Palladium-catalysed Heck-type alkenylation reactions in the synthesis of quinolines. Mechanistic insights and recent applications

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Palladium-catalysed Heck-type alkenylation reactions in the synthesis of quinolines. Mechanistic insights and recent applications.

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Quinoline and quinolone cores are present in a wide variety of pharmaceuticals, agrochemicals and materials, as well in ligands/catalysts in asymmetric synthesis. Transition-metal catalysed based approaches have played a pivotal role in the development of the catalytic methods for their synthesis. This review presents recent developments on palladium-catalysed Mizoroki-Heck reaction and its dehydrogenative variant (the Fujiwara-Moritani reaction), a C-H activation reaction that does not require the use of prefunctionalized coupling parterns for the synthesis of quinoline frameworks. The mechanistic understanding of both type of reactions, and how the different reaction conditions affect the outcome and the regioselectivity for the synthesis of the quinoline core, which is crucial to achieve target-oriented synthesis successfully, is discussed through selected examples.

1. Introduction

Quinoline and quinolone frameworks, as well as their dihydro/tetrahydro counterparts, are important motifs widely found in biologically active natural products, pharmaceuticals or agrochemicals[1], such as antimalarial chloroquine or hydroxychlorquine,[2] which have recently attracted much attention regarding their use as anti-COVID-19. Relevant examples include also tipifarnib, a farnesyltransferase inhibitor (FTI) for treatment of cancer,[3] the antioxidant ethoxyquin that is used as food preservative[4] or the 3-(4-arylquinolin-3-yl) acrylates that are maxi-K channel openers used in the treatment of ischemia, asthma or migraine,[5] as well as azapodophyllotoxins with potent antitumor activities (Figure 1).[6] Quinoline derivatives have also been used in the manufacture of dyes and as organic optoelectronic materials.[7] Besides, Cinchona-alkaloid derivatives are important ligands and catalysts in asymmetric catalysis.[8]

Great efforts have been devoted to the development of methods for the preparation of these privileged heterocycle cores, and consequently several reviews on the synthesis and applications of quinolines have been published.[9] Synthetic routes to quinoline derivatives usually involve multiple steps and/or highly functionalized substrates and present low functional group compatibility.

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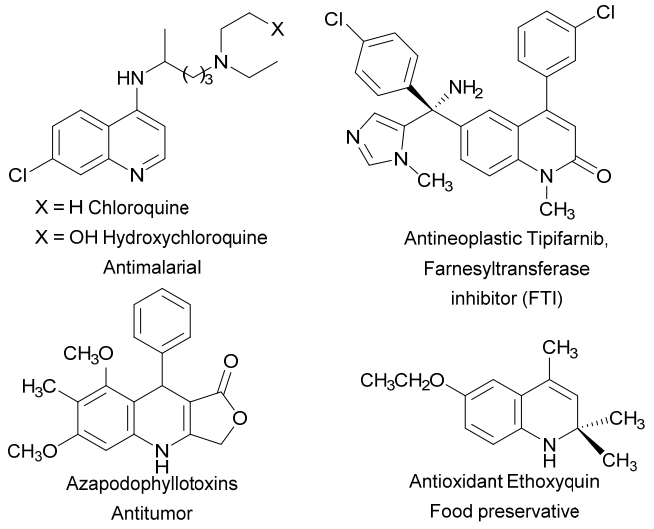


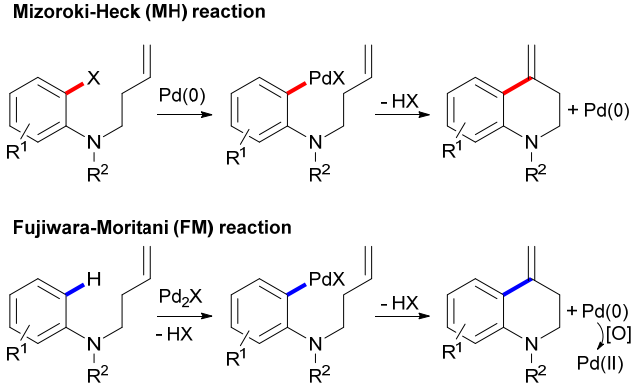
Figure 1. Representative examples of biologically active quinoline derivatives.

For example, our group has reported the enantioselective synthesis of 2,4-disubstituted tetrahydroquinolines *via* intramolecular carbolithiation of *N*-alkenyl substituted 2-iodoanilines, which requires working under strict anhydrous conditions at very low temperature (-90 ºC).[10] Therefore, both academy and industry demand more efficient strategies for the construction of these scaffolds. In this context, catalytic synthesis of quinoline derivatives has emerged as an alternative to classical methods that has enabled to overcome the above-mentioned drawbacks. An excellent example is the development of transition-metal-catalysed cross-coupling reactions that has had a huge impact on pharmaceutical research,[11] though now the goal has moved to the design of more environmentally friendly approaches: C–H bond activation reactions.[12] In particular, the Mizoroki-Heck (MH)

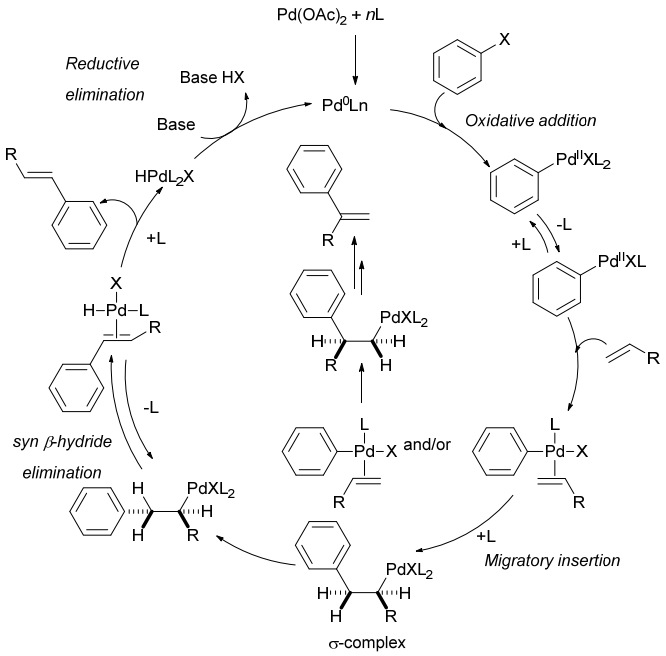
reaction[13] and its dehydrogenative or oxidative variant, also known as Fujiwara-Moritani (FM) reaction,[14] stand out among the approaches for the assembly of these heterocycles.[15] The MH reaction is a Pd(0)-catalysed cross-coupling reaction between (hetero)aryl or vinyl halides or triflates with alkenes (Scheme 1), while its dehydrogenative variant employs Pd(II) catalysis for the oxidative coupling of two C(sp^2)-H bonds (an alkene and an arene); however, it requires an oxidant to regenerate the active catalytic species (Scheme 1). Therefore, the FM reaction is an atom-economical variation of the Heck reaction that avoids the use of prefunctionalised coupling partners, thus minimizing the complications and waste associated with their preparation. Although the general catalytic cycles are now reasonably well established, some key catalyst features and experimental conditions responsible for selectivity remain challenging. In this review, we will focus on the mechanistic understanding of both previously mentioned palladium-catalysed reactions, and how the different reaction conditions affect the outcome and the regioselectivity for the synthesis of the quinoline core, which is crucial to achieve target-oriented synthesis successfully.

2. Intramolecular Mizoroki-Heck reaction in the synthesis of the quinoline core

The mechanism of the MH reaction has been widely studied.[16] The most generally accepted catalytic cycle involves four main steps (Scheme 2): (a) the oxidative addition of the *in situ* generated Pd(0) to C-X bonds of aryl halides or triflates, (b) migratory insertion, (c) *syn*-β-hydride elimination and (d) reductive elimination. The Heck-type reactivity depends on the ability of the Pd(0) species to undergo oxidative addition to C-X bonds of aryl halides or triflates and the subsequent addition of the ArPdX intermediates to unsaturated bonds,[17] being either the oxidative addition or the complexation/insertion process the rate determining steps



Scheme 1. Intramolecular Mizoroki-Heck and Fujiwara-Moritani reactions.



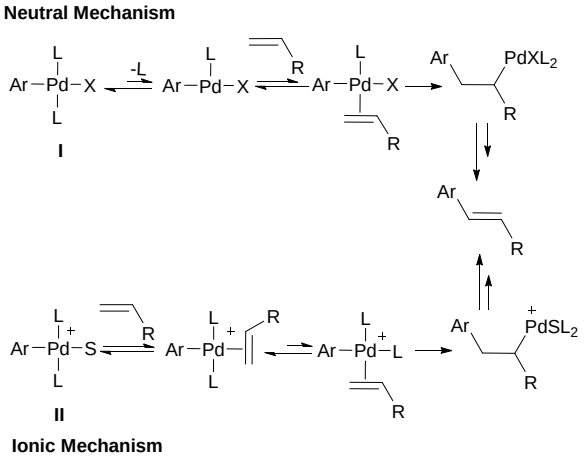
Scheme 2. General catalytic cycle for the Mizoroki-Heck reaction

A wide variety of palladium complexes may be used as catalysts, such as $Pd(PPh_3)_4$, $Pd(dba)_2$ and $Pd_2(dba)_3$, which provide directly catalytically active Pd(0) species. Besides, Pd(0) species can be *in situ* generated by reduction of Pd(II) precatalysts, such as $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$, in the presence of phosphine ligands, whose function is to keep the catalyst stable at a (0) oxidation state, by forming species like PdL_4 and PdL_2. However, the use of ligand-free MH reaction is interesting due to economic, environmental and chemical reasons (high toxicity, difficulty to be recovered, high price, etc.). Additionally, fully coordinated palladium complexes present lower reactivity, so, an increase of catalyst loading is usually needed to obtain reasonable reaction rates. Both organic (trialkylamines) and inorganic bases (NaOAc, $NaHCO_3$, etc.) are used to regenerate the catalytic active Pd(0) species. After the pioneering work of Mizoroki[18] and Heck,[19] many modifications to the original reaction conditions have been introduced to improve the selectivity, *e.g.* use of tetraalkylammonium salts (Jeffery protocol)[20] or either silver[21] or thallium[22] salts. In addition, it has been demonstrated that the efficiency of the catalyst can be increased carrying out the reaction under pressure or microwave assisted conditions.

