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Palladium-Catalyzed Oxidative Arene C-H Alkenylation Reactions Involving Olefins

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Abstract

Palladium-catalyzed selective C-H alkenylation reaction has been established as a central synthetic transformation to enable the construction of carbon–carbon bonds in an efficient, atom-economical, and environmentally friendly way. It provides a powerful alternative to classical cross-coupling reactions for the construction of conjugated organic molecules, including late-stage functionalization. The knowledge of mechanisms, the use of different strategies to control site-selectivity, and the development of efficient chiral catalysts for C-H alkenylation reactions has expanded the application of this tool for the synthesis of molecules of increased complexity.

Keywords: C-H activation; palladium; alkenylation; catalysis

Palladium-catalyzed oxidative C-H alkenylation: the Fujiwara-Moritani reaction

The **Mizoroki-Heck reaction** (see Glossary) [1] is recognized as a fundamental transformation in organic synthesis due to its broad applicability for the formation of $C(sp^2)$-$C(sp^2)$ bonds. However, it requires the pre-installation of a carbon-(pseudo)halide (C-X) bond in the substrate. Consequently, the oxidative variant of the Heck reaction, the **Fujiwara-Moritani reaction**, has recently gained much attention. This reaction, first described by Fujiwara and Moritani in the late 1960s [2], consists of the palladium-catalyzed alkenylation of $C(sp^2)$-H bonds and can be efficiently employed for the synthesis of highly functionalized aromatic molecules, including late-stage functionalization, in an atom-economical way [3-8]. The oxidative coupling of an arene and an alkene takes place *via* palladium(II) catalysis, *i.e.* a C-C bond is formed starting from two inert C-H bonds, avoiding the need for prefunctionalization. (Figure 1A).

The reaction proceeds through C-H activation of the aryl ring to form a σ-aryl-Pd(II) intermediate, which would coordinate to the olefin partner (Figure 1B). Subsequent 1,2-migratory insertion to the Pd(II)-aryl bond and β-hydride elimination would give the alkenylated arene. The generated Pd(II)-hydride is transformed into a Pd(0) species after reductive elimination, so an oxidant is required to recover the catalytically active Pd(II) species [2]. Among the mechanisms proposed for the C-H metalation step, the most common pathways go through the transition states exemplified in Figure 1C for the metalation of benzylamines [9]. The first mechanism involves the formation of an aryl-Pd(II) species through the electrophilic palladation of the arene [10], so the electronic properties of the arene play a fundamental role. The second mechanism [11-12] consists of a proton abstraction via a concerted and intramolecular transfer of a hydrogen atom to a base (**CMD, concerted metalation-deprotonation**).

Organic molecules possess a wide range of C-H bonds, which is what makes the Fujiwara-Moritani reaction a very attractive method for their functionalization. However, the main challenge is to achieve high site-selectivity towards just a given C-H bond. Irrespective of the mechanism operating in the C-H activation process, three main strategies for the control of regioselectivity are utilized [13], involving substrate-control and/or catalyst-system-control (Figure 1D):

1) Advantage can be taken of the electronic properties of the arene. Typically, a palladium(II) source is employed without the aid of directing groups and/or ligands. Usually, high loadings of the aryl coupling partner are required. When this strategy is operating, the alkenylation reaction is thought to occur through electrophilic palladation or acetate-mediated CMD (Figure 1D, i).

2) Functional groups (directing groups, DG) can be attached to the substrate that are able to coordinate to the Pd(II) center, approaching it to a specific C-H site. In this strategy, palladation of the C-H bond usually takes place *via* acetate-mediated CMD (Figure 1D, ii).

3) The last approach consists of the use of ligands to tune the properties of the Pd(II) catalyst. Pyridine-based ligands and mono-protected amino acids (MPAA) are the most commonly used ones. When pyridine ligands are employed, the dehydrogenative coupling is usually proposed to proceed through a similar scenario as that one described in Figure 1D (i), although with higher catalytic efficiency (Figure 1D, iii) [14]. On the other hand, *N*-acetyl amino acids would replace the acetate, being its *N*-acetyl group responsible for the proton abstraction (Figure 1D, iv) [15].

Selected examples of the application of these strategies will be shown in the following sections.

Regioselectivity driven by substrate control

When the Fujiwara-Moritani reaction is carried out over simple arenes, a common proposal is that the C-H activation step takes place *via* **electrophilic metalation**. That can be formally considered as an aromatic electrophilic substitution and thus, may lead to mixtures of regioisomers. This issue can be overcome through the adjustment of the electronic properties of the arene by tuning its substituents, though achieving complete site-selectivity may become a major challenge depending on the substrate. Nevertheless, the CMD mechanism cannot be ruled out, since depending on the substitution pattern of the arene, both pathways would lead to similar (if not the same) regioselectivities. For example, when benzene derivatives were alkenylated with allyl amines the regioselectivity completely depended on their electronic properties: electron-rich arenes led to *ortho*- and *para*-products predominantly, while electron-deficient arenes gave the *meta*-product selectively (Figure 2A) [16]. In contrast, the *para*-selective palladium(II)-catalyzed alkenylation of tertiary anilines could be achieved by tuning free aniline concentration using AcOH as co-solvent (Figure 2B) [17]. Thus, the amine moiety

did not act as a chelating/directing group to activate the *ortho* C-H site. DFT calculations support an electrophilic metalation process towards the *para*-position of the arene.

Positional control ruled by the electronic nature of the arene is a very common approach for heteroaromatic substrates, since they possess very active C-H sites, as illustrated by the intermolecular Fujiwara-Moritani reaction of indoles [18]. C-3 alkenylation occurs due the more nucleophilic character of that site, as shown in an elegant synthesis of indolo[3,4-*a*]pyrrolo[3,4-*c*]carbazole-6,8-diones starting from indoles and maleimides [19] (Figure 2Ca). The indole core is firstly palladated at C-3, followed by alkenylation with the maleimide. The cascade reaction follows by palladation at C-2 and C-H arylation with another indole, and thermal cyclization releases the polycyclic compound (Figure 2Ca). A related procedure has been applied to the synthesis of carbazoles via regioselective triple successive oxidative Heck reactions, where the process also starts by regioselective C-3 alkenylation of indole (Figure 2Cb) [20]. In contrast, the alkenylation of indole can be switched from C-3 to C-2 in the presence of acetic acid, which favors the migration of the C3-PdX bond to the highly activated 2-position of the iminium ion intermediate [21].

