Palladium/Brønsted Acid Catalysis for Hydrofunctionalizations of Alkynes: From Tsuji-Trost Allylations to Stereoselective Methodologies

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(Article begins on next page)

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"Palladium/Brønsted Acid Catalysis for Tsuji-Trost Functionalizations with Alkynes"

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Please see the orginal article in its version of records at the following link:

Abstract: Alkynes are one of the most abundant feedstocks for chemical transformations. By merging palladium and Brønsted acid catalysts, they are converted into reactive allylmetal species, which become suitable for Tsuji-Trost functionalizations with complete atom-economy. This approach, which overcomes the limitations of traditional methods that suffer from the formation of over-stoichiometric amounts of by-products, has been disclosed for developing new C–C and C–Het bond forming methodologies. Within this review, we aim to survey the latest advancements in this area including applications in polymer chemistry, deuterium-labeling and stereoselective catalysis.

1. Introduction

The Tsuji-Trost reaction is one of the most powerful and exploited catalytic synthetic methodology in organic chemistry.[1] The ability of late-transition metals such as palladium, rhodium, and ruthenium to form electrophilic π-allyl species,[2] in the presence of substrates containing a leaving group at the allylic position, was exploited to develop a broad range of novel transformations. Despite considerable progress in this area of research, the most important limitation of this method relies on the formation of over-stoichiometric amounts of by-products, which impacts the atom-economy of the catalysis.[3] This issue is inherently linked to the use of allylic electrophiles as substrates. Following precedent studies conducted on stoichiometric transformations,[4] at the beginning of the nineties, the research group of Trost pioneered this field. These seminal works discovered the abilities of alkyne derivatives[5] to generate electrophilic π-allyl species with complete atom-economy.[6] Key to success was the combination of palladium catalyst and simple carboxylic acids. Despite the lack of strong experimental evidence, it is generally accepted that palladium(0) pre-catalysts could undergo oxidative addition by Brønsted acids to form hydrido-palladium(II) complexes.[7] However, a pathway involving a proton-transfer from the acid to a Pd(0)-alkyne complex appear to be likely at work under certain reaction conditions.[8] The in-situ formation of a palladium(II)-hydride enabled a sequence of elementary steps enclosed in two discrete catalytic cycles. In the first cycle, the catalytically active species **A** hydropalladates the alkyne forming a vinyl-palladium(II) intermediate **B**, which subsequently isomerizes to the corresponding allene **C** via a β-hydrogen elimination step. Then, allene **C** enters the second catalytic cycle delivering an electrophilic π-allylpalladium species **D** via a subsequent hydropalladation. Finally, the addition of a nucleophile to **D** forms the allylic product along with a palladium(0) species upon reductive elimination (Scheme 1).
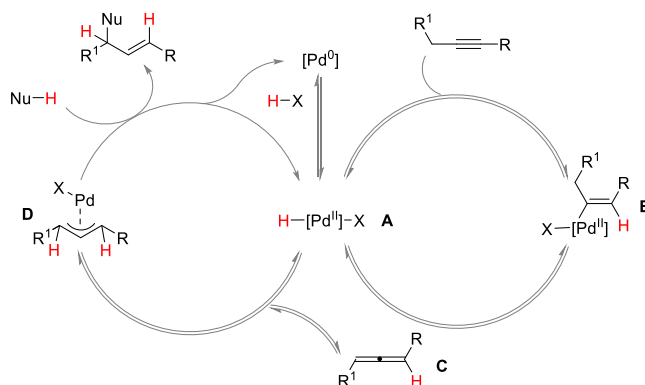
Scheme 1. General mechanism for Tsuji-Trost allylations with alkynes.

From an historical perspective, this approach has been widely investigated by the group of Yoshinori Yamamoto, which importantly contributed to this field.[9] As an example, by employing aryl propyne derivatives, several Tsuji-Trost allylations were reported using *C*-,[10] *O*-,[11] and *N*-centered nucleophiles (Scheme 2, a).[12]
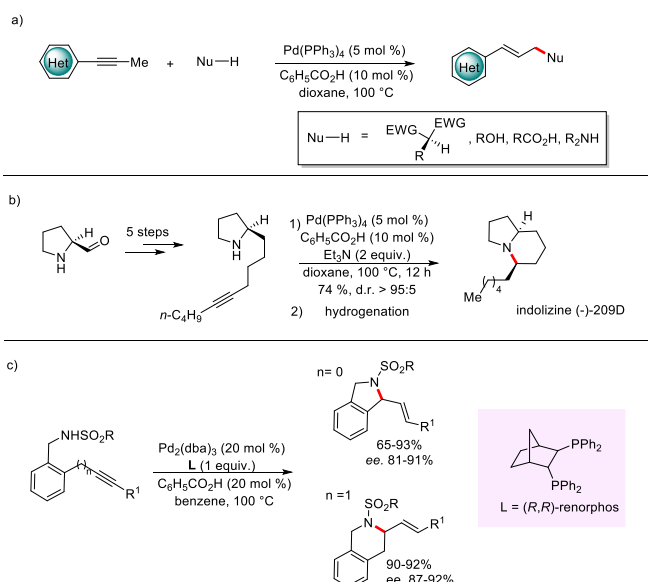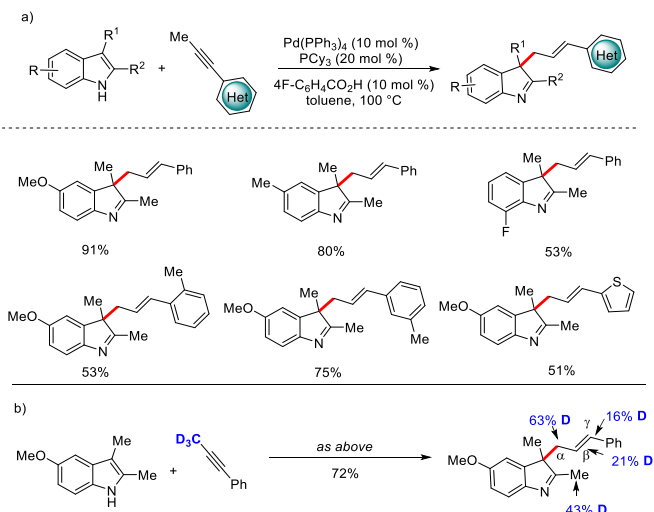
Scheme 2. Pd-catalyzed addition of nucleophiles to alkynes (a); Total synthesis of indolizine (-)-209D alkaloid (b); Enantioselective amine allylation with alkynes (c).

The synthetic utility of this approach was highlighted by applying the alkyne hydroamination methodology as the key step in the total synthesis of indolizidine alkaloid (-)-209D (Scheme 2, b).[13] Interestingly, a stereoselective variant of these transformations was also amenable in the presence of stoichiometric amounts of a chiral diphosphine ligand. Although high catalyst loadings were required, chiral palladium catalysts enabled the synthesis of a broad family of enantiomerically enriched heterocycles through intramolecular allylations of alkynes (Scheme 2, c).[14] Since these discoveries, many research groups started to investigate in this direction exploiting the reactivities of different transition metals in the presence of Brønsted acids and alkynes.[15] This approach, that could be utilized also by employing allene or 1,3-diene derivatives,[16] presents notable synthetic advantages since the synthesis of these unsaturated hydrocarbons is often substrate-dependent or not high-yielding.[17] In this scenario, the use of synthetically flexible palladium catalysts, still represents the most eligible choice, allowing for the discovery of a wide number of catalytic reactions. While several, competent reviews offer an account of this area of research, within this work we aim to show the emerging progress obtained by merging palladium complexes and Brønsted acids for catalytic functionalizations of alkynes. Furthermore, in a dedicated chapter, we will discuss the latest advancements in asymmetric transformations using alkynes and parental substrates such as 1,3-dienes and allenes.

2. C–C Bond Formations

2.1. Intermolecular C–C Bond Formations

As early as 2016, the group of Lin and Yao exploited the properties of electrophilic π-allyl-palladium(II) intermediates, generated from alkynes and in-situ formed hydropalladium(II) species for dearomative, allylic alkylations of indoles (Scheme 3, a).[18] A palladium-hydride catalyst obtained by the combination of Pd(PPh₃)₄ and user-friendly 4-F-benzoic acid, led to a platform of three-dimensional indolenines bearing a congested quaternary stereocenter with excellent atom- and step-economy. Mechanistic investigations were performed in the presence of a deuterated 1-phenyl-1-propyne derivative (Scheme 3, b).

The observed incorporation of deuterium at the γ-position of the product indicated that the insertion of the alkyne to the palladium-hydride catalyst and β-hydrogen elimination from intermediate **B** were reversible (see Scheme 1). Following these studies, Lin and co-workers attempted the dearomatization of β-naphtols by using a similar catalytic system and stoichiometric amounts of an inorganic base (Scheme 4, a).[19] Important mechanistic hints were obtained performing controlling experiments. A reaction conducted in the presence of phenyl allene led to the formation of the corresponding product in comparable yields under optimized conditions, suggesting that the allene is an intermediate of the catalytic process. On the other hand, the use of a phenylallyl acetate as the electrophile failed to deliver any product, probing a pathway involving two-fold palladium(II)-hydride insertions/β-hydrogen eliminations steps (Scheme 4, b).
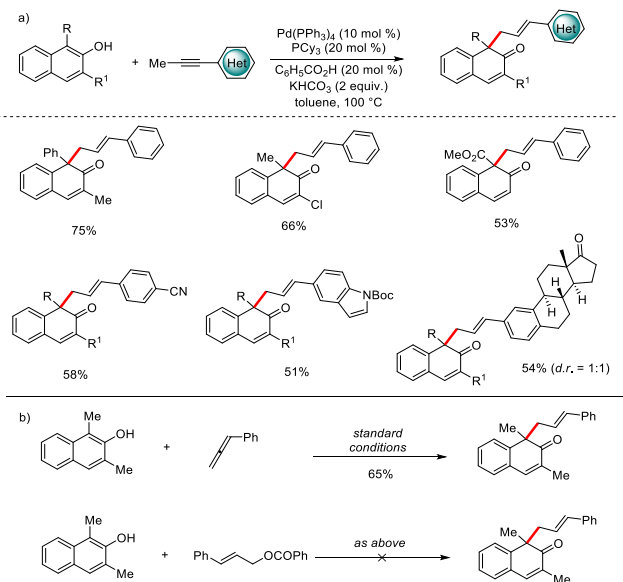

Scheme 4. Redox-neutral Pd(0)-catalyzed dearomatization of β-naphthols with alkynes (a); Mechanistic studies (b).

