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Steering Site-Selectivity in Transition Metal-Catalyzed C-H Bond Functionalization: the Challenge of Benzanilides

Rafael Gramage-Doria^{*[a]}

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Abstract: Selective C-H bond functionalizations catalyzed by metal complexes have completely revolutionized the way in which chemical synthesis is conceived nowadays. Typically, the reactivity of a transition metal catalyst is the key to control the site-, regio- and/or stereo-selectivity of a C-H bond functionalization. Of particular interests are molecules that contain multiple C-H bonds prone to undergo C-H bond activations with very similar bond dissociation energies at different positions. This is the case of benzanilides, relevant chemical motifs that are found in many useful fine chemicals, in which two C-H sites are present in chemically different aromatic fragments. In the last years, it has been found that depending on the metal catalyst and the reaction conditions, the amide motif might behave as a directing group towards the metal-catalyzed C-H bond activation in the benzamide site or in the anilide site. The impact and the consequences of such subtle control of site-selectivity are herein reviewed with important applications in carbon-carbon and carbon-heteroatom bond forming processes. The mechanisms unraveling these unique transformations are discussed in order to provide a better understanding for future developments in the field of site-selective C-H bond functionalization with transition metal catalysts.

Rafael Gramage-Doria received his PhD in 2012 from the University of Strasbourg in the group of Dominique Matt and Dominique Armspach where he obtained the SAUAS PhD award (2013). He did postdoctoral research with Joost Reek at the University of Amsterdam after securing a NWO-Rubicon Fellowship and in 2014, he joined the group of Takashi Ooi at Nagoya University. In 2015 he was appointed CNRS senior researcher (Charge de Recherche) in the group of Christian Bruneau at the University of Rennes, where he obtained the Habilitation diploma (2019). His research activities include transition metal catalysis for fine chemicals, C-H bond functionalization, supramolecular and coordination chemistry, and supramolecular catalysis.



1. Introduction

Controlling chemical reactivity at specific positions is of fundamental relevance for the advancement of our knowledge in chemical synthesis.^[1] In this respect, C-H bond functionalizations contribute significantly in this direction as it represents one of the most sustainable entries enabling sophisticated molecular structures to be obtained from straightforward building blocks.^[2] During the last decades, a wide array of transition metal complexes have been recognized as fascinating catalysts to activate and functionalize a broad

variety of aromatic C-H bonds into more useful C(sp²)-C and C(sp²)-heteroatom bonds.^[3] Usually, transition metal-catalyzed aromatic C-H bond functionalizations are sought in such a way that one C-H bond is preferentially activated with respect to the other ones by means of chelation-assisted directing groups and/or the stereo-electronic properties of the substrate of interest.^[3] A classic approach is the use of molecular substrates containing a single aromatic fragment in which the C-H bond functionalization can occur. Traditionally, the installation of a rationally-designed directing group at close proximity of the desired aromatic C-H bond to be functionalized enables the metal catalyst to tackle regio-selectivity issues (i.e. *ortho* vs *meta* vs *para*).^[4]

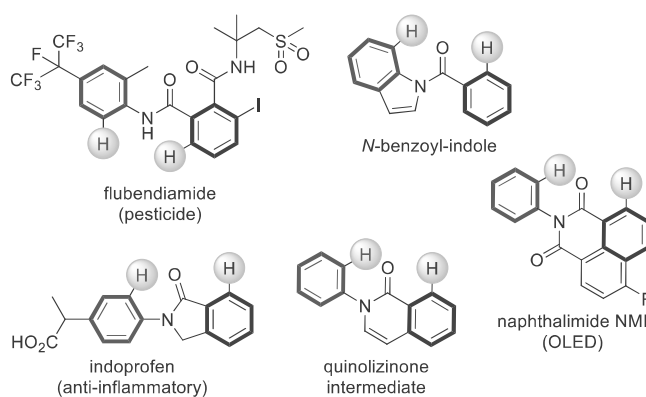
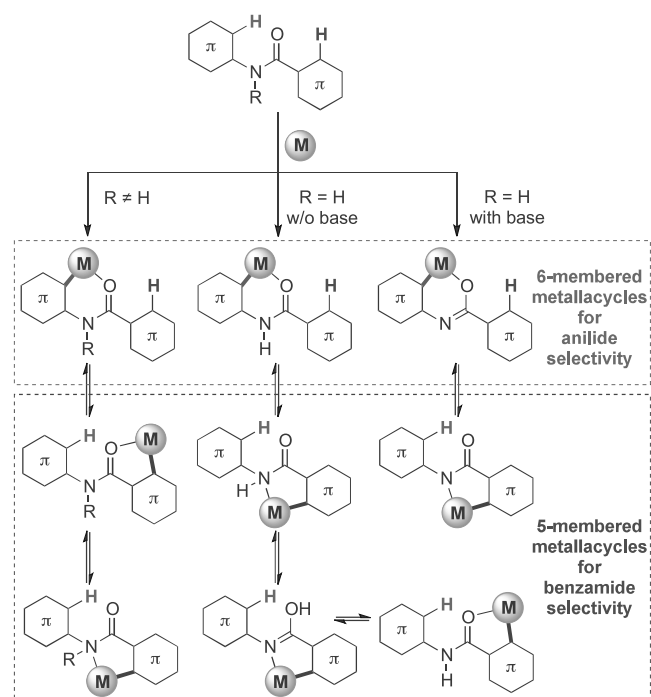


Figure 1. Relevant molecules featuring the benzanilide motif highlighting the two chemically different aromatic C-H bonds.

An increasing level of complexity appears when the molecule of interest contains two aromatic C-H sites in which the functionalization can occur. Besides regio-selectivity, site-selectivity is herein an appealing case for exploiting transition metal-catalyzed C-H bond functionalizations.^[5] In this context, benzanilides (or phenylbenzamides) are one of the best examples. They contain a single amide motif linking two aromatic entities that in turn, result to be chemically different. Importantly, benzanilide-containing derivatives are present in a myriad of useful chemicals with applications ranging from biology to materials sciences, despite being key intermediates in the synthesis of very sophisticated molecules (Figure 1).^[6]

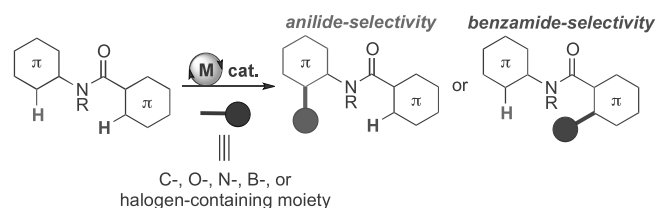
Consequently, targeting site-selective C-H bond functionalizations with benzanilide derivatives is highly interesting because it facilitates the access to molecules that otherwise will require long and tedious synthetic sequences generating significant amounts of chemical waste. In the last years, the amide group from benzanilides has been identified as a promising directing group for controlling the *ortho*-selectivity in transition metal-catalyzed C-H bond functionalizations. The action mode of this amide group is manifold (Scheme 1).^[7] For instance, the oxygen lone pair of the carbonyl group can interact with the metal catalyst leading to five-membered metallacycles for benzamide site-selectivity or six-membered ones for anilide

site-selectivity. Such behavior is upgraded in terms of efficiency when considering secondary amides. In this case, due to amide tautomerization, the nitrogen can bind to the metal catalyst preferentially leading to benzamide site-selectivity *via* the formation of five-membered metallacycles. Additionally, under specific reaction conditions the amide group can undergo deprotonation leading to a negative charge in the nitrogen atom or in the oxygen atom that will translate in a different type of coordination to the metal catalyst, thus leading to different site-selectivity. Finally, it is important to note that in the case of benzanilides in which the amide group is part of a cyclic structure, different geometries and torsion angles might be relevant for accessing different site-selective C-H bond activation steps. Clearly, the directing ability of the amide group from benzanilides is rich and versatile for providing a plethora of possibilities in terms of C-H bond activations using transition metal catalysts and appropriate coupling partners.



Scheme 1. Action modes of the (secondary or tertiary) amide as directing group for controlling the site-selectivity in benzanilide derivatives *via* transition metal-catalyzed C-H bond functionalizations.

In this review, the advances leading to site-selective C-H bond functionalizations by means of transition metal catalysts at the benzanilide platform (up to 2019 included) are discussed (Scheme 2). Particular attention is paid to the role of the amide group for enabling the transition metal catalyst to reach a given site-selectivity. Those cases in which the amide group is part of a more elaborated, strong directing group (i.e. pyridine, quinoline, triazole, oxazoline, etc.) or the benzanilide derivatives are highly functionalized with chemical substituents at specific positions (i.e. halides, alcohols, amines, etc.) dictating the selectivity of the reactions are not herein considered as it is meaningless to consider the site-selectivity in these scenarios.^[7]

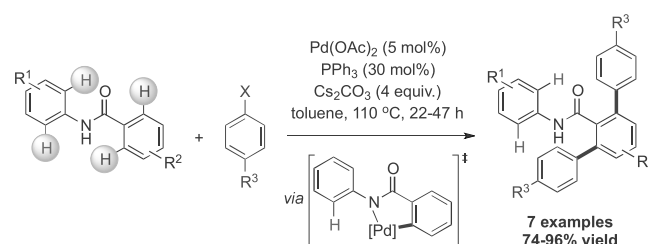


Scheme 2. Site-selective transition metal-catalyzed C-H bond functionalization of benzanilides.

2. C-C Bond-Forming Reactions

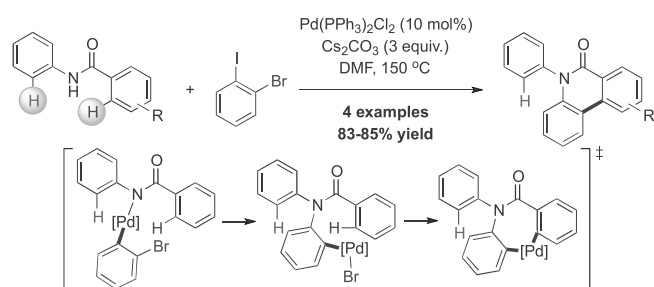
2.1. C-H Bond Arylation Reactions

As it is the case for many type of directing groups, transition metal-catalyzed C-H bond arylations represent the most active area of research for benzanilide derivatives as well.^[8] In 2000, the first examples of successful C-H bond arylations of benzanilides in an intermolecular manner were reported by Miura and co-workers.^[9] Benzanilide derivatives reacted with a variety of aryl bromides and aryl triflates, respectively, leading to *ortho*-arylated products under palladium catalysis (Scheme 3). Exclusive benzamide site-selectivity was observed for the resulting products, which was rationalized by the formation of 5-membered palladacycle intermediates. The active catalyst was formed in-situ upon mixing Pd(OAc)₂ complex with triphenylphosphine as the ligand. The reaction was performed in the presence of a base (Cs₂CO₃) and bis-arylation was mainly observed in apolar solvents (toluene or *o*-xylene), whereas the products resulting from mono-arylation were better formed in polar solvents such as *N,N*-dimethylformamide (DMF). Interestingly, the reaction was compatible with ether and chloride functional groups.



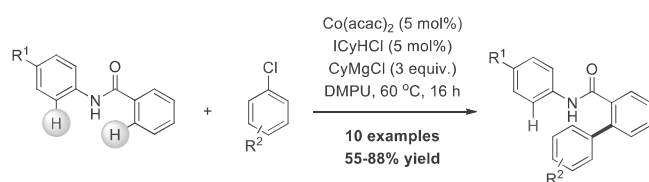
Scheme 3. Benzamide site-selective *ortho*-C-H bond arylation of benzanilides highlighting the *N*-coordination to palladium.

Recently, a very similar palladium-catalyzed strategy was reported by Banerji and co-workers for the synthesis of appealing phenanthridones from 1-bromo-2-iodobenzene through a tandem N-H/C-H bond arylation sequence (Scheme 4).^[10] The mechanism of such reaction likely undergoes *via* a Buchwald-Hartwig palladium-catalyzed amination followed by an intramolecular palladium-catalyzed C-H bond arylation. The reaction was compatible with chloride and nitro groups.



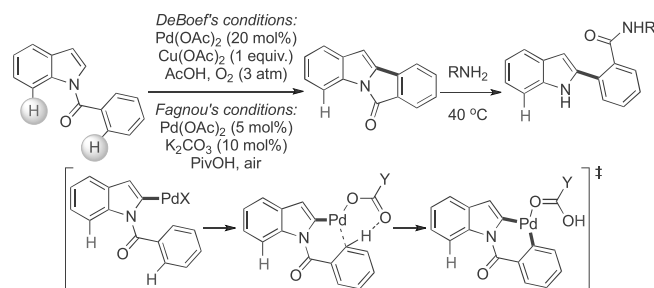
Scheme 4. Palladium-catalyzed tandem C-H/N-H bond arylation with benzamide site-selectivity highlighting the *N*-coordination to palladium.

In 2015, Ackermann and co-workers showed that cobalt catalysts enabled the C-H bond arylation of benzamides with benzamide site-selectivity (Scheme 5).^[11] Interestingly, the catalysis employed readily available aryl chlorides as coupling partners and the active catalyst required the use of a specific *N*-heterocyclic carbene pre-ligand (ICyHCl). Compared to the previous two examples (Schemes 3-4),^[9,10] the reaction temperature in this case was milder (60 °C). However, three equivalents of an organomagnesium (CyMgCl) had to be used.



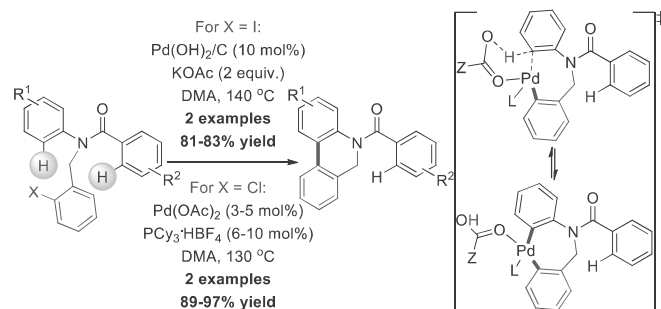
Scheme 5. Cobalt-catalyzed C-H bond *ortho*-arylation with benzamide site-selectivity. DMPU = *N,N*-Dimethylpropyleneurea.