Pyrroles have a limited application for the Fujiwara-Moritani reaction due to their instability in acidic and oxidative conditions, although examples involving the alkenylation of this privileged framework have been reported with C-2 *vs*. C-5 regioselectivity control [22]. C-4-alkenylated pyrroles could be selectively obtained without the use of directing groups or specific *N*-protecting groups. The reaction proceeded efficiently with a free NH or with electronically diverse *N*-substituents, using electron-deficient alkenes or styrenes as coupling partners (Figure 2Da) [23]. C-5-alkenylation of 2-acylpyrroles could also be accomplished (Figure 2Db) [24] using an *N*-protecting group. The metalation event takes place *via* electrophilic palladation although the coordinating effect of the *N*-protecting group cannot be ignored. Related heterocycles, such as furans, thiophenes [25] or even selenophenes [26] have been regioselectively alkenylated at the C-2/C-5 position.

Regioselectivity driven by the use of directing groups

The most common strategy to achieve site-selectivity in the C-H bond activation step is the incorporation of **directing groups** to the substrate. Those motifs are σ-chelating groups with Lewis basic heteroatoms, which can coordinate to the Pd (II) center and bring it close to a specific C-H bond (usually *ortho* to the directing group) forming palladacycles [27-29]. The

major drawback of this strategy lies on the presence of an additional functionality in the final product. Therefore, the use of directing groups that can be easily removed once the reaction has taken place is utterly desirable [30].

Amides are common directing groups in intermolecular Pd(II)-catalyzed alkenylation reactions [31]. It is even possible to use an acetamide as a **transient** and **traceless directing group**. As shown in Figure 3A, an acetamide-directing group is generated *in situ* from the corresponding aniline, which undergoes *ortho*-olefination with acrylates. In the course of the reaction, the amide is hydrolyzed and subsequent cyclization affords quinolones in a one-pot procedure (Figure 3A) [32].

Alternatively, the directing group may be further transformed and embedded in a more complex structure. Thus, a careful design of the reaction conditions may allow directing groups to undergo cascade reactions once the coupling with the olefin partner has occurred. This is illustrated in the synthesis of phenanthridines and carbazoles via Pd (II)-catalyzed C-H bond activation of biaryls with an iminoquinone as directing group and internal oxidant or co-oxidant [33]. The benzamide-directed olefination of 2-amidophenols with acrylates leads to 4-alkenyl benzoxazoles through acid-catalyzed condensation of the phenol and the amide director, once the alkenylative coupling has taken place (Figure 3B) [34]. Related reactivity can be accomplished using a carboxylate directing group [35], which may also be used as traceless directing groups. For instance, carboxylate-directed olefination of dearomatized benzoic acids with acrylates and styrenes provides the corresponding vinylarenes, followed by rearomatization upon decarboxylation (Figure 3C) [36]. A Pd/Ag bimetallic system is proposed to play a key role in the tandem decarboxylative C-H olefination process followed by rearomatization.

Sulfonamide-based auxiliary groups have also been effectively used as directors for intermolecular Fujiwara-Moritani/cyclization cascade reactions. A representative example is the reaction between *N*-tosyl-2-aminobiphenyls and 1,3-dienes for the diastereoselective synthesis of dibenzo[*b,d*]azepines with two different stereogenic elements. In contrast to the reactions of alkenes, the transformation is proposed to proceed through migratory insertion of the aryl-Pd(II) species (formed after C-H palladation of the arene) to the diene, followed by reductive elimination of the intermediate palladacycle (Figure 3D) [37]. Related cascade reaction between *N*-sulfonamidoarylcarboxamides and 1,3-dienes afforded 3,4-

dihydroisoquinolones [38]. Besides, the (2-pyridyl)sulfonyl framework stands out as a widely employed directing group. The versatility and usefulness of this moiety lies not only on its capability of efficiently coordinating the palladium center, but also on the fact that it can be easily removed and derivatized [39-40]. This group was initially used in the intermolecular Fujiwara-Moritani reaction for the directed C-2 alkenylation of indoles with different olefin coupling partners. The methodology was also found effective for the mono- and di-alkenylation of the pyrrole nucleus (Figure 3Ea). This framework has also been utilized as the *N*-protecting/directing group for the alkenylation of simple arenes (Figure 3Eb-c) [41-43].

Ligand assistance in the control of regioselectivity

Besides the examples shown in the previous sections, there are still problems associated with the control of regioselectivity. The control provided by the substrate leads in many cases to low regioselectivities, as not only electronic factors take part, and offers a narrow scope of the aromatic coupling partners. In the case of directing-group control, the problem is that not all the directors can be efficiently removed. Therefore, the development of ligands for the oxidative Heck reaction has been an important breakthrough, since they are able to improve the site-selectivity and reactivity, sometimes in combination with directing groups [44]. Among the ligands used nowadays, two classes stand out: pyridine-based ligands [45] and mono-protected amino acids (MPAA) [46], which can be used both in the non-directed (without directing groups) or directed (with directing groups) Fujiwara-Moritani reactions. Selected examples to illustrate both strategies will be disclosed.

Non-directed ligand-assisted Fujiwara-Moritani reaction

In the past decade, pyridine derivatives have been developed as ligands for the Pd(II) center to modulate reactivity and site-selectivity in the olefination of different arenes without the aid of directing groups [45. Recently, the use of pyridone-based ligands for the non-directed site-selective Pd(II)-catalyzed C-H alkenylation of simple arenes and heteroarenes with electron-deficient alkenes [47], utilizing the aromatic substrate as the limiting reagent, led to the olefinated products in good yields. Less-reactive electron-deficient arenes can also be olefinated affording the *meta*- substituted products with moderate to good regioselectivities (Figure 4A) [48]. In addition, the dual activation enabled by the combination of pyridine ligands and protected amino acid (*N*-acetyl-glycine) has allowed the efficient alkenylation of a wide variety of arenes [49].

