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Asymmetric Pd(II)-Catalyzed C–O, C–N, C–C Bond Formation Using Alkenes as Substrates: Insight into Recent Enantioselective Developments

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This Review summarizes the advances in the catalytic enantioselective mono- and difunctionalization of alkenes, highlighting the fundamental role of ligands. Several types of asymmetric reactions have been developed involving different bonds formation, C–O, C–N and C–C, highlighting the urgency to go ahead in the search for new ligands and synthetic methodologies in order to improve the control over the reaction selectivity and activity and thus, to increase the applications in the synthesis of heterocyclic scaffolds and biologically active compounds. The Review is organized into paragraphs, which discuss the type of bond formed during the nucleopalladation, C–O, C–N, C–C bonds, and the type of reaction involved.

1. Introduction

Starting from the discovery of the Wacker process,[1] where the presence of Pd(II) facilitates the addition of oxygen to ethylene, Pd(II)-catalyzed addition of nucleophiles on sp^2 carbon has become a benchmark in metal-catalyzed alkenes functionalization.[2–4] Using simple substrates, such as alkenes, transformations involving C–O, C–N and C–C bond formation have been made feasible, including intra- and intermolecular process. These reactions generally rely on the strong interaction of Pd(II) salts with the π-orbitals of the alkenes, as well as of alkynes and arenes.[5] In function of the nucleophile involved in the nucleopalladation two possible mechanism are involved: (1) Wacker/aza-Wacker-type reactions for C–O and C–N bonds formation and (2) Heck-type reactions for C–C bonds (Scheme 1). In the first case, the coordination with the double bond (**A**) and the consequent nucleopalladation (NP) leads to the formation of a Pd(II)-alkyl intermediate **B**. The nucleopalladation generates a new stereocenter, which can be lost after reductive elimination, if a hydrogen on the newly formed C–Nu bond is present on the same plane and side of the Pd-species (*syn*-coplanar elimination), affording the classical Wacker product **3**. However, the β-hydride elimination from the new C–Nu bond formed can be prevented if the rotation in **B** is forbidden (i.e. in case of cyclic alkenes).

Moreover, if the hydrogen is substituted with an alkyl group or an electron-withdrawing group (EWG) is located on R^3, β-hydride elimination will occur further away from the newly formed C–Nu bond, preserving the stereocenter. In the Heck-type cycle (Scheme 1, right), addition of the carbon nucleophile to the Pd-catalyst is occurring as first step, affording **C**, then the intermediate **B** is given only after migratory insertion on the alkenes **1**. Thus, the development of a new enantioselective Pd(II)-catalyzed functionalization has become particularly attracting. However, even if Pd(II) offers great advantages compared to Pd(0) in terms of functional group compatibility and air and moisture tolerance, the need of oxidative conditions in order to reestablish the catalyst active species is not compatible with the most common used chiral phosphines,[6] which are known to provide high level of enantiocontrol.[7] Moreover, phosphine ligands attenuate the electrophilicity and σ-donating properties of Pd(II), making it less reactive. The use of nitrogen-containing ligand, able to coordinate the Pd center with weaker interactions turned out to be fruitful for this purpose. For this reason, in the last decades of the 20th century several chiral 1,3-diamines, as well as (−)-sparteine, have been used as ligands in combination with Pd(II)-salts.[8] However, control over enantioselectivity was barely achieved.[9] Despite (−)-sparteine is naturally occurring, the lack of success and difficulty in achieving the corresponding (+)-derivative, highlighted the urgent need to introduce new ligands which can tolerate oxidizing conditions, while preserving the Pd(II)-electrophilicity. In 1986 the first pyridine oxazoline (Pyox) ligand was synthetized by Brunner and coworkers[10] and followed by new generations of ligands, such as Box[11,12] and Phox,[13] where the oxazoline nuclei was kept as the chiral coordinating group.[14] Despite Pyox ligands were firstly described, their special properties remained enclosed until recent years, where reinvestigation of their features and electronic optimization of the initial backbone, allowed to develop new powerful asymmetric reactions. For example, Liu's group, by designing new generations of Pyox ligands substituted at the C-6 position of the

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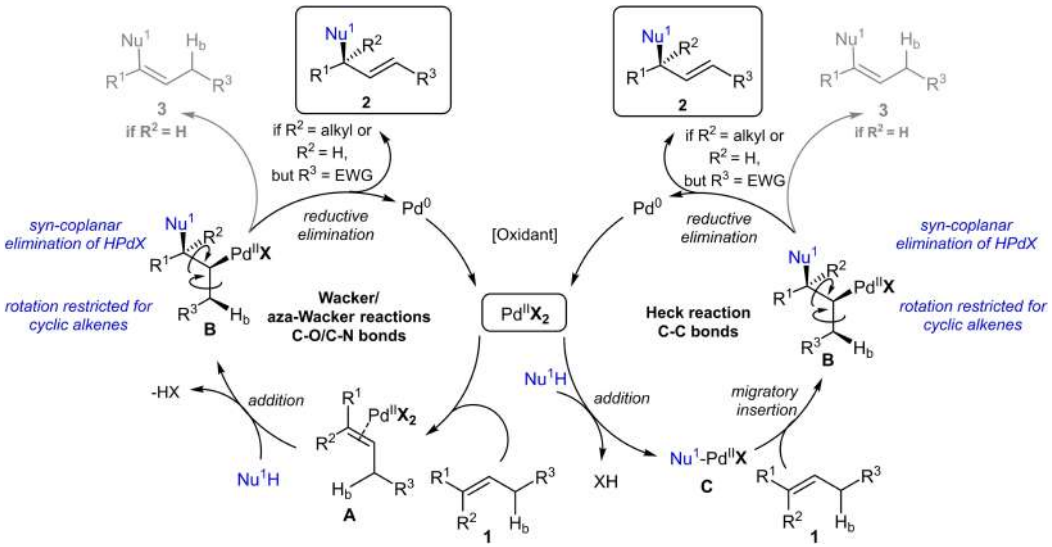
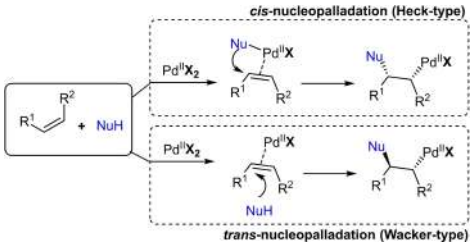


Scheme 1. Pd(II)-catalytic cycles illustrating Wacker and aza-Wacker process (left) and Heck pathway (right).

pyridine,[15] has uncovered the potential of Pd(II) in enantioselective difunctionalization of alkenes, which previously suffered of low reactivity and enantioselectivity.

Finding the perfect ligand in Pd(II)-catalyzed alkene functionalization is not the only challenge. In fact, nucleopalladation can proceed through two different stereochemical pathway: *cis*- or *trans*-nucleopalladation[16] (Scheme 2).

Since the energy difference between the two possible pathways can be really low, in some case both mechanisms might operate contemporary, increasing the difficulties in developing high level of enantioselectivity.



Scheme 2. Schematic representation of *cis*- and *trans*-nucleopalladation.

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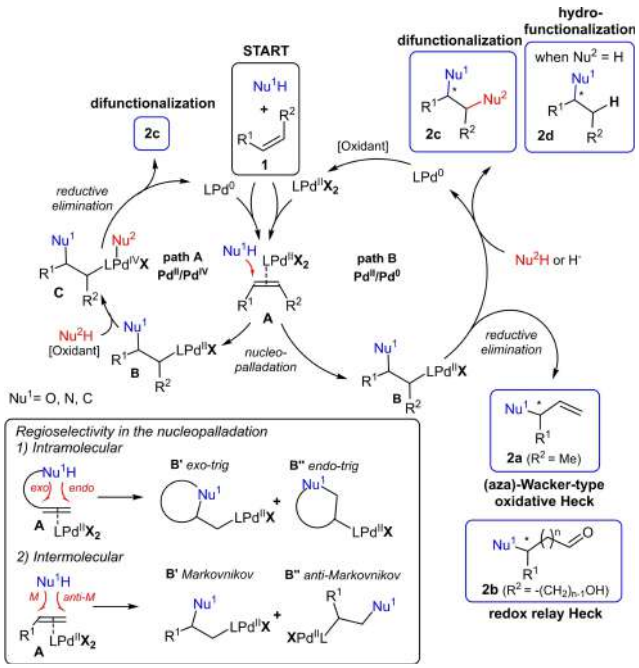
Reaction conditions, including palladium source, type of oxidants and nucleophiles, solvents and additives, can also have a critical role and decisive impact on the mechanism and final outcome. Indeed, starting from alkenes **1** in function of the oxidant employed, two types of pathway are possible, Pd(II)/Pd(0) (path B) or Pd(II)/Pd(IV) (path A) (Scheme 3). While the former is common in the presence of molecular oxygen and quinones as oxidizing agents, the Pd(IV) specie is usual formed in the presence of strong oxidant as hypervalent iodines I(III), Selectfluor and *N*-fluorobenzenesulfonimide (NFSI) (Scheme 3, path A). The discussed Wacker- and Heck-type products, resulting from the β-hydride elimination, are not the only products which can be obtained after nucleopalladation of alkenes (Scheme 1). Indeed, after the initial formation of the alkyl palladium specie **B**, different scenarios are possible: (1) in absence of a second nucleophile, the reductive elimination affords, in function of the bond formed in the nucleopalladation step (C–O, C–N, C–C), Wacker-type, aza-Wacker-type and Heck products (**2a**), respectively; (2) when a particular class of substrates is employed, redox-relay Heck reactions might also take place, affording products **2b**; (3) in the presence of a second nucleophile, alkenes difunctionalization can be achieved, allowing the construction of complex molecules in one step (**2c**). If hydride sources, such as silanes or alcohol solvents, are used in the reaction mixture, (4) hydrofunctionalization are possible, too (**2d**). All the possible outcomes, which can be obtained starting from the alkene substrate **1**, underlines the infinite potential of the palladium catalyst and at the same time shows that the optimization of reaction conditions is an urgent requirement in order to prevent undesired side reactions, give regioselectivity and enantioselectivity. Together with fine-tuning of reaction conditions and ligand design, substrates design has also been reclaimed as valuable approach to avoid off-target reactions (i.e. see paragraph 4.2.3 Redox-Relay Heck).



Scheme 3. Different scenarios in Pd(II)-catalyzed alkene functionalization.

Considering all these potential scenarios and the challenging, concerning the asymmetric Pd(II)-alkenes functionalization, the present review provides a tool for developing new enantioselective strategies, by discussing the recent progresses in this field. Since most of the asymmetric Pd(II)-alkene functionalization carried out by Hayashi, Zhang, Stahl, Sasai, Overman, Stoltz, Sigman has been already discussed in the review of 2011,[2] herein we will focus on the last 10 years, describing the recent developments on the oxidative Pd(II)-functionalization of alkenes, involving the formation of a quaternary stereocenter on the double bond.

2. Enantioselective C–O Bond Formation

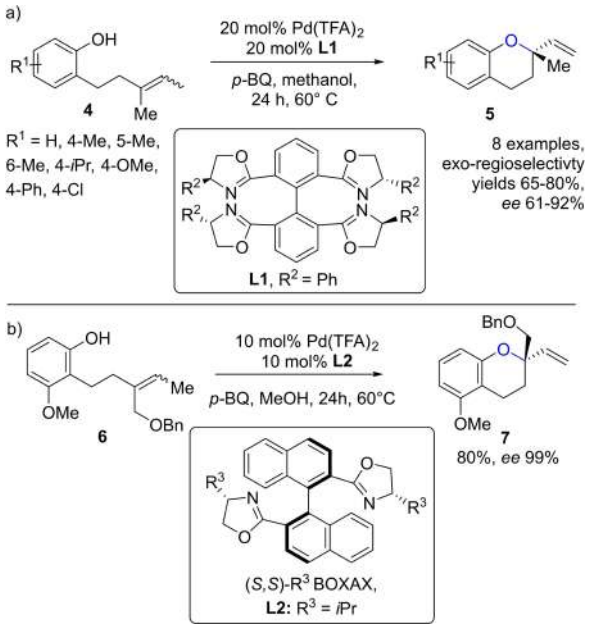
Developing a catalytic system which allows effective oxypalladation of alkenes in oxidative conditions is not so straightforward. Primary and secondary alcohols can be easily oxidized to the corresponding aldehyde or ketone derivatives in the presence of Pd(II) catalysts,[17] as well as phenols can undergo quinone formation with consequent undesired side reactions.[18] Thus, the development of catalysts that promote effective oxypalladation requires good chemoselectivity.

2.1. Wacker-Type Reactions

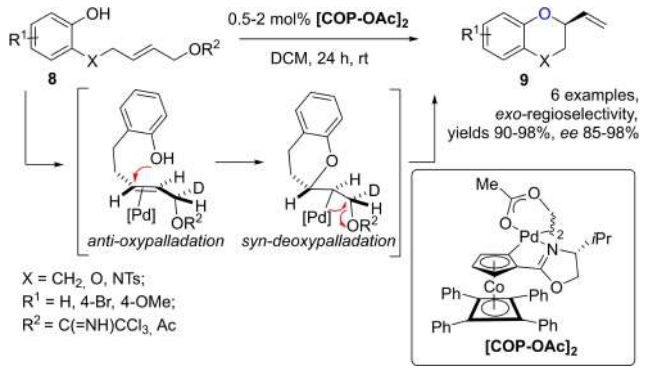
During the first decade of the 21th century, on the basis of the pioneering work of Hosokawa and Murahashi on the enantioselective Pd(II)-catalyzed alkene functionalization,[19] the Wacker-type oxidation of phenols and alcohols in enantioselective manner have been widely developed mostly using substituted alkenes, in order to prevent β-hydride elimination from the newly formed C–O bond. For the enantioselective version of these reaction, initially β-pinene, and (–)-sparteine were employed as chiral ligands, but satisfying results were achieved only with specific substrates geometry. The employment of novel binaphthyl derived bisoxazoline ligand (BOXAX) and cobalt oxazoline palladacyle COP–OAc gave better enantiocontrol (up to 99%), compared to other natural products and bisoxazoline ligands, such as BOX and PyBOX.

2.1.1. Intramolecular Wacker-Type Reactions

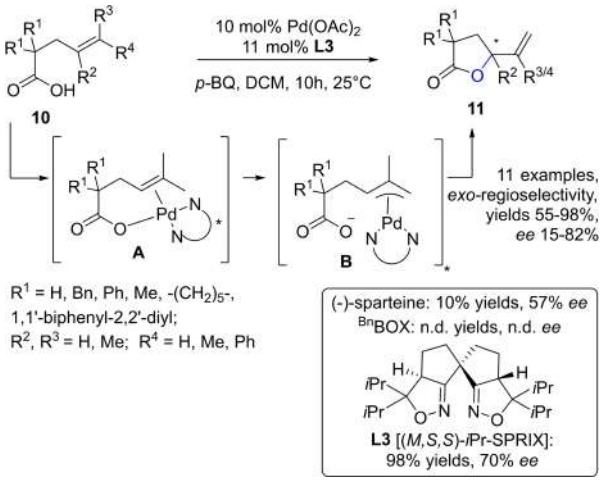
In 2007, Zhang *et al.* introduced novel biphenyl oxazoline ligands **L1**, and demonstrated their applications in the Wacker-type cyclization of *ortho*-tetrasubstituted allylphenols and trisubstituted allylphenols and allylnaphthols.[20–22] The ligand with phenyl-substituted tetraoxazoline **L1** showed remarkably higher catalytic activity and enantioselectivity compared with other substitutions, including Bn, *i*Pr and *t*Bu (Scheme 4a). Thus, employing the optimized catalytic system, 20 mol% $Pd(TFA)_2$ with ligand **L1** (1:1 ratio) in the presence of *p*-benzoquinone (*p*-



Scheme 4. Enantioselective synthesis of vinyl chromans **5** and **7**.



Scheme 5. Asymmetric synthesis of compounds **9** using catalytic chiral cobalt and dipalladium complex, [COP–OAc]$_2$



Scheme 6. Intramolecular cyclization of alkenoic acids **10** using Pd(II)/**L3** catalytic system.

BQ) in MeOH at 60°C, vinylchromans **5** could be synthetized in moderate yield and satisfying *ee* (61–92%).[23] It is especially significant that this type of ligand do not own any axial chirality due to their molecular symmetry, but only one diastereoisomer is obtained upon Pd-complexation (chelation-induced axial chirality).[24] Applying a similar strategy for the construction of the chroman unit, Tietze and coworkers synthetized secalonic acid E,[25] using binaphthyl derived bisoxazoline ligand **L2**, (*S,S*)-*i*Pr–BOXAX (Scheme 4b). By employing Pd(TFA)$_2$ (10 mol%) in the presence of the chiral ligand **L2** and *p*-BQ, the 5-methoxy-substituted chroman ring **7** could be obtained with >99% *ee*, and irrespective of the *E/Z* ratio of the starting material **6**, contrary to a previous work.[26]

Overman and Solomon, starting from their former work,[27] described a [COP–OAc]$_2$-catalyzed intramolecular Wacker-type reaction for the synthesis of 2-vinylchromanes, 2-vinyl-1,4-benzodioxanes, and 2,3-dihydro-2-vinyl-2*H*-1,4-benzoxazines in high yields (90–98%) and excellent enantiomeric purities (87–98% *ee*)[28] ([COP–OAc]$_2$ = oxazolinylcyclopentadienyl cobalt and dipalladium complex). However, the substrates **8** were preactivated by inserting in the allylic position a trichloroacetimidate as leaving group (Scheme 5). The authors demonstrated through deuterium labeling experiments that an *anti*-oxypalladation/*syn*-deoxypalladation mechanism was operative, in compliance with previous DFT analysis.[29]

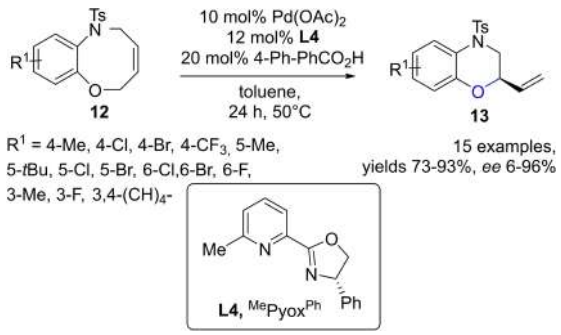
Sasai and coworkers described an intramolecular oxidative cyclization of 4-pent-1-enoic acid **10**, using spiro bis(isoxazoline) ligand **L3**, SPRIX, for obtaining optically active γ-alkenyl-γ-lactones **11**.[30] Indeed, all the attempts made in the presence of (−)-sparteine, (*R,R*)-Bn–BOX, (*S,S*)-*i*Pr–BOXAX, and (*R*)-BINAP were unsuccessful (Scheme 6). SPRIX in particular with its unique isoxazoline coordination sites on the rigid spiro backbone, possess low σ-donor ability, preserving the Lewis acidity of Pd salts.[31] The employment of 15 mol% of (*M,S,S*)-*i*Pr–SPRIX **L3** and 2 equiv. of *p*-BQ at 0°C led to a quantitative formation of **11**, with 82% *ee*. The mechanism could proceed either *via* oxypalladation (Wacker type) or C–H bond activation. The no reactivity of the 2,2-diphenylpent-4-enoic acid and the different intermolecular kinetic isotope effect (KIE) between deuterated and non-deuterated substrates led to the conclusion that the reaction proceeded *via* a π-allyl Pd intermediate **B** and thus likely through C–H bond activation.

The construction of benzoxazine nuclei is useful from pharmaceutical point of view, since chiral 3,4-dihydro-2*H*-1,4-benzoxazines are key structural elements in numerous natural products and bioactive molecules. Different asymmetric Pd-catalyzed reactions have been developed to achieve these motifs, including aminohydroxylation of 1,3-dienes (Pd(II)-catalyzed)[32] and allylic substitution,[33] instead ring contraction reaction remains elusive. Employing a benzo-fused cyclooctenes **12**, as substrates, it was possible to straightforwardly obtain enantio-enriched vinyl-substituted benzooxazines **13** through a particular ring contraction reaction with a *O*-chemoselective pathway.[34] Pyox substituted with a methyl at the C-6 position

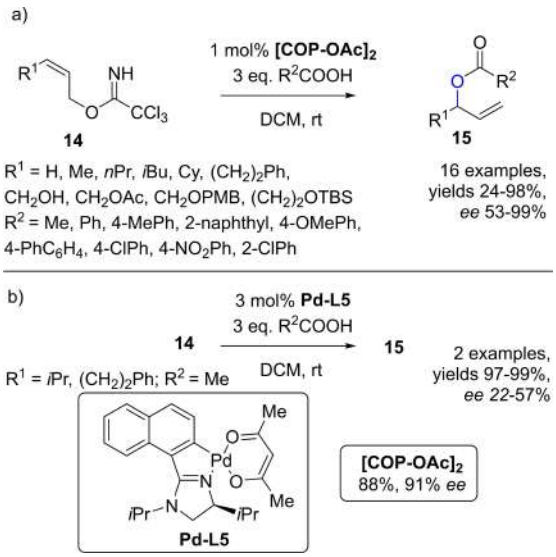
of the pyridine and with the phenyl on the oxazoline ring, ^{Me}Pyox^{Ph} **L4**, was used as chiral ligand (Scheme 7). The presence of 20 mol% of an acidic additive, 4-Ph–$PhCO_2H$, was also necessary to increase both reactivity and enantioselectivity (up to 93% yield, 96% *ee*). Regarding the substrate tolerance, the benzo[*b*][1,4]oxazocine with substitutions on the 3-position of the phenyl ring gave poor results in terms of enantioselectivity.

