σ-Alkyl-Pd(II) Species For Remote C–H Functionalization

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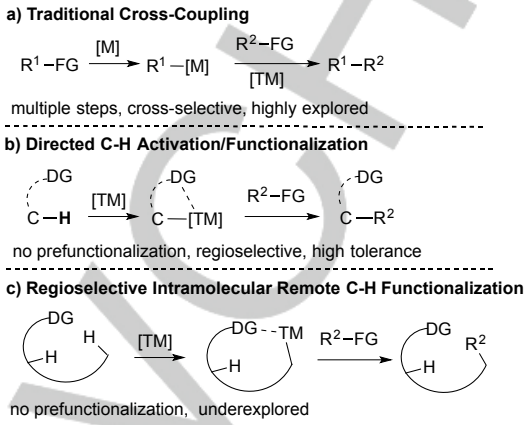
Abstract: The transition-metal-directed C–H activation processes have traditionally required the installation of suitable coordinating groups to place the metal in close proximity to an specific neighbouring or remote C(sp^2)–H or C(sp^3)–H moiety of the molecular structure. Alternatively, substitution of C−H bonds at positions previously thought inaccessible are now performed through domino processes *via in situ* generated σ-alkyl-Pd(II) species. This concept article highlights on recent developments which utilize these σ-alky-Pd(II)-species for remote C−H functionalization to reinvigorate new C−C bond formation in cascade fashion *via* use of catalytic palladium metal.

Introduction

A remarkable progress has been made in the past three decades toward efficient C−C and C−Heteroatom bond formation *via* traditional cross-coupling and C−H activation approaches.[1] As a consequence, there is no dearth of literature in the organic chemist's toolbox to functionalize C(sp)−H, C(sp^2)−H and C(sp^3)−H bonds encompassing limitations with desired substitution pattern and in regioselective fashion.[2] Despite the increasing use of such synthetic methods and the tremendous progress made in direct functionalization of C(sp^2)−H and C(sp^3)−H bonds located nearby to suitable directing groups, only recent advancements have shed light on the activation of remote C(sp^2)−H and C(sp^3)−H moieties[3] within the molecular structure, which had previously been thought inaccessible (Scheme 1).

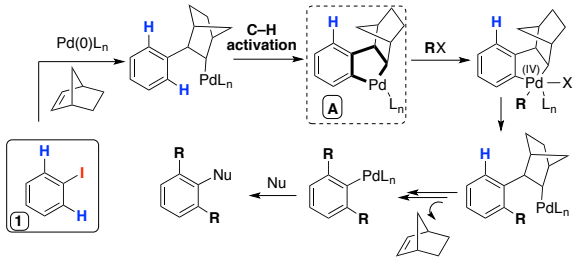
Unreactive remote C−H moieties have thus become an enticing target to be harnessed by transition-metal catalysis.[4] This goal has been partially achieved in some cases (such as *meta*- and *para*-C−H of aromatic rings or γ-, and δ-positions in aliphatic chains) by installing suitable coordinating groups to guide the metal toward the desired C–H moiety. A broad range of directing groups have so far been explored in the C–H activation arena, nevertheless their installation and/or removal from the core substrate can have a considerable synthetic cost, hence diminishing the efficiency of the overall functionalization process. The continuous efforts to achieve greener transformations have boosted the search for new reaction systems involving directing groups which can be reversibly linked to the substrate or, furthermore, the use of catalytic amounts of directing group precursors.[5]

Addressing this issue, the use of 2-norbornene as an auxiliary



Scheme 1. Types of regioselective TM-catalyzed functionalizations.

ligand in Pd-catalysis[6] has proven to be a tremendously versatile strategy for the dual *ortho*- and *ipso*-functionalization of aryl halides (Scheme 2). This approach relies on the ability of 2-norbornene to insert reversibly into the Pd–C bond of palladated arenes. Hence, upon carbopalladation of 2-norbornene, the norbornyl-Pd moiety can promote the activation of the *ortho* C–H bond, leading to the formation of a key C(sp^2),C(sp^3)–palladacyle (**A**, Scheme 2). Several electrophilic reagents such as alkyl, aryl or alkynyl halides or *O*-benzoyl hydroxylamines can add oxidatively to the intermediate **A**, to further evolve through the C–C or C–N bond formation respectively.[6] The process can be repeated if a second *ortho* C–H bond is available in the starting halo arene. The cascade reaction ends with the extrusion of 2-norbornene and final coupling with a nucleophilic partner such as a boronic acid or an alkene.



