Comparative analysis of palladium, nickel and copper phosphane/carbene catalysts in Suzuki-Miyaura couplings: Mechanistic insights and reactivity trends

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Abstract

Suzuki-Miyaura coupling is a useful synthetic method of the formation of new carbon-carbon bonds between an organic halide and a boronic acid (or boronate ester), generally catalyzed by palladium compounds in the presence of an external base. In the search of more sustainable and green chemistry processes, precious metals such as palladium are currently being replaced by base metal analogues, which produce more affordable and accessible catalytic platforms. In this work, the catalytic cycle of the Suzuki-Miyaura coupling reaction between phenyl bromide and phenylboronate has been studied by computational means for different combinations of metal/ligand systems. Three transition metals: palladium, nickel, and copper, and four monodentate ligands, including two phosphanes (PMe_3 and $P(CF_3)_3$) and two N-heterocyclic carbenes (1,3-bis(methyl)imidazol-2-ylidene and 1,3-bis(trifluoromethyl)limidazol-2-ylidene), have been used to construct and explore the reaction for monoligated catalytic species. Overall, the palladium systems display the lowest activation barriers for the Suzuki-Miyaura reaction, with nickel producing the second-best catalysts. On the other hand, copper seems to produce slightly worse systems, with reaction barriers over 25 kcal mol^{-1} for all the ligands.

Keywords: Suzuki-Miyaura, cross-coupling, palladium catalyst, nickel catalyst, copper catalyst, phosphane ligands, NHC ligands.

Classical cross-coupling reactions

Cross-coupling reactions represent a fundamental class of chemical transformations in organic synthesis that involve the formation of a new bond between two different organic moieties, typically in the presence of a transition metal catalyst. In these reactions, two distinct substrates, often referred to as coupling partners, undergo a selective coupling process to generate a single product that contains the newly formed bond.[1-2] The significance of cross-coupling reactions in organic synthesis lies in their versatility, efficiency, and ability to construct complex molecular architectures with high levels of control and selectivity. Some of the most important features of cross-coupling reactions are:

1. **Wide variety of Carbon-Carbon and Carbon-Heteroatom bonds can be formed**: Cross-coupling reactions enable the selective formation of carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds, including C-C, C-N, C-O, C-S, and C-X (X = halogen) bonds, through different approaches combining a plethora of transition

metal catalysts, ligands, and organic substrates. This versatility allows assembling complex molecular scaffolds from readily available starting materials, facilitating the synthesis of natural products, pharmaceuticals, agrochemicals, and materials with tailored properties.

2. **Functional group tolerance and modularity**: Cross-coupling reactions are highly modular and compatible with a wide range of functional groups, allowing for the incorporation of diverse structural motifs into target molecules. This tolerance towards functional groups enables chemists to perform selective transformations in the presence of sensitive functionalities, expanding the synthetic toolbox for complex molecule synthesis.
3. **Stereochemical control and regioselectivity**: Many cross-coupling reactions exhibit excellent stereochemical control and regioselectivity, enabling the precise construction of chiral centers and the selective formation of bonds at specific positions within a molecule. This level of control is essential for the synthesis of enantiomerically pure compounds and complex molecular architectures with defined stereochemical arrangements.
4. **Catalytic efficiency and mild reaction conditions**: Transition metal catalysts employed in cross-coupling reactions facilitate the formation of new bonds under mild reaction conditions, typically at ambient temperature and atmospheric pressure. This catalytic efficiency minimizes waste generation, reduces energy consumption, and enhances the sustainability of synthetic processes, aligning with the principles of green chemistry.
5. **Impact on materials science and drug discovery**: Cross-coupling reactions have revolutionized the fields of drug discovery and materials science by providing efficient methods for the synthesis of pharmaceutical intermediates, bioactive compounds, functional materials, and molecular probes. The rapid development of new catalytic systems and reaction methodologies has expanded the synthetic capabilities of chemists, accelerating the pace of innovation in these interdisciplinary areas.