2.1.2. Intermolecular Wacker-Type Reactions

Examples regarding intermolecular nucleophilic attack to alkenes are not numerous and often activated alkenes were required. In particular, on this latter Overman carried out an extensive work on the use of a particular complex, $[COP–OAc]_2$, for the enantioselective synthesis of branched allylic ether or esters, starting from prochiral (*E*)-allylic trichloroacetimidates in the presence of different oxygen nucleophile, such as phenols and carboxylic acids.[27,35] Since the same substrates are also used for the [3,3]-sigmatropic rearrangement, the intramolecular *N*-attack could also be observed, mostly when (*E*)-alkenes were employed. In 2010, the Overman's group applied the developed system to investigate different carboxylic acids and di- and trisubstituted alkenes. (*Rp,S*)-$[COP–OAc]_2$ catalyst was superior in terms or reactivity, chemoselectivity and enantioselectivity, over a different range of palladium complexes, including cationic palladium diamine complex, palladium dichloride phosphinooxazolines and bis-oxazoline complexes, where really poor reactivity and enantioselectivity were observed. Good enantioselectivity was realized also with the palladacyclic COP complexes $[(Rp,S)$-$COP–Cl]_2$, but with really low yields, since this complex catalyzed asymmetric rearrangement of allylic trichloroimidate quite faster, especially in the presence of the *E* alkene isomer. Moreover, trisubstituted alkenes proven to not be tolerated. (Scheme 8a).[36] In order to test new complexes as catalysts for the rearrangement of prochiral *(E)*-allylic trichloroacetimidate and the S_N2 allylic substitution of acetic acid with prochiral (*Z*)-allylic trichloroacetimidate a new family of air- and moisture-stable enantiopure C,N-palladacycles (PIN–acac complexes, **Pd**–**L5**) was prepared, starting from 2-iodo-1-naphthoic acid and enantiopure β-aminoalcohols.[37] A structural feature of the C,N-palladacycle



Scheme 7. Ring contraction of **12** as route to access 1-vinyl substituted benzooxazine **13**.



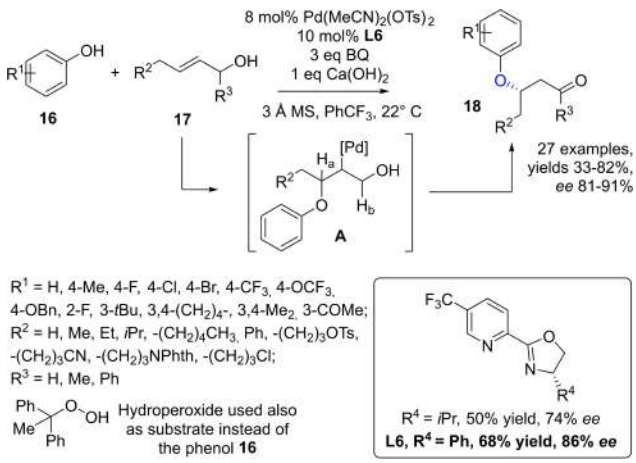
Scheme 8. Intermolecular nucleophilic attack of external acids on allylic trichloroacetimidates **14**, and comparison between two different catalysts, **Pd**–**L5** and **[COP**–**OAc]$_2$**.

catalyst motifs **Pd**–**L5** is the projection of steric bulk, arising from *i*Pr substituents on the imidazoline ring, both above and below the palladium square-plane coordination sphere, with the aim to control better enantioselectivity. Analogous to COP catalysts, an *anti*-acetoxypalladation/*syn*-deoxypalladation mechanism was operative, but with poor enantiocontrol (Scheme 8b).

Despite the challenges arising from developing enantioselective intermolecular Pd-catalyzed alkene functionalization, recently Sigman described an asymmetric intermolecular coupling of oxygen nucleophiles **16** and allylic alcohols **17** to give β-aryloxycarbonyl compounds **18**, using a chiral pyridine oxazoline-ligated palladium catalyst (**Pd**–**L6** or Pd–$^{5-CF3}$–Pyox).[38] A broad substrates scopes, including various phenols and allylic alcohol, as well as alkyl hydroperoxide were tolerated under the reaction conditions (Scheme 9). The specific design of the substrates, bearing an alcohol functional group on the allylic position of the alkene, makes the H_b more acidic than H_a in **A**, directing the β-hydride elimination process and thus, leading to the successful synthesis of β-alkoxyaldehyde and ketone derivatives **18** (*ee* up to 91%).

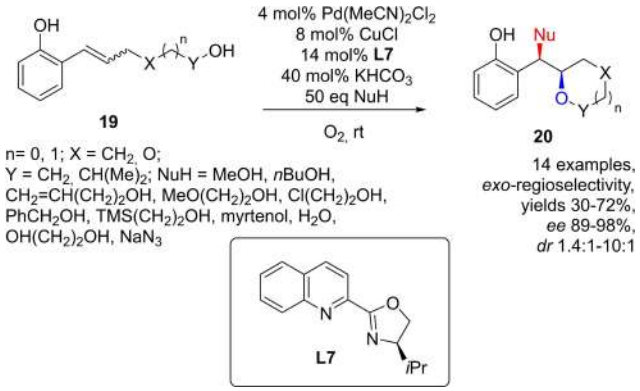
2.2. Difunctionalization Reactions

The formation of two carbon–heteroatom bonds across an unsaturated system in one-pot process with full control of selectivity (regio-, diastereo-, and enantioselectivity), is challenging as well as extremely desired in organic chemistry. The generation of molecular complexity, as functionalized heterocycles and functionalized aliphatic chains in rapid manner from simple alkene precursors[39–44] requires fine-tuning of reaction conditions. Some years ago the possibility to add functional groups at the desired site in a regio-, diastereo- and

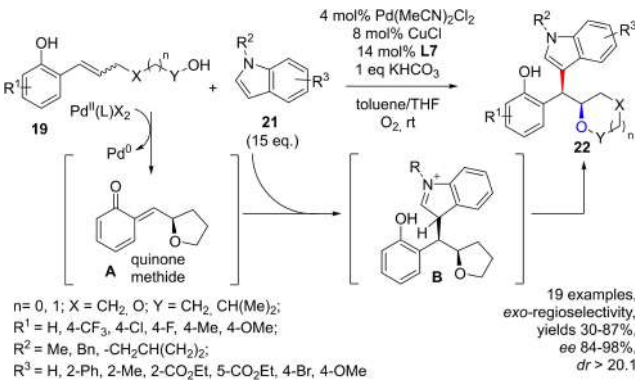


Scheme 9. Oxypalladation of phenols **16** on alkenols **17**, affording **18** through redox-relay strategy.

enantioselective manner was an ideal scenario, but the recent developments have shown that some limits can be exceeded.[45]



Scheme 10. Enantioselective difunctionalization of *o*-vinyl–phenols **19** through an intra-intermolecular attack.



Scheme 11. Pd(II)-catalyzed asymmetric oxycarbofunctionalization of *o*-vinyl–phenols **19**.

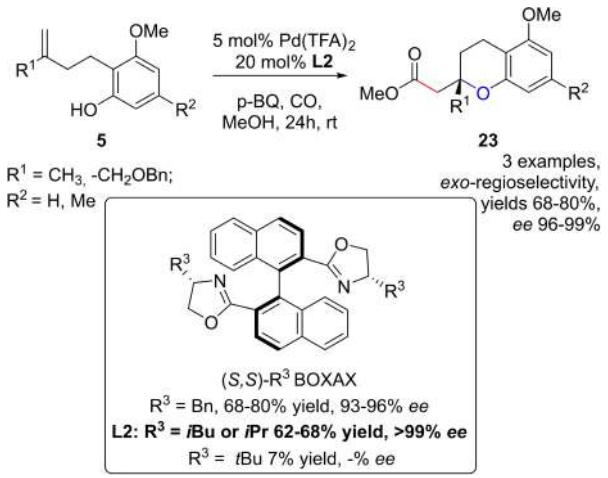
2.2.1. Intra-intermolecular Difunctionalization

Pd(II)-catalyzed enantioselective alkene difunctionalization involving the oxygen as nucleophile have been established by Sigman in 2007,[46] proposing a parallel approach to the standard osmium-catalyzed Sharpless dihydroxylation.[47] Using *o*-vinyl–phenols **19** as substrates, the presence of a second double bond, given by the phenol ring conjugated with the alkene involved in the reaction, allowed the difunctionalization process taking advantage of the formation of a quinone methide intermediate (see **A** in Scheme 11). The instability of the quinone methide specie favored the attack by a second external nucleophile, in this case methanol, furnishing the difunctionalized product **20** (Scheme 10).[48] In particular, the use of 4 mol% $Pd(MeCN)Cl_2$ in combination with 14 mol% *i*PrQuinox, **L7**, and CuCl (8 mol%) enabled to reach 98% *ee*. The high ligand loading compared to the palladium catalyst was necessary to prevent loss due to copper coordination.

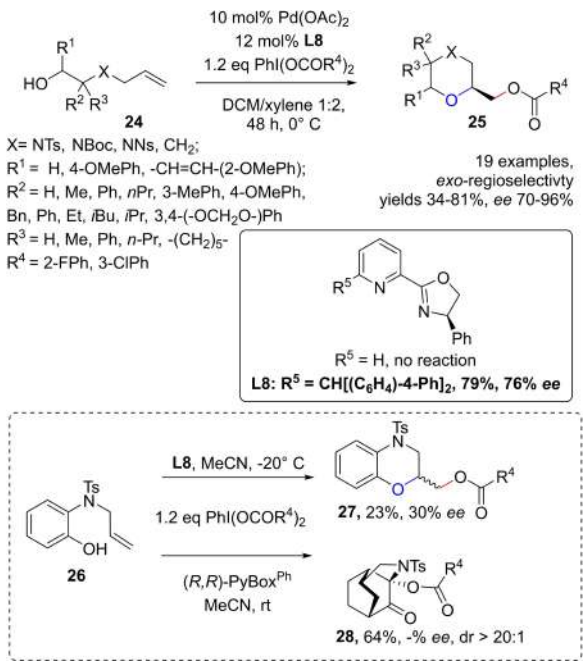
When methanol was replaced by *N*-methylindole **21** as nucleophile, the enantioselective difunctionalization afforded **22** with excellent enantio- and diastereoselectivity (Scheme 11).[49] The domino reaction consisted in the intramolecular alkoxylation with the contemporary quinone methide formation **A** and subsequent aromatic substitution of the indole with quinone, **B**. The reaction was compatible also with *N*-methylpyrrole, however in all the cases the *N*-protection of the indole was required.

Tietze carried out extensive work on the application of enantioselective domino-Wacker/carbonylation/methoxylation reaction for the construction of natural products, including (−)-Blennolide A and C, (−)-gonytolide C and (−)-Diversonol, starting from a *o*-substituted phenols **5**.[26,50,51] In particular, the intramolecular alkoxylation step on the double bond was the key step for the formation of a new stereocenter at the C-4 position of the chromane. Using, $Pd(TFA)_2$, as Pd(II) source, *p*-BQ as oxidant under an atmosphere of carbon monoxide in methanol, compound **23** was obtained in good yield (Scheme 12). Excellent enantioselectivity was obtained thanks to the presence of chiral BOXAX ligands, **L2**. In particular, by tuning the steric properties of BOXAX, it was possible to achieve enantioselectivity of 99%, when (*S,S*)-*i*Bu–BOXAX was employed.[50] While Bn and *i*Pr substitution gave similar results, the use of the *t*Bu substitution dropped drastically the reactivity (≈7% yields).

As above reported, enantioselective dioxygenations on different alkenes have been studied widely, while those on terminal alkenes remain rare. Beccalli and coworkers published recently an oxidative Pd-catalyzed intra-intermolecular dioxygenation of (aza-)alkenols **24**, with total *exo*-regioselectivity (Scheme 13).[52] In this case not only C_6-modified Pyox ligand **L8** was fundamental for the outcome of the reaction,[15] but also the employment of aromatic hypervalent-iodine was necessary to increase the enantioselectivity from 34% to 76% *ee*. The authors hypothesized the formation of a more stable $Pd(OAc)_2$-ligand complex when $PhI(mcba)_2$ was employed. Additionally, steric hindrance at the C_6 position of Pyox was more fruitful in terms of reactivity. This strategy allowed to obtain enantioen-



Scheme 12. Enantioselective domino-Wacker/carbonylation/methoxylation reactions for the synthesis of the chromane unit **23**.



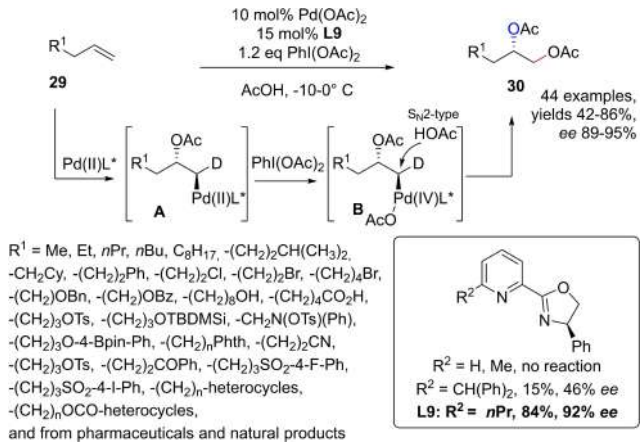
Scheme 13. Intra-intermolecular dioxygenation of (aza)-alkenols **24** and ligand effect on the cyclization of **26**.

riched acyloxy-substituted morpholines and pyrans **25**, giving access to β-aminoacids, as well as natural product (+)-centrolobine as natural product. When the protocol was extended to more oxidation sensitive and challenging substrates such as phenols **26**, the enantioselectivity observed was only 30%.[18] Conversely, in the presence of a commercially available tridentate ligand, (*R,R*)-PyBOX^{Ph}, a side reaction promoted by the hypervalent iodine was observed.

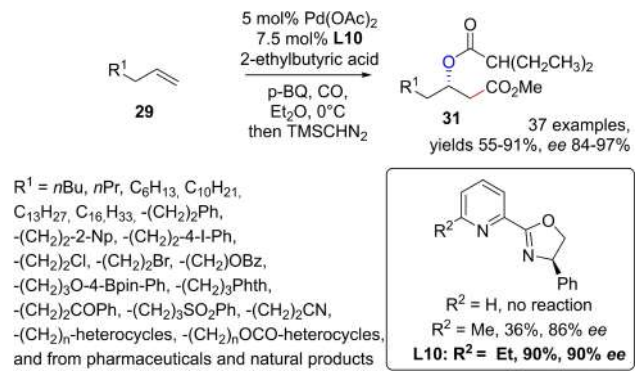
2.2.2. Inter-intermolecular Difunctionalization

It is known that developing an enantioselective process is quite challenging, mostly when the substrates does not bring any chiral information[53] and the geometry of the system is quite straightforward. For this reason, a Pd-catalyzed enantioselective difunctionalization of 1-propene and 1-butene is almost thought-provoking. However, by fine tuning the properties of the ligand, the Liu's group in 2021[54] could develop an inter-intermolecular asymmetric difunctionalization of terminal mono-substituted alkenes **29** (Scheme 14). The mild method developed, based on the use of $Pd(OAc)_2$, C_6-ethyl-substituted Pyox ligand, ^{Pr}Pyox^{Ph} **L9**, and $PhI(OAc)_2$ in dried acetic acid (HOAc) allowed to obtain diacetoxy-substituted compounds **30**. Some mechanistic studies were carried out to understand the stereochemistry of the oxypalladation step. Starting from the *trans*-deuterated substrates **29**, the authors concluded that a *trans*-oxypalladation followed by a sequential S_N2-type nucleophilic attack by the acetate group was preferred (A and B intermediates in Scheme 14).

Similarly, they reported an inter-intermolecular Pd(II)-catalyzed enantioselective oxycarbonylation of alkenes,[55] with high reactivity and excellent enantioselectivity (Scheme 15). Before,



Scheme 14. A Pd(II)/**L9**-catalyzed inter-intermolecular asymmetric diacetoxylation of terminal mono-substituted alkenes **29**.



Scheme 15. A Pd(II)/**L10**-catalyzed inter-intermolecular asymmetric oxycarbonylation of mono-substituted alkenes **29**.

in order to prevent chemoselectivity issues, the presence of directing groups was required[56,57] and asymmetric oxycarbonylation of alkenes were exclusively reported in an intramolecular manner.[48,50] Using **L10** ligand, bearing an ethyl group at the C_6-position of pyridine, in combination with $Pd(OAc)_2$, *p*-BQ, 2-ethylbutyric acid and CO as nucleophilic sources, products **31** could be isolated with yield up to 91 % and *ee* up to 97 %.

2.3. Hydrooxygenation

Catalytic asymmetric hydrooxygenation of alkenes, as way to directly access to chiral C–O bonds, is attractive as much as challenging. Only recently, hydrooxygenation of alkenes has been reported with high enantiocontrol using a Pd(II)-catalyst in the presence of hydrogen donors, as silanes.[58] The design of a moderately sterically hindered Pyox ligand bearing a propyl group, **L9** ($^{Pr}Pyox^{Ph}$), was crucial for both reactivity and enantioselectivity (Scheme 16). Also the kind of oxidant had to be finely optimized, since strong oxidant, as $PhI(OAc)_2$, NFSI, and Selectfluor, could afford the undesired dioxygenations, too. The reducing agent features, might also be not too strong, since source of hydrogen may favor the formation of palladium hydride (PdH) species, leading to the *anti*-Markovnikov products **33** with no stereocenter formation and reduction side products, **34**. Thus, carrying the reaction in a mixture of 1,1,2,2-tetrachloroethan (TCE) and water (3:1), triethoxysilane, $(EtO)_3SiH$ as reducing agent, $Pd(OAc)_2$/**L9** as catalytic system and *p*-BQ as mild oxidant, a broad scope of optically active esters **32** was obtained through a selective Markovnikov hydrooxygenation.

3. Enantioselective C–N Bond Formation

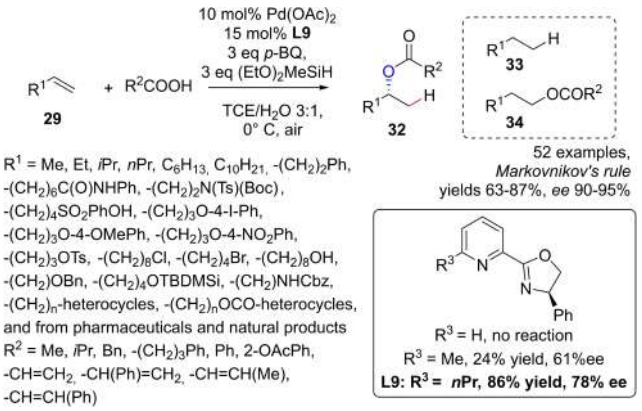
The Pd(II)-catalyzed amination reactions of C–C double bonds are a powerful and economical pathway to build heterocycles.[59] To improve this strategy, the classical aza-Wacker-type reaction has been developed investigating the effect of the ligands on palladium catalysts to switch the regioselectivity and extending the reactivity to the 1,2-difunctionalization of alkenes.

3.1. Aza-Wacker-Type Reactions

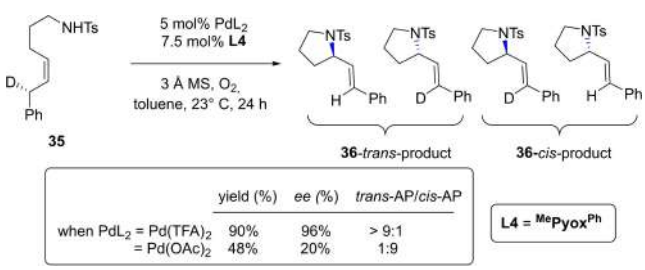
As mentioned in the introduction, the asymmetric Pd(II)-catalyzed oxidative alkenes functionalization are associated with the stereochemical course of nucleopalladation, where the possibility of *cis*- or *trans*-nucleopalladation results in the formation of diastereomeric intermediates, which might have significant consequences on the control of the enantioselectivity.[60] Different studies showed that the improved enantioselectivity was obtained in aminopalladation (AP), when the *trans*-AP was preferred. Indeed, systems, as $Pd(OAc)_2$/(−)-sparteine and $Pd(TFA)_2$/(−)-sparteine, known to afford products exclusively arising from *cis*-AP of the alkene,[61] failed to give high enantioselectivity for a wide range of Pd-catalyzed oxidative asymmetric functionalization. Thus, in order to offer more detailed information about the stereochemical course of the AP in the presence of Pd(II), Stahl and coworkers carried out NMR studies using deuterium-labeled substrate **35** in the presence of Pd(II) salts and the Pyox ligand, $^{Me}Pyox^{Ph}$. Results pointed out that the ligand plays a determining role in switching the nucleopalladation from *cis*- (in absence of ligand) to *trans* when combined with $Pd(TFA)_2$ as catalyst (Scheme 17). The use of $Pd(OAc)_2$, instead of $Pd(TFA)_2$, led also to a loss of yields and *ee*, (20 % instead of 96 %), since in this case the *cis*-aminopalladation was preferred. Thus, a neutral-donor ligand, as Pyox, alters the stereochemical course of NP when combined with the suitable anionic ligand (OAc, TFA), as well as the presence of an acid or basic environment. Indeed, addition of bases has shown to favor *cis*-AP.[62,63]

3.1.1. Intramolecular aza-Wacker-Type Reactions

Conversely to the above-mentioned asymmetric Wacker-type cyclizations, aza-Wacker-type variants have become feasible only recently, despite their longstanding interest. Particularly outstanding is the contribute of Hegedus and Stahl.[64–67] In 2012, Zhang reported the formation of isoindolinones and isoquinolin-1(*2H*)-ones **38** bearing an α-tetra-substituted carbon



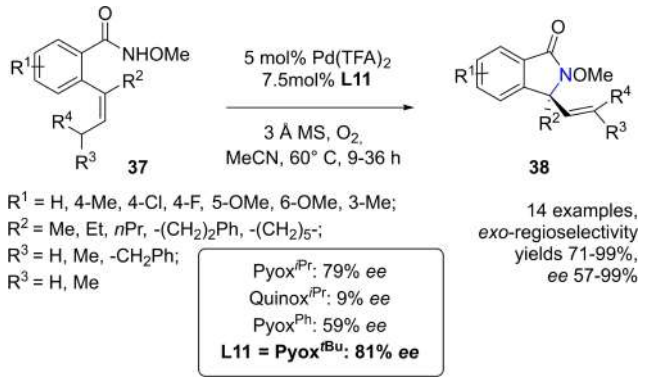
Scheme 16. The first enantioselective Pd(II)-catalyzed hydrooxygenations of alkenes **29**.



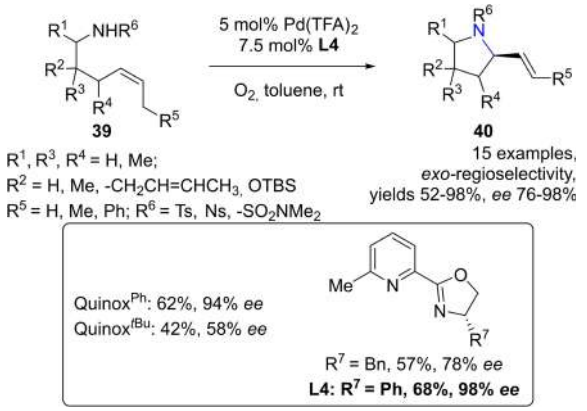
Scheme 17. Deuterium-labeling studies: *cis*- versus *trans*-aminopalladation in Pd(II)-catalyzed alkene functionalization.

stereocenter, as improvement of the already established α-trisubstituted amines.[68] Starting from trisubstituted olefins **37**, the heterocycles were obtained in high yield and high *ee* using the chiral Pyox^{tBu} ligand, together with Pd(TFA)$_2$ as the metal source (Scheme 18). On the contrary, Quinox^{iPr}, gave low yield and low level of enantioselectivity; while MeCN turned out to be the best solvent. Despite the ability of MeCN to coordinate strongly through its nitrogen atom to the metal center, the increased temperature might favor the fast dissociation, likely promoting the Pd-chiral ligand complex formation.