Scheme 2. Reaction mechanism of the Pd-catalyzed norbornene-mediated C–H activation (Catellani reaction).

This Concept article focuses on the intramolecular carbopalladation of alkenes as a synthetic strategy to carry out C–H activation at remote locations within the molecular structure. The introduction of substrates bearing tethered alkenes in palladium catalysis constitutes a valuable route for the *in situ* generation of suitable σ-alkyl-Pd groups, which are able to further perform an intra- or intermolecular[7] C–H activation,

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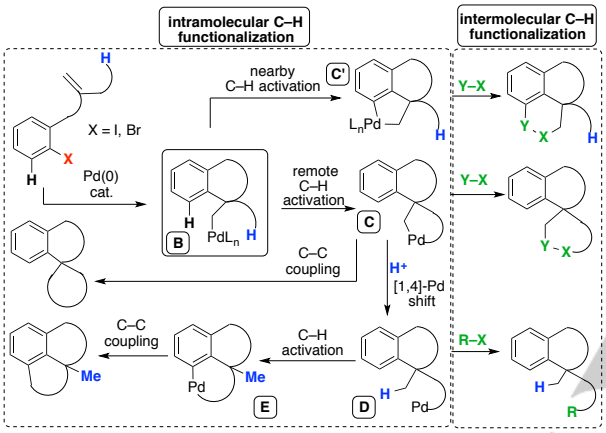
leading to interesting cascade reactions. This approach represents an excellent entry to complex carbo- and heterocyclic molecular structures in a single step through the judicious design of the starting materials. Alternatively, the σ-alkyl-Pd moieties can be generated via amino- or oxa-palladation of alkenes.[8] The subject under review can be structured in two different types of transformations (Scheme 3): a) those where the cascade process is entirely intramolecular and b) those where a second coupling partner is incorporated to the reaction. Additionally, two different kinds of processes can be distinguished, those where the alkyl group of intermediate **B** (generated upon the initial carbopalladation of the alkene) remains in the final cascade organic product, and those where the species **B** evolves through a [1,4]-Pd shift, transferring the reactive metallated position within the molecular structure.

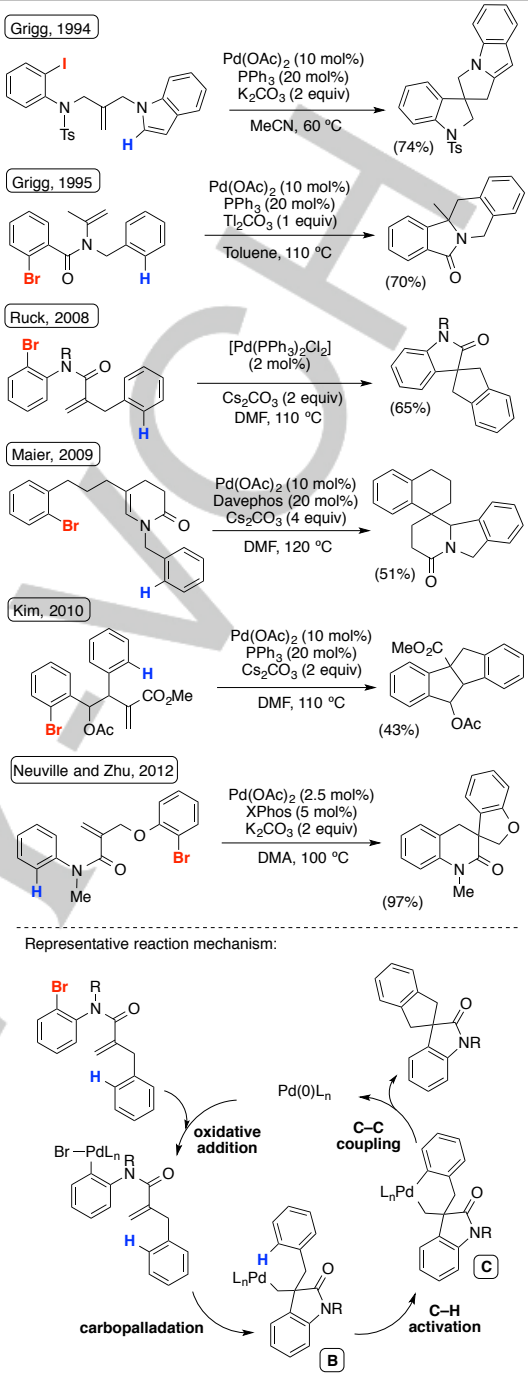


Scheme 3. Synthetic routes for nearby and remote C–H functionalization through intramolecular carbopalladation of alkenes.