Prompted by these findings, the same group reported on a synthetic approach for the α-allylation of ketones using a cooperative catalytic system based on palladium(0) and L-proline catalysts.[20] The method, applicable for a broad range of substrates with high functional group tolerance, required a stronger Brønsted acid such as 4-toluensulphonic acid. Mechanistic investigations supported the formation of an enamine intermediate, resulting from the condensation of the ketone with L-proline, which is responsible of the nucleophilic attack on the electrophilic π-allylpalladium(II) species (Scheme 5).
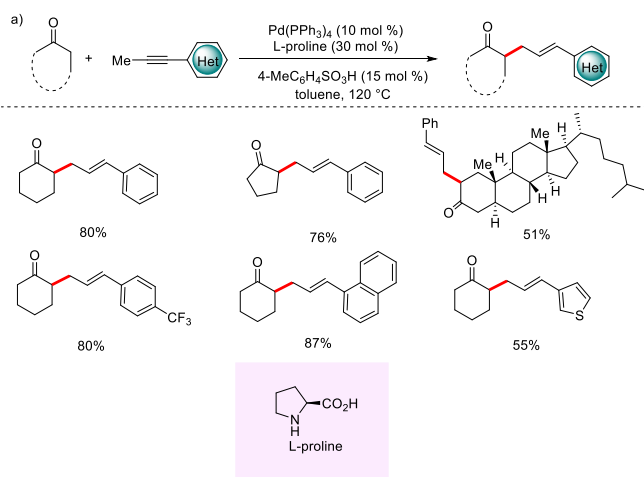
Scheme 5. Cooperative palladium/proline-catalyzed allylic alkylation of ketones with alkynes.

A general strategy for palladium-catalyzed allylic alkylations of *C*-centered nucleophiles was recently developed using *N*-heterocyclic carbene (NHC) ligands.[21] This method, that does not require the presence of commonly employed carboxylic acids as additives, was found amenable for the regioselective allylation of a broad family of pronucleophiles such as azalactones, oxindoles and α-cyanophosphonates (Scheme 6). The authors proposed the in-situ formation of a catalytically active hydridopalladium(II) species through ligand exchange of Pd(OAc)$_2$ with free IPr·HCl, in the presence of an inorganic base.
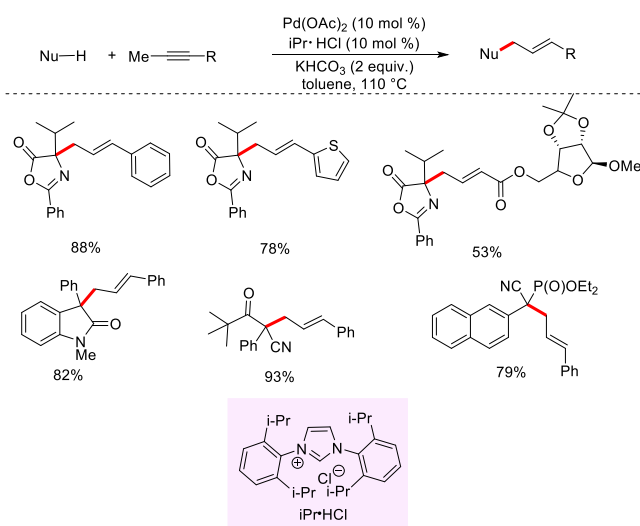
Scheme 6. Palladium−NHC-catalyzed allylic alkylation of nucleophiles with alkynes.

The robustness of this approach was further reflected by the development of a strategy for the palladium-catalyzed allylic alkylations using water as the most environmentally friendly and cost-effective solvent.[22] This strategy exploits "on-water" conditions,[23] in which insoluble substrates in aqueous phase, were vigorously stirred together. Using Cy-Johnphos as the ligand and benzoic acid as co-catalyst, a variety of *C*-centered nucleophiles such as indolinones and ketones were allylated in good yields and displaying an ample functional group tolerance. Importantly, the methodology was applicable to the selective modification of drug molecules such as edaravone, phenylbutazone and barbituric acid derivatives (Scheme 7).
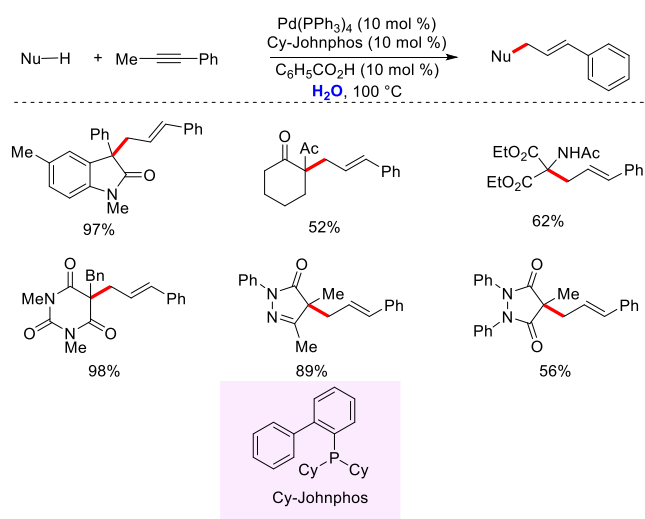
Scheme 7. Pd-catalyzed allylic alkylation of alkynes in H$_2$O.

The redox-neutral chemistry of alkynes, in the presence of palladium-hydride species, was explored by the group of Chen for the synthesis of 1,4- and 1,5- dienes, which are convenient architectures to trigger Cope-like rearrangements (Scheme 8).[24]
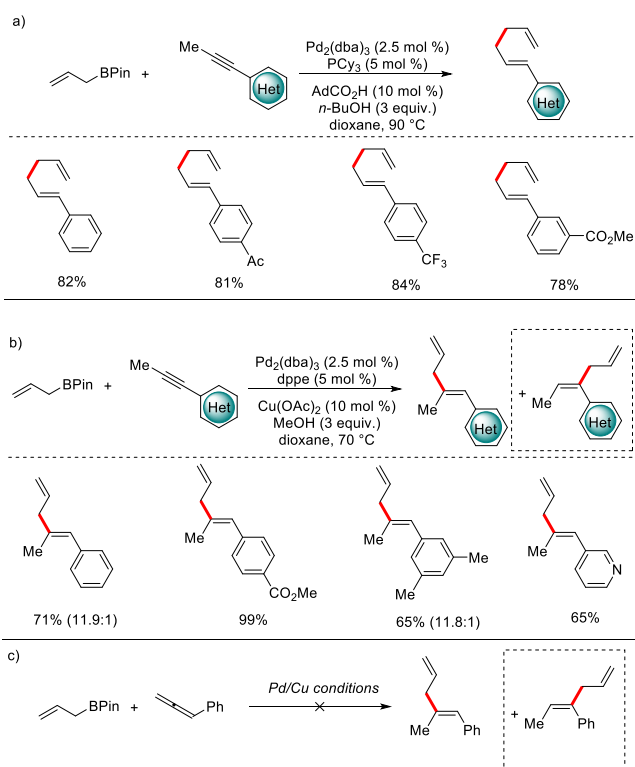
Scheme 8. Regioselective Pd-catalyzed hydroallylation of alkynes for the synthesis of 1,5-dienes (a) and 1,4-dienes (b).

A careful interplay of reaction conditions was necessary to control the regioselectivity of the process, using simple alkynes and allylboron reagents. Particularly, the use of a monophosphine ligand along with adamantyl carboxylic acid promoted a tandem isomerization of the alkyne to the corresponding allene intermediate. A subsequent allyl-allyl coupling lead to 1,5-dienes (Scheme 8, a), under the most typical reaction pathway (see Scheme 1). Contrarily, a biphosphine ligand such as diphenylphosphinoethane (dppe) hindered the β-H elimination step that forms the allene intermediate. The presence of Cu(OAc)$_2$ as an additive favored a vinyl-allyl coupling instead, thus providing 1,4-dienes by promoting a transmetallation with the allylboron reagent (Scheme 8, b). This mechanistic hypothesis was supported by a reaction performed using phenylallene as the reaction pattern that failed to deliver the expected product (Scheme 8, c).

Transition metals-catalyzed C–H activation methodologies represent one of the most employed tools to install allyl groups on (hetero)arenes.[25] These approaches often require the use of allyl electrophiles (i.e., acetates, halides, ethers among others). Recently, an atom-economical approach was reported by Minami and co-workers for the C–H allylation of arenes using 1-substituted aryl-propynes.[26] Here, the use of a carboxylic acid as co-catalyst, is crucial to promote both the formation of a reactive π-allylpalladium intermediate and the corresponding carboxylate, which is responsible of a concerted-metalation deprotonation (CMD) C–H activation step (Scheme 9).[27]
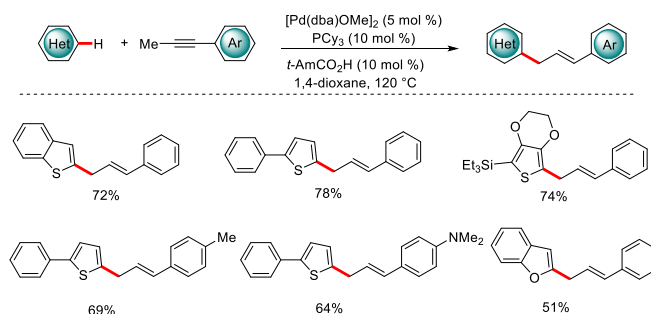
Scheme 9. Palladium/carboxylic acid-catalyzed C–H allylation of heteroarenes.

