] Using the complex Co($\mathbf{L_{14}}$*)Cl_2 in combination with catalytic amounts of $ZnCl_2$ as a Lewis acid, a variety of chiral 1-aminoindenes were prepared, generally in high yields and ee values. Electronically biased unsymmetrical internal alkynes (e.g., aryl alkyl alkynes) reacted with complete regioselectivity. However, the use of alkynes with potentially coordinating

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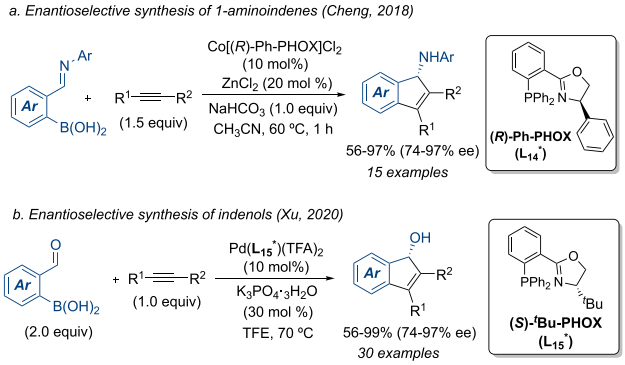
Scheme 25. Metal-Catalyzed Asymmetric Annulation of Alkynes with *ortho*-Carbonylated Arylboronic Acids to Access Indenes



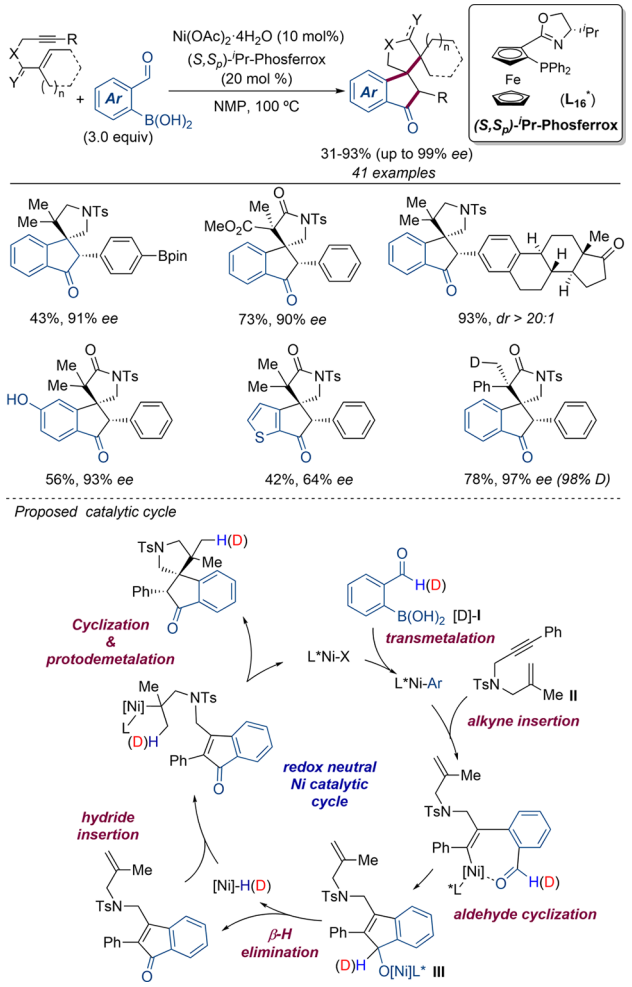
heteroatoms inhibited the asymmetric induction, likely causing decoordination of the chiral ligand.

The access to enantioselective 1-hydroxyindenes by regioselective coupling of alkynes with arylboronic acids containing an *ortho*-carbonyl moiety was pioneered by Hayashi in 2005 employing Rh catalysis in combination with chiral diene ligands.[71b] Subsequent Pd- and Ni-catalyzed versions were reported by the groups of Lu[71e] and Lam,[73] respectively. Recently, Xu has reported a complementary asymmetric annulation of 2-formyl arylboronic acids with internal alkynes using the chiral (S)-^{t}Bu-PHOX ($\mathbf{L_{15}}$*)/palladium(II) complex as a catalyst (Scheme 25b).[74] Despite the high reactivity, a main drawback of this method is the low regioselectivity attained for unsymmetrical internal alkynes, even those electronically and/or sterically biased.

The Kong group has extended this approach to the regio-, diastereo-, and enantioselective construction of *N*-containing spirocycles,[75] which are recognized as privileged structural motifs in pharmaceuticals.[76] This protocol exploits the Ni-catalyzed annulation reaction between *o*-formyl arylboronic acids with 1,6-enynes in combination with a hydrogen-borrowing reductive cyclization of the resulting dienone (Scheme 26). This redox neutral domino catalytic transformation[77] offers a new disconnection pathway for the synthesis of enantioenriched spiroindanones. $Ni(OAc)_2 \cdot 4H_2O$ and (S,S_p)-^{i}Pr-phosferrox ligand ($\mathbf{L_{16}}$*) provided the best results. The use of polar aprotic solvents was required to attain high regioselectivity. An excellent synthetic performance was observed for a wide variety of both 1,6-enynes and aryl boronic acids, with tolerance to boronate ester substituents being remarkable. The synthetic usefulness of this transformation was demonstrated in gram-scale experiments, providing good yields. Interestingly, the use of labeled 2-(CDO) boronic acids enabled the access to otherwise difficult to prepare deuterated spirocycles in a single step.

The authors suggested a catalytic cycle in which the formation of an Ar—Ni intermediate by transmetalation of the boronic acid (**I**) with the nickel catalyst is followed by *syn*-insertion across the C≡C triple bond of **II**. The resulting alkenyl-Ni complex undergoes an intramolecular nucleophilic addition to the aldehyde, yielding intermediate **III**. This species can undergo β-hydride elimination to deliver a Ni—H complex with concomitant formation of the indanone product. Then, 1,2-addition of the Ni^{II}—H species to the unactivated alkene followed by spirocyclization via 1,4-addition to the enone moiety affords a C(sp^3)—nickel intermediate which

Scheme 26. Ni-Catalyzed Cascade Synthesis of Enantiomerically Enriched Spiroindanones via 1,5-Enyne Arylative Cyclization



undergoes protodemetalation to give the spiroindanone product while regenerating the active nickel catalyst. The use of deuterated arylboronic acid ([D]-**I**) in the model reaction with substrate **II** led to exclusive deuterium incorporation at the terminal carbon of the olefin moiety, suggesting that a hydrogen-transfer pathway is operative. Furthermore, crossover experiments between deuterated and nondeuterated indanols pointed to an intramolecular hydrogen-transfer mechanism. A KIE value of 3.2 in parallel independent reactions of **II** with **I** and [D]-**I** is suggestive of β-hydrogen elimination of the alcohol being the rate-determining step in this process.

4.2. *anti*-Selective Methods. Metal-catalyzed cyclization involving *anti*-carbometalation of alkynes remains rare because of the inherent *syn*-selectivity of alkyne migratory insertion.[78] However, elegant protocols of *anti*-addition of arylboronic acids to alkynes and subsequent nucleophilic addition of the resulting alkenyl-metal to a tethered electrophilic group have been described in recent years. The first example of this unconventional selectivity was reported by Tsukamoto in 2006 employing Pd catalysis.[79] Since then, new types of cyclizations have provided expanded access to complex carbo- and heterocyclic structures, although the development of reliable methods has not been well-established until recently. Ni-based catalytic systems have demonstrated a superior reactivity and

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selectivity in this chemistry, allowing *anti*-1,2-dicarbofunctionalization of alkynes.

Most of these methods rely on alkynes containing a proximal electrophile (Figure 2). *syn*-1,2-Addition of an organometallic

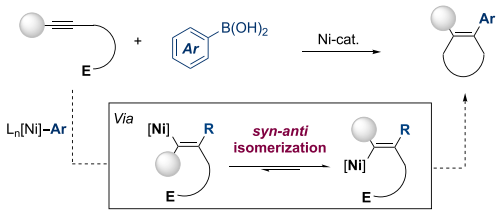
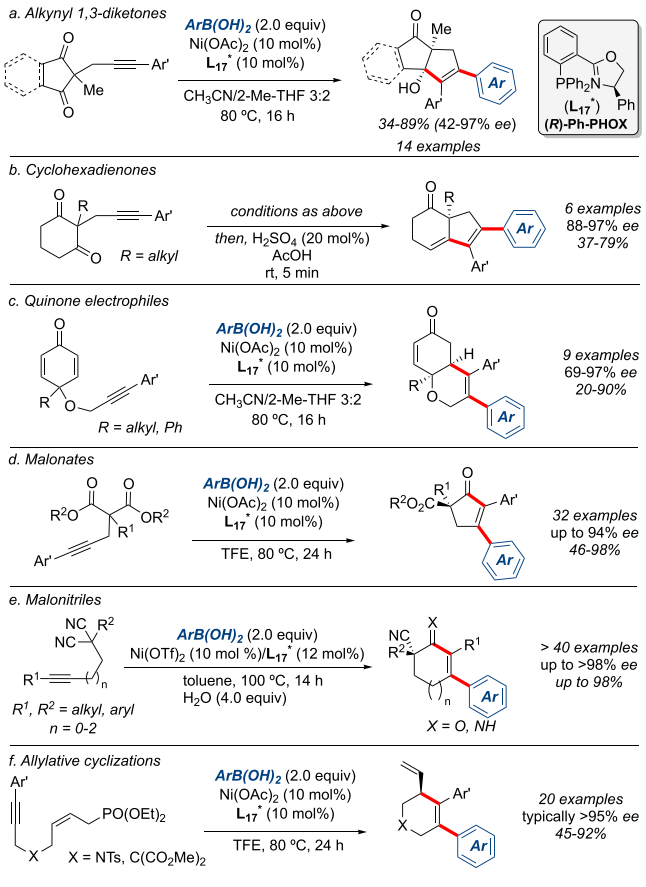


Figure 2. Strategy for *anti*-carbometallative cyclization.

species across the triple bond, in which the metal is regioselectively positioned distal to the electrophile (typically controlled by an aryl substituent), leads to an alkenyl-metal intermediate that cannot satisfy the geometric requirements for cyclization. Instead, reversible *syn*-to-*anti* isomerization provides the reactive formal *anti*-carbometalation intermediate that possesses the correct geometry for cyclization and rapidly evolves toward the *anti*-difunctionalization product.

The first example using Ni catalysis was the asymmetric arylative cyclization of 1-propargyl-1,3-cyclopentadienones with arylboronic acids in the presence of the chiral phosphinooxazoline ligand $\mathbf{L_{17}}$* described by Lam (Scheme 27a).[15] A number of fused 5,5-bicyclic products were obtained

Scheme 27. Ni-Catalyzed Asymmetric Arylative Cyclization of Alkynes Enabled by Reversible Alkenyl-Nickel *E*/*Z* Isomerization



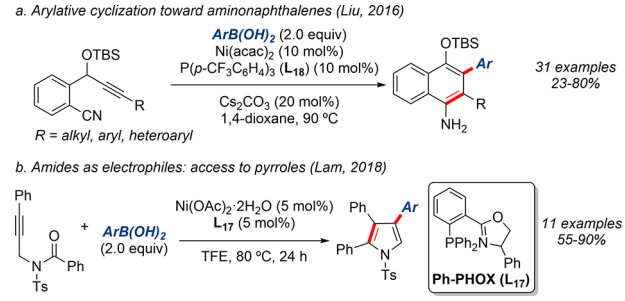
in good yields and high enantiomeric excesses using $Ni(OAc)_2$ as a precatalyst. The P,N-ligand was not only important for achieving high asymmetric induction but also found to be highly effective in terms of reactivity and regiocontrol. When 1,3-cyclohexadiones were used, significant dehydration of the initial cyclization products was observed. For this reason, the method was redirected toward the enantioselective synthesis of the corresponding 1,3-dienes by driving the dehydration to completion under acidic conditions (Scheme 27b). Quinones were also found to be suitable substrates, leading to the formation of fused 6,6-bicyclic cores (Scheme 27c). This methodology was also extended to malonate esters, which gave the corresponding cyclopentenone adduct with high yield and diastereo- and enantioselectivity by using $\mathbf{L_{17}}$* (Scheme 27d).[80]

Liu disclosed a highly enantioselective arylative cyclization of alkynyl-containing malononitriles to afford cyclic enones with a nitrile-containing all-carbon quaternary center (Scheme 27e).[81] The use of the phosphinooxazoline ligand L_{17}* was crucial for both reactivity and enantiocontrol. Interestingly, other arylboron sources such as boroxines or potassium trifluoroborate salts reacted efficiently, but Bpin esters failed, probably due to sluggish transmetalation under base-free conditions.

Alkynes containing a tethered (*Z*)-allylic phosphate were also found to be excellent substrates for arylative cyclizations with arylboronic acids under Ni catalysis (Scheme 27f).[82] The reaction produces chiral 6-membered aza- and carbocycles with very high asymmetric induction. Unlike other related Ni-catalyzed allylic substitutions, which are thought to proceed through allylnickel intermediates, migratory insertion of the alkene into the carbon−nickel bond of (*Z*)-alkenyl-Ni species followed by *β*-phosphate elimination was suggested to be operative in this reaction.

In addition, Liu and co-workers have tuned up this protocol toward the arylation of OTBS-protected propargyl alkynols bearing an *ortho*-cyanophenyl group at the propargylic position (Scheme 28a).[83] After a first Ni-promoted aryl-metalation of

Scheme 28. Ni-Catalyzed Arylative Cyclization/Aromatization of Functionalized Alkynes



the alkyne, the corresponding *syn*-to-*anti* isomerization occurs, and the alkenyl-metal intermediate inserts into the C≡N triple bond of the nitrile, leading to the 1-aminonaphthalene products. The reaction was highly useful for aryl-substituted alkynes, and both arene and heteroarene groups could be easily installed. The regioselectivity seems to be controlled by the electronic effect of the aryl group attached at the alkyne. Alkyl-substituted alkynes delivered the desired product, albeit with lower yields. Recently, the synthesis of densely substituted pyrrole derivatives from *N*-tosyl alkynamides has been reported

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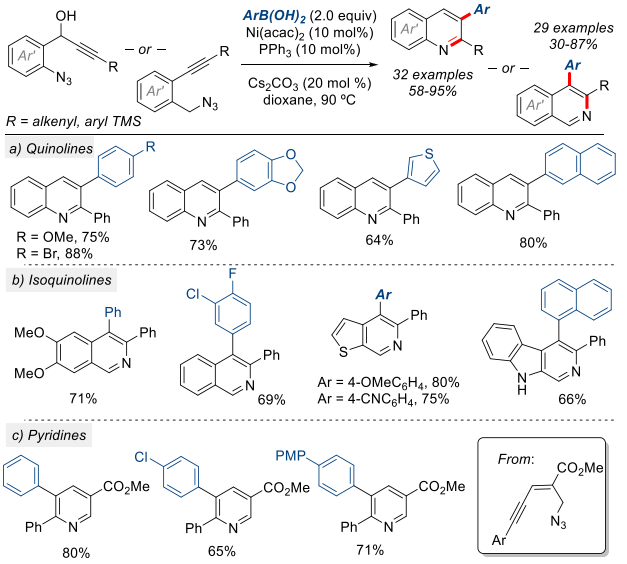
employing this formal *anti*-dicarbofunctionalization strategy (Scheme 28b).[84] Interestingly, when the amide group was replaced by a ketone, the reaction delivered valuable tetrahydropyridines with high asymmetric induction.[85]

Unlike previous methods where the alkenyl-metal intermediate is captured by a carbon electrophile, trapping this intermediate with a noncarbon center electrophile has been recently explored as a new way to access heterocycles. A salient example of this chemistry using azides as a nitrogen electrophilic system has been described by Reddy and coworkers (Scheme 29a).[86] *ortho*-Azidophenyl propargylic alcohols were cyclized to 2,3-diaryl quinolines via arylation with aryl boronic acids under Ni^{II} catalysis.