Intramolecular C–H activation through σ-alkyl-Pd(II) intermediates

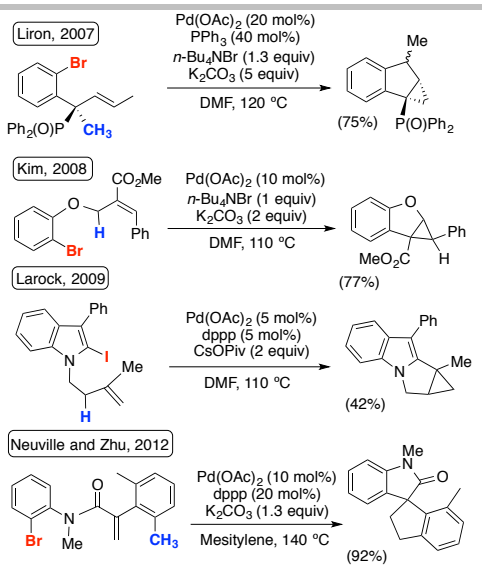
The cascade reactions involving C–H activation assisted by either 2-norbornene (Scheme 2) or alkenes tethered to aryl halides (Scheme 3) share some common features that allow these transformations to proceed. First, the β-hydride elimination from the carbopalladated intermediates **A** or **B** is not feasible (due to conformational constrains or the absence of beta-hydrogen atoms, respectively); and second, the *in situ* generated σ-alkyl-Pd(II) intermediate places the metal in close proximity to a C–H moiety present in the substrate, promoting its metallation and further functionalization.

The use of σ-alkyl-Pd(II) intermediates of type **B** (Scheme 3) for intramolecular C–H activation was first disclosed by Grigg and co-workers[9] for substrates bearing tethered activated heterocycles (Scheme 4). Since then, a wide range of scaffolds has been synthesized using this strategy by varying the substitution pattern of the starting materials (Scheme 4). These reactions lead to the formation of interesting polycyclic and spirocyclic structures and have been successfully applied in the synthesis of complex scaffolds containing heterocyclic moieties, such as indoline, tetrahydrofuran and oxoindole derivatives.[10] Interestingly, the σ-alkyl-Pd(II) species **B** can carry out the activation not only in aromatic C–H bonds, but also in more challenging aliphatic C(sp^3)–H moieties (Scheme 5). Generally,

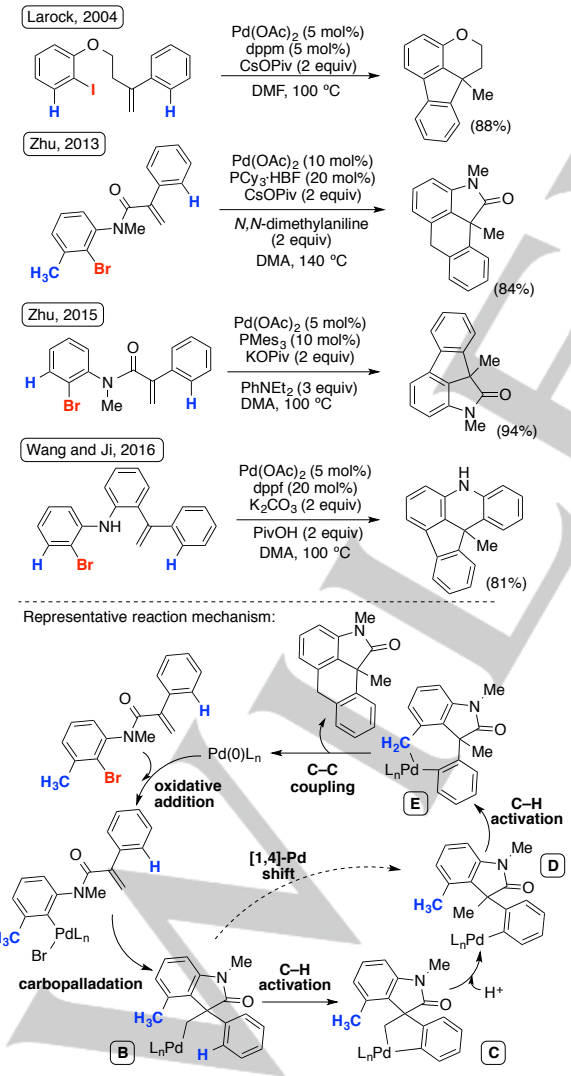


Scheme 4. Intramolecular cascade remote C(sp^2)–H activation involving σ-alkyl-Pd species.