Polyfluoroarenes could be amenable to C–H functionalization as well. In the presence of SPhos as ligand and CsOPiv as base, the C–H allylation of a broad family of fluoroarenes was accomplished in high yields and good regioselectivity (Scheme 10, a).[28]
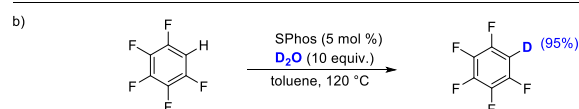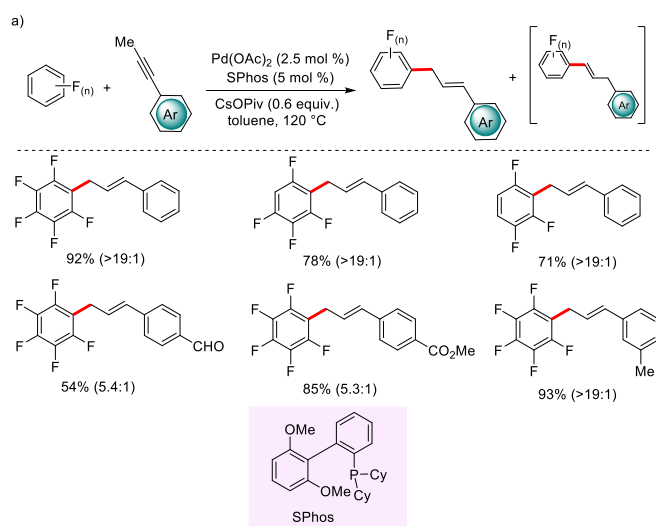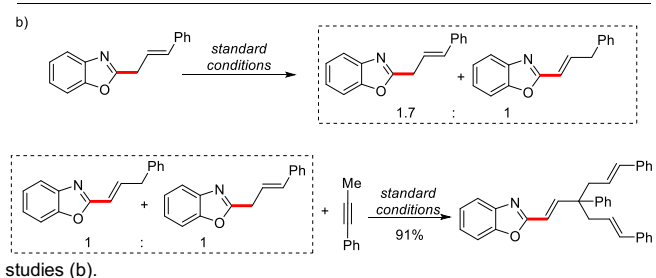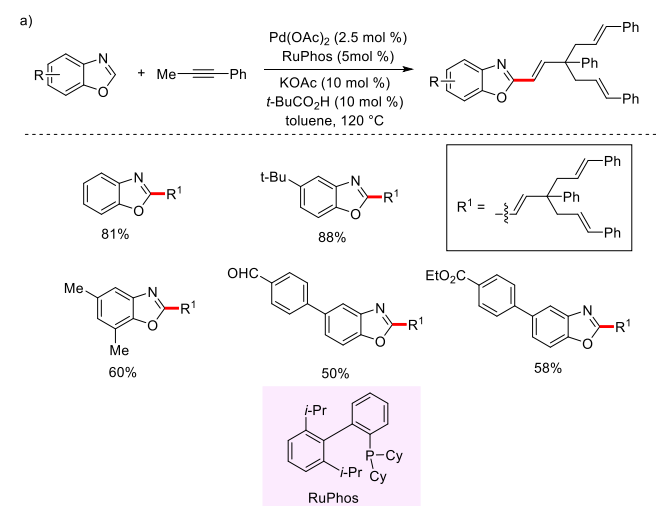
Scheme 10. Palladium-catalyzed C−H allylation of electron-deficient polyfluoroarenes with alkynes (a); H/D exchange experiment (b).

Mechanistic studies were conducted and, particularly, the H/D exchange reaction of pentafluorobenzene with 10 equiv of D_2O was studied (Scheme 10, b). High deuterium incorporation was observed in the absence of the palladium catalyst, indicating that the inorganic base is responsible of the C–H cleavage of the polyfluoroarene. This step produces pivalic acid as co-product, which led to the formation of the catalytically-active hydridopalladium(II) species.

The reactivity of palladium catalysts, in the presence of heteroarenes, was further explored developing a direct C–H trisallylation of azoles (Scheme 11, a).[29] This method led to pharmaceutical relevant, C2-alkenylated azoles containing an all-carbon quaternary center. Mechanistic studies revealed that allylated benzoxazole, formed by an initial C–H activation step, could isomerize under a palladium-catalyzed regime. Subsequently, when a mixture of mono-allylated intermediates was submitted to standard conditions, the tris-allylated compound was delivered in high yields with full conversion of the starting materials. These evidences suggested that the isomerization takes place prior to a two-fold C(sp^3)–H allylation process (Scheme 11, b).

Scheme 11. Palladium/acid-catalyzed C−H trisallylation of azoles (a); Mechanistic studies (b).

The use of alkynes as nucleophilic π-allyl precursors for Tsuji-Trost allylations, in the presence of palladium catalysts, is far less developed with respect to their common reactivity as electrophiles. In this context, an umpolung strategy was recently developed for the allylic alkylations of isatin derivatives.[30] Here, a crucial role is played by a metal reagent. Indeed, in the presence of Pd(PPh$_3$)$_4$ as

the catalyst and a stoichiometric amount of acetic acid, indium is able to play the role of both a reductant and a Lewis acid, enabling the synthesis of allylated oxindoles in good yields with a broad substrate scope (Scheme 12, a). Differently from the dearomatization of naphtols, here a model reaction performed with phenylallyl acetate led to the formation of the target product. This outcome supported a mechanism that might occur through the in-situ formation of allylic electrophiles intermediates (Scheme 12, b).
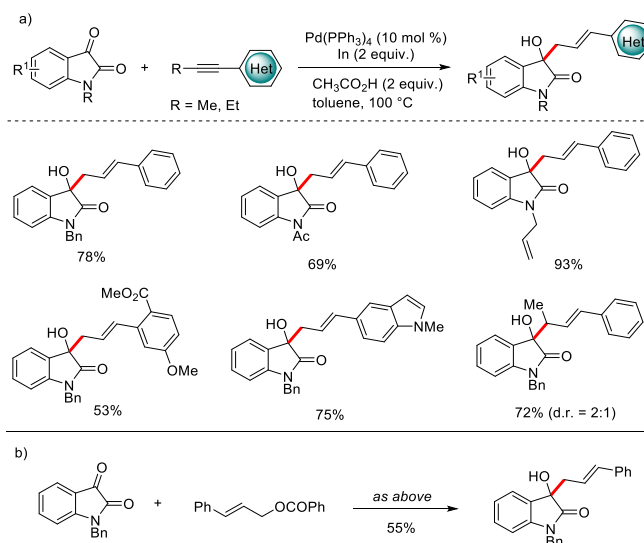
Scheme 12. Indium-mediated Pd-catalyzed allylic alkylation of Isatins with alkynes (a); Control experiment with phenylallyl acetate (b).

2.2. Intramolecular C–C Bond Formations

Intramolecular hydroarylations of alkynes are well-consolidated approaches to build heterocycles with high levels of atom economy.[31] In this context, *N*-unprotected propargylic tryptamine derivatives were exploited by Maestri and co-workers for the synthesis of tetrahydrocarbolines (THC) with complete regioselectivity and high functional group tolerance (Scheme 13, a).[32] Mechanistic studies and control experiments using an allenamide intermediate[33] (Scheme 13, b) supported a synergy between Pd(0) and benzoic acid catalysts which enabled a sequential isomerization of the alkyne to the corresponding allene derivative and a subsequent indole C–H activation.
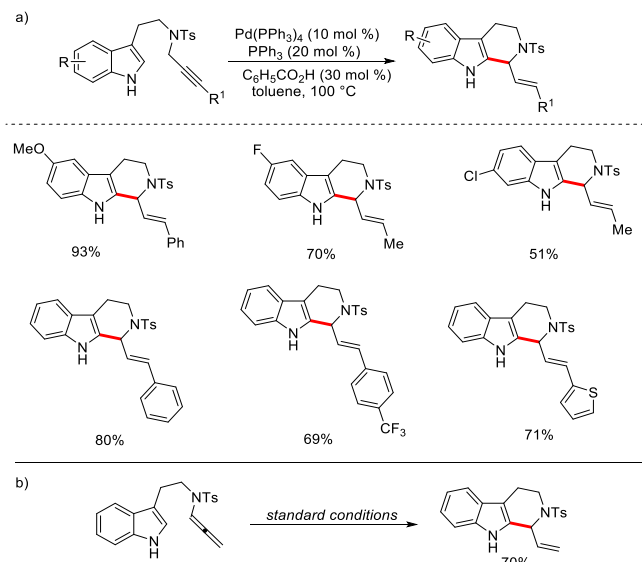
Scheme 13. Synthesis of carbolines via palladium/carboxylic acid joint catalysis (a); Control experiment with allenamide (b).

In analogy, intramolecular allylic alkylations of ketones were realized by Dong and co-workers.[34] The reaction allowed for the synthesis of both *endo*- and *exo*-bridged bicyclic cyclohexanones (Scheme 14, a). Indeed, by controlling the nature of the ligand and the acid additive employed as co-catalyst with palladium, both diastereoisomers could be obtained with good control (Scheme 14, b). Mechanistic probes were conducted through deuterium labeling experiments. Particularly, when deuterated substrates were submitted to the reaction conditions, deuterium incorporation was observed into the corresponding products to various degrees. This deuterium scrambling indicated the activation of the propargylic proton, invoking a reaction pathway involving alkyne/allene isomerization and Pd(II)-π-allyl complex formation (Scheme 14, c).