Overall, cross-coupling reactions represent a keystone of modern synthetic chemistry, offering powerful tools for the construction of complex molecules and the exploration of chemical space. Their significance in organic synthesis is underscored by their widespread use in academia, industry, and research laboratories, driving advancements in diverse fields of science and technology. The relevance of cross-coupling reactions was corroborated by the award of the the Nobel Prize in Chemistry 2010 to Profs. Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki “for palladium-catalyzed cross couplings in organic synthesis”.[3] The field of cross-coupling chemistry has undergone significant development since its inception, with several key historical milestones contributing to its evolution. These historical developments and milestones represent pivotal moments in the advancement of cross-coupling chemistry, demonstrating the transformative impact of transition metal-catalyzed reactions on organic synthesis. Subsequent research efforts have built upon these foundational discoveries, leading to the development of new catalyst systems, reaction methodologies, and applications in diverse areas of science and technology. Next, some of the most representative cross-coupling processes involving the formation of new carbon-carbon bonds, along with their most relevant key points, are briefly described:

The Heck coupling (1972):[4-5] The Heck reaction, reported by Prof. Richard F. Heck in 1972, in which the work of Prof. Tsutomu Mizoroki was acknowledged, is a palladium-catalyzed cross-coupling reaction that enables the selective formation of carbon-carbon bonds between aryl or vinyl halides and alkenes or alkynes (Scheme 1).

[Insert Figure 1 here]

Scheme 1. General Heck coupling reaction between an aryl halide and a terminal alkene.

Palladium catalysts play a central role in promoting the Heck reaction by activating both the aryl (or vinyl) halide and the alkene or alkyne substrates. The choice of palladium species and ligand can significantly influence the reaction rate, selectivity, and functional group tolerance. Common phosphane ligands used in Pd-catalyzed Heck reactions include triphenylphosphane (PPh_3) and its derivatives, such as phosphanooxazolines and diphenylphosphanobinapthyl ligands (BINAP).[6] An external base is needed to carry out this transformation; the most common candidates for this role tend to be triethylamine, potassium carbonate, and sodium acetate. This reaction typically exhibits high regioselectivity, with the C-C bond formation occurring predominantly at the less hindered position of the alkene or alkyne substrate. The Heck reaction is known for its broad functional group compatibility, tolerating a wide range of functional groups including ethers, esters, ketones, nitriles, and heterocycles. However, some functional groups, such as acidic protons or strong electron-withdrawing groups, may interfere with the reaction and require special considerations. This coupling has found extensive applications in organic synthesis for the construction of biaryl compounds, substituted alkenes, and complex molecular architectures. It is widely used in pharmaceuticals, agrochemicals, materials science, and fine chemical synthesis.

The Kumada reaction (1972):[7] Named after Prof. Makoto Kumada, this cross-coupling process is a powerful synthetic method that enables the formation of carbon-carbon bonds between organic halides and organomagnesium compounds (Grignard reagents) under the catalysis of a transition metal, typically palladium or nickel (Scheme 2).

[Insert Figure 2 here]

Scheme 2. General Pd-catalyzed Kumada coupling between an aryl halide and an arylmagnesium halide.

The Kumada coupling is compatible with a wide range of functional groups, including sensitive moieties such as esters, ketones, nitriles, and halides. Both organic halides and organomagnesium reagents can be readily prepared or commercially available, providing easy access to diverse coupling partners. Organic halides such as alkyl halides, aryl halides, vinyl halides, and heteroaryl halides can be used as electrophiles, while various Grignard reagents, including alkylmagnesium halides and arylmagnesium halides, serve as nucleophilic partners. This reaction typically employs palladium[8] or nickel[9] catalysts in the form of complexes with phosphane ligands. However, catalytic systems based on other transition metals, such as silver, copper and iron, have also been developed for this type of reactions.[10-12] The Kumada coupling has been widely

utilized in the synthesis of natural products, pharmaceuticals, agrochemicals, and functional materials. It enables the construction of diverse molecular architectures, including biaryl compounds, substituted alkenes, and complex polycyclic structures.