Inspired from the seminal work from Itahara,^[12] in 2007 DeBoef and co-workers reported a palladium-catalyzed intramolecular aerobic oxidative coupling of *N*-benzoylindoles (Scheme 6).^[13] The reaction proceeded with benzamide site-selectivity leading to a type of bioactive tetracycle type of lactams^[14] that can also undergo cleavage of the N-C(O) bond with primary amines accessing biologically-privileged scaffolds (Scheme 6).^[15] Fagnou and co-workers described the same reactivity but with a more affordable catalytic system as it did not require the use of any copper salt and catalytic amounts of K₂CO₃ were enough in the presence of an air atmosphere (Scheme 6).^[16] The mechanism of this C-H bond arylation is proposed to follow a Pd(0)/Pd(II) catalytic cycle with initial regioselective palladation at the C-2 position of the indole fragment followed by a concerted metalation-deprotonation (CMD) palladation in the *ortho*-C-H bond of the benzamide ring prior to reductive elimination to provide the final product (Scheme 6). Later, Oestreich and co-workers reported similar findings using 40 mol% of a pyridine-containing ligand.^[17] The same type of reaction was found to occur under basic conditions, that is 1 equivalent of KOAc in toluene^[18] or using K₂CO₃ as an additional additive in 10 mol% loading.^[19]



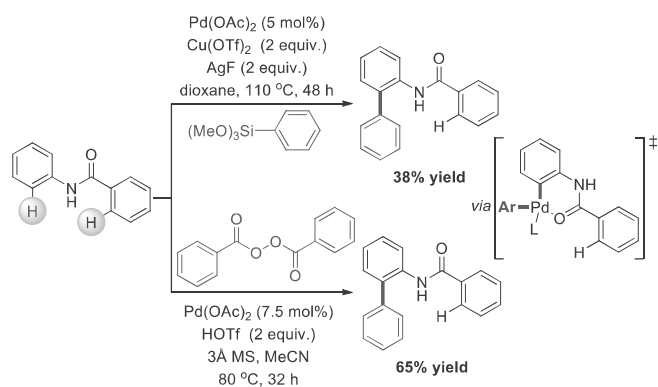
Scheme 6. Palladium-catalyzed intramolecular C-H bond *ortho*-arylation with benzamide site-selectivity and its associated key mechanistic steps. X = carboxylate or carbonate ligand. Y = Me, ^tBu or O.

Considering C-H bond arylations with anilide site-selectivity, Fagnou and co-workers reported the first examples by means of palladium catalysis in 2005 (Scheme 7).^[20] It consisted in an intramolecular C-H bond arylation using Pd(OH)₂/C (Pearlman's) as catalyst in the presence of two equivalents of KOAc. With this affordable reaction conditions, excellent yields of the corresponding products were obtained (Scheme 7). Although the initial palladium pre-catalyst is heterogeneous in nature, mechanistic studies indicate that the true active catalyst is an homogeneous one that is in-situ formed under these reaction conditions. A year later, they showed that the same type of transformation was possible using less reactive aryl chlorides with Pd(OAc)₂/PCy₃ as the catalytic system in the presence of K₂CO₃ instead of KOAc (Scheme 7).^[21] In both cases depicted in Scheme 7, the reaction likely starts with an oxidative addition to the aryl-halide bond, followed by halide/base exchange and a CMD step assisted by the presence of a palladium-ligated base, either acetate or carbonate (Scheme 7).^[21-22] For the above described examples,^[12-22] it is relevant to note that the formation of thermodynamically accessible five-membered rings (Scheme 6) or six-membered rings (Scheme 7) may trigger the site-selectivity of the reaction to some extent.



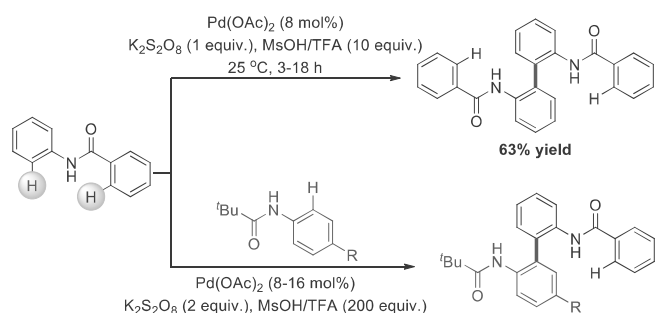
Scheme 7. Intramolecular palladium-catalyzed C-H bond *ortho*-arylation with anilide site-selectivity. DMA = *N,N*-dimethylacetamide, Z = Me (for acetyl ligand) or O⁻ (for carbonate ligand).

The intermolecular version with anilide site-selectivity was tackled in 2007 by Shi and co-workers employing also a palladium catalyst, but with trimethoxyphenylsilane as the aryl source (Scheme 8).^[23] Although exclusive anilide site-selectivity was observed, the yield was rather low (38%). In addition, the catalysis required over-stoichiometric amounts of $\text{Cu}(\text{OTf})_2$ and AgF . Cu^{2+} and/or Ag^+ were claimed to behave as chemical oxidants in the last step of the catalytic cycle in order to regenerate the active palladium(II) catalyst whereas fluoride anions might assist in the transmetallation step for activating the arylsilane partner. Wang and co-workers achieved the same site-selectivity but using benzoylperoxide as the aryl source under palladium catalysis and CO_2 extrusion (Scheme 8).^[24] The catalysis was more efficient, leading to the arylated product in 65% yield with HOTf as the only additive. The same site-selectivity but with higher reactivity (up to 79% yield) was reported later with other aryl sources such as benzoic acids,^[25] arylsulfonyl chlorides,^[26] and aryl diazonium salts under organic photoredox catalysis at room temperature.^[27] In all these cases, a six-membered cyclopalladate intermediate with the carbonyl motif behaving as directing group is likely operating for the control of the site-selectivity of this type of C-H bond arylations (Scheme 8). A copper-catalyzed C-H bond arylation of benzanilides with diaryliodonium salts was developed too, the mechanism of which, however, proceeds *via* a Friedel-Crafts pathway.^[28]



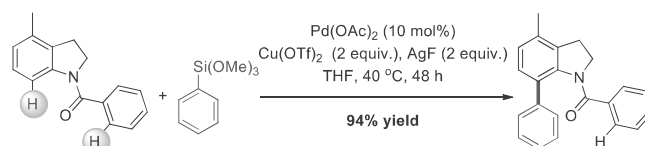
Scheme 8. Intermolecular palladium-catalyzed C-H bond *ortho*-arylation with anilide site-selectivity highlighting the *O*-coordination to palladium. OTf^- = trifluoromethanesulfonate.

Under oxidative conditions, homo- and cross-coupling reactions between benzanilide derivatives with palladium catalysts at room temperature were reported by Lu and co-workers (Scheme 9).^[29] These types of (pseudo)dimerization occurs at the *ortho*-C-H bonds from both anilide rings selectively. The homo-coupling reaction was also found to proceed with an heterogeneous catalyst ($\text{Pd}/\text{Al}_2\text{O}_3$) under O_2 atmosphere.^[30]



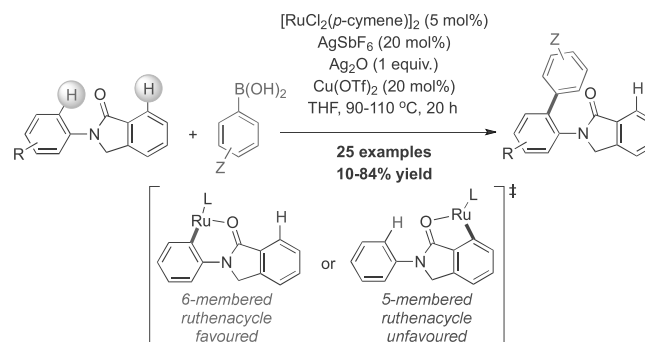
Scheme 9. Homo- and cross-coupling, palladium-catalyzed C-H bond *ortho*-arylation with anilide site-selectivity. MsOH = methanesulfonic acid.

Similar to the above-described work from Shi (Scheme 8),^[23] *N*-benzoylindoline, which contains a benzanilide core, was found to react with trimethoxyphenylsilane under palladium catalysis leading to a C-H bond arylation with anilide site-selectivity (Scheme 10).^[31] This time, the catalysis was performed with THF as the solvent and a milder temperature of 40 °C, although the loading of palladium pre-catalyst was doubled.



Scheme 10. Palladium-catalyzed C-H bond *ortho*-arylation with anilide site-selectivity using *N*-benzoylindoline as substrate.

Boronic acids were found to be suitable aryl sources to afford C-H bond *ortho*-arylated benzanilides with anilide site-selectivity. This was demonstrated with ruthenium catalysts using *N*-arylisindolinones (Scheme 11).^[32] Mono-arylated products exclusive formed with a broad functional group tolerance in both coupling partners. Preliminary mechanistic experiments indicate that the site-selectivity of the catalysis for this type of substrates arises from their preference to likely access six-membered ruthenacycle intermediates in the C-H activation step over five-membered ones. The same reactivity was observed with potassium phenyltrifluoroborate as coupling partner instead of boronic acids.

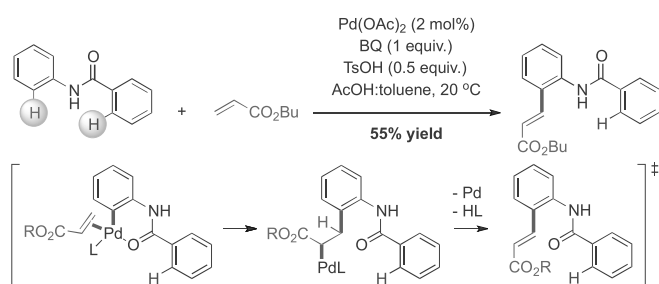


Scheme 11. Ruthenium-catalyzed C-H bond *ortho*-arylation with anilide site-selectivity using *N*-arylisindolinones as substrates highlighting the *O*-coordination to ruthenium. $\text{L} = \eta^6\text{-}p\text{-cymene}$.

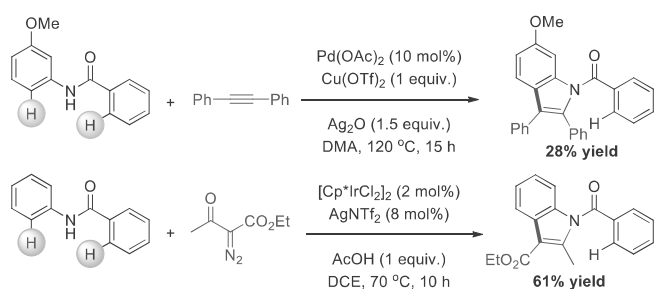
2.2. C-H Bond Alkenylation Reactions

After C-H bond arylations, C-H bond alkenylations undoubtedly constitute an appealing entry towards the formation of new carbon-carbon bonds. In 2002, de Vries, van Leeuwen and co-workers reported the first example of C-H bond *ortho*-alkenylation of benzanilide (Scheme 12).^[33] Butylacrylate was employed as the alkene source under palladium catalysis. This oxidative coupling led to exclusive C-H bond alkenylation at the anilide ring in the presence of benzoquinone (BQ) as chemical oxidant and *para*-toluenesulfonic acid (TsOH). Interestingly, the

reaction was carried out at room temperature and the presence of acetic acid was required to get highly active palladium species. The reaction is likely assisted by coordination of the carbonyl group to palladium leading to six-membered palladacycle species. Alkene insertion and β -hydride elimination leads to the C-H bond alkenylated product with Heck regio-selectivity (Scheme 12). Then, a number of related reaction conditions were reported. For instance, using catalytic amounts of copper salts under an oxygen atmosphere,^[34] employing selectfluor and trifluoroacetic acid,^[35] and even under non-acidic conditions.^[36] An heterogeneous palladium-containing polyoxometalate catalyst led to the same reactivity without the use of any extra reagents.^[37] Such type of reactivity enabled the access to 4-alkenyl benzoxazoles from readily available 2-amidophenols^[38] and implementation in fullerene functionalization has been demonstrated too.^[39] Similarly, switching the alkene source for an alkyne derivative such as diphenylacetylene leads to the formation of original indoles, although in a modest yield (Scheme 13).^[40] Structurally-related indoles can also form *via* an iridium-catalyzed C-H bond functionalization employing a diazo compound (i.e. ethyl 2-diazo-3-oxobutanoate) as a coupling partner (Scheme 13).^[41] The site-selectivity of the reaction appears to be determined by the formation of six-membered iridacycles similar to the palladium ones described in Scheme 12.



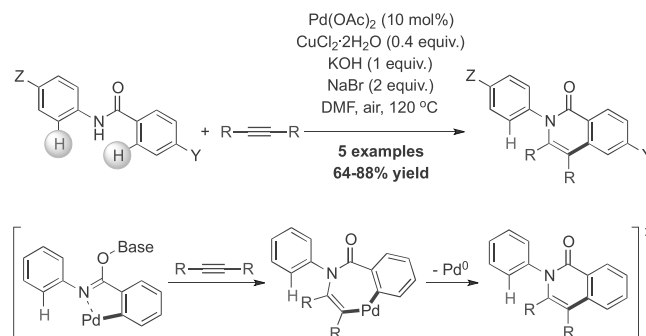
Scheme 12. Palladium-catalyzed C-H bond *ortho*-alkenylation with anilide site-selectivity highlighting the *O*-coordination to palladium. L = anionic ligand (*para*-toluenesulfonate or acetate).



Scheme 13. Palladium-catalyzed C-H bond *ortho*-alkenylation leading to indoles (top) and an iridium-catalyzed version (bottom). DCE = 1,2-dichloroethane, Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl.

