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Direct C–H Arylation

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Abstract: Bonds between hydrogen and carbon atoms are the most frequent type of bonds in organic molecules. The ability to replace hydrogen atoms by making other types of bonds to carbon atoms can enable simpler access to complex organic molecules by substituting multistep synthetic sequences. The use of transition metal catalysts to activate C–H bonds is particularly attractive as it offers control over the reactivity and selectivity through catalyst design. However, such functionalization includes the difficult breaking of strong C–H bonds that are not activated by the presence of other groups. Additionally, the common presence of a number of C–H bonds in a molecule raises the issue of site-selectivity because differentiation of C–H bonds that are in sterically and electronically similar environments is a challenge. We discuss selected recent developments that are a part of the long-term research interest in mild and selective C–H activation reactions with a focus on the replacement of C–H bonds with C–aryl groups and an emphasis on the work of our group.

Keywords: C–H activation · C–H arylation · Palladium · Spatial anion control

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1. Introduction

The formation of carbon–carbon bonds between two aromatic groups has a prominent role in synthetic organic chemistry because of the frequent occurrence of biaryl motifs in organic compounds, such as in pharmaceuticals, organic materials, organocatalysts, and ligands for transition metals.[1] Consequently, the formation of Ar^1–Ar^2 bonds is of continuing interest in the area of organic synthetic methodology (Ar^1 and Ar^2 represent aryl groups). While the initial focus was on enabling such reactivity in general,[2] the examples of current efforts include site- and enantio-selective catalysts, challenging substrates, mild conditions, and the use of earth-abundant first-row transition metals.[1] Catalysts based on a wide range of transition metals are known to enable reactions that join two aryl groups by using two starting molecules, Ar^1–FG^1 and Ar^2–FG^2, which can transfer the aryl groups to a transition metal (Scheme 1a, FG^1 and FG^2 represent suitable functional groups). The most common catalytic systems for such cross-coupling reactions are based on transition metals palladium and nickel and some of the most widely used methods are named after the researchers who contributed to their discovery and development. Prominent examples include Suzuki-Miyaura, Negishi, and Corriu-Kumada cross-coupling reactions,[2] in which the FG^1 groups in a nucleophilic Ar^1–FG^1 cross-coupling component are based on boron, zinc, and magnesium, respectively (Scheme 1a). The FG^2 groups in an electrophilic Ar^2–FG^2 coupling component are commonly halogens (I, Br, Cl), but can also be more complex groups, such as sulfonates, which are used to transform OH groups of phenols into suitable functional groups for cross-coupling.

The direct use of Ar–H bonds for the formation of Ar^1–Ar^2 bonds removes the need for the presence of a FG group on one (or both) of the coupling partners (Scheme 1b).[3–7] In this approach, simple arenes can serve as the substrates for the formation of biaryl motifs. Even more desirably, complex molecules, such as bioactive compounds, for which the installation of a FG would require additional steps or a completely new multistep synthetic strategy, could be used as the substrates (Scheme 1b). However, the utilization of C–H bonds that are not in proximity to a suitable activating group[8–12] is difficult as exemplified by the lack of reactivity of such bonds during common transformations in organic synthesis. In addition, with complex molecules, the catalysts must enable the reactivity of C–H bonds while keeping usually more reactive functional groups intact.

Next to the reactivity, the second major challenge for the direct use of C–H bonds is site-selectivity.[13–17] Due to the usual presence of more than one C–H bond in a molecule, catalysts capable of selectively activating a particular C–H bond are required. However, control over reaction site-selectivity is a general challenge in organic chemistry. Even transformations of common groups, such as alcohols, for which numerous synthetic transformations are available, present a site-selectivity issue when one among more electronically and sterically similar groups needs to be transformed.[18–23] However, the site-selective transformation