2.1. Regioselectivity in the Mizoroki-Heck reaction. Synthesis of aromatic quinolines vs their dihydro derivatives.

To account for differences in the regioselectivity derived from the *syn* insertion of the Ar-Pd(II)-X complex to the alkene, two different mechanistic pathways have been proposed, termed as “cationic” and “neutral”, depending on the formal charge on the first-formed palladium(II)-alkene complex generated. In the neutral mechanism (non-polar route), a neutral palladium species is formed by dissociation of one ligand, while in the cationic mechanism (polar route) a loss of the X group leads to

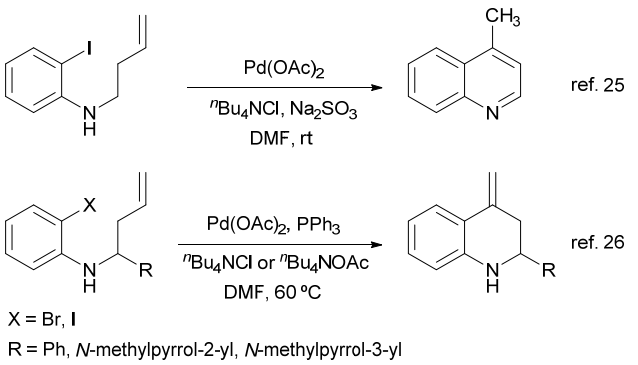
the formation of a cationic palladium species which undergoes *syn* addition (Scheme 3).



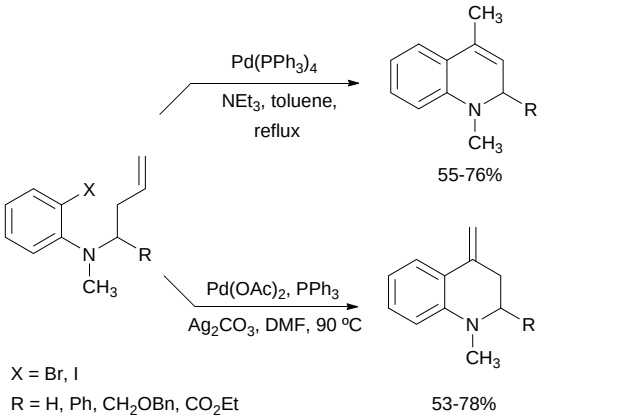
Scheme 3. Cationic (or polar) vs. neutral MH pathways.

The mechanistic pathways change depending on the precatalysts, ligands, additives, etc. used, which can generate different palladium species or intermediates after the oxidative addition step. Thus, when $Pd(OAc)_2$/n PPh_3 (n>2) is used, the *trans* complex (X = OAc) formed (after the oxidative addition step) is easily dissociated, so a cationic Heck reaction pathway takes place *via* an electrophilic palladium (II) species, $[ArPd\text{-}(PPh_3)_2]^+$ (II). Similar electrophilic palladium(II) species have been reported when using bidentate phosphines as dppp instead of PPh_3, though in this case thallium salts are needed as iodide ion scavengers. However, when $Pd(PPh_3)_4$ is employed, the intermediate *trans* complex (X = I) has an iodide ligand, thus favoring a Heck-type α,β-insertion reaction, via a neutral mechanism.[23]

The regioselectivity in the intramolecular variant of the MH reaction is also influenced by the ring size and the preference for *exo* processes, which can be explained by the strain in the approach of the arylpalladium intermediate. In fact, *endo*-trig cyclisations are rare and have been reported when the *exo* processes are blocked. An illustrative example can be found in the synthesis of the 4-methylenequinolone reported by Smalley,[24] where even having severe congestion surrounding the most substituted alkene carbon, the reaction always proceeded via a 6-*exo*-trig process. In the same way, the cyclisation of *N*-benzyl-*N*-(2-iodophenyl)-*N*-but-3-enamide led to the 4-methylquinolone derivative either using $Pd(dba)_2/PPh_3$ or ligandless Jeffery's conditions that would favor *endo* ring formation. One of the first examples of intramolecular MH reaction was described by Larock,[25] who reported the 6-*exo*-trig ring closure of *N*-homoallyl-2-iodoaniline to give 4-methylquinoline, *via in situ* isomerization and oxidation of the initially formed methylenetetrahydroquinoline, using a phosphine-free catalytic system. However, we have shown that it is possible to avoid isomerization and oxidation isolating 2-(hetero)aryl substituted 4-methylenetetrahydroquinolines in moderate to good yields using modified Jeffery's conditions[26] (Scheme 4).



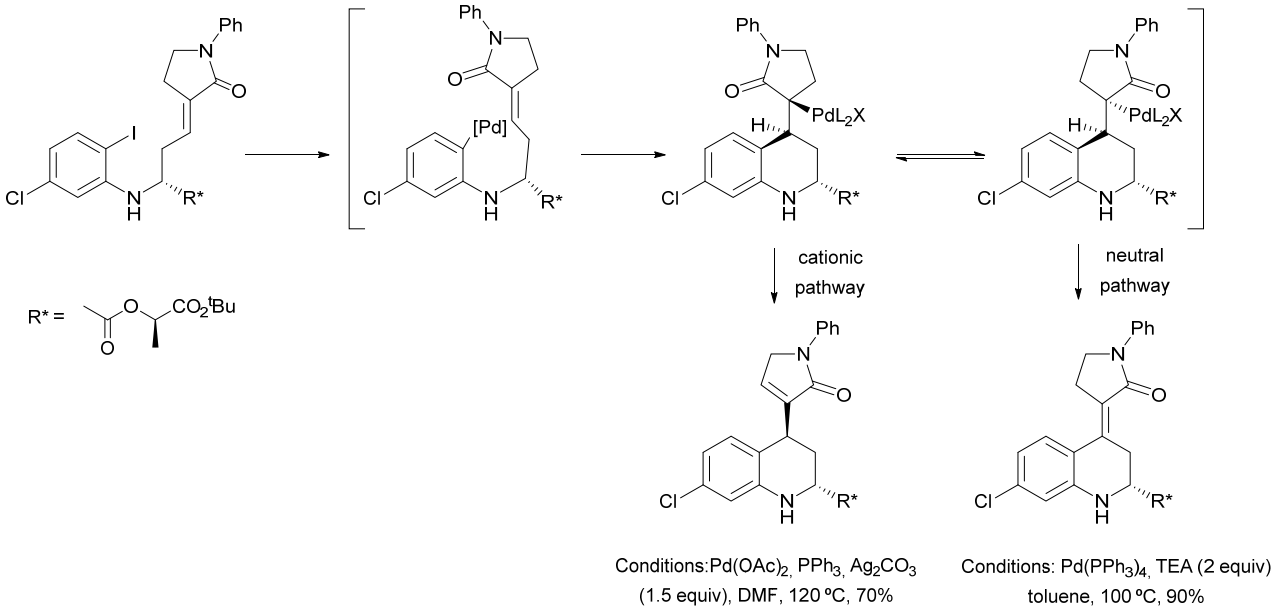
Scheme 4. Intramolecular 6-*exo*-trig MH reaction: synthesis of quinolines *vs.* dihydroquinolines.



Scheme 5. Cationic *vs.* neutral MH pathways in the intramolecular MH reaction of unactivated alkenes

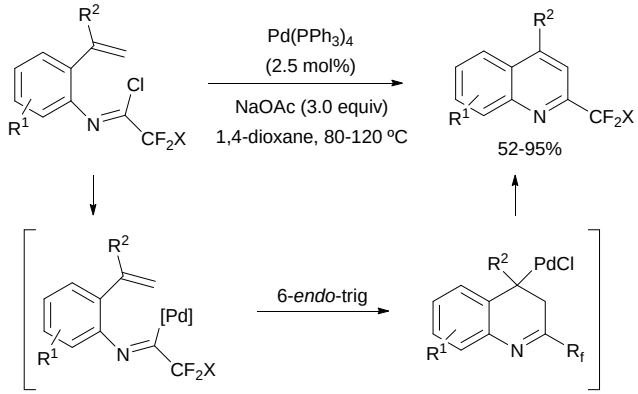
Besides, the isomerization could be also controlled in the cyclisation of *N*-methyl-*N*-alkenyl substituted 2-haloanilines by choosing the adequate catalytic system (Scheme 5). When non-substituted alkenes are used, the reaction can switch to the synthesis of hydroquinolines with an exocyclic or endocyclic double bond. Modified Jeffery´s conditions [$Pd(OAc)_2$, PPh_3, $AgCO_3$], led to the quinoline with the *exo* double bond, while the regioselectivity was shifted to the *endo* product when the reaction proceeded via a neutral mechanism using $Pd(PPh_3)_4$. In the first case, the use of silver salts is crucial to avoid reinsertion of the palladium hydride species formed after β-elimination to give the more stable 1,2-dihydro derivative (Scheme 5).