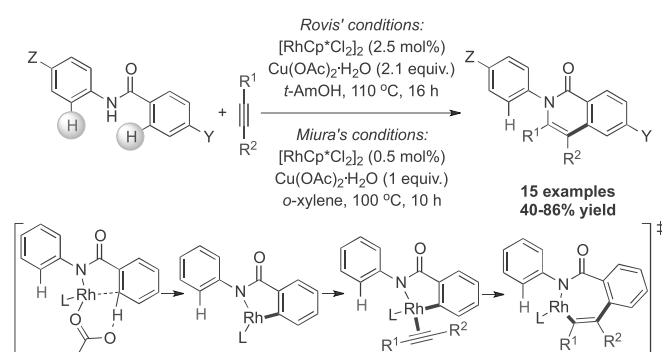
Alternatively, Huang and co-workers reported a reverse site-selectivity for the reaction of benzanilides with alkynes.^[42] In the presence of a base and a copper co-catalyst, the palladium catalyst enables the C-H bond functionalization at the benzanilide ring with an intramolecular cyclization step leading to *N*-arylisquinolones in good yields (Scheme 14).

Experimental mechanistic studies suggest the formation of five-membered palladacycle intermediates in the site-determining C-H bond activation step. In the presence of air, copper salts likely serve to re-oxidize Pd(0) species into the catalytically active Pd(II) species after the formal reductive elimination step (cyclization/annulation). An heterogeneous Pd/C-based catalytic system has been reported using similar reagents with the same site-selectivity.^[43]



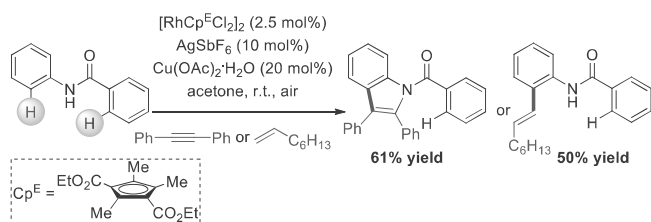
Scheme 14. Palladium-catalyzed C-H bond *ortho*-alkenylation with benzanilide site-selectivity employing alkynes as coupling partners highlighting the *N*-coordination to palladium. R = Ph, Et.

Besides palladium catalysts, rhodium catalysts are rather efficient for C-H bond alkenylations with benzanilides. In 2010, the groups of Rovis and Miura, independently, reported a pioneering rhodium-catalyzed oxidative cycloaddition with alkynes *via* C-H/N-H functionalization (Scheme 15).^[44,45] The catalysis was found to be site-selective as only the *ortho*-C-H bond in the benzanilide ring underwent functionalization forming *N*-arylisquinolones. Unsymmetrical alkynes led to mixtures of regio-isomers with the smaller substituent (i.e. alkyl vs aryl) preferentially near to the C-H bond being functionalized. Mechanistic investigations indicate that (1) a Rh(I)/Rh(III) catalytic cycle is operating and (2) the turnover-limiting step is the C-H bond activation with the alkyne insertion step being irreversible. The rhodium-mediated C-H bond activation step likely occurs *via* a CMD mechanism with a rhodium-coordinated acetate ligand enabling the deprotonation in the substrate. An alternative protocol using Ag₂CO₃ as chemical oxidant instead of Cu(OAc)₂ has been reported.^[46] A greener approach was developed using [Cp*Rh(MeCN)₃][BF₄]₂ as the pre-catalyst in the presence of K₂CO₃, air and water.^[47] Additionally, Ackermann and co-workers showed that the same site-selectivity was reached using [RuCl₂(*p*-cymene)]₂ as the pre-catalyst with identical reaction conditions as the ones developed by Rovis' group [i.e. Cu(OAc)₂·H₂O in *t*-AmOH] at the expenses of a higher catalyst loading (5 mol%).^[48] The nickel-catalyzed version was accomplished by Chatani and co-workers who found a catalytic system based on Ni(OTf)₂, PPh₃ and *t*BuOK.^[49]



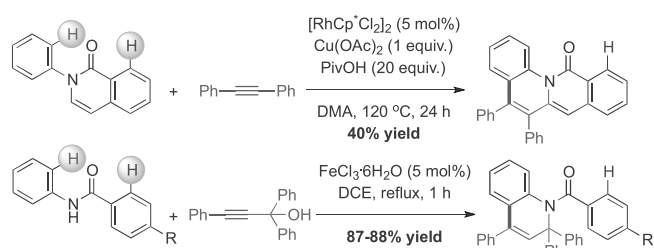
Scheme 15. Rhodium-catalyzed C-H bond *ortho*-functionalization with benzamide site-selectivity employing alkynes as coupling partners highlighting the *N*-coordination to rhodium. L = Cp*.

In 2014, Tanaka and co-workers reported a reversal in the site-selectivity of the above-described reaction by switching the electronic properties of the Cp ligand attached to the rhodium catalyst (Scheme 16).^[50] The key rhodium catalyst contained an electron-deficient η^5 -cyclopentadienyl ligand (Cp^E). In the presence of catalytic amounts of silver(I) and copper(II) salts in acetone solvent under air at room temperature, benzanilide reacted with diphenylacetylene with anilide site-selectivity leading to indoles. This catalytic system preferentially performs annulation across the electron-rich ring (anilide) over the electron-deficient one (benzamide). These results clearly indicate that tuning the electron-properties of the ligand on rhodium impact the site-selectivity of the reaction. A six-membered rhodacycle similar to the palladium one reported in Scheme 12 may account for the site-selectivity observed in this C-H bond functionalization. Importantly, this strategy was extended to perform the very challenging oxidative olefination with unactivated alkenes (Scheme 16).^[51] In addition, the same site-selectivity was observed using activated alkenes (i.e. acrylates) with a catalytic system based on [RhCp*Cl₂]₂ and AgSbF₆ (or AgOTf) in the presence of NaOAc (or Ag₂CO₃).^[52,53]



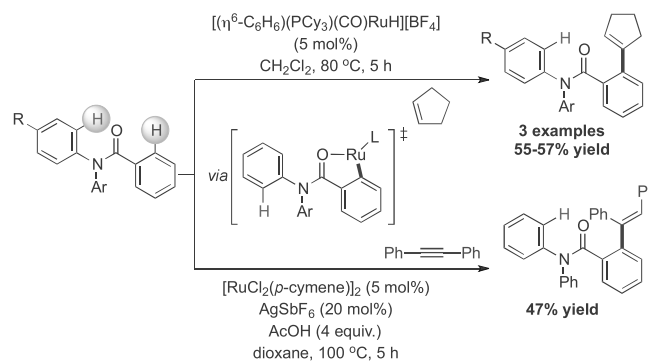
Scheme 16. Rhodium-catalyzed C-H bond *ortho*-functionalization with anilide site-selectivity employing a representative alkyne and a terminal alkene, respectively.

In 2017, You and co-workers described a rhodium-catalyzed annulation of pyridinones and alkynes with anilide site-selectivity enabling the synthesis of aromatically-fused quinolinones (Scheme 17).^[54] Structurally-related products were obtained *via* an iron-catalyzed reaction with 1,1,3-triphenylpropargyl alcohol as coupling partner using benzanilide derivatives (Scheme 17).^[55] The reaction, however, does not proceed *via* a formal metal-catalyzed C-H bond activation but rather *via* a Friedel-Crafts mechanism which shows the higher inner reactivity of the anilide ring *versus* the benzamide ring.

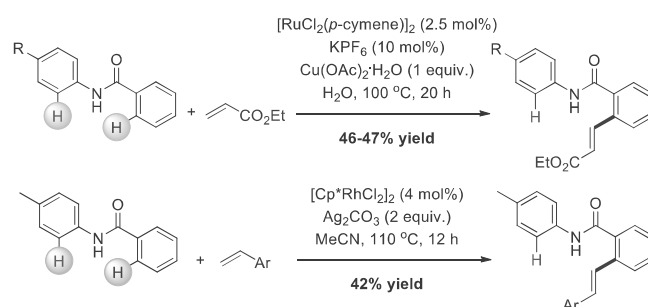


Scheme 17. Rhodium-catalyzed C-H bond *ortho*-functionalization with anilide site-selectivity for a pyridinone derivative (top) and iron-catalyzed access to 1,2-dihydroquinolines (bottom). R = H, Me.

In this context, ruthenium catalysts have shown its ability to perform C-H bond alkenylations as well (*vide supra*).^[48] Different reports have shown the preference of ruthenium catalysts to enable C-H bond alkenylations using benzanilide derivatives with excellent site-selectivity for the benzamide ring. In 2010, Yi and co-workers reported a ruthenium(II)-catalyzed oxidative coupling involving unactivated alkenes such as cyclopentene (Scheme 18).^[56] Several kinetic and spectroscopic evidences indicate that the C-H bond functionalization is fast and that the C(sp²)-C(sp²) bond forming step is the rate-limiting one. The carbonyl group from the amide fragment is essential for enabling catalytically-productive five-membered ruthenacycle species. A similar type of ruthenacycle intermediates were exploited by Miura, and co-workers for the site-selective hydroarylation of alkynes (Scheme 18).^[57] This time, the reaction was performed with [RuCl₂(*p*-cymene)]₂ as the pre-catalyst and catalytic amounts of AgSbF₆ in dioxane. They showed that the catalysis was more efficient in the presence of 4 equivalents of AcOH as protons participate in the last elementary step of protonolysis in the catalytic cycle. The same pre-catalyst was used by Ackermann and co-workers in water media to promote C-H bond alkenylations with benzamide site-selectivity using acrylates as coupling partners (Scheme 19).^[58] The same site-selectivity was accomplished with a rhodium catalyst using a less reactive styrene derivative as shown by Li and co-workers under non-optimized reaction conditions (Scheme 19).^[59]

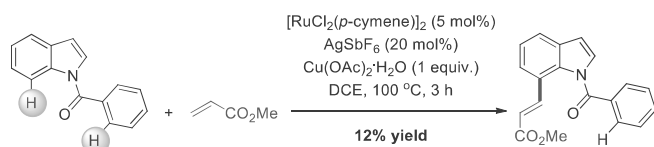


Scheme 18. Ruthenium-catalyzed C-H bond *ortho*-alkenylation with benzamide site-selectivity using cyclopentene and an alkyne, respectively, highlighting the *O*-coordination to ruthenium. L = η^6 -C₆H₆ or η^6 -*p*-cymene.

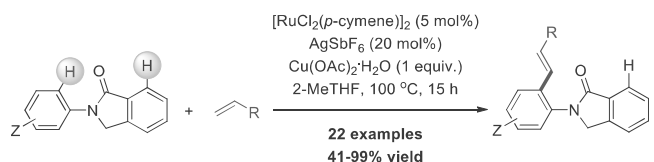


Scheme 19. Benzamide site-selective C-H bond *ortho*-alkenylation using acrylates in water under ruthenium catalysis (top) and using a styrene derivative under rhodium catalysis (bottom). R = H, F. Ar = 4-Cl-C₆H₄.

Ruthenium catalysts enabling anilide site-selectivity for C-H bond alkenylations remain rare (*vide supra*)^[48] and it has been observed as a side-product for C2-alkenylations with *N*-benzoylindoles (Scheme 20).^[60] A more general design has been reported recently, in which *N*-aryl-isoindolinones appeared to be excellent substrates enabling C-H bond alkenylations with anilide site-selectivity (Scheme 21).^[61] Exclusive mono- and *ortho*-selectivity was obtained for acrylate and styrene derivatives as coupling partners, respectively. Phthalimides led to the same site-selectivity but with lower reactivity, as it was the case when using alkynes as coupling partners. In this case, the geometry of the directing group is critical to locate the ruthenium center at close proximity of the C-H bond from the anilide ring as stated before for related C-H bond functionalizations (Scheme 11).^[32] Importantly, the potential of the catalysis was exemplified in the late-stage functionalization of indoprofen. Double C-H bond alkenylations were feasible albeit with low yield (20%).

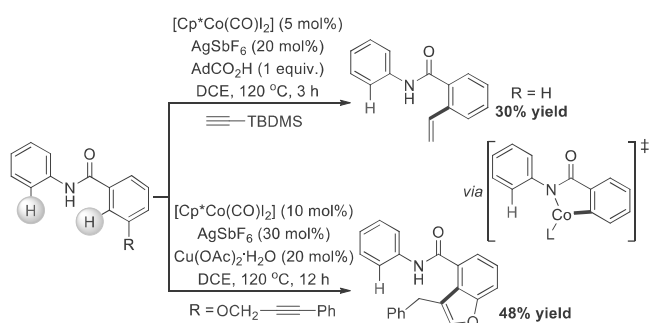


Scheme 20. Ruthenium-catalyzed C-H bond *ortho*-alkenylation with anilide site-selectivity as a side-product.



Scheme 21. Ruthenium-catalyzed C-H bond *ortho*-alkenylation with anilide site-selectivity for benzanilides comprising a *N*-aryl-isoindolinone core.

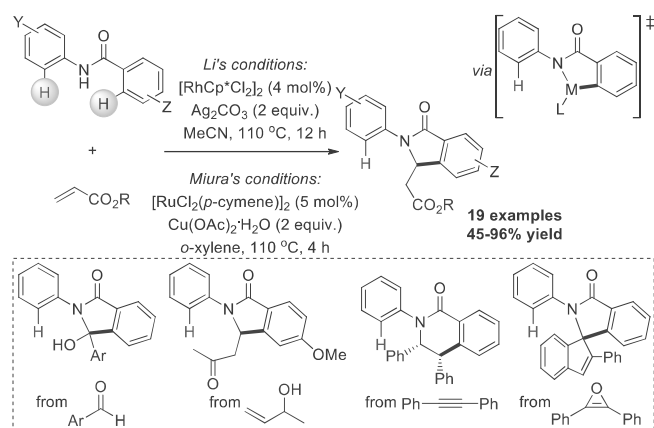
Organometallic cobalt species have merged as a promising type of catalysts for C-H bond functionalizations. For instance, [Cp*Co(CO)₂] complex displayed modest activity as a pre-catalyst with benzamide site-selectivity for the vinylation of secondary benzanilides (Scheme 22).^[62] The same cobalt complex led to the same site-selectivity for the intramolecular cyclization of alkynes (Scheme 22).^[63] In both cases, it was reasoned that five-membered cobaltacycles are formed during the C-H bond activation step.