The Sonogashira coupling (1975):[13] The Sonogashira coupling, named after the chemist Prof. Kenkichi Sonogashira (although Profs. L. Cassar[14] Richard F. Heck[15] independently discovered it), is a widely used palladium-catalyzed cross-coupling process that enables the formation of C-C bonds between terminal alkynes and aryl or vinyl halides (typically bromide or iodide) under mild reaction conditions (Scheme 3).

[Insert Figure 3 here]

Scheme 3. General Sonogashira reaction between an aryl halide and an arylmagnesium halide.

This reaction is particularly valuable for the synthesis of conjugated diynes and substituted alkynes, which are important structural motifs in natural products, pharmaceuticals, and materials science.[16] Palladium catalysts, often in the form of palladium(II) complexes with phosphane ligands, play a central role in promoting the Sonogashira coupling reaction. Additionally, copper(I) salts or complexes serve as co-catalysts to accelerate the transmetalation step and enhance the efficiency of the reaction. The usage of an external base, key to activate the terminal alkyne, is required in this process; the usual species employed for this purpose are alkylamines (di- and triethylamine) potassium carbonate or cesium carbonate may be used as well. This reaction has broad substrate scope, accommodating various terminal alkynes and aryl or vinyl halides. Both electron-rich and electron-poor aryl halides can participate in the reaction, providing access to diverse substituted alkynes with different substitution patterns and functional groups. Over the years, various advancements and modifications of the Sonogashira coupling have been reported to improve reaction efficiency, selectivity, and sustainability. These include the development of new palladium catalysts, ligands, and reaction conditions, as well as the exploration of alternative coupling partners and reaction methodologies.[17-18]

The Negishi coupling (1977):[19] Prof. Ei-ichi Negishi developed the Negishi coupling, which involves the cross-coupling of organozinc reagents with organic halides or pseudohalides (such as bromides, chlorides, or triflates) in the presence of a palladium catalyst and a suitable ligand (Scheme 4).

[Insert Figure 4 here]

Scheme 4. General Negishi coupling between an aryl halide and an arylzinc halide.

The Negishi coupling provides a versatile method for the formation of C-C bonds, particularly in the context of challenging substrates and complex molecular architectures. Organozinc (including alkenyl, aryl, and alkyl groups) reagents, derived from the reaction of organohalides with zinc metal or zinc salts, serve as nucleophilic partners in the Negishi reaction. These reagents are typically prepared in situ and can be derived from

various organic halides, including aryl, vinyl, and alkyl derivatives.[20] As in other cross-coupling reactions, the preferred catalytic species for the Negishi coupling consist of different combinations of palladium(II) salts and phosphane ligands; alternatively, a nickel catalyst may be employed.[21] This catalytic process is characterized by a broad functional group compatibility, tolerating a wide range of functional groups, *i.e.* esters, ethers, nitriles, and heterocyclic fragments. The Negishi reaction has found a diverse range of applications in organic synthesis for preparing biaryl compounds, substituted alkenes, and other, more complex, molecular scaffolds.

The Stille coupling (1978):[22] Prof. John K. Stille pioneered this cross-coupling reaction, which involves the palladium-catalyzed cross-coupling of organostannanes with organic halides or pseudohalides (including bromides, iodides, triflates and sulfonates), in the late 1970s (Scheme 5).

[Insert Figure 5 here]

Scheme 5. General Stille coupling between an aryl halide and an organotributyltin compound.