Directed ligand-assisted Fujiwara-Moritani reaction

This is the most common scenario when ligand-aided Pd(II)-catalyzed alkenylations are carried out, and thus, several ligands have been utilized combined with different directing groups. The ligand has to be carefully designed, since it has to generate a pre-transition state where the Pd(II) is coordinated to both the ligand and the substrate (Figure 4B). Therefore, a matched coordinative affinity of both the directing group and the ligand should be achieved, avoiding over-coordination of any of those components to the metal center [9]. With these precepts in mind, a wide variety of *N*-monoprotected amino acids (MPAA), which enhance the efficiency and the C-H activation step rate, have been developed [46,50]. Furthermore, those ligands could also affect the regioselectivity of the transformation. Thus, when the phenylacetic acid shown Figure 4C was alkenylated using *N*-formyl-isoleucine (For-Ile-OH) as ligand, the olefination at the C-H bond *ortho* to the methoxyl group was highly favored, being the reaction unselective in the absence of the ligand [51]. The combination of a bidentate directing group in a benzyl phosphonamide with a MPAA has also allowed the use of unbiased unactivated alkenes in these olefination reactions, with a broad scope regarding both the arene and the aliphatic alkene [52].

Beyond the development of several *ortho*-selective functionalization reactions [50,29], directing groups have also been designed to allow selective *meta*- [53] and *para*-alkenylations with the aid of MPAAs [54]. Selected examples are shown in Figures 4D [Figure 4Da [55], b [56], and c [57] and 4E [58-59]. Remote functionalization on various heterocyclic systems has also been achieved using related templates [60]. Although these templates provide an effective method for the functionalization of distal C-H bonds, the main drawback is that they are covalently bonded to the substrate, meaning that a specific functional group is required to anchor those directing groups to the starting molecule. With the aim of overriding this disadvantage, the design of a bifunctional template capable of directing the *meta*-C-H functionalization through a reversible coordination with a heterocyclic substrate has been developed (Figure 4Fa) [61]. This bifunctional template was able to coordinate two different metal centers. Thus, one metal center allows the template binding to substrate and the other one promotes the C-H cleavage. Thus, intermolecular *meta*-olefination of different 3-phenylpyridine derivatives was achieved using a MPAA as ligand. A related concept based only in palladium coordination was developed for the template directed C-5 selective olefination of thiazoles (Figure 4Fb) [62]. These templates coordinate the heterocycle into the cavity while a nitrile acts as a directing group for the metalation of a distal position in the heterocycle. This protocol has been efficiently applied for the functionalization of diverse

heterocycles (i.e. quinolines, benzothiazoles or benzoxazoles) [63]. A different strategy, based on the use of a **transient directing group**, has also been used for the *m*-alkenylation of biarylic aldehydes and amines (Figure 4Fc) [64].

Intramolecular Fujiwara-Moritani reaction

Although the intermolecular Fujiwara-Moritani reaction has been studied for decades, its intramolecular variant is still relatively underexplored and mainly focused on the use of electron-rich (hetero)arenes. Regarding the regioselectivity of the alkene insertion, these intramolecular transformations usually take place through *exo* processes, due to the strain involved in the approach of the arene to the intramolecular coupling partner. For instance, an indole bearing a butenyl chain tethered to the C-3 position was subjected to an intramolecular aerobic Pd(II)-catalyzed C-H alkenylation reaction, using pyridine-based ligands to construct 5-membered rings *via* 5-*exo*-trig processes [65] (Figure 5A). Electron-rich arenes have also efficiently undergone cyclization. For example, furans could be obtained through 5-*exo*-trig cyclization of a variety of allyl phenyl ethers with the assistance of pyridine ligands (Figure 5B) [6. Similarly, chromanes could be synthetized through 6-*exo*-trig cyclization of butenyl ethers [67-68].

Nitrogen-containing heterocycles can also be obtained. Acrylamides undergo-5-*exo*-trig cyclization to form oxindoles, even with substituted alkenes (Figure 5C) [69]. An electron-rich arene was essential for the reaction to take place, as well as a free N-H and a tri- or tetra-substituted olefin motif. In contrast, the reactivity could be switched in related substrates to the β-position of the alkene generating 2-quinolones *via* an unprecedented 6-*endo*-trig cyclization (Figure 5D) [70]. These quinolones could be further functionalized via a subsequent intermolecular C-3 alkenylation. The same approach was later applied to the synthesis of coumarins starting from the corresponding aryl cinnamates [71]. Dihydroquinolines could also be obtained via a 6-*endo*-trig intramolecular Fujiwara-Moritani reaction using *N*-protected allylanilines as the substrates. 1,2- or 1,4-Dihydroquinolines were selectively obtained depending on the alkene substitution pattern (Figure 5E) [72]. To account for the *endo*/*exo* selectivity of these cyclizations, two alternative mechanistic pathways could be proposed. On the one hand, the reaction could proceed through arene metalation-alkene insertion (analogous to the intermolecular mechanism depicted in Figure 1B). Alternatively, an alkene activation-arene insertion mechanism may occur (Figure 5Fa) in which an initial Pd(II) alkene activation would be followed by *anti* nucleophilic attack of the arene to the Pd(II) complex. Thus, both

pathways may differ in the stereochemical outcome. There is stereochemical support for a mechanism involving initial palladation of the (hetero)arene [65-66] or attack of the heteroarene to the palladium-complexed olefin [73]. In the case of the unusual 6-*endo* cyclization of anilines (Figure 6E), DFT studies have shown that the reaction proceeds via prior activation of the alkene, being the coordination of the remote protecting group to the palladium center crucial to favor the formation of the six-membered ring. The computed energy difference between the TS for the 6-*endo* cyclization and the 5-*exo* counterpart was always high (3.0−10.0 kcal/mol), ensuring a complete regioselectivity, confirming experimental data (Figure 6Fb) [72].

Enantioselective variants of the Fujiwara-Moritani Reaction

The ligand-assisted Fujiwara-Moritani reaction has also been employed for the generation of stereogenic centers, taking advantage of the strategy used in the asymmetric variant of the Mizoroki-Heck reaction. The use of substituted olefins as coupling partners can lead to the generation of quaternary stereocenters by driving the hydride elimination to a contiguous β′-position. Oxazoline-containing pyridine (PyrOx) or nicotine (NicOx) chiral ligands have been used in inter [74] and intramolecular [75] reactions of indoles, in which high enantiocontrol was achieved with an SPRIX ligand, with two isoxazoline moieties (Figure 6A) [76].