Scheme 14. Pd-catalyzed stereodivergent intramolecular α-allylic alkylation of ketones with alkynes (a,b); Deuterium-labelling experiments (c).

2.3. Isomerizations

Metal-catalyzed alkyne isomerizations offer a valuable synthetic methodology to deliver 1,3-dienes with good stereoselectivities and complete atom-economy. The strategy thus represents an important alternative tool to the more established cross-coupling reactions.[35] Noteworthy, one of the earliest examples of catalytic isomerization of alkynes was realized combining palladium(0) species and carboxylic acids in the presence of acyl-alkynes, or related substrates with strong electron-withdrawing (EWG) groups.[36] A recent application of this concept could be found in the total synthesis of [^{15}N$_5$]-Cylindrospermopsin, a toxic alkaloid produced by cyanobacterial algal blooms.[37] Indeed, the synthesis of the key intermediate was realized by a palladium/benzoic acid mediated isomerization of an arylalkyne (Scheme 15).
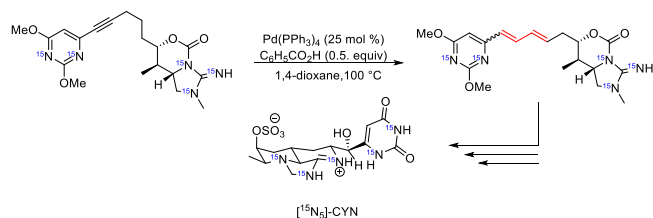
Scheme 15. Synthesis of key intermediate in the total synthesis of [^{15}N$_5$]-Cylindrospermopsin via palladium/benzoic acid mediated isomerization of alkynes.

A considerable advance in this area was recently reported by Maestri and co-workers using propargylamide derivatives.[38] Hence, in-situ formed palladium(II)-hydride species enabled a sequential bidirectional isomerization involving the α-C(sp^3) of alkynyl fragments to form 1,3-dienes and 1,3-trienes with good regiocontrol (Scheme 16, a). Mechanistically, the model 1,3-diene substrate could be obtained by submitting the allenamide to the optimized conditions, probing the former as an intermediate in the catalytic cycle (Scheme 16, b).
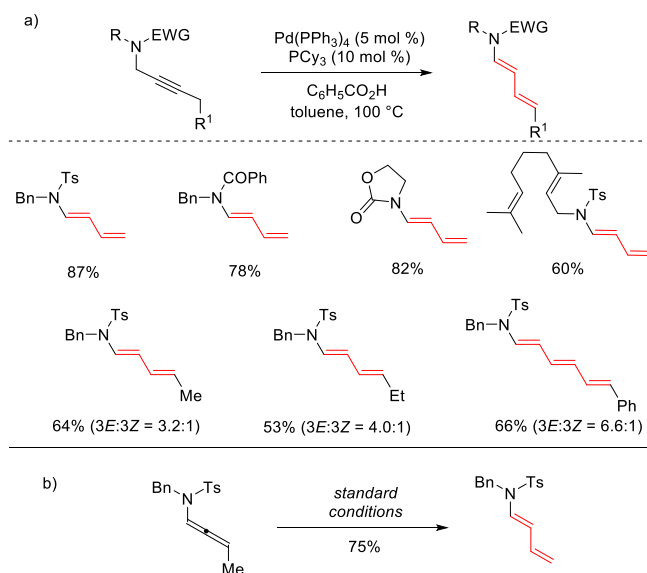
Scheme 16. Bi-directional alkyne isomerization via Pd(0)/carboxylic acid catalysis: expedient access to 1,3-dienes (a); Control experiment with allenamide intermediate (b).

3. C–Het Bond Formations

The use of *N*- and *O*-centered nucleophiles for palladium-catalyzed allylic alkylations using alkynes is well established. In this context, recent investigations focused on synthetic modifications of natural occurring heterocycles. These molecules present different Lewis basic functionalities and hence, many possible reaction sites. Therefore, the chemoselective functionalization of these entities results highly challenging. Recently, Gao and co-workers reported on the use of palladium(II)-hydride catalyst for *N*-allylation of tautomerizable heterocycles with alkynes.[39] This simple protocol allowed for the chemoselective synthesis of differently substituted quinazolinones, pyrimidines, pyridines and benzoxazolines with good yields and complete atom economy (Scheme 17).
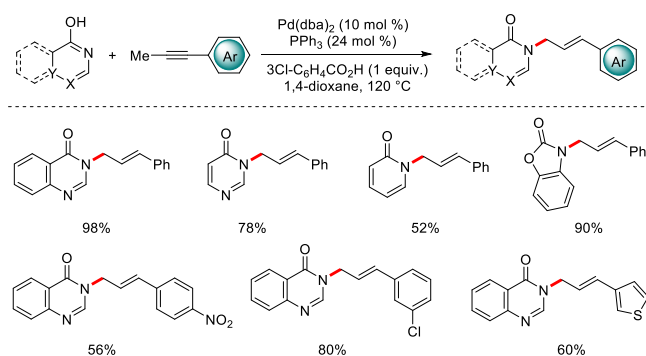
Scheme 17. Pd-catalyzed allylation of tautomerizable heterocycles with alkynes.

Under the same catalytic system, *N*-allylation of aminophenols was subsequently reported by the same group.[40] This represents a nice example of chemoselectivity in palladium-catalyzed allylation methodologies since both phenols and anilines were reported as suitable reactive nucleophilic patterns for *O*- and *N*- allylations. This approach afforded *E*-selective, *N*-allylic products with complete chemoselectivity in the presence of *meta*-, *ortho*- and *para*-aminophenols (Scheme 18, a). Interestingly, terminal alkynes could be employed as well, delivering the target product in moderate yields (Scheme 18, b). In fact, these substrates are less prone to undergo isomerization to the corresponding allenes as a consequence of their propensity to form σ-alkynyl-palladium(II) transient species.[41]
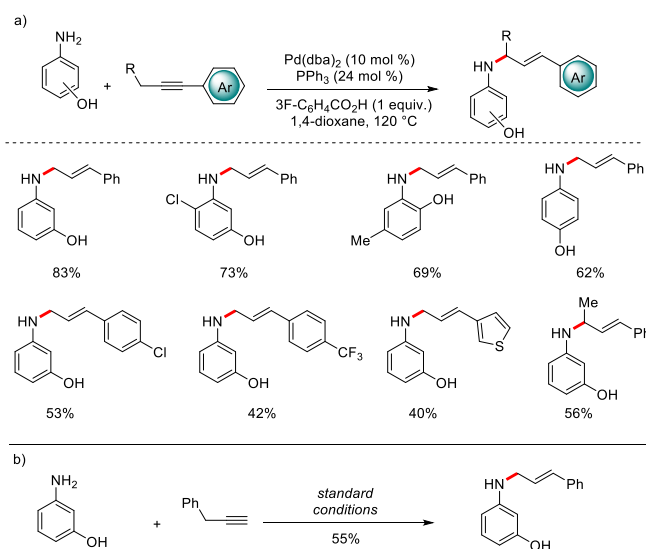
Scheme 18. Pd-catalyzed allylation of tautomerizable heterocycles with alkynes.

Sulfur-containing building blocks represent a key structural motif in medicinal chemistry and material science.[42] However, metal-catalyzed C–S bond forming reactions are often challenging to be realized due to not trivial catalyst poisonings.[43] As in example, Lu and co-workers developed a palladium-catalyzed Tsuji-Trost allylation using sulfonyl hydrazides as precursors of sulfinic anions (Scheme 19).[44] The use of *meta*-clorobenzoic acid as a stoichiometric additive led to the synthesis of a broad family of allylic sulfones with linear regioselectivity, producing H_2 and N_2 as the sole by-products.
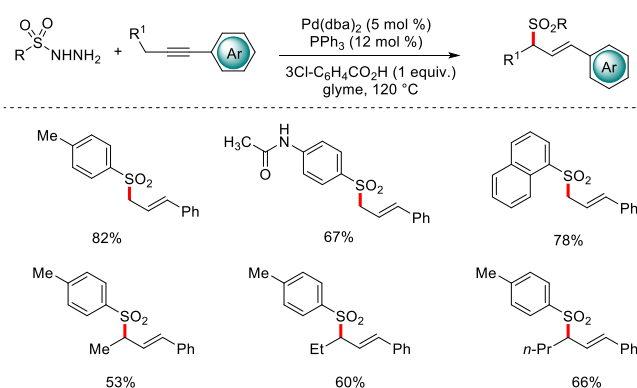
Scheme 19. Synthesis of allyl sulfones via Pd-catalyzed hydrofunctionalization of alkynes.