Scheme 22. Benzamide site-selective, cobalt-catalyzed C-H bond *ortho*-alkenylation of benzanilide derivatives highlighting the *N*-coordination to cobalt. Ad = 1-adamantyl, TBDMS = *tert*-butyldimethylsilyl, L = Cp*.

2.3. C-H Bond Alkylation Reactions

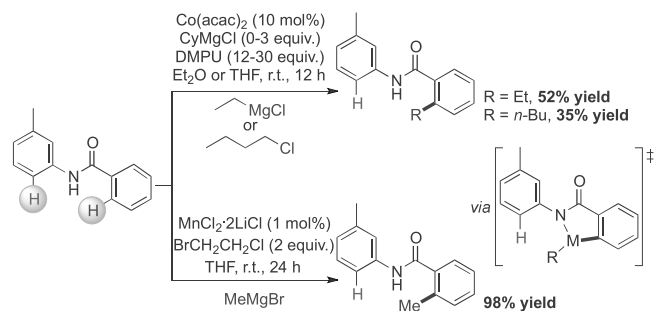
In 2010, Li and co-workers reported the first examples of site-selective C-H bond alkylations of benzanilides (Scheme 23).^[65] Electron-withdrawing olefins (i.e. acrylates, acrylonitriles, α,β -unsaturated ketones) underwent oxidative coupling at the aromatic C-H bond belonging to the benzamide ring followed by an intramolecular Michael reaction (nucleophilic cyclization) forming a series of γ -lactams. This tandem reaction was tolerant to a wide variety of functional groups as shown also by Wang in 2016.^[63] The same type of reaction occurred under ruthenium catalysis as shown by Miura and co-workers with similar levels of efficiency (Scheme 23).^[64] Similar to C-H bond alkenylations (*vide supra*), the C-H bond activation step likely involved formation of five-membered metallacycle.^[68,59] This intramolecular cascade approach was later extended to different coupling partners (benzaldehydes, allylic alcohols, alkynes, diphenylcyclopropanone) leading to complex structures such as 3-hydroxyisoindolin-1-ones,^[65] isoindolinones,^[66] *cis*-3,4-dihydroisoquinolinones,^[67] and spiroisoindolinones (Scheme 23).^[68] Importantly, these examples show that the site-selectivity of the catalysis is favored also because they lead to thermodynamically affordable five-membered rings. The other site-selectivity will hypothetically lead to much less stable four-membered rings that do not form so far.



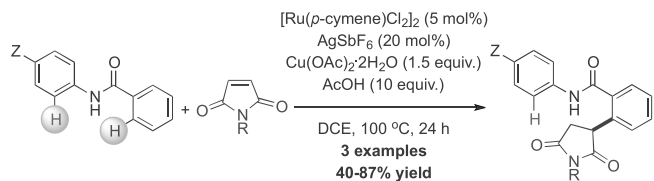
Scheme 23. Benzamide site-selective, metal-catalyzed C-H bond *ortho*-alkenylations highlighting the *N*-coordination to rhodium or ruthenium. L = Cp* for M = Rh or L = η^6 -*p*-cymene for M = Ru. R = alkyl or benzyl. Ar = 4-CF₃-C₆H₄.

Intermolecular C-H bond alkylations with benzamide site-selectivity were pioneered by Nakamura and co-workers with a series of cobalt- and manganese-catalyzed methodologies for methylation, ethylation and *n*-butylation (Scheme 24).^[69-71] The formation of five-membered metallacycles is postulated to be at the origin of such site-selectivity. A palladium-catalyzed version for *n*-butylation gave rise to very poor results (12% yield)^[72] and a rhodium-catalyzed methylation employing MeBF₃K as a more benign alkylating agent was reported too (43% yield).^[73] The same site-selectivity was observed with allylbromides under

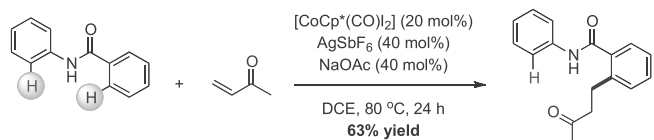
rhodium catalysis.^[74] Moreover, *N*-substituted maleimides were found to be appropriate partners leading to alkylated products upon a formal hydroarylation *via* ruthenium catalysis as it was shown by Prabhu and co-workers (Scheme 25).^[75] In 2018, Hamilton and Whiteoak studied the difference between the reactivity of benzamides and anilides, respectively, by DFT calculations under cobalt catalysis, before being applied experimentally to the benzamide (Scheme 26).^[76] This work demonstrated full benzamide site-selectivity upon reaction with 3-buten-2-one.



Scheme 24. Cobalt- and manganese-catalyzed C-H bond *ortho*-alkylation with benzamide site-selectivity highlighting the *N*-coordination to cobalt or manganese. M = Co or Mn.

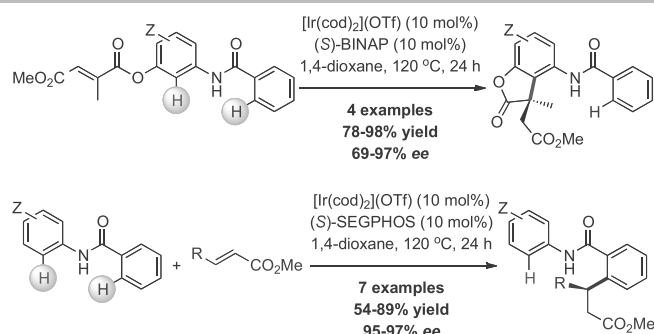


Scheme 25. Ruthenium-catalyzed C-H bond *ortho*-alkylation with benzamide site-selectivity. Z = H, OMe. R = Et, Bn.



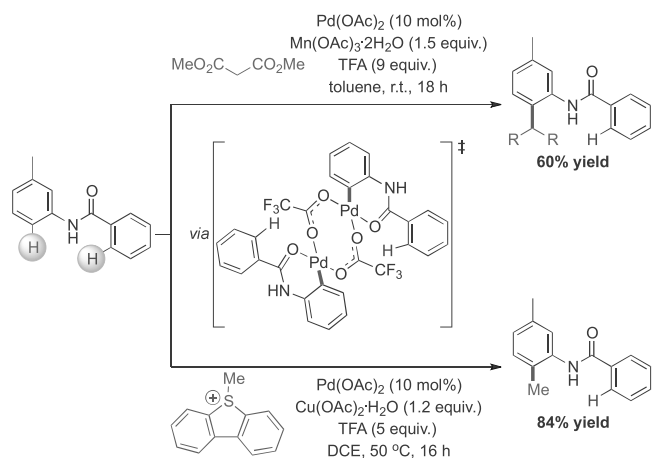
Scheme 26. Cobalt-catalyzed C-H bond *ortho*-alkylation with benzamide site-selectivity using 3-buten-2-one as coupling partner.

A reversal in the site-selectivity of cyclization reactions leading to formal C-H bond alkylations in the anilide ring are not trivial,^[77] besides some radical-based reactions with iron^[78] and copper catalysts.^[79-82] Regarding C-H bond functionalizations, Shibata and co-workers disclosed a highly enantioselective intramolecular C-H conjugate addition between benzanilides and β -substituted acrylates under iridium catalysis (Scheme 27).^[83] For that, they employed $[\text{Ir}(\text{cod})_2]\text{OTf}$ (cod = 1,5-cyclooctadiene) complex as catalyst precursor and (*S*)-BINAP as the chiral ligand. The intermolecular version was accomplished using (*S*)-SEGPHOS as the chiral ligand but leading exclusively to benzamide site-selectivity.



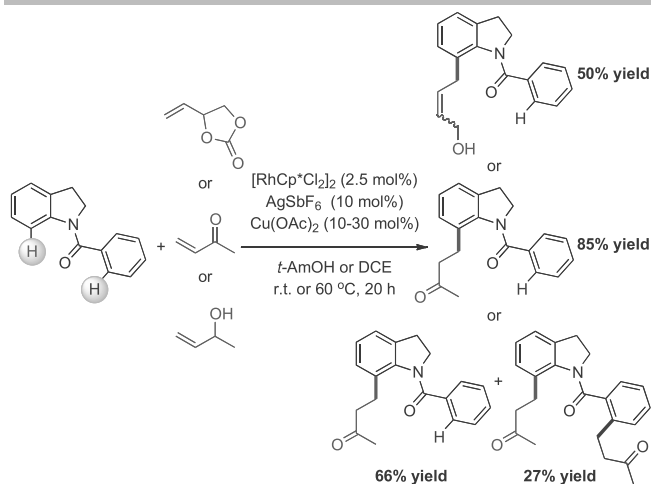
Scheme 27. Iridium-catalyzed enantioselective C-H bond *ortho*-alkylation of benzanilides. Z = H, Me, Cl, OMe. R = Me, ⁿPent, Ph.

Intermolecular C-H bond alkylations of benzanilides with anilide site-selectivity have been achieved in a limited number of cases. For instance, in 2013, Yu and co-workers described a palladium-catalyzed oxidative cross-coupling using β -keto esters as the alkyl source (Scheme 28).^[84] The key mechanistic findings are that dinuclear palladium(II) species might be involved in the C-H bond activation step and that mononuclear palladium(IV) species precede the reductive elimination step. The overall mechanism involved a Pd(II)/Pd(IV) catalytic cycle similar to seminal observations reported by Sanford and Dong, independently, for other substrates.^[85-86] Recently, Novak and co-workers reported a palladium-catalyzed C-H bond methylation using an original sulfonium salt as reagent (Scheme 28).^[87]



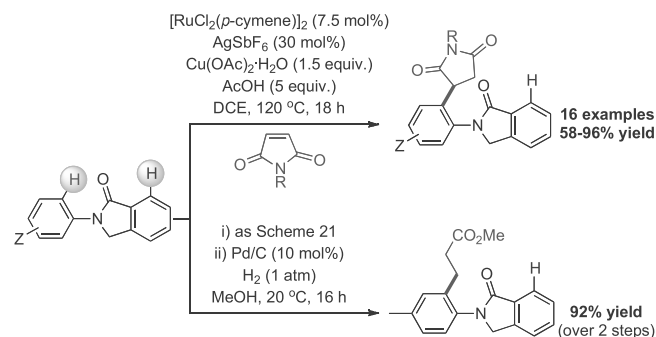
Scheme 28. Palladium-catalyzed C-H bond *ortho*-alkylation with anilide site-selectivity using β -keto ester and sulfonium salt partners, respectively, highlighting the *O*-coordination to palladium. R = CO₂Me.

The same site-selectivity was observed by Kim and co-workers with rhodium catalysis. 4-vinyl-1,3-dioxolan-2-one was used as a coupling partner leading to the corresponding allylic alcohol in moderate yield^[88] and a higher reactivity was obtained using enones (Scheme 29).^[89] Similar observations were found with allylic alcohols, however, C-H bond functionalization at the benzamide ring took place to some extent as well (Scheme 29).^[90]



Scheme 29. Rhodium-catalyzed C-H bond *ortho*-alkylation with anilide site-selectivity using different allyl partners.

Ruthenium catalysts enabling C-H bond alkylations in the anilide ring of benzamides are also scarce. For instance, *N*-arylisindolinones were found to react with *N*-arylisindolinones giving rise to the product resulting from C-H bond *ortho*-alkylation in the anilide ring (Scheme 30).^[91] In a complementary strategy, it was shown that products resulting from C-H bond *ortho*-alkylation in the anilide ring can be prepared upon a sequence involving ruthenium-catalyzed C-H bond alkenylation and palladium-catalyzed hydrogenation (Scheme 30).^[61]

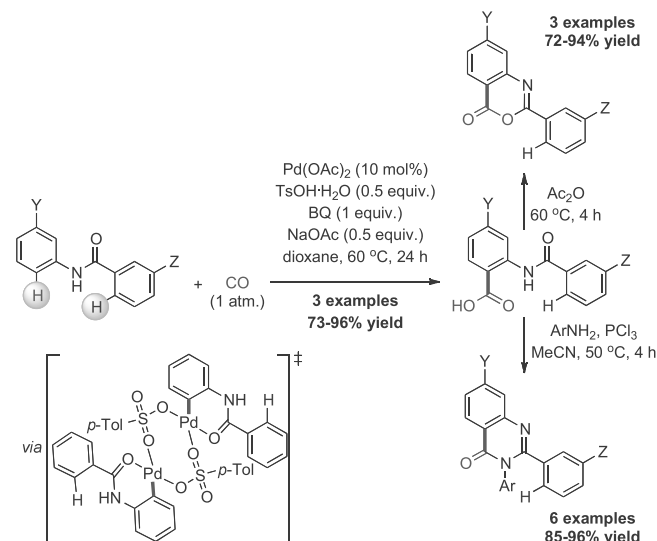


Scheme 30. Ruthenium-catalyzed C-H bond *ortho*-alkylation with anilide site-selectivity. R = alkyl, benzyl, (hetero)aryl.

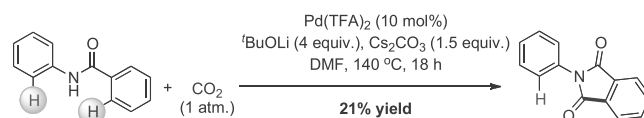
2.4 C-H Bond Acylation Reactions.