A straightforward intramolecular oxidative amidation of alkenes **39** was reported in the presence of Pd(TFA)$_2$, Pyox ligand and O_2 as oxidant, enabling the formation of 2-vinyl-*N*-Ts-pyrrolidines **40** in high yields and enantioselectivities.[69] The best ligand was ^{Me}Pyox^{Ph}, **L4**, which yielded product **40** in 68% yield and 98% *ee* (Scheme 19). The ability of the ligand to control the stereochemical pathway of the reaction was also tested in the presence of chiral substrates. Interestingly, the *cis*-substituted pyrrolidine was the favored product in the presence of the achiral ligand with a ratio 7:1, while in the presence of the chiral ones the same *cis* was formed exclusively when (*R*)-**L4** was used and the *trans*-diastereomer was favored when (*S*)-**L4** was employed (*dr* 1:7 *cis/trans*, 23% yield).



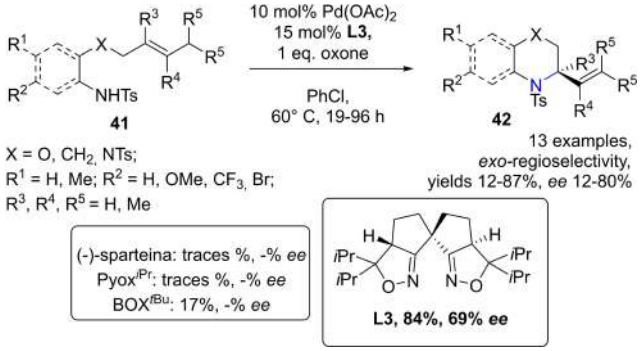
Scheme 18. Asymmetric aza-Wacker type intramolecular cyclization of *N*-methoxy-2-vinylbenzamides **37**.



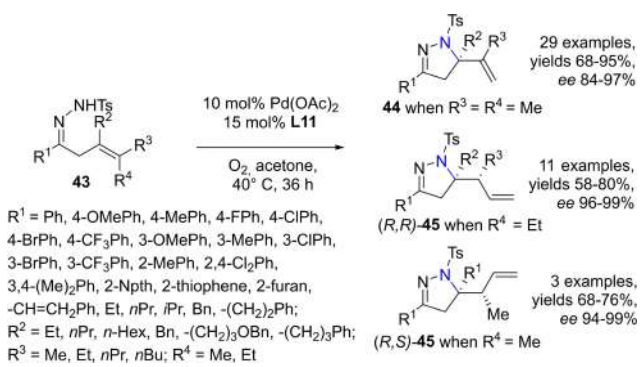
Scheme 19. Intramolecular *exo*-cyclization of aminoalkenes **39** in the presence of **L4**.

The same authors envisioned to use SPRIX ligands for the construction of six-membered nitrogen heterocycles through an enantioselective aza-Wacker-type reaction (Scheme 20). Starting from alkenyl sulfonamides **41** the desired cyclized products **42** could be obtained with **L3**, while other commonly used ligands, such as (*S,S*)-*t*Bu–BOX, (−)-sparteine, (*S*)-*i*Pr–Pyox, and (*S*)-BINAP were ineffective.[70] Thus, morpholines, piperazines, piperidines, and their benzo-fused derivatives were synthetized using as optimized reaction conditions, 10 mol% of Pd(OAc)$_2$, 15 mol% of (*P,R,R*)-*i*Pr–SPRIX (**L3**), 1 equiv. of oxone in chlorobenzene at 60°C.

Zhang *et al.* described a challenging cyclization of *N*-Ts hydrazine-tethered tetrasubstituted olefins **43**, affording chiral pyrazolines **44** bearing a tetrasubstituted carbon stereocenter (Scheme 21).[71] The formation of a second stereocenter was also given when the chain on the outer carbon of the double bond was elongated from methyl to ethyl, *n*Pr and *n*Bu. Not so many asymmetric aza-Wacker-type cyclization, affording vicinal stereocenters, have been developed,[72] ought to firstly the need to use challenging substrates as tetrasubstituted alkenes and secondly to the "chain-walking" requirement. Both diastereomers (*R,R*)-**45** and (*R,S*)-**45** could be prepared. (*R,R*)-products were obtained when both substituents on the outer carbon atom of the olefin, were larger than a methyl group, with the alkyl substituent in *cis* to the intranucleophilic group undergoing β-hydride elimination; on the other hand, (*R,S*)-**45** were achieved



Scheme 20. The use of SPRIX.as chiral ligand for the cyclization of aliphatic or benzo-fused aminoalkenes **41**.



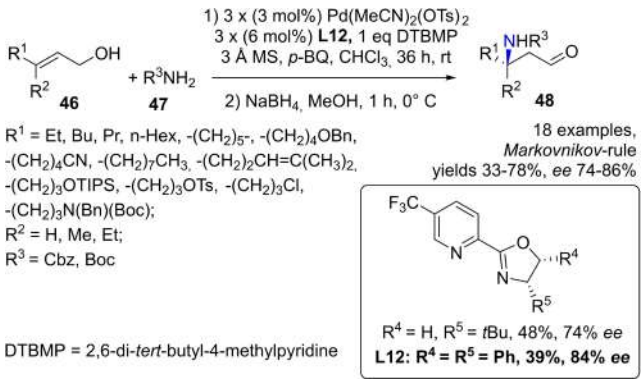
Scheme 21. Formation of two vicinal stereocenter by means of Pd(II)-catalyzed reactions on *N*-Ts hydrazine-tethered tetrasubstituted olefins **43**.

when one of the two substituent was a methyl group. In all the cases, the β-hydride elimination proceeded selectively at the methylene side.

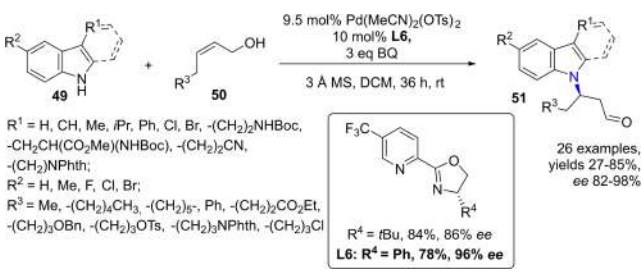
3.1.2. Intermolecular aza-Wacker-Type Reactions

The described intermolecular aza-Wacker-type reactions are both based on chain-walking strategies. The oxidation of the alcohol to the aldehyde is known as redox-relay reaction, which is the result of the migration of the double bond after the Wacker-type product formation[73] (more detailed description is given at Paragraph 4.2). In 2019 Sigman and coworkers reported a Pd-catalyzed enantioselective Markovnikov addition of carbamates to allylic alcohols for the construction of α-tertiary and α-secondary amines, **48** (Scheme 22). The reaction may generate a range of β-amino alcohols and β-amino acids, after reduction and oxidation of the aldehyde, respectively. Notably, enantioselective syntheses of α-tertiary amines are quite rare. In the conditions employed, $Pd(MeCN)_2(OTs)_2$ in combination with **L12** and Cbz–NH_2 as nucleophile, enantioselectivity up to 85% was reached, and mechanistic studies showed that the C–N bond formation occurs *via* a *syn*-aminopalladation mechanism.

Starting from *Z*-alkenols **50** and indoles as nucleophiles, the same authors developed an enantioselective strategy for the functionalization of the indole on the amino function, instead of the nucleophilic C-2 and C-3 positions (Scheme 23).[74] The presence of the hydroxyl group in β-position preserves the formed stereocenter by preventing the formation of the traditionally observed enamine products. Chain-walking was compatible until homoallylic alcohol, further elongation of the alcohol chain did not afford the desired product, indicating a likely competitive β-hydride elimination towards the newly formed C–N bond. Polar solvents as DMF resulted in the complete suppression of the reactivity. In order to simplify the substrate scope 3-substituted indoles were initially investigated, furnishing the relative product in good yields (47–78%). However, when 3-H indole and 3-Me indole were employed, yields decreased to 30% but excellent enantioselectivity was still obtained (98% *ee*). Nucleophiles with similar pK_a, as oxazolidinone, were tolerated, too.



Scheme 22. Asymmetric redox-relay strategy for the synthesis of β-amino aldehydes **48**.



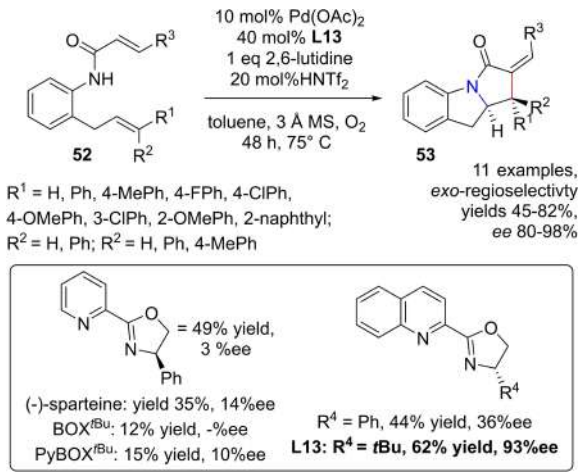
Scheme 23. *N*-functionalization of indoles **49** with alkenols **50** to yield aldehydes **51** through redox-relay strategy.

3.2. Difunctionalization Reactions

Using different type of alkenes, difunctionalization processes involving generally the formation of C–N and C–C bonds, have been developed through intra- or intermolecular processes.[75] In order to make this efficient strategy enantioselective, the use of chiral ligands has been exploited and addition of more challenging nucleophiles has been accomplished.

3.2.1. Intra-intramolecular Difunctionalization

The enantioselective oxidative cascade cyclization of unsaturated anilides **52** was described by Yang *et al.*,[72] as approach to achieve enantioenriched indolines **53** with excellent diastereoselectivities ($dr > 24:1$) (Scheme 24). $Pd(MeCN_2)Cl_2$/Quinox^{tBu} system has been proven to be the optimal, while (−)-sparteine, C_2-symmetric BOX and PyBOX ligands were not efficient for this reaction. Supported by the stereochemical outcomes, the aminocarbofunctionalization of all substrates essentially yielded



Scheme 24. Pd(II)-catalyzed cascade reaction for the asymmetric synthesis of tricyclic systems **53**.

only one diastereoisomer among the four possible, as result of a *syn*-amidopalladation,

Using alkene-tethered aliphatic acrylamides **54** as substrates, a cascade cyclization was achieved, as a result of C–N and C–C bonds formation (Scheme 25).[76] In this case, the use of the bidentate ligand (*S,S*)-diPhPyox **L14** was fundamental to induce high enantioselectivity (up to 93% *ee*), while (−)-sparteine and other bidentate ligand as SPRIX[77] were inefficient. The use of $Pd(TFA)_2$, instead of $Pd(OAc)_2$ as well as the employment of aromatic solvent in the presence of a base were necessary to ensure high enantioselectivity. Conversely to the previous work,[72] here an *anti*-aminopalladation was operative, and computational studies showed that stabilizing noncovalent CH/π and arene–arene interactions observed only in one of the four possible transition states between the substrate and the C4–phenyl group on the oxazoline ring may be responsible for the observed high selectivity.

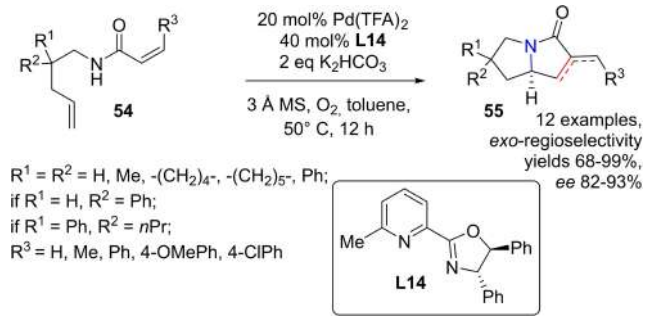
In 2014, the homologous of the substrate **54**, the *N*-(2,2-disubstituted hex-5-en-1-yl)acrylamides **56**, was submitted to an unprecedented combination of $Pd(TFA)_2$ with a chiral Quinox^{tBu} ligand **L13** and a chiral phosphoric acid **PA1**, reporting a synergistic effect able to afford chiral 6,5-bicyclic heterocycles **57**, through a highly efficient asymmetric oxidative tandem cyclization (Scheme 26).[78] In order to explain the synergistic effect given by the chiral Brønsted acid and the chiral ligand with the palladium catalyst, a Pd(II)-complex coordinating both chiral ligand and chiral phosphate is postulated, where the alkene substrate coordinates to the Pd(II) and the cinnamamide is activated by hydrogen bonding with phosphoric acid.

Difunctionalization involving a C–H activation step has also been described by the Liu's group.[79] Starting from *o*-vinyl substituted benzanilides **58**, various indolines containing a quaternary stereogenic center **59** were synthesized in high yield with excellent enantioselectivity, through an asymmetric Pd(II)-catalyzed intramolecular oxidative aminoarylation of alkenes (Scheme 27). The reaction conditions involved the use of quinoline–oxazoline chiral ligands **L15**, fundamental to increase yields and *ee*, in combination with Ag_2CO_3 as oxidant and phenylglyoxylic acid (PGA) as additive, in THF as solvent.

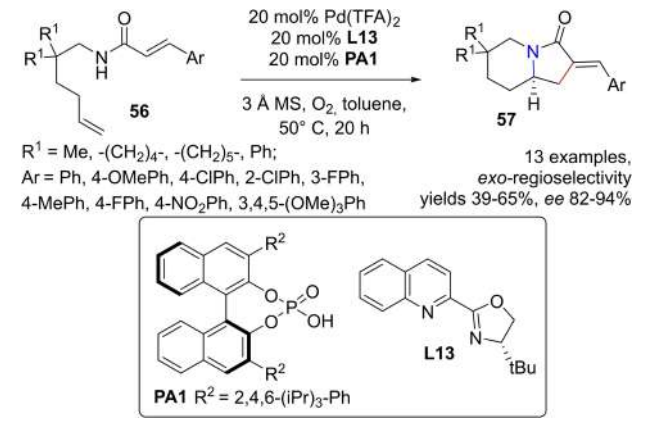
3.2.2. Intra-intermolecular Difunctionalization

Pd-catalyzed alkene difunctionalization reactions of a particular class of substrates, namely *o*-vinylphenols, have been widely studies by Sigman and coworkers (as discussed in the Paragraph 2.2.1). The key features of this system is the ability of the Pd(II)-alkyl intermediate derived from nucleopalladation to undergo a redox reaction, forming Pd(0) and an *ortho*-quinone methide intermediate, which might be attacked by a second nucleophile, restoring the phenolic form. In 2012 an amino-carbofunctionalization variant has been developed, where the presence of phenols tethered to *N*-Ts-aminoalkenes **60** allowed to obtain pyrrolidine derivatives **61**, functionalized on the methylene-bridge with the nucleophile of interest.[80] The process was completely diastereo- and enantioselective with values >99% *ee* and >20:1 *dr* (Scheme 28). In the case of the methyl carbamate-protected substrate, low yield and poor stereoselection was obtained, due likely to the Lewis basic properties of the carbamate able to displace the chiral Quinox^{iPr} ligand, **L7**.

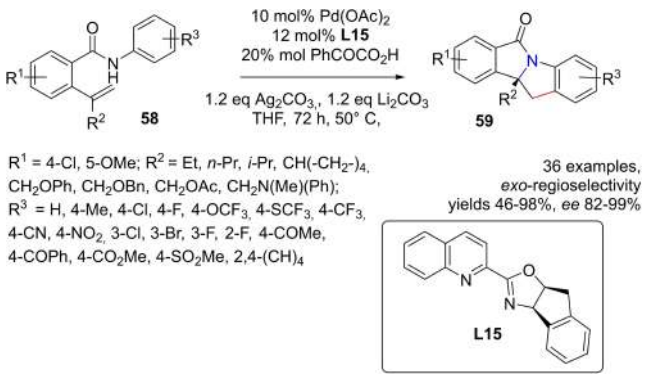
Some years later excellent enantioselectivity was also obtained in the diamination of unactivated alkenes-tethered to amides or carbamates **62** using PyBOX^{Ph} and Quinox^{Ph} ligands, $Pd(TFA)_2$ as catalyst and NFSI as both oxidant and nucleophilic



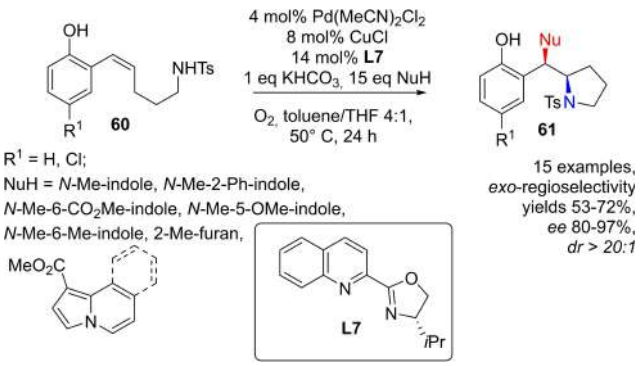
Scheme 25. Alkene-tethered acrylamides **54** as substrates for the Pd(II)-catalyzed synthesis of pyrrolizin-3-ones **55**.



Scheme 26. Synergistic effect of chiral phosphoric acid **PA1** and Pyox ligand **L13** in the enantioselective synthesis of indolizin-3-ones **57**.



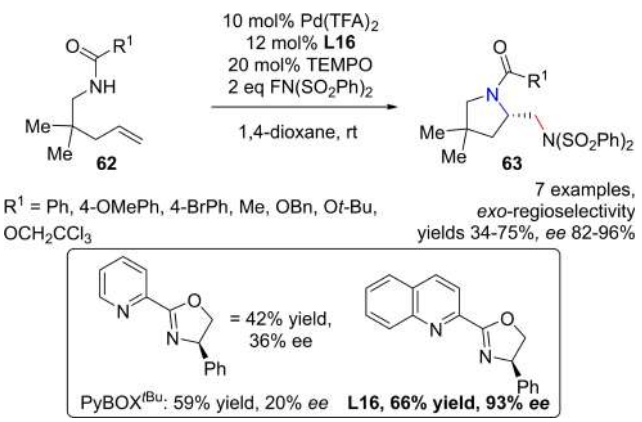
Scheme 27. Synthesis of indolines **59**, employing $Pd(OAc)_2$ in the presence of **L15**.



Scheme 28. Use of *o*-vinylphenols **60** as "smart" substrates for the preparation of pyrrolidine derivatives **61** through a carboamination process.

source (Scheme 29).[81] Geminal disubstitution on the backbone generally gave good yields and high enantioselectivity, monosubstituted substrates also gave excellent enantioselectivity but modest yield and diastereoselectivity. In order to understand the high selectivity observed, mechanistic experiments were carried out. Only one of four possible diastereomeric aminopalladation products **63** was formed, in particular the one resulting from a *cis*-aminopalladation. The X-ray analysis of the alkylpalladium complex showed that steric effect of quinoline in **L16** may play a role in lengthening the quinoline–Pd bond, which is beneficial for developing efficient enantioselective oxidative Pd(II)-difunctionalization.

Therefore, in order to enhance reactivity and enantioselectivity by increasing the Pd–ligand bond, Liu's group envisioned to introduce a sterically bulky group into the C_6-position of Pyox. Thus, in 2018, a new pyridine–oxazoline (Pyox) ligand **L17** was synthesized, featuring a *ortho*-(1-phenyl)benzyl substitution on the pyridine ring, **L17**.[15] Compared to the commercially ones, as ^{H}Pyox, this ligand features less electron-donating properties towards the Pd(II), without altering its electrophilicity. The ligand was tested in the aminoacetoxylation of alkenes, using $Pd(OAc)_2$ and $PhI(OAc)_2$ as nucleophile source

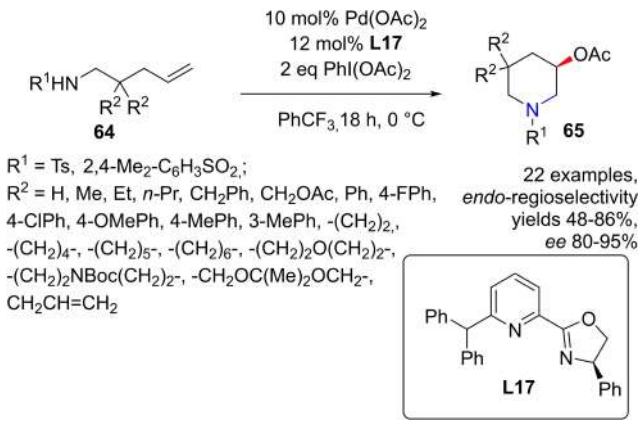


Scheme 29. Asymmetric intramolecular amination of alkenes-tethered to anilides **62**, followed by intermolecular nucleophilic attack.

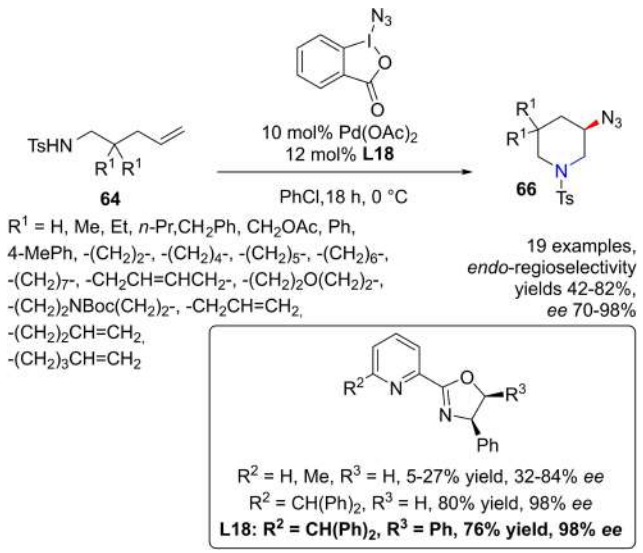
and oxidant. 6-*Endo* aminoacetoxylation was mainly observed, through *trans*-aminopalladation (Scheme 30). The choice of the substrates **64** was crucial, indeed, only the aminoalkenes bearing a disubstitution on the β-position, participating in the Thorpe-Ingold effect, gave exclusively 6-*endo* cyclization step, preventing the formation of 5-*exo*-products.