The peculiar reactivity of alkynoic acids and secondary amides enabled unprecedented intramolecular cascade cyclizations, providing a wide range of six-membered heterocycles functionalized with a quaternary allylic stereocenter.[45] This type of transformations were

achieved using a simple palladium(0) precursor and a properly chosen Buchwald-type ligand (Scheme 20, a). Mechanistic information was provided using deuterium labeling experiments. Particularly, submitting a model substrate under the optimal reaction conditions, high deuterium incorporation was observed at the terminal vinylic carbon. This, along with further studies, led the authors to propose the formation of an allenyl-palladium(II) carboxylate as the key intermediate of the cascade reaction (Scheme 20, b).

a)

Y = OH, L = t-BuXPhos

82%   88%   47%

Y = NHPh, L= JohnPhos

77%   97%   55%

t-BuXPhos   Johnphos

b)
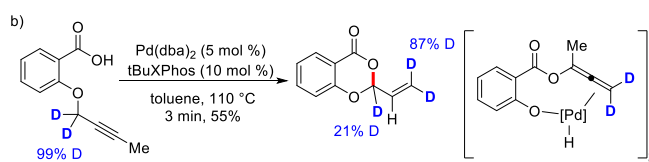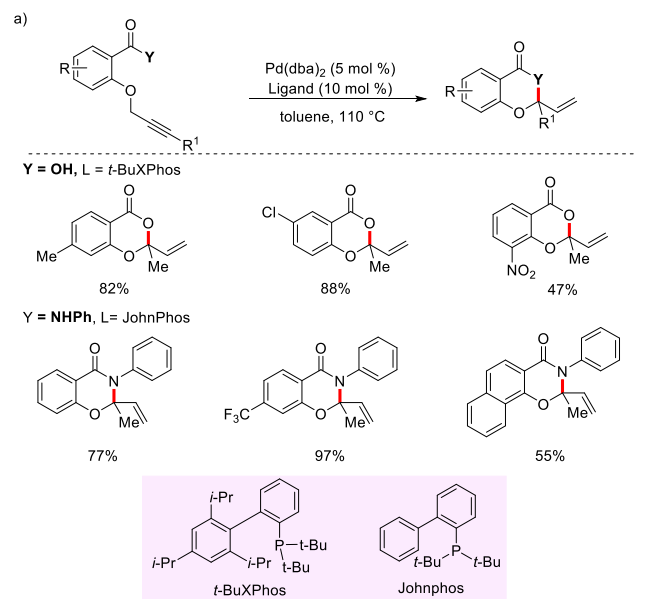
Scheme 20. Palladium-catalyzed cyclization of alkynoic acids and amides (a); Deuterium-labelling experiments (b).

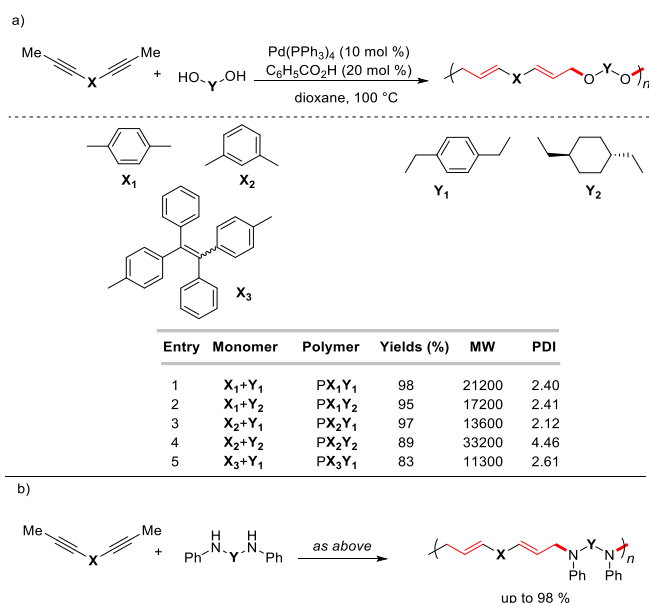Interestingly, the use of palladium(II)-hydride catalysts in the presence of internal diynes was exploited in polymer chemistry, too. Hence, the use of *O*-nucleophiles such as diols led to the synthesis of regio- and stereo- regular functional poly(allylic ethers) with high average molecular weights (MW up to 33200).[46] The synthesis of these polymers proceeded with high yields and complete *E*-selectivity. Noteworthy, the materials obtained by this process possess excellent film-forming ability and showed high refractive indices which could prompt their applications as 2D fluorescent photo-patterns (Scheme 21, a). This approach was recently extended using a diphenyldiamine derivative as nucleophilic pattern for the synthesis of poly(allylictertiaryamines) under a palladium/carboxylic acid catalysis regime (Scheme 21, b).[47] The synthesis of these material proceeded in high yields, molecular weights (MW up to 25600) and with complete atom-economy.

a)

Entry	Monomer	Polymer	Yields (%)	MW	PDI
1	X_1+Y_1	PX_1Y_1	98	21200	2.40
2	X_1+Y_2	PX_1Y_2	95	17200	2.41
3	X_2+Y_1	PX_2Y_1	97	13600	2.12
4	X_2+Y_2	PX_2Y_2	89	33200	4.46
5	X_3+Y_1	PX_3Y_1	83	11300	2.61

b)

up to 98 %

Scheme 21. Pd/benzoic acid-catalyzed regio- and stereoselective polymerization of internal diynes and diols.

4. Other Alkyne Derivatives

1,3-Dienes represents a key structural motif in synthetic organic chemistry since their main core is present in many biologically relevant molecules. Furthermore, they are commonly employed to design novel catalytic transformations to even more complex targets. For these reasons, strategies for their synthesis are always on high demand. Recently, the reactivity of alkyne derivatives such as skipped enynes and cyclopropylacetylenes, under palladium/carboxylic acid catalysis, has been exploited for the synthesis of highly decorated 1,3-dienes. Mechanistically, transformations involving skipped enynes[48] could occur through two distinct catalytic cycles. In the first one, a sequence of hydropalladium insertions and β-H eliminations lead to a vinyl-allene intermediate of type **F**. The latter could enter the second catalytic cycle, forming a π-allylpalladium intermediate of type **G** after subsequent hydropalladation. Hence, the presence of an allyl substituent in the alkyne derivative, allows a π-σ-π isomerization to form kinetically favored allylmetal species **H**.[49] This intermediate could finally react with an external nucleophile, leading to the target 1,3-diene product (Scheme 22).
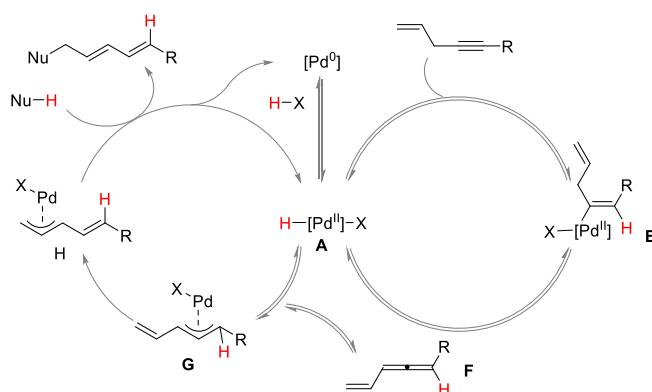
Scheme 22. Plausible mechanism for allylation with skipped enynes.

Thus, skipped enynes were employed for palladium-catalyzed allylations using *C*-, *N*- and *O*-centered pro-nucleophiles. The transformation proceeded under the most classical conditions using Pd(PPh$_3$)$_4$ and benzoic acid as the catalysts and diversely decorated dienes were synthesized in high yields and regioselectivities (Scheme 23).[50]
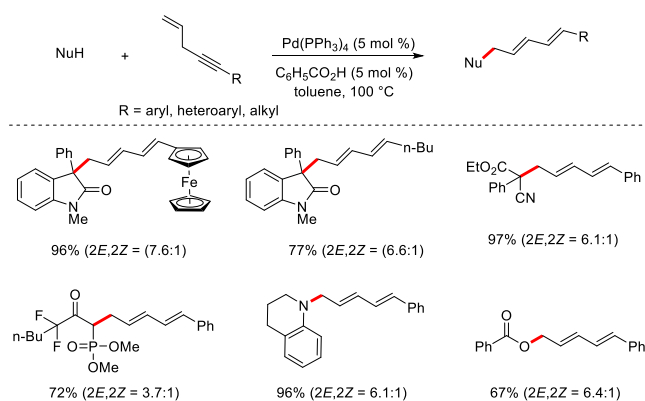
Scheme 23. Palladium-catalyzed allylic alkylation of pronucleophiles with skipped enynes.

This family of substrates was subsequently employed to devise a novel methodology for the catalytic dearomatization of indoles.[51] Remarkably, this transformation occurred without the need of pre-installed leaving groups or the presence of external extra oxidants. A typical catalytic system based on palladium(0) precursor, pivalic acid and a monophosphine ligand, led to the synthesis of a broad family of 1,3-dienes with good *E/Z* selectivity and yields (Scheme 24). A reaction performed in the presence of an eneallene substrate delivered the dearomatized heterocycle in good yields (Scheme 24, b), providing mechanistic information on the nature of the intermediate formed in the catalytic cycle (see Scheme 22).
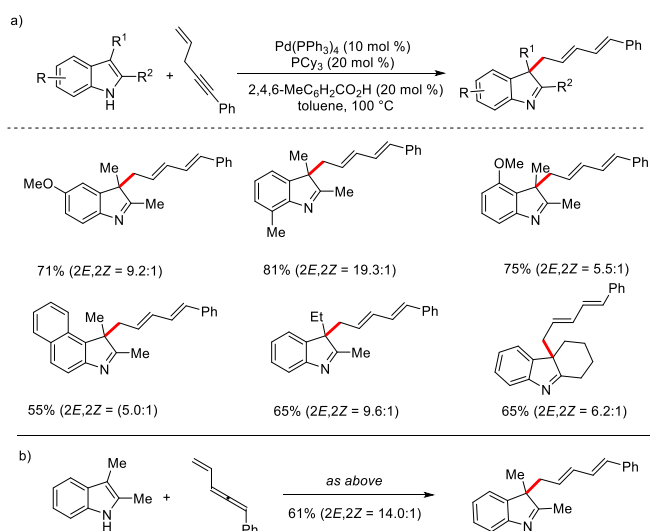
Scheme 24. Indole dearomatizations with skypped enynes.