In 2010, Yu and co-workers reported a seminal work on C-H bond acylations of benzamides with anilide site-selectivity (Scheme 31).^[92] They found that Pd(OAc)₂ was an excellent pre-catalyst to perform C-H bond carboxylations in the presence of CO leading to *ortho*-carboxylated chemicals. Additionally, these products can easily undergo post-functionalizations affording complex structures such as benzoxazinones and quinazolinones. In the catalysis, BQ served as a chemical oxidant and TsOH as the ligand. From the mechanistic viewpoint, they managed to isolate a catalytically productive intermediate consisting of a six-membered palladacycle in which coordination of the oxygen lone pair from the amide unit took place, although a dimeric palladium intermediate is more likely to operate. Further studies supported a Pd(0)/Pd(II) catalytic cycle.^[92] In alternative protocols, CO was

replaced by a more benign *N,N*-dimethyloxamic acid giving lower yields^[93] and using diethyl azodicarboxylate (DEAD) instead of CO led to the product resulting from *ortho*-C-H ethoxycarboxylation (R-CO₂Et) with the same anilide site-selectivity.^[94] A reversed site-selectivity with a palladium catalyst was reported using CO₂ in a poor yield.^[95] In this case, an intramolecular reaction cascade occurred leading to *N*-phenylphthalimide (Scheme 32).

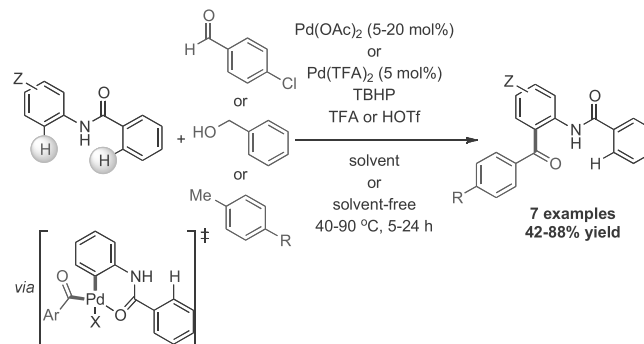


Scheme 31. Palladium-catalyzed C-H bond *ortho*-carboxylation with anilide site-selectivity using CO and useful derivatizations, highlighting the O-coordination to palladium. Y = H, OMe, -OCH₂O-. Z = H, Cl. R = H, OMe, 3,5-bis(trifluoromethyl).

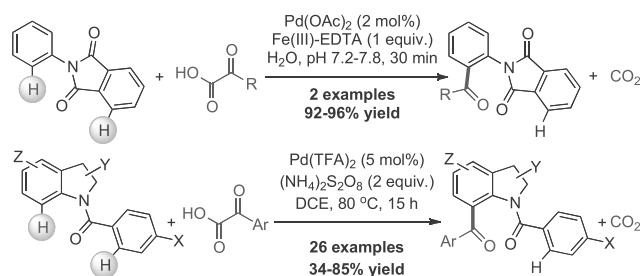


Scheme 32. Palladium-catalyzed C-H bond *ortho*-carboxylation with benzamide site-selectivity using CO₂.

Inspired by the pioneering contribution from Yu (*vide supra*),^[92] a number of new methodologies based on palladium catalysts under oxidizing conditions appeared employing different coupling partners as the source of acyl groups. The formation of these acyl groups is manifold. They can be obtained in the presence of *tert*-butyl hydroperoxide (TBHP) from benzaldehyde derivatives,^[96-97] benzylic alcohols,^[98] toluene derivatives,^[99-101] (Scheme 33) or from decarboxylation of α -oxocarboxylic acids (Scheme 34).^[102-103] All these reactions share the formation of a common catalytic intermediate prior to the reductive elimination step, namely a six-membered palladacycle bearing an acyl group (Scheme 32).

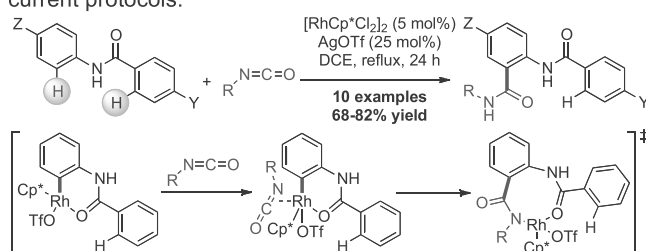


Scheme 33. Palladium-catalyzed C-H bond *ortho*-arylation with anilide site-selectivity highlighting the O-coordination to palladium. Z = H, Me. R = H, Cl. solvent = toluene or HOAc/DMA or DMSO.



Scheme 34. Palladium-catalyzed C-H bond *ortho*-acylation with anilide site-selectivity for phthalimides (top) and indolines (bottom). R = Ph, N(Me)(OMe).

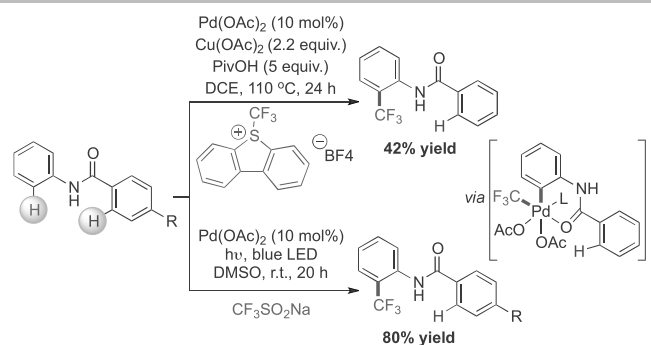
Besides palladium catalysts, there is a noteworthy case of a catalytic system based on rhodium leading to acylated benzanilides. Wang and co-workers reported the *ortho*-C-H bond functionalization of benzanilides with anilide site-selectivity using isocyanates as coupling partners.^[104] The catalysis was compatible with a variety of functional groups and the key catalytic intermediates were postulated to involve six-membered rhodacycles (Scheme 35). This methodology is appealing because unsymmetric diamides are not trivial to synthesize with current protocols.



Scheme 35. Rhodium-catalyzed C-H bond *ortho*-acylation with anilide site-selectivity highlighting the O-coordination to rhodium. R = alkyl, aryl. Z = H, Me, OMe, Cl, I, NO₂. Y = H, Me, OMe.

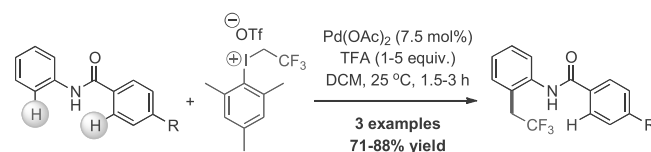
2.5 C-H Bond Fluoroalkylation Reactions.

Fluoride-containing building blocks are particularly relevant for biomedical applications.^[105] As such, C-H bond functionalizations of benzanilides employing fluorinated coupling partners have been tackled, leading mostly to products resulting from anilide site-selectivity. A first contribution was made by Shi and co-workers in 2013, who developed a palladium-catalyzed *ortho*-C-H bond trifluoromethylation of benzanilide utilizing Umemoto's reagent as the trifluoromethyl source (Scheme 36).^[106] Recently, a more efficient methodology was introduced by Wang using a rather safe and stable reagent, namely CF₃SO₂Na, under visible-light-induced palladium catalysis (Scheme 36).^[107] In both cases, a six-membered palladacycle species with oxidation state +4 on palladium was postulated to precede the reductive elimination step with an overall catalytic cycle involving Pd(II)/Pd(IV) species.

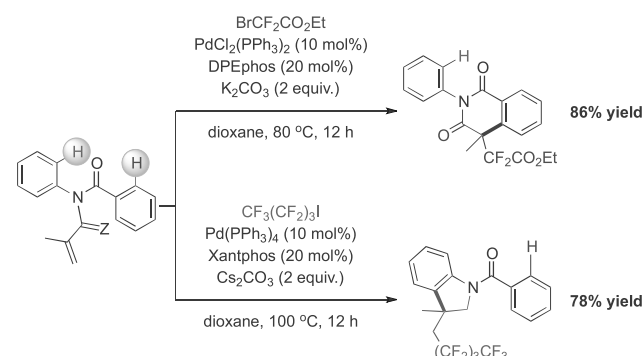


Scheme 36. Palladium-catalyzed C-H bond *ortho*-trifluoromethylation with anilide site-selectivity highlighting the O-coordination to palladium. R = H, OMe.

A palladium-catalyzed *ortho*-C-H bond trifluoroethylation with anilide site-selectivity was reported by Novak and co-workers using the very original mesityl(trifluoroethyl)iodonium triflate reagent as the "CF₃CH₂" source (Scheme 37).^[108] The reaction was fast and took place under very mild conditions. Two complementary palladium-catalyzed protocols have been described involving an intramolecular cyclization with different site-selectivity (Scheme 38).^[109-110]



Scheme 37. Palladium-catalyzed C-H bond *ortho*-trifluoroethylation with anilide site-selectivity. R = H, OMe, NO₂.

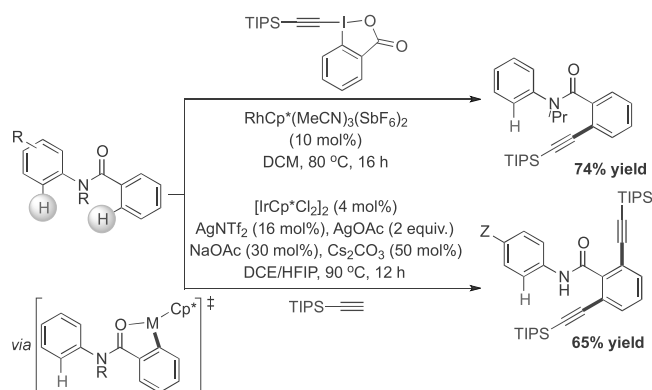


Scheme 38. Palladium-catalyzed C-H bond *ortho*-functionalization involving fluorinated groups with different site-selectivity. Z = O, CH₂.

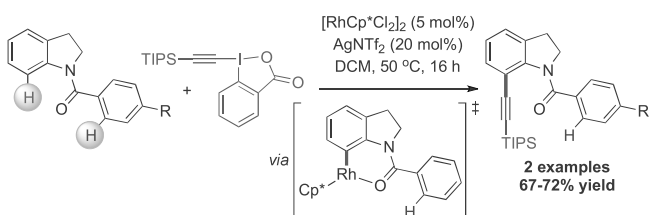
2.6 C-H Bond Alkynylation Reactions.

Alkynylated compounds are key synthons in the synthesis of more elaborated molecular structures since the alkenyl fragment can readily be engaged in further derivatizations *via* well-known protocols (i.e. the Sonogashira cross-coupling).^[111] Unfortunately, the site-selectivity of the C-H bond alkynylation of benzanilide derivatives have been rarely studied. The group of Glorius reported the first observations dealing with rhodium catalysis.^[112] Benzanilide reacted with 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (TIPS-EBX) affording the *ortho*-C-H bond alkynylated product with exclusive benzamide site-selectivity (Scheme 39). A two-fold *ortho*-C-H bond alkynylation was achieved using an iridium catalyst and

(triisopropylsilyl)acetylene as reagent (Scheme 39).^[113] In both cases, a five-membered metallacycle is sought to be responsible for the observed site-selectivity. The reversed site-selectivity was achieved only for structurally pre-disposed indolines under rhodium catalysis using TIPS-EBX reagent (Scheme 40).^[114] In this case, the site-selective determining intermediate was evoked to be a six-membered rhodacycle due to the molecular geometry adopted by the substrate.



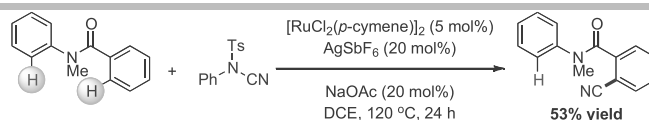
Scheme 39. C-H bond *ortho*-alkynylation with benzamide site-selectivity with rhodium and iridium catalysts highlighting the O-coordination to the metal. M = Rh or Ir. Z = SO₂NH₂.



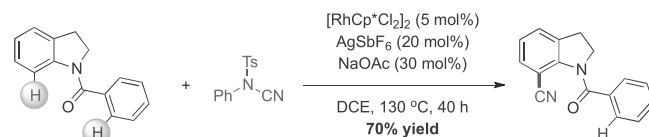
Scheme 40. Rhodium-catalyzed C-H bond *ortho*-alkynylation with anilide site-selectivity highlighting the O-coordination to rhodium. R = H, Me.

2.7 C-H Bond Cyanation Reactions.

In 2014, Ackermann and co-workers noted that the ruthenium-catalyzed cyanation using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as coupling partner proceeded with benzamide site-selectivity leading to the cyanated product in a moderate yield (Scheme 41).^[115] Similar reactions conditions but swapping ruthenium for rhodium led to anilide site-selectivity for indolines, as it was shown by Kim and co-workers (Scheme 42).^[116] The carbonyl group coordinates to the metal catalyst enabling different site-selective determining C-H bond activations in each case (five-membered ruthenacycle vs six-membered rhodacycle, *vide supra*). NCTS is an efficient partner for these transformations, although stoichiometric amounts of PhNHTs are formed as side-products at the end of the reaction.



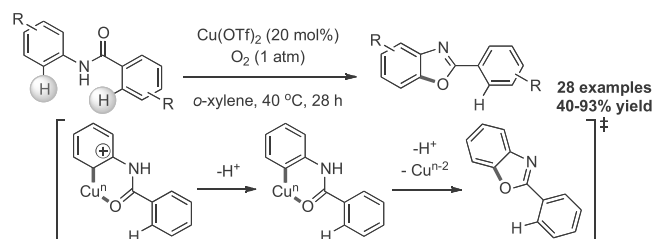
Scheme 41. Ruthenium-catalyzed C-H bond *ortho*-cyanation with benzamide site-selectivity.



Scheme 42. Rhodium-catalyzed C-H bond *ortho*-cyanation with anilide site-selectivity.

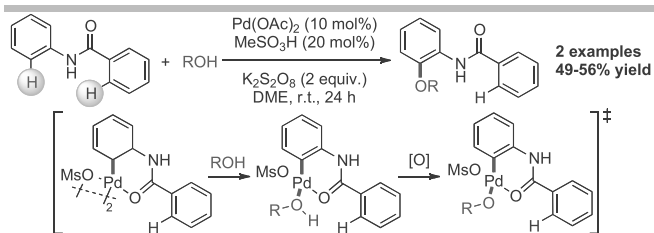
3. C-O Bond Forming Reactions.