Mono-protected amino acids are another common family of ligands employed for the asymmetric Fujiwara-Moritani reaction. These ligands have been used in desymmetrization methodologies [77] and in the generation of stereocenters based on atoms other than carbon (e.g., silicon) [78]. In a different approach, the enantioselective C-H olefination of racemic phenylacetic acids bearing α-hydroxyl and α-amino substituents *via* kinetic resolution has been accomplished (Figure 6B) [79]. In this case, *N*-Boc-L-threonine (Boc-L-Thr(Bz)-OH) was used as ligand, affording the corresponding olefinated *S*-configured products and the *R*-configured unreacted substrates in high enantiomeric excesses.

The asymmetric Fujiwara-Moritani reaction is not exclusively limited to the generation of central chirality; it has also been applied for accessing enantioenriched compounds with axial and planar chirality. Different strategies have been applied for atroposelective alkenylations. The enantioselectivity can be controlled using of chiral ligands, as illustrated in the synthesis of axially chiral vinyl arenes using MPAAs and an easily removable ketoximine ether as the

directing group [80]. On the other hand, chiral spirophosphoric acids (such as STRIP) have been used as chiral anionic ligands for the atroposelective alkenylation of quinoline derivatives (Figure 6C) [81]. DFT calculations suggested that the chiral phosphate acted as counteranion to stabilize Pd, being the enantioselectivity determined by the CMD type C−H bond cleavage step.

An alternative is the use of a chiral auxiliary that acts as a directing group for a diastereoselective alkenylation. Thus, chiral sulfoxide-directed alkenylations constitute an excellent example, as the directing group is easily introduced, exerts a high stereocontrol, and can be easily eliminated [82]. A further evolution of this strategy is the use of transient chiral directing groups, e.g., simple and inexpensive amino acids, as *t*-leucine. The chiral amino acid reacts reversibly with the racemic biarylic carbonyl compound to form the corresponding imines. C-H activation would occur preferentially in one diastereomer affording an axially enantioenriched palladacycle, which would be *in situ* hydrolyzed after alkenylation (Figure 6D) [83]. A related strategy using also *t*-leucine has been described for the control of C-N axial chiralitys in the olefination of *N*-arylindoles [84].

Regarding planar chirality, an elegant method for the enantioselective oxidative Heck alkenylation of ferrocenecarboxylic acid was developed employing the carboxylate group present in the molecule as director and *N*-acetyl-L-phenylalanine as ligand. Under the optimized reaction conditions, the olefinated ferrocenecarboxylic acids were obtained in good yields and enantiomeric excesses (Figure 6E) [85]. The *N*-protecting group of the MPAA played a crucial role in the reactivity and selectivity of this transformation, observing that bulky functionalities led to lower yield and enantioselectivities.

Concluding remarks

As it has been highlighted throughout this short review, the palladium-catalyzed selective C-H alkenylation reaction is nowadays a central synthetic transformation for the formation of $C(sp^2)$-$C(sp^2)$ bonds in an efficient atom-economical way, and provides a powerful alternative to classical cross-coupling reactions for the construction of conjugated organic molecules. Its efficacy to accomplish the olefination of a wide range of aromatic scaffolds has been confirmed by its application to the formation of complex molecules, as exemplified in the synthesis of (+)-lithospermic acid [86], dragmacidin F [87], elavatine A [88] or the tricyclic core of the indoxamycin family of secondary metabolites [89]. Besides, the implementation of this

reactivity in tandem or cascade processes would allow the preparation of molecules with increased complexity in a single procedure [90].

The knowledge of the mechanisms involved and the development of strategies to control selectivity will indeed expand the application of this tool in natural product, fine chemical, and drug synthesis. In this context, the discovery of new and more efficient ligands to enhance reactivity and improve selectivity (both regio- and stereoselectivity) will continue to be of great importance. The development of nondirected methods has already allowed the application of these reactions to the late-stage functionalization of natural products or drugs (Figure 7A) [48,91]. However, the high temperatures usually required for the olefination may be incompatible with its use in late-stage functionalization of complex molecules. In this context, the development of milder procedures to promote the olefination reaction is an important goal. The use of non-conventional techniques, such as ultrasound, has recently allowed the *meta*-functionalization of a broad variety of substrates not only significantly reducing the reaction time and temperature, but also improving the yields and regioselectivities (Figure 7B) [92]. Along these lines, the recent discovery of a photoredox protocol that merges palladium and organo-photocatalysis constitutes an important breakthrough. This strategy has been applied to non-directed, and to *o*-, *m*-, and *p*-directed olefinations,. Visible light acts as both an oxidant and an activator enabling highly regioselective olefination of a broad scope of (hetero)arenes, including late-stage functionalization (Figure 7C) [93].

Besides these recent important methodological advances, the reaction conditions should still be improved for large-scale industrial applications, with more efficient catalytic systems (higher turnover numbers) and environmentally friendly oxidants (e.g., oxygen). Advances along these lines are expected. The use of heterogeneous catalysis in non-conventional solvents, such as γ-valerolactone (GVL), a biomass derived polar solvent, or the implementation of continuous flow systems are indeed important steps towards sustainability (Figure 7D) [94]. Besides, the utilization of cheaper, earth-abundant and less toxic first row transition-metals to replace palladium (e.g., high-valent cobalt complexes [95]) can also open the door to new directions in C-H alkenylation reactions, as new reactivities and improved selectivities could be expected. The possibility to functionalize alkene C(sp^2)-H bonds [96-97] and more demanding C(sp^3)-H bonds [98] would certainly expand its application.

Thus, C-H alkenylation has the potential to impact not only synthetic chemistry, but also material science and medicinal chemistry by improving the efficacy and sustainability of the synthesis of conjugated organic materials or pharmaceuticals.

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Declaration of interests

The authors declare no conflict of interests.

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Figure captions.