Scheme 29. Ni-Catalyzed Arylative Cyclization/ Aromatization of Functionalized Alkynes



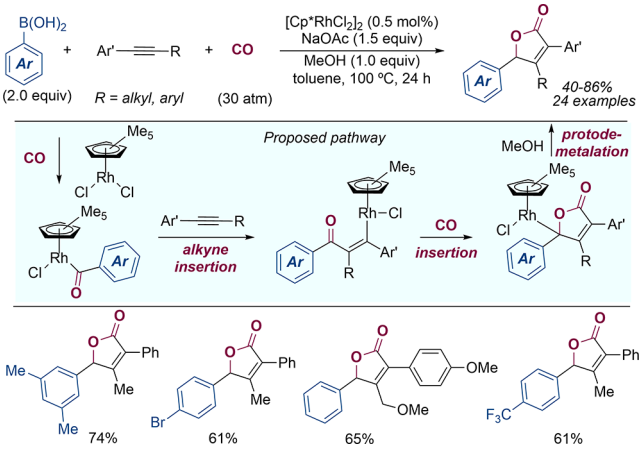
The same group extended this protocol to a series of selectively substituted diaryl isoquinoline, pyridine, and indene derivatives from diarylacetylenes with azide, carbonyl, and cyanide tethers, respectively (Scheme 29b).[87] Additionally, this approach was also applied to the synthesis of a variety of substituted pyridines in a predictable manner (Scheme 29c). The method is amenable to a variety of alkynes and boronic acids with different steric and electronic properties. The use of nitriles in a similar process has allowed the synthesis of 1-aminoisoquinolines.[88]

5. CARBOARYLATION BY INTERMOLECULAR TRAPPING OF ALKENYL-METAL INTERMEDIATES

5.1. Cascade Processes. The development of general methods capable of achieving intermolecular difunctionalization of internal alkynes in a selective way, thus providing stereodefined tetrasubstituted olefins, remains a significant challenge.[89] This goal can be achieved by trapping the alkenyl-metal intermediate resulting from carbometalation of the triple bond with an external electrophile. However, potential incompatibilities and interferences often limit the scope of suitable electrophiles in this transformation. These include the following: (i) the organoboron reagent must react faster with the alkyne than with the trapping electrophile, and (ii) the reaction of the alkenyl-metal intermediate with the electrophile must proceed faster than its transmetalation with the organoboron reagent.

Based on this strategy, Guan has reported the synthesis of butenolides by Rh-catalyzed coupling of internal alkynes with aryl boronic acids under a CO atmosphere, regarded as the oxa-Pauson-Khand reaction (Scheme 30).[90] After trans-

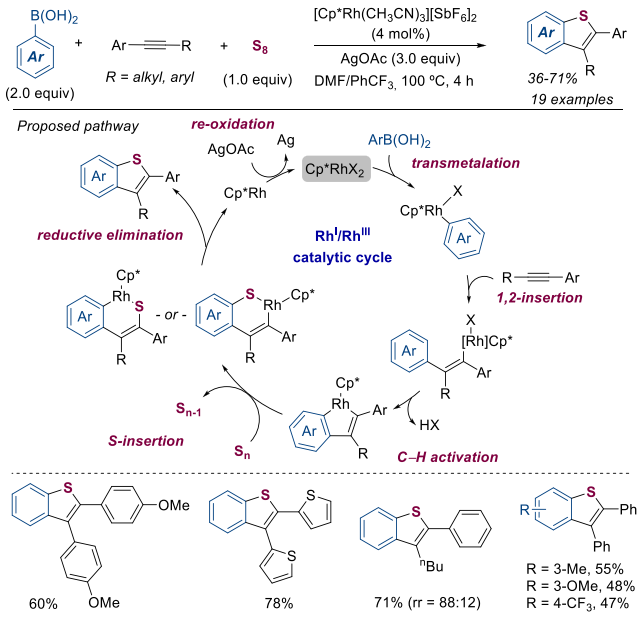
Scheme 30. Rh-Catalyzed Intermolecular oxa-Pauson-Khand Reaction



metalation from boron to Rh followed by insertion of one molecule of CO, the resulting aryl-acyl-rhodium species inserts into the C≡C triple bond in a regiocontrolled fashion directed by the aryl substituent. Further insertion of another CO molecule into the C(sp^2)-Rh bond and protodemetalation by MeOH delivered the corresponding butenolide.

Nishii and Miura have disclosed a Rh-catalyzed three-component coupling reaction of arylboronic acids, alkynes, and elemental sulfur (S_8) leading to benzo[*b*]thiophene derivatives (Scheme 31).[91] The thiophene annulation proceeds via the sequential alkyne insertion, C—H activation, and then

Scheme 31. Rh-Catalyzed Three-Component Assembly of Benzothiophenes Using Elemental Sulfur as an Electrophile



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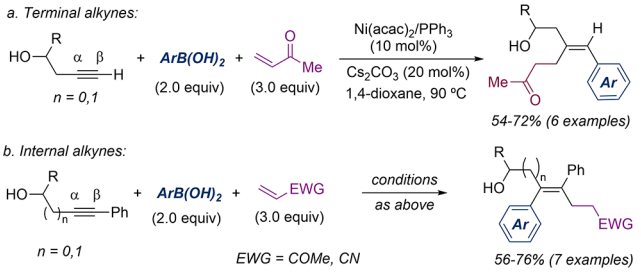
interception of the metallacycle intermediate by sulfur atom transfer. High regioselectivity was observed for electronically biased aryl alkyl alkynes.

As previously mentioned in Section 2, Reddy reported the Ni-catalyzed hydroarylation of alkynols with arylboronic acids.[25] The otherwise rapid protodenickelation of the carbometalated intermediate species could be prevented by trapping it with Michael-type acceptor olefins, providing the corresponding 1,2-dicarbofunctionalization product in useful yields (Scheme 32). The reaction between the alkenyl-Ni

Scheme 32. Ni-Catalyzed Arylation of Alkynes and Trapping the Carbometalation Intermediates with Michael-Type Electrophiles

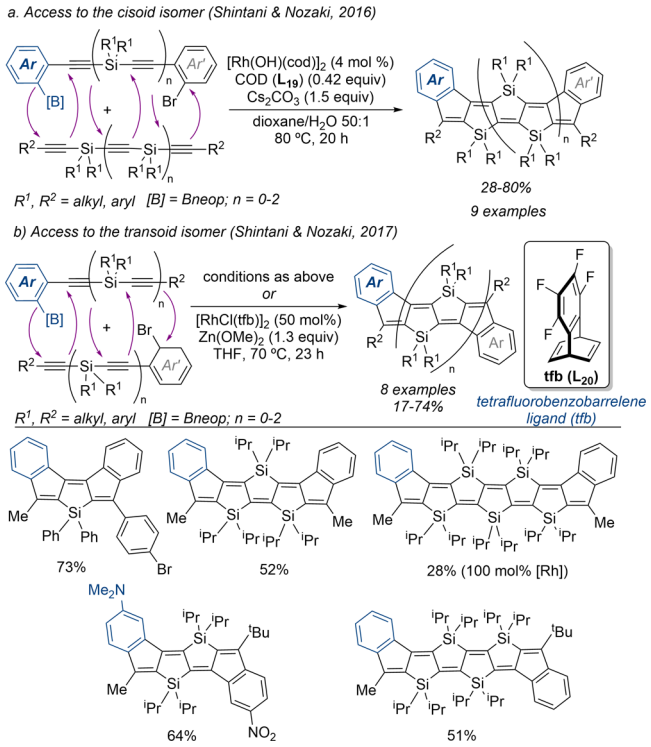


species with the activated alkene seems to be faster than the *syn*-to-*anti* isomerization since only the *syn*-product was observed. Interestingly, the regioselectivity of the insertion event appears to be controlled by the substitution at the alkyne. Terminal alkynes delivered the β-arylation products (regioselectivity controlled by the OH directing group), whereas internal aryl alkynes showed aryl incorporation at the α-position (regioselectivity controlled by the aryl substituent). Although the authors suggested that the opposite regioselection is determined purely by steric factors, electronic factors due to the polarization of the triple bond in aryl-substituted alkynes cannot be ruled out.[36a,b]

5.2. Construction of Fused Polycyclic Structures. Shintani, Nozaki, and co-workers described the synthesis of quinoidal fused oligosilole derivatives via the so-called Rh-catalyzed stitching reaction (Scheme 33).[92] The high efficiency of the process lies in the ability to couple—in an orchestrated fashion—two different unsymmetrical oligosilenes. One of them must contain an aryl boron moiety, which initiates the cascade process by transmetalation with the Rh species. The newly formed Rh intermediates then undergoes sequential insertion to a different oligosilene partner in an intermolecular fashion. Once the two oligosilenes are assembled, a cascade process of multiple 1,2-insertion steps takes place, leading to a final alkenyl-rhodium intermediate which can react via oxidative addition with a C−X bond present at each one of the oligosilene partners. Further reductive elimination yields the desired unsymmetrical fused oligosilene. The access to the cisoid isomers can be achieved when both the boron and the halide groups are present in the same oligosilene (Scheme 33a).

On the contrary, when the initiating boron and the terminal halide groups are in different oligosilenes, the reaction provides access to the transoid isomer using the tetrafluorobenzobarrelene ligand ($\mathbf{L_{20}}$, Scheme 33b).[93] These products can be further derivatized to the corresponding dianion by reduction with alkali metals.[94] In 2017, the same group reported the

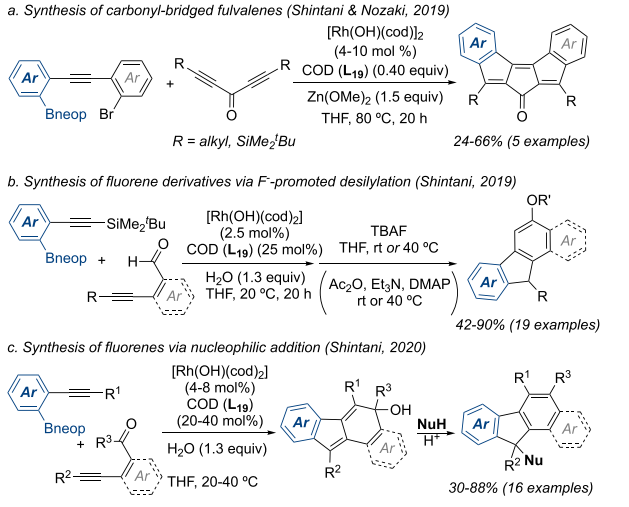
Scheme 33. Synthesis of Quinoidal Fused Oligosiloles by a Rhodium-Catalyzed Stitching Reaction (Neop, Neopentyl Glycolate; COD, 1,5-Cyclooctadiene)



synthesis of dibenzo[*a*,*e*]fulvalenes employing a similar strategy.[95]

This reactivity has been extended to the synthesis of unsymmetrical carbonyl-bridged dibenzofulvalenes employing bis(alkynyl)ketones (Scheme 34a).[96] Although the structural

Scheme 34. Synthesis of Fulvalenes by a Rhodium-Catalyzed Stitching Reaction (COD: 1,5-Cyclooctadiene)



scope in the original paper was restricted to 6 examples, further derivatization of the products increased the accessible chemical space. The reaction also tolerated the introduction of heteroatoms as bridging groups such as Si and Ge, as well as functional groups such as SO_2 and P(O)Ph, albeit in lower yields for the latter two cases (33% and 17%, respectively).

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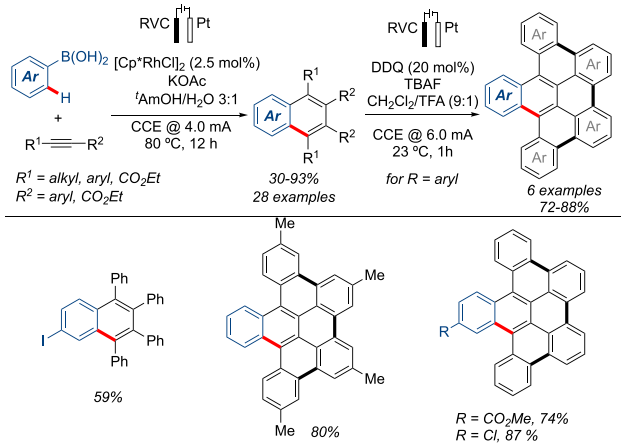
In a related process, Shintani developed a strategy en route to fluorene derivatives in which the halide partner was substituted by an electrophilic carbonyl group that readily promoted an intramolecular cyclization of the alkenyl-rhodium intermediate (Scheme 34b).[97] Subsequent fluoride-promoted desilylation yielded the corresponding fluorene derivatives in a one-pot process with high yields and a broad substrate scope. α,β-Unsaturated ketones and imines were also found to be efficient electrophilic partners. More recently, the same group has described a variation of the method that allows coupling in a single sequence the rhodium-catalyzed stitching reaction with a remote nucleophilic substitution, which enables the incorporation of both heteroatom and carbon nucleophiles under acidic conditions (Scheme 34c).[98]

Ackerman and co-workers[99] have studied the synthesis of nonplanar polycyclic aromatic hydrocarbons (PAHs) from diaryl alkyne via the combination of Rh-catalyzed C−H activation of boronic acids followed by a [2 + 2 + 2] cycloaddition with electrocatalytic cyclodehydrogenation in which electricity functions as a sustainable oxidant (Scheme 35). High levels of double regioselectivity toward symmetrical

Scheme 35. Rhodium- and Electrocatalysis for C−H Activation/Benzannulation towards PAH Derivatives



products was attained with challenging unsymmetrical alkynes, which was ascribed to attractive noncovalent interactions in the key migratory-insertion transition state. The corresponding adduct was further treated with catalytic amounts of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) under electrochemical conditions for the rapid access to the π-extended systems, which led to a variety of PAHs. The synthetic utility of this method was showcased by the chemoselective C−H functionalization/annulation of sensitive iodo-substituted boronic acids.

PART II: ORGANOBORON AS TRAPPING AGENTS OF CATALYTIC METAL SPECIES

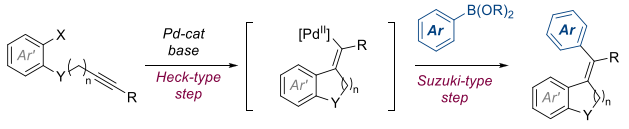
This part of the review focuses on distinct alkyne functionalization strategies in which the organoboron reagent participates in the last step of the functionalization of the triple bond by trapping the *in situ* generated unsaturated metal intermediates such as alkenyl-, allenyl-, or allyl-metal species through a Suzuki-type reaction. This approach has resulted in elegant methods for 1,2-difunctionalization of alkynes (Section 6) and coupling of propargylic alcohol derivatives toward the synthesis of allenes and 1,3-dienes (Section 7).

6. DIFUNCTIONALIZATION STRATEGIES VIA TERMINATING SUZUKI-TYPE COUPLING

6.1. *syn*-Selective Methods. Methods for practical catalytic 1,2-dicarbofunctionalization of alkynes in a regio- and stereoselective manner remain an important goal in organic synthesis. Pioneering studies developed by Chatani[100] and Larock[101] showcased the potential of using alkynes bearing aryl halides in combination with boronic acids under Rh or Pd catalysis, respectively, for the synthesis of heterocycles. These seminal contributions fueled the development of novel protocols exploiting this reactivity during the last two decades.[102] Despite these advances, issues related to a competing reaction between the boronic acid and the aryl halide still remain. Additionally, the regioselectivity of alkyne insertion is often not well-controlled for unsymmetrical alkynes, leading to mixtures or regioisomers. Another important limitation often encountered is the inability to incorporate terminal alkynes, largely producing homocoupling products and/or Sonogashira-type coupling with the aryl reagent.

This chemistry has found extensive applications in the Heck−Suzuki-type cascade reaction enabling the synthesis of carbo- and heterocyclic platforms in a single synthetic step (Scheme 36).[103,104] In these cases, the cyclization step is

Scheme 36. Pd-Catalyzed Heck−Suzuki-Type Cascade Reaction for the Synthesis of Carbo- and Heterocycles



favored due to structural constraints associated with the intramolecular process, thus minimizing the competing intermolecular Suzuki-type cross-coupling without the involvement of the C≡C triple bond.

Gulea and Suffert applied this cyclocarbopalladation/cross-coupling cascade approach to sulfur-containing alkynes bearing a pendant aryl bromide unit, thus providing an efficient access to sulfur heterocycles decorated with a stereodefined tetrasubstituted exocyclic double bond (Scheme 37a).[105] This transformation is especially challenging because the thiophilicity of palladium often leads to poisoning of the catalyst.[106] Conditions were found to circumvent this issue that were compatible with different organoboronic acids, such as aryl-, vinyl-, allyl-, and cyclopropyl boronic acids, thereby enabling the introduction of a large variety of substituents. Products resulting from direct Suzuki coupling between the aryl bromide and the boron reagent were observed in some instances, albeit in low yields. The process works efficiently via either 5-*exo* or 6-*exo*-dig cyclization.