The reaction of the same substrate **64**, in the presence of azides as nucleophiles has also been reported.[82] Readily accessible 1-azido-1,2-benziodoxol-3(1H)-one (ABX) has been used as azidating reagent; thanks to its oxidative properties, no further oxidant was necessary to be added. In particular, the use of an electrophilic azide turns out to be fundamental, since the addition of azide anions, as $TMSN_3$ and Bu_4NN_3, to the standard conditions completely inhibited the reaction. The use of sterically bulky chiral ligand **L18** was crucial in order to obtain successful reaction (Scheme 31).

A different Pyox with a sterically bulky group into the *ortho*-position of the pyridine, **L19**, was identified as the best ligand

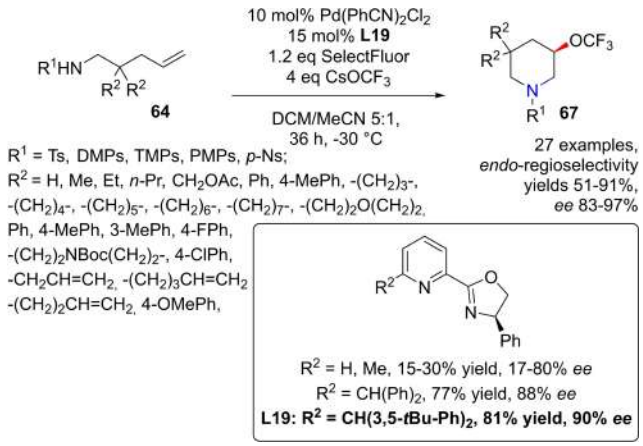


Scheme 30. Aminoacetoxylation of aminoalkenes **64** in the presence of the novel ligand **L17**.

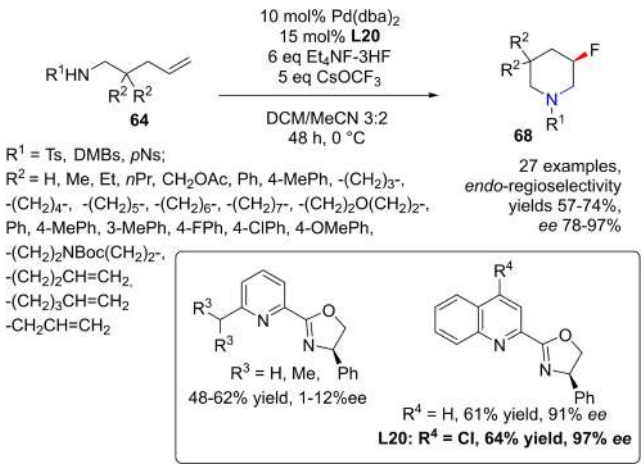


Scheme 31. *Endo*-cyclization of **64** in the presence of ABX for the azide-functionalization of piperidine **66**.

to obtain aminotrifluoromethoxylation starting from the same alkenes **64** using $Pd(PhCN)_2Cl_2$ as catalyst, **L19** and $CsOCF_3$ as readily accessible and stable trifluoromethoxide source.[83] In fact, the replacement of $AgOCF_3$ with $CsOCF_3$ not only offered a more stable alternative, but prevented the poor enantioselectivity obtained in the presence of the silver salt, due to its coordination ability to the ligand, leading to a naked Pd(II) specie (Scheme 32). Since the steric hindrance of the ligand may be responsible of the catalyst-ligand complex dissociation, an extra amount of **L19** was required for the successful asymmetric reaction. Additionally, performing the reaction in a mixed solvent (DCM/MeCN, v/v = 5:1) at −30°C allowed to obtain the desired product **67** up to 91% yield and 97% *ee*. Moreover, the type of protecting group on the nitrogen turned out to be fundamental. Indeed, while sulfonamide and phenyl amine substrates gave rise exclusively to the *endo*-product, the same authors showed that using Boc (*tert*-butyloxycarbonyl) as protecting group, the pyrrolidine ring was solely obtained, through a 5-*exo* aminotrifluoromethoxylation process.[84]



Scheme 32. Use of Pyox ligand **L19** with substituent at the C_6-position of the pyridine as optimal ligand for the preparation of 3-trifluoromethoxy piperidines **67**.



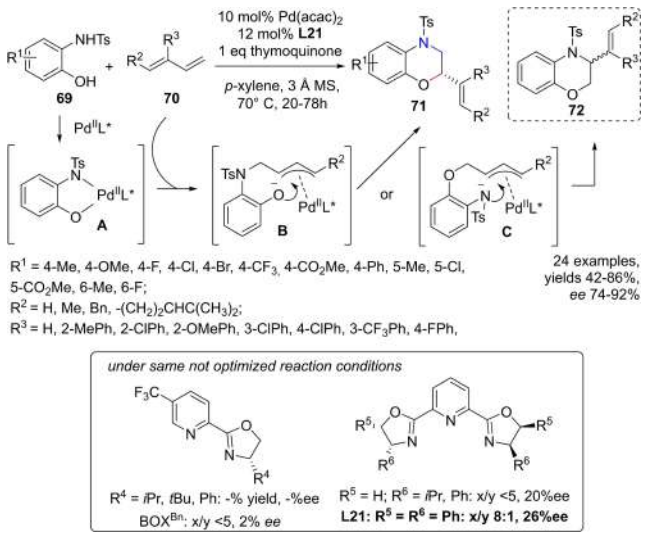
Scheme 33. Aminofluorination of aminoalkenes **64** as synthetic method to access chiral 3-fluoro piperidines **68**.

Similarly, β-substituted fluorine-containing piperidines **68** have been obtained, describing the first asymmetric Pd(II)-catalyzed aminofluorination of unactivated alkenes (Scheme 33).[63] In this case, the chiral quinoline–oxazolines (Quinox, **L20**) proved to give higher enantioselectivity. $Et_4NF \cdot 3HF$ was employed as a readily accessible nucleophilic fluoride source and, compared to $AgHF_2$, was found to play an essential role in the enantioselective control. Surprisingly, $CsOCF_3$, used in this case as additive, improved the *ee* value up to 97%.

3.2.3. Inter-intermolecular Difunctionalization

Starting from 1,3-dienes **70** and *N*-tosyl-2-aminophenols **69**, a straightforward approach has been developed to directly achieve chiral 3,4-dihydro-2*H*-1,4-benzoxazines **71** in high yield and enantioselectivity through a Pd(II)-catalyzed asymmetric intermolecular aminohydroxylation.[32] Due to the di-nucleophilic nature of the substrate **69**, both aminopalladation and oxypalladation might occur, affording respectively products **71** and **72** (Scheme 34). The use of aromatic solvents, such as toluene and *p*-xylene, could optimize the **71**/**72** ratio from 14/3 up to 89/1. The use of *p*-xylene, together with thymoquinone as oxidant and chiral PyBOX ligand **L21** allowed to reach *ee* up to 92% and 86% yields. In this case the palladium catalyst had a multifunctional role: (1) to promote the first step regioselectively through the formation of a π-allyl palladium complex, **B** (or **C**); (2) to induce an asymmetric intramolecular allylation, affording the final product. Substrates **69** bearing various substituents were well tolerated.

A regioselective asymmetric 1,2-diamination of 1,3-dienes with readily available dialkylureas **73** has been reported by using a chiral pyridine–oxazoline ligand to give 4-vinylimidazolidin-2-ones **74** in high yields and with excellent levels of enantioselectivity (up to 99% yield, 97% *ee*).[85] The phenyl-



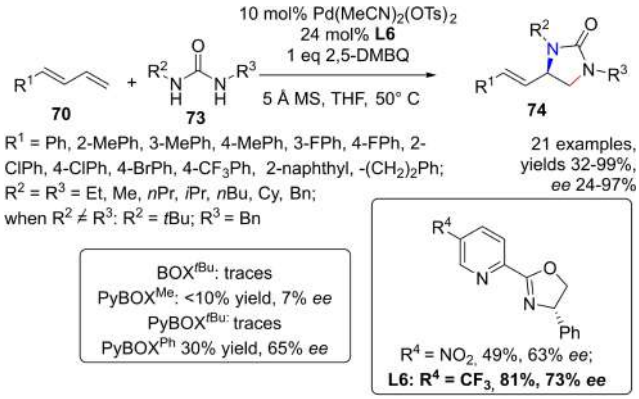
Scheme 34. Regioselective intermolecular aminohydroxylation of *N*-Ts-2-aminophenols **69** with dienes **70** in the presence of $Pd(acac)_2$ and **L21**.

substituted Pyox **L6** resulted the highly active catalyst; $Pd(OAc)_2$ and $Pd(MeCN)_2Cl_2$ were not able to catalyze the process, while $Pd(MeCN)_2(OTs)_2$, a highly dissociated palladium(II) species, was highly compatible with the chiral ligand to make the diamination reaction of 1,3-dienes proceed stereoselectively (Scheme 35).

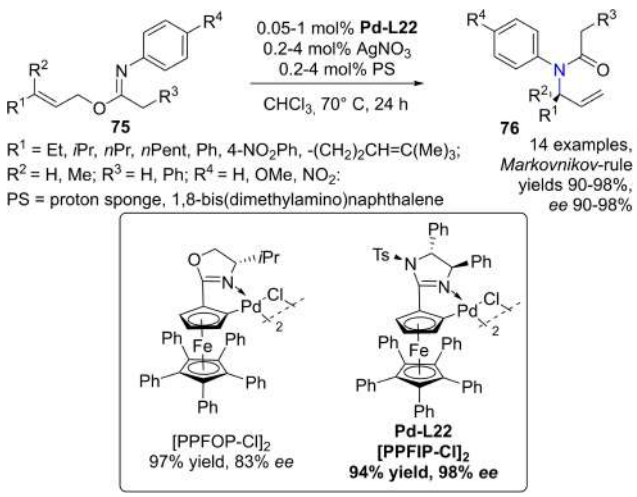
3.3. Rearrangement of Allylic Imidates

In 1974, Overman firstly described the synthesis of branched chiral allylic trihaloacetamides through the rearrangement of the corresponding allylic trichloroacetimidate known as Overman rearrangement, in the presence of $[COP–Cl]_2$.[86,87] Until the first decade of the 21th century different paper have been published on this strategy by using catalytic amounts of soft Lewis acids.[88] However, the use of COP–X in cyclopalladation is not always fruitful, indeed the sensitivity of the cobalt-based sandwich complexes towards the substitution pattern of the substrate and the poor chances to modify the electron density when compared to ferrocenes, limit the reactivity to a define class of substrates, like halogenated ones and acetimidates bearing α-unbranched alkyl substituents at the 3-position of the allyl group.[89] To this purpose, valuable is the work made by Peter's group,[90,91] where different class of catalyst complexes have been developed, based on the ferrocene moiety, describing the first Pd(III) complexes acting as enantioselective catalysts.[92] Thus, a non-halogenated alternative of the Aza-Claisen rearrangement has been developed, making use of acetamidates **75** to furnish branched chiral allylic products **76** with high levels of enantio- and regioselectivity with the chloride bridged dimeric pentaphenylferrocene based imidazoline palladacycle $[PPFIP–Cl]_2$ **Pd–L22** as precatalyst (Scheme 36).[93] Activation of $[PPFIP–Cl]_2$ precatalyst was ensured by treatment with $AgNO_3$. Heating the reaction mixture up to 70 °C allowed to reduce the reaction time from 3 days to 24 hours and to increase yields up to 93%, without influencing the enantioselectivity. The developed reaction offered a broad substrates scope, including the use of trisubstituted alkene giving tetrasubstituted allylic acetamides.

Worth to mention is the application of the concept of asymmetric counter anion-directed catalysis (ACDC), where chiral TRIP counter anion (**PA2**) together with simple cyclopalladated benzyl amines **L23** were used instead of Pd–ferrocene complexes to catalyzed the Overman rearrangement in high enantioselectivity (up to 98%) (Scheme 37).[94]



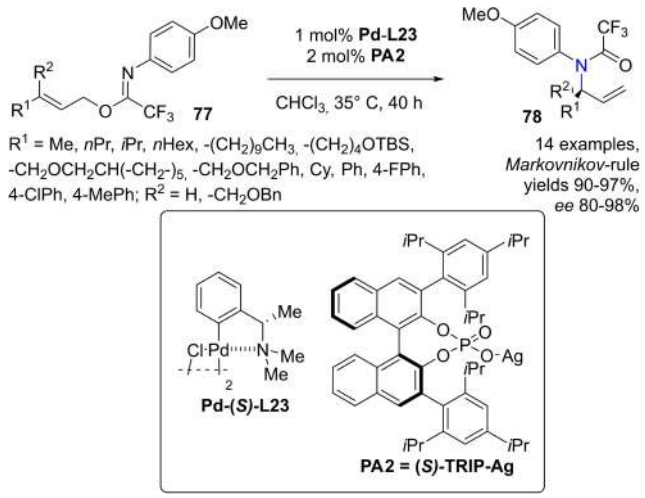
Scheme 35. Diamination of dienes **70** with dialkyl ureas **73**, using $Pd(MeCN)_2(OTs)_2$/**L6** as catalytic system.



Scheme 36. Rearrangement of allylic imidates **75** in the presence of new ferrocene-based imidazoline palladacycle, **Pd–L22**.

3.4. Hydroamination

Not so many examples have been reported in enantioselective Pd(II)-catalyzed hydroamination of alkenes and mostly, these findings are limited to specific class of substrates as styrenes or α,β-unsaturated carbonyl compounds. In 2000 Hartwig reported the first example of an enantioselective hydroamination of styrenes catalyzed by a Pd(II) species, in the presence of BINAP. Mechanistic studies showed that the reaction proceeds through



Scheme 37. ACDC driven by (***S***)**-TRIP–Ag** in the presence of palladacycle **L23** for the allylic rearrangement of acetimidates **77**.

alkene insertion into a palladium hydride to form an η^3-benzyl intermediate which undergoes subsequent external nucleophilic attack of the π-allyl specie affording the branched substituted product.[95,96]

Similarly, in 2015 Liu and Chen reported a Pd-catalyzed asymmetric hydroamination of styrenes **79** under oxidative reaction conditions, in which NFSI was used as the nitrogen source as well as the oxidant, and pyridine–oxazoline ligands, instead of phosphine, were used as chiral ligands.[97] Starting from initial encouraging results with the commercially Pyox ligand (^{H}Pyox^{iPr}) about activity (70% yield, *ee* 0%), it was gratifying to find out that substitution at the C-6 (**L24** and **L25**) led also to an increase of the enantioselectivity up to 50% (Scheme 38). Further optimization, including solvent screening, catalyst loading and addition of triethyl orthoformate, furnished the product in 75% yield and 87% *ee*. Deuterium labeling experiment showed that a quick reversible migratory insertion of styrene into the palladium hydride is occurring, which could explain the low enantioselectivity for some substrates. In particular, after migratory insertion of styrene into the palladium hydride species to form the benzyl–Pd intermediate **A**, oxidized by NFSI to Pd(IV), the reductive elimination from **B** provides the final product **80**. The presence of an alcohol is required as source of hydride.

Recently, a Pd(II)-catalyzed hydroamination of β-nitrostyrene with methoxyamine has been reported to occur in aqueous buffer and at room temperature.[98] Specifically, Pd–phenanthroline complex was used, exploiting the ability of the phenanthroline to intercalate within DNA helix and thus, providing a chiral proximity through non-covalent interactions satisfying enough to afford enantioselectivity >75% into the final product.

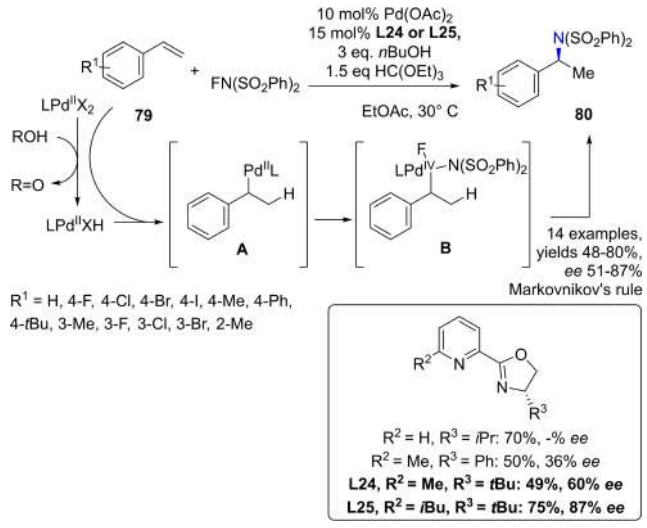
4. Enantioselective C–C Bond Formation

The direct functionalization of alkenes in coupling reactions involving the formation of C–C bond allowed to increase the complexity of the scaffold and at the same time to offer an efficient and economical strategy for the synthesis of polyheterocyclic systems and natural products. The recent literature reported intra- and intermolecular processes with particular attention to the stereoselective impacts. Within this type of reactions, the difunctionalization of alkenes was a further improvement of the strategy.

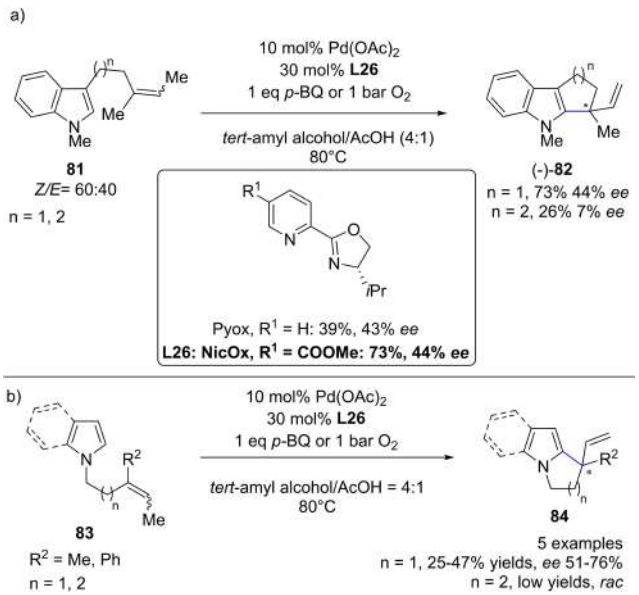
4.1. Fujiwara-Moritani Cross-Coupling

One of the first examples of enantioselective intramolecular C–C bond formation under oxidative Pd(II)-catalyzed conditions, was applied on the indole annulation, starting from indoles **81**, bearing an olefin pendant in position C3 (Scheme 39a). The best ligand for stereoselectivity was the nicotine derivative NicOx, **L26** clearly superior to the conventional pyridine derivative Pyox ligand and among different oxidants, *p*-BQ gave the best result.[99] Also the synthesis of the new NicOx ligand was described.

The reaction was extended to indoles and pyrroles in which the alkene was tethered on the N1, **83** (Scheme 39b). In these cases, while the five-membered ring were formed in decent yields (25–47%) and good enantiomeric excesses (51–76%), the formation of the six-membered ring would not even occur, due probably to a different reaction mechanisms.



Scheme 38. Enantioselective hydroamination of styrenes **79** in the presence of NFSI as oxidant and nucleophilic source.



Scheme 39. Indole annulation to give compounds **82** and **84** through the use of unconventional **L26** ligand.

4.2. Oxidative Heck Reactions

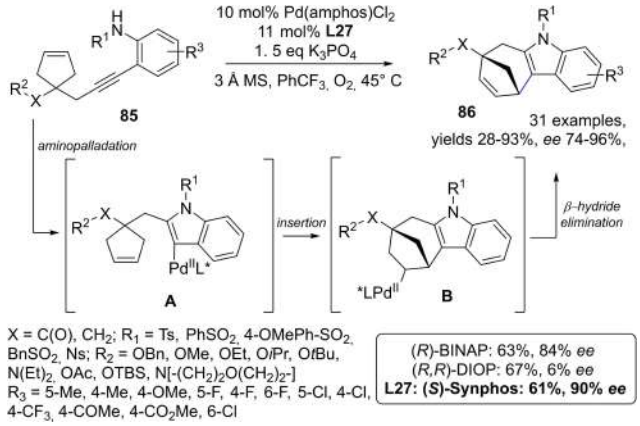
Classical oxidative Heck reaction leads to the formation of conjugated unsaturated systems, making use of cross-coupling reaction between an alkene and a nucleophilic carbon source, as arylboronoic acids.[100] Since, in this kind of reactions no carbon stereocenter is formed, in the presence of the appropriate ligand only desymmetrizations of the starting material are possible.[101,102] Thus, design of the substrates is a crucial aspect for developing oxidative Heck reactions where quaternary stereocenter are newly formed. One of the common strategies foresees the use of alkenes substituted with R groups, in such a way that β-hydride elimination is not occurring at the newly formed Csp^3, but rather at the proximal H-available carbon position, preserving the new stereocenter formed. Other approaches consist of the presence of directing groups as well as design of alkenes with specific electronic properties given by an electron-withdrawing group (EWG), located at $-(CH_2)_n-$ distance from the C=C bond. The presence of EWG, by altering the electronic properties of the alkenes, act as "thermodynamic sink" and allows the "chain-walking" of the double bond, through repetitive migratory insertion and β-hydride elimination steps (Scheme 40). Moreover, arylboronic acids or organostannanes are commonly employed as nucleophilic carbon source, affording intermediate **A**, through transmetallation, able to undergo migratory insertion on the alkene **I**.

4.2.1. Intramolecular Heck Reactions

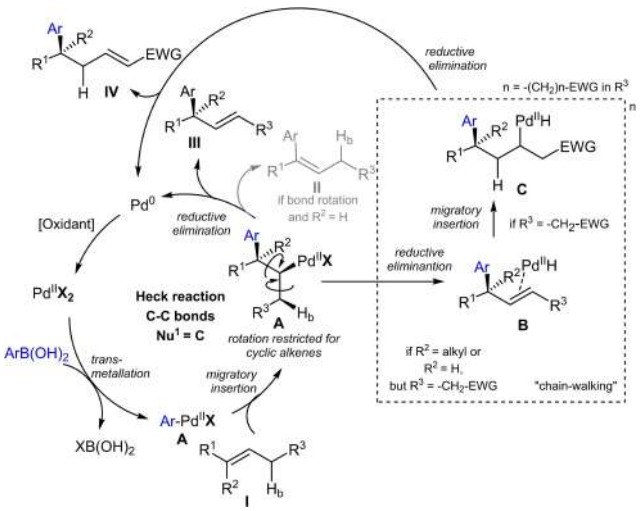
Starting from substituted *o*-alkynyl anilines **85**, the cascade aminopalladation-triggered Heck-type reaction was exploited to obtain indole-fused bicyclo[3.2.1]octanes **86**, bearing all–carbon quaternary bridgehead stereocenter.[103] The optimized reaction conditions suggested the use of Pd(amphos)Cl_2 as catalyst, (*S*)-Synphos (**L27**) as ligand, $PhCF_3$ as solvent, at 50 °C, in the presence of K_3PO_4 as base and molecular sieves (Scheme 41). The attempt to replace the sulfonyl group with Boc or Ac resulted in no reactivity. In this case, some control experiments to explore the reaction mechanism proposed the coordination of the Pd(II) with the triple bond and the aminopalladation step forming the intermediate **A**, which underwent intramolecular double bond insertion to generate the species **B**. The β-H elimination furnished product **86** and the Pd–H species. The Pd(II) was regenerated *via* reductive elimination and oxidation with O_2.