In 2008, Nagasawa and co-workers reported the first examples of a site-selective C-H bond functionalization of benzanilides leading to products resulting from a C-O bond forming process.^[117] Indeed, they showed that a variety of benzanilide derivatives reacted in an intramolecular fashion giving rise to 2-arylbenzoxazoles under copper catalysis and an atmosphere of oxygen, the latter being an oxidant to re-generate the catalytically active copper(II) species (Scheme 43). In a subsequent study they showed that oxygen could be switched by air at the expenses of replacing *o*-xylene by *o*-dichlorobenzene as the solvent.^[118] The mechanism of the reaction was postulated to involve six-membered copper species *via* electrophilic aromatic substitution followed by a C-O coupling event. This represents the single example for intramolecular site-selective C-O bond formation *via* C-H bond functionalization using benzanilide derivatives.



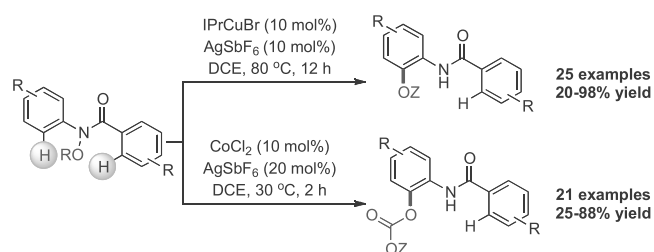
Scheme 43. Copper-catalyzed intramolecular oxidative C-O coupling of benzanilide derivatives with anilide site-selectivity highlighting the O-coordination to copper.

On the other hand, intermolecular reactions have been more explored. In fact, a palladium-catalyzed C-H bond *ortho*-alkoxylation with anilide site-selectivity was reported in 2012 (Scheme 44).^[119] Interestingly, the C-O bond formation involved the use of readily affordable alcohols as coupling partners. Modest yields of the alkoxyated derivatives were obtained and the reaction was presumed to proceed involving a Pd(II)/Pd(IV) catalytic cycle.



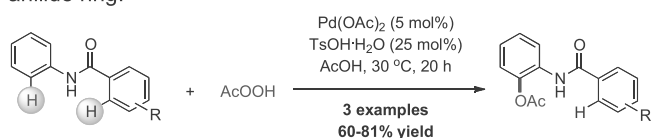
Scheme 44. Palladium-catalyzed C-H bond *ortho*-alkoxylation with anilide site-selectivity highlighting the O-coordination to palladium. R = Me, ⁱPr.

Nakamura and co-workers described an original [1,3]-alkoxy rearrangement of *N*-alkoxybenzanilide derivatives.^[120] The reaction, which was catalyzed by a carbene-copper(I) complex, led to a formal C-H bond *ortho*-alkoxylation with exclusive anilide site-selectivity (Scheme 45). The same group reported the [1,3]-alkoxycarbonyloxy rearrangement catalyzed by a cobalt salt (Scheme 45).^[121] The metal catalyst (either copper or cobalt) serves likely as a Lewis acid.

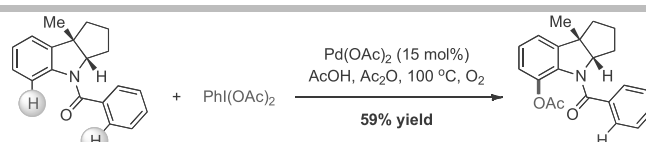


Scheme 45. Copper- and cobalt-catalyzed C-H bond *ortho*-alkoxylation and *ortho*-alkoxycarbonyloxylation with anilide site-selectivity. R = Z or C(O)OZ where Z = alkyl or benzyl. IPr = 1,3-(2,6-diisopropylphenyl)imidazol-2-ylidene.

Recently, Hii and co-workers reported a palladium-catalyzed C-H bond *ortho*-acetoxylation using peracetic acid (AcOOH) as coupling partner, which was conceived as an atom-economical reagent (Scheme 46).^[122] For benzanilide derivatives, exclusive anilide site-selectivity was reached under very mild reaction conditions. Interestingly, only one equivalent of water was formed as side-product which is important from a sustainable point of view. Considering acetoxylation reactions, Movassaghi and co-workers reported one example of a biologically-relevant *N*-acylindoline using (diacetoxyiodo)benzene as the acetate source (Scheme 47).^[123] They observed the exclusive formation of the acetoxyated product resulting from the *ortho*-C-H functionalization in the anilide ring.

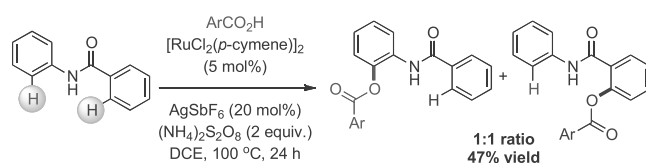


Scheme 46. Palladium-catalyzed C-H bond *ortho*-acetoxylation with anilide site-selectivity. R = H, 4-Me, 3-Br.

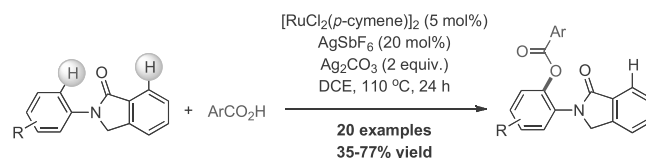


Scheme 47. Palladium-catalyzed C-H bond *ortho*-acetoxylation with a biologically-relevant *N*-acylindoline derivative.

Regarding C-H bond *ortho*-benzoylations of benzanilide derivatives, Jeganmohan and co-workers showed that the reaction was not site-selective as the two possible products formed in a 1:1 ratio under a ruthenium-based catalytic system (Scheme 48).^[124] This finding highlights the challenges associated to site-selective C-O bond forming reactions involving benzanilides. This issue is somehow circumvented using *N*-arylisoindolinones, which contain a benzanilide motif.^[125] Similar reactions conditions as the ones developed by Jeganmohan led to exclusive C-H bond *ortho*-benzoylations with anilide site-selectivity (Scheme 49). Although a good functional group tolerance was demonstrated, the conditions were not compatible for acetoxylation or benzyloxylation and no reactivity was observed with *N*-arylphthalimides. Six-membered ruthenacycles similar to those from Scheme 11 were claimed to occur for the C-H bond activation step.



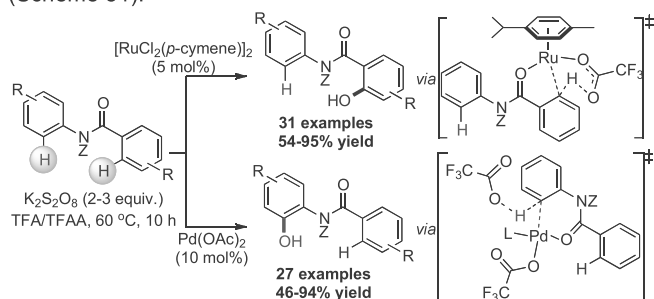
Scheme 48. Ruthenium-catalyzed C-H bond *ortho*-benzoylation of benzanilide. Ar = 4-NO₂-C₆H₄.



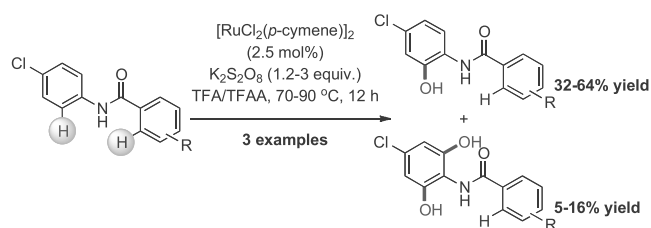
Scheme 49. Ruthenium-catalyzed C-H bond *ortho*-benzoylation with anilide site-selectivity.

A last type of C-O bond forming reaction tackled with benzanilide derivatives is the very relevant C-H bond hydroxylation. Particularly, Rao and co-workers reported a catalyst-controlled regio-divergent strategy to obtain exclusively the product resulting from a given site-selectivity for *N*-protected benzanilides.^[126] Typically, *para*-cymene-coordinated ruthenium catalysts enabled the C-H bond *ortho*-hydroxylation in the benzamide ring, whereas palladium catalysts enabled the C-H bond hydroxylation in the anilide ring (Scheme 50). Such findings were rationalized by the different coordination geometries adopted by each metal catalyst in the C-H bond activation step according to DFT calculations. The ruthenium catalyst seems to prefer a piano stool geometry involving a five-membered ring while the palladium catalyst displays a square planar geometry involving a six-membered ring (Scheme 50). The opposite site-selective determining intermediates are not favorable due to the steric shielding between the substrate and the metal catalyst. The same group also reported the C-H bond

ortho-hydroxylation of *N*-H benzanilides.^[127] The catalysis enabled anilide site-selectivity with ruthenium catalysts and a mixtures of mono- and di-hydroxylated products formed depending on the substituents from the benzamide fragment (Scheme 51).

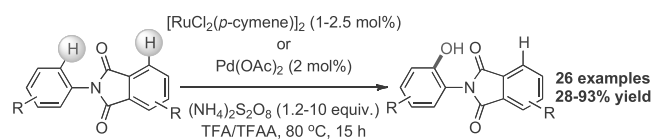


Scheme 50. Regio-divergent metal-catalyzed C-H bond *ortho*-hydroxylation of *N*-protected benzanilide derivatives highlighting the *O*-coordination to ruthenium or palladium. Z = Me, Et, Bn.

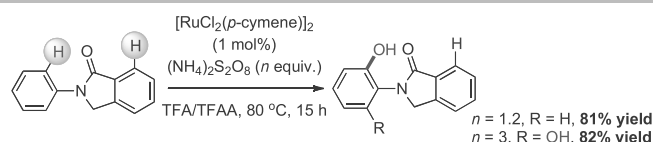


Scheme 51. Ruthenium-catalyzed C-H bond *ortho*-hydroxylation of *N*-H benzanilide derivatives.

Alternatively, *N*-arylphthalimide derivatives were found to be suitable partners to provide exclusively mono-hydroxylated products with anilide site-selectivity regardless of the equivalents of oxidant being used (Scheme 52).^[128] The reactions, which were catalyzed by ruthenium or palladium catalysts, were tolerant to a broad scope of functional groups. Interestingly, no di-hydroxylated products were formed. On the other hand, *N*-arylisoindolinones, which are less sterically-demanding substrates, did give rise to di-hydroxylated products when using up to 3 equivalents of oxidant (Scheme 53). In these examples, the site-selectivity of the reaction is controlled by the pre-disposed carbonyl group that enforces formation of six-membered metallacycle intermediates at the anilide ring rather than five-membered ones at the benzamide ring. (*vide supra*, Scheme 11).



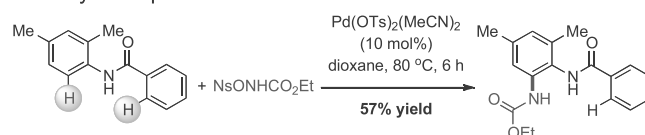
Scheme 52. C-H bond *ortho*-mono-hydroxylation of *N*-arylphthalimide derivatives with anilide site-selectivity with ruthenium or palladium catalysts.



Scheme 53. Oxidant-controlled, ruthenium-catalyzed C-H bond *ortho*-hydroxylation of *N*-arylisoindolinone with anilide site-selectivity.

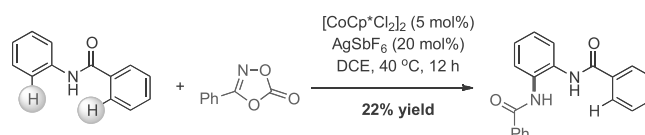
4. C-N Bond Forming Reactions.

C-N bond formation have also been accomplished with benzanilide derivatives. In all cases to date, only anilide site-selectivity has been reached with different transition metal catalysts *via* C-H bond functionalization strategies. In 2010, Yu and co-workers described the first successful example of a C-N bond forming reaction.^[129] They showed that a palladium(II) pre-catalyst enabled the C-H bond *ortho*-amidation using ethyl *N*-nosyloxycarbamate (NsONHCO₂Et) as a source of “NHCO₂Et” moieties (Scheme 54). The C-H bond activated species are postulated to be similar to those reported in Scheme 31, namely, dimeric six-membered palladacycles *via* coordination of the carbonyl lone pair to the metal center.

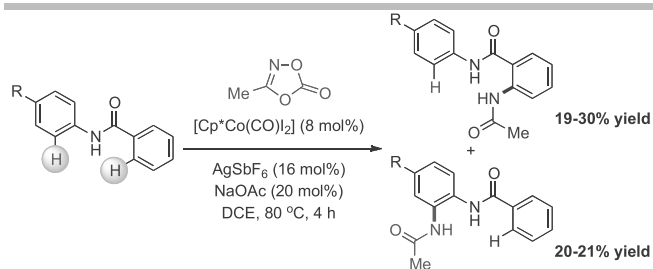


Scheme 54. Palladium-catalyzed C-H bond *ortho*-amidation with anilide site-selectivity.

An alternative type of reagents suitable for C-H bond amidation are 3-substituted 1,4,2-dioxazol-5-ones. Chang and co-workers demonstrated that C-H bond *ortho*-amidation with anilide site-selectivity were feasible employing cobalt catalysts, although with a low yield (Scheme 55).^[130] Only traces of product were observed by replacing the cobalt complex [CoCp*Cl₂]₂ for [RuCl₂(*p*-cymene)]₂ as the pre-catalyst. Analogously, Whiteoak and co-workers showed that the presence of catalytic amounts of NaOAc as a base have little impact in the site-selectivity of this transformation (Scheme 56).^[131] Indeed, they showed that both possible products form in comparable yields and side-products displaying C-H bond over-amidation at both aromatic sites were also detected in some cases. DFT calculations suggested that the catalytically active species involved half-sandwich cobaltocene-coordinated intermediates. Overall, these observations indicate the difficulty to access this type of transformation in a site-selective and efficient manner.