A similar strategy has been applied to access different heterocycles.[107] For example, the Donnart group devised the synthesis of five- and six-membered silacycles by Heck−Suzuki coupling of silylalkynes bearing a tethered aryl bromide with aryl boronic acids (Scheme 37b).[108] Both aryl- and heteroaryl groups could been installed, along with different substituents at both the silicon moiety and the alkyne group. Finally, Matoušová and co-workers disclosed a two-step process involving a domino cyclization/Suzuki cross-coupling followed by halocarbocyclization to provide polycyclic compounds

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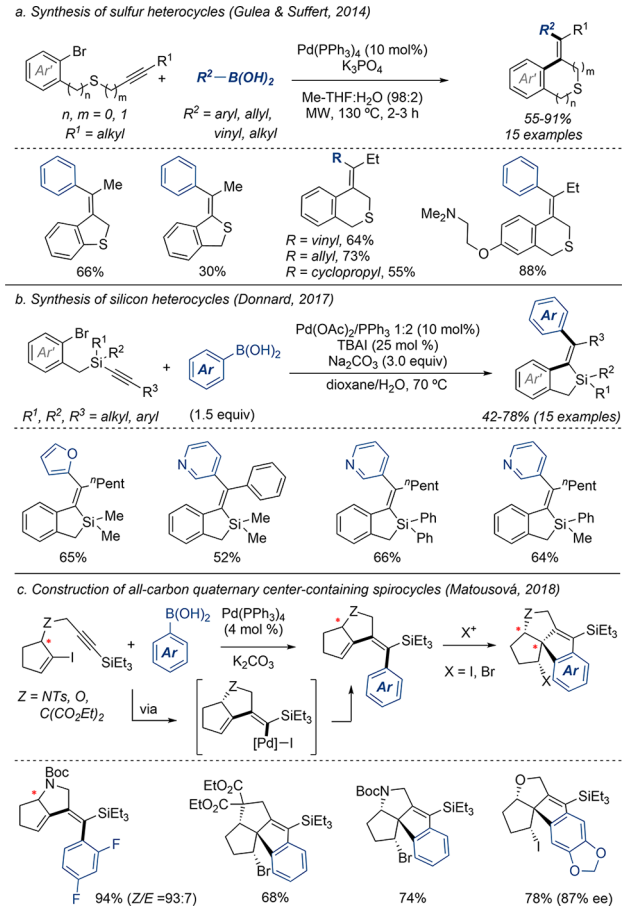
Scheme 37. Pd-Catalyzed Cyclocarbopalladation/Cross-Coupling Cascade for the Synthesis of (Hetero)cyclic Ring Systems

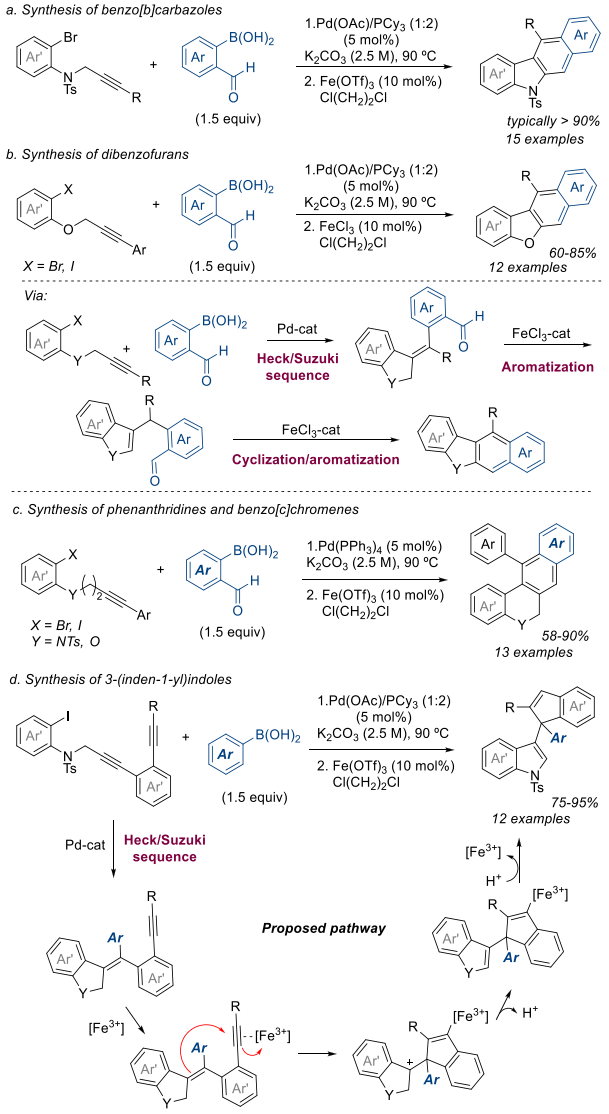


(Scheme 37c).[109] In the global process, three new C−C bonds and a stereochemically defined all-carbon quaternary center were formed with excellent stereoselectivity.

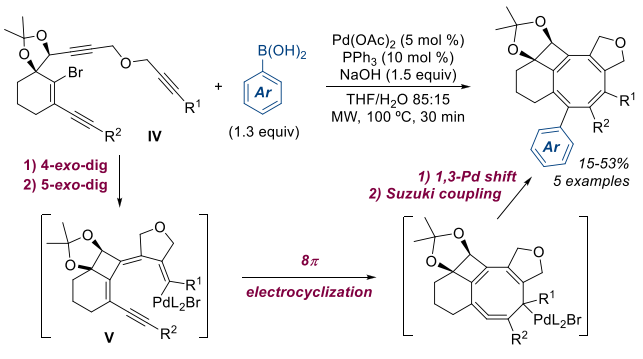
Nowadays, this cascade protocol has been reinterpreted to allow the construction of novel heterocyclic structures or the design of more complex multisequential transformations using *ortho*-functionalized arylboron reagents. For instance, Java and co-workers have established a one-pot protocol for the synthesis of π-extended aromatic frameworks. The first step consists of a Heck−Suzuki coupling reaction between alkynes containing an aryl halide moiety with *o*-formylboronic acids, followed by an Fe-catalyzed isomerization/cyclodehydration. This strategy was applied to the synthesis of benzo[*b*]carbazole derivatives,[110] dibenzofurans,[111] 3-(inden-1-yl)indoles,[112] benzo-phenanthridines, and benzo[*c*]chromenes[113] (Scheme 38).

More recently, Suffert, Blond, and co-workers envisioned the access to the cyclooctatetraene core from the reaction of alkenyl bromides **IV** with arylboronic acids through a polycyclization cascade process involving three alkyne moieties (Scheme 39).[114] Substrate **IV** undergoes two cyclocarbopalladations, first a 4-*exo*-dig and then a 5-*exo*-dig cyclization, providing intermediate **V**. Then, an 8π-electrocyclization followed by a 1,3 π-allyl palladium shift takes place ended by a Suzuki cross-coupling to yield the final cyclooctatetraene product. Different electron-rich and electron-poor arylboronic acids could be installed in the final cyclic structure, as well as

Scheme 38. One-Pot Pd-Catalyzed Heck−Suzuki Coupling and Fe-Catalyzed Isomerization/Cyclodehydration



Scheme 39. Pd-Catalyzed Domino Polycyclization Ended by a Suzuki Reaction towards Cyclooctatetraenes



heteroaromatic boronic acids including those containing basic nitrogen atoms.

A related intermolecular reaction involving coupling of three components is much more challenging and remains underdeveloped. Wen and co-workers have designed a cascade,

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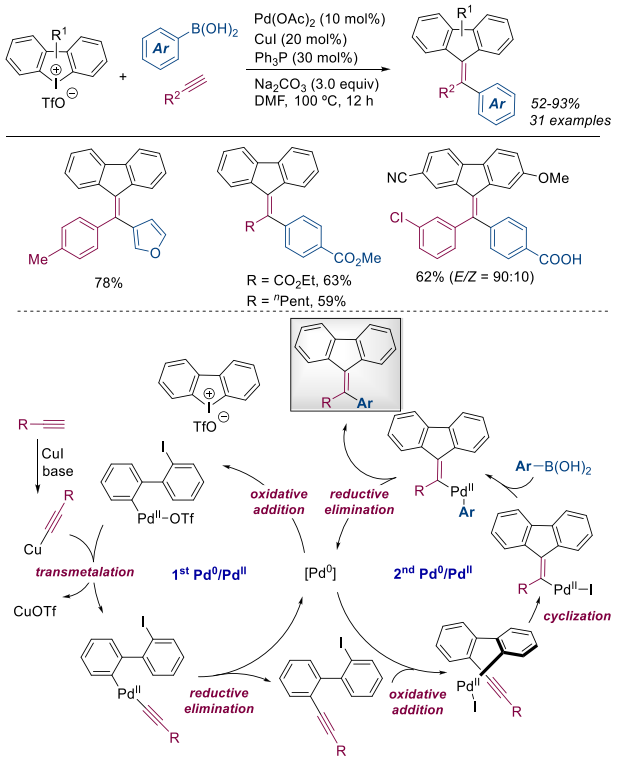
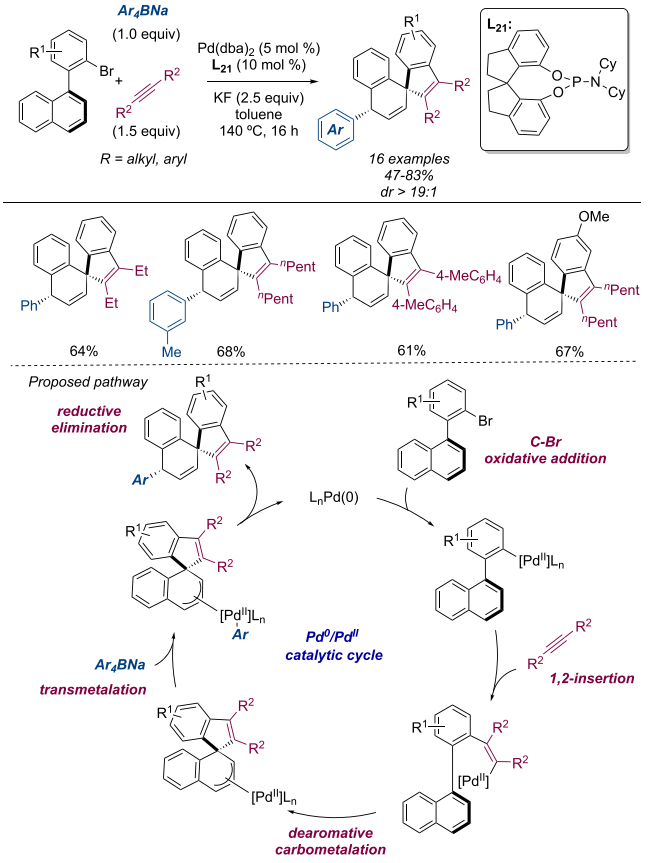
multicomponent reaction outcome for the synthesis of tetrasubstituted methylidenefluorenes (Scheme 40).[115] This

Scheme 40. Pd/Cu-Catalyzed Three-Component Cascade Reactions for the Synthesis of Methylidenefluorenones



Scheme 41. Dearomative Difunctionalization of Naphthalenes through a Palladium-Catalyzed Heck/Anionic-Capture Sequence



reaction relies on the use of cyclic diphenyliodonium triflates and combines Pd and Cu catalysis. A first alkynylation of the iodonium triflate, via oxidative addition to Pd^0, transmetalation with an alkynyl-Cu^I species, and reductive elimination, provides the strategic intermediate alkyne that then undergoes a Heck−Suzuki coupling with a boronic acid through a second Pd^0/Pd^{II} catalytic cycle to afford the methylidenefluorene skeleton. Both aryl and alkyl alkynes are compatible in this reaction. Interestingly, the method can be applied to unsymmetrical cyclic diphenylene-iodoniums to give isomeric methylenefluorenes, with high chemoselectivity being observed in cases where the electronic properties of the two aryl rings are markedly different.

The ability of the intermolecular Heck−Suzuki sequence to access carbospirocycles has been described recently by Hong, Jia, and co-workers (Scheme 41).[116] This group envisioned a cascade process involving an intramolecular dearomative carbometalation of a naphthalene unit that acts as a masked conjugated diene, followed by diastereoselective intermolecular cross-coupling of the *in situ* formed π-allyl-metal species with the organoboron reagent. The use of phosphoramidite-type ligands $\mathbf{L_{21}}$ with steric hindrance at the amino moiety was found to play a key role for achieving high chemoselectivity toward the desired product over other competitive reaction pathways including intramolecular naphthalenyl C−H arylation, intermolecular Suzuki coupling, 1,2-difunctionalization, and dearomative reductive Heck reaction. Equally important is the use of KF as a base, since poor results are obtained employing other bases such as Na_2CO_3, Cs_2CO_3, K_3PO_4, or CsF. Additionally, sodium tetraaryl borates (Ar_4BNa) proved to be more reactive than the aryl boronic acid derivatives, leading to higher yields. Under the optimized conditions, a range of 1,4-dihydronaphthalene-based spirocycles bearing oxindole, dihydrobenzofuran, or indene subunits are easily obtained in moderate to excellent yields. Remarkably, both alkyl and aryl internal alkynes reacted smoothly under the optimized reaction conditions. DFT calculations revealed that it is the facile exergonic insertion of the naphthalene double bond that disrupts the sequence of direct Suzuki coupling, leading to the domino Heck−Suzuki coupling reaction. The steric repulsions between the aryl group of the forming C−C bond and the spiro-scaffold disfavor the intrinsic regioselectivity toward 1,2-difunctionalization, allowing the observed 1,4-difunctionalization.

Along similar lines, Wu and co-workers have reported the Pd-catalyzed intermolecular, four-component carbonylative 1,2-dicarbofunctionalization of internal alkynes using boronic acids, aryl iodides, and CO.[117] Tetrasubstituted α,β-unsaturated ketones and benzofulvenes can be obtained in a highly regio- and stereocontrolled manner using $Pd(acac)_2/P(o\text{-tolyl})_3(\mathbf{L_{22}})$ as a catalytic system, in combination with $Cu(TFA)_2$ as a Lewis acid (Scheme 42a). Interestingly, a 1:1 mixture of Ac_2O and HCO_2H was found to be a practical CO surrogate that avoids handling toxic CO gas. The reaction proved to be general for a different array of substituted boronic acid and aryl halides. The use of unsymmetrical dialkyl alkynes led to regioisomeric mixtures. In contrast, electronically differentiated 1-alkyl-2-arylalkynes delivered the corresponding product with a decent regioselectivity (Scheme 42a).