4.2.2. Intermolecular Heck Reactions

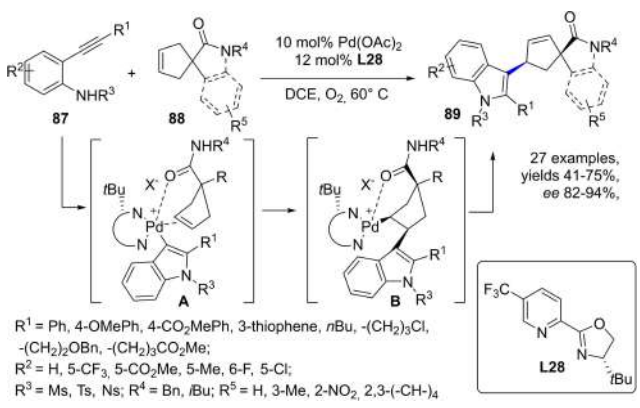
Among the stereoselective domino reactions, the use of *o*-alkynylanilines **87** with prochiral cyclopentene **88** allowed to access to indole–cyclopentene conjugates **89** bearing two stereocenters in high diastereo- and enantioselective manner, through an aminopalladation-oxidative Heck reaction (Scheme 42).[104] The reaction was performed with Pd$(OAc)_2$ in the presence of chiral bidentate Pyox ligand **L28** ($^{5-CF3}$Pyox^{tBu})



Scheme 41. Asymmetric synthesis of indole-fused bicyclo[3.2.1]octanes **86**, through aminopalladation and subsequent carbopalladation of *o*-alkynyl anilines **85**.



Scheme 40. Representative scheme of oxidative Heck reactions with β-hydride elimination occurring at a different site from the newly formed C–C bond.

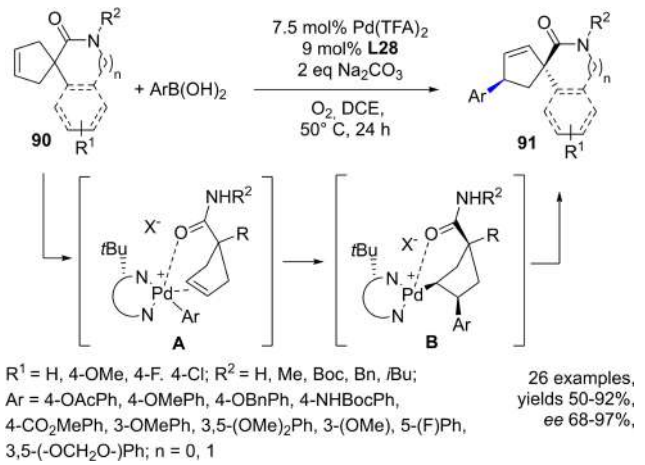


Scheme 42. Cascade reaction for the synthesis of indole–cyclopentene conjugates **89**, exploiting the amide on **88** as directing group.

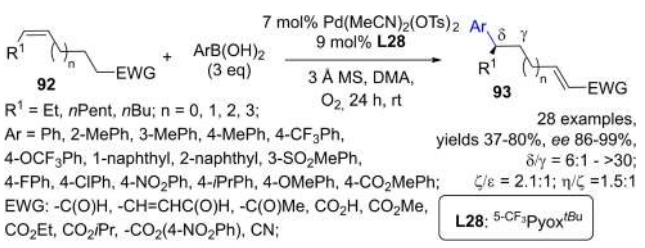
and O_2 as terminal oxidant, in DCE at 60°C. In order to define the stereoselectivity, the presence of the carboxamide group was mandatory due to the coordination of the indolylPdX species **A** to the double bond of **88** directed by the amide function. In this way the face selectivity of the subsequent *syn*-carbopalladation was driven, generating the Pd(II) complex **B**. Subsequent β-hydride elimination, decomplexation and reductive elimination of HX generated the indole derivative **89.**

Similar *cis*-isomers were obtained with excellent diastereo- and enantioselectivity, starting from 4,4-disubstituted cyclopentene **90** and arylboronic acids, using Pyox ligand, **L27**, in DCE at 50°C (Scheme 43). The carboxamide function was an essential directing group for the coordination in the pentacoordinated Pd complex **A** in which the steric repulsion was minimized. The subsequent *syn*-carbopalladation of **A** followed by the decomplexation of **B** afforded the product **91**.[105]

Sigman *et al.* described a chain-walking strategy,[106] using $Pd(MeCN)_2(OTs)_2$/Pyox (**L28**) as catalytic system, O_2 as oxidizing agent, in DMA. Thus, enantioselective and site-selective Pd-catalyzed arylation of alkenes tethered to carbonyl derivatives **92** was described as route to access to α,β-unsaturated systems, **93**. Starting from phenylboronic acid and (*Z*)-dec-4-enal, excellent enantioselectivity was obtained with the conditions already in-hand (Scheme 44). On the other hand, site-selectivity was fine-tuned by screening different solvents, in particular DMA gave the best results with δ/γ ratio of 15. Either electron-rich and electron-deficient aryl substituted boronic acids gave in this case site selectivity >9:1 for the δ-products. The same protocol was extended to the desymmetrization of cyclic enones[107] for the construction of chiral α,β-unsaturated δ-lactams, as important pharmaceutical core, starting from cyclic enelactam.[108]



Scheme 43. Stereoselective synthesis of compounds **91** starting from 4,4-disubstituted cyclopentene carboxamides **90**.



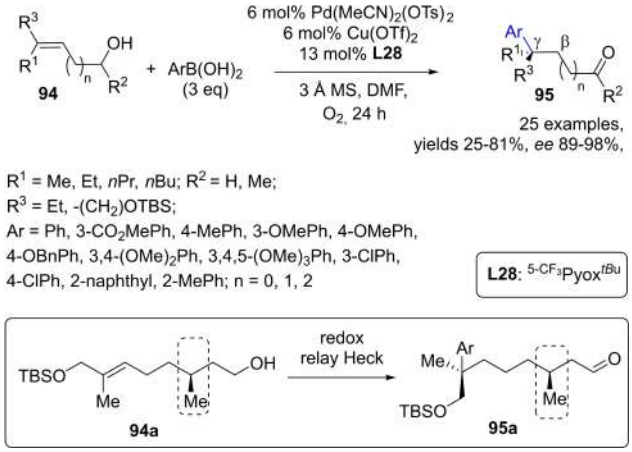
Scheme 44. Asymmetric arylation of alkenes **92** with β-hydride elimination driven by EWG located at $(-CH_2-)_n$ distance.

4.2.3. Redox-Relay Heck Reactions

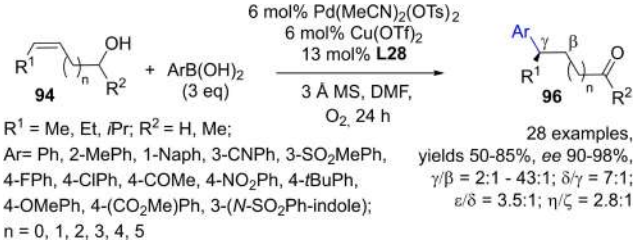
Among the oxidative Heck reactions, redox-relay Heck reactions represents a powerful strategy to build new chiral stereocenter along aliphatic chain and far away from functional groups, as aldehydes and ketones, paving the ways to unexplored building blocks. The Sigman's group developed several enantioselective redox-relay Heck reactions of di- and tri-substituted alkenyl alcohols using aryldiazonium salts,[109] arylboronic acids,[110] and alkenyl triflates,[111] to provide carbonyl compounds that contain remote alkenyl/alkynyl/aryl stereocenters. The key feature of these reactions is the "chain-walking", induced by the presence of the nucleophilic alcohol that acts as thermodynamic sink. The mechanism behind the chain-walking has been supported by computational studies,[112,113] demonstrating that (1) the product resulting from γ-insertion is thermodynamically stabilized (addition favored on the carbon further away from the EWG) and (2) the resulting aldehyde does not participate in migratory insertion.

To achieve the announced result, a key requirement was the employment of electron-withdrawing group ($-CF_3$) at the pyridine C-5 position of the Pyox ligand, which prevents the formation of the traditional Heck product (as seen in Scheme 9 and Scheme 44). In fact, the electronic features of the Pd-ligand complex allow repeated β-hydride eliminations and reinsertions, where the palladium migrates closer to the electronegative oxygen, without never dissociating. Ligation of the Pd-complex on the same face of the alkenes through the whole relay process has been demonstrated with *d*-labeling experiments, but in particular employing the chiral substrates **94a**, the product **95a** was obtained in high diastereoselectivity, without affecting the second stereocenter (Scheme 45).[110]

Moreover, since both carbons on the double bond might participate in the nucleophilic addition, site-selectivity is given by slight differences in the electronic structure of the reacting olefin as well as by steric effects, making the C_γ the favorable site for the insertion of the nucleophilic carbon and the C_β for the palladation. A highly selective asymmetric redox-relay oxidative Heck reaction was reported using achiral or racemic acyclic alkenols and boronic acid derivatives. In this case the regioselectivity of the initial migratory insertion was highly dependent on the electronic nature of the boronic acid and subtle electronic effects of the alkenyl alcohol **94**, specifically the boronic acid with the cyano group at the 3-position displayed the highest γ/β ratio (49:1), while the ones with the methoxy group in *para*-position gave the lowest selectivity (2.1:1) (Scheme 46). Also elongation of the alkenes chain led to decrease selectivity (from 16:1 for γ/β to 2.8:1 for η/ζ).[114]



Scheme 45. Redox-relay Heck strategy for the enantio- and diastereoselective synthesis of quaternary stereocenter in compound **95**.

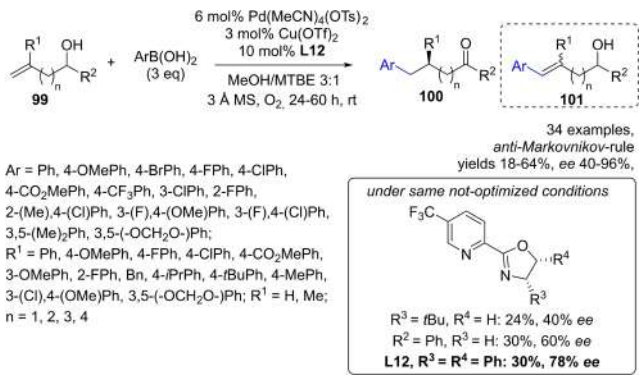


Scheme 46. Regioselective arylation in the γ-position of alkenes **94** in function of electronic properties of alkenes **94** and of aryl boronic acids.

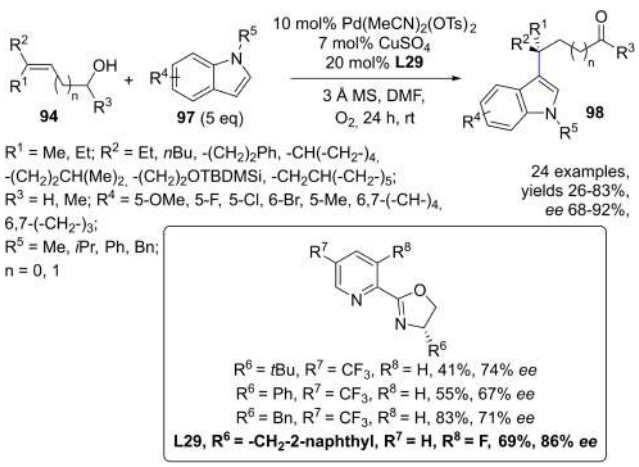
Intermolecular dehydrogenative Heck arylation was extended to the trisubstituted alkenes in combination with *N*-protected indoles **97** as coupling agents, for the construction of remote quaternary stereocenters (Scheme 47).[115] In this case, the design of a new 2-naphthyl Pyox ligand, **L29**, featuring an extended aromatic moiety, which might take part in putative π-interactions, was fundamental to achieve excellent enantioselectivity in **98** (92% *ee*).

Selecting 1,1-disubstituted homoallylic alcohols **99** as substrates, an enantioselective redox-relay Heck reaction forming the 1,2-diaryl carbonyl derivatives **100**, instead of the styrenyl product **101**, thermodynamically stable and already described under similar conditions,[116] has been developed.[117] The design of a new ligand, bearing two vicinal phenyl substituent on the oxazoline ring, **L12**, overcame the propensity to form the trisubstituted styrene, leading at the same time to higher enantioselectivity for the products **100** (Scheme 48).

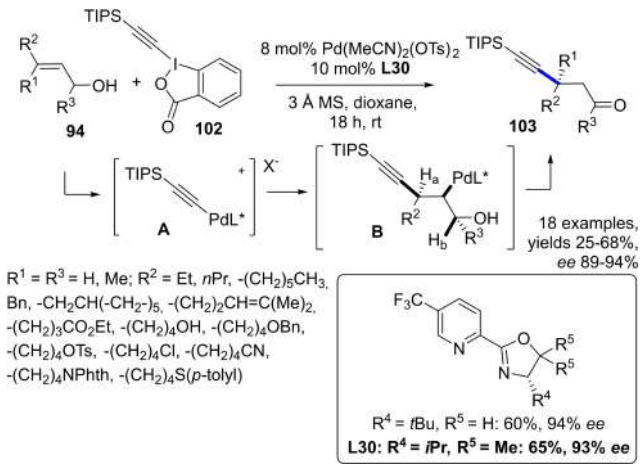
In 2017, enantioselective alkynylation of di- and trisubstituted alkenols **94** was also described, allowing the formation of challenging propargylic stereocenters in **103**.[118] The design of a new ligand, featuring an *i*Pr group and a *gem*-dimethyl moiety on the oxazoline portion (**L30**) improved slightly yield, compare to $^{5-CF3-}$Pyox^{tBu}, maintaining high enantioselectivity. Benziodoxole derived triisopropylsilyl variant **102** (TIPS–EBX) was identified as best alkynyl source (Scheme 49). Also in this case, complete selectivity for the formation of the alkynyl aldehyde, rather than the classical Heck-type product or the homocoupling product, was obtained, through the suggested mecha-



Scheme 48. Selective *anti*-Markovnikov addition of aryl boronic acids to yield 1,2-diaryl carbonyl compounds **100**.



Scheme 47. *N*-Me indoles **97** as coupling partners in enantioselective remote functionalization of aldehydes and ketones **98**.



Scheme 49. Asymmetric β-alkynylation by using hypervalent iodine **102** in the presence of Pd(II)/**L30** catalytic system.

nism involving Pd–alkynyl species **A** followed by alkenol insertion to give **B** and β-hydride elimination of H_b.

Chain walking reactions using different electron withdrawing group as thermodynamic sink have been explored, too. However, in these cases, no oxidation to the aldehyde occurs and thus the redox relay is not taking place. Nevertheless, since the following reactions are a conceptual development of the previous ones they will still be discussed in this paragraph. Therefore, the use of an aromatic group, usually alkenylbenzenes, was exploited as way to access styrenes with remote stereocenters.[119] However, in this case a palladium (0) source was required due to the coupling with the alkenyl triflates. Instead, using amide as EWG, interruption of the chain-walking was observed.[120] Using as substrates homoallylic protected amines **104**, it was possible to selectively interrupt the "chain-walking" process, allowing the divergent formation of the preferred allylic products **105** over the ene amide-type products **106** (Scheme 50). Supported by DFT studies and labeling experiments the authors hypothesized that a combination of the reversible nature of the chain-walking process, involvement of the carbonyl in the displacement of the alkene through ligand exchange, or the stabilization of intermediate Pd–alkyl species might take part in the product determining step. The instability of intermediates that would lead to the ene amide-type products **106**, afforded the selective formation of allylic products **105**, specifically for homoallylic imides, biscarbamates, sulfonamides, and trifluoroacetamides. On the other hand, the formation of the ene product **106**, together with diarylation step was observed when alkyl and aryl amides were employed.

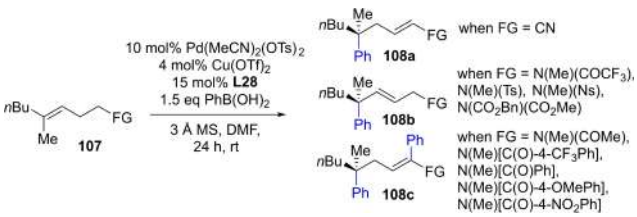
Therefore, the remote functional group attached to an alkene and the chain length between the two groups can have considerable impact on the selectivity and the chain-walking. In particular, functional group (FG), ranging from amides, imides, sulfonamides, nitriles, carbamates, ketones and alcohols, can modulate either the binding affinity for the alkene **107** or the barrier of the migratory insertion of the aryl–palladium species into the alkene. The lack of a direct correlation between the rates observed and the calculated transition states suggested that the migratory insertion was not always the rate-limiting step. DFT calculations could be used to predict the impact of the terminal group on the rate of the reaction.[121] Thus the predictive model could be used to design diene substrates that can undergo site-selective functionalization, based on the nature of the terminal group **108 a**–**c** (Scheme 51).

4.3. Hydrocarbofunctionalization

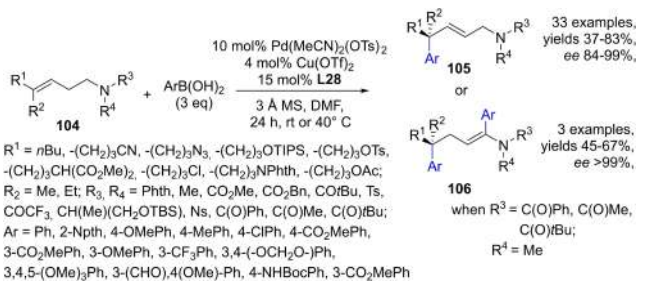
Hydrocarbofunctionalization reactions have been reported mainly using styrenes as substrates, few cases involving β,γ-unsaturated amides, bearing 8-aminoquinoline (8-AQ) as directing group and addition to α,β-unsaturated carbonyls, known as Hayashi-Miyaura reaction. Asymmetric hydroarylation of styrenes and dienes **109** with boronic esters or organostannanes has been reported by Sigman, performing the reaction in the presence of $Pd(MeCN)_2Cl_2$ (2.5 mol%), bisoxazoline (10 mol%), using oxygen as oxidant in *i*PrOH, at 55°C (Scheme 52). The best results in term of *ee* was obtained with (*S*)-*i*PrBOX, **L31**. However the *ee* didn't exceed the 59% and yields of **110** stayed in a range between 28 and 53%.[122]

On the other hand, nitrostyrenes **111** were suitable substrates for the addition of arylboronic acids affording β,β-diaryl substituted nitroalkanes **112** with good enantioselectivity and yields (up to 96%). The optimized conditions consisted of 5 mol% $Pd(TFA)_2$, *i*Pr–IsoQuinox as chiral ligand (**L32**), in MeOH as solvent under air atmosphere. The *ee* decreased using electron-deficient arylboronic acids (Scheme 53).[123]

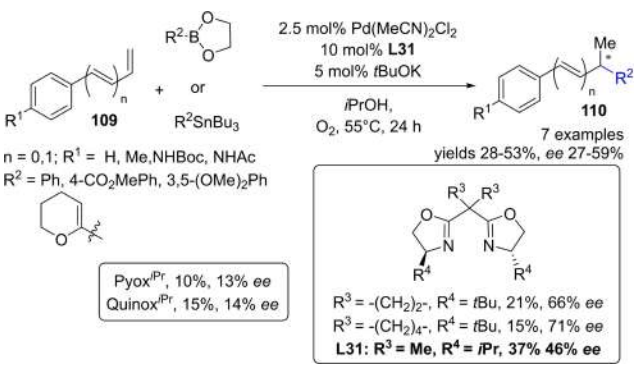
Working on unactivated alkenes, the introduction of the bidentate 8-aminoquinoline directing group to the substrates, **113**, was critical to address the regioselectivity in intermolecular hydrofunctionalization of the double bond and the presence of a chiral monodentate oxazoline ligand (MOXin, **L33**) provided



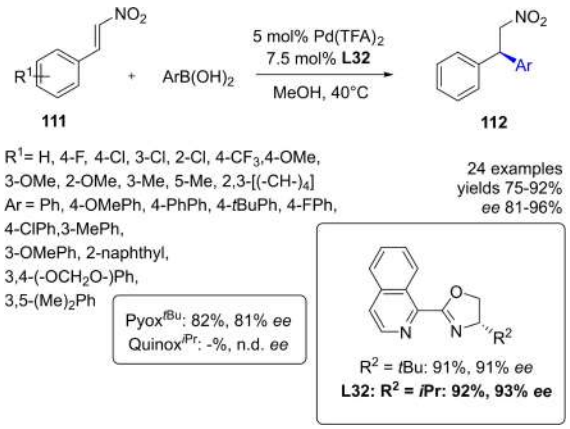
Scheme 51. Summary of the different outcomes investigated in function of the FG located at $(–CH_2–)_2$ distance from the olefin.



Scheme 50. Divergent reactivity of amides **104** in function of the $–R^3$ and $–R^4$ substituents, yielding allylic **105** or diarylated ene-products **106**.

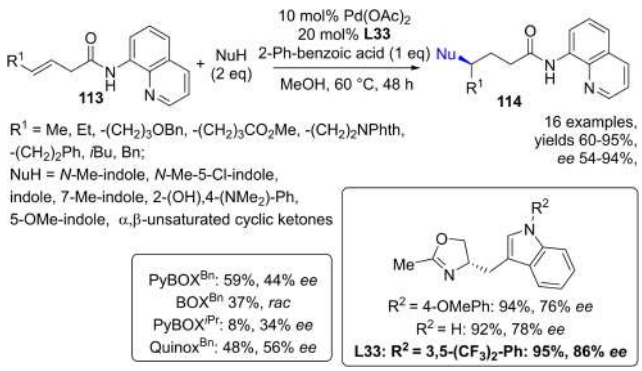


Scheme 52. Hydrocarbofunctionalization of styrene derivarives **109** in the presence of BOX ligand.