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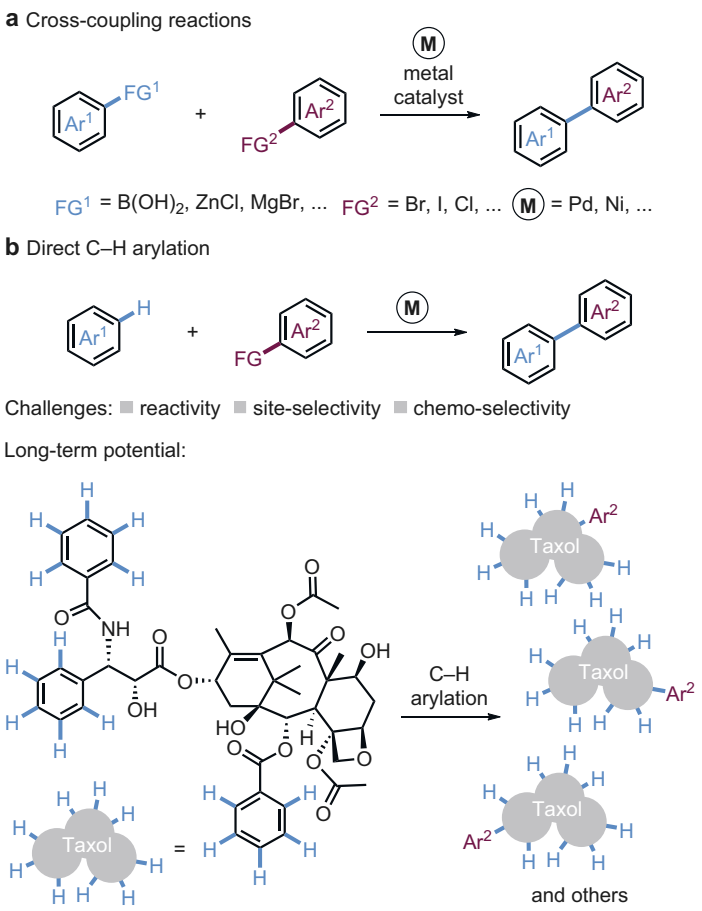


Scheme 1. Traditional and direct routes to biaryls.

of C–H bonds, where, through catalyst design, different C–H sites could be targeted selectively, is a highly valuable long-term goal. Such capability to utilize the usually unreactive sites in a molecule could offer shorter strategies for organic synthesis. With complex molecules, derivatives that are not easily accessed otherwise could be obtained directly, for example, in order to improve or modify biological activity in drug discovery (Scheme 1b).

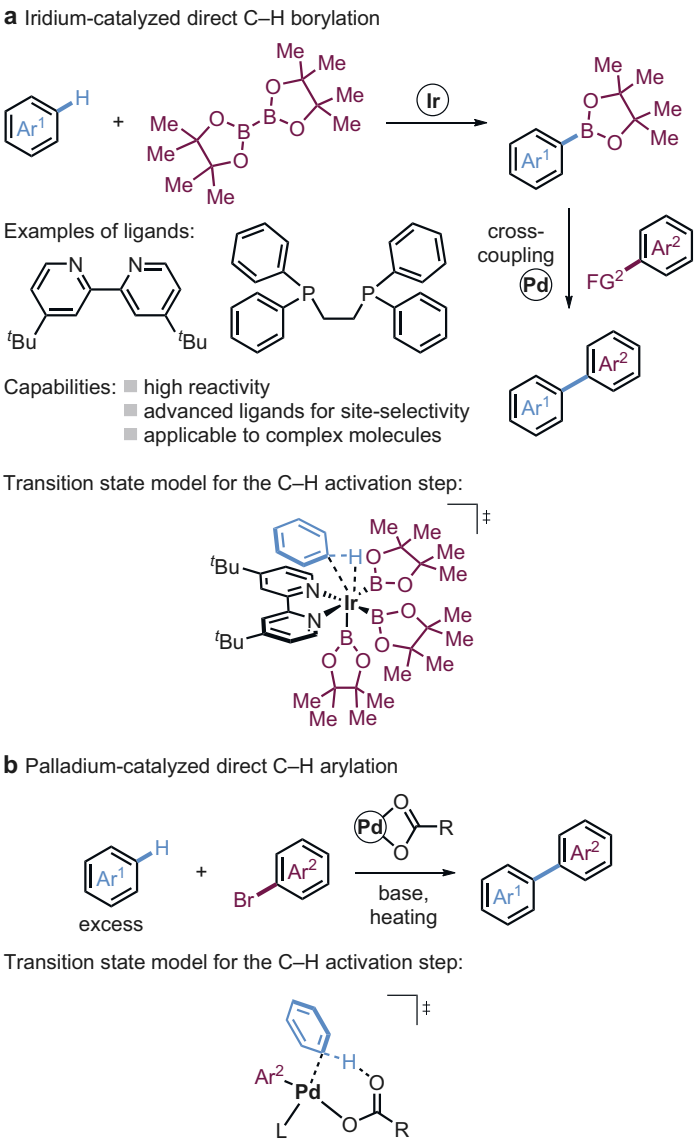
2. Direct C–H Activation

Despite the decades-long interest in their synthetic potential, C–H activation reactions, the reactions in which a C–H bond is cleaved at a transition-metal center (M) in a concerted process to directly form an intermediate with a M–C bond,[24] are difficult without the use of directing groups.[15,25] The directing groups bind to a second coordination site on the metal center and facilitate the C–H activation step by making the process intramolecular, while at the same time providing control over the site-selectivity. Catalysts capable of direct intermolecular C–H activation without the need for excess substrate are less developed and, in particular, systems that can operate in mild conditions and are compatible with various functional groups are rare.[26] Although there has been a significant recent progress in C–H activation of C(sp^2)–H bonds in arenes, the activation of C(sp^3)–H bonds at transition metal centers without the use of excess substrate represents an even greater challenge.