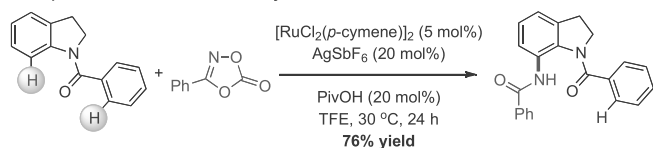


Scheme 55. C-H bond *ortho*-amidation with cobalt catalysts with anilide site-selectivity.



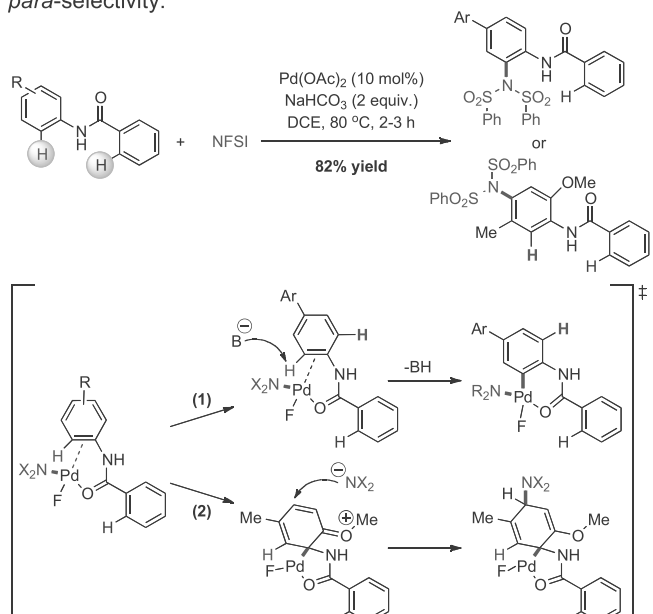
Scheme 56. Cobalt-catalyzed C-H bond *ortho*-amidation in the presence of a base. R = H, Cl, Me, OMe.

The same type of amidating reagents were used by Prabhu and co-workers under ruthenium catalysis to functionalize indolines. Due to the restricted flexibility of the substrate, site-selective C-H bond *ortho*-amidation in the anilide ring was achieved in a good yield (Scheme 57).^[132] The key ruthenacycle species participating in the C-H bond activation step is equivalent to the rhodacycle shown in Scheme 40.



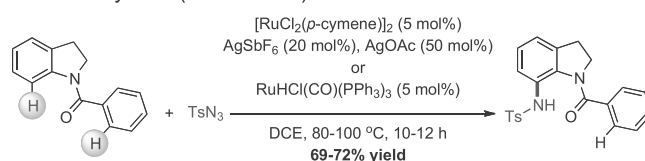
Scheme 57. Ruthenium-catalyzed C-H bond *ortho*-amidation with anilide site-selectivity.

In 2010, Zhang and co-workers reported a unique example of a C-H bond *ortho*-sulfonimidation of benzanilides under palladium catalysis using *N*-fluorobenzenesulfonimide (NFSI) as the nitrogen source (Scheme 58).^[133] Interestingly, C-H bond *para*-sulfonimidation was observed for a methoxy-substituted benzanilide derivative. The catalysis exclusively provided the products resulting from anilide site-selectivity. The authors suggested a common palladium species for the C-H bond activation step. Then, depending on the substituents on the anilide ring two pathways were postulated to access each regioisomer: (1) reductive elimination *via* a Pd(II)/Pd(0) cycle for *ortho*-selectivity or (2) dearomatization of a spiro-palladacycle that undergoes sulfonimidation and hydrogen elimination for *para*-selectivity.

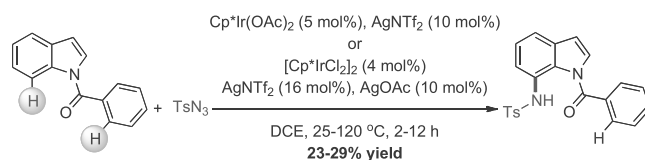


Scheme 58. Palladium-catalyzed C-H bond sulfonimidation with anilide site-selectivity highlighting the *O*-coordination to palladium. Ar = *p*-tolyl. X = SO₂Ph. B = base (OAc⁻ or HCO₃⁻).

Ruthenium(II)-based catalysts appeared to be suitable for C-H bond *ortho*-sulfonamidation with anilide site-selectivity (Scheme 59). Two complementary methodologies were provided for indolines. In one case [RuCl₂(*p*-cymene)]₂ is used as the pre-catalyst in the presence of silver salts,^[134] and in the other case, RuHCl(CO)(PPh₃)₃ is enough to reach comparable efficiencies.^[135] These methodologies were not appropriate for indole derivatives. Alternatively, iridium catalysts enabled C-H bond *ortho*-sulfonamidation with anilide site-selectivity although in modest yields (Scheme 60).^[136-137]

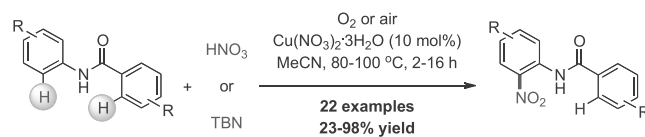


Scheme 59. Ruthenium-catalyzed C-H bond *ortho*-sulfonamidation with anilide site-selectivity for *N*-benzoylindoline.



Scheme 60. Iridium-catalyzed C-H bond *ortho*-sulfonamidation with anilide site-selectivity for *N*-benzoylindole.

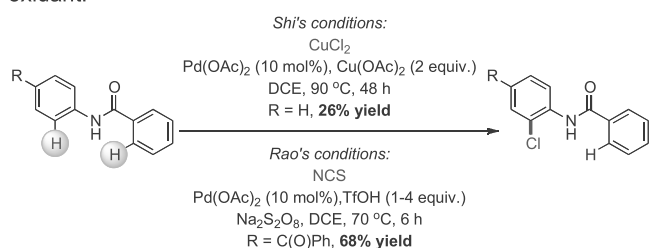
Several examples of nitration reactions with benzanilides have been disclosed. In particular, copper salts operating under a radical mechanism are convenient. Carretero and co-workers showed that Cu(NO₃)₂ behaves as an excellent pre-catalyst for the C-H bond *ortho*-nitration of benzanilides with anilide site-selectivity (Scheme 61).^[138] Different mono-substituted derivatives were obtained in good yields and di-nitration was demonstrated as well. For benzanilides substituted in *ortho* position at the anilide ring, mixtures of *ortho*- and *para*-nitration were observed. Interestingly, it was possible to replace the hazardous nitric acid reagent for a more benign *tert*-butyl nitrite (TBN) obtaining similar yields of *ortho*-nitrated products with the same site-selectivity (Scheme 61).^[139] Alternatively, a copper(I)-based catalytic system enabling in-situ azidation-oxidation with azidotrimethylsilane and *tert*-butyl hydroperoxide enabled similar reactivity as the copper(II) catalysts from Scheme 61.^[140] One example under silver catalysis has been reported too.^[141]



Scheme 61. Copper-catalyzed C-H bond *ortho*-nitration with anilide site-selectivity.

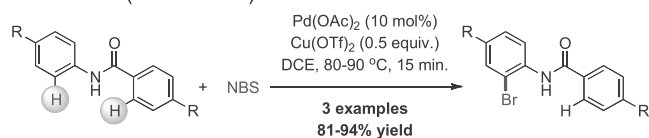
5. C-H Bond Halogenation Reactions

Few examples have been reported for the site-selective C-H bond halogenation of benzanilide derivatives and all of them relying on palladium catalysis. In 2006, Shi and co-workers reported a seminal contribution showing that palladium(II) pre-catalysts afforded the product resulting from the C-H bond *ortho*-halogenation in the anilide ring although in a low yield (Scheme 62).^[142] The reaction was carried out in the presence of over-stoichiometric amounts of Cu(OAc)₂ and CuCl₂, the former being the oxidant and the latter being the source of chlorides. The key C-H bond activated species seems to involve dimeric cyclopalladated complexes structurally similar to the ones in Scheme 28. In 2013, Rao and co-workers reported a copper-free protocol for the C-H bond *ortho*-chlorination with anilide site-selectivity under palladium catalysis (Scheme 62).^[143] This time, the reaction required the use of stoichiometric amounts of *N*-chlorosuccinimide (NCS) with TfOH and Na₂S₂O₈ as the co-oxidant.



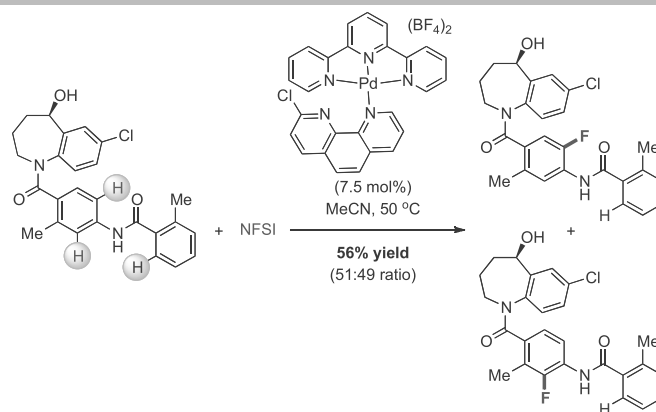
Scheme 62. Palladium-catalyzed C-H bond *ortho*-chlorination with anilide site-selectivity.

Palladium catalysts were efficient for the C-H bond *ortho*-bromination with anilide site-selectivity as it was shown by Kapur and co-workers.^[144] *N*-bromosuccinimide (NBS) was employed as the source of bromide in the presence of Cu(OTf)₂ and they noted that the reactions were fast, being accomplished in only 15 minutes (Scheme 63).



Scheme 63. Palladium-catalyzed C-H bond *ortho*-bromination with anilide site-selectivity. R = H or Me.

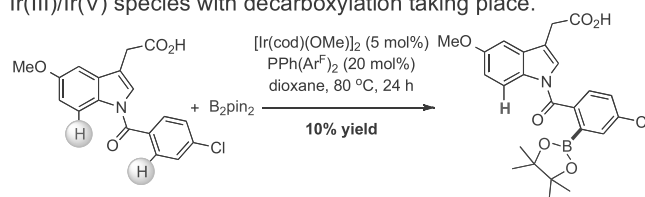
In 2018, Ritter and co-workers developed a rationally-designed palladium(II)-based catalytic system that enabled electrophilic aromatic C-H bond *ortho*-fluorinations (Scheme 64).^[145] They reported one example for a biologically-relevant benzanilide derivative, namely, tolvaptan. This compound is particularly challenging as it contains two benzanilide fragments. The catalysis was highly site-selective as only the *ortho*-C-H bonds from the anilide ring in the central core reacted leading to a statistical mixture of regioisomers. The reaction was performed with *N*-fluorobenzenesulfonimide (NFSI) as the source of fluorides under very mild conditions.



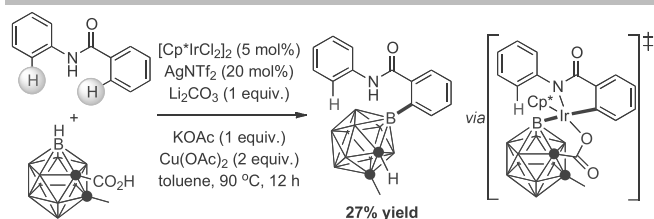
Scheme 64. Palladium-catalyzed C-H bond *ortho*-fluorination with anilide site-selectivity for tolvaptan.

6. C-H Bond Borylation Reactions

Borylation reactions *via* transition metal catalyzed C-H bond functionalization strategies is rather appealing as the boron-containing motifs are easily transformable into more elaborated carbon-carbon or carbon-heteroatoms bonds.^[146] Regarding benzanilide derivatives only a couple of examples have been reported. The first one deals with an iridium-catalyzed C-H bond borylation using the biologically relevant indomethacin.^[147] By means of an original analytical approach employing LC-HR-MS/MS coupled with reaction-driven data processing, it was reported a low yield for the C-H bond *ortho*-borylation with benzamide site-selectivity (Scheme 65). In a second example, a carboxylic acid-containing carborane (1-COOH-2-CH₃-o-C₂B₁₀H₁₀) was found to react with benzanilide affording a B-C cross-coupled product with benzamide site-selectivity (Scheme 66).^[148] In-depth mechanistic studies highlight the role of the carboxylate fragment to assist the B-H activation step and further C-H bond activation *via* a five-membered iridacycle with an overall mechanism involving Ir(III)/Ir(V) species with decarboxylation taking place.



Scheme 65. Iridium-catalyzed C-H bond *ortho*-borylation with benzamide site-selectivity for indomethacin. pin = pinacolato. Ar^F = 3,5-bis(trifluoromethyl)phenyl.



Scheme 66. Iridium-catalyzed C-H bond *ortho*-borylation with benzamide site-selectivity using a carborane coupling partner highlighting the *N*-coordination to iridium. • = carbon atoms. vertex = borane atoms.

7. An attempt of “site-selectivity rules” for *ortho*-C-H bond functionalization of benzanilide derivatives.

As it is clearly seen above in detail, the mechanisms governing each site-selectivity are not always trivial and may vary depending on (1) the presence of additives/ligands, (2) pH conditions and/or (3) coupling partners. In view to provide a sort of general overview, Tables 1 and 2 summarize the main findings that have been accomplished for site-selective *ortho*-C-H bond functionalizations of benzanilides derivatives, which are the most studied so far. It is expected that these guidelines will serve to select reaction conditions to those that are entering in the field of C-H bond functionalization using metal catalysts or to those who are searching for a specific site-selectivity for synthetic purposes. In addition, the remaining challenges are also highlighted, indirectly suggesting future research directions.