On the other hand, for alkenes with electron-withdrawing groups, the intramolecular MH reaction takes place at the β-position of α,β-unsaturated amides, like in 1,4-additions. There are several examples in the literature of the cyclisation of *N*-butenylaniline derivatives that lead to the synthesis of 2-substituted tetrahydroquinolines with *exo* α,β-unsaturated amide moieties at the C-4 position, regardless of the pre-catalyst used.[26,27]



Scheme 6. Cationic *vs.* neutral MH pathways in the intramolecular MH reaction of activated alkenes

Interestingly, Di Fabio and Alvaro were able to switch the outcome of the reaction from the 4-alkylidenetetrahydroquinoline to its isomeric derivative with a tertiary stereocenter at the C-4 position of the tetrahydroquinoline unit by changing the catalytic system. Thus, the intramolecular MH reaction on α,β-unsaturated lactams shown on Scheme 6 allowed the diastereoselective synthesis of enantiopure tetrahydroquinolines, starting from a chiral pool aldehyde. The authors explained the regiocontrol in the formation of the double bond by the different mechanistic pathways: polar [$Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF] or neutral [$Pd(PPh_3)_4$, toluene]. Although both products have an α,β-unsaturated system, the 4-alkylidenetetrahydroquinoline is the most thermodynamically stable regioisomer (Scheme 6).[28]



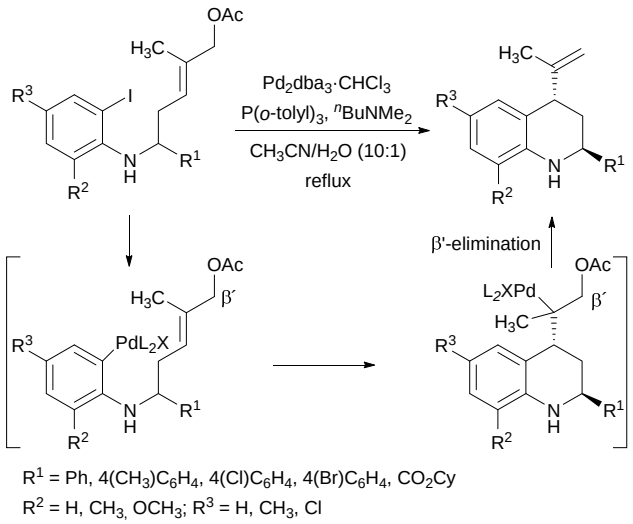
R^1 = H, 3-CH_3, 4-CH_3, 2-OCH_3, 4-OCH_3, 3-Cl, 4-Cl, 2-Br, 4-Br, 4-NO_2, 4-F
R^2 = Ph, 4-F-C_6H_4, 4-Cl-C_6H_4, CH_3, Et, *n*Bu,Cy
R^3 = H, F, Cl, CF_3

Scheme 7. Intramolecular 6-*endo*-trig MH reaction of imidoyl halides

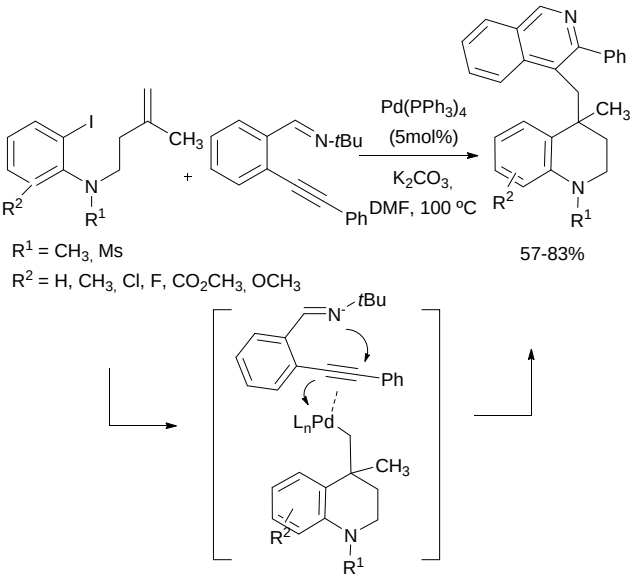
A different approach for the synthesis of the quinoline core involves the 6-*endo*-trig Heck cyclisation reaction using imidoyl halides (instead of aryl halides) with a tethered α-substituted alkene that led to the selective construction of 2-fluoroalkyl quinolines (Scheme 7). In this case, it is necessary to avoid the 5-*exo*-trig process by introducing a substituent in the alkene, so that the intermediate palladium species cannot undergo β-elimination, while reductive elimination of the C-Pd(II)-Cl group to form a C-Cl would be disfavored. Thus, oxidative addition of the imidoyl chloride to a Pd(0) center, followed by intramolecular insertion of the alkene and β-elimination would afford the six-membered heterocycle.[29]

2.2. Construction of tertiary and quaternary centers *via* Mizoroki-Heck reaction

The control of the β-hydride elimination step in the Mizoroki-Heck reaction allows the construction of stereocenters. Several strategies have been used to direct the elimination to another β´ position, such as blocking the β-hydride elimination using cyclic or substituted acyclic alkenes, and using allylic derivatives (esters, ethers, silanes, boronates) to favor either a tautomerisation or an elimination reaction.[30] The intermolecular MH coupling of aryl (pseudo)halides with allyl esters has been widely explored. Besides, enantioselective variants using chiral phosphine ligands (*i.e.* (*R*)-BINAP) have also been developed.[31] However, there are few examples of the intramolecular variant and, to our knowledge, only one example of its application in the synthesis of quinoline derivatives has been reported. Thus, Lautens described the use of allyl acetates as coupling partners in the intramolecular MH reaction for the generation of a tertiary stereocenter *via* elimination of β´-acetoxy group, which led to the diastereoselective synthesis of *trans*-2,4-disubstituted tetrahydroquinolines (Scheme 8).[32]



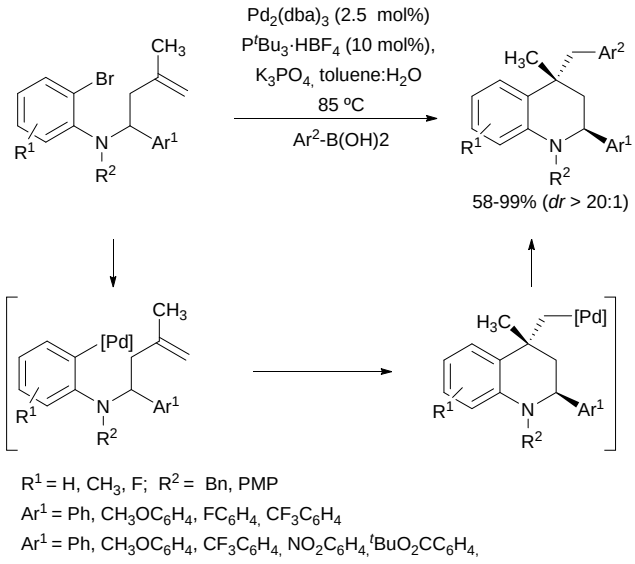
Scheme 8. Generation of tertiary stereocenters via β′-leaving group elimination



Scheme 10. Domino Heck/intermolecular cross-coupling reaction

2.3. Cascade reactions

On the other hand, β-hydride elimination can also be avoided by involving the alkylpalladium intermediate in another coupling reaction, *i.e.* a cascade reaction. Among the few examples of construction of six-membered heterocycles by intramolecular Heck/Suzuki cascade reaction, we can find the diastereoselective synthesis of 2,4,4-trisubstituted tetrahydroquinolines through cyclisation of functionalized *o*-bromoanilines with boronic acids (Scheme 9).[33] The σ-alkylpalladium(II) intermediate obtained after the initial 6-*exo* carbopalladation process participates in a second intermolecular cross-coupling reaction with a boronic acid. It is crucial to select the adequate catalytic system and experimental conditions to avoid the direct cross-coupling reaction between the aryl halide and the boronic acid. In this case, tertiary amines had to be used as substrates, since with secondary amines the direct cross coupling was the main pathway.



Scheme 9. Intramolecular Heck/intermolecular Suzuki cascade reaction.

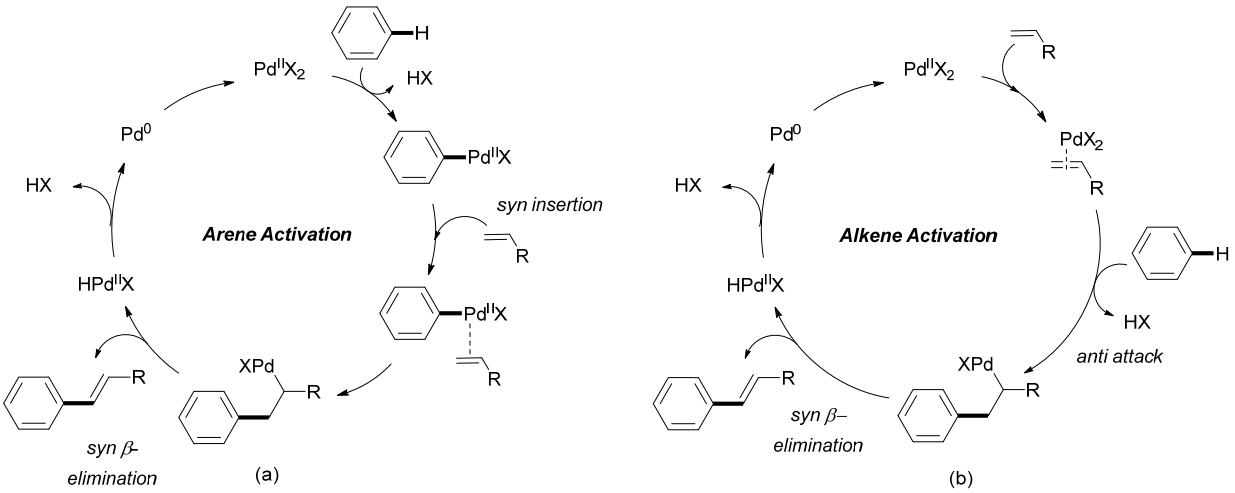
As shown in Scheme 10, the intermediate alkylpalladium(II) species can also be involved in the reaction with alkynes that incorporate a nucleophilic group to form two cycles, two C-C and a C-N bond in a single step, affording functionalized (isoquinol-4-yl)methyltetrahydroquinolines.[34]