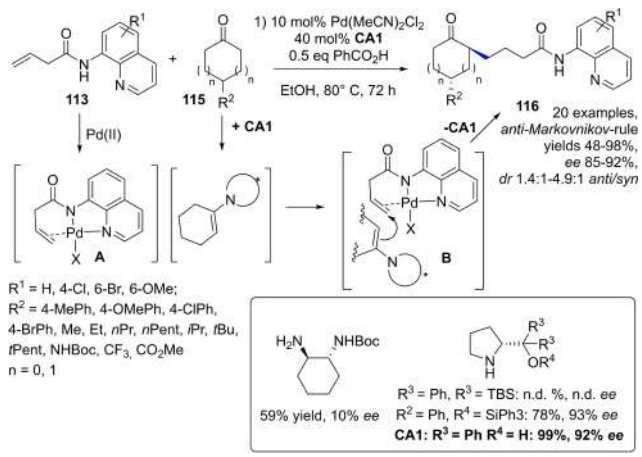


Scheme 53. Asymmetric synthesis of β,β-diaryl substituted nitroalkanes **112** through Pd(II)-catalyzed reactions.

an important advance in the enantioselectivity of asymmetric catalysis (Scheme 54). Various indoles reacted at C3 position to give products **114** through γ-addition.[56]



Scheme 54. Chiral monodentate oxazoline ligand, **L33**, and 8-AQ as directing group for the regio- and enantioselective synthesis of **114**.



Scheme 55. *Anti*-Markovnikov addition of cyclic ketones **115** to alkenyl amides **113** using chiral amine as chiral information.

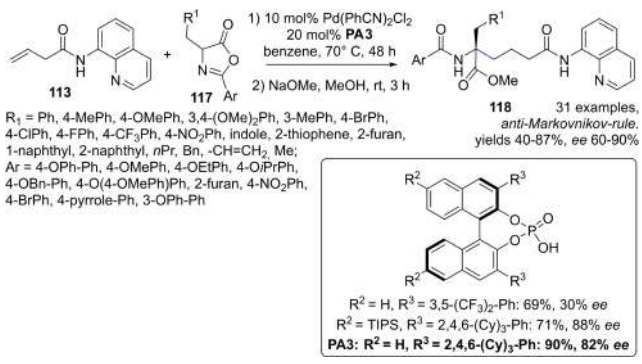
Addition of enolizable cyclic ketones to the above substrates **113** has been realized with total regioselectivity and high stereocontrol exploiting the cooperative catalytic effect of Pd(II) and chiral amine **CA1**. Specifically, the enamine generated from a chiral amine might be reactive enough to attack the alkene–Pd complex (**A**), leading to an enantio- and regioselective Wacker-type reaction with the formation of the desired product (Scheme 55). Using 4-substituted cyclohexanones, the desymmetrization of the process allowed the formation of two stereogenic centers in a single step, in a diastereomeric ratio from 1.8/1 to 4.9/1 and high enantioselectivity for the major diastereomer.[124] DFT calculations showed that the origin of the stereoselectivity is determined at the nucleophilic addition step.

The use of non-conjugated alkenes and carbonyl pronucleophiles as reaction partners in a Wacker-type reaction would represent a powerful approach towards enantioselective α-alkylation (Scheme 56). In this contest, the use of azalactones **117** as masked amino acid pronucleophiles and chiral phosphoric acids **PA3** as chiral ligand allowed the synthesis of **118** through an enantioselective addition (*ee* up to 90%). The use of nonpolar solvent was critical for the stereoinduction.[125]

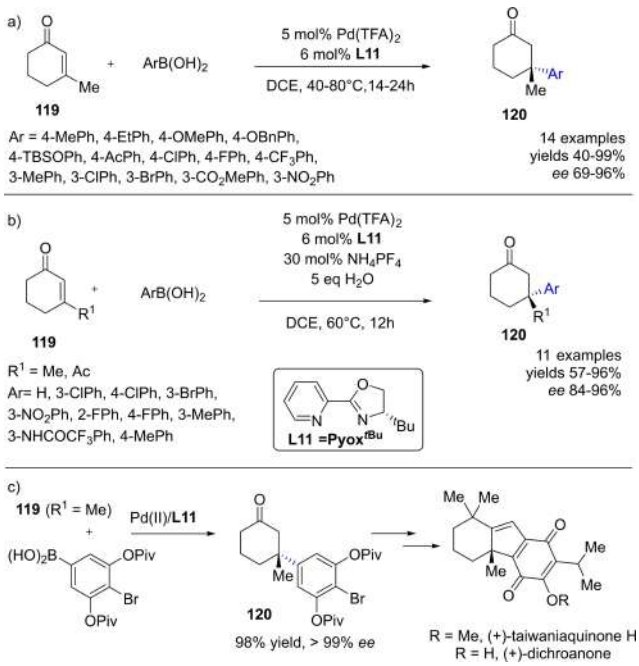
4.3.1. Hayashi-Miyaura Reaction (Conjugate Addition to α,β-Unsaturated Carbonyls)

The research group of Stoltz did a very extensive study on the palladium-catalyzed asymmetric conjugate addition of cyclic electron-poor alkenes involving the arylboronic acids, reporting both mono- and di-functionalization processes.

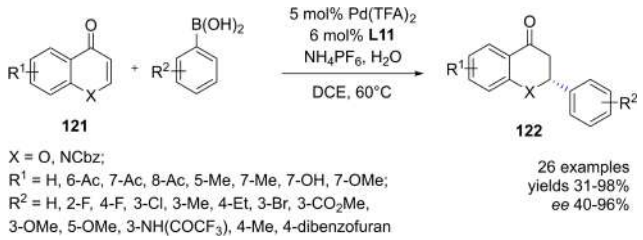
The α,β-unsaturated carbonyl compounds **119** were used in enantioselective conjugate addition with arylboronic acids to deliver β,β-disubstituted cyclic ketones **120** containing quaternary stereocenter in high *ee*. Five-, six- and seven-membered ring enones were reacted with a wide variety of commercially available arylboronic acids. The reaction was performed with $Pd(TFA)_2$ (5 mol%) in the presence of the chiral $Pyox^{tBu}$ as ligand (6 mol%), in DCE (Scheme 57a).[126] The procedure has been later improved with the addition of NH_4PF_6 and water, which accelerated the reaction and allowed to lower the temperature (Scheme 57b).[127]



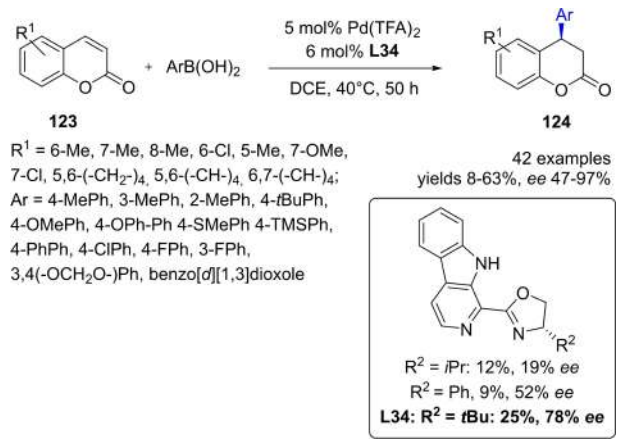
Scheme 56. Addition of azalactones **117** to alkenes **113** as route to access chiral amino acids **118**.



Scheme 57. Enantioselective addition of aryl boronic acids to α,β-unsaturated cyclic ketones **119** as route to access tricyclic terpenoids.



Scheme 58. Asymmetric conjugate addition to chromones and 4-quinolones **121**.



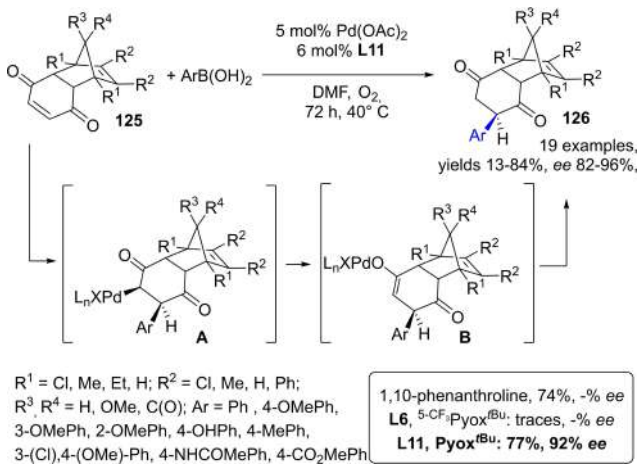
Scheme 59. Pd-catalyzed addition of arylboronic acids to coumarins **123** using *t*Bu–carboline–oxazoline **L34** as ligand.

When the reaction was performed on a small scale, the moisture present in the air was sufficient to drive the reaction to completion. The scale-up of the reaction demonstrated that the reaction needed the presence of water as proton donor to replace the palladium in position 2 of the ketone **119**. At the same time, also the addition of salt additives containing weakly coordinating counterions for the palladium led to an increase in reaction rate. The ammonium hexafluorophosphate gave the optimal combination of short reaction time and high *ee*. Computational study gave elucidation on the reaction mechanism, involving the transmetalation from boron to palladium and justifying the enantioselectivity controlled mainly by the steric repulsion of the *t*Bu substituent of the oxazoline ligand and the C-2 of the ketone.[128] This synthetic strategy was applied in the asymmetric total syntheses of the tricyclic diterpenoids (+)-dichroanone and (+)-taiwaniaquinone H (Scheme 57c).[129]

The same protocol was applied also to chromones and 4-quinolones **121** affording 2-aryl derivatives **122**, through the enantioselective conjugate addition of arylboronic acids (Scheme 58).[130]

Very recently, Li reported the first Pd-catalyzed asymmetric addition of arylboronic acids to coumarins **123** providing 4-aryl-3,4-dihydrocoumarins **124** (Scheme 59). The protocol, involving $Pd(TFA)_2$ and chiral *t*Bu–carboline–oxazoline ligand **L34**, was compatible with either electron-withdrawing or electron-donating groups on the arylboronic acids and on the substituted coumarins. Limitations were observed with the use of aliphatic boronic acids.[131]

Then, Lee *et al.* reported the reaction of polycyclic cyclohexenediones **125** as substrates able to produce, through conjugated addition and desymmetrization, up to five stereocenters simultaneously (Scheme 60). The process was completely regioselective, also because symmetric α,β-conjugated polycyclic cyclohexenediones were employed. Only in the case of substrates bearing not sterically bulky group on R^1 and R^2 position, the β-hydride elimination was observed, yielding the classic Heck product. The desired quaternary carbon formation



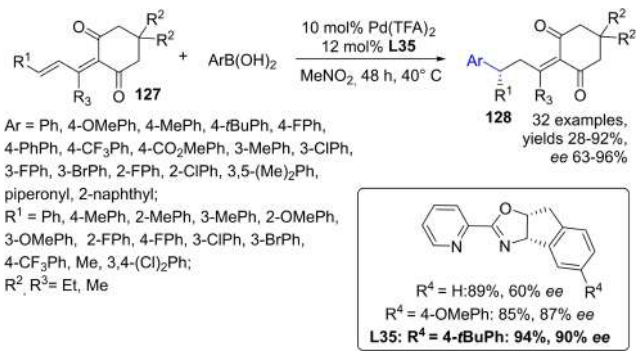
Scheme 60. Pd-catalyzed addition to polycyclic cyclohexenediones **125**, affording up to five stereocenters in **126**.

was probably due to the steric hindrance in the *endo* face of the substrates, favoring the Pd-enolate isomerization step (**B**) and consequent decomplexation.[132]

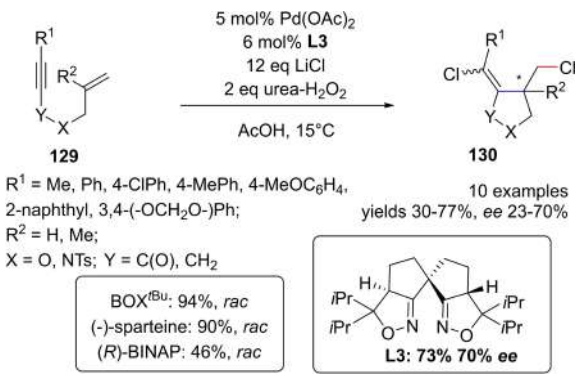
If 1,4-conjugate additions of boronic acids to α,β-unsaturated carbonyl compounds have been well studied, conversely, 1,6-conjugate additions have not been widely reported due to the difficult to control the regioselectivity and enantioselectivity (Scheme 61).[133] To this aim, Meldrum acid-derived dienes **127**, bearing electron-deficient or electron-rich substituents, were used in coupling reaction with arylboronic acids providing 1,6-addition with high enantioselectivity by the use of a new chiral In–Pyox–**L35** bearing an extended arm. The best catalyst was $Pd(TFA)_2$ in $MeNO_2$ as solvent.

4.4. Difunctionalization Reactions

The efficiency of the domino reactions as strategy for the skeleton difunctionalization is widely recognized, both as intramolecular and intermolecular processes.



Scheme 61. Meldrum acid-derived dienes **127** as substrates in aryl boronic addition using In–Pyox, **L35**, as ligand.



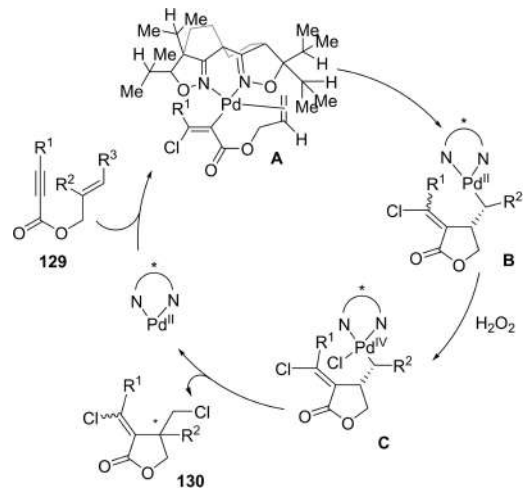
Scheme 62. Cascade reaction of 1,6-enynes **129** in the presence of Pd(II)-catalyst and SPRIX ligand **L3**.

4.4.1. Intra-intermolecular Difunctionalization

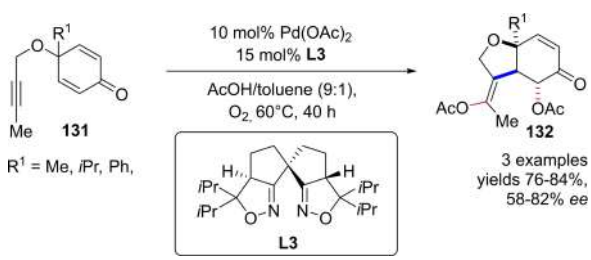
The domino reaction of 1,6-enynes **129**, in the presence of Pd(II)-catalyst, H_2O_2 as oxidant and LiCl as nucleophile, afforded chlorinated α-methylene-γ-lactones **130** through a dichlorination-cyclization process. Respect to the previous reported racemic synthesis,[134] the use of chiral ligand SPRIX **L3** showing high stability under oxidative conditions, was crucial to obtain enantioselectivity (Scheme 62). No enantioselectivity was observed with other known chiral ligands.[135]

After the initial chloropalladation at the triple bond, the insertion of the olefin produced a σ-alkyl Pd(II) species **B** then oxidized to Pd(IV) **C**. The nucleophilic attack by Cl^- afforded the product and regenerated the catalytic active Pd(II) specie. The enantioselectivity was controlled in the step of intramolecular olefin insertion. Coordination of the olefin to avoid steric repulsion towards the (*M,S,S*)-*i*Pr–SPRIX provided the intermediate **A**, from which the major (*R*)-enantiomer was obtained (Scheme 63).

Also alkynyl cyclohexadienones **131** are suitable substrates for difunctionalization process, consisting of a cyclization step with C–C bond formation followed by a diacetoxylation, exploiting the same ligand (**L3**) but with the advantage to use oxygen as oxidant (Scheme 64).[136]



Scheme 63. Mechanism and related intermediates affording compound **130** from 1,6-enynes **129**.



Scheme 64. Intramolecular asymmetric cyclization of alkynyl cyclohexadienones **131** in the presence of **L3** and subsequent enantioselective acetoxylation.

4.4.2. Inter-intermolecular Difunctionalization

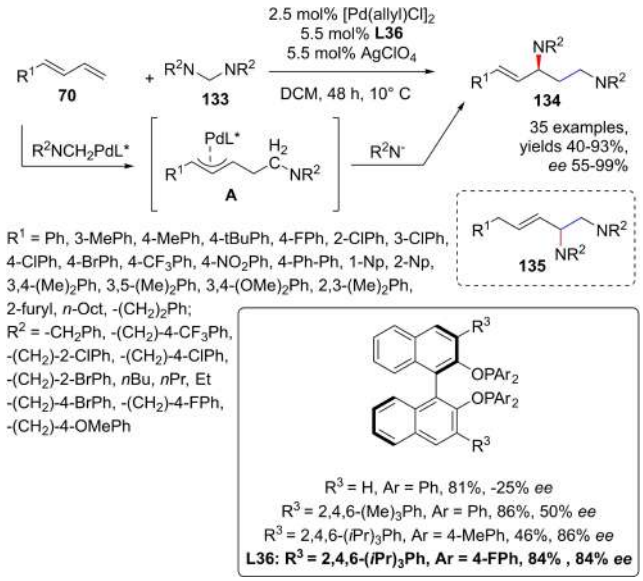
A 1,2-difunzionalizations of dienes **70** with aminals **133** has been developed through a chiral palladium complex ligated with BINOL-derived chiral diphosphinite **L36**.[137] This Pd-catalyzed cascade reaction proceeds *via* a C–N bond activation, aminomethylation, and asymmetric allylic amination reaction. Therefore, the role of the chiral palladium complex is crucial in the allylic amination reaction, rather than the palladation step (Scheme 65). On the contrary, all the ligand widely used in Pd-catalyzed asymmetric allylic alkylations, such as diphosphine, monophosphine, chiral phosphine–oxazoline-type P,N ligands did not give good results. Deuterium migration was observed during *d*-labeled experiments, and for this reason the authors speculated that β-hydride elimination from **A** and reinsertion to form allylic–Pd intermediate **B** were most likely involved. This mechanism could also explain the formation of the 1,1 aminomethylated product **135** beside the main product **134**. The **134**/**135** ratio could be increased by increasing the steric hindrance on the BINAPO, **L36**.

A particular cascade reaction to access chiral 2-vinyl–indolines **137** was reported starting from aryl ureas **136** and 1,3-dienes **70**, based on the *ortho* C–H activation and the urea acting as directing group for the alkene insertion. The use of a new chiral sulfoxide–oxazoline (SOX) ligand **L37** bearing single chiral center on the sulfur was the optimal ligand for the stereocontrol of the allylation step. Electron-rich phenyl ureas gave higher yields, implying the C–H activation process might go through an electrophilic palladation pathway (Scheme 66). The indoline derivatives **137** resulted in high yields and enantioselectivity (up to 90% *ee)* performing the reaction with $Pd(MeCN)_2(OTs)_2$ as catalyst, in THF as solvent and using 2,5-dimethyl–benzoquinone (2,5-DMBQ) as oxidant.[138]

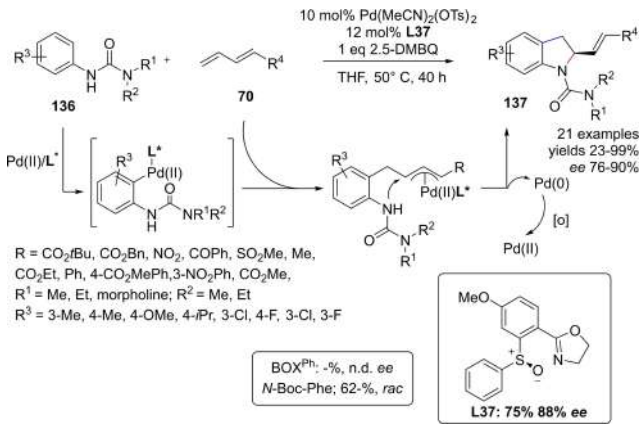
Among the 1,2-difunctionalization, the enantioselective version of carboboration of alkenes has been developed using as substrates unactivated alkenyl carbonyl compounds **113**, bearing as directing group the 8-aminoquinoline, substituted *N*-methylindoles **97** as nucleophile and B_2pin_2 as boron coupling partner (Scheme 67). The reaction conditions included $Pd(OAc)_2$ as catalyst and monodentate oxazoline ligand **L33**, in the presence of BQ/O_2 as oxidant and NaF (2 equiv), at 45°C for 5d. Screening of the solvents showed that a mixture of HFIP/THF/DMF 2:2:1 improved both yields and *ee*. The alkylboronate products **138** were obtained with moderate to high enantioselectivity. The reaction proceeded through five- and six-membered palladacycle intermediates to insert a secondary boron group to the β or γ positions relative to the carbonyl group. Upon complexation, the facile *E/Z* isomerization can justify the stereoconvergence of *Z*- and *E*-alkenes.[139]

The same reaction provided better results in terms of yields and *ee*, using chiral monodentate oxazoline (MOX) **L38** as ligand, TFE as solvent and 2 equiv. of potassium trifluoroacetate (KTFA) as additive (Scheme 68).[57]

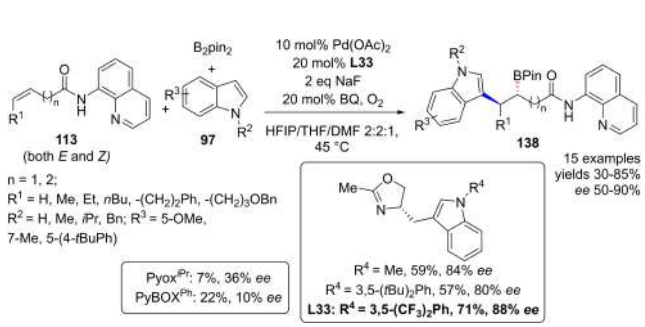
Considering the synthetic interest of the β-*tert*-functional carbonyls, an efficient synthetic alternative to the nucleophilic addition of boron derivatives to α,β-unsaturated systems has been developed (Scheme 69). The strategy consisted on the cross-coupling between alkenylboronates **140** and carbamoyl chloride **141**, by a reaction that involved acyl palladium complexes to promote a 1,2-metallate shift as key step for the



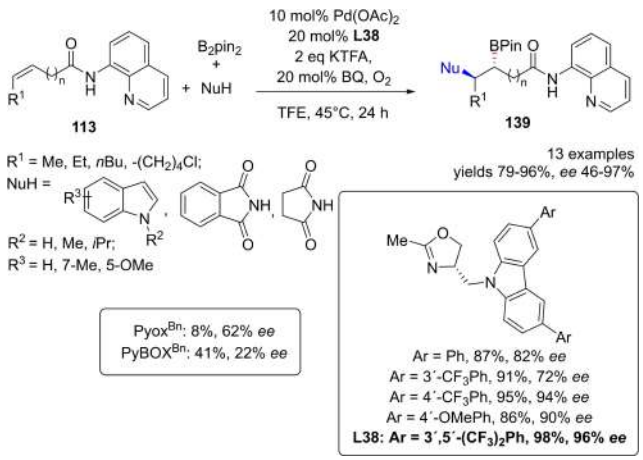
Scheme 65. BINOL-derived chiral diphosphinite **L36** as Pd(II)-ligand in the1,2-difunctionalizations of dienes **70** with aminals **133**.