Table 1. Summary of the site-selectivity observed for transition metal-catalyzed C-H bond functionalizations with benzanilides derivatives.^[a-c]

C-C Bond Formation	Anilide site-selectivity	Benzamide site-selectivity
Arylation with Ar-X	Pd(OAc) ₂ /PCy ₃ (intramolecular)	Pd(OAc) ₂ /base/oxidant
Arylation with Ar-[Si]	Pd(OAc) ₂ /base/oxidant	elusive
Arylation with (Ar-CO) ₂	Pd(OAc) ₂ /acid	elusive
Arylation with Ar-B(OH) ₂	[RuCl ₂ (<i>p</i> -cymene)] ₂ /oxidant	elusive
Alkenylation with alkenes	Pd(OAc) ₂ /acid/oxidant or [RuCl ₂ (<i>p</i> -cymene)] ₂ /oxidant (cyclic benzanilides)	[RuH(C ₆ H ₆)(PCy ₃)(CO)][BF ₄] or [RuCl ₂ (<i>p</i> -cymene)] ₂ /oxidant or [RhCp*Cl ₂] ₂ /base
Alkenylation with alkynes	Pd(OAc) ₂ /oxidant or [Cp*RhCl ₂] ₂ or [RhCp*Cl ₂] ₂ /acid/oxidant	Pd(OAc) ₂ /base or [RhCp*Cl ₂] ₂ /oxidant or [RuCl ₂ (<i>p</i> -cymene)] ₂ /oxidant or acid or Ni(OTf) ₂ /PPh ₃ /base or [CoCp*(CO) ₂] ₂ /acid or oxidant
Alkenylation with carbenes	[IrCp*Cl ₂] ₂ /acid	elusive
Alkylation with alkenes	[RhCp*Cl ₂] ₂ /oxidant or [RuCl ₂ (<i>p</i> -cymene)] ₂ /oxidant/acid (cyclic benzanilides)	[RhCp*Cl ₂] ₂ /base or [RuCl ₂ (<i>p</i> -cymene)] ₂ /oxidant/acid or [CoCp*(CO) ₂] ₂ /base or [Ir(cod)] ₂ (OTf)/SEGP HOS or [Ir(cod)] ₂ (OTf)/BINAP (intramolecular)
Alkylation with R(Mg)X	elusive	Co(acac) ₂ /base or MnCl ₂
Alkylation with β-keto esters	Pd(OAc) ₂ /oxidant/acid	elusive
Alkylation with [R-S(Ar) ₂] [†]	Pd(OAc) ₂ /oxidant/acid	elusive
Acylation with CO _x	Pd(OAc) ₂ /oxidant/acid (with CO)	Pd(TFA) ₂ /base (with CO ₂)
Acylation with ArCHO	Pd(OAc) ₂ /acid	elusive
Acylation with Ar-CH ₂ OH or Ar-Me	Pd(TFA) ₂ /TBHP/acid	elusive
Acylation with RCOCO ₂ H	Pd(OAc) ₂ /oxidant or Pd(TFA) ₂ /oxidant	elusive
Acylation with RNCO	[RhCp*Cl ₂] ₂	elusive
Alkynylation	[RhCp*Cl ₂] ₂ (cyclic benzanilides)	RhCp*(MeCN) ₃ (SbF ₆) ₂ or [IrCp*Cl ₂] ₂ /base
Cyanation	[RhCp*Cl ₂] ₂ (cyclic benzanilides)	[RuCl ₂ (<i>p</i> -cymene)] ₂ /base
Fluoroalkylation	Pd(OAc) ₂ /oxidant/acid or Pd(PPh ₃) ₄ /Xantphos/base	PdCl ₂ (PPh ₃) ₂ /DPEphos/base

^[a]The reactions considered herein are intermolecular unless otherwise stated.

^[b]The first chemical from the reaction conditions corresponds to the transition metal pre-catalyst.

^[c]The reagents displayed in italics indicate that they are optional.

Table 2. Summary of the site-selectivity observed for transition metal-catalyzed C-H bond functionalizations with benzanilides derivatives.^[a-c]

C-X Bond Formation	Anilide site-selectivity	Benzamide site-selectivity
Hydroxylation	Pd(OAc) ₂ /oxidant/acid or [RuCl ₂ (<i>p</i> -cymene)] ₂ /oxidant/acid (for N-H benzanilides and cyclic benzanilides)	[RuCl ₂ (<i>p</i> -cymene)] ₂ /oxidant/acid
Alkoxylation with ROH	Pd(OAc) ₂ /oxidant/acid	elusive
Acetoxylation	Pd(OAc) ₂ /acid with AcOOH or Pd(OAc) ₂ /acid with PhI(OAc) ₂	elusive
Benzyloxylation with ArCO ₂ H	[RuCl ₂ (<i>p</i> -cymene)] ₂ /base (cyclic benzanilides)	elusive
Intramolecular alkoxylation	Cu(OTf) ₂ /O ₂ or IprCuBr or CoCl ₂	elusive
Amidation with NsONHCO ₂ Et	Pd(OTs) ₂ (MeCN) ₂	elusive
Amidation with dioxazolone	[RuCl ₂ (<i>p</i> -cymene)] ₂ /acid (cyclic benzanilides) or [CoCp*Cl ₂] ₂ (poor yield)	[CoCp*(CO)] ₂ (poor yield)
Amidation with NFSI	Pd(OAc) ₂ /base	elusive
Amidation with TsN ₃ (cyclic benzanilides)	[RuCl ₂ (<i>p</i> -cymene)] ₂ /base or [RuHCl(CO)(PPh ₃) ₃] or IrCp*(OAc) ₂ (poor yield)	elusive
Nitration with HNO ₃ or TBN or TMSN ₃ /TBHP	Cu(NO ₃) ₂ or CuI	elusive
Chlorination with NCS	Pd(OAc) ₂ /oxidant/acid	elusive
Bromination with NBS	Pd(OAc) ₂ /oxidant	elusive
Fluorination with NFSI	Pd(L1)(L2)(BF ₄) ₂ ^[d]	elusive
Borylation	[Ir(cod)(OMe)] ₂ /PPh(ArF) ₂ with B ₂ pin ₂ (poor yield)	[IrCp*Cl ₂] ₂ /oxidant/base with R ₂ BH (poor yield)

^[a]The reactions considered herein are intermolecular unless otherwise stated.

^[b]The first chemical from the reaction conditions corresponds to the transition metal pre-catalyst.

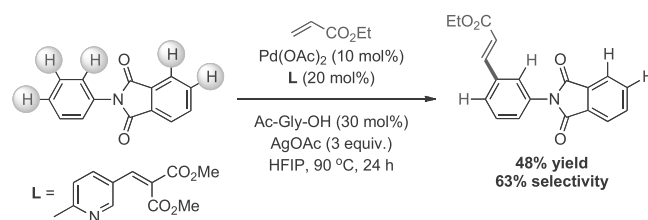
^[c]The reagents displayed in italics indicate that they are optional.

^[d]L1 = 2,2':6',2''-terpyridine, and L2 = 2-chloro-1,10-phenanthroline.

8. Beyond *ortho*-selectivity

The examples below undoubtedly testify the preference for *ortho*-selective transformations due to the coordinating ability of the amide bond as manifold directing group in C-H bond functionalizations of benzanilides. Interestingly, some studies have investigated C-H bond *meta*-functionalizations with additional control of the site-selectivity for benzanilides. van Gemmeren and co-workers described a palladium-catalyzed olefination protocol enabling high levels of *meta*-selectivity in aromatic C-H bonds.^[149] When applied to *N*-arylphthalimide, a modest yield was obtained but with a high preference for *meta*-selectivity in the anilide ring (Scheme 67). Recently, a palladium-

catalyzed methodology inspired by contributions from Yu^[150] and Catellani,^[151] respectively, showed the incorporation of a norbornene unit to the anilide ring from benzanilide with a simultaneous *meta*- and *para*-regioselectivity (Scheme 68).^[152]

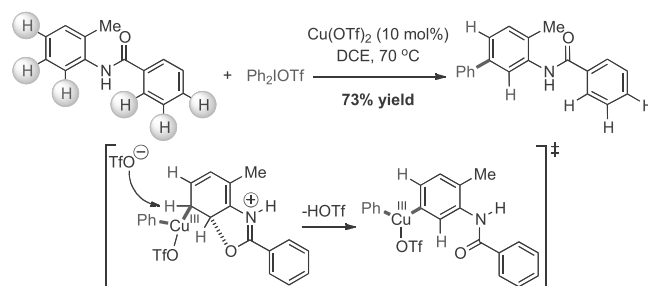


Scheme 67. Palladium-catalyzed C-H bond *meta*-olefination with anilide site-selectivity of *N*-arylphthalimide. HFIP = hexafluoroisopropanol.



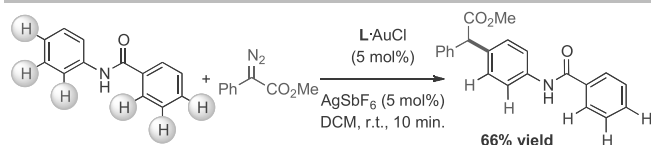
Scheme 68. Palladium-catalyzed norbornene incorporation to benzanilide with benzamide site-selectivity. L = 4-phenylpyridine.

Recently, Gaunt and co-workers reported a C-H bond *meta*-arylation using first-row transition metal catalysis.^[153] It was disclosed that a copper catalyst enabled such transformation using Ph₂IOTf as the arylating reagent. For benzanilide, the reaction delivered the compound resulting from functionalization in the anilide ring (Scheme 69). The key mechanistic feature was to reach such site- and regio-selectivity by means of an unprecedented dearomatization oxycupration step.

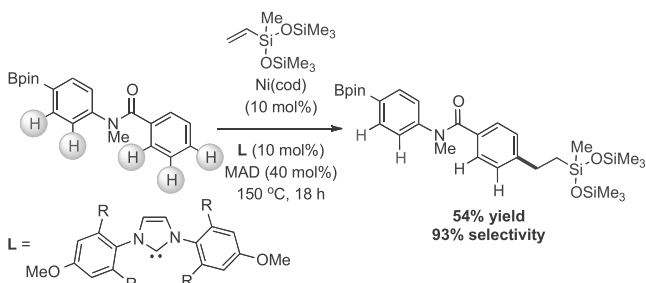


Scheme 69. Copper-catalyzed C-H bond *meta*-arylation with anilide site-selectivity.

In 2014, a gold-catalyzed C-H bond *para*-functionalization with α -aryl- α -diazoacetates was reported.^[154] When applied to a benzanilide derivative, this *para*-functionalization occurred with exclusive anilide site-selectivity (Scheme 70). The role of the ligand was essential for the success of the reaction and a phosphite ligand was preferred. Two years later, Nakao and co-workers developed an appealing strategy to furnish C-H bond *para*-alkylated derivatives with benzamide site-selectivity.^[155] More precisely, an aluminum complex (i.e. MAD) was engaged in transient coordination to the ketone, while a nickel-carbene catalyst participated in the C-H bond *para*-functionalization (Scheme 71).



Scheme 70. Gold-catalyzed C-H bond *para*-alkylation with anilide site-selectivity. L = (2,4-^tBu₂C₆H₃O)₃P.



Scheme 71. C-H bond *para*-alkylation with benzamide site-selectivity via cooperative nickel/aluminum catalysis. MAD = methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide). R = CH(3,5-(CH₃)₂C₆H₃)₂.

9. Conclusion

In the last two decades a broad knowledge of the reactivity of benzanilide derivatives in C-H bond *ortho*-functionalization with transition metal catalysts have been accumulated. The usefulness and versatility of these type of amides as powerful directing groups has enabled challenging site-selective *ortho*-C-H bond functionalizations. At this stage, the control of the site-selectivity for carbon-carbon bond formation is rather well established with different methodologies. The creativity to introduce original reagents as new carbon-sources appeared to be useful to circumvent some reactivity issues. This is true also for carbon-heteroatom bond forming reactions, although they remain under-studied with respect to the carbon-carbon ones. A key observation is that the reactivity of benzanilides is not only controlled by the stereoelectronic effects at each aryl group, but most importantly, by the transition metal catalyst generated under different reaction conditions which translates into a different mechanistic pathways. Most of the successful catalytic systems herein reviewed are based on expensive and scarce metal complexes (Pd, Rh, Ru, Ir, Au, etc.), although more benign ones such as Co, Cu or Fe have started to be considered for this type of site-selective transformations.^[156] In the future it would be desirable, to apply green chemistry rules to these processes in view to reduce the waste of chemicals and the energy input of the reactions regarding the temperature and the time.^[157] Besides, some fundamental niches still do exist. For example, the reversal of the site-selectivity observed for some type of benzanilides. In particular, the ones involving cyclic amides and imides such as *N*-benzoyl-indoles and -indolines, and *N*-aryl-isoindolinones and -phthalimides, in which no examples for benzamide site-selectivity are known to date. Additionally, the site-selectivity for *meta*- and *para*-C-H bond functionalization of benzanilides is in its infancy compared to substrates based on strong directing groups such as the nitrogen-containing ones (i.e. pyridine, imine, etc.).^[158] New methodologies based on catalytic systems displaying original action modes and rationally-designed reagents will probably constitute two complementary strategies to overcome the

remaining challenges in this field. It will be interesting as well to see real applications of the current protocols in the late-stage functionalization of fine chemicals as well as in material sciences.^[159]

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Keywords: benzamide • anilide • C-H functionalization • transition metals • homogeneous catalysis

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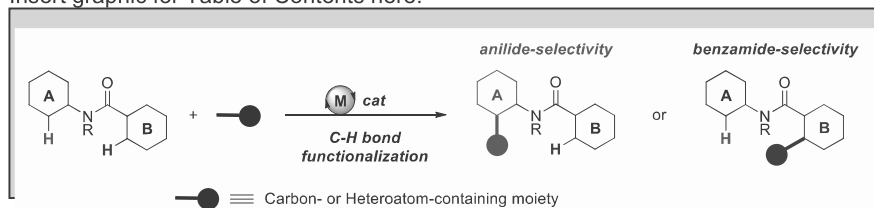
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Full control of the site-selectivity in C-H bond functionalizations is as desirable as challenging in transition metal catalysis. This is especially true for benzanilide derivatives, which are one of the most important building blocks in organic synthesis. The developments of these methodologies are discussed emphasizing the action mode that the transition metal-based catalysts display in order to reach a given site-selectivity.

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