the reaction proceeds through the 5- or 6-*exo-trig* cyclization (depending on the length of the pendant chain of the substrate) to give the σ-alkyl-Pd(II) intermediate of type **B** (Schemes 3 and 4). The availability of a C(sp^2)–H or C(sp^3)–H moiety nearby the metallic atom leads to the formation of suitable *C,C*-palladacyclic complexes (**C**, Schemes 3 and 4) with sizes commonly ranging from 4 to 7 members. Cámpora and co-workers characterized a five-membered C(sp^2),C(sp^3)–palladacycle arising from the intramolecular C(sp^2)–H activation of a σ-alkyl-Pd(II) complex.[11] The cascade terminates with the reductive elimination of Pd(0) and concomitant C–C bond formation (Scheme 4).[12]



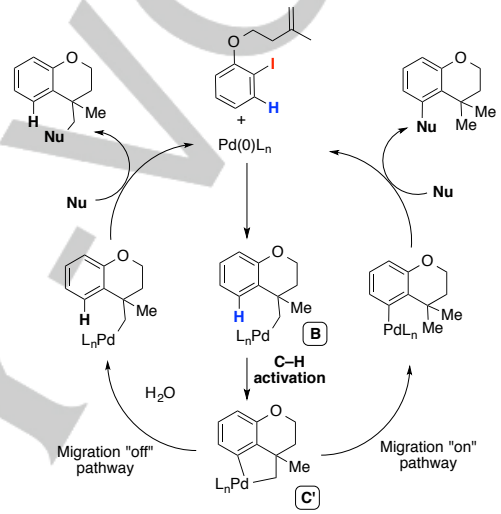
Scheme 5. Intramolecular cascade remote (Csp^3)–H activation involving σ-alkyl-Pd species.



Scheme 6. Intramolecular cascade C–H activation involving σ-alkyl-Pd species which evolve through [1,4]-Pd shift.

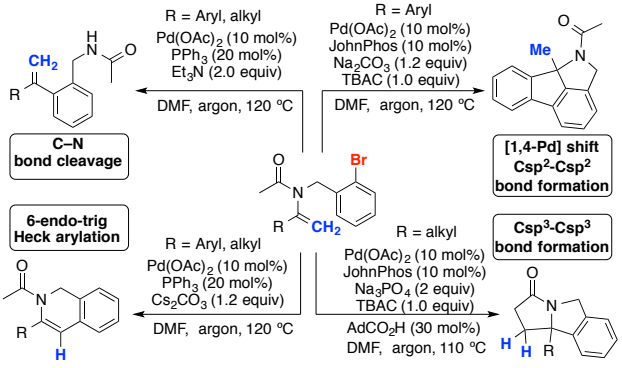
In some cases the σ-alkyl-Pd(II) intermediates are transient species which undergo a formal [1,4]-Pd shift,[13] involving the exchange of the reactive metallated position with a nearby C–H moiety present in the molecular structure (Schemes 3 and 6). The new organometallic intermediate can either be captured by a nucleophile present in the reaction mixture, or continue to perform a C–H activation step in a different fragment of the substrate (Schemes 6).

Jia and coworkers[13b] studied in detail the mechanism and experimental conditions to control the [1,4]-Pd migration for alkyl ether substrates (Scheme 7). They found that the *C,C*-palladacycle complex of type **C'** could undergo selective protonolysis of the C(sp^2)–Pd over the C(sp^3)–Pd bond in the presence of (excess) water.



Scheme 7. Influence of water on the [1,4]-Pd migration

Remarkably, Xu, Loh and co-workers[14] recently reported four possible Pd-catalyzed transformations for 2-Br-benzylimines substrates (Scheme 8). Interestingly, the reaction pathway could be switched form [1,4]-Pd shift to C(sp^3)–H activation with the appropriate substrate design and control of the experimental conditions.