3. Intramolecular Fujiwara-Moritani reaction in the synthesis of the quinoline core

The Fujiwara-Moritani reaction takes place *via* Pd(II) catalysis. The reaction is proposed to proceed through C-H activation of the aryl ring to form a σ-aryl-Pd(II) intermediate (arene activation) (Scheme 11a). Then, the olefin partner would coordinate to the Pd(II) species, followed by 1,2-migratory insertion to the Pd(II)-aryl bond. As in the MH reaction, the formed Pd(II)-hydride is transformed into a Pd(0) species after reductive elimination so, in this case, an oxidant is required in order to recover the catalytically active Pd(II) species.[14] Alternatively, some of these Pd(II)-catalysed C-H alkenylations have been shown to proceed through a mechanism that does not involve a C-H activation event, but a prior coordination of the olefin to the Pd(II) species, followed by subsequent nucleophilic attack of the arene ring and β-hydride elimination to give the alkenylated arene (Scheme 11b).[14]

3.1. Regioselectivity in the C-H activation step

Due to the large number of C-H bonds present in organic molecules, one of the major challenges of the oxidative Heck reaction consists of achieving selectivity in the C-H activation step. During the past decades, different mechanisms have been proposed for the C-H metalation process that would proceed through three different transition states, as disclosed by Yu and co-workers in 2010 (Figure 2). [35]



Scheme 11. Schematic catalytic cycles for the Fujiwara-Moritani reaction.

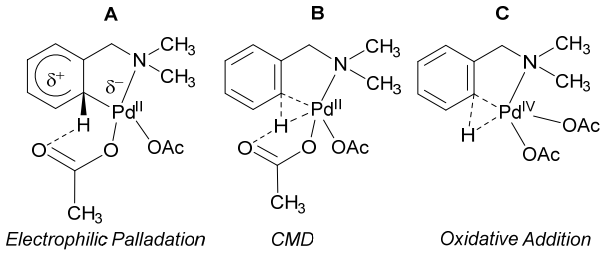


Figure 2. Mechanistic pathways for the C-H arene activation step in the FM reaction

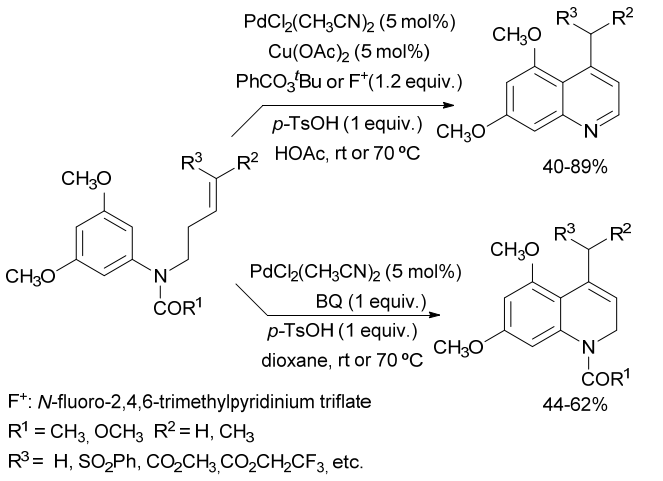
The first mechanism involves the formation of an aryl-Pd(II) species through the electrophilic palladation of the aromatic ring (Figure 2a). In this case, the C-H activation step would take place via an electrophilic aromatic substitution, followed by a fast deprotonation that leads to rearomatisation. That way, the aryl-Pd(II) species is formed by the transference of a proton to an acetate bounded to the palladium(II) centre. Therefore, the electronic properties of the arene substrate play a fundamental role in the C-H activation. The second mechanism proposed (Figure 2b) is a Concerted Metalation-Deprotonation (CMD), which consists of a proton abstraction that takes places by means of a concerted and intramolecular transfer of a hydrogen atom to a base. The last mechanism (Figure 2c) is based on the oxidative addition of the C-H bond to the Pd(II) centre and involves the formation of a Pd(IV) species, that provides the aryl-Pd(II) species after reductive elimination

Regardless of the mechanism operating in the C-H activation step, there are three main strategies for the control of the regioselectivity: to take advantage of the electronic properties of the arene substrate, to use directing groups and to employ ligands for the Pd(II) centre. These strategies have been used in a variety of methodologies for the synthesis of quinolines, dihydroquinolines or even quinolones. Those examples will be herein disclosed placing the accent on the proposed mechanistic pathway for each case.

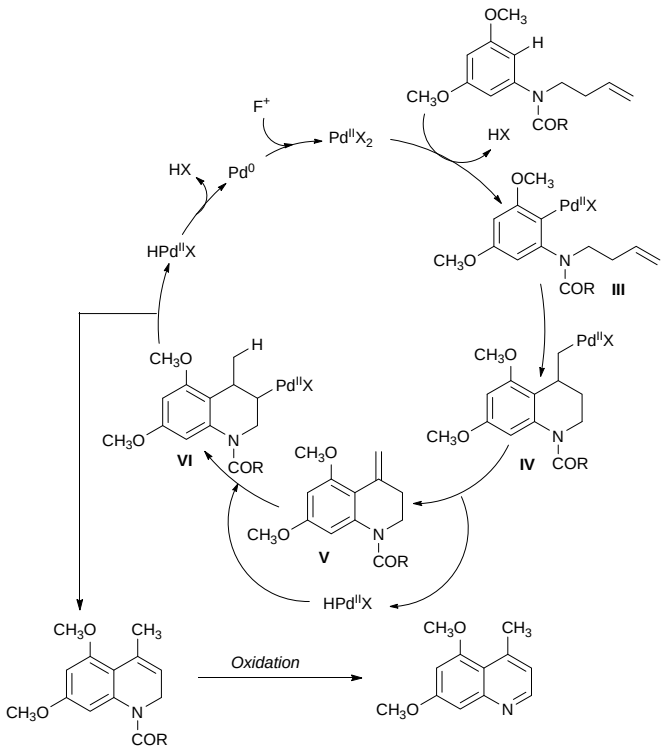
3.1.1. Regioselectivity control by the electronic properties of the arene.

When simple substituted arenes or heteroarenes are employed as substrates in the Pd(II)-catalysed alkenylation reaction in the absence of directing groups and/or ligands, it is commonly agreed that the C-H activation step proceeds through an electrophilic aromatic substitution. Accordingly, the regioselectivity of that step completely depends on the electronic properties of the substrate. However, the main drawback of this method lies on the fact that not a wide scope of the arene can be achieved, as the reaction only works with electron-donating substituents in C(sp^2)-H bonds placed in their *ortho* and/or *para* positions.[36]

In our group, this strategy has proved to be efficient in its intramolecular variant for the synthesis of quinoline and dihydroquinoline derivatives. As discussed above for the MH reaction, in the intramolecular FM reaction, *exo*-trig cyclisations are usually favored being also determinant the size of the formed ring. In this context, we recently reported the intramolecular palladium(II)-catalysed C-H alkenylation reaction of *N*-butenylanilines (protected as acetamides or carbamates) for the regioselective preparation of quinolines and dihydroquinolines via 6-*exo*-trig processes (Scheme 12).[37] There is no competition with the 7-*endo*-trig cyclisation. The reaction can be directed either to the quinoline or to the 1,2-dihydroquinoline using the same catalyst $PdCl_2(CH_3CN)_2$ and changing the oxidant and the solvent. Thus, when $PhCO_3{}^tBu$ or *N*-fluoro-2,4,6-trimethylpyridinium triflate (F^+) were used as oxidants in acetic acid, deprotection of the carbamate/amide and further oxidation took place leading the aromatic derivative. When milder reaction conditions were employed (BQ as oxidant in dioxane), the elimination of the *N*-protecting group could be avoided, obtaining the corresponding 1,2-dihydroquinolines.



Scheme 12. 6-*Exo*-trig intramolecular FM reaction of *N*-butenylanilines. Synthesis of quinolines *vs.* dihydroquinolines

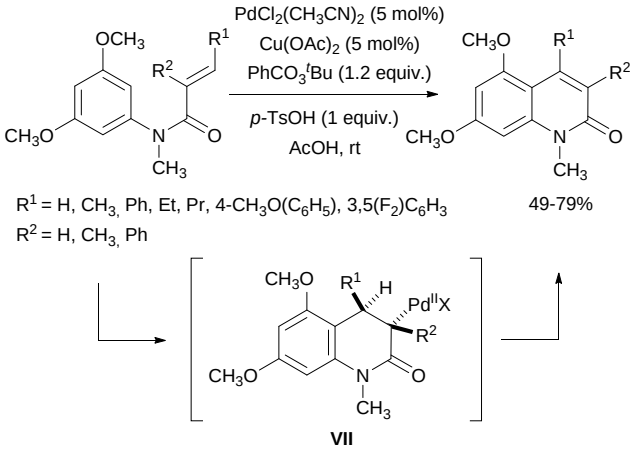


Scheme 13. 6-*Exo*-trig intramolecular FM reaction of *N*-butenylanilines.