Currently, the most advanced catalytic systems for direct C–H activation of arenes utilize iridium centers coordinated by nitrogen and phosphorous donor atoms of the ligands.[27,28] With the iridium-based systems, the C–H activation step is most often followed by the functionalization of the Ir–C bond that gives products with C–B bonds (Scheme 2a). The installation of a C–B bond in place of a C–H bond enables numerous further synthetic transformations, including the use of C–B bonds in the classical cross-coupling chemistry (Scheme 1a). Furthermore, the mild reaction conditions, which include low temperatures, the use of non-polar solvents, and the absence of additives, enable the exploitation of weak intermolecular interactions between the substrate and the catalyst that can result in the control over site-selectivity.[29–36]

Because of the well-developed functionalization chemistry of Pd–C bonds in catalytic reactions, including the palladium-catalyzed cross-coupling reactions, there is a significant ongoing effort directed at developing catalytic Pd centers that enable the direct formation of Pd–C bonds starting from C–H bonds. The use of palladium in oxidation state II for the activation of C–H bonds is known for over 50 years and one of the well-studied transformations is the Fujiwara–Moritani reaction, an oxidative coupling of arenes with olefins.[37–40] This transformation was initially reported in 1967, but only recently, in 2017 and 2018, general catalytic systems that do not require excess arene were reported.[41–43]

The use of palladium catalysts for the formation of aryl–aryl bonds was extensively developed by the Fagnou group, who in 2006 reported that the replacement of acetates in $Pd(OAc)_2$ with sterically demanding pivalate anions ($((CH_3)_3CCO_2^-)$) results in the formation of a catalytically more competent active species (Scheme 2b).[44] The coordinated pivalate anion was proposed to be directly involved in the cleavage of the C–H bond in a six-



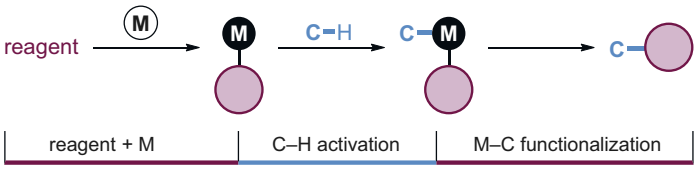
Scheme 2. Comparison of direct C–H borylation and direct C–H arylation systems.

membered concerted metalation-deprotonation (CMD) transition state (Scheme 2b).[44–47] The intermolecular C–H activation on simple palladium-carboxylates was studied computationally by the Sakaki group earlier in 2000[48] and geometrically similar transition states were proposed for related intramolecular C–H activation reactions.[49–56] A report by the Hartwig group showed that, for the intermolecular C–H activation, the coordinated carboxylates are involved in the transition state without the involvement of added ligands such as phosphines.[57]

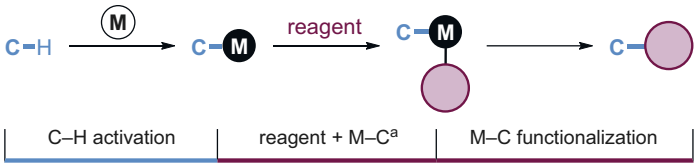
3. Reagent-first and C–H-first Mechanisms

In both the iridium C–H borylation reactions and the example of a palladium-based system in Scheme 2, in the C–H activation transition states, the active metal species contains bound groups that originate from the functionalization reagents. With iridium, the Bpin group is bound to the metal center prior to the C–H activation step, while with palladium, the Ar^2 group, which will be subsequently transferred to the Ar^1 group, is present. Such mechanistic sequence, in which the reagent binding precedes the C–H activation step could be generalized and is referred to here as the *reagent-first mechanism*. The reagent-first mechanisms can be contrasted with processes in which the C–H bond is cleaved prior to the reaction of the reagent with the metal center, for which the term *C–H-first mechanism* is used here (Scheme 3). The two mechanistic scenarios are relevant for the catalyst design and include specific advantages and challenges, as illustrated here with the consideration of the two scenarios for the design of palladium-catalyzed mild direct C–H arylation reactions.

Reagent-first mechanism:



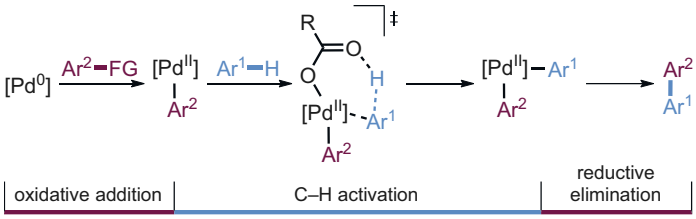
C–H-first mechanism:



Scheme 3. Classification of C–H activation reactions based on the sequence of the reaction steps that involve the reagent and the C–H bond. M represents a metal center in a certain oxidation state and further appropriately coordinated by anionic and neutral donors. M in a black circle represents the metal center in the same or in higher oxidation states, depending on the mechanism of the C–H activation step and on the type of the functionalization reagent. [a]Different M–C bond functionalization steps can be involved.