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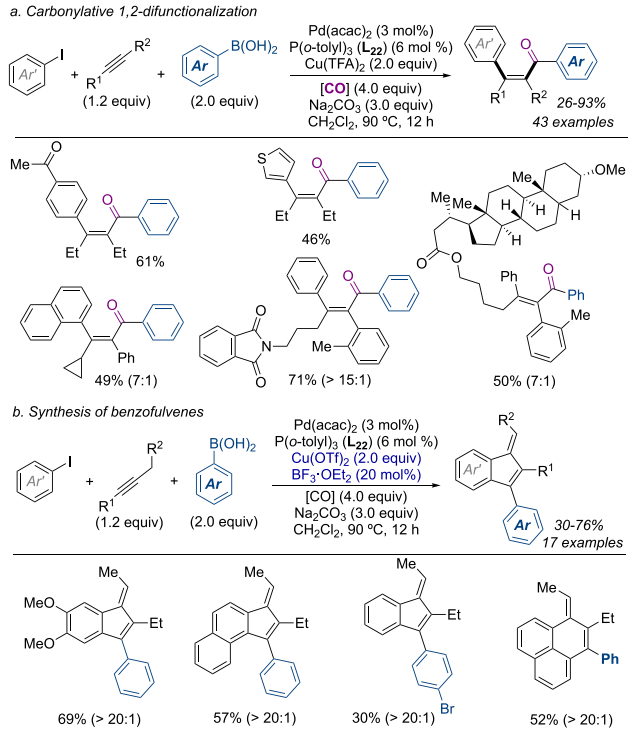
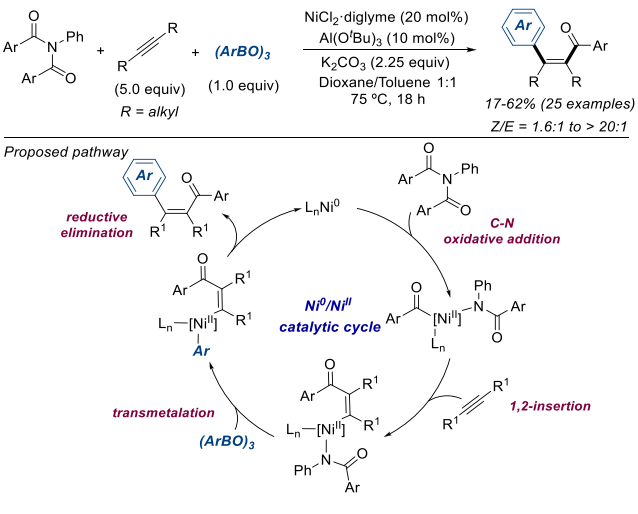
Scheme 42. Pd-Catalyzed Multicomponent Synthesis of Enones and Fulvenes



Interestingly, of the more acidic $Cu(OTf)_2$ as the additive resulted in a different reaction outcome leading to the benzofulvene derivatives (Scheme 42b). The combination of $Cu(OTf)_2$ as the additive (2 equiv) and $BF_3{\cdot}Et_2O$ as a cocatalyst (20 mol %) was found to provide better reaction yields. Control experiments demonstrated that no benzofulvene product was obtained under the $Cu(OTf)_2$ conditions (in the absence of $BF_3{\cdot}Et_2O$).

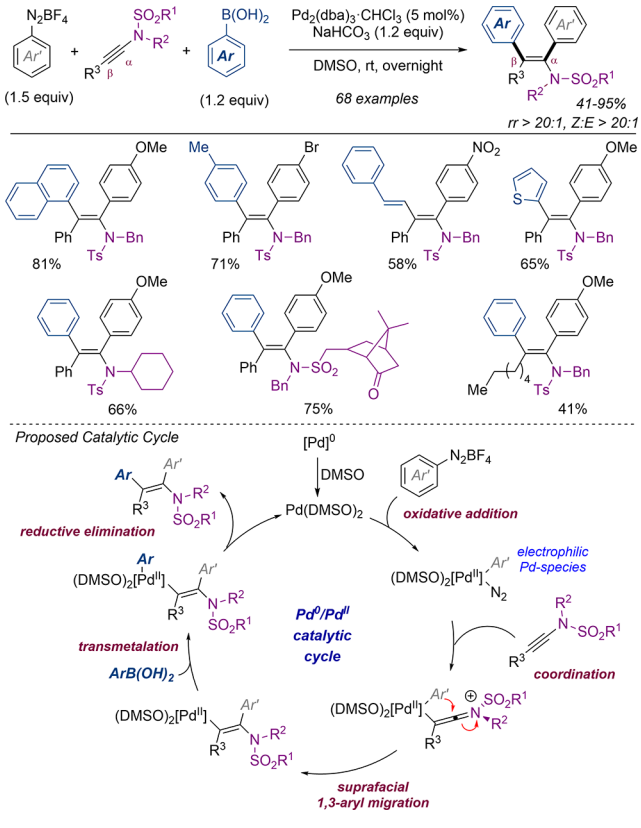
The Stanley group has developed an alternative method for the stereocontrolled 1,2-carboacylation of internal alkynes employing nickel catalysis, in which electrophilic amides served as selective acylating agents (Scheme 43).[118] Although initial studies were performed using aryl boronic acids as nucleophiles (the corresponding boronic ester derivatives did not react under the optimized reaction conditions), the anhydrous triaryl boroxines provided better *Z*-stereoselectivities. This observation was rationalized by the formation of Ni—H intermediates by protonation with the OH bond of the boronic acid, which could be responsible for the *Z* to *E* isomerization process. A study of different Lewis acids to minimize the coordination of the enone product to the catalytically active nickel species identified $Al(O^tBu)_3$ as particularly effective. High functional group compatibility was found for both the amide and boroxine counterparts, whereas the scope of alkynes seems to be limited to symmetrical dialkyl alkynes (1-phenylpropyne led to a low yield). From a mechanistic point of view, the authors postulated that the reaction starts with oxidative addition of the N—C═O bond to a Ni^0 species to give an acyl-Ni^{II}-amido intermediate which then inserts into the triple bond, generating an alkenyl-Ni^{II} intermediate. Transmetalation with the aryl boroxine and final reductive elimination yield the final product.

Scheme 43. Ni-Catalyzed Carboacylation of Internal Alkynes with Amides



Concomitantly with the Cu-catalyzed umpolung difunctionalization of ynamides by regioselective *syn*-carbometalation/cyclization previously discussed in Section 4.1 (Scheme 20), Gandon, Sahoo, and co-workers have reported an intermolecular three-component umpolung difunctionalization of ynamides via Pd-catalyzed coupling with aryl diazonium salts (electrophile) and aryl boronic acids (nucleophile, Scheme 44).[119] The reaction employs $Pd_2(dba)_3$ as a catalyst in combination with $NaHCO_3$ as a base in DMSO as a solvent. DFT studies support a mechanism initiated by oxidative addition of the aryldiazonium salt to an *in situ* generated $Pd(DMSO)_2$ catalytically active complex. The resulting

Scheme 44. Three-Component Pd-Catalyzed Umpolung Functionalization of Ynamides



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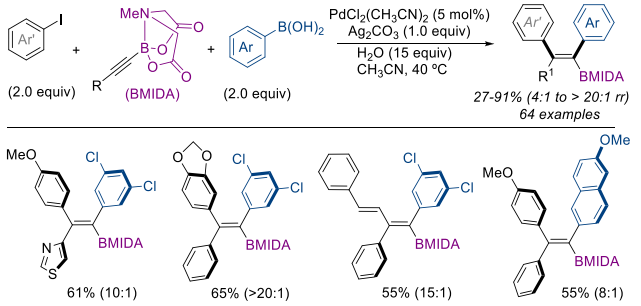
cationic Pd^{II} intermediate then coordinates to the ynamide accompanied by ligand exchange with N_2 to form a ketiminium complex. The suprafacial 1,3-aryl migration from Pd to the C═N bond generates a Pd-enamide intermediate. Further transmetalation with the boronic acid and reductive elimination yield the final product. Consistently good results were obtained regardless of the electronic character of the boronic acids, including alkenyl boronic acids. Regarding the scope of aryldiazonium salts, electron-rich substrates were more effective, likely because of the poor stability of electron-deficient ones.

A challenging intermolecular alkyne dicarbofunctionalization reaction was devised by Wang, Glorius, and co-workers using arylethynyl *N*-methyliminodiacetyl (MIDA) boronates (Scheme 45).[120] This approach circumvents the issues of

Scheme 45. *N*-BMIDA-Directed Pd-Catalyzed Three-Component Coupling of Internal Alkynes, Aryl Iodides, and Boronic Acids

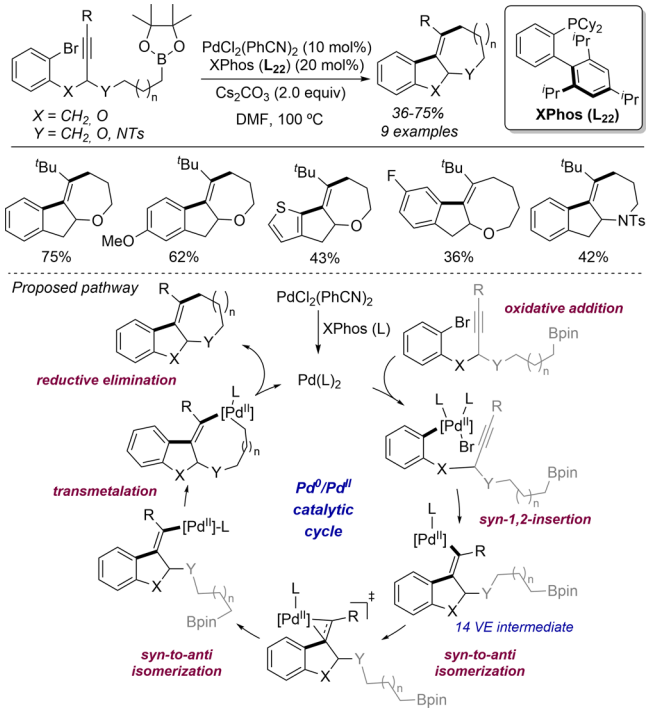


selectivity control and side reactions. In particular, the three-component reaction of arylethynyl-BMIDA substrates with an aryl iodide and a boronic acid in the presence of $PdCl_2(CH_3CN)_2$ as a catalyst and Ag_2CO_3 as a base in DMSO delivered the corresponding tetrasubstituted alkenyl boronate with excellent yields and selectivity. The BMIDA group was required to gain high reactivity; other boron sources such as the Bpin, potassium trifluoroborates, and Bdan (dan = 1,2-diaminonaphthalene) led to decomposition under the optimized conditions. An important aspect of this strategy lies in the chemical versatility of the C−B bond toward its transformation into C−C, C−X, or C−H bonds via cross-coupling or protodeborylation reactions, thus providing a modular, regio- and stereoselective access to tri- and tetrasubstituted aryl alkenes. The excellent regioselectivity was proposed to arise from a hyperconjugative effect via donation of the σ_{C-Pd} electron pair to the p orbital of the boron unit.

6.2. *anti*-Selective Methods. An even more difficult challenge in alkyne difunctionalization is to find a way for accessing products with an opposite configuration at the double bond. In this regard, there are two main strategies employed for achieving formal *anti*-carbometalation intermediates as direct precursors of the *anti*-isomer of the emerging double bond: (i) conjunctive cross-coupling methods[121] through *syn*-insertion of catalytically generated organometallic species followed by further *syn*-to-*anti* thermodynamically favored isomerization, and (ii) π-electrophilic activation with a transition metal[23] followed by an *anti*-nucleophilic attack to the activated alkyne. The *in situ* generated alkenyl-metal intermediate through either of the two mechanisms can react with the corresponding organoboron reagent by transmetalation, furnishing the *anti*-1,2-dicarbofunctionalization product after reductive elimination.

Regarding the former pathway, namely, *syn*-to-*anti* isomerization of the intermediate alkenyl-metal species, the Werz group has designed alkyne systems that are able to undergo formal *anti*-carbopalladation.[122] Strategically, substitution with −SR, alkynes, ^{t}Bu, or silyl groups was required to prevent other competing pathways, for example, β-hydride elimination. Additionally, sterically encumbered monodentate phosphine ligands were found to be crucial for the formation of the 14 valence electron palladium species required for the *syn*-to-*anti*-isomerization in the coordination sphere of the metal center after insertion of Ar−Pd^{II} species. Interception of the resulting transient alkenyl-palladium species via Suzuki cross-coupling finally results in the *anti*-dicarbofunctionalization product.[123] Under a scenario meeting those requirements, the construction of seven- and eight-membered rings having embedded a tetrasubstituted double bond was achieved in moderate to good yields from *tert*-butyl-substituted alkynes decorated with an aryl bromide and an aliphatic boronic ester unit as domino precursors (Scheme 46). $PdCl_2(PhCN)_2$ with XPhos ligand

Scheme 46. Intramolecular *anti*-Carbopalladation/Suzuki Coupling Cascade for Accessing Medium Ring Systems



L_{22} was used as the precatalyst system, with Cs_2CO_3 as a base in polar aprotic solvents such as DMF or DMA. TBS-protected alkynes delivered a poor yield because of deprotection of this group under the reaction conditions.

The proposed mechanism starts with the oxidative addition of the Ar−Br bond to a Pd^0 species, thus generating an aryl-Pd^{II} intermediate which reaches the 14 valence electron counting in the Pd-center by the presence of the XPhos ligand L_{22} which promotes dissociation of the bromide anion. Then, a *syn*-addition of the aryl-Pd^{II} into the pendant alkyne occurs with concomitant isomerization toward the *anti*-isomer. This isomerization is proposed to take place via an η^2-alkenyl transition state. Final Suzuki coupling with the alkyl boronate

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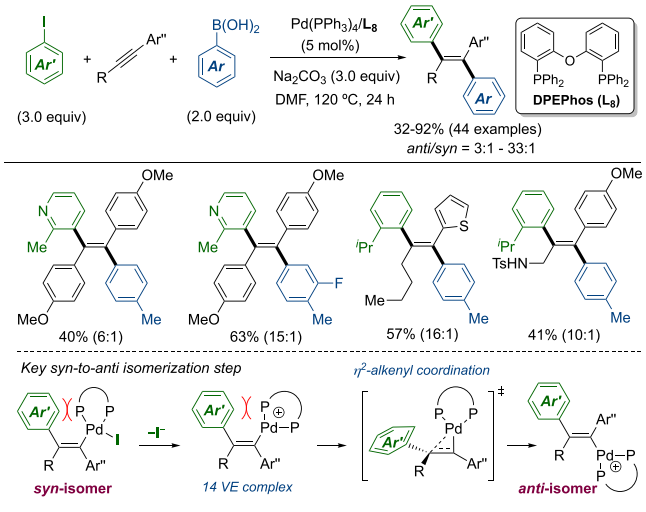
furnishes the diorganopalladium(II) intermediate which upon reductive elimination delivers the cyclized product.

A striking feature of these reactions is that rapid trapping of the alkenyl-palladium species by the organoboron reagent is a crucial step for the *anti*-carbopalladation to take place, thus functioning as the driving force of the reaction. This thermodynamically favored process, in which two new C−C bonds are created, compensates the energy required to promote the *syn*-to-*anti* isomerization; otherwise, the organopalladium species could undergo protodemetalation.[11]

A related intermolecular variant of this process involving the coupling of three or more components is much more challenging and remains an underdeveloped process. A primary reason for this scarcity is that the stereoselectivity is difficult to control because the trapping of the *syn*-addition intermediate is a potential competing process (see examples above in Section 6.1). Lan, Cheng, and co-workers managed to overcome this difficulty and have developed a three-component protocol that enables the intermolecular formal *anti*-carbopalladation of alkynes employing aryl iodides as electrophiles along with boronic acids (Scheme 47).[124] This method allows for the preparation of all-carbon tetrasubstituted alkenes with high levels of *anti*-stereocontrol and regioselectivity.

Scheme 47. Pd-Catalyzed Intermolecular *anti*-Selective Dicarbofunctionalization of Internal Alkynes

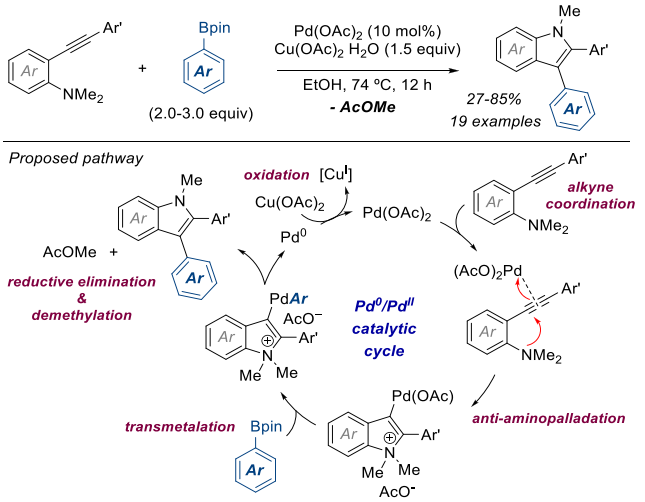


Addressing the stereoselectivity issue was achieved using a bulky phosphine ligand such as DPEPhos $\mathbf{L_8}$ that imposes a very crowded environment around the palladium center in the alkenyl-metal intermediate. Indeed, release of the steric strain caused by the proximity of the bulky Pd-complex and the aryl substituent on the adjacent carbon is the thermodynamic driving force of the isomerization toward the *anti*-addition intermediate which avoids such steric congestion. The combination of $Pd(PPh_3)_4$ with DPEPhos ligand $\mathbf{L_8}$ in DMF at 120 °C provided the best results. As expected, the use of aryl iodides with substitution at the *ortho* position resulted in better stereoselectivities due to their increased steric demand. Different electron-releasing and electron-withdrawing groups were well tolerated at the aryl boronic acid counterpart. However, the use of nonconjugated unsymmetrical internal alkynes delivered poor regioselectivities.