The procedure can be applied to both unsubstituted and substituted alkenes, although for α,β-unsaturated esters higher temperatures (70ºC) and a stronger oxidant were required. As expected, in all the cases, electron-donating substituents at the C-3 and C-5 positions of the aromatic ring are needed for the cyclisation to perform well (Scheme 12). The proposed mechanism was thought to involve aromatic metalation by electrophilic palladation to form species **III**, followed by *syn* migratory insertion of the alkene and β-hydride elimination to give tetrahydroquinoline **VI**, along with palladium hydride. That palladium hydride species would then perform migratory insertion into the exocyclic olefin of **V** to form intermediate **VI**, which would evolve via β-hydride elimination to produce the corresponding 1,2-dihydroquinoline. The obtained Pd(II) hydride species undergoes reductive elimination to form Pd(0) that is afterwards reoxidised to the catalytically active Pd(II) species (Scheme 13). However, a mechanism involving a prior activation of the alkene followed by arene insertion cannot be discarded.[38]

Pd(II)-catalysed cyclisations of *N*-arylacrylamides generally prefer to proceed through 5-*exo*-trig processes to form oxindoles.[39] Even when β-hydride elimination is not allowed, the Pd(II)-aryl intermediate prefers to capture a nucleophile[40] or to undergo C-H alkylation.[41] However, we were able to find the adequate catalytic system to switch the reaction to the β-position of the alkene (the most reactive position in the intermolecular reactions), generating quinolones via an unprecedented 6-*endo*-ring closure. Thus, we have developed an efficient method for the synthesis of quinolones starting from *N*-arylacrylamides as substrates using $PdCl_2(CH_3CN)_2$ as catalyst and $PhCO_3tBu/Cu(OAC)_2$ as oxidant (Scheme 14).[42] This palladium (II)-catalysed intramolecular alkenylation takes place with high efficiency at room temperature. Furthermore, the reaction could be carried out not only in a 2% wt. aqueous solution of PTS, but also in water, obtaining the quinolones in good yields, though the cyclisation required longer reaction times (24 h). Several substitution patterns in the alkene are well tolerated in this transformation; that way, both 4-substituted and 3,4-disubstituted quinolones could be efficiently obtained. Nonetheless, alkenes bearing electron-deficient substituents do not perform well, probably due to acidic decomposition of the substrate.

The mechanistic pathway would involve a selective 6-*endo*-trig cyclisation process that would provide intermediate **VII**, leading to the corresponding quinolone after β-hydride elimination (Scheme 14). Although the reaction was initially proposed to occur through palladation of the aromatic ring followed by cyclisation onto the alkene, an alkene activation-arene insertion cannot be discarded, as in the previous *exo* cyclisation.



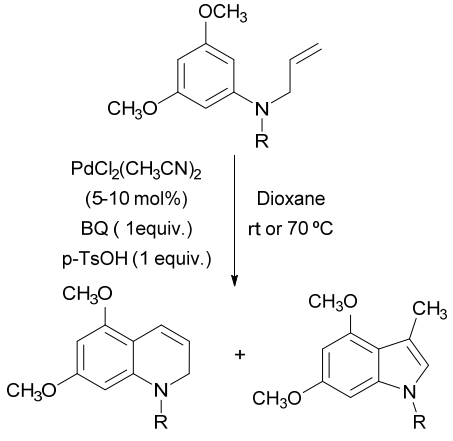
Scheme 14. Intramolecular 6-*endo*-trig FM reaction of acrylamide derivatives

In any case, either an electrophilic palladation of the arene or an electrophilic aromatic substitution to the Pd(II) activated alkene should take place, as the reaction only works well with electron rich aromatic rings, mainly *N*-(3,5-dimethoxyphenyl) acrylamides. This is probably the main drawback of this 6-*endo*-trig cyclisation of *N*-arylacrylamides for the synthesis of quinolones.

3.1.2. Regioselectivity control by the use of directing groups

Directing groups are σ-chelating groups that contain Lewis basic heteroatoms, which are able to coordinate to the palladium centre and to approach it to a specific C-H bond, forming palladacycles. Although most of them enable the activation of C-H bonds in their *ortho* position,[43] there are also directing groups that have been specially designed to activate *meta,*[44] *para* C-H bonds or even remote positions.[45] The use of directing groups in transition metal-catalysed alkenylative couplings,[46] and more specifically in palladium (II)-catalysed reactions,[47] has been widely spread. This methodology for the control of regioselectivity in the C-H activation step has also been applied to the synthesis of the quinoline core.

In the context of our study on the intramolecular FM reaction, our group recently reported an efficient method for the synthesis of 1,2- and 1,4-dihydroquinolines via Pd(II)-catalysed 6-*endo* intramolecular C-H alkenylation reaction of *N*-protected allylanilines.[48] We demonstrated the necessity of a coordinating protecting group on the nitrogen atom, a remote directing group that, along with the electronic properties of the arene, controlled not only the regioselectivity of the C-H activation step but also the size of the ring formed, also improving the reactivity.



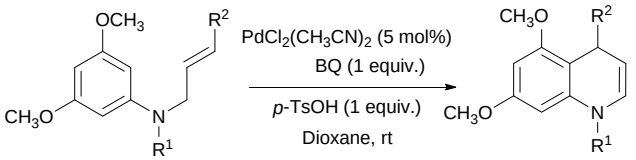
	1,2-dihydroquinoline[a]	*indole*[a]
R = CH_3	nr	nr
R = CO_2CH_3	85%	-
R = CO_2CH_2Ph	68%	-
R = SO_2Tol	87%	-
R = CO_2tBu	57%	15%
R = $COCH_3$	85%	10%

[a]*Isolated % yield*

Scheme 15. Intramolecular 6-*endo*-trig FM reaction directed by the remote *N*-protecting group**.**

Thus, a great influence of the *N*-protecting group on the FM reaction outcome was observed. The reaction of *N*-protected anilines with a tethered allyl group took place via an unusual 6-*endo*-trig process leading to the corresponding 1,2-dihydroquinolines in good yields (Scheme 15), except for the *N*-methyl derivative. However, the 5-*exo*-trig products, the indoles, were isolated as minor products in the reaction of the *N*-Boc and *N*-acetyl protected derivatives, and in the last case higher catalyst loadings and higher temperatures were required. Nevertheless, when substituted alkenes were used, the 1,4-dihydroquinolines were obtained (Scheme 16), with the only exception of the methyl-bearing *N*-tosyl allylaniline. In that case, the 1,2-dihydroquinoline proved the major product (64%), obtaining the 1,4-dihydroquinoline as minor product (26%). The palladium catalyst showed an improved reactivity in the case of aryl-substituted alkenes when a mono-protected amino acid (MPAA) was employed as ligand (Boc-Val-OH). However, the regioselectivity of the reaction completely changed when there were electron-withdrawing groups in the terminal position of the alkene (Scheme 16). Under the standard conditions, conjugated alkenes did not react, and with an increase of the catalyst loading (10 mol%) and heating to 70 ºC the reaction followed a 5-*exo*-trig pathway leading to the indoles in moderate to good yields.

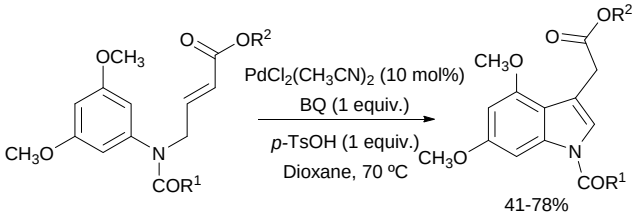
DFT studies were carried out in order to explain these results and get insight on the mechanism of the reaction. Activation energy calculations of several palladium complexes with different electronic properties for the two possible mechanistic pathways (arene-palladation/alkene insertion and alkene activation/arene insertion) were too high, though the activation barriers were lower when palladium (II) is coordinated to the alkene, followed by nucleophilic attack of the arene. However, in all the cases, preferential 5-*exo*-trig insertions were favoured, in contraposition to experimental observations



42-91%

R^1 = CO_2CH_3, $CO_2{}^tBu$, SO_2Tol

R^2 = CH_3, CH_2Ph, Ph, $4(CH_3)C_6H_4$, $4({}^tBu)C_6H_4$, $4(OCH_3)C_6H_4$, $4(F)C_6H_4$, $2(CH_3)C_6H_4$, 2-naphthyl



41-78%

R^1 = OCH_3, $OC(CH_3)_3$

R^2 = OCH_3, OEt, O^nBu, O^tBu, OCH_2Ph

Scheme 16. Intramolecular 6-*endo*-trig vs. 5-*exo*-trig FM reactions. Unactivated vs. activated alkenes

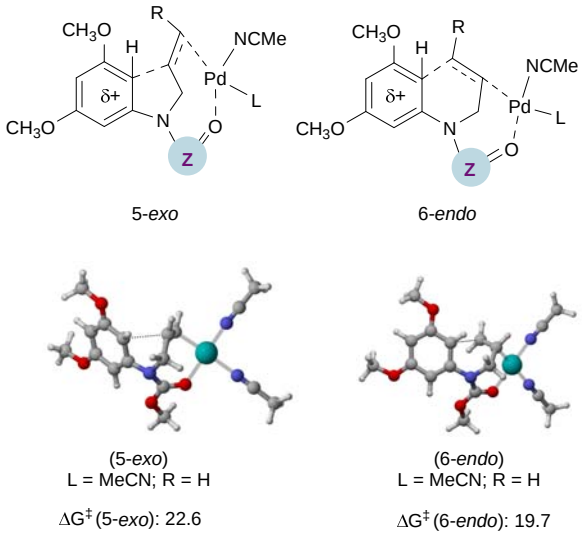
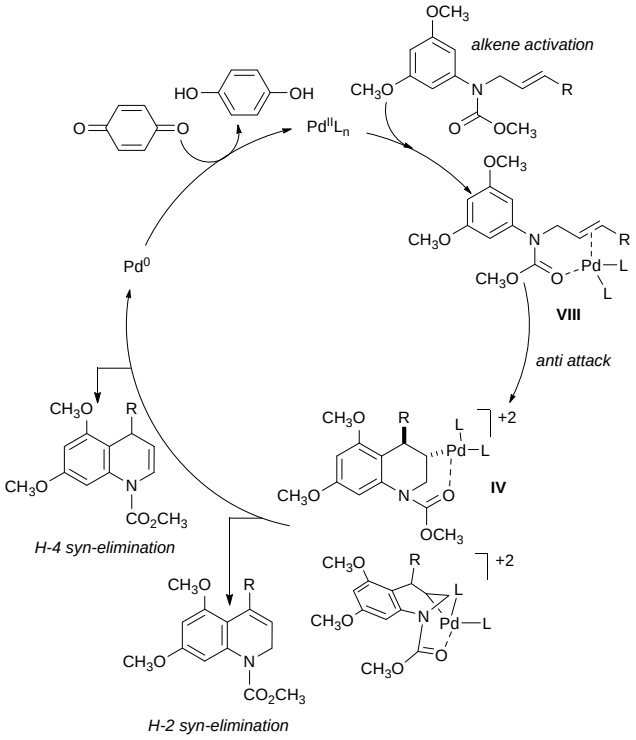