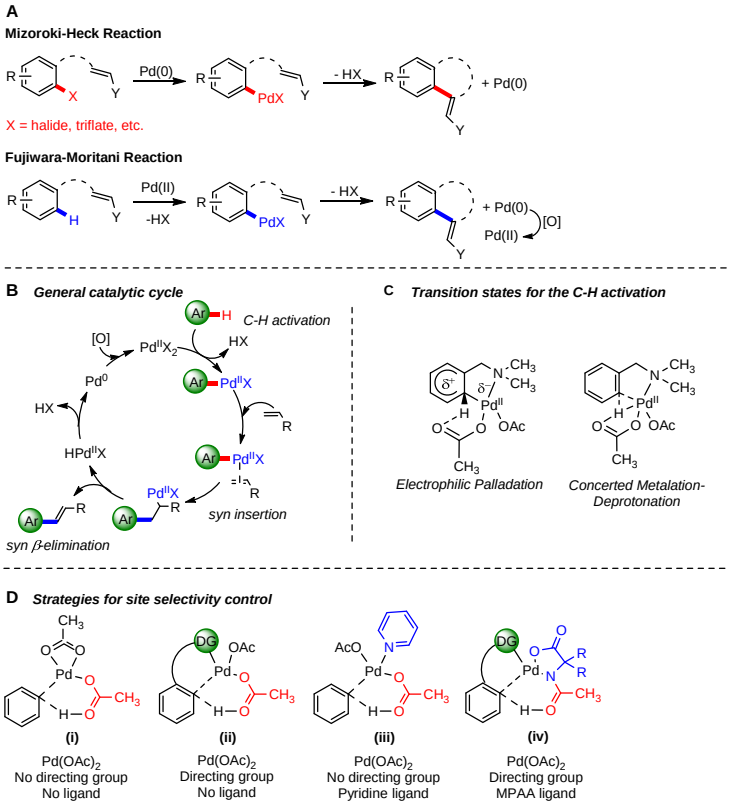

Figure 1. The oxidative C-H alkenylation reaction. (A) The Mizoroki-Heck and the Fujiwara-Moritani reactions for the alkenylation of arenes. (B) General catalytic cycle for the Fujiwara-Moritani reaction. (C) Mechanistic proposals for the C-H activation event (transition states represented). (D) Approaches for regioselectivity control in the C-H activation event.

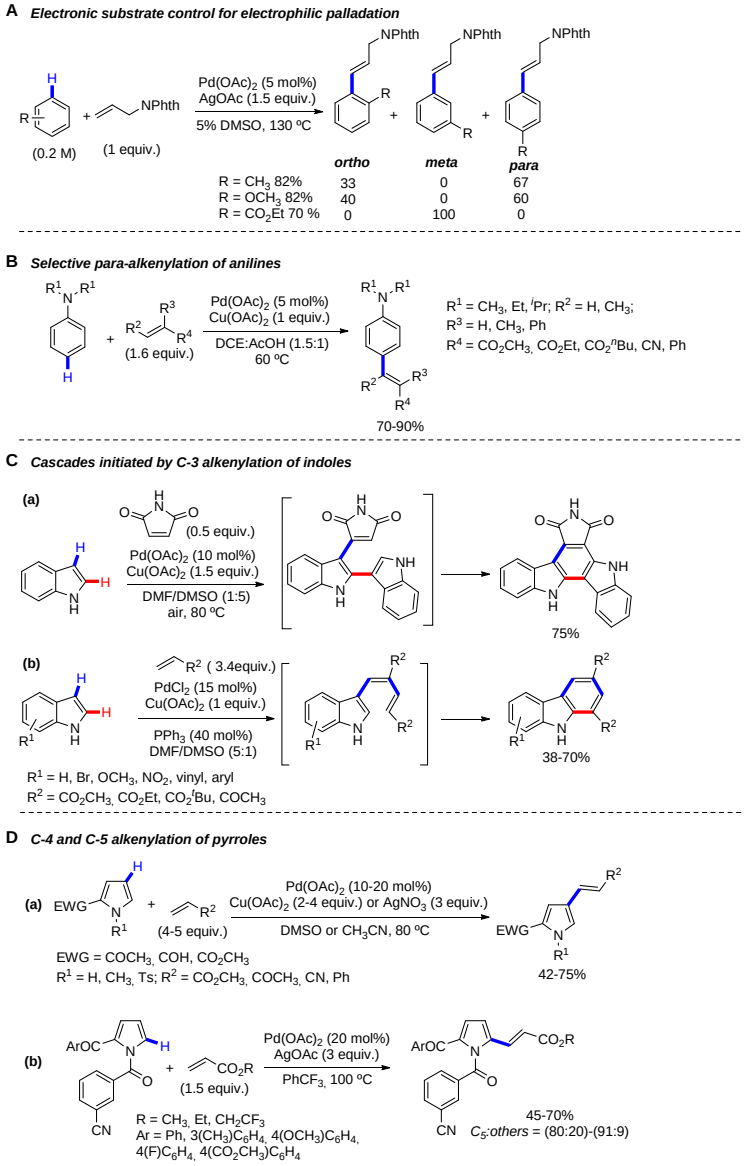

Figure 2. Regioselectivity driven by substrate control. (A) Effect of the electronic properties of the arene in the regioselectivity of the alkenylation. (B) Selective *p*-alkenylation driven by an amino group. (C) Selective C-3 alkenylation of indoles. Application in the synthesis of (a) indolo[3,4-*a*]pyrrolo[3,4-*c*]carbazole-6,8-diones and (b) substituted carbazoles. (D). C-4 (a) and C-5 (b) olefination of pyrroles