The mechanism for this process was studied by DFT calculations. After oxidative addition of the aryl iodide to a Pd^0 complex, the *syn*-1,2-insertion into the alkyne takes place. Further steric clashing-promoted *syn*-to-*anti* isomerization ensures the formation of the desired tetracoordinated *anti*-alkenyl palladium(II) species. This is proposed to occur via a three-membered ring-type transition state involving cationic Pd species formed upon dissociation of iodide. Final transmetalation with the boronic acid and reductive elimination furnishes the tetrasubstituted alkene with the concomitant regeneration of the catalytically active Pd^0 species. Interestingly, as in the case of Werz's protocol,[123] the *syn*-to-*anti* isomerization was suggested to take place via a 14 valence electron palladacyclopropene intermediate in which rotation of the alkenyl group in the transition state can be considered as an η^2-alkenyl ligand donating 4 electrons to the palladium center.

Nucleopalladation of a metal-coordinated triple bond and further trapping of the alkenyl-palladium(II) intermediate provide an alternative mechanistic approach to formal *anti*-functionalization products. For example, Lee has developed an intramolecular aminopalladation-initiated cascade reaction of alkynes for the synthesis of 2,3-diaryl indoles combining *ortho*-alkynyl anilines and arylboronic acids (Scheme 48).[125] In this

Scheme 48. Pd-Catalyzed Intramolecular Aminopalladation-Initiated Cascade Reaction towards Indole Synthesis



case, the Pd atom behaves as a π-acidic Lewis catalyst, triggering an *anti*-aminopalladation of the alkyne. The resulting Pd^{II} species then reacts with a boronic ester via transmetalation followed by reductive elimination to give the indole product along with a Pd^0 species. As Pd^{II} was required for catalysis, stoichiometric amounts of $Cu(OAc)_2$ were used as an external oxidant.

An interesting enantioselective version of this approach has been reported by Zhu and co-workers using the chiral bisphosphine QuinoxP ligand $\mathbf{L_{23}}$*, thus opening the access to axially chiral indole derivatives (Scheme 49).[126] A broad substrate scope and high asymmetric inductions were typically achieved. Stoichiometric experiments were performed to clarify the potential reaction pathway and the chirality transfer from the $\mathbf{L_{23}}$*Pd^{II} species. A proposed model suggests that the highly sterically demanding *tert*-butyl groups in the ligand are spatially disposed in order to avoid the interaction with the larger group at the *ortho* position.

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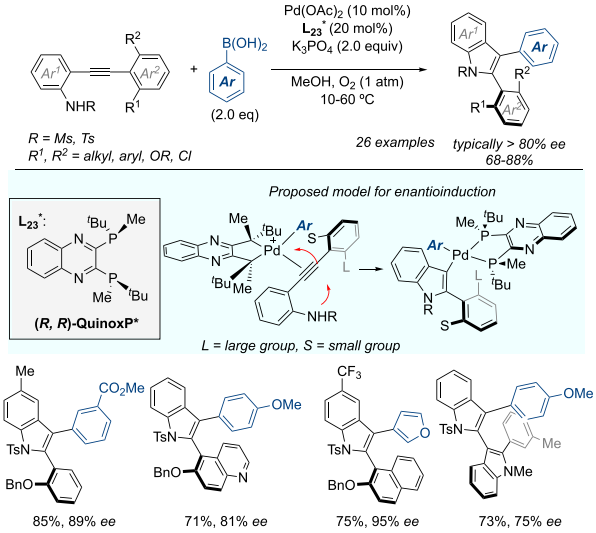
Scheme 49. Pd-Catalyzed Asymmetric Synthesis of Axially Chiral Indoles through Formal *anti*-Alkyne Difunctionalization

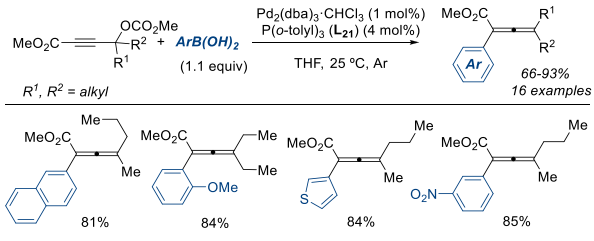


7. FUNCTIONALIZATION OF PROPARGYLIC FUNCTIONALITIES

Pd-catalyzed coupling of propargylic compounds bearing a good leaving group such as propargylic halides, esters, or carbonates with organoboronic acids is one of the most straightforward approaches for the synthesis of allenes, alkenes, and dienes.[127] These reactions typically proceed via decarboxylation to give a key allenyl complex which undergoes transmetalation with the organoboron reagent followed by reductive elimination.[128]

Recently, Ma and co-workers have reported the arylation of propargylic carbonates bearing an ester functionality attached to the C≡C triple bond (Scheme 50).[129] Complete

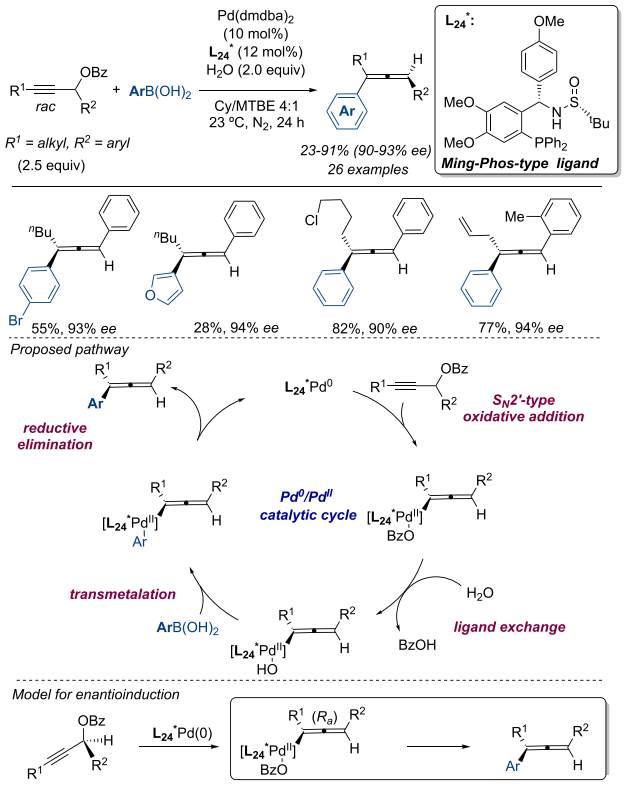
Scheme 50. Synthesis of Tetrasubstituted 2,3-Allenoates from 3-Alkoxycarbonyl Propargylic Carbonates



chemoselectivity toward formation of the allene product was observed, with no detectable quantities of the alkyne hydroarylation product. This latter mode of reactivity is the main pathway typically encountered under related conditions and represents a potential side reaction due to the high reactivity of alkynoate toward addition of aryl-palladium species.[11] The method tolerated a variety of steric and electronic changes to both reaction partners, including heteroaromatic rings. Importantly, this work offers an efficient and versatile means of generating tetrasubstituted allenes, an appealing family of substrates in organic synthesis.

More recently, the same group has described the first enantioselective synthesis of axially chiral allenes employing this approach (Scheme 51).[130] For this purpose, the benzoate

Scheme 51. Pd-Catalyzed Enantioselective Syntheses of Trisubstituted Allenes via Coupling of Propargylic Benzoates



group at the propargylic position was found to be particularly effective. Ligand screening revealed the Ming-Phos **L$_{24}$*** as the more reactive and effective one; other chiral ligands, particularly those based on bisphosphines, delivered poor yields or no desired product. The palladium source was also equally important: the Pd^{II}-based precatalyst gave no reactivity or very low yields, in comparison with Pd^0 precatalysts. The overall mechanistic pathway is believed to start with an oxidative addition of the propargylic benzoate to a Pd^0 center via an S$_N$2′-type reaction, generating the allenic-Pd^{II} intermediate. The addition of 2 equiv of water was found to be crucial, which is believed to be responsible for the generation of hydroxo-palladium(II) species (via ligand exchange with the benzoate group), which are more reactive for transmetalation with the boronic acid. Finally, after reductive elimination, the desired allene is obtained with concomitant regeneration of the required Pd^0 active catalyst.

A positive nonlinear effect was found for the Ming-Phos ligand **L$_{24}$*** at both low and high conversions, suggesting that the active catalyst would be a Pd^0 species with more than one ligand bound to it. Based on these observations, a combination of a dynamic kinetic resolution and a kinetic resolution process was hypothesized to be responsible for the high degree of asymmetric induction. It was proposed that both enantiomers of the allenyl-Pd^{II} intermediate, formed by oxidative addition of the racemic benzoate to Pd^0, would be in a dynamic interconversion via an allyl-type species. Different aryl groups could be installed satisfactorily from the aryl boronic source, including alkenyl substrates. The main restriction was found in the nature of alkynyl (R^1) and propargyl (R^2) substituents: the reaction failed with alkynes carrying an aryl substituent (R^1 =

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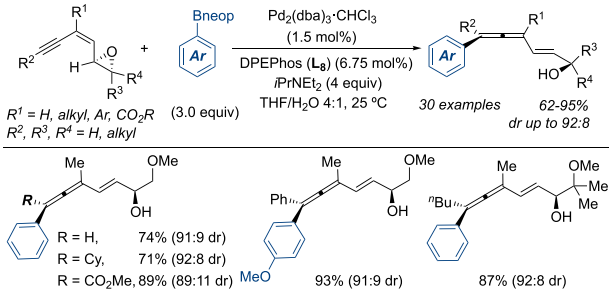
Ar) or alkyl chains at the propargylic position (R^2 = alkyl). This method is not suitable for the construction of tetrasubstituted allenes.

Conjugated enynes carrying a leaving group at the allylic carbon can also be used for the synthesis of allenes. This family of compounds typically undergoes aryl metalation with the metal being regioselectively placed at the carbon conjugated with the double bond. Subsequent 1,3-metal migration generates the allenic structure with the concomitant formation of an alkyl-metal intermediate suitable for a final coupling with either a nucleophile or an electrophile to afford the allene product. Artok and co-workers have described the addition of organoboron reagents to epoxy-1,3-enynes using Pd catalysis (Scheme 52).[131] In this case, the authors proposed that the

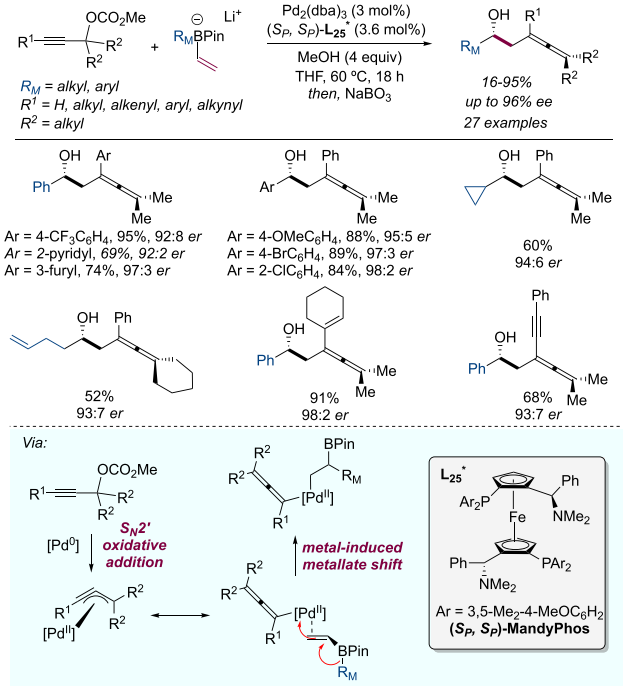
Scheme 52. Pd-Catalyzed Arylative Allenation of Conjugated Enyne Oxiranes



reaction starts with the formation of an oxa-allyl-palladium(II) species, which undergoes transmetalation with the boronic acid. Subsequent reductive elimination yielded the allenol product. High reaction yields and diastereoselectivities were achieved irrespective of the nature of the substituents attached to the alkyne moiety (H, alkyl, aryl, or an ester group). The transformation was chemoselective to the formation of the allenol product instead of the arylative ring opening of the epoxide, which was detected in low conversions, especially when the alkyne is attached to an aliphatic chain.

Stereospecific 1,2-metalate rearrangement is a unique reactivity mode of boronate esters which has been extensively exploited in enantioselective conjunctive cross-coupling by merging an alkenyllithium reagent, an organoboronic ester, and an organic electrophile.[132] In 2016, Morken introduced the concept of palladium-induced metalate rearrangement wherein 1,2-migration of an alkyl or aryl group from boron to the vinyl α-carbon occurs concomitantly with C−Pd σ-bond formation. The resulting chiral organometallic intermediate can be exploited in subsequent bond-forming processes.[133] Using this strategy, Morken has described the enantioselective synthesis of allenols by Pd-catalyzed conjunctive cross-coupling using propargyl carbonates as electrophiles (Scheme 53).[134] The reaction was proposed to start with a first oxidative addition of the propargyl carbonate to a Pd^0 complex via an S_N2' process. The resulting intermediate reacts with the nucleophilic boronate reagent to deliver the enantioenriched borylated allene. Remarkably, this strategy enables the introduction into the substrate of two nucleophilic reagents along with the boron moiety. Because of the lability of the boron group, the crude reaction was treated under oxidative C−B bond cleavage to yield the corresponding allenols. More recently, the same group has reported a strategy for accessing trisubstituted allenols controlling both central and axial

Scheme 53. Pd-Catalyzed Enantioselective Conjunctive Cross-Coupling with Propargylic Carbonates



chirality via 1,4-difunctionalization of borylenynes with aryl halides.[135]

In comparison with substrates bearing a good leaving group such as propargylic halides, esters, or carbonates, coupling of propargylic alcohols is less well developed. This paucity stems from the difficulty associated with the oxidative addition step of the transition metal catalyst. In 2016, the Kimber group reported a strategy toward the synthesis of 1,3-dienes employing terminal propargylic alcohols in combination with aryl boronic acids (Scheme 54).[136] A Lewis acid−base interaction between the alcohol and the organoboron species was proposed as the activation mode to promote the oxidative addition to the palladium complex, upon which the allene product is released via reductive elimination. Additionally, a Pd−H complex is likely formed under the reaction conditions by oxidation of the Pd^0 complex with the $B(OH)_3$ generated during the formation of the allene. This reactive hydridic species can undergo 1,2-insertion into the allene, forming a transient alkyl-Pd^{II} intermediate which further evolves via β-hydrogen elimination to deliver the 1,3-diene product. Therefore, the overall catalytic cycle consists of an auto tandem process in which the palladium species is involved in both processes, namely, the cross-coupling event in which the allene is obtained, and the subsequent Pd−H-catalyzed allenyl-diene isomerization. To demonstrate the formation of the Pd−H species by reaction with the boric acid, control experiments were performed treating the preformed allene product with different boron-containing additives. These experiments revealed that the presence of boric acid was crucial to attain such a reactivity profile, indicating that the release of $B(OH)_3$ is an important step in the first catalytic cycle which then triggers the formation of the reactive Pd-hydride. Different aryl boronic acids could be satisfactorily installed, leading to the *E*-1,3-diene product with excellent stereoselectivity and good to high reaction yields. However, the presence of halides or