Figure 3. Computed activation energy for the cyclisation after alkene activation by the Pd complexes

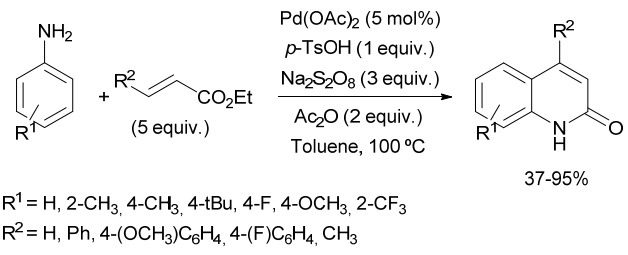
However, if the coordination of the oxygen of the carbamate protecting group to the palladium centre is considered, a complete inversion of the *endo*/*exo* selectivity is observed in agreement with the experimental results. The *endo* regioselectivity is general for terminal and substituted alkenes, and the energy difference with respect to the 5-*exo* counterparts is always high (3.0-10.0 kcal/mol), ensuring a complete regioselectivity. An example is shown in Figure 3. The sense of regioselectivity seems logical, as the coordination of the protecting group to the palladium would induce a larger strain in the 5-*exo*-trig cyclisation. This coordination would also explain the formation of indoles when *N*-acetyl and *N*-Boc protecting groups are employed (Scheme 17): (1) acetamides are less coordinating than carbamates and (2) the bulkiness of Boc may hamper the coordination to the metal center, affecting negatively the regioselectivity of the cyclisation. DFT studies of the *syn* β-hydride elimination also explain the regioselectivity in the formation of 1,2-dihydro- or 1,4-dihydroquinolines. The calculations demonstrated that, in most cases, the reactions would take place under kinetic control. The formation of the more stable 1,2-dihydroquinoline is only favored when the alkene has no substituents. Therefore, the following mechanistic pathways could be proposed: (1) formation of a palladium/alkene complex **VIII**, (2) electrophilic insertion of the arene through a 6-*endo* process that would be favored by the coordination of the *N*-protecting to the palladium and (3) *syn* β–hydride elimination of either H-2 or H-4 to give 1,2-dihydro- or 1,4-dihydroquinolines, respectively (Scheme 17).



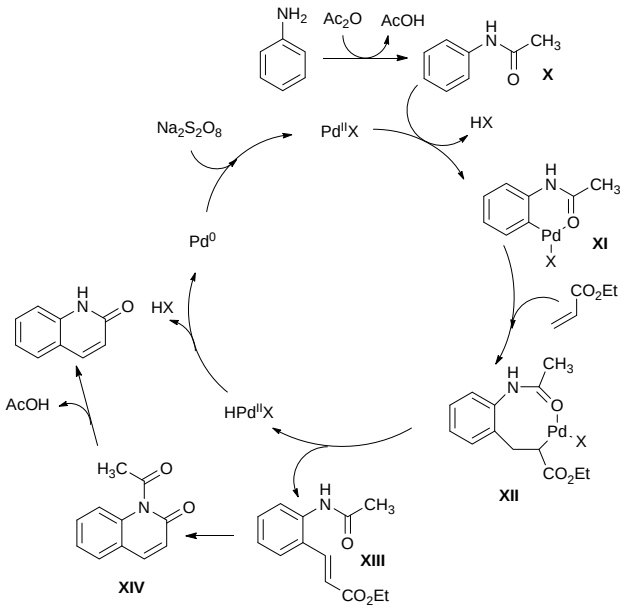
Scheme 17. Mechanism for intramolecular 6-*endo*-trig FM reaction of *N*-allylanilines. Regioselectivity controlled by a remote *N*-protecting group**.**

On the other hand, Liu and co-workers developed an interesting intermolecular FM/intramolecular amidation cascade reaction for the synthesis of quinolones, starting from different anilines and acrylates and taking advantage of an *in situ* formed acetamide directing group, which could be eliminated in the course of the reaction (Scheme 18).[49] The transformation proved to be highly efficient with anilines bearing alkyl and electron-rich substituents on the aromatic ring using cinnamates as coupling partners. Interestingly, this methodology was applied to the synthesis of Tipifarnib.

The aniline substrate is proposed to undergo *in situ* amidation by Ac_2O to form the corresponding acetamide **X** (Scheme 19). The newly formed amide group would act as a directing group, favoring palladation in the *ortho* position to form **XI**. Afterwards, migratory insertion takes place to the acrylate providing species **XII**, which gives **XIII** by β-hydride elimination.



Scheme 18. Intermolecular FM directed by a transient acetamide group, followed by intramolecular amidation**.**



Scheme 19. Liu's mechanism for intermolecular FM directed by a transient acetamide group, followed by intramolecular amidation

The intermolecular C-H alkenylation product **XIII**, under the acidic conditions, would isomerize and undergo intramolecular amidation to give **XIV**, which would be hydrolised *in situ* to afford the quinolone. In order to check the viability of the mechanism, intermediate **XIII** was synthesized and treated with 1 equivalent of *p*-TsOH in toluene at 100 ºC for 36 h. That way, the corresponding quinolone was obtained quantitatively.

3.1.3. Regioselectivity control by the use of ligands for the Pd(II) centre

The third method for the control of the regioselectivity consists of the use of ligands for the metal center that can enhance the reactivity and selectivity of the Pd(II)-catalysed alkenylation reaction. In this context, several ligands have been applied combined with different directing groups.[35,50] In those cases the ligand has to be carefully designed:[35] If the substrate contains a too-strongly-coordinating directing group, the coordination of the ligand to the metal center would be avoided (Figure 4a); however, if the ligand coordinates too strongly to the palladium, the directing group would not be able to perform its work (Figure 4b). Therefore, the design of a ligand that would be capable of generating a pre-transition state where the Pd(II) is coordinated to one molecule of the ligand and one molecule of the substrate is utterly desirable (Figure 4c).

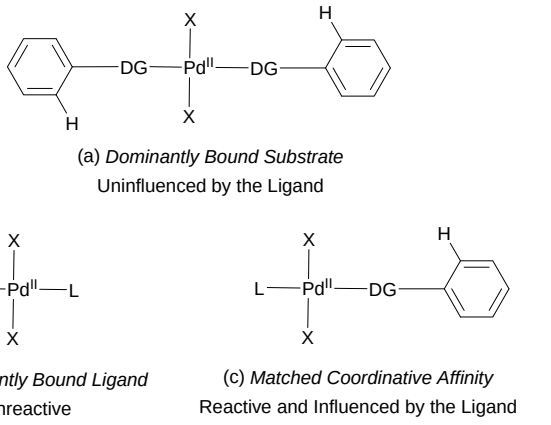
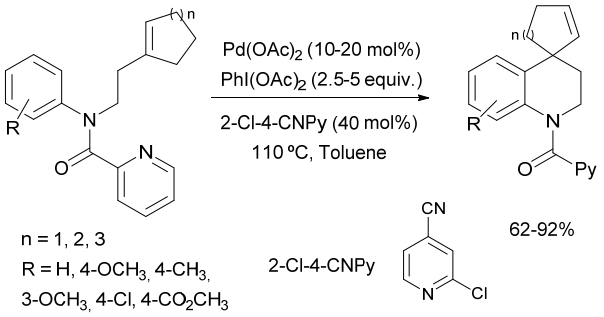


Figure 4. Different types of Pd(II)-complexes. Effect of the directing group and ligand.

An example of the ligand-aided FM reaction for the synthesis of quinolines, is the work developed by He and co-workers. Different cycloalkene-bearing anilines, using picolinamide as the *N*-protecting group, were subjected to a 6-*exo*-trig intramolecular reaction to obtain the corresponding spiro-tetrahydroquinolines (Scheme 20).[51] The use of the pyridine ligand proved to be essential, since the yield increased from 20% to 80%. This reaction showed to be efficient and compatible not only with electron-rich substituents, but also with electron- withdrawing groups in the aniline ring. Nevertheless, in the last cases, the catalyst loading and the oxidant equivalents had to be doubled, probably due to the lower nucleophilicity of the aromatic ring. Furthermore, different ring sizes were tolerated in the cycloalkene moiety.

The need of picolinamide as *N*-protecting/directing group was also demonstrated. It was observed that when a free NH or *N*-methyl group were used, the reaction did not take place. When coordinating protecting groups, such as *N*-tosyl or *N*-Boc, were employed, the substrate underwent allylic acetoxylation.