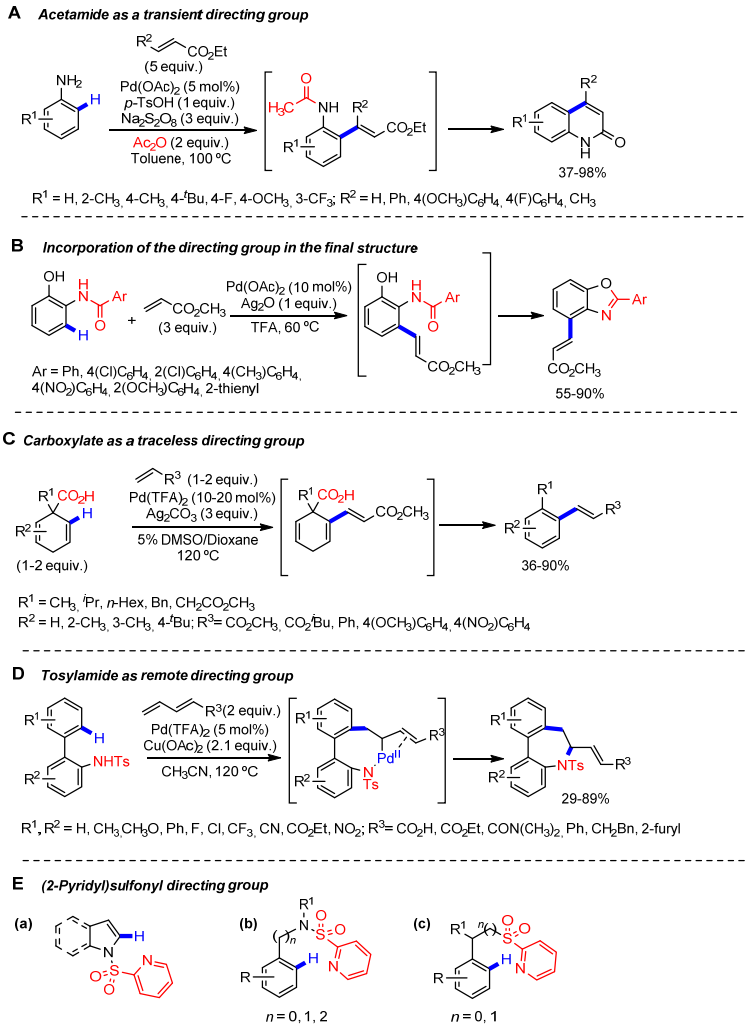

Figure 3. Regioselectivity control by Directing Groups (DG). (A) Use of an acetamide as a transient and traceless directing group. (B) Incorporation of the directing group into the structure of a more complex molecule. (C) Carboxylic acid as traceless directing group. (D) *N*-Tosyl directing group for the alkenylation of biphenyls with dienes. (E) (2-Pyridyl)sulfonyl directing group for the alkenylation of heteroarenes and arenes.

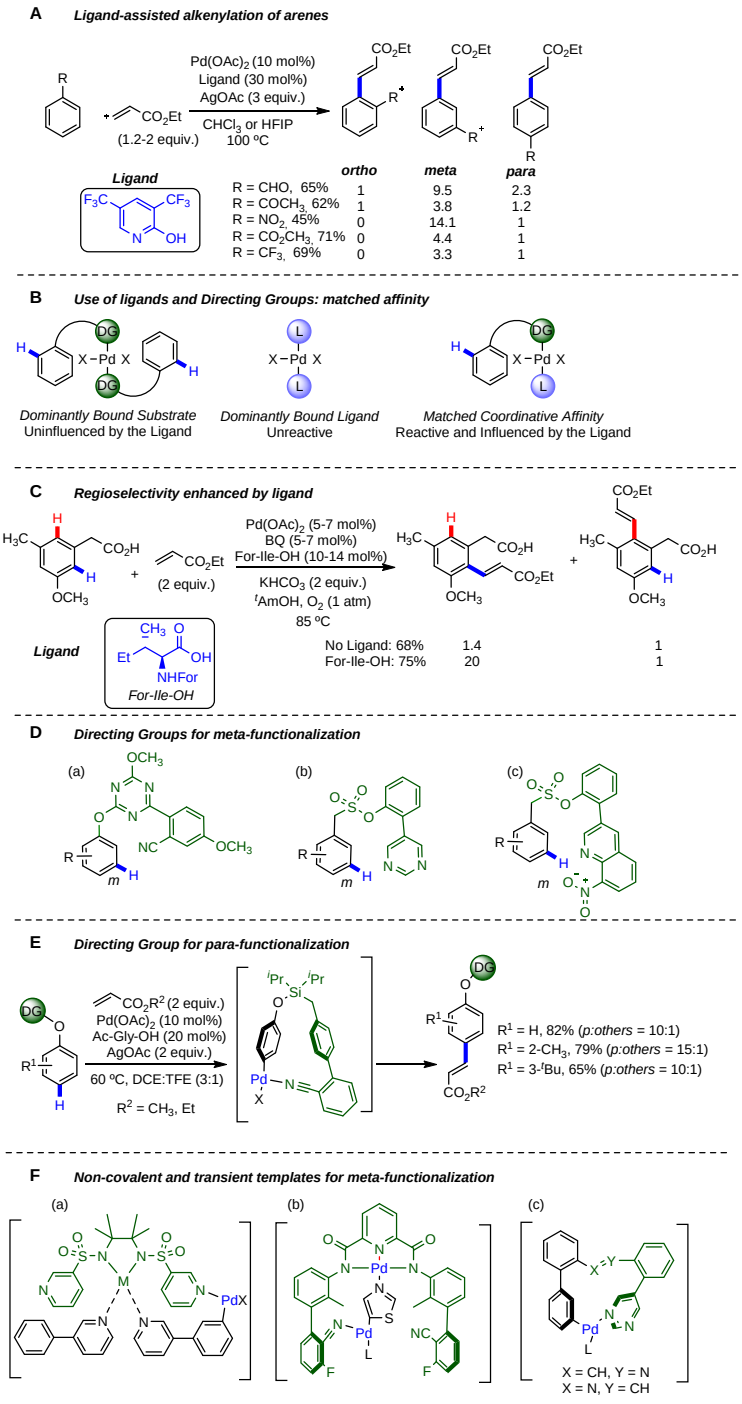

Figure 4. **Ligand assistance in regioselectivity contro**l. (A) Ligand-assisted alkenylation of simple arenes. (B) Directed ligand-assisted functionalization. Matched coordinative affinity of the directing group and the ligand. (C) *ortho*-Directed alkenylation. Regioselectivity enhanced by the ligand. (D) *meta*-Directed alkenylation. (E) *para*-Directed alkenylation. (F) (a), (b) *meta*-Functionalization through non-covalent interaction. (c) *m*-Functionalization mediated by a Transient Directing Group.