Skipped enynes could be also employed for *N*-allylation reactions.[51] Indeed, the same authors demonstrated that, by changing the nature of the Brønsted acid catalyst, it was possible to switch the selectivity of the transformation. The use of a less coordinating phosphate anion, along with a sterically encumbered phosphine ligand, led to a family of *N*-functionalized 1,3-dienes with high chemoselectivity (*N/C* > 20:1) and functional group tolerance (Scheme 25).
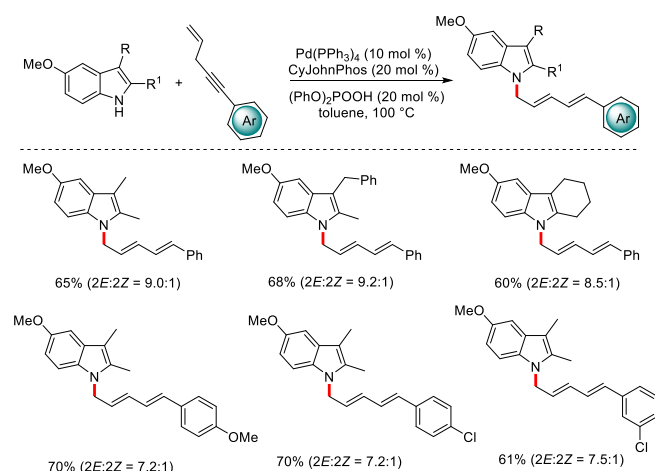
Scheme 25. Regioselective Pd-catalyzed *N*-allylation of indoles with skipped enynes.

The use of ring strain is of particular interest in synthetic organic chemistry since its inherent properties could be employed to design complex structures.[52] Thus, cyclopropylacetylenes could offer many opportunities. Hence, the reactivity of this class of compounds has been recently investigated for the synthesis of 1,3-dienes using palladium catalysis. The rationale behind this approach relies on the formation of vinyl palladium(II) intermediates of type **I** that easily undergo the cleavage of the C–C bond of the strained ring to form alkyl-palladium(II) species **J**. This intermediate produces via β-H elimination a key vinyl-allene species **F** that could enter a second catalytic cycle as previously illustrated for skypped enynes (Scheme 26).
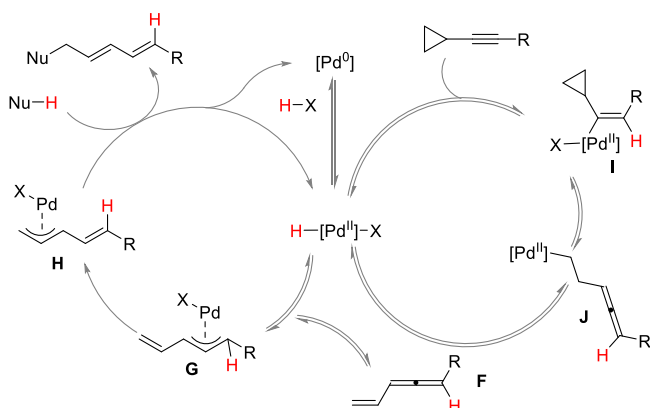
Scheme 26. Plausible mechanism for allylation with cyclopropylacetylenes.

With these premises, the group of Lu explored the reactivity of cyclopropylacetylenes to functionalize the naturally occurring oxindole scaffold. In the presence of commercially available *meta*-chlorobenzoic acid, a family of 1,3-diene oxindole intermediates, bearing a quaternary stereocenter at the C3 position, were synthesized with good yields and high regioselectivities (Scheme 27, a).[53] Preliminary results supported the feasibility of an enantioselective protocol, too. In fact, using a chiral biphosphine ligand, the oxindole product could be isolated with promising enantiomeric excess (Scheme 27, b)
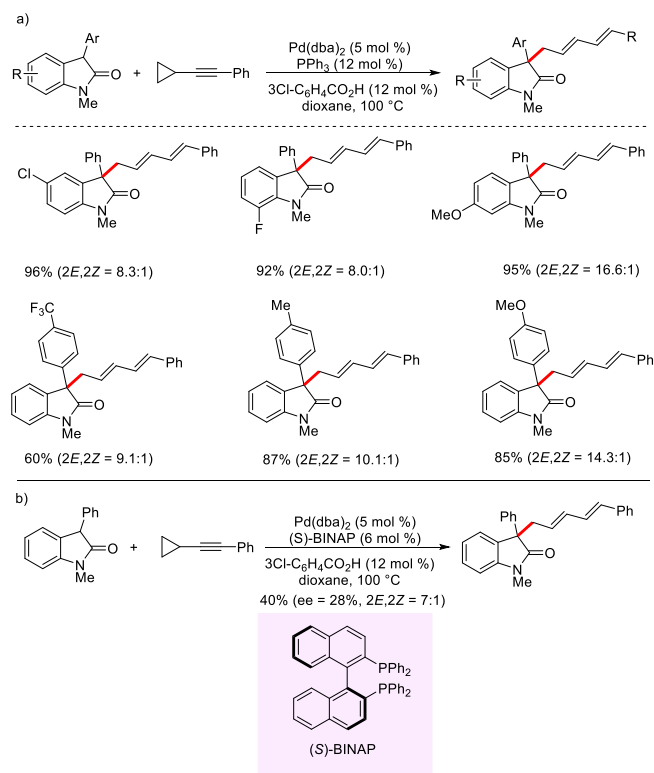
Scheme 27. Palladium-catalyzed allylation of cyclopropyl acetylenes to construct 1,3-dienes.

The attractiveness of the methodology was further explored by the same group reporting allylic dearomatizations of indoles (Scheme 28, a). Under the same catalytic protocol, 1,3-diene indolenine frameworks could be obtained in good yields and regioselectivity through a cascade strategy involving sequential C–C bond activation/allylic alkylation.[54] Under slight modified conditions that required the use of an inorganic base, the dearomatization of β-naphtols could be achieved as well (Scheme 28, b).
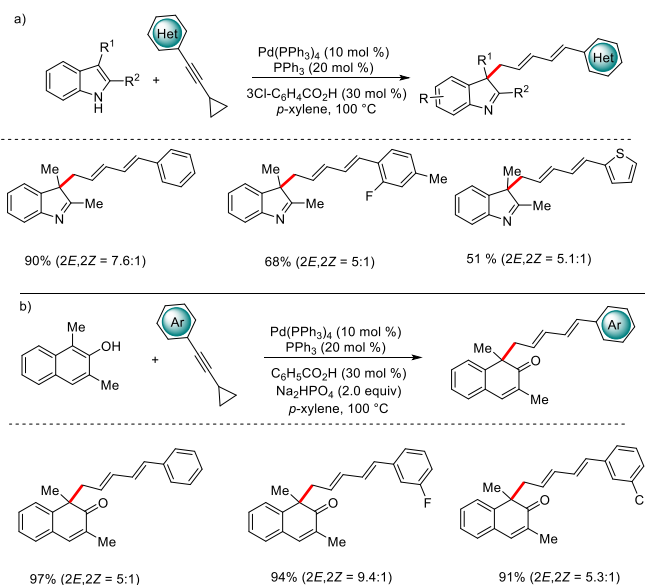
Scheme 28. Palladium-catalyzed dearomatizations of indoles with cyclopropylacetylenes (a); Dearomatizations of naphtols (b).

5. Deuterium-labeling

Recently, deuterium incorporation methodologies are playing an important role in modern synthetic chemistry. In fact, C–D bonds are considered as non-radioactive, bio-isosteric, iso-electronic replacement for ubiquitous C–H bonds in organic molecules.[55] For these reasons, a plethora of catalytic methodologies have been reported for H/D scrambling. In this context, strategies for the synthesis of deuterated olefins are particularly attractive due to their abundance in nature and their use as substrates for further transformations. However, most of deuterium labeling of olefins occur using costly metals such as rhodium, iridium, and ruthenium or employing hazardous deuterium sources such as deuterated solvents or D$_2$.[56] The reactivity of palladium catalysts in combination with carboxylic acids might represent a viable alternative since it allows transformations using water as the solvent. Particularly, a sequence of insertions and β-H-eliminations could be exploited to install deuterium on olefinic C–H bonds.
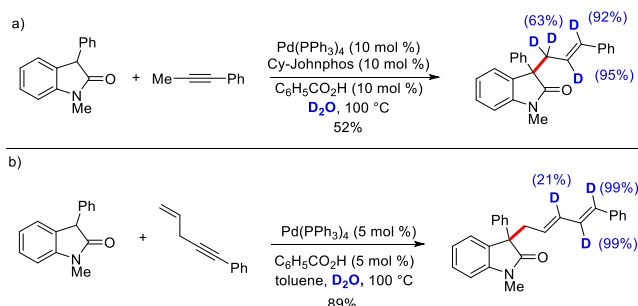
Scheme 29. Palladium/benzoic acid catalysis for the synthesis of deuterated olefines.