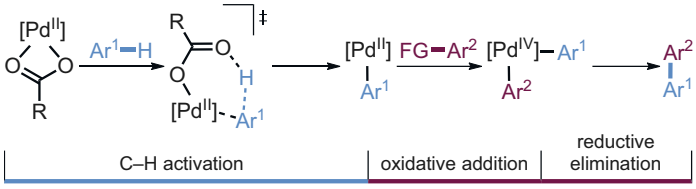
The catalytic system in the initial report by the Fagnou group,[44] as well as the number of subsequent C–H arylations of arenes that utilize aryl bromides as the arylation reagents operate by the reagent-first mechanism (Scheme 4a). An initial oxidative addition of aryl bromides to a palladium(0) site is generally feasible and the reagents are widely available. However, the presence on the catalyst of an aryl group that originates from the reagent (Ar^2) could be expected to strongly influence the C–H activation reactivity in the subsequent C–H activation step. The lower electron-deficiency of the Pd(II) center in the Pd(II)-Ar^2 species could result in a generally less-reactive Pd(II) site, compared with the sites that contain other coordinated groups instead of Ar^2. Furthermore, the exact active species for the C–H activation step is different for different arylation reagents, with the electronic and steric properties of the Ar^2 group resulting in variable reactivity of the resulting Pd(II)-Ar^2 species for the C–H activation.

a Reagent-first mechanism for C–H arylation



- easier oxidative addition of the arylation reagent at Pd^0
- Pd^{II} species for C–H activation is influenced by the properties of Ar^2

b C–H-first mechanism for C–H arylation



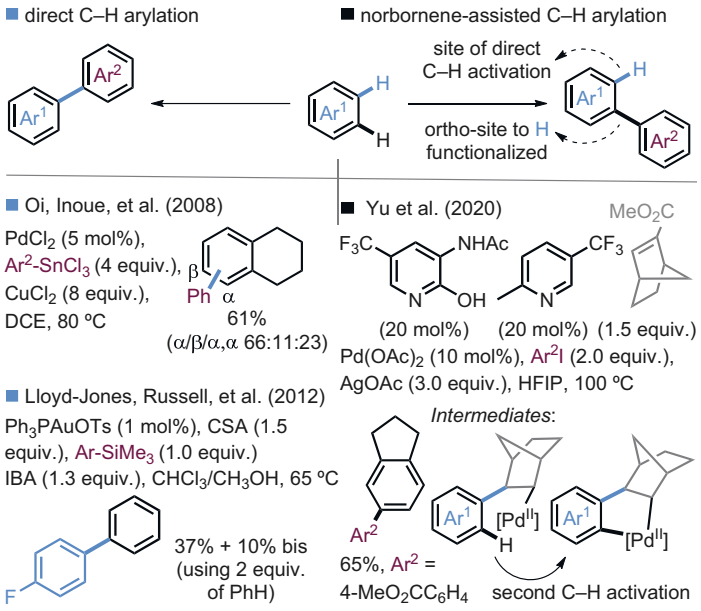
- general highly reactive Pd^{II} species for C–H activation can be designed
- more difficult oxidative addition at Pd^{II}

Scheme 4. Two mechanistic pathways for C–H arylation reactions with palladium.

In the C–H-first mechanism, a Pd(II) species, the structure of which is independent of the substrate or the arylation reagent used, is initially involved in the C–H activation step (Scheme 4b). This scenario, compared with the reagent-first mechanism, potentially simplifies the catalyst design as a single structure of the active species is relevant for the activation of the C–H bonds. However, in this scenario, the subsequent functionalization steps are also challenging as oxidative additions to Pd(II) species to form Pd(IV) intermediates are much more difficult compared with the corresponding oxidative additions to Pd(0) centers. The arene-limited C–H olefination reactions can be considered to proceed through the C–H-first mechanism (Scheme 3), but involve a functionalization process in which the palladium center remains in oxidation state II.[41,42]

4. Prior Work on C–H Arylation of Arenes as Limiting Substrates

Here, we include prior examples of C–H arylation reactions of non-activated arenes. Compared to benzene, both electron-rich arenes, such as alkoxyarenes, and some electron-deficient arenes, such as fluoroarenes, can be considered as activated substrates for the C–H activation through the CMD mechanism.[45,58–60] In certain cases, mildly to moderately electron-rich dialkyl- and trialkyl-arenes proved suitable.[61] For example, the direct arylation of simple dialkyl arenes with arylstannanes was reported in 2008 by Oi, Inoue, and coworkers using a palladium catalyst in copper(II)- and chloride-rich conditions (Scheme 5, left).[62] The reaction does not include any carboxylate-type anions and the C–H activation was proposed to proceed at a Pd(IV) center. In 2012, Lloyd-Jones, Russell, and coworkers described a gold-catalyzed C–H arylation of electron-rich arenes, which proceeds through an electrophilic aromatic substitution mechanism.[63,64] Interestingly, benzene was



Scheme 5. C–H arylation of simple arenes.

a suitable substrate, although two equivalents were used (Scheme 5, left).