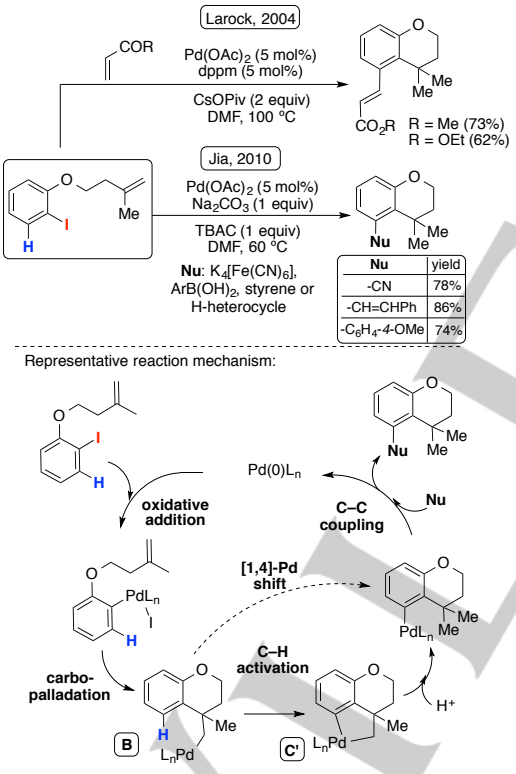


Scheme 8. Cascade reactions reported by Xu and Loh and co-workers.

Intermolecular coupling involving remote C–H activation through σ-alkyl-Pd(II) species

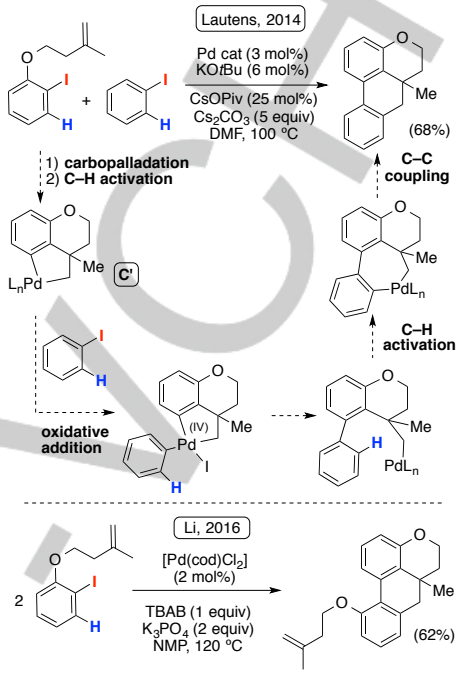
The introduction of a second coupling partner in the cascade reactions involving σ-alkyl directed C–H activation is much less explored than the exclusively intramolecular processes described above. Nevertheless, the increasing interest and recent progress in this area suggests that further developments can be expected in the near future.

An early report by Larock and co-workers[13a] showed that σ-alkyl-Pd(II) species (arising from intramolecular carbopalladation of alkenes tethered to the starting iodoarene) could successfully mimic the norbornyl group to functionalize the *ortho* C–H position of the arene, establishing a precedent for this type of intermolecular cascade reactions. In this case the σ-alkyl-Pd(II) intermediate evolved through formal [1,4]-Pd shift, leading to a C(sp^2)–Pd bond which was further cross-coupled with activated olefins (Scheme 9). In addition, Jia and co-workers[13b,c] employed this concept to further expand the diversity in terms of C–H functionalization of C(sp^2)-Pd intermediate *via* Heck and Suzuki reactions and coupling with nucleophiles such as cyanide or activated heterocycles.



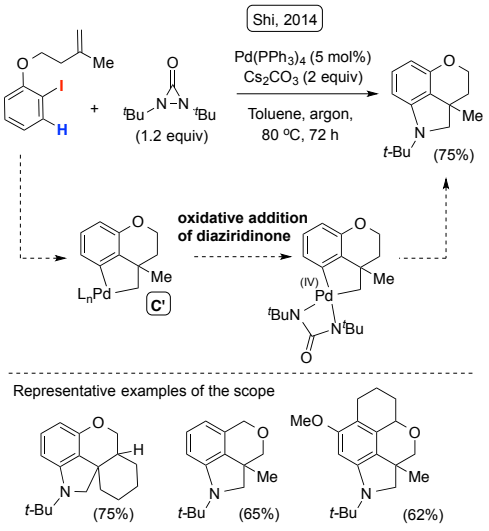
Scheme 9. Intermoleular C–H functionalization carried out through σ-alkyl-Pd intermediates.