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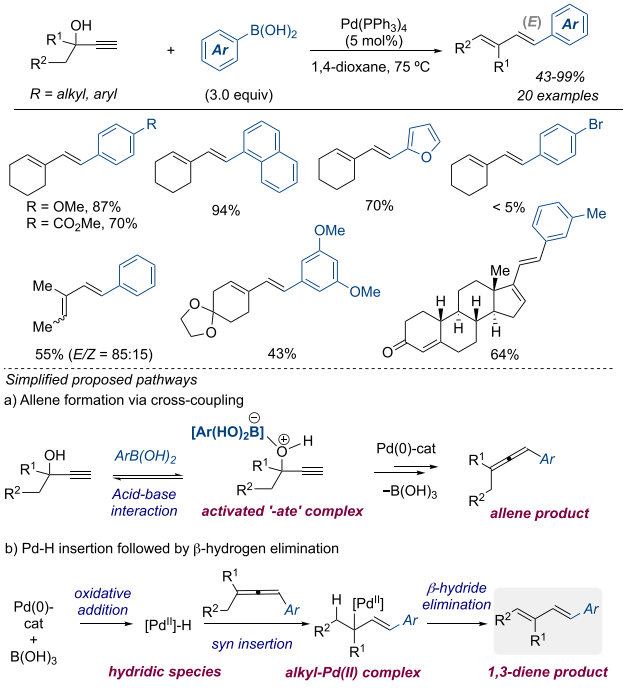
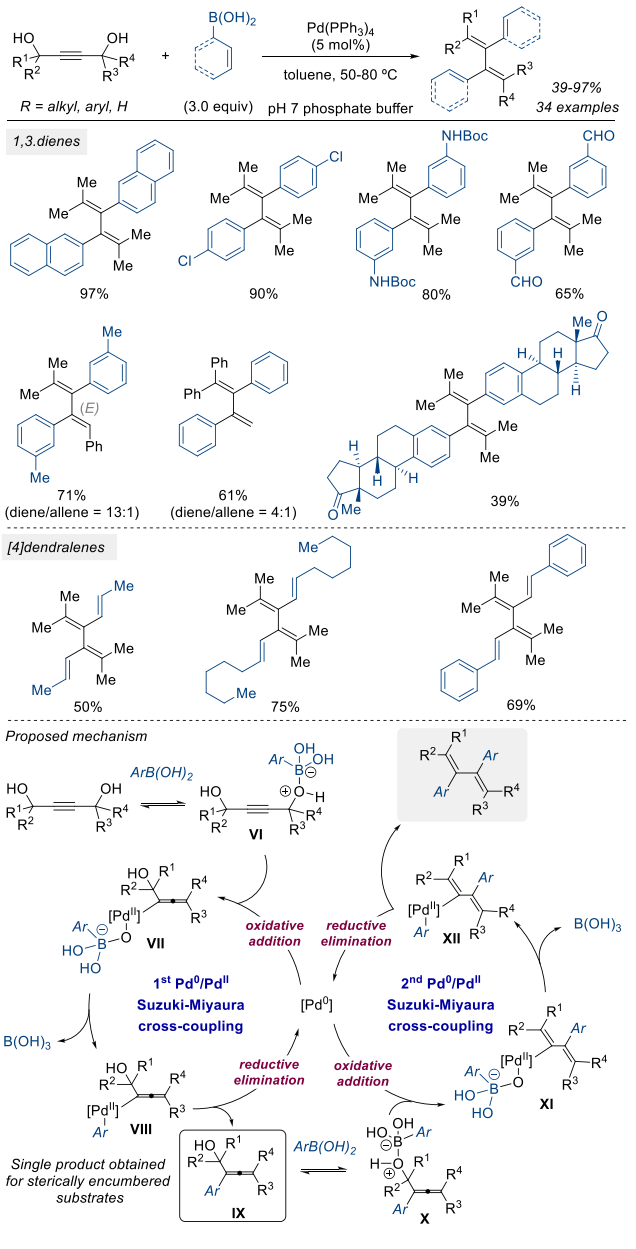
Scheme 54. Pd-Catalyzed Synthesis of 1,3-Dienes from Propargylic Alcohols



Scheme 55. Pd-Catalyzed Two-Fold Suzuki−Miyaura-Type Cross-Coupling Sequence of Propargylic Diols



pseudohalides at the boronic acid counterpart was not well tolerated.

Concomitantly with the previous method, Sherburn and co-workers described a similar strategy for the synthesis of 1,3-dienes via a Pd-catalyzed 2-fold cross-coupling sequence between propargylic diols and organoboron reagents (Scheme 55).[137] The reaction tolerates a broad range of aromatic boronic acids and proceeds with perfect control of regio- and stereoselectivity. The presence of water or using a pH 7 aqueous buffer is needed to get clean conversion. Substrates bearing a secondary alcohol moiety provided excellent *E* stereoselectivity in the newly formed C=C double bond. Alkynes having a single primary alcohol were also tolerated, albeit minor quantities of the allene byproduct were formed as a result of an allylic transposition. In contrast, unsubstituted, simple but-2-yne-1,4-diol failed to react. Alkenyl boronic acids were also suitable coupling partners for this transformation, leading to the corresponding [4]dendralene products as single stereoisomers.

The proposed mechanism involves a Suzuki−Miyaura-like 2-fold cross-coupling sequence between the propargylic diol and either the aryl or alkenyl boronic acid (Scheme 55). As in the previous case, the formation of an activated Lewis acid/base complex (**VI**) between the alcohol and the boron reagent facilitates insertion of Pd^0 into the propargyl C−O bond via S_N2' oxidative addition to deliver an allenic σ-palladium complex **VII**. This intermediate evolves by the release of $B(OH)_3$ toward the allenyl-Pd^{II} intermediate **VIII**, from which allenol **IX** is obtained via reductive elimination, thus completing the first cross-coupling. After that, a second catalytic cycle proceeds through a similar activated Lewis acid/base complex **X**, via the intermediates **XI** and **XII** to give the 1,3-diene product. Remarkably, the steric hindrance at either the propargyl diol or the organoboron reagent precludes the formation of the 1,3-diene, and only the allenol product arising from the first catalytic cycle is obtained.

The functionalization of propargylic substrates by a reaction with an organoboron reagent has been also employed as a strategy for the synthesis of 1,4-dienes (also known as skipped dienes), which are thermodynamically less favorable. This goal was achieved by Nechab and co-workers in the context of atropodiastereoselective synthesis of indenes by using a diverse family of aryl boronic acids (Scheme 56).[138] The reaction is based on an auto tandem Pd-catalyzed process in which the use of 1,5-enynes **XIII** with a carbonate group at the propargylic position allows for a first cross-coupling with an arylboronic acid, thus generating a 1,5-enallene species **XIV**. This intermediate, which is the major product at room temperature, then engages in a second Pd-catalyzed cycloisomerization between the allene fragment and the pendant allyl moiety in an ene-type reaction upon heating up to 100 °C. This process occurs via a first oxidative cyclometalation involving the bicoordinated species **XV**, delivering the

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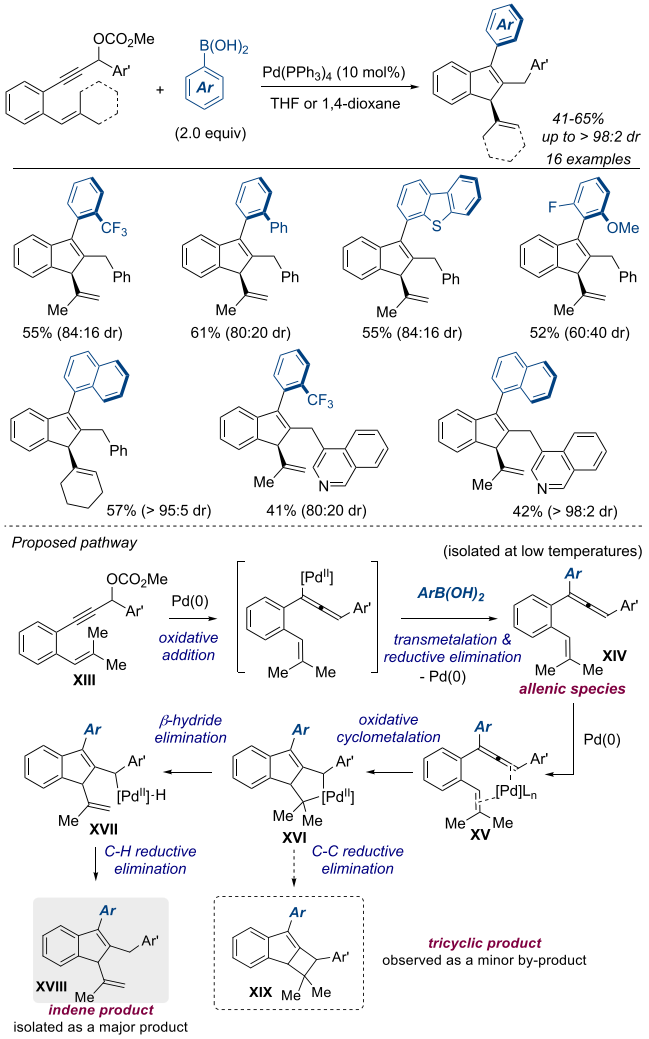
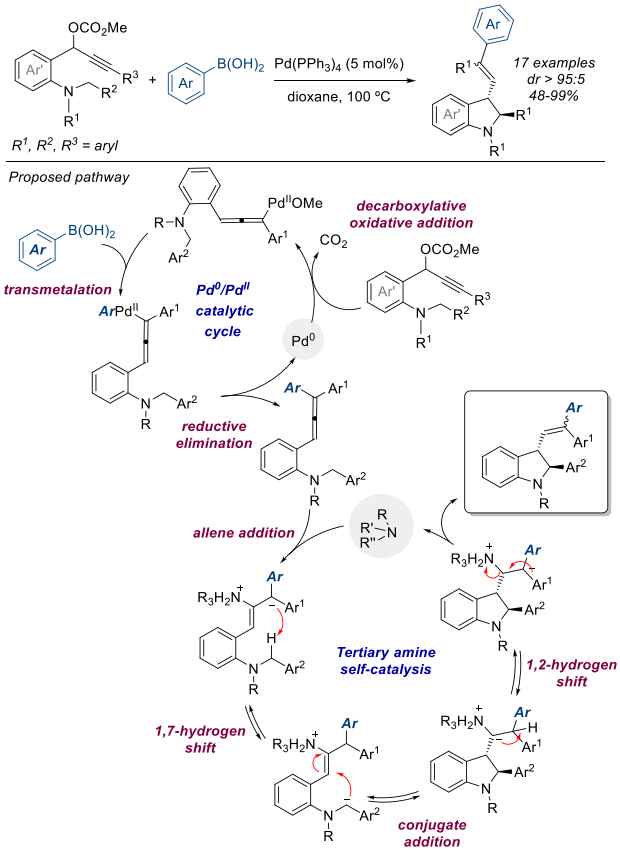
Scheme 56. Pd-Catalyzed Atroposelective Cross-Coupling and Cycloisomerization of Propargyl Carbonates



intermediate **XVI**. Further β-hydride elimination results in the formation of the alkyl-Pd^{II} **XVII**, which furnishes the indene product **XVIII** via reductive elimination. This cyclization step takes place in an atropodiastereoselective fashion when using *ortho*-substituted and naphthalene-derived boronic acids, allowing the generation of both central and axial stereogenic centers, in a process in which C(sp^2)−C(sp^2) and C(sp^2)−C(sp^3) bonds are created in a single synthetic step. However, the enantioselective version of this reaction has not been reported yet. Interestingly, the resulting intermediate **XVI** can evolve via a C−C reductive elimination pathway, generating the tricyclic byproduct **XIX**, which can be isolated as the minor product of this transformation.

In 2017, Lim reported the use of propargyl carbonates bearing a tertiary amine moiety (diaryl benzyl amine) for the synthesis of indolines by a reaction with aryl boronic acids under Pd catalysis (Scheme 57).[139] Initial arylative allenylation of the alkyne unit, likely via S_N2' attack of Pd^0 on the propargylic carbonate, followed by transmetalation and reductive elimination from the resulting allenyl-Pd^{II} intermediate gives the trisubstituted allene intermediate. Then, the tertiary amine initiates autocatalysis by nucleophilic attack to the allene moiety followed by proton migration, nucleophilic addition, 1,2-H shift, and elimination of the tertiary amine to

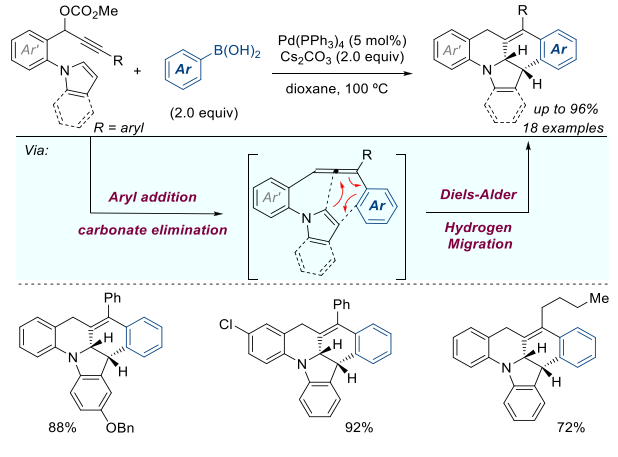
Scheme 57. Tandem Pd/Amine-Catalyzed Addition of Boronic Acids to Propargylic Carbonates for the Synthesis of Indolines



deliver the corresponding indoline skeleton with good results and high *anti/syn* stereoselectivity.

A related protocol has been described by Lim from a propargyl compound containing 2-indolylphenyl moieties leading to cyclic systems with up to 6 fused rings in a single synthetic step with excellent yields (Scheme 58).[140] This method involves three sequential steps triggered by Pd^0-catalyzed allenylation of propargyl carbonate followed by a Diels−Alder cyclization and hydrogen migration processes to

Scheme 58. Synthesis of Polycyclic Ring Systems Triggered by Pd^0-Catalyzed Allenylation of Propargyl Carbonates



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furnish benzo[*b*]indolo[3,2,1-*de*]acridines. The base (Cs_2CO_3) seems to be essential for the H-migration.

PART III: TRANSITION-METAL-CATALYZED RADICAL ADDITION/COUPLING REACTIONS

Transition-metal-catalyzed radical addition/coupling reactions of alkynes with organoboron reagents have provide innovative methods to synthesize various kinds of functionalized alkenes in a regio- and stereodefined fashion. These single-electron transfer (SET) processes allow the addition of alkyl electrophiles that are most challenging to realize using traditional 2-electron-based cross-coupling processes. However, the selectivity control of reactive radical intermediates is still a great challenge in these transformations. The following section will discuss recent advances in this emerging field.

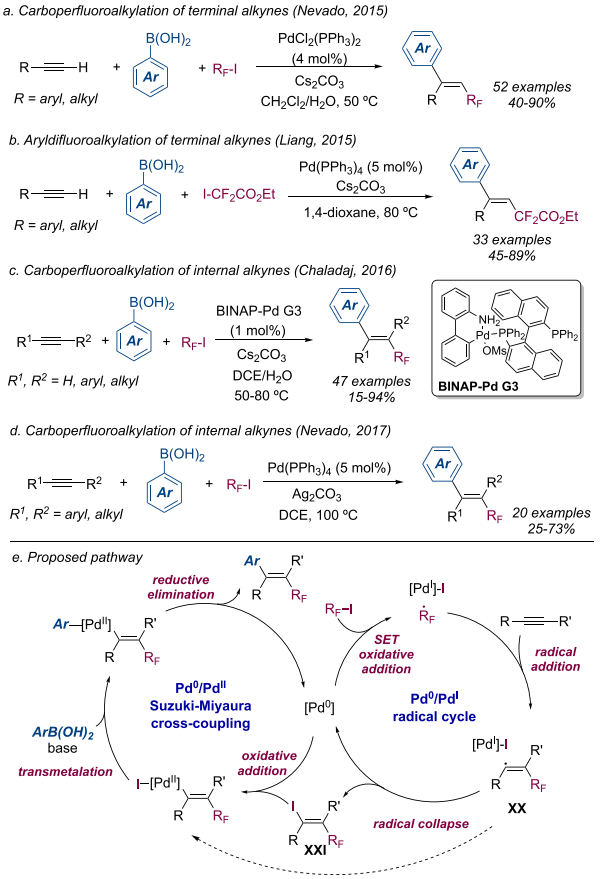
8. DIFUNCTIONALIZATIONS TRIGGERED BY RADICAL ADDITIONS

Transition-metal-catalyzed radical addition/coupling provides a powerful alternative mechanism for alkyne difunctionalization that addresses the limitation of *syn*-selectivity imposed by migratory insertion at the catalytic metal. These reactions typically favor *anti*-addition, which is dominated by steric factors of vinyl radicals in the coupling step.[141]

The ability of fluorinated alkyl halides to undergo radical formation under transition metal catalysis was exploited by Halszedine in 1950 for the radical addition of iodotrifluoromethane to acetylene.[142] This seminal work triggered the development of many protocols for fluoroalkyl radical addition to alkynes[143] driven by the wide-range significance of perfluoroalkylated compounds in different fields of chemistry.[144] In the past several years, this approach has evolved to more sophisticated multicomponent transformations enabling difunctionalization of both terminal and internal alkynes. Boronic acids were found to be excellent nucleophilic coupling partners, in combination with perfluoroalkyl halides under Pd or Ni catalysis. Tri- or tetrasubstituted alkenes containing perfluoroalkyl groups can be prepared through this strategy with high levels of regio- and stereocontrol.