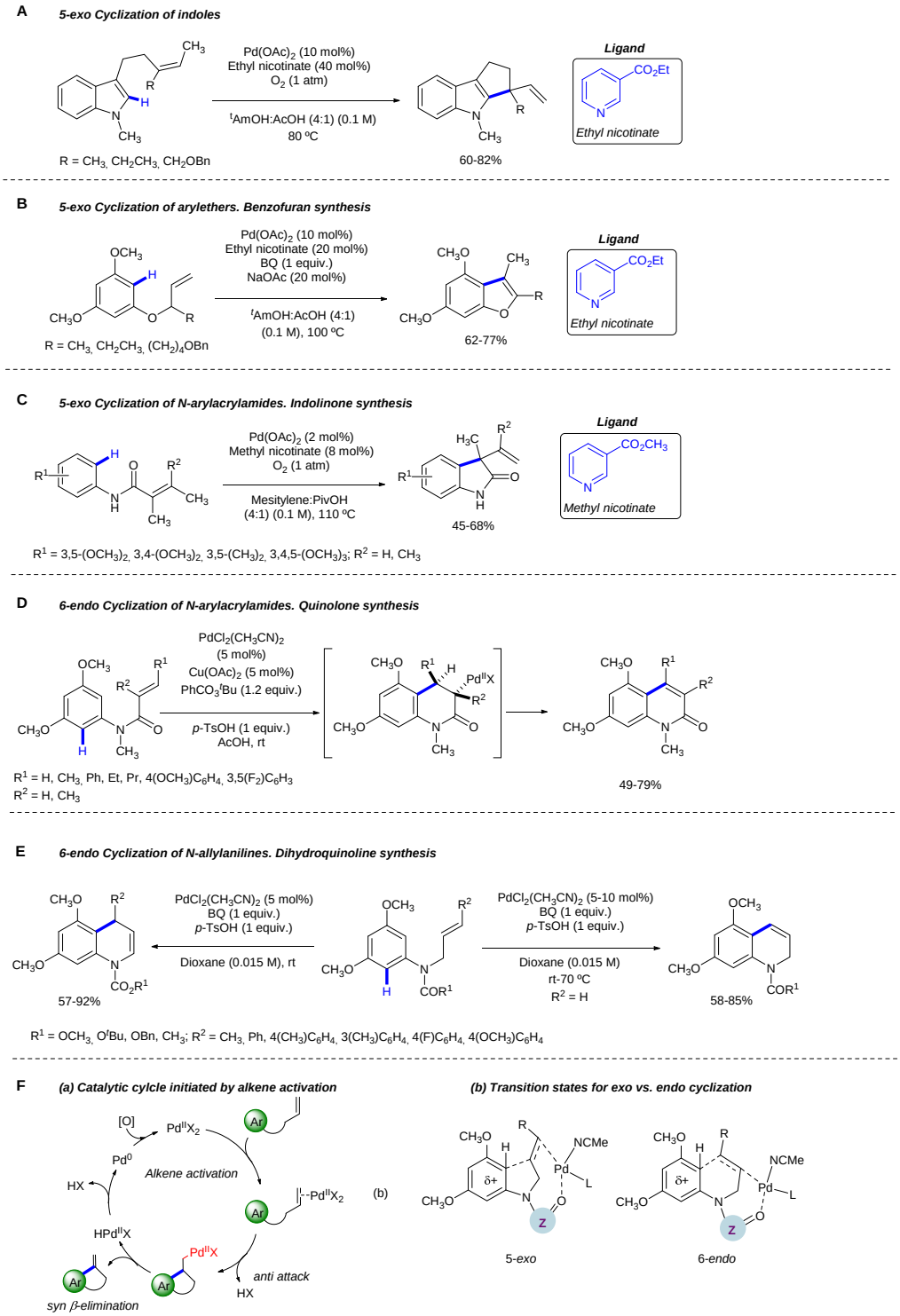

Figure 5. Intramolecular Fujiwara-Moritani reaction. (A) Ligand-assisted intramolecular 5-*exo*-trig cyclization of indole. (B) Ligand-assisted intramolecular 5-*exo*-trig cyclization of allyl aryl ethers. (C) Ligand-assisted intramolecular 5-*exo*-trig cyclization of acrylamides. (D) Intramolecular 6-*endo*-trig cyclization of acrylamides. (E) Intramolecular 6-*endo*-trig cyclization of allylanilines. (F)(a) Alternative alkene activation- arene insertion mechanism for the cyclization reactions. (b) 5-*exo vs.* 6-*endo* TS for the cyclization of allylanilines. Influence of the distal coordination of the protecting group on regioselectivity.

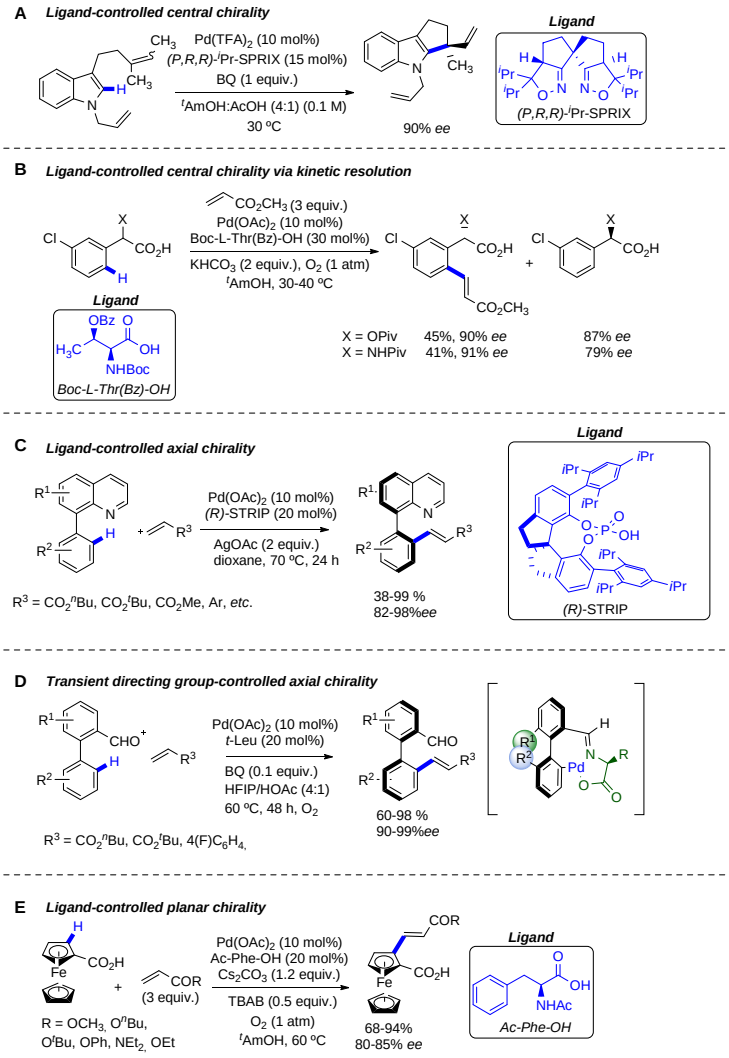

Figure 6. Enantioselective Fujiwara-Moritani reactions. (A) Ligand-controlled enantioselective generation of a quaternary stereocenter. (B) Enantioselective alkenylation via kinetic resolution. (C) Ligand-controlled atroposelective synthesis of axially chiral biaryls (D) Atroposelective synthesis of axially chiral biaryls controlled by a chiral transient directing group. (E) Planar chirality control: enantioselective alkenylation of ferrocene carboxylic acid.