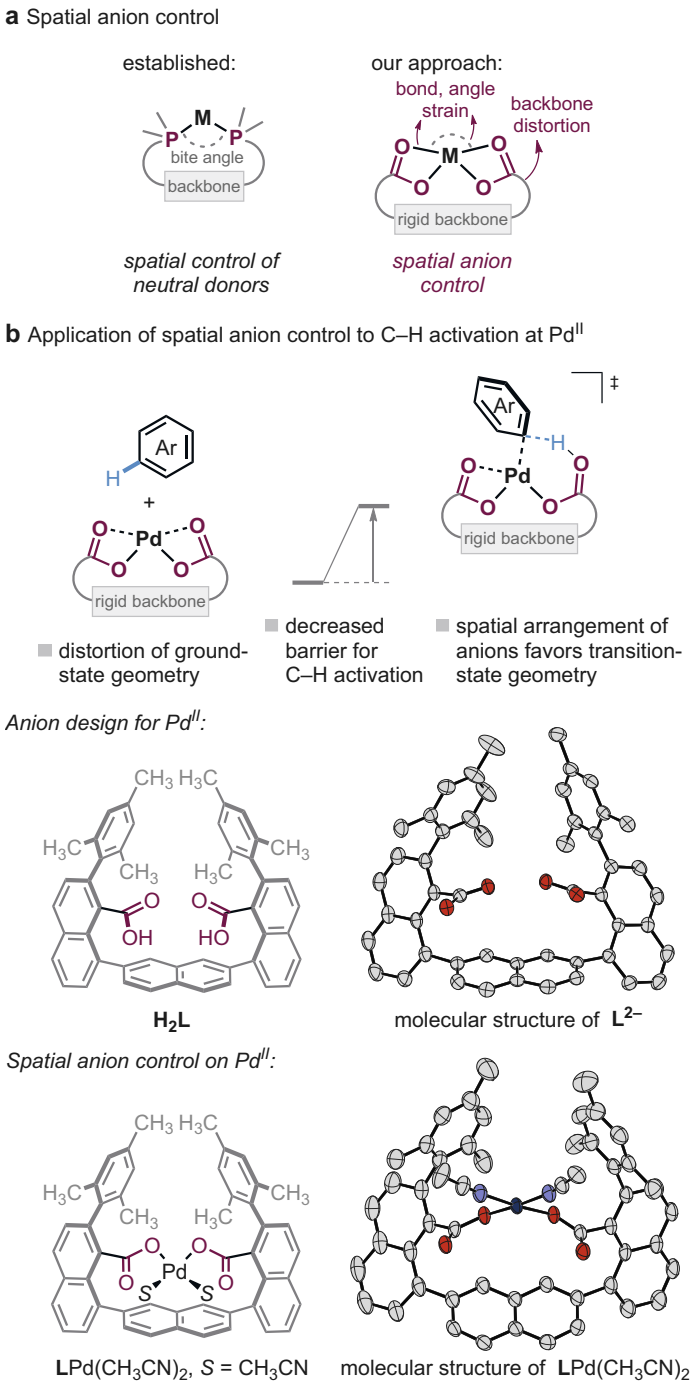
Based on their earlier work with alkoxyarenes as substrates,[65] in 2020, the Yu group reported a C–H arylation reaction with simple arenes that was enabled by the use of a norbornene derivative as an additive (Scheme 5, right).[66,67] The reaction enabled C–H arylation of fluoroarenes and dialkylarenes as limiting substrates, but required excess arene for simple substrates, such as benzene, for which it delivers products of 1,3-bis-arylation instead. The mechanism of the reaction does not involve a direct C–H activation/M–C functionalization sequence, but proceeds through a Catellani-type[68] norbornene relay process in which the initial intermolecular C–H activation step is followed by a norbornene insertion into the M–C bond and a subsequent intramolecular second C–H activation. This sequence, in comparison with the arylation by the direct C–H first mechanism (Scheme 4b), forms a more electron-rich Pd(II) center, thus likely facilitating the oxidative addition of the arylation reagent.