The first transition-metal-catalyzed one-pot three-component reaction involving the addition of perfluoroalkyl iodides (R_F–I) and boronic acids to alkynes was reported in 2015 by the Nevado group exploiting the ability of palladium(0) to act as a single electon donor and promote radical reactions (Scheme 59a).[145] Shortly after, the Liang group reported a similar procedure for aryl fluoroalkylation of terminal alkynes involving ethyl 2,2-difluoro-2-iodoacetate as a radical precursor (Scheme 59b).[146] The Wu group has recently extended this three-component reaction to 2-iodo-2,2-difluoroacetophenones as electrophilic radical precursors.[147] The incorporation of the difluoromethylene group (CF_2) into organic compounds is attractive because not only does it act as a bioisostere for mimicking the electronic features of an ethereal oxygen atom, but it also is a lipophilic hydrogen-bond donor.[148] Because of the mild conditions, the broad scope and functional group tolerance are remarkable in all cases. However, both methods are limited to terminal alkynes (alkyl- and aryl-alkynes). Subsequently, Chaładaj reported a method for Pd-catalyzed carboperfluoroalkylation broadly applicable to both terminal and internal alkynes, providing access to tri- and tetrasubstituted perfluorinated alkenes in good yields and excellent stereoselectivities (Scheme 59c).[149] The key to success for the

Scheme 59. Pd-Catalyzed Radical Difunctionalization of Alkynes via Addition of Perfluoroalkyl Electrophiles and Boronic Acids



observed reactivity arose from the utilization of BINAP-ligated palladacyclic precatalysts based on the 2-aminobiphenyl scaffold, previously developed by Buchwald for C–C and C–N cross-coupling reactions.[150]

Later, Nevado and co-workers also devised a method for stereoselective carboperfluoroalkylation of internal alkynes in which the use of silver bases was key to enabling the reaction.[151] Remarkably, only traces of product were detected using Cs_2CO_3, which was the base of choice in their previous studies with terminal alkynes (Scheme 59d). It is interesting to note that whereas alkenyl boronic acids coupled efficiently with terminal alkynes, this reagent class seems not to be suitable partners for internal alkynes. Another limitation associated with the use of internal alkynes is that only unsymmetrical aryl-alkyl alkynes allowed achieving high regioselectivity (R_F positioned far from the Ar substituent); for most unsymmetrical dialkyl-substituted alkynes, regioselectivities were poor.

Chaladaj and co-workers formulated a mechanistic hypothesis based on two catalytic cycles involving Pd^0/Pd^I and Pd^0/Pd^{II}, operating in an auto tandem fashion (Scheme 59e).[149] In the first cycle (Pd^0/Pd^I), SET from the Pd^0 catalyst to R_F–I results in homolytic scission of the C–I bond with the formation of a radical pair between the alkyl radical R_F and a Pd^I intermediate. The R_F• species then adds to the triple bond of the alkyne, generating the alkenyl radical **XX** which is trapped by the Pd^II species to give the alkenyl iodide **XXI**. The second cycle consists of a classical Suzuki coupling of the

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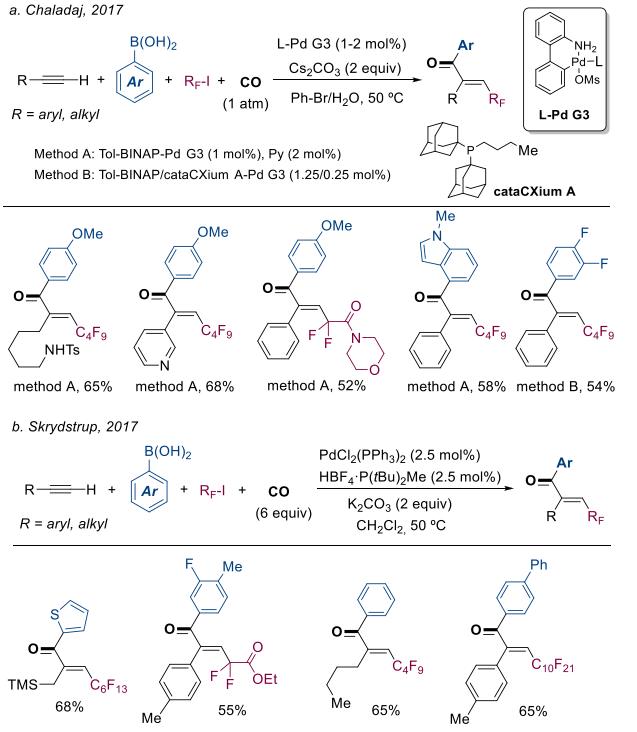
iodide **XXI** with the aryl boronic acid. This mechanistic scenario involving the formation of alkenyl iodide **XXI** is based on the observation that this species can be detected during the reaction progression and is readily formed when the internal alkyne reacts with R_F–I in the presence of a catalytic amount of arylboronic acid (10 mol %) under otherwise identical conditions, evolving to the corresponding coupling product upon the subsequent addition of boronic acid to the mixture. However, similar control experiments performed by the Nevado group in their study with terminal alkynes determined that the alkenyl iodide was not produced.[145] Consequently, the authors proposed the recombination of alkenyl radical **XX** with either $Pd^{I}I$ or $ArPd^{I}$ species generated in the SET step, to give alkenyl-Pd^{II}–Ar species (transmetalation with the boronic acid may occur prior to or after radical trapping), from which reductive elimination eventually generates the dicarbofunctionalized product. Further mechanistic studies by Nevado suggest a mechanistic dichotomy for the reaction of terminal vs internal alkynes: the intermediacy of alkenyl iodide species **XXI** is likely involved for the latter, whereas recombination of alkenyl radical intermediates with Pd^{I} species seems to be favored for the former.[151] Nevertheless, the operative mechanism seems to be quite substrate-dependent, since Wu detected small amounts of the alkenyl iodide in the iodoalkylation of terminal aryl alkynes at the early stages of the reaction, which gradually decreases with time, suggesting that the formation of this alkenyl iodide is involved in the reaction.[147]

The high stereoselectivity in the case of terminal alkynes can be ascribed to the less steric demand in the alkenyl radical **XX** for recombination with Pd^{I} radical species *anti* to the incorporated R_F group. For internal alkynes, the high *anti*-stereocontrol seems to be determined by a more stable *cis* arrangement between R^1 and R_F in the intermediate alkenyl radical **XX**.

In 2016, Liang and co-workers extended their Pd-catalyzed aryldifluoroalkylation of terminal alkynes[146] to a four-component process incorporating carbon monoxide as the fourth reactant to promote a carbonylation as an additional step in the presence of alcohols or amines as nucleophiles.[152] Subsequently, the groups of Chaladaj[153] and Skrydstrup[154] reported independently a similar four-component carbonylative carboperfluoroalkylation of terminal alkynes using (hetero)arylboronic acids as nucleophiles (Scheme 60). A series of perfluorinated enones can be prepared with good yields and excellent regio- and stereoselectivities under mild reaction conditions from both aryl- and alkylalkynes. Chaladaj's procedure exploits the good performance of the Buchwald-type Pd-precatalyst L-Pd-G3 used in the previously developed three-component carboperfluoroalkylation of alkynes (Scheme 60a). However, it was found that the application of the more sterically demanding Tol-BINAP ligand (1 mol %, used in combination with 2 mol % of pyridine) improved the selectivity toward the enone product. Furthermore, a combination of two palladium species Pd G3 ligated by Tol-BINAP (0.75 mol %) and the hindered electron-rich phosphine ligand cataCXium A (1.5 mol %) was required for achieving complete conversion in reactions involving electron-deficient arylboronic acids. The authors speculated that, in the presence of carbon monoxide, transmetalation of electron-deficient boronic acids with the palladium(II) species is sluggish. The Pd complex bonded to cataCXium A could facilitate the transfer of the aryl group from the boronic acid

Scheme 60. Pd-Catalyzed Carbonylative Radical 1,2-Difunctionalization of Terminal Alkynes by Insertion of CO



and then either relay it to the other catalytically active Tol-BINAP complex or promote carbonylative coupling by itself.

A reaction mechanism involving two independent catalytic cycles, analogous to that previously described for the three-component reaction, shown in Scheme 59, was proposed in which the alkenyl iodide intermediate undergoes a common carbonylative Suzuki coupling through oxidative addition to Pd^0, coordination and insertion of CO to the alkenylpalladium complex, and then transmetalation of the resulting acylpalladium intermediate with the (hetero)arylboronic acid and reductive elimination.

Skrydstrup adapted the Nevado three-component arylperfluoroalkylation of terminal alkynes to a carbonylative process (Scheme 60b).[154] Again, the use of a bulky, strong σ-donating $P(^tBu)_2Me$ phosphine ligand (as its HBF_4 salt) in combination with $Pd(PPh_3)_2Cl_2$ (2.5 mol %) was needed to achieve the desired reactivity. The catalyst system required 6 equiv of CO from COgen (9-methyl-9*H*-fluorene-9-carbonyl chloride) and K_2CO_3 as a base. Interestingly, this method was adapted to the preparation of ^{13}C-labeled enones by employing ^{13}C-labeled COgen. In their mechanistic hypothesis, the authors did not consider the intermediacy of alkenyl iodide species and proposed a direct trapping of the alkenyl radical with Pd^{I} species to give the key alkenyl-Pd^{II} intermediate that follows the typical carbonylative mechanism.

This strategy has been recently applied by Zhang and co-workers to the radical cascade aryldifluoroalkylation/cyclization of 1,6-enynes with ethyl difluoroiodoacetate, as an efficient means of generating CF_2-containing indoles, benzofuranes, and benzothiophenes (Scheme 61).[155] This tandem process involves the formation of a heterocyclic skeleton with the incorporation of two important functional groups through the formation of one C(sp^3)–CF_2 bond and two C–C bonds in one step. Interestingly, the wide bite angle of the diphosphine

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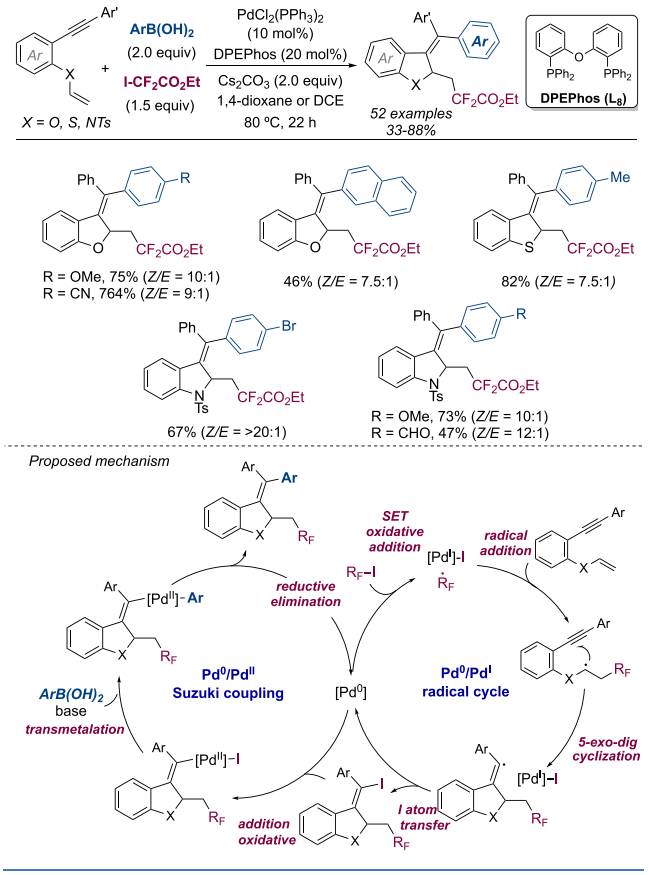
Scheme 61. Pd-Catalyzed Intermolecular Cascade Insertion of Boronic Acids and Perfluoroalkyl Electrophiles with Enynes

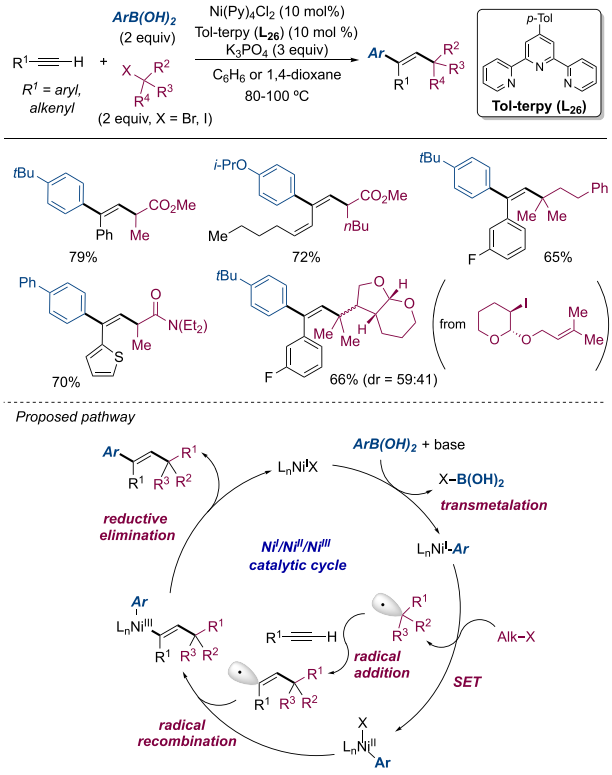


ligand DPEPhos ($\mathbf{L_8}$) was found to produce a significant improvement in reactivity. The aromatization of the resulting cyclization products could be afforded via a subsequent $Fe(OTf)_3$-catalyzed double bond isomerization process.

This reaction was proposed to occur by initial addition of the RCF_2 radical, generated along with Pd^I species by reduction of ethyl difluoroiodoacetate by Pd^0, to the double bond[156] of the 1,6-enyne moiety. The resulting alkyl radical intermediate undergoes an intramolecular 5-*exo*-dig cyclization to give a vinyl radical which could evolve to the alkenyl iodide intermediate via atom transfer of iodine from ICF_2CO_2Et or $I-Pd^I$ species with the release of Pd^0. This alkenyl iodide then enters in a classical Suzuki coupling Pd^0/Pd^{II} redox catalytic cycle. Support for the intermediacy of the alkenyl iodide intermediate comes from control experiments performed in the absence of boronic acid, which showed its formation in good yield with moderate stereoselectivity (Z/E = 2:1). Interestingly, when this mixture was treated with the arylboronic acid under the standard conditions, the arylation product was obtained with improved *Z*-stereoselectivity (Z/E = 10:1). This observation was ascribed to an isomerization via $TS_{syn\text{-}anti}$ in the cross-coupling process.

The above dicarbofunctionalizations of alkynes catalyzed by palladium complexes seem to require activated perfluoroalkyl iodides as alkyl donors. The greater ability of nickel complexes, in combination with multidentate nitrogen ligands, to generate alkyl radical species from nonactivated alkyl halides by single electron transfer[157] was exploited by Nevado and co-workers in their Ni-catalyzed three-component dicarbofunctionalization of terminal alkynes with boronic acids and alkyl halides.[158] The air- and moisture-stable precatalyst $NiCl_2(Py)_4$, in combination with a tridentate *tert*-pyridine ligand $\mathbf{L_{26}}$, provided the best results (Scheme 62). This method offers a remarkable

Scheme 62. Ni-Catalyzed Radical 1,2-Difunctionalization of Terminal Alkynes



functional group tolerance and wide scope, providing trisubstituted alkenes in a highly regio- and stereocontrolled manner in favor of the *anti*-addition product. Both activated (α-halocarbonyl derivatives) and unactivated (tertiary) alkyl halides could be efficiently incorporated across triple bonds. Unactivated primary or secondary alkyl iodides containing an alkene group (i.e., δ-iodoalkenes) delivered the corresponding cyclization/addition/coupling products with high *anti*-addition stereocontrol but low diastereoselectivity in the newly formed five-membered ring. However, this method was not applied to terminal alkyl-alkynes.