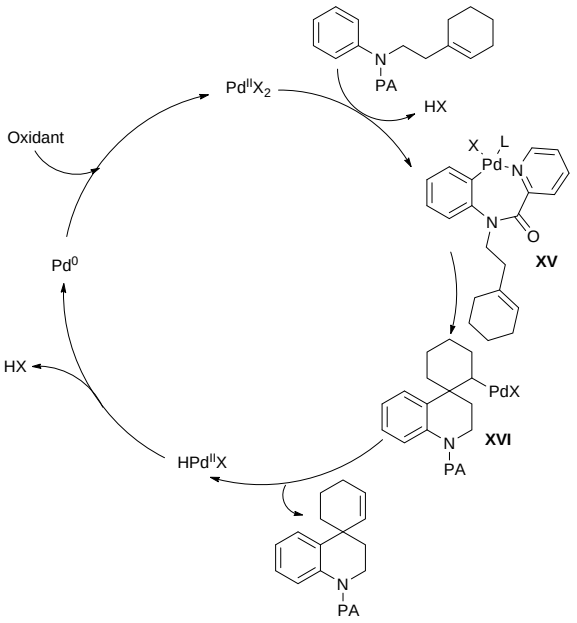
These results suggest that the coordination of Pd(II) to the pyridine ring is necessary for the reaction to proceed. In order to try to determine the mechanism operating in the reaction, kinetic isotopic experiments were carried out.



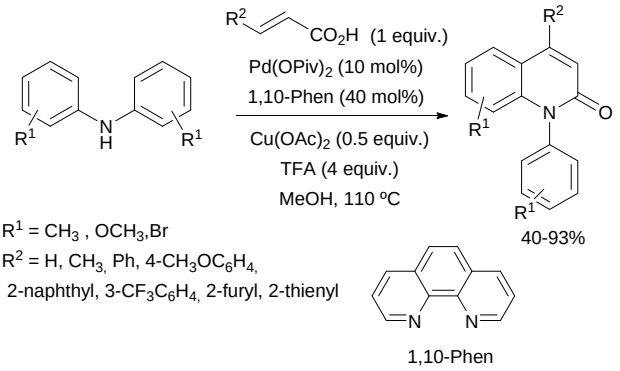
Scheme 20. Intramolecular 6-*exo*-trig FM reaction controlled by both the *N*-protecting group and the pyridine ligand

When using an aniline deuterated in the alkene moiety, no deuterium-migration product was obtained (K_H/K_D= 1.1), while when arene was deuterated, a kinetic isotopic effect of K_H/K_D = 3.4 was observed. These results suggest that the aryl C(sp^2)-H activation is the rate-limiting step. Thus, the reaction may proceed as depicted in Scheme 21. Firstly, as corroborated by the kinetic isotope experiments, C-H activation would take place in the arene, presumably thanks to both, the picolinamide *N*-protecting/directing group and the ligand. The intermediate **XV** formed would then undergo migratory insertion to the olefin, obtaining **XVI**. After β-hydride elimination, the tetrahydroquinoline is formed, along with palladium hydride. After reductive elimination and reoxidation of Pd(0), the active Pd(II) species is recovered**.**

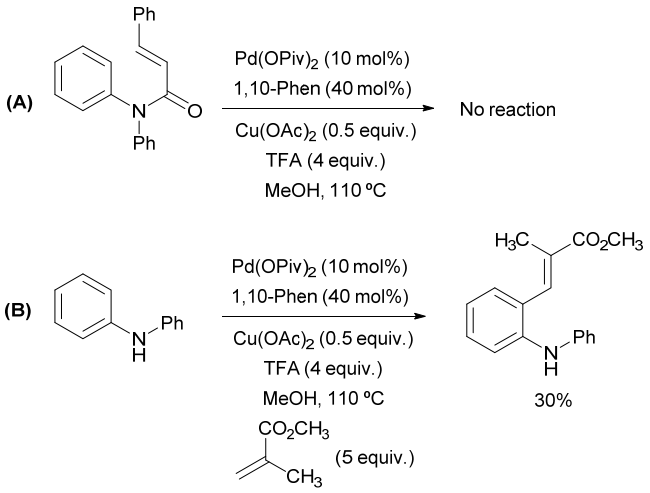
Besides the intramolecular FM reaction, closely related approaches that involve an intermolecular C-H alkenylation for quinoline synthesis have also been described. Some selected examples are discussed. Maiti and co-workers developed an intermolecular FM/amidation cascade reaction to synthesize 4-substituted quinolones starting from diarylamines and α,β-unsaturated carboxylic acids (Scheme 22) using 1,10-phenanthroline as ligand.[52] Even though the use of those substrates may lead to complications in the FM reaction (since intermediates derived from α,β-unsaturated acids are prompt to undergo easy decarboxylation), it was found that TFA could prevent that process, allowing the formation of quinolones. The reaction proceeded smoothly when a variety of cinnamic acids were employed. Based on different competition experiments carried out, they found that electron rich diphenylamines and electron rich acrylic acids underwent the reaction preferentially over their neutral or even electron-deficient counterparts.



Scheme 21. Mechanistic proposal for the intramolecular FM reaction controlled by both the *N*-protecting group and the pyridine ligand.

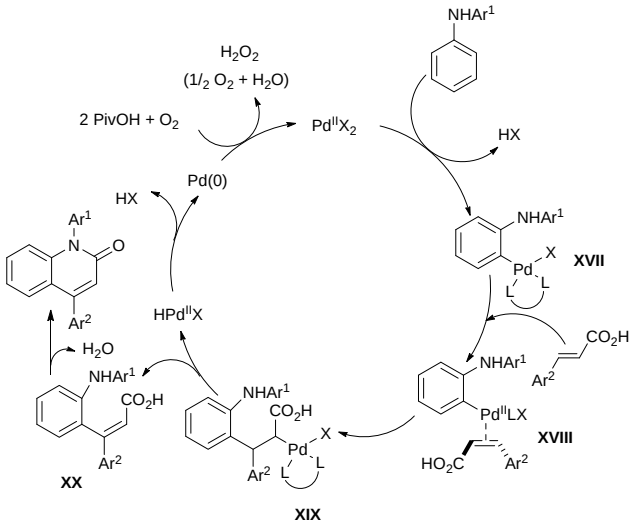


Scheme 22. Intermolecular FM reaction/intramolecular amidation cascade reaction. C-H alkenylation controlled by a phenathroline ligand



Scheme 23. Different experiments for the elucidation of the reaction mechanism

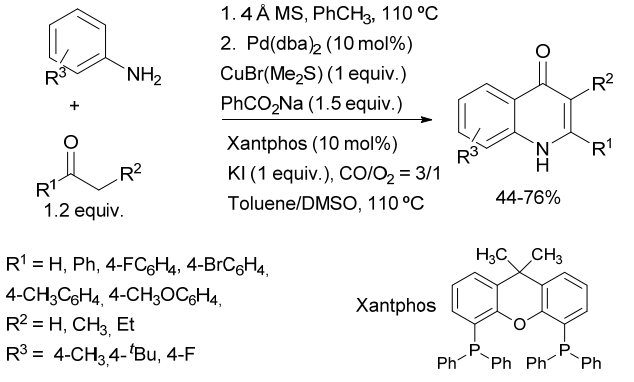
Experiments carried out with deuterium-labelled compounds showed that the cyclisation of diphenylamines with just one deuterated ring took place preferentially at the non-deuterated ring (K_H/K_D = 4.0), while when both aromatic rings were deuterated, a kinetic isotopic effect of K_H/K_D = 4.3 was observed. These results indicate that the C-H activation step is irreversible and may be the rate-limiting step. Besides, *N,N*-diphenylcinnamide failed to give the corresponding quinolone under the standard reaction conditions (Scheme 23a). Nonetheless, when methyl methacrylate was reacted with *N,N*-diphenylamine, the corresponding alkenylation product was provided (Scheme 23b). Those results may indicate that the intermolecular alkenylation is the first step, followed by subsequent intramolecular amidation. The proposed mechanism is depicted in Scheme 24. Initially, the *ortho*-palladation of the diarylamine, which is favored by electron-rich aromatic rings, takes place. The formed intermediate **XVII** would then coordinate to the corresponding acrylic acid obtaining **XVIII**, which is transformed into **XIX** after migratory insertion. Subsequent β-hydride elimination would provide **XX** and palladium hydride. After reductive elimination, the Pd(0)



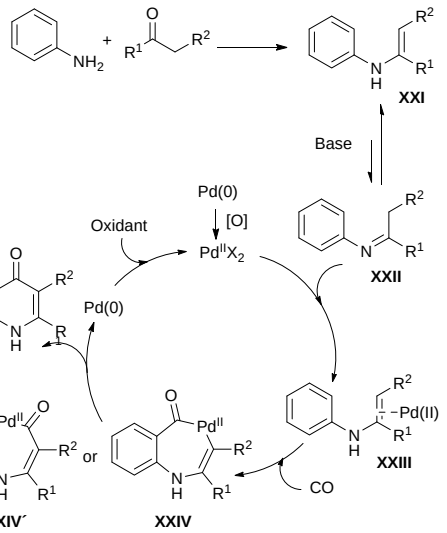
Scheme 24. Maiti's mechanism for the intermolecular FM reaction controlled by a phenathroline ligand, followed by intramolecular amidation.

obtained is reoxidized to recover the Pd(II) species. Alkenylation product **XX** undergoes TFA-catalysed intramolecular amidation to give the quinolone. It is worth to mention that when carrying out the reaction in the absence of TFA, intermediate **XX** undergoes decarboxylative coupling to give a 1,3-diarylindole instead of the quinolone.