5. The Development of Mild C–H Arylation

5.1 *Spatial Anion Control for the Design of Pd(II) Catalysts for C–H Activation*

The observation of the beneficial effect of different carboxylates in the initial reports by the Fagnou group and the provided mechanistic insights by the same group and by the Hartwig group,[44,57] together with the early computational studies by the Sakaki group[48] indicated that palladium centers coordinated only by carboxylate anions might be potent sites for C–H activation. However, despite the use of a number of advanced sterically-demanding carboxylates following the work by the Fagnou group,[69–71] the development of highly active catalysts for direct C–H arylation reactions remained a challenge. We hypothesized that the bifunctional role of the catalyst in the C–H activation step of the CMD mechanism, where a precise spatial positioning of the palladium center and the carboxylate anions is required, could offer an opportunity for rational anion design. In particular, a design that imparts spatial anion control around the metal center through the use of anions that are geometrically restrained by a rigid backbone could impact the relative energies of the intermediates and the transitions states.[25,72] For example, an unfavorable anion geometry could destabilize the active catalytic species through bond and angle strain in the coordination sphere and through the distortion of the ligand backbone (Scheme 6a), thus making it more reactive. If at the same time, the anion geometry would impart less strain in the CMD transition state, the barrier for C–H activation would be reduced (Scheme 6b). This strategy could potentially unlock the full potential of palladium-carboxylates for C–H activation, and more broadly, the spatial anion control could be applied to other metals. It could be of general consequence for catalytic reactions by subtly modulating spatial arrangements and relative energies of catalytic intermediates and transition states.[72]

The 'outer' oxygen atoms of the two carboxylates that are oriented towards the substrate in the transition state have a larger separation compared to their distance in the symmetrical ground state Pd(II) carboxylate (Scheme 6b), while the two other 'inner' oxygen atoms remain similarly positioned. This consideration implies that



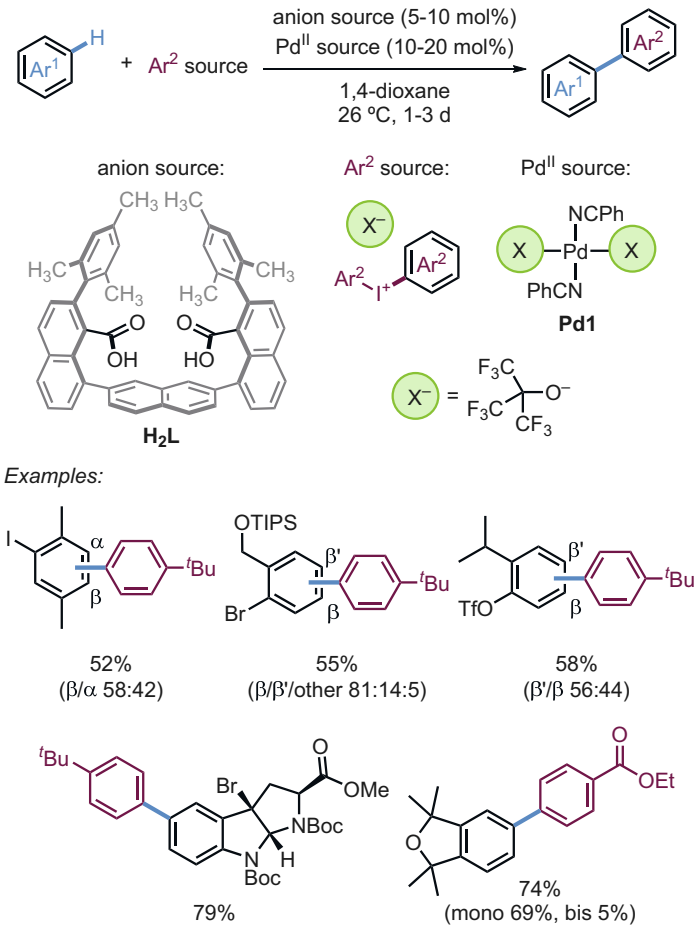
Scheme 6. Spatial anion control, the general concept and the application to C–H activation on Pd^{II}.[72]

the lowering of the barrier of the transition state could be accomplished with a placement of two carboxylates in a plane in a bent position, such that the C–CO_2^- bonds of the two carboxylates close an angle of less than 180°.

Our reported design for the spatial anion control on a palladium(II) center is shown in Scheme 6b and includes the placement of two 1-naphthyl carboxylic acid groups at the 2- and 7-positions of the central naphthalene linker, while the bulky mesityl groups prevent the bridging coordination modes of the carboxylates.[72] The crystal structures of the anion and of the corresponding Pd(II) complex showed how a bent arrangement of the carboxylates favors geometries in which the two 'outer' O atoms are significantly more separated compared with the two inner O atoms, as required in the CMD transition state for C–H activation (Scheme 6b).