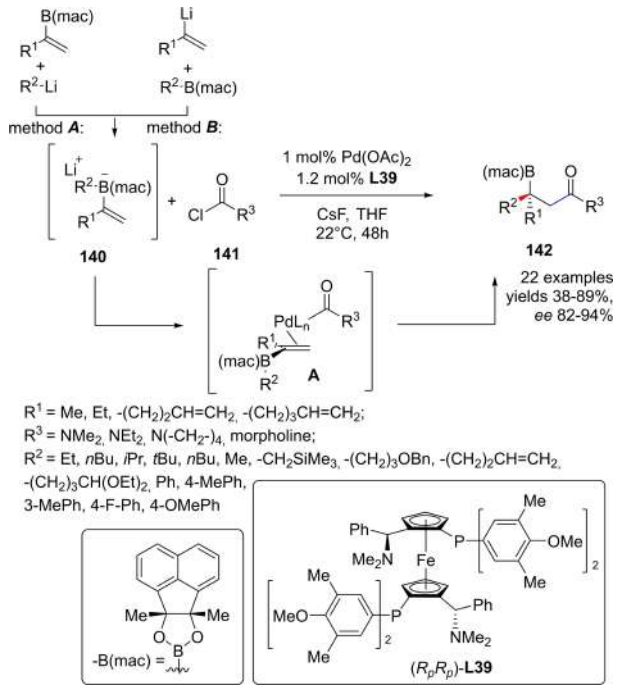
Scheme 66. Domino reaction of aryl ureas **136** in the presence of dienes **70**, yielding chiral 2-vinyl–indolines **137**.



Scheme 67. Carboboration of alkenyl amides **113** bearing 8-AQ as directing group, using monodentate ligand **L33**.



Scheme 68. Synergistic effect of ligand **L38** and 8-AQ in controlling enantio- and regioselectivity of **139**, respectively.



Scheme 69. 1,2-Difunctionalization of activated alkenes **140** in the presence of ferrocene **L39** ligand and by using carbamoyl chloride **141** as second partner.

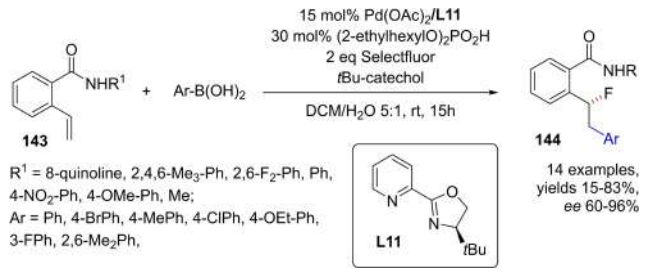
coupling. Moreover, the presence of MandyPhos as ligand (**L39**), resulted in a high level of enantioselectivity.[140] The use of "mac" diol ligand on **140**, addition of CsF and H_2O enabled the reaction on both aliphatic and aromatic substrates. Cesium fluoride would undergo ion exchange with lithium complex to furnish a more reactive cesium complex, water improved the solubility of CsF.

A great wealth of data are reported in literature on the alkenes difunctionalization involving arylboronic derivatives. Asymmetric fluoroarylation of styrenes **143** was realized in the presence of boronic acid and Selecfluor as the fluorine source (Scheme 70).[141] The substrates exploited the presence of *o*-amide substituents as directing group, in particular the amide arising from 8-quinoline amine stabilizes the metal intermediate. The methylene chloride was the solvent of choice, no coupling product was formed in toluene, DMF, THF, MeCN and AcOEt. Water was found to increase the reaction rate, therefore the ideal solvent consisted of a biphasic mixture DCM/H_2O (5:1 v/v), helping also to keep the product **144** away from further oxidation.[142]

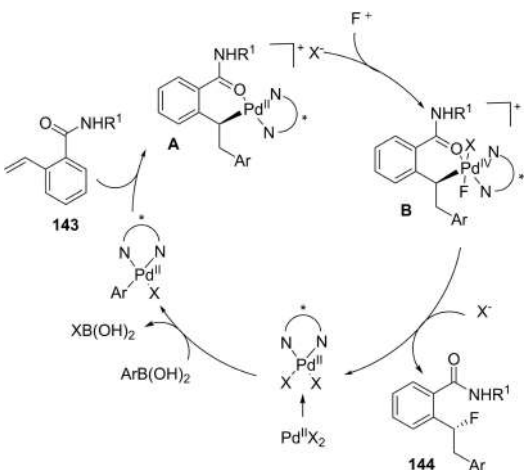
The mechanism proceeded through an oxidative Heck-type coupling involving Pd(II)/Pd(IV) oxidation process.[141] In order to obtain enantioselectivity in the fluoroarylated product **144**, the 2,2′-pyridine–oxazoline chiral ligand was the best choice for good to excellent results (Scheme 71).

The same mechanism was entailed in the fluoroarylation process of unactivated aminoalkenes **145** with the formation of chiral benzylic fluorides **146**, exploiting three-component coupling reaction, in the presence of arylboronic acids and Selecfluor, affording the 1,1-fluoroarylation product **146** with total regioselectivity and satisfying enantioselectivity with the formation of chiral benzylic fluorides (Scheme 72). The reaction proceeded smoothly in CH_2Cl_2/H_2O (5:1 v/v), using the Pd-$(MeCN)_2Cl_2$/4,4′-dibenzyl-2,2′-bisoxazoline (**L40**) catalytic system and in the presence of phenylacetonitrile as additive.[143]

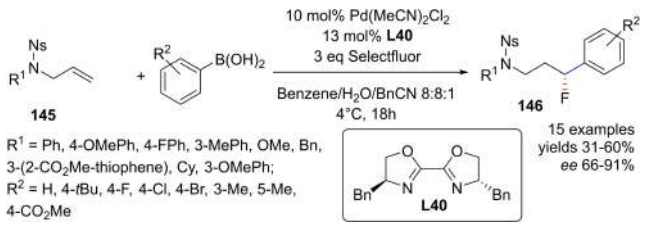
Using the chromenes **147** as substrates, the arylfluorination reaction reported a divergent regioselectivity affording both



Scheme 70. Pd(II)-catalyzed asymmetric fluorination of styrenes **143**.

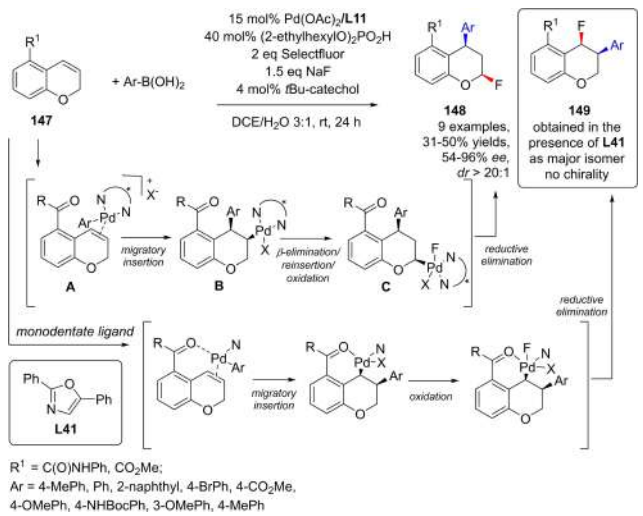


Scheme 71. Mechanism involved in the carbofluorination of styrenes **143**.

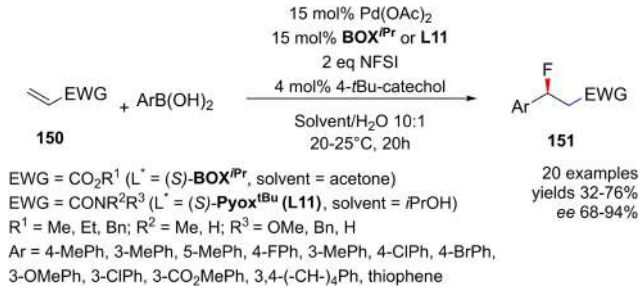


Scheme 72. 1,1-Difunctionalization of unactivated aminoalkenes **145** using **L40** as chiral ligand.

the 1,2- and 1,3-difunctionalization depending on the ligand used and the presence of a directing group on the substrate. In fact, to obtain the 1,3-arylfluorinated product **148**, the presence of electron-withdrawing group in position 4 of the chromene was mandatory. (Scheme 73)[144] The presence of a strong bidentate ligand, such as the 4,4′-di-*tert*-butyl-2,2′-bipyridine or Pyox^{tBu} (**L11**), favors the transmetallation step of the arylboronic acid and the formation of the subsequent cationic palladium specie **C**. The subsequent migration and oxidation afforded the 1,3-disubstituted product. The selectivity for the 1,2-product



Scheme 73. Ligand effect on the regioselective carbofluorination of chromenes **147**.



Scheme 74. 1,1-Difunctionalization of activated alkenes **150** by using Pd(II)-catalyst and **BOX** or **Pyox** ligand in function of the substrate.

149 was enhanced by the presence of monodentate ligands, such as oxazole **L41** and pyridines.

More in general, the fluoroarylation addition of α,β-unsaturated carbonyl derivatives **150** has been developed exploiting the arylboronic acids and *N*-fluorobenzenesulfonimide with the formation of β,β-fluoroarylated product **151** (Scheme 74). In this case, the reaction conditions previously reported with the use of Selectfluor as fluorine donor, didn't give the addition. The reaction was performed with $Pd(OAc)_2$, 15 mol%, bisoxazoline or pyridine–oxazoline Pyox^{tBu} (**L11**) as ligand in acetone/H_2O 10:1 or *i*PrOH/H_2O 10:1 at r.t., depending on the electron-withdrawing group present on the double bond (ester or amide). Also in this case, the presence of water was mandatory and the mechanism run through Pd(II)/Pd(IV) intermediate.[145]

5. Perspective and Outlook

The significant steps, which have been made in the last years, regarding asymmetric Pd(II)-catalyzed reactions, have shown that the role of Pd(II) goes further beyond the classic Wacker oxidation of ethylene and that different reaction pathways, including Wacker aza-Wacker and Heck process as well as difunctionalization and cascade reactions, can be obtained starting from simple substrates, like alkenes. Design of new ligands and modification of preexisting motifs has not only allowed the success of transformations in higher yields but has also enabled to provide new stereocenters in high enantioselectivities. Reactions and goals, which were challenging some years ago, have been recently made feasible, highlighting the continuous crescendo of this field. With the present review, we want to offer a manual to draw the key aspects regarding reaction conditions optimizations (see Table 1), providing a tool for developing new enantioselective transformations.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: (aza)-Wacker reaction · Enantioselectivity · Oxidative Heck reaction · Alkenes · Palladium

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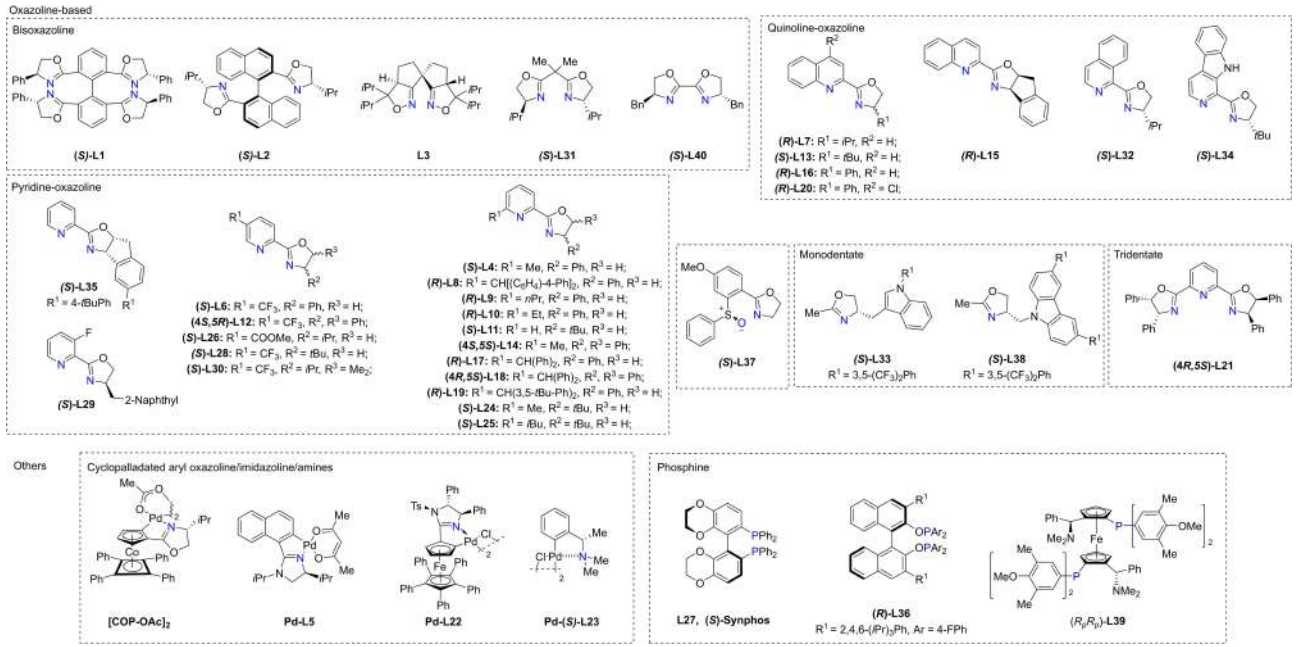
Table 1. Summary of the key aspects and critical parameters for enantioselective Pd(II)-catalyzed functionalization.[a]



Type of reaction	Substrate	Pd source	Lig	[c]*cis trans*	[c]*Selectivity*	[Ox]	Additive	Solvent	Critical Parameters	Ref.
C–O bond formation										
Wacker-type	Alkene tethered to phenol	$Pd(TFA)_2$	**L1, L2**	–	*exo*	*p*-BQ	–	MeOH	Type of substitution on the oxazoline ring.	[23,25]
Wacker-type	Alkene tethered to phenol	–	**[COP–OAc]$_2$**	*trans*	*exo*	–	KF (in few examples)	DCM	No significant differences among complexes tested.	[28]
Wacker-type	Alkene tethered to carboxylic acid	$Pd(OAc)_2$	**L3**	–	*exo*	*p*-BQ	–	DCM	Type of ligand.	[30]
Wacker-type/Ring contraction	5,6-dihydro-2*H*-benzo[*b*]-[1,4]oxazocine	$Pd(OAc)_2$	**L4**	–	*exo*	–	4-Ph–$PhCO_2H$	toluene	Substitution on the C-6 position of the pyridine on the ligand; presence of an acid additive	[34]
Wacker/Rear-range-ment	Allylic trichloro-acetimidate	–	**[COP–OAc]$_2$, Pd–L5**	–	*endo*	–	–	DCM	Competitive *N*-attack through a rearrangement of the substrate, in function of the anion on the ligand.	[36,37]
Wacker-type	Phenol/alkenol	$Pd(MeCN)_2(OTs)_2$	**L6**	*cis*	–	*p*-BQ	$Ca(OH)_2$/ 3 Å MS	$PhCF_3$	Substitution on C5 of pyridine in **L6** with of EWG. Type of oxidant.	[38]
Difunctionalization	Vinyl phenol	$Pd(MeCN)_2Cl_2$	**L7**	–	*exo*	O_2	CuCl, $KHCO_3$	toluene/ THF	Type of solvent.	[48] [49]
Difunctionalization	Alkene tethered to phenol	$Pd(TFA)_2$	**L2**	–	*exo*	*p*-BQ	–	MeOH	Type of substitution on the oxazoline ring.	[26,50,51]
Difunctionalization	(Aza)-alkenols, *N*-allyl amino-phenol	$Pd(OAc)_2$	**L8**	*cis*	*exo*	$PhI(mcba)_2$	–	xylene/ DCM	Type of oxidant and substitution on Pyox with bulky group. *T* (°C). Apolar solvent. Only terminal alkenes.	[52] [18]
Difunctionalization	Terminal Alkene	$Pd(OAc)_2$	**L9**	*trans*	*Mark*	$PhI(OAc)_2$	–	AcOH	Type of oxidant and substitution on C6 of pyridine in **L9** with aliphatic group. *T* (°C)	[54]

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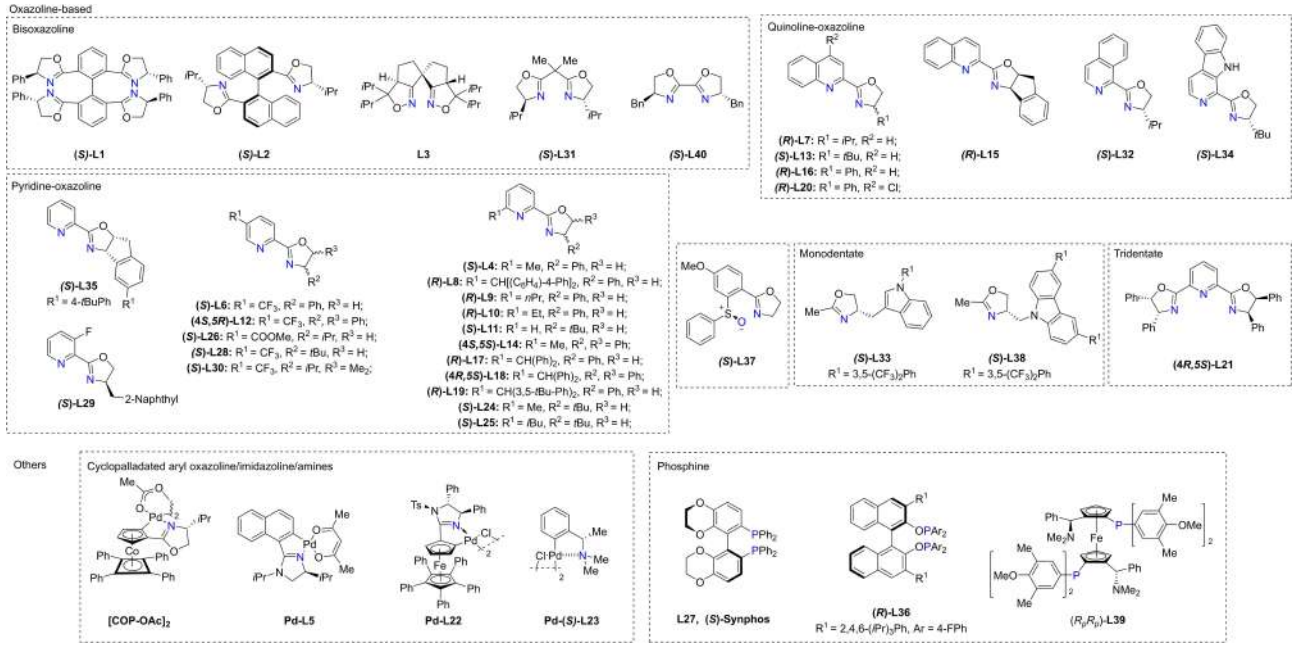
Table 1. continued



Type of reaction	Substrate	Pd source	Lig	[c]*cis trans*	[c]*Selec-tivity*	[Ox]	Additive	Solvent	Critical Parameters	Ref.
Difunctionalization	Terminal alkene	$Pd(OAc)_2$	**L10**	–	*Mark*	$PhI(OAc)_2$	–	AcOH/ Et_2O	Type of oxidant and substitution on C6 of pyridine in **L10**.	[55]
Hydrooxy-genation	Terminal alkene	$Pd(OAc)_2$	**L9**	–	*Mark*	*p*-BQ	–	TCE/ H_2O	Type of hydrosilanes, carboxylic acids and substitution on *C6* of Py in **L9.**	[58]
C–N bond formation										
aza-Wacker	Aminoalkene	$Pd(OAc)_2$ $Pd(TFA)_2$	**L4**	*cis* *trans*	*exo*	O_2	3 Å MS	toluene	*Cis* or *trans* in function of the Pd salt. Type of substitution on Pyox ligand.	[60] [69]
aza-Wacker	Vinyl benzamide	$Pd(TFA)_2$	**L11**	*cis*	*exo*	O_2	–	MeCN	Pd(II) specie. Herein **L7** is a poor ligand. Polar solvent are preferred.	[68]
aza-Wacker	Alkenyl sulfona-mide	$Pd(OAc)_2$	**L3**	–	*exo*	oxone		PhCl	Type of oxidant and ligand.	[70]
aza-Wacker	*N*-Ts-hydrazine tethered to al-kene	$Pd(OAc)_2$	**L11**	*cis*	*exo*	O_2	–	acetone	Type of solvent. Herein **L24** is a poor ligand.	[71]
aza-Wacker	Alkenols and benzylamine/ indole	$Pd(MeCN)_2(OTs)_2$	**L12** **L6**	*cis* *cis*	*Mark*	*p*-BQ *p*-BQ	DTBMP -/3 Å MS	$CHCl_3$ DCM	Type of oxidant and of base. Type of oxidant and without base.	[73] [74]
Difunctionalization	Anilide	$Pd(OAc)_2$	**L13**	*cis*	*exo*	O_2	2,6-lutidine MS, $HNTf_2$	toluene	Type of ligand: BOX, PyBOX and Pyox without C6 substitu-tion are poor ligand.	[72]
Difunctionalization	*N*-alkenyl acrylamide	$Pd(TFA)_2$	**L14**	*trans*	*exo*	O_2	3 Å MS, K_2HCO_3	toluene	Presence of phenyl groups on the oxazoline side of the ligand.	[76]
Difunctionalization	*N*-alkenyl acrylamide	$Pd(TFA)_2$	**L13**	*trans*	*exo*	O_2	**PA1**, 3 Å MS	toluene	Presence of a bulky phosphoric acid (PA).	[78]