The groups of Lautens and Shi have extended this chemistry to the functionalization of the two Pd–C bonds present in the C(sp^2),C(sp^3)-palladacycle intermediate of type **C'**, avoiding the protonolysis leading to the [1,4]-Pd shift described above. The authors introduced a second iodoarene in the reaction system,[15b] leading to an impressive double C–H activation process accomplished with the assistance of the σ-alkyl-Pd(II) moiety (Scheme 10). Building on these results, Li and co-workers[15c] have recently demonstrated the intermolecular homodimerization version of the C–H activation process using the same starting material, which leads to fused polycycles (Scheme 10).



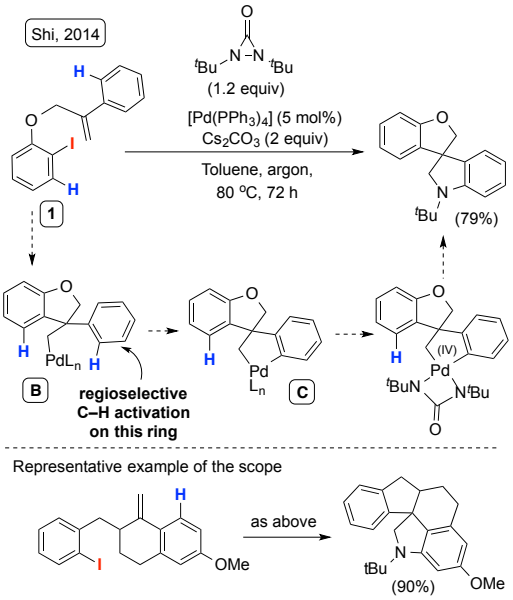
Scheme 10. Intermolecular C–H functionalization carried out through σ-alkyl-Pd intermediates.

Recent seminal report by Shi and co-workers[15a] demonstrated the synthesis of spiro or fused indoline derivatives *via* oxidative addition of intermediates of type **C'** to a diaziridinone derivative and subsequent C–N bond formation through reductive eliminations (Scheme 11). Noteworthy, the mechanistic pathways of the coupling reactions with both iodoarenes and diaziridinones involve Pd(IV) species.



Scheme 11. Synthesis of fused indolines through the use of diaziridinone *via* σ-alkyl-Pd(II) intermediates.

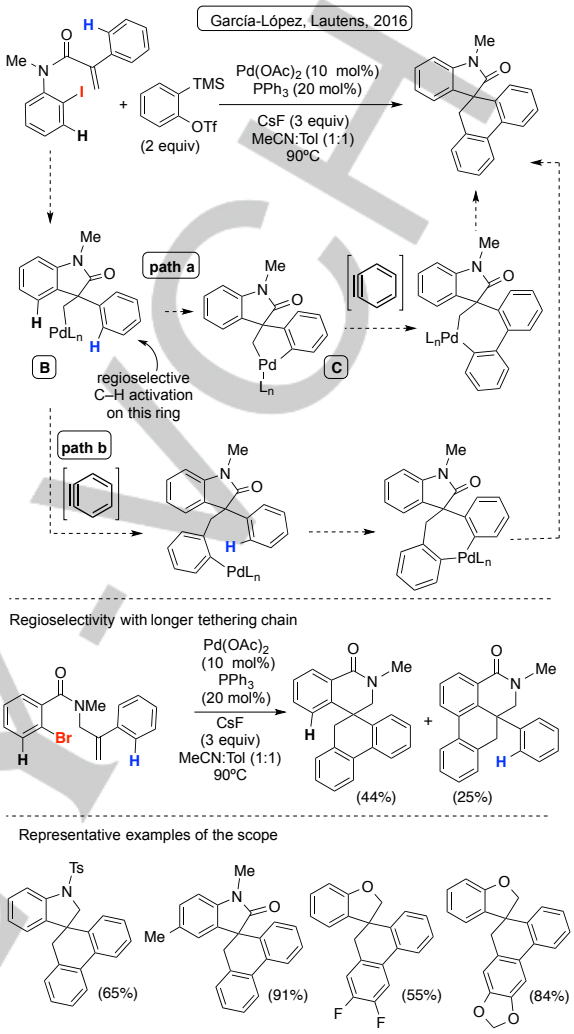
Shi assessed the first functionalization of a remote C–H bond with a second coupling partner via σ-alkyl-Pd(II) intermediates (Scheme 12). The 5-*exo*-*trig* carbopalladation of the alkene **1** evolved through the formation of a key spiro-palladacycle of type **C**, which was further cross-coupled with the diaziridinone reagent, leading to an interesting spiro-heterocyclic scaffold. Remarkably, this transformation was carried out regioselectively on the remote C–H bond rather than the nearby C–H moiety present in the starting iodoarene.