5.2 *Mild C–H Arylation*

In addition to the design of a dicarboxylate based on the 1,2':7',1"-ternaphthalene backbone, in order to avoid interference of other coordinating species with the spatial anion control, we developed a class of palladium precatalysts and arylation reagents that contain nonafluoro-*tert*-butoxide anions.[72] The $(CF_3)_3CO^-$ anion is a bulky monodentate counteranion that can be replaced from a Pd(II) center by carboxylates and acts as a terminal base that accepts the H^+ after the C–H activation step. The use of the designed anion (**H_2L**), Pd(II) (**Pd1**), and Ar^2 ($Ar^2{}_2IOC(CF_3)_3$) sources for the direct C–H arylation resulted in a catalytic system that enables the reactivity at room temperature and shows compatibility with a broad range of functional groups (Scheme 7).[72] Simple non-activated arenes, such as benzene, are readily arylated and even aryl-iodides and -triflates, which are highly reactive reagents for the traditional Pd(0)-based cross-coupling reactions (Scheme 1a), are suitable substrates for the C–H activation. Furthermore, the mild reaction conditions enable C–H arylation of functionally rich molecules and late-stage diversification of pharmaceutically relevant compounds. The site-selectivity of the direct C–H arylation is under the combined influence of steric and electronic effects, with exposed and electron-rich sites being preferentially functionalized (Scheme 7).



Scheme 7. Direct C–H arylation.[72]

5.3 *Site-selectivity next to Small Alkyl Groups*

The site-selectivity of direct C–H activation processes that do not include directing interactions, such as hydrogen bonding,[29–36,73,74] with functional groups can be rationalized by the consideration of two general selectivity modes. In the selectivity mode I, a preference for sterically exposed sites is observed, and in the selectivity mode II, electronically activated positions are more reactive. In most systems, the combined influence of these two modes determines the site-selectivity of the C–H activation step.[41–43,75–78] However, it is important to note that the final product distribution of a C–H functionalization reaction might also be determined by other steps of the catalytic cycle, in which case a different site-selectivity might be observed.[79]

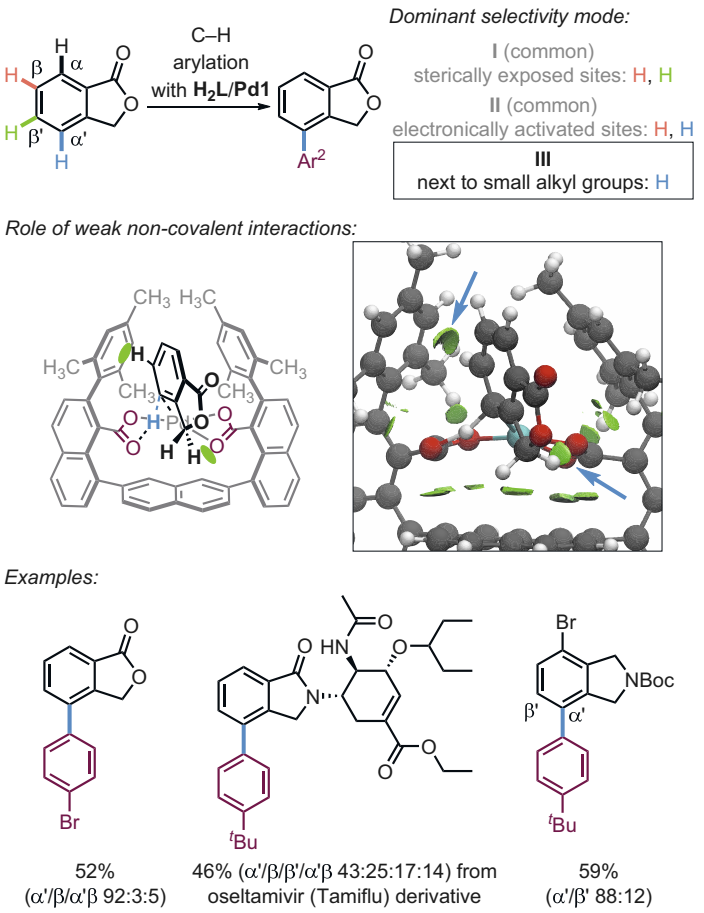
Interestingly, the C–H arylation of substrates such as phthalide with our catalytic system shows preference for the C–H site next to the alkyl group (labeled as the α' site) (Scheme 8).[80] This selectivity cannot be predicted by the consideration of either, the selectivity mode I, which would predict the β and the β' as the major reaction sites, the selectivity mode II, in which case the β and the α' would be similarly reactive, or their combined influence, which would favor the β site. The functionalization of sterically more demanding positions without directing interactions between a functional group on the substrate and the catalyst is rare not only in C–H activations, but also in numerous other methods for the functionalization of arenes.