A related approach for the synthesis of the quinoline core is the Pd(II)-catalysed oxidative carbonylation reaction. Lei and co-workers carried out efficiently the synthesis of 4-quinolones starting from anilines and ketones under CO/O_2 atmosphere (Scheme 25).[53]



Scheme 25. Pd(II)-catalysed oxidative carbonylation reaction of anilines and ketones under ligand control



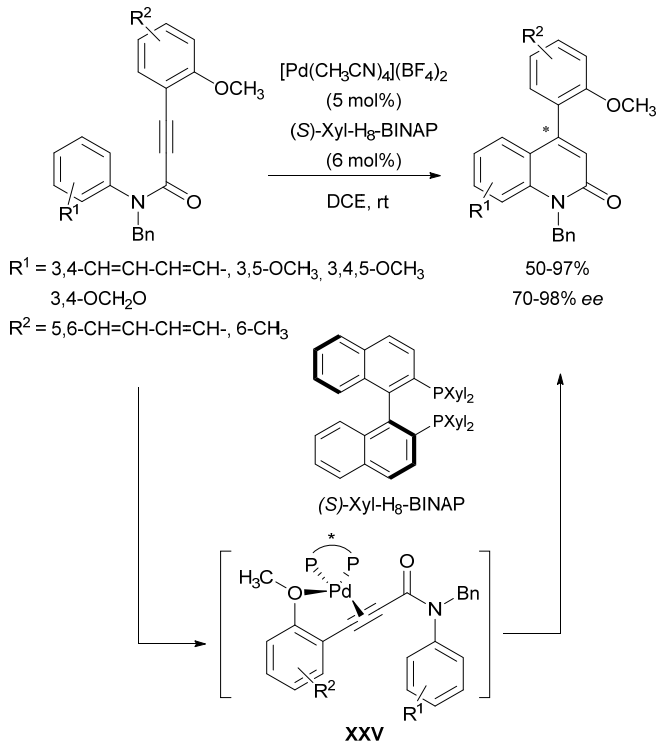
Scheme 26. Lei's mechanism proposal for the Pd(II)-catalysed oxidative carbonylation reaction of anilines and ketones under ligand control

A condensation reaction would take place between the aniline and the ketone to form the corresponding imine **XXI**, which would then isomerize to enamine **XXII**. This intermediate is thought to undergo coordination to Pd(II) followed by insertion of CO, providing **XXIV** or **XXIV´**. After reductive elimination of either species, the corresponding 4-quinolone is obtained (Scheme 26)

4. Other selected palladium-catalysed approaches to quinoline synthesis

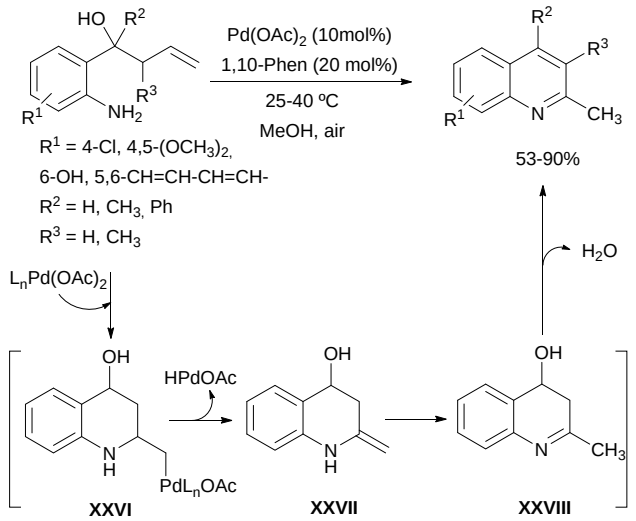
Besides the MH and the FM reactions discussed in the previous sections, a plethora of methods based on the activation of C-H bonds have been employed for the synthesis of quinolines, that include very different approaches involving C-C formation, such as alkyne hydroarylation,[54,55] or the aza-Wacker reaction[56] and the oxidative amination of C(aryl)-H bonds that involve C-N bond formation.[57] The detailed discussion of these procedures is beyond the scope of this review, but only some selected interesting approaches for the formation of quinolines will be presented to provide a wider picture.

The hydroarylation of alkynes is an interesting alternative to the C-H alkenylation reaction with alkenes. In this context, Fujiwara and co-workers developed a Pd(II)-catalysed procedure to obtain quinolones starting from *N*-phenylpropiolamides.[54] The enantioselective formation of different 4-aryl quinolones, with control of the axial chirality using a cationic Pd(II)/*(S)*-Xyl-H_8-BINAP system is also possible (Scheme 27).[55] The reaction requires the presence of an alkoxy group in the C-2 position of the aryl ring attached to the alkyne. This fact proved that the coordination of the Pd(II) to the oxygen is required and the reaction was proposed to proceed through intermediate **XXV**.



Scheme 27. Enantioselective intramolecular Pd(II)-catalysed hydroarylation of *N*-phenylpropiolamides using *(S)*-Xyl-H_8-BINAP as ligand

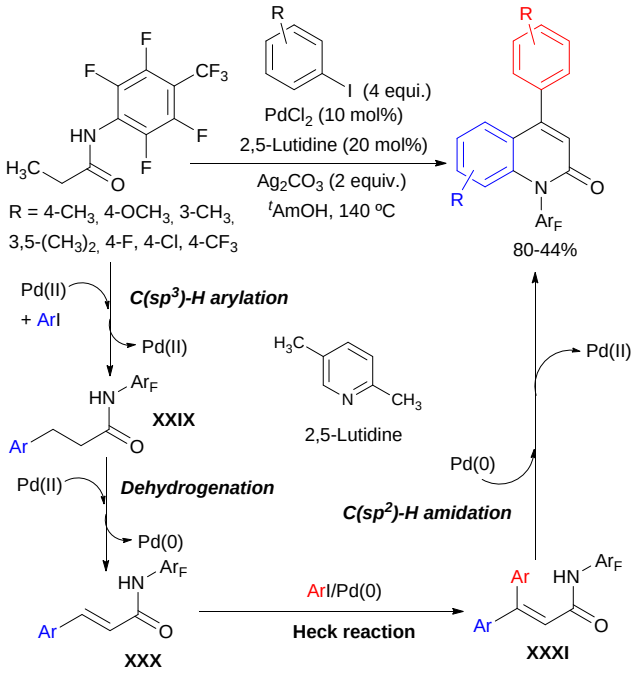
An interesting approach for the synthesis of the quinoline core through the intramolecular aza-Wacker reaction was developed by Wang and co-workers. 2-Methylquinolines could be efficiently obtained from the 1-(2-aminophenyl)but-3-en-1-ols using 1,10-phenantroline as a ligand (Scheme 28).[58] A plausible mechanism of the reaction is depicted in Scheme 28.



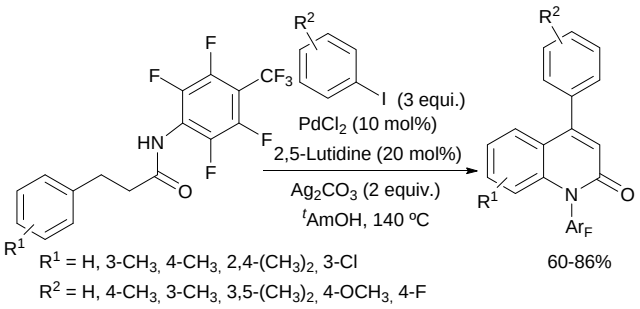
Scheme 28. Wang´s synthesis of 2-methylquinolines by the intramolecular aza-Wacker reaction.

After coordination of the palladium (II) catalyst to both the amine and alkene moieties, aminopalladation to the olefin would take place yielding **XXVI**. The subsequent β-hydride elimination provides **XXVII**, and after isomerization of the double bond to the endocyclic position, **XXVIII** undergoes dehydration to form the quinoline.

Besides, Yu and co-workers[59] developed an efficient method for the formation of the quinolone core based on the intramolecular amidation of C(aryl)-H bonds. They were able to synthesize different 4-arylquinolones starting from the corresponding propionamides. In this cascade reaction three C-C bonds and a C-N bond are formed with the aid of a pyridine-based ligand (Scheme 29). When two identical aryl rings were introduced, the reaction proceeded smoothly. When two different aryl groups were installed, mono-arylation took place, followed by subsequent intramolecular amidation (Scheme 30). In all the cases, the aryl ring introduced by means of the aryl iodide was installed at the C-4 position of the quinolone. This selectivity proves that the insertion of the second arene occurs after the dehydrogenation process, through a stereospecific Heck reaction. The reaction mechanism is proposed to proceed as depicted in Scheme 29: Firstly, the arylation of the C(sp^3)-H bond takes place to form intermediate **XXIX**, which then undergoes Pd(II)-induced dehydrogenation providing **XXX**. The second aryl group is afterwards installed by a Heck reaction, *trans* to the amide group, giving **XXXI**. That way, intramolecular amidation would take place selectively at the firstly-introduced arene (the one that is *cis* to the amide group) forming the quinolones. To prove this mechanism, the authors independently synthesized intermediate **XXX** and subjected it to the reaction conditions, obtaining the corresponding quinolones.



Scheme 29. Yu´s synthesis of quinolones by the intramolecular formation of C-N bonds.



Scheme 30. Synthesis of quinolones bearing non-identical arene rings.

5. Conclusions and outlook

In the last years, major progress has been achieved in palladium-catalysed reactions (Mizoroki-Heck reaction and its dehydrogenative variant) for the synthesis of quinolone and quinoline derivatives, both in the development of new synthetic methods and their mechanistic understanding. DFT calculations have helped to gain more insight into the mechanism of these transformations, however, it continues to be difficult to rationalize the effect of different parameters. More studies are needed to achieve this goal, which will help to select the most adequate catalyst or experimental conditions in target-oriented synthesis.

Undoubtedly, the intramolecular Mizoroki-Heck reaction is an excellent tool for the synthesis of heterocycles that has been widely applied in the synthesis of quinoline derivatives. Although different strategies to control the β-elimination step and thus generate tertiary and quaternary stereocentres have been reported, the development of enantioselective variants for the construction of the quinoline core is an important issue that has not yet be addressed.

On the other hand, although transition-metal direct C-H functionalization/activation of C(sp^2)-H bonds has emerged as an efficient, atom-economical, and environmentally friendly synthetic tool for the preparation of complex multifunctional molecules, there are not many examples of the synthesis of quinolines involving the inter- or intramolecular formation of C-C bonds, driven by C-H bond activation. The main problem of this strategy lies on the control of regioselectivity; however, nowadays, different removable or non-removable directing groups and efficient ligands have been reported that may help to overcome this drawback.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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