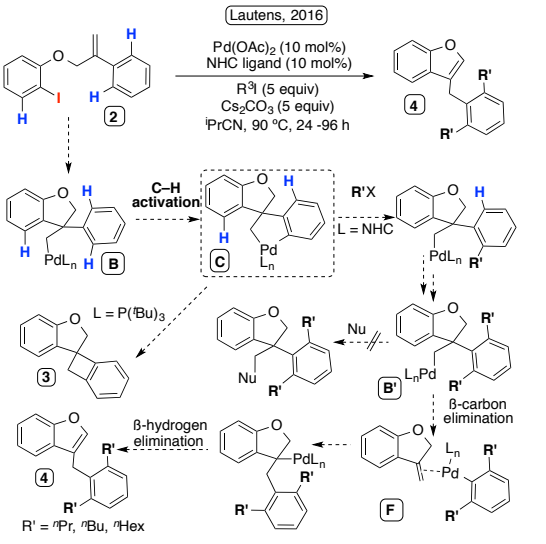
Scheme 12. Synthesis of spiro-indolines through remote amination *via* σ-alkyl-Pd(II) intermediates.

Complementary methodologies[16] have shown that both Pd-bonded carbons of intermediate of type **C** can be cross-coupled with unsaturated species such as arynes, showcasing the versatility of the palladium-catalyzed remote C–H functionalization (Scheme 13). Interestingly, the regioselectivity of the remote C–H over the nearby C–H functionalization is influenced by the length of the alkenyl tethering chain. This cascade reaction could take place through two different pathways (Scheme 13). One path would involve the insertion of the aryne into the spiro-palladacycle **C**, while the second possibility would imply the trapping of the σ-alkyl-Pd(II) intermediate **B** with the aryne followed by a C–H activation step. The mechanism of this reaction has been investigated in detail through the isolation of the spiro-palladacycle intermediate of type **C** and additional experiments which ruled out the second pathway.[16b]

Lautens and co-workers have recently taken this chemistry one step further by using the *in situ* generated σ-alkyl-Pd(II) group to perform a C–H alkylation on a remote site of the molecule (Scheme 14).[17] First, the authors assessed the regioselective metallation of the remote C–H bond by screening the conditions to get the strained 4,5-spirocycles **3** from the alkenylated substrates **2** (Schemes 3 and 14). Subsequently, several attempts to extrapolate the reactivity of the norbornyl-Pd system (Scheme 2) to the new σ-alkyl-Pd(II) intermediate were carried out. Surprisingly, whilst in the norbornene-mediated process both *ortho*- and *ipso*-positions of the ring are sequentially



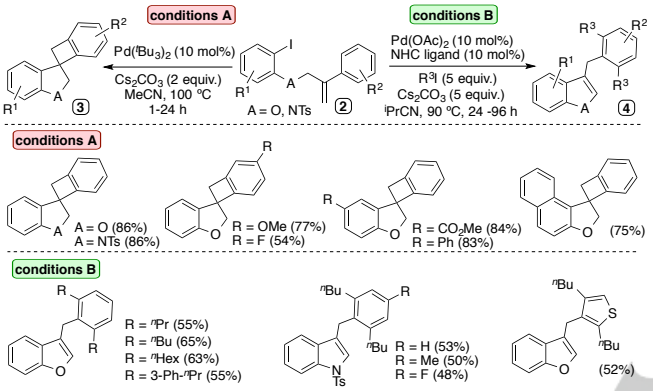
Scheme 13. Trapping of arynes generated in situ with σ-alkyl-Pd(II) species.