The mechanistic studies of the reaction with phthalide as the substrate showed the C–H activation to be the site-determining step of the reaction.[80] Furthermore, the computational analysis of the transition states indicated the involvement of weak non-covalent interactions, including a C–H···π interaction and a C–H···O interaction (Scheme 8). The $C–H_{alkyl}\cdots O_{carboxylate}$ interaction can be expected to be present even for simple palladium-carboxylate catalysts and such selectivity was indeed also observed in experiments that used $Pd(OAc)_2$.[80] Therefore, we suggested that the site-selectivity for sites *ortho* to small alkyl groups might be a distinct and general selectivity mode for C–H activation, termed as selectivity mode III in the used classification (Scheme 8).[80]

The C–H arylation with selectivity mode III was demonstrated on a diverse range of arenes, many of which represent pharmaceutically relevant compound classes, such as phthalide, isoindolinone, and isoindoline derivatives, and benzosultams (for a few examples, see Scheme 8).[80] Such selectivity is observed in molecules that contained endocyclic methylene groups and is favored by the presence of electron-withdrawing substituents and smaller fused alkyl rings, but is not the dominant influence when non-cyclic alkyl groups are present. The potential generality of the selectivity mode III could open a strategy to access C–H sites that are not favored by other arene functionalization reactions.

5.4 *Catalytic Cycle*

The computational and mechanistic studies performed up to now suggest that the C–H arylation in our system proceeds through a Pd(II)/Pd(IV) catalytic cycle (Scheme 9).[72,80] The active species **PdL**, which is formed from the anion source **H_2L** and the palladium(II) source **Pd1**, enables the C–H activation through the CMD mechanism to form a Pd^{II}-aryl species. The $(CF_3)_3CO^-$ anion present in the arylation reagent $Ar^2{}_2IOC(CF_3)_3$ removes the proton after the C–H activation step, which results in the formation of an ion pair containing the diaryliodonium cation and an



Scheme 8. Site-selective C–H arylation *ortho* to small alkyl groups. Partial plot for attractive non-covalent interactions with $sign(\lambda_2)\rho <$ –0.006 (green) is shown.[80]

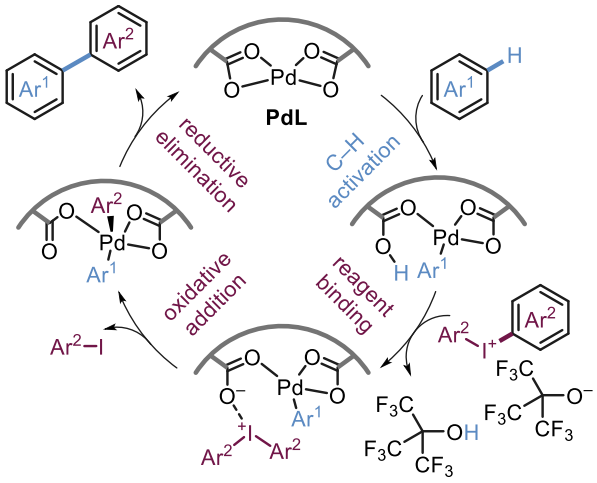
anionic palladium(II) site. The oxidative addition,[81–83] which might be facilitated by the formation of this ion pair, results in the formation of a Pd(IV) species which delivers the product after a facile reductive elimination step.

The absence of other anions and cations that might interfere with the spatial anion control or the formation of the $[Ar^2{}_2I][Ar^1PdL]$ ion pair could be crucial for the success of the mild C–H arylation reaction. For example, the reactivity is inhibited by the presence of acetate anions,[72] which are commonly used in other C–H activation systems, but can bind to Pd(II) in a more stable non-strained κ^2 mode compared with L^{2-}.

6. Conclusion

Since the initial work by the Fagnou group in 2006, the direct C–H arylation of non-activated arenes as limiting substrates has been a challenge in the area of C–H activation. In 2020, our group introduced a catalytic system that was based on spatial anion control on palladium, which enabled C–H arylation of a wide range of functionally rich substrate classes at room temperature, while before even arylation of benzene as a limiting substrate was a challenge.[72] The use of carboxylate-based anions on palladium also revealed an uncommon but potentially general mode of site-selectivity in which the C–H sites next to small alkyl substituents are activated in preference to sterically exposed and electronically activated sites.[80]

Mild direct C–H functionalization reactions, such as the well-developed iridium-catalyzed C–H borylation, offer a transformative technology for organic synthesis. Our work demonstrates that catalysts that are based on palladium-carboxylate active sites can enable challenging C–H functionalization reactivity in mild conditions and sets the stage for the development of site-selective catalysts for the modification of complex molecules.



Scheme 9. Proposed catalytic cycle.[72]

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