A proof of concept was already demonstrated by Lin, Yao, and co-workers in recent contributions.[22,50] Using a typical catalytic system, they succeed to label up to two C(sp^2)–H bonds with deuterium, using alkynes and enynes as substrates and D$_2$O as the safest reagent (Scheme 29). Prompted by these findings, Maestri and co-workers reported a protocol based on palladium and benzoic acid catalysis to convert simple alkynes in to highly polydeuterated olefins.[57] The methodology was applied for the synthesis of diversely decorated d-1,3-dienes (Scheme 30, a) and exploited to access bioactive, deuterium-enriched, amminonaphto- and anthra- quinones (Scheme 30, b) under thermal Diels-Alder conditions. Using a modified catalytic system, in the presence of additional triphenylphosphine as the ligand, d-THC could be synthesized as well in good yields and deuterium incorporation (Scheme 30, c). Mechanistic studies provided evidence of in situ formation of a Pd(II)–D catalyst that enabled a concerted sequence of productive elementary steps (insertion, β-hydrogen elimination) that finally led to the corresponding polydeuterated compound. Remarkably, the chemoselectivity observed (1,3-diene vs THCs) was mainly ascribed to the nature of the N-substitution pattern [alkyl vs tryptamine] of the alkyne fragment.
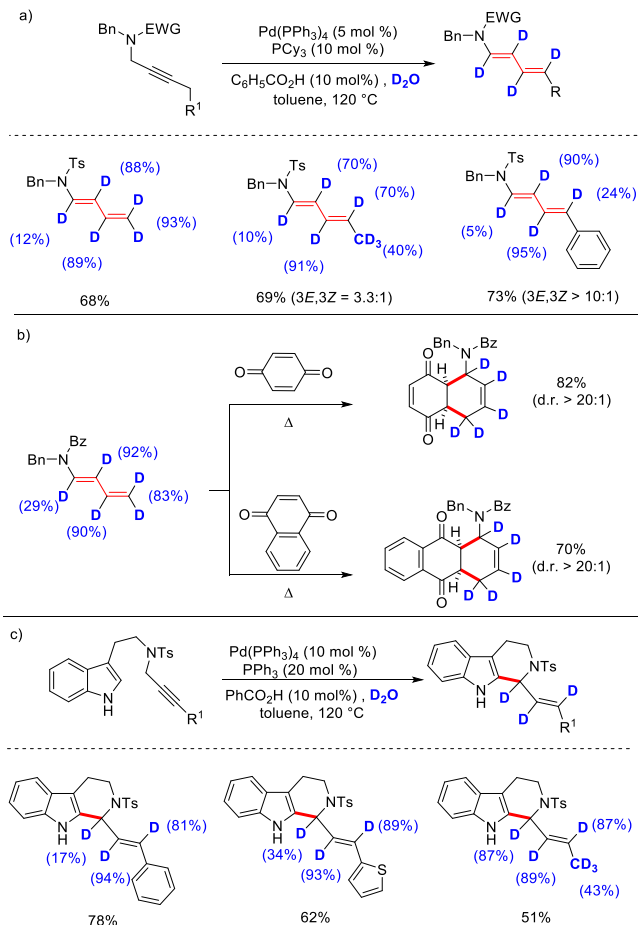
Scheme 30. Palladium/benzoic acid catalysis for isomerization/polydeuteration of alkynes.

6. Asymmetric Transformations

Asymmetric functionalizations of carbonyl compounds at the α- position[58] represent one of the most important transformation in organic synthesis. In this context, cooperative catalysis[59] has been largely exploited for asymmetric α-alkylation of aldehyde derivatives. Parallelly, the functionalization of ketones is more challenging and only recently new concepts such as SOMO catalysis[60] or photo-organocatalysis[61] have been applied to solve these issues. Generally, α-allylation of carbonyls has been often achieved using allylic electrophiles. Thus, the use of alkynes as electrophilic π-allyl-metal precursors, under a palladium catalysis regime, represents a higher atom-economical approach to develop enantioselective allylation protocols. Following precedent studies,[20a] the group of Zhao recently reported the first example of asymmetric α-alkylation of ketones using alkynes. This goal was achieved by combining enamine catalysis with a chiral biphosphine hydropalladium(II) species, formed by a reversible oxidative addition of palladium(0) to *para*-toluensulfonic acid. This ternary catalytic system led to the corresponding allylated ketones with good enantioselectivities (Scheme 31).[62]
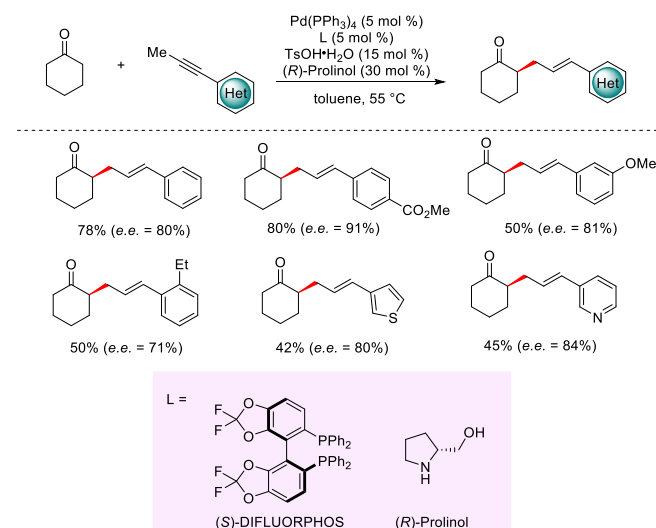
Scheme 31. Enantioselective, palladium-catalyzed α-allylation of ketones with alkynes.

Skypped enynes could be employed as well.[63] Here, the stereoselection was totally in charge of an atropoisomerically chiral phosphoric acid which in-situ generates a chiral π-allylpalladium(II) phosphate that undergoes nucleophilic addition by the enamine.[59] This asymmetric counteranion-directed catalytic protocol enabled the conversion of a wide range of alkynes and enolizable aldehydes into a diverse spectrum of chiral α-quaternary aldehydes in high yields and enantioselectivities (Scheme 32).
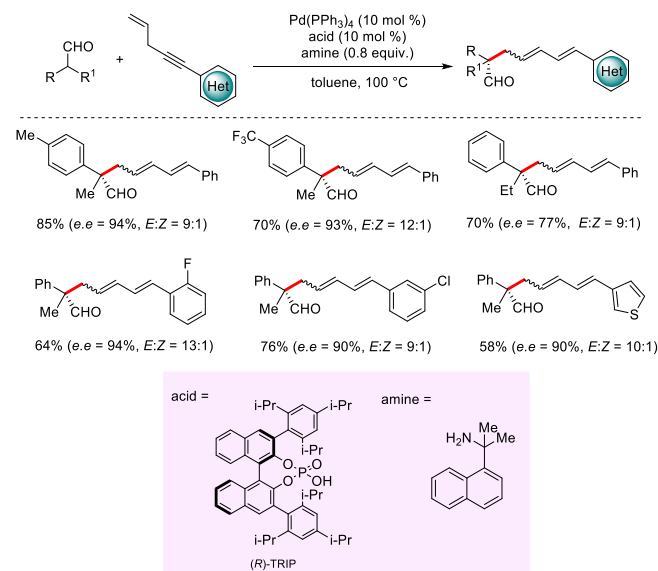
Scheme 32. Enantioselective, palladium-catalyzed α-allylation of aldehydes with skypped enynes.

Finally, by employing readily available cyclopropylacetylenes, an asymmetric regioselective α-pentadienylation reaction of aldehydes was recently developed.[64] The catalytic system consisted of a chiral bidentate phosphine ligand, along with a chiral Brønsted acid in the presence of a palladium(0) precursor.[59] As for the previously discussed examples, the use of an achiral amine was nonetheless sufficient to achieve high levels of steroinduction. α-Pentadienylated aldehydes were afforded with high yields and enantioselectivities as well as excellent *E*/*Z* ratios (Scheme 33).
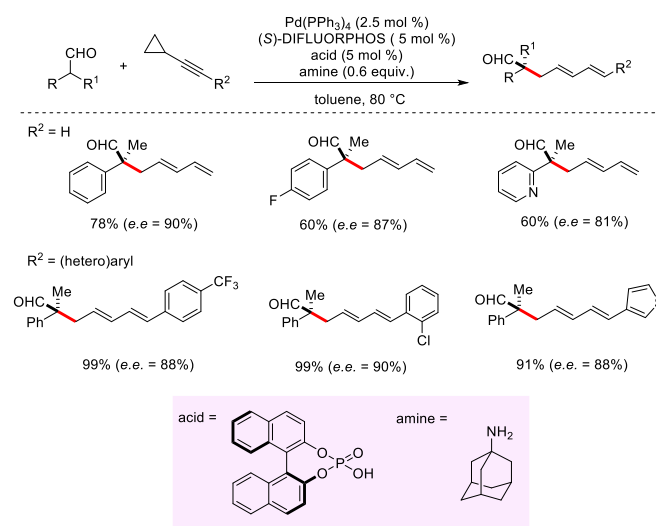
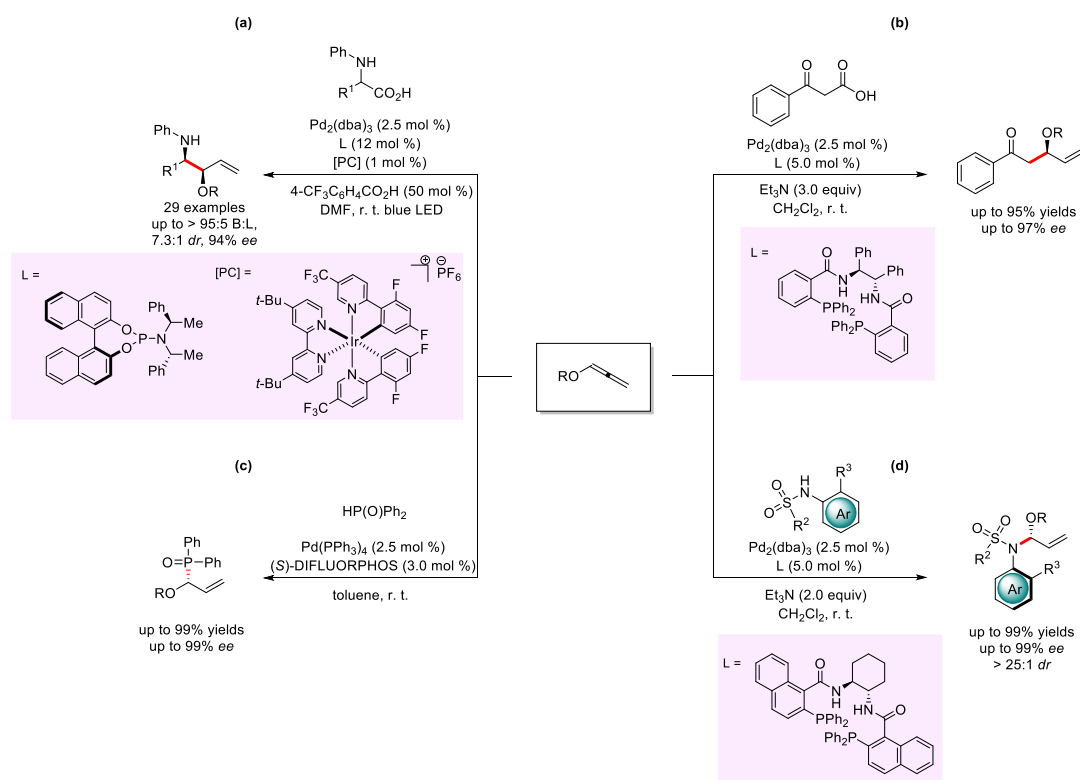**Scheme 33.** Enantioselective, palladium-catalyzed α-allylation of ketones with cyclopropylacetylenes.