Scheme 14. Remote C–H alkylation *via* σ-alkyl-Pd(II) intermediates.

coupled with an alkyl halide and a nucleophile respectively, only the C(sp^2)–Pd bond of the intermediate **C** could be functionalized with the alkyl halide in the present substrates. The expected coupling of the nucleophile and the C(sp^3) bonded to Pd did not take place. Instead, the 3-substituted benzofuran derivatives **4** were obtained in moderate yield (Scheme 14).

The synthesis of derivatives **4** was optimal when using a catalytic system involving an NHC ligand, although the use of diverse phosphine ligands also afforded moderate yields of the desired product. The scope of the reaction included substrates bearing both electron-withdrawing and donating groups, with an ether or amino-tethered alkene and different acyclic alkyl iodides, leading to a variety of interesting 3-substituted furan and indole scaffolds (Scheme 15).



Scheme 15. Scope of the spirocyclization and remote C–H functionalization.

Surprisingly, although a clear parallelism in the reaction mechanism leading to the C–H activation event in the cases of the norbornyl-Pd(II) (**A**) and the σ-alkyl-Pd(II) (**C**) intermediates can be established, the behaviour of both toward alkyl halides is rather different. While the norbornyl-Pd(II) derivative **A** undergoes the oxidative addition of the alkyl halide to give a Pd(IV) intermediate followed by C–C bond formation (Scheme 2), the σ-alkyl–Pd(II) **C** evolves through the direct *ipso*-carbon alkylation, as suggested by mechanistic DFT calculations (Scheme 14). This alkylation process can occur twice if the aryl ring contains a second C–H position available. The increasing steric hindrance built around the Pd atom upon the alkylation step has a crucial role in the evolution of the reaction in both cases. The norbornyl system extrudes 2-norbornene leading to an *ipso*-palladated arene which can be then cross-coupled with a range of nucleophiles (Scheme 2). The σ-alkyl-palladated complex arising from **B'** also undergoes a β-carbon elimination to produce a terminal olefin and a palladated arene (Scheme 14). In contrast to the norbornene case, the regioselective carbopalladation of the new olefin can take place to give a less hindered intermediate **F**, from where β-hydride elimination terminates the cascade process. These last steps occur fast enough to avoid the cross coupling of intermediate **B** with suitable nucleophiles when present in the reaction mixture.

Summary and outlook

The use of σ-alkyl-Pd(II) moieties generated *in situ* to direct the C–H functionalization far beyond the nearby bonds of the starting reactive site in the molecular structure results in a highly innovative strategy to achieve novel transformations via multiple C–C bond formation in a cascade manner.Taking into account the tremendous utility of the Pd/norbornene approach to *ortho*-C–H functionalization in terms of possible coupling partners, several interesting questions raise in the horizon of this new mode for remote C–H activation. For instance, 1) the behaviour and reaction mechanism of the C(sp^2),C(sp^3)–palladacycles of type **C** toward species such as secondary alkyl or aryl halides or other electrophilic reagents, used with huge success in the norbornene system, or toward other unsaturated species; 2) the elucidation of the factors governing the regioselectivity in the remote *vs ortho* C–H activation; 3) the screening of conditions and ligands which permit the cross-coupling with nucleophiles culminating the cascade process; or 4) the development of stereoselective reactions in those cases where chiral centers are generated. Moreover, further developments in this area would be expected through the design of substrates with different functional groups to guide the transition metal through the molecular structure in order to achieve the desired remote functionalization in a cascade fashion.

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Dedicated to Prof. Anamik Shah on occasion of his 62nd birthday.

Keywords: Remote • C–H activation • palladium • catalysis • cascade • spirocycles

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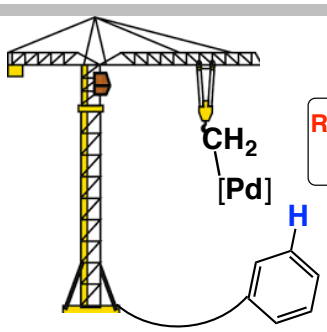
CONCEPT

Remote Destination - Substitution of C−H bonds at positions previously inaccessible are now performed *via* σ-alkyl-Pd(II) species. A specially designed substrate directs the carbopalladated species resulting from intramolecular cyclization towards C−H activation at remote position.



REMOTE C–H ACTIVATION GUIDED BY ALKYL-Pd SPECIES

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Page No. – Page No.

σ-Alkyl-Pd(II) Species For Remote C–H Functionalization