The Stille coupling offers advantages such as high functional group tolerance and compatibility with a wide range of substrates. Organostannanes, which are organotin compounds, serve as nucleophilic partners in the Stille reaction. These compounds are typically prepared from the reaction of organohalides with tin-based reagents such as tributyltin hydride or tributyltin chloride.[23] Despite concerns about the toxicity of organostannane reagents, the Stille coupling has been extensively utilized in the synthesis of complex molecules and materials. The typical catalysts for this reaction are palladium(0) species bearing monodentate or bidentate phosphane ligands. As for its applications in organic synthesis, this reaction can be employed to prepare biaryl compounds, vinylarenes, and other structurally diverse organic molecules, and also for synthesizing polymeric structures[24] and natural products.[25]

The Suzuki-Miyaura coupling (1979):[26-27] The Suzuki-Miyaura reaction, proposed by Prof. Akira Suzuki and Prof. Norio Miyaura, involves the palladium-catalyzed cross-coupling of arylboronic acids or boronate esters with aryl halides or vinyl halides, providing compounds with new carbon-carbon bonds (Scheme 6).

[Insert Figure 6 here]

Scheme 6. General Suzuki-Miyaura reaction between an aryl halide and an arylboronic acid.

The most usual catalysts to promote this reaction are combinations of palladium(II) salts (or palladium(0) precursors) with phosphane ligands, either mono- or bidentate. Boronic acids, organotrifluoroborates and boronate esters serve as nucleophilic partners in this coupling reaction.[28] These compounds are typically prepared by carboboration or hydroboration, allowing for an efficient generation of molecular complexity. An external base needs to be added to the reaction mixture; several studies have been carried out

and have determined that this species has different roles in the reaction course: formation of transient Pd intermediates, generation of borate compounds that favor transmetalation, and acceleration of the reductive elimination stage.[29] The scope of the Suzuki-Miyaura coupling includes most functional groups, including ethers, esters, nitriles, and many more. This coupling process has been widely used to synthesize biphenyl compounds, polyolefins and styrenes. In addition, this reaction shows some remarkable advantages over other similar processes. These advantages include the improved availability of common boronic acids, milder reaction conditions, the lower toxic nature of boronic acids over organotin and organozinc reagents, and the possibility of employing water as the reaction medium,[30] which makes this coupling more eco-friendly, economical, and applicable towards water-soluble reactants.

The Hiyama reaction (1988): The Hiyama coupling is a palladium-catalyzed cross-coupling reaction that allows the formation of carbon-carbon bonds between organosilicon compounds (typically silicon-containing organohalides or siloxanes) and organic halides (Scheme 7). This process was reported by Prof. Tamejiro Hiyama in the late 1980s.[31]

[Insert Figure 7 here]

Scheme 7. General Hiyama coupling between an aryl halide and an organic trimethoxysilane.

The preferred catalysts for the Hiyama coupling are palladium(0) complexes or reducible palladium(II) salts (such as $[Pd_2Cl_2(allyl)_2]$, often combined with P-ligands or N-heterocyclic carbenes. Organosilicon compounds used in this reaction typically include silicon-containing organohalides (*e.g.* arylsilanes, alkylsilanes), silanols or siloxanes.[32] The employment of an external base or fluoride anions, for instance by adding tetrabutylammonium fluoride (TBAF), is key for activating the C-Si bond of the organosilane reagent.[33] Using this type of compounds offers several advantages over the classical organometallic counterparts in terms of stability, ease of handling, and compatibility with a wide range of functional groups. The scope of the reaction is broad and allows reacting several aryl, vinyl, and allylic halides with different organosilicon reagents containing aryl or alkenyl groups.

Furthermore, some examples of classical cross-coupling reactions involving the formation of new carbon-heteroatom bonds are:

The Ullmann condensation (1905):[34] This coupling reaction, named after the German chemist Fritz Ullmann who first reported it in 1905, is a venerable organic reaction that involves the coupling of different nucleophilic species with electrophilic aryl halides (such as aryl chlorides, bromides, or iodides) in the presence of a copper catalyst to form aryl ethers, aryl thioethers, aryl nitriles, and aryl amines. Thus, this type of reaction allows the construction of new C-N, C-O and C-S bonds, among others including also C-C couplings (Scheme 8).[35]

[Insert Figure 8 here]

Scheme 8. General C-O Ullmann coupling between an aryl halide and an alcohol.