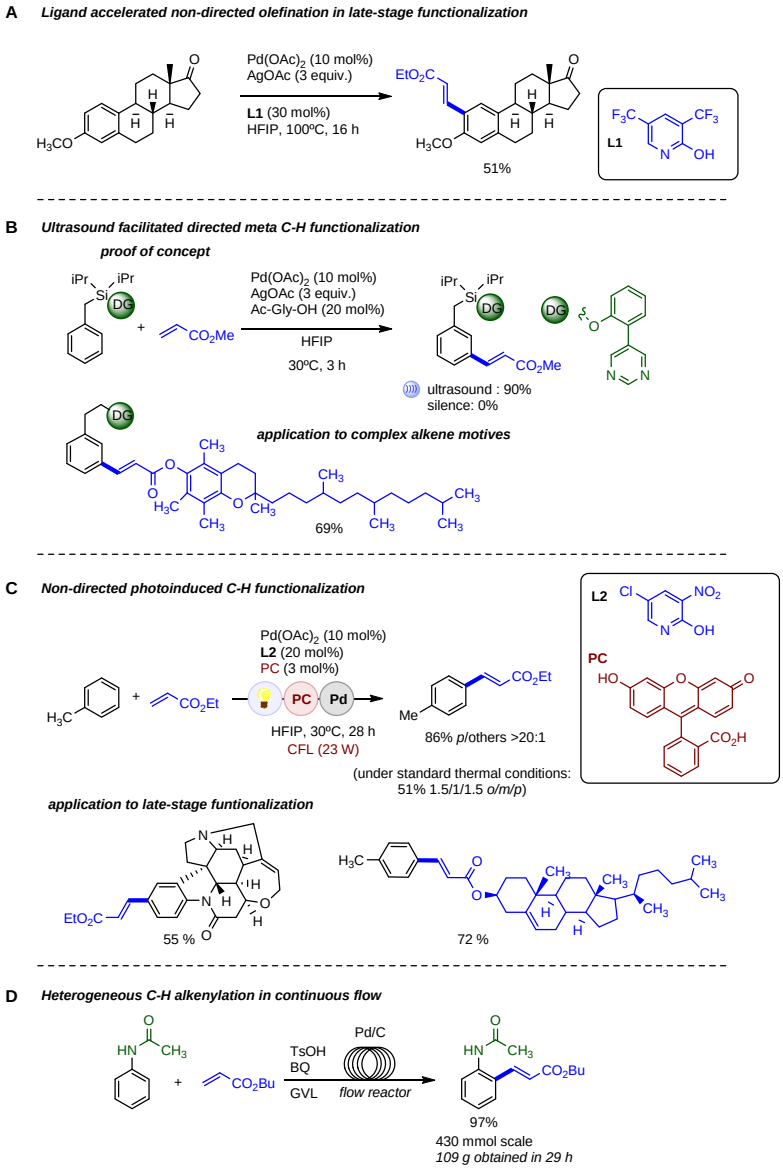

Figure 7. Future perspectives. (A) Ligand accelerated olefination in late-stage functionalization. (B) Use of non-conventional techniques: ultrasound facilitated C-H functionalization. (C) Photoinduced regioselective olefination. (D) Heterogeneous olefination in continuous flow using a biomass-derived reaction medium

Highlights

Palladium-catalyzed oxidative arene C-H alkenylation reactions with alkenes has increased the toolbox of synthetic reactions for C-C bond formation to provide access to biologically relevant molecules and drugs in an efficient, atom economical and environmentally friendly way.

The use of easily removable or transient directing groups and/or ligands allows to control the site selectivity to achieve selective functionalization of $C(sp^2)$-H bonds at the *ortho*, *meta*, *para*, and even remote positions, also improving the reactivity.

The intramolecular variant of these C-H alkenylation reactions can led to the construction of a variety of heterocyclic systems via *exo* or *endo* processes

Ligand design is key to achieve enantioselective C-H alkenylation reactions to generate central, axial, and planar chirality

Outstanding Questions Box

Is it possible to improve regio- and enantioselectivity of Pd(II)-catalyzed C(sp^2)-H alkenylations by careful design of directing groups and ligands?

Is it possible to extend Pd(II)-catalyzed C-H alkenylations to site selective functionalization of C(sp^3)-H bonds?

May C–H activation reactions impact the way in which organic molecules are synthetized?

Is it possible to address the issues associated with scaling up C-H alkenylation for industrial application, thus facilitating the advance of modern medicine and manufacturing?

Is it possible to selectively alkenylate a wide range of C-H bonds using earth-abundant first-row transition-metals?

Glossary

CMD (concerted metalation-deprotonation): mechanistic pathway where the C–H activation takes place via simultaneous metalation and deprotonation processes.

Directing group*:* σ-chelating group with Lewis basic heteroatoms, which can coordinate to the metal center and bring it close to a specific C–H bond.

Electrophilic metalation: mechanistic pathway where the C–H activation step takes place via an electrophilic aromatic substitution

Fujiwara-Moritani reaction: Pd(II)-catalyzed oxidative direct coupling reaction between two C(sp^2)–H bonds, an (hetero)arene and an alkene, to generate a new double C-C bond.

Mizoroki-Heck reaction: Pd(0)-catalyzed cross-coupling reaction of an (hetero)aryl or vinyl halide or pseudohalide with an alkene to generate a new double C-C bond

Transient directing group: directing group generated *in situ* in a reversible and temporary way from a functional group of the substrate.

Traceless directing group: directing group that assists the functionalization of the substrate and thereafter is removed in a single step.