These asymmetric methodologies represent the only examples present in literature since 2008[14a] that involve the use of alkynes as versatile substrates able to undergo isomerization/allylation sequences. However, other unsaturated hydrocarbons such as 1,3-dienes and allenes proved to be feasible patterns for stereoselective Tsuji-Trost functionalizations under the palladium/Brønsted acid catalytic regime. Since recent, authoritative reviews cover these methodological aspects,[16] we found interesting to present here the very recent advancements using these unsaturated analogues.

Hence, 1,3-dienes are prone to undergo insertion of metal-hydride species forming electrophilic π-allylmetal species which can undergo attack by an external nucleophile, generating a chiral compound. Since preliminary discoveries that reported only modest enantiomeric excess,[64] much progress has been achieved in recent times.[65] As in example, novel C–C bond forming reactions involve the use of a synergistic palladium/amine catalytic system for the α-allylation of enolizable aldehydes.[66] The presence of a Brønsted acid such as Et₃N·HBF₄ and a phosphoramidate ligand was mandatory to form a chiral allyl-palladium(II) intermediate that could be trapped by an asymmetric enamine nucleophile. Interestingly, by the choice of an appropiate combination of the catalysts, both *syn* and *anti* stereoisomers could be obtained (Scheme 34, a). Similarly, azalactones could be exploited as suitable nucleophiles, as well. Here, the best reaction conditions were achieved using an oxazoline-based P,N-chiral ligand (Scheme 34, b).[67] Important contributions have been reported also involving the formation of chiral allylic sulfones. In this context, the use of sulfonyl hydrazides as nucleophiles required the presence of substoichimetric amounts of *para*-tolunesulfonic acid to promote the formation of the palladium-hydride active species (Scheme 34, c).[68] Mechanistic information supported the formation of a key allyl hydrazide intermediate that subsequently evolve into the chiral sulfone by the assistance of the palladium catalyst. In a complementary manner, sulfinic acid could be exploited as well to enable the same reactivity using an atropoisomeric bidentate phosphine ligand (Scheme 34, d).[69] Importantly, computational experiments revealed that the reaction is initiated by a direct transfer of a hydrogen atom from the sulfinic acid to the 1,3-diene. This occurs *via* a ligand-to-ligand hydrogen transfer (LLHT) process[70] rather than a more usual palladium-hydride intermediate.
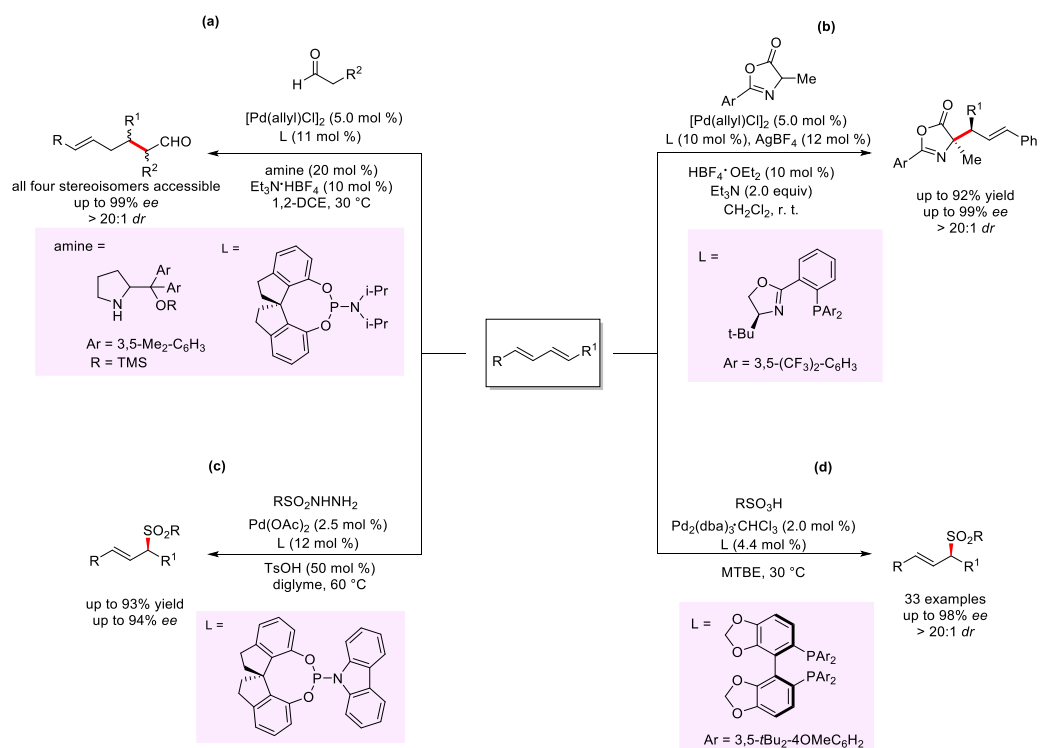
Scheme 34. Enantioselective, palladium/Brønsted acid-catalyzed, Tsuji-Trost functionalizations using 1,3-dienes.

As depicted in Scheme 1, allenes could be directly delivered, from the corresponding alkynes, by a one-fold metal-hydride insertion/β-hydrogen elimination. This observation and pioneristic contributions by Trost and co-workers,[71] prompted their use in asymmetric palladium/Brønsted acid catalysis.[16] Recently, novel approaches for the stereoselective synthesis of C–C and C–Het bonds have been developed using inherently more reactive alkoxyl-substituted allenes. In example, a dual palladium/photoredox strategy, enabled regio- and enantioselective decarboxylative hydroaminomethylation of allenes (Scheme 35, a).[72] A broad family of vinyl 1,2-aminoethers was delivered with good branched to linear selectivity and high enantiomeric excess. Within this work, the authors proposed a mechanism that involve the formation of a chiral allyl-palladium(II) species that subsequently undergoes a slow decarboxylation via a reductive quenching process of the blue-light-excited Ir(III)* complex. This step, that proceeded through a single-electron transfer (SET) process,[73] generates an aminoalkyl radical that rebounds with the allyl-palladium(II) intermediate, forming a palladium(III) species. Final reductive elimination to palladium(I) and regeneration of Pd(0) via reduction of Pd(I) by the Ir(II) complex, close the catalytic cycle delivering the final product. Here, the stereoselection was totally in charge of the phosphoramidate ligand. Interestingly, β-Ketoacids could be amenable substrates for the asymmetric addition to allenes (Scheme 35, b).[74] An interplay of reaction conditions that required the use of a base and a chiral Trost-type ligand, led to a branch-selective decarboxylative pathway leading to γ,δ-unsaturated ketones that present a stereogenic heteroatom substituent at the β-position. Stereoselective C–Het bond formation might become suitable exploiting allenes, too. In fact, tautomeric phosphine oxides were found excellent pattern for asymmetric palladium-catalyzed hydrophosphinylation of allenes (Scheme 35, c).[75] This method, that required the use of bidentate chiral phosphine ligand, led to the synthesis of a broad family of allylic phosphine oxides and late-stage functionalization of cholesterol. Mechanistic information was provided by deuterium-labeling studies that supported a LLHT pathway. Finally, atroposelective hydroamination of allenes, under palladium/Brønsted acid catalysis, led to the synthesis of axially chiral sulfonamides (Scheme 35, d).[76] Following precedent studies by Rhee and co-workers,[77] acidic sulfonamide derivatives, substituted at the *ortho*-position with several functional groups, were exploited to enable this transformation in the presence of a Trost-type chiral ligand. The high diastereoselectivity realized with this catalytic system were rationalized to be function of a more thermodynamically stable *syn*-Pd(π-allyl) intermediate that is subsequently attacked by sulfonamide anions to form the expected product.

Scheme 35. Enantioselective, palladium/Brønsted acid-catalyzed, Tsuji-Trost functionalizations using allenes.

7. Summary and Outlook

The development of sustainable synthetic methodologies is nowadays of paramount importance in the organic chemistry community. The possibility to exploit alkyne derivatives as versatile electrophilic patterns for Tsuji-Trost-type functionalizations represents an ideal opportunity to develop novel catalytic methodologies with high atom economic and efficiency. Within this manuscript, a survey of the recent advances achieved combining simple Brønsted acids and popular palladium catalysts has been described. Particularly, by means of relatively simple catalytic systems, a broad number of synthetic manipulations of alkyne derivatives affording more complex unsaturated structures could be achieved with high yields, regio- and chemo-selectivities. In this scenario, many other challenges need to be addressed, particularly if compared to the use of other metal counterparts in the presence of alkynes.[78] In fact, a strong ligand effect has been displayed by many catalytic manifolds, suggesting that the development of a new generation of ligands will be mandatory to enable novel C–Het bond formation methodologies. Furthermore, the use of established chiral Brønsted acids[79] or the design of newly ones, will be the key to realize novel enantioselective functionalizations. We hope that this overview will open new perspectives in this area of research, which has recently witnessed a kind of renaissance, prompting the development of novel catalytic methodologies.

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