Originally, these reactions were conducted at elevated temperatures, often refluxing in aprotic polar solvents such as nitrobenzene, N-methylpirrolidone or N,N-dimethylformamide, and required long reaction times. However, with the advent of modern catalytic systems, the Ullmann reaction has been optimized to proceed under milder conditions. The typical catalysts employed in nowadays consist of copper(I), sometimes copper(II), salts usually stabilized by the employment of bidentate N-donor ligands.[36] The Ullmann coupling exhibits a relatively broad substrate scope, accommodating various aryl halides and functional groups. Typically, all kinds of aryl chlorides, bromides, and iodides can serve as viable coupling partners, although their electron-poor versions are preferred.[37] Since different carbon-heteroatom bonds can be furnished with these reactions, the Ullmann reaction has found widespread applications in the synthesis of pharmaceuticals, agrochemicals, and natural products.

The Buchwald-Hartwig amination (1994):[38-39] The Buchwald-Hartwig amination, developed by Prof. Stephen L. Buchwald and Prof. John F. Hartwig, enables the palladium-catalyzed coupling of aryl halides or pseudohalides with amines to form new carbon-nitrogen bonds (Scheme 9).

[Insert Figure 9 here]

Scheme 9. General Buchwald-Hartwig amination reaction between an aryl halide and a primary amine.

The Buchwald-Hartwig reaction fundamentally employs palladium catalysts bound to different P-ligands. The first ligand reported to facilitate this transformation was P(*o*-tolyl)$_3$, which was subsequently replaced by more sophisticated ligands such as 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[40] and 1,1′-bis(diphenylphosphino)ferrocene (DPPF)[41] bidentate species. Later, bulky tri- and di-alkyl phosphane ligands (including the famous biaryl systems) were employed to enhance the performance of the process.[42-43] More recently, this coupling process has been reported to proceed with N-heterocyclic carbene ligands.[44] Amines, usually primary or secondary, serve as nucleophilic partners in the Buchwald-Hartwig amination reaction. Additionally, other nitrogen-containing nucleophiles such as amides and sulfonamides can also be used as coupling partners in certain variations of the reaction. This reaction needs an additional base to proceed, the typical bases employed range from the traditional alkoxydes to hydroxides, carbonates, and phosphates. While the Buchwald-Hartwig amination now encompasses a broad range of aryl and amine coupling partners, the conditions necessary for each specific reaction remain primarily dependent on the nature of the substrates. The Buchwald-Hartwig amination has found extensive applications in organic synthesis for the construction of aniline derivatives, amino acids, peptides, and other nitrogen-containing compounds.

The Chan-Lam reaction (1998):[45-47] The Chan-Lam coupling, reported nearly at the same time by Prof. Dominic Chan, Prof. Patrick, Y. S. Lam and Prof. David Evans, is a versatile

cross-coupling reaction that enables the formation of C-N and C-O bonds through the coupling of aryl or heteroaryl halides with aryl amines or aryl alcohols, respectively. This reaction represents an efficient and practical method for the synthesis of aniline derivatives and functionalized aromatic amines and ethers, which are valuable building blocks in organic synthesis, pharmaceuticals, and materials science (Scheme 10).

[Insert Figure 10 here]

Scheme 10. General Chan-Lam coupling between an aniline and an arylboronic acid.

Copper catalysts play a crucial role in promoting the Chan-Lam coupling. Usually, copper(I) or copper(II) species are used as catalysts, along with suitable ligands, typically N-donors, to enhance catalytic activity and selectivity.[48] This reaction is essentially an aerobic oxidative coupling, in which dioxygen from air acts as the oxidizing species within the catalytic cycle. The Chan-Lam coupling typically proceeds under mild reaction conditions, with the reaction carried out at ambient temperature or slightly elevated temperatures. This mildness allows for the tolerance of many functional groups, including sensitive functionalities such as esters, ketones, and amides, making the reaction compatible with complex molecular architectures.[49] The Chan-Lam coupling exhibits a broad substrate scope, allowing the activation of several aryl and heteroaryl halides, primary and secondary aryl amines, and aromatic alcohols. This coupling process can be efficiently employed to furnish new compounds and intermediates key to the preparation of pharmaceuticals, dyes, polymers, and agrochemicals.