Control experiments pointed to a radical mediated process. On the other hand, reactions with Ni^0 or Ni^{II} precatalyst in the absence of boronic acid or with a substoichiometric amount of the boronic acid failed to provide alkenyl halide, suggesting that a simple [Ni]/L system is not responsible for the C–X activation. The authors proposed a Ni^I/Ni^{III} catalytic cycle in which the active Ni^I species produced *in situ* undergoes transmetalation with the $ArB(OH)_2$ reagent producing the $Ar-Ni^I$ intermediate. SET from this complex to the R–X reagent produces an R radical that adds to the alkene to give an alkenyl radical. This alkenyl radical is intercepted by the $ArNi^{II}X$ species formed in the SET step to afford the key Ni^{III} species, which undergoes reductive elimination to produce the corresponding trisubstituted alkene while regenerating Ni^I.

The same research group reported a related Ni-catalyzed *anti*-selective carbosulfonylation reaction of terminal (hetero)-aryl alkynes using a related catalyst system (Scheme 63).[159] In

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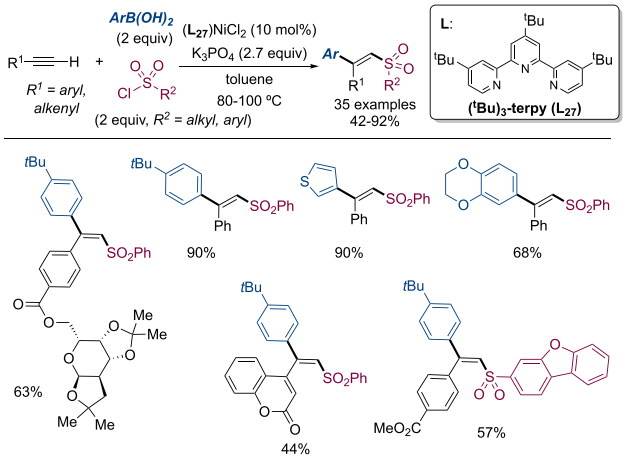
Scheme 63. Ni-Catalyzed Radical 1,2-Carbosulfonylation of Terminal Alkynes

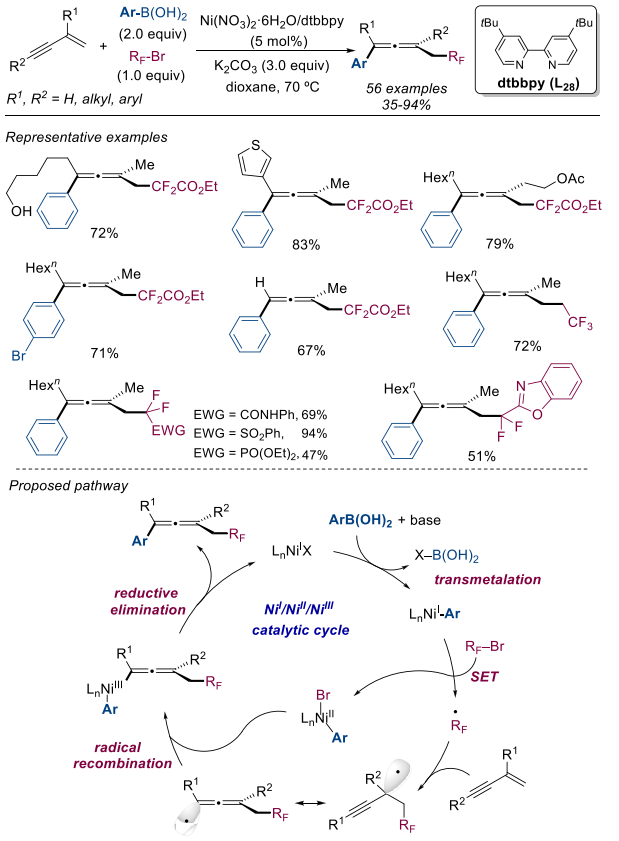


this case, however, the preformed complex of a tri*tert*-butyl-substituted terpyridine ligand $\mathbf{L_{27}}$ provided significantly higher yields than the combination $NiCl_2(Py)_4/\mathbf{L_{27}}$. β,β-Disubstituted alkenyl sulfones were obtained with complete regio- and stereocontrol by the simultaneous addition of aryl and sulfonyl groups (from arylboronic acid and sulfonyl chloride, respectively) across the triple bond in a radical-mediated process. The mild reaction conditions allow for excellent functional group tolerance, thus notably expanding the scope of the alkyne carbosulfonylation. Because no method is without limitations, this protocol was not applicable to alkyl-substituted terminal alkynes or internal ones, while vinyl or alkyl boronic acids were not suitable coupling partners either.

While control experiments strongly supported the radical nature of this reaction, the alkenyl chloride as putative reaction intermediates resulting from a nickel-mediated halosulfonylation could not be detected when performing the reaction in the absence of the boronic acid under either Ni^{II} or Ni^{0} precatalysts. Furthermore, when an independently prepared sulfonylated alkenyl chloride was subjected to the standard conditions in the presence of the arylboronic acid, no Suzuki coupling was observed, thus ruling out its participation as a productive intermediate. Based on these observations, the authors proposed a catalytic cycle very similar to that shown in Scheme 62. The $Ar-Ni^{I}$ species was hypothesized to reduce via SET the sulfonyl chloride to generate a sulfonyl radical that adds reversibly to the terminal position of the alkyne. In much the same way, the resulting alkenyl radical then recombines with an $Ar-Ni^{II}$ halide complex generated in the SET step to generate a Ni^{III} complex which delivers the product through reductive elimination while regenerating Ni^{I}.

Nickel catalysts have also been demonstrated to be capable of generating different fluoroalkyl radicals from fluoroalkyl halides. Exploiting this feature, the Wang group has recently devised a Ni-catalyzed 1,4-carbofluoroalkylation of 1,3-enynes to access structurally diverse fluoroalkylated allenes (Scheme 64).[160] Various 1,3-enynes, fluoroalkyl bromides, and arylboronic acids participated in this three-component reaction. The synthetic potential of the resulting multisubstituted allenes was demonstrated through their derivatization into different fluorinated carbo- and heterocycles. $Ni(NO_3)_2{\cdot}6H_2O$, in combination with the bipyridine ligand $\mathbf{L_{28}}$, was found to provide best reactivity, although other Ni^{II} precatalysts also functioned well.

Scheme 64. Ni-Catalyzed Difunctionalization of 1,3-Diynes towards the Synthesis of Tetrasubstituted Allenes



Control and radical clock experiments supported the participation of fluoroalkyl radicals in the catalytic cycle. Propargyl bromide or allenyl bromide intermediates could not be detected when performing the reaction with substoichiometric amounts of boronic acids, which suggests that 1,2- and 1,4-ATRA (atom transfer/radical addition) processes are not operative. Competitive experiments with boronic acids showed no dependence of electronic effects on the reaction rate, suggesting that boronic acids were unlikely involved in the rate-limiting step. In contrast, competition experiments between fluoroalkyl halides showed that reaction rate decreases in the order: R−I > R−Br > R−Cl, indicating that a nickel-centered inner-sphere electron-transfer process led to the rate-determining halogen-atom abstraction from the alkyl halide.

A catalytic cycle was proposed in which the reaction is believed to proceed via the reaction of an $Ar-Ni^{I}$ species formed *in situ* with the alkyl halide, generating a fluoroalkyl radical in a SET process, leading to a fluorinated alkyl radical ($R_F\bullet$) and an $Ar-Ni^{II}$ species (rate-determining step). The R_F radical intermediate adds to the alkene moiety of the 1,3-enyne, to form a stabilized allenyl radical which collapses with the previously formed $ArNi^{II}X$ species, thus yielding the substituted allene after reductive elimination.

Almost simultaneously, a copper-catalyzed 1,4-dicarbofunctionalization of 1,3-enynes using alkyl diacyl peroxides as masked alkyl electrophiles and aryl boronic acids as nucleophiles was reported by Bao and co-workers for the synthesis of tetrasubstituted allenes (Scheme 65).[161] The use of tridentate chiral Py-Box ligand $\mathbf{L_{29}}$ resulted a key element for success; other commonly used N-donor ligands such as

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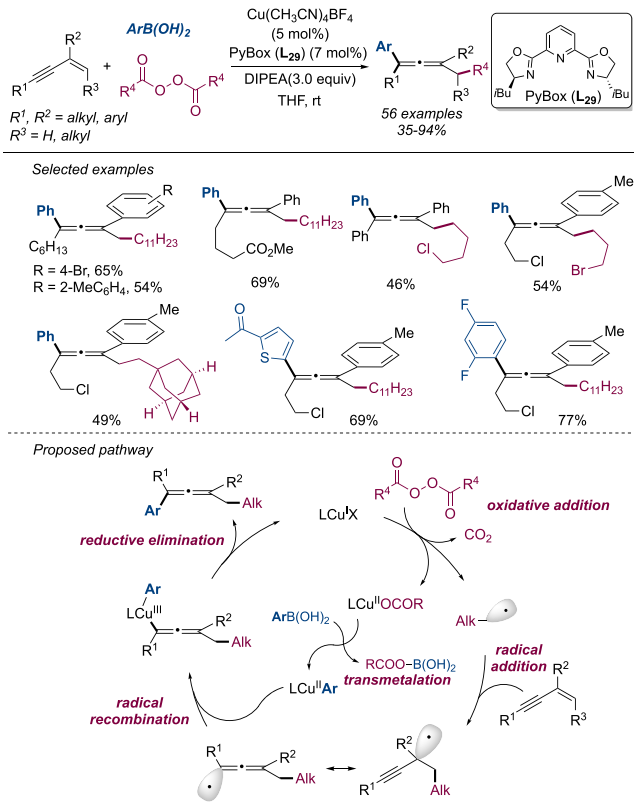
Scheme 65. Cu-Catalyzed Difunctionalization of 1,3-Enynes Employing Diacyl Peroxides as Masked Electrophiles



bipyridine (bipy), phenantroline, bisoxazoline (Box), or bipyoxazoline ligands failed to afford the 1,4-arylalkylation product. Despite the chiral nature of the ligand, enantioselectivities were not satisfactory, and a racemic ligand was generally used. A variety of 1,3-enynes were compatible with this catalytic system, including those containing internal alkynes and terminal alkynes, albeit in these cases with relatively lower yields. Regarding the boron partner, aryl and thienyl-derived boronic acids participated efficiently in the reaction, whereas alkylboronic acids were found to be unreactive. Primary and secondary alkyl diacyl peroxides can be employed, though the latter led to lower yields.[162]

Control experiments suggested that an allenyl radical might be involved. The mechanistic proposal suggests a similar pathway to that reported by Wang in the previous example,[160] but following a general $Cu^{I}/Cu^{II}/Cu^{III}$ redox course. However, in this case, the Cu^{I} catalyst assists the formation of the alkyl radical from the alkyl diacyl peroxide via a SET process, generating a Cu^{II} species. This alkyl radical adds to the alkene moiety of the 1,3-diene to give a propargyl radical, which is a resonance structure of the corresponding allenyl radical. The Cu^{II} species generated in the SET step can undergo transmetalation with $Ar-B(OH)_2$ to afford $Ar-Cu^{II}$ species that could combine with the allenyl radical leading to a Cu^{III} species from which the 1,4-difunctionalization product is generated by reductive elimination, along with the active Cu^{I} catalyst. An alternative outersphere mechanism was also considered by the authors where a radical homolytic substitution between the $Ar-Cu^{II}$ species and the allenyl radical would lead to the product while regenerating the Cu^{I} catalyst.

SUMMARY AND OUTLOOK

The catalytic functionalization of alkynes with organoboron reagents has experienced an explosive growth in the past decades, as a highly versatile means for the construction of multisubstituted olefins. This Review summarizes recent developments in the field through a discussion of the principal strategies from a mechanistic perspective. Although palladium catalysis has dominated this research area, more and more first-row transition metal catalysis is being incorporated into the field, and it will be a focus of future investigations, offering different mechanistic pathways and being complementary in scope and reactivity.

The impressive progress achieved has been mainly guided by the discovery of new reactivity modes or by achieving increased levels of structural complexity through cascade processes. However, the vast majority of reported protocols rely on the use of either symmetrical alkynes or electronically biased alkynes (e.g., alkyl aryl disubstituted alkynes or propyolate-type alkynes) to achieve site-selectivity. Unactivated unsymmetrical dialkyl alkynes have been scarcely investigated, and control over regioselectivity for this substrate class remains an important limitation that precludes the more general application of this chemistry. Although some methods based on removable directing groups have emerged in recent years that enable high regioselective hydroarylation, future research toward the development of complementary strategies and extending the range of transformations is imperative. In addition to regiocontrol, overcoming the inherent *syn*-selectivity of alkyne migratory insertion is a considerable challenge. A handful of strategies exploit an intramolecular trapping of the *anti*-alkenyl-metal intermediate, formed upon reversible *E*/*Z* isomerization of the *syn*-carbometalation species, either with a heteroatom-containing substituent or with an electrophile near the alkyne. Another innovative strategy to overcome this limitation was devised by merging, in a tandem fashion, an initial thermodynamically favored *syn*-selective Pd-catalyzed hydroarylation with a kinetically controlled Ir-photocatalyzed *syn* → *anti* photoisomerization. In addition to these substrate-controlled solutions, a catalyst-controlled approach has recently appeared that offers hope that new methods will likely emerge in the years to come.

In spite of the wealth of reactivity that has been established, another general restricting limitation that becomes apparent throughout the entire Review is that the use of organoboron reagents is mainly limited to (hetero)aryl derivatives, with isolated examples of alkenylboron cross-coupling. However, the use of alkylboron reagents remains conspicuously absent from this chemistry, which is possibly due to their slow rate of transmetalation, a problem innate to the two-electron nature of this process. Distinct modes for activation of the organometallic complexes through SET provide a viable solution to this hurdle, and this emerging strategy will notably expand the scope of the field.

Highly selective 1,2-difunctionalization of alkynes through tandem processes has also achieved significant accomplishments. In these transformations, the organoboron reagent can either initiate the cascade process as precursors of catalytically competent organometallic species that insert across the C≡C triple bond (Sections 2−5) or participate in the last step of the functionalization of the triple bond by trapping *in situ* generated alkenyl-metal intermediates (Sections 6−8). Despite these undisputed advances, several challenges and limitations

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remain to be addressed. For example, control of chemoselectivity is an issue of concern in these processes. While most of the reported reactions rely on intramolecular initiating or terminating steps, thus leading to cyclic products, moving toward fully intermolecular coupling reactions involving three or more components is a daunting task due to the increased number of possible competing side reactions. Intermolecular multicomponent reactivity and expanding the scope of the electrophilic species will also capture considerable attention in future research. On the other hand, although some efficient enantioselective variants have been developed, especially for the synthesis of chiral allenes, this area is still in its infancy, and considerable progress (including general access to the more challenging tetrasubstituted allenes and other atroposelective strategies) is expected in the next several years.

Functionalization of propargylic derivatives has experienced significant progress. However, most of the reported procedures give rise to the corresponding allenic systems or subsequent rearranged derivatives. In sharp contrast, propargylic substitution reactions have received much less attention. This latter reactivity should be expanded, driven by the synthetic versatility of the resulting propargylic alcohols.

Finally, the 1,2-difunctionalization of alkynes through radical addition has developed rapidly into a robust tool for the preparation of multifunctional tri- and tetrasubstituted alkenes. These reactions typically favor *anti*-addition, which is dominated by steric factors of vinyl radicals in the coupling step. Recent research has nicely extended to the more challenging internal alkynes the Pd^0-catalyzed three-component radical addition/coupling reaction with perfluoroalkyl iodides (R_F–I) and boronic acids. Current limitations associated with this substrate class that remain to be solved are the failure of alkenylboronic acid derivatives to take part in the reaction and the poor regiocontrol observed for unsymmetrical dialkyl-substituted alkynes. More sophisticated difunctionalization via four-component transformations involving CO as additional partner has also been designed, although their applicability to internal alkynes is yet to be demonstrated. The ability of nickel complexes with multidentate nitrogen ligands to generate alkyl radical species from nonactivated alkyl halides has also been elegantly exploited in the 1,2-difunctionalization of conjugated terminal alkynes, providing access to chemical space that is not feasible via Pd catalysis. The extension of this reactivity profile to the coupling with terminal alkyl-alkynes and internal alkynes is awaited. These SET-mediated processes have also been applied to the 1,4-dicarbofuncionalization of conjugated enynes, resulting in chiral allenes. The development of enantioselective versions of this reaction and the discovery of new reactivities, among other exciting developments, are expected in this rapidly evolving research area.

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