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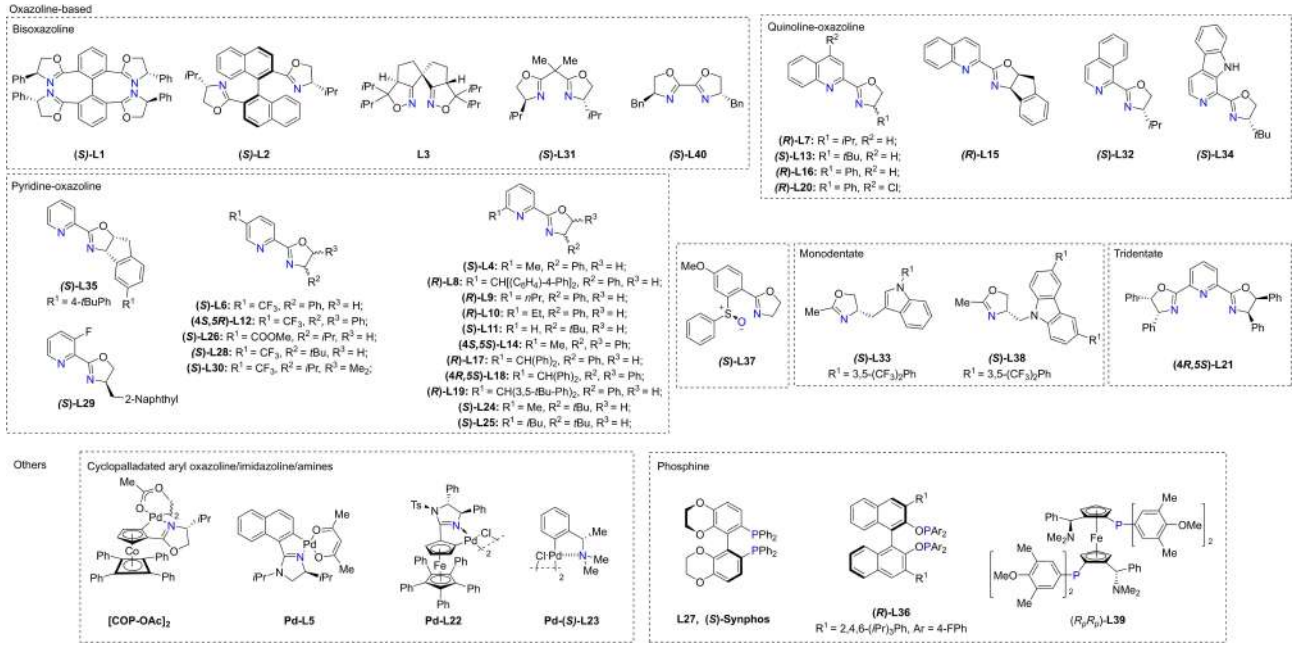
Table 1. continued



Type of reaction	Substrate	Pd source	Lig	[c]*cis trans*	[c]*Selectivity*	[Ox]	Additive	Solvent	Critical Parameters	Ref.
Difunctionalization	Vinyl benzamide	$Pd(OAc)_2$	**L15**	*cis*	*exo*	$AgCO_3$	Li_2CO_3 PGA	THF	Quinox ligand are preferred over Pyox. Type of oxidant and addition of PGA	[79]
Difunctionalization	Vinyl phenol	$Pd(MeCN)_2Cl_2$	**L7**	*trans*	*exo*	O_2	$KHCO_3$	Toluene/ THF	AP influenced by nucleophile nature. Different reactivity of *E/Z* alkene.	[80]
Difunctionalization	*N*-alkenyl amide or carbamate	$Pd(TFA)_2$	**L16**	*cis*	*exo*	NFSI	TEMPO	Dioxane	In general bidentate ligand were preferred, in particular Quinox ones.	[81]
Difunctionalization	Terminal amino-alkene	$Pd(OAc)_2$	**L17, L18**	*trans*	*endo*	I(III)[c]	–	aromatic solvent	Type of substitution on C6 pyridine of Pyox (and type of azide source for Ref. [82]). Presence of base is detrimental for Ref. [15].	[15] [82]
Difunctionalization	Terminal amino-alkene	$Pd(PhCN)_2Cl_2$ $Pd(dba)_2$	**L19**, **L20**	*trans*	*endo*	Selectfluor $PhI(OPiv)_2$	$CsOCF_3$	DCM/ MeCN	Substitution on C6 pyridine of Pyox, OCF_3 and F source, PG and *T* (°C)	[63,83]
Difunctionalization	Aminophenol/ diene	$Pd(acac)_2$	**L21**	–	*anti-Mark*	Thymoquinone	3 Å MS	xylene	Chemoselectivity. Tridentate ligand and aromatic solvent are preferred.	[32]
Difunctionalization	Urea/diene	$Pd(MeCN)_2(OTs)_2$	**L6**	*trans*	*anti-Mark*	2,5-DMBQ	3 Å MS	THF	Pd(II) salts: highly dissociated Pd are preferred. Type of oxidant and ligand.	[85]
Rearrang. Imidates	Allylic Imidate	–	**Pd–L22**	–	*endo*	–	$AgNO_3$, PS	$CHCl_3$	Amount of catalyst.	[93]
Rearrang. Imidates	Allylic Imidate	–	**Pd–L23**	–	*endo*	–	**PA2**	$CHCl_3$	Presence of **PA2**. Type of cyclopalladated catalyst.	[94]
Hydro-amination	Styrene/NFSI	$Pd(OAc)_2$	**L24** or **L25**		*Mark.*	NFSI	$HC(OEt)_3$	EtOAc	Aliphatic substitution on C6-posiiton pyridine of Pyox. Substituent on *ortho*-position of substrate are not tolerated.	[97]
C–C bond formation										
Fujiwara-Moritani	Alkenyl indole	$Pd(OAc)_2$	**L26**	–	*exo*	*p*-BQ or O_2	–	alcohol/ AcOH	In general low *ee*, but higher than commercially available Pyox.	[99]
Oxidative Heck	Alkene tethered to alkynylanilide	$Pd(amphos)Cl_2$	**L27**	*cis*	–	O_2	K_3PO_4 3 Å MS	$PhCF_3$	Inorganic base and nonpolar solvents are preferred. Type of Pd salts.	[103]

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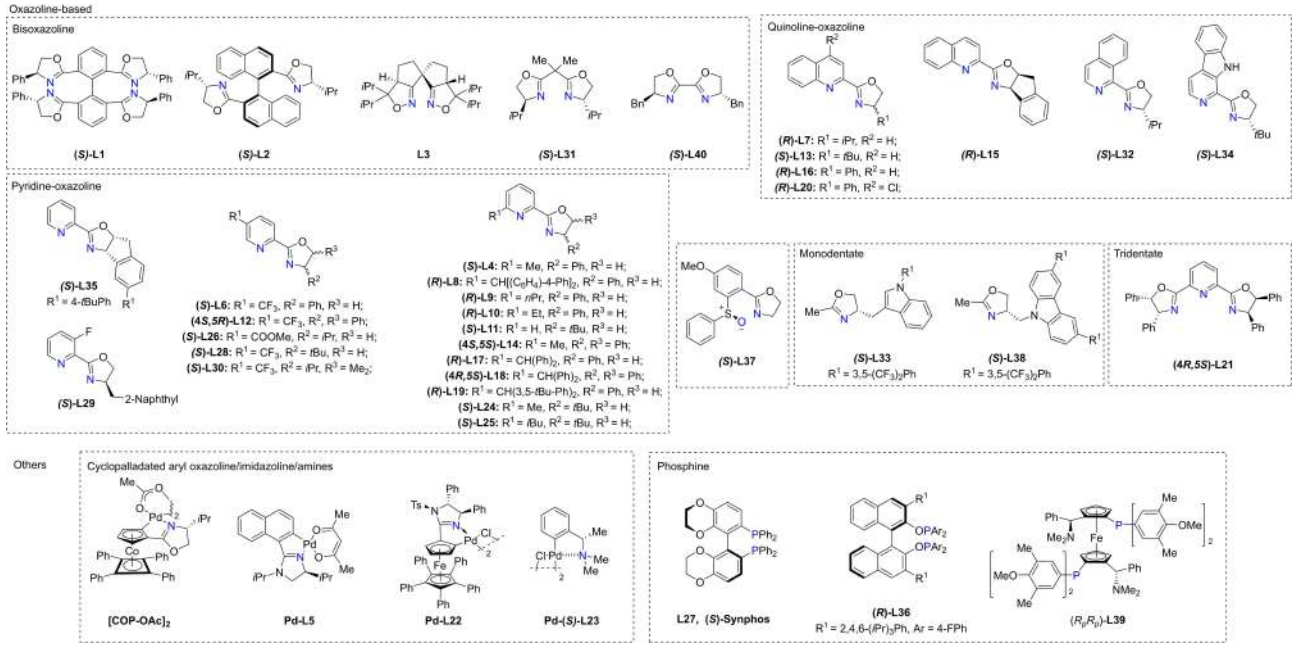
Table 1. continued



Type of reaction	Substrate	Pd source	Lig	[c]*cis trans*	[c]*Selectivity*	[Ox]	Additive	Solvent	Critical Parameters	Ref.
Oxidative Heck	Alkynylanilide and cyclopentene	$Pd(OAc)_2$	**L28**	*cis*	–	O_2	–	DCE	$Pd(TFA)_2$ and $Pd(OPiv)_2$ are detrimental. EWG on the lligand.	[104]
Oxidative Heck	Cyclopentene/ boronic acid	$Pd(TFA)_2$	**L28**	*cis*	–	O_2	Na_2CO_3	DCE	$Pd(OAc)_2$ and K^+ and Cs^+ counter anion in the organic base are detrimental.	[105]
Oxidative Heck	Alkenol and boronic acid	$Pd(MeCN)_2(OTs)_2$	**L28**	*cis*	–	O_2	3 Å MS	DMA	Presence of 3 Å MS is required. Type of substitution on C5 pyridine of Pyox.	[106]
Redox-Relay Heck	Alkenol and boronic acid	$Pd(MeCN)_2(OTs)_2$	**L28**	*cis*	*Mark.*	O_2	$Cu(OTf)_2$ 3 Å MS	DMF	Amount of 3 Å MS (mg/mmol). Steric and electronic properties of substrates.	[110,114]
Relay	Alkenol and indole	$Pd(MeCN)_2(OTs)_2$	**L29**	*cis*	*Mark.*	O_2	$CuSO_4$ 3 Å MS	DMF	Type of substitution on Pyox ligand: EWG and bulky group are preferred.	[115]
Heck	Alkenol and boronic acid	$Pd(MeCN)_2(OTs)_2$	**L12**	*cis*	*anti-Mark*	O_2	$Cu(OTf)_2$ 3 Å MS	MeOH/ MTBE	Type of solvent and ligand. Steric and electronic properties of substrates.	[117]
Relay	Alkenol and TIPS–EBX	$Pd(MeCN)_2(OTs)_2$	**L30**	*cis*	*Mark.*	TIPS–EBX	3 Å MS	dioxane	Pd(0) source is detrimental. Type of ligand and solvent.	[118]
Hydrocarbofunctional	Alkene/stannane/ boronic acid	$Pd(MeCN)_2Cl_2$	**L31**	*cis*	*Mark.*	O_2	*t*BuOK	*i*PrOH	Type of ligand and substitution on BOX.	[122]
Hydrocarbofunctional	Nitrostyrene and boronic acid	$Pd(TFA)_2$	**L32**	–	–	air	–	MeOH	Alcohol solvents are preferred. Type of ligand.	[123]
Hydrocarbofunctional	Alkene bearing 8-AQ/indole	$Pd(OAc)_2$	**L33**	–	–	Ar or air	2-Ph-benzoic acid	MeOH	Higher *T* (°C) are preferred. The additive is crucial for high yield. Monodentate ligand are required.	[56]
Hydrocarbofunctional	Alkene bearing 8-AQ/ketone	$Pd(MeCN)_2Cl_2$	**CA1**	*trans*	*anti-Mark*	–	Benzoic acid	EtOH	Type of chiral amine and additive. Type of Pd(II) counter anion	[124]

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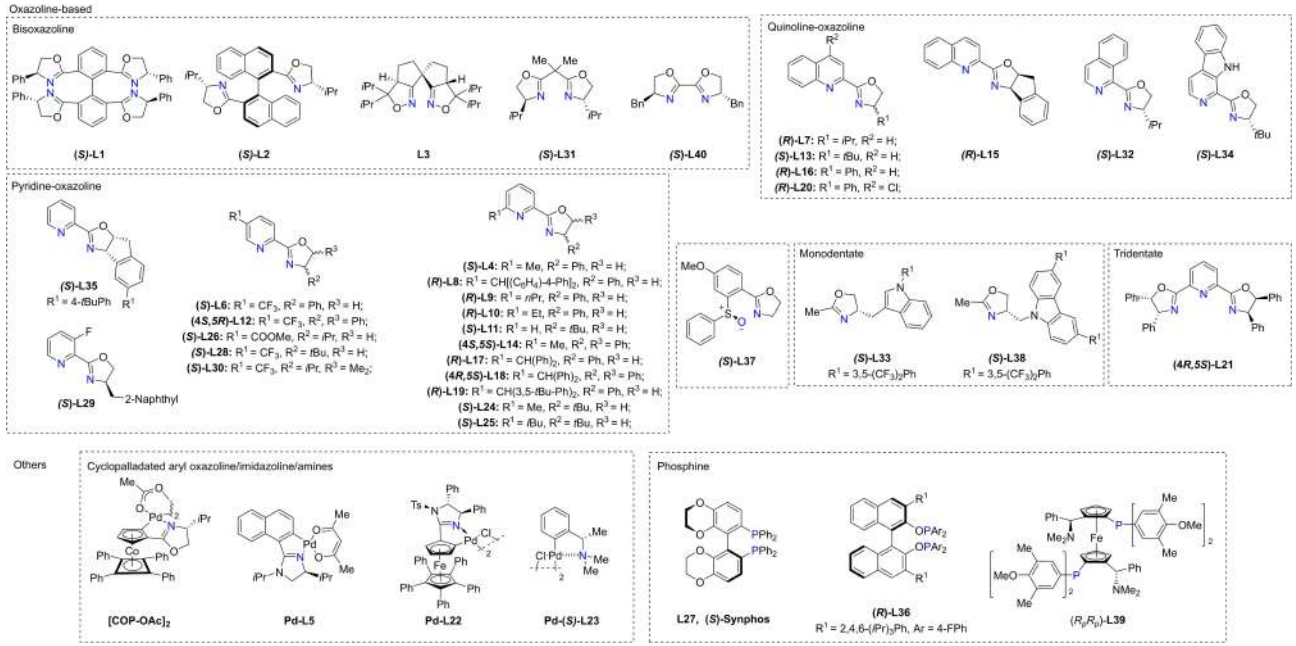
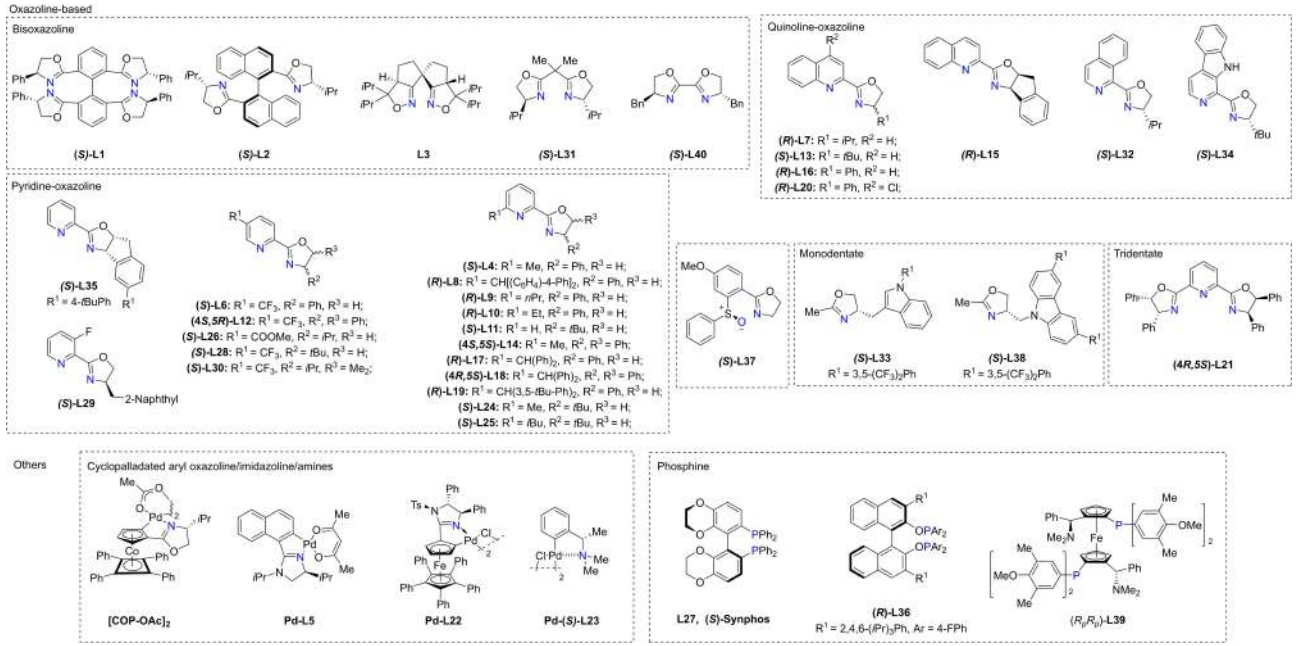
Table 1. continued



Type of reaction	Substrate	Pd source	Lig	[c]*cis trans*	[c]*Selectivity*	[Ox]	Additive	Solvent	Critical Parameters	Ref.
Hydrocarbofunctional	Alkene bearing 8-AQ/azalactone	$Pd(MeCN)_2Cl_2$	**PA3**	*trans*	*anti-Mark*	–	–	benzene	Steric hindrance on **PA3** plays a crucial role.	[125]
Hayashi-Miyaura	α,β-unsaturated ketone/ boronic acid	$Pd(TFA)_2$	**L11** **L34**	*cis*	*Mark.*	–	NH_4PF_6 H_2O	DCE	Type of Pd source. Pyox ligand and nonpolar solvents, in particular halogenated, are preferred. Inert gas.	[126–131]
Hayashi-Miyaura	α,β-unsaturated ketone/ boronic acid	$Pd(OAc)_2$	**L11**	*cis*	–	O_2	–	DMF	Side Heck reaction when *endo*-face of substrate is not sterically hindered.	[132]
Hayashi-Miyaura	γ,δ-unsaturated ketone/ boronic acid	$Pd(TFA)_2$	**L35**	*cis*	–	–	–	$MeNO_2$	Type of substitution on the ligand.	[133]
Difunctionalization	1,6-enyne	$Pd(OAc)_2$	**L3**	–	*exo*	Urea–H_2O_2	LiCl	AcOH	Use of SPRIX ligand.	[135]
Difunctionalization	alkynyl cyclo-hexadienone	$Pd(OAc)_2$	**L3**	–	*exo*	O_2	–	AcOH/ toluene	Type of oxidant. Ratio AcOH/toluene > 1:1.	[136]
Difunctionalization	Diene and ami-nal	$[Pd(allyl)Cl]_2$	**L36**	–	*anti-Mark*	–	$AgClO_4$	DCM	Steric hindrance on the ligand. Lower *T* (°C) is beneficial.	[137]
Difunctionalization	Diene and urea	$Pd(MeCN)_2(OTs)_2$	**L37**	–	*anti-Mark*	2,5-DMBQ	–	THF	Quinone oxidants are preferred. P,N Pyox ligands are detrimental.	[138]
Difunctionalization	Alkene bearing 8-AQ/indole/ B_2pin_2	$Pd(OAc)_2$	**L33**	*trans*	–	O_2/BQ	NaF	HFIP/ THF/ DMF	Use of monodentate ligand and solvent mixture are beneficial.	[139]
Difunctionalization	Alkene bearing 8-AQ/NuH/ B_2pin_2	$Pd(OAc)_2$	**L38**	*trans*	–	O_2/BQ	KTFA	TFE	Higher *T* (°C), K^+ in KTFA and fluorinated solvent are beneficial.	[57]

Table 1. continued



Type of reaction	Substrate	Pd source	Lig	[c] *cis* *trans*	[c] *Selectivity*	[Ox]	Additive	Solvent	Critical Parameters	Ref.
Difunctionalization	Alkenyl boronate/carbamoyl chloride	$Pd(OAc)_2$	**L39**	–	*anti-Mark*	–	CsF	THF	Presence of CsF is fundamental. Classic pinacolate ligand and ethyl chloroformate are not tolerated.	[140]
Difunctionalization	Styrene	$Pd(OAc)_2$	**L11**	–	*anti-Mark*	Selectfluor	(2-ethylhexylO)$_2$PO$_2$H *t*Bu-catechol	DCM/H_2O	Type of Pd(II)-salts and ligand.	[141]
Difunctionalization	*N*-allyl amine/boronic acid	$Pd(MeCN)_2Cl_2$	**L40**	*cis*	*anti-Mark*	Selectfluor	–	benzene H_2O/BnCN	Type of Pd(II)-salts and nitrile used as solvent. Solvent mixture ratio.	[143]
Difunctionalization	Chromene/boronic acid	$Pd(OAc)_2$	**L11**	*cis*	–	Selectfluor	NaF (2-ethylhexylO)$_2$PO$_2$H *t*Bu-catechol	DCE/H_2O	1,3- or 2,1-regiselectivity dependent on ligand and substrates. EWG on boronic acid and amide directing group favors 1,3-selectivity.	[144]
Difunctionalization	Alkene/boronic acid	$Pd(OAc)_2$	**L11** **BOX^{iPr}**	*cis*	*anti-Mark*	NFSI	*t*Bu-catechol	*i*PrOH/H_2O	Selectfluor is detrimental as well as lack of water, ligand and additive.	[145]

[a] PGA = $PhCOCO_2H$; AP = aminopalladation; PG = Protecting Group; DMBQ = 2,5-dimethyl-1,4-benzoquinone; PS = proton sponge [i.e. 1,8-bis(dimethylamino)naphthalene], KTFA = potassium trifluoroacetate. [b] Nucleopalladation; [c] Markovnikov or *anti*-Markovnikov's rule (in case of difunctionalization, the attribution is made in function of the first step); [c] [d] I(III) = $PhI(OAc)_2$, IBX–N_3.

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