Base metal-catalyzed cross coupling reactions

Of course, cross-coupling reactions continue to be hot a research topic, and many different new and improved metal-catalyzed platforms for building chemical bonds are reported on a regular basis. Nowadays, more than 90% of the chemical processes, including most of the commodities produced, involve a catalytic transformation.[50] This should not be surprising since catalysis is associated with additional advantages such as decreased energy input, diminished environmental impact, and overall monetary benefit in industrial chemical processes. The ubiquitous presence of transition metal catalysts largely results from a combination of their efficiency, distinct modes of reactivity, and the predictable control of both activity and selectivity upon ligand modification. Second- and third-row transition metals, often called precious metals, are the obvious choices for building up catalytic processes and they have become quite popular in homogeneous catalysis due to their fantastic properties in terms of stability, selectivity, and characterization. Typical precious metals employed in catalysis are ruthenium, rhodium, palladium, silver, osmium, iridium, platinum, and gold. Despite the prevalence of precious metals in catalysis, there are problems associated with their continued use in catalytic processes.[51] The first one is related to the scarcity of precious metals and its heterogeneous distribution around the globe, which makes them expensive and dependent on the supplying channels. The second problem with precious metals is that their usage also has significant –direct and indirect– implications for the environment. The mining and refinement of low-grade metal ores often results in an increased use of fossil fuels and CO_2 emissions, and to make things worse, the scarce precious metals are rarely recycled. The natural replacement for precious metals in catalysis are the first-

row transition (or base) metals: titanium, vanadium, chromium, manganese, iron, cobalt, nickel, and copper, which should be the ideal candidates for achieving a sustainable development for cross-coupling catalysis in the long term.[52] These metals present clear advantages in terms of pricing and global availability, and most of them show lower toxicity than their precious metal counterparts. Although precious-to-base metal migration has largely increased in the last years, there are some disadvantages that stand in the way of a faster replacement. These problems are often related to the inherent reactivity of base metals, which leads to problems with their stability, selectivity, and scope. However, when properly controlled, base metal catalysts can provide similar or even better results than those obtained with precious metals. Although there are many challenges associated with the usage of base metals as catalysts for reactions that have historically relied on precious metals, the potential future benefits for both our society and the environment are substantial and clearly justify the precious-to-base metal replacement in homogeneous catalysis. In terms of applicability, many classical cross-coupling reactions can be currently performed with base metal homogeneous catalysts; Table 1 shows the availability (including one recent example) of cross-coupling processes that employ late base transition metal catalysts for carbon-carbon bond formation.

Table 1. Availability of cross-coupling reactions promoted by late base transition metal catalysts.

Reaction	Fe	Co	Ni	Cu
Heck	✓[53]	✓[54]	✓[55]	✓[56]
Kumada	✓[57]	✓[58]	✓[59]	✓[60]
Sonogashira	✓[61]	✓[62]	✓[63]	✓[64]
Negishi	✓[65]	✓[66]	✓[67]	✓[68]
Stille	✓[69]	×	✓[70]	✓[71]
Suzuki-Miyaura	✓[72]	✓[73]	✓[74]	✓[75]
Hiyama	✓[76]	✓[77]	✓[78]	✓[79]

General reaction mechanism of cross coupling reactions

Most cross-coupling processes typically proceed through a general mechanism that involves three key steps (Scheme 11): oxidative addition (**OA**), transmetalation (**TM**), and reductive elimination (**RE**). Although the specific details may vary depending on the type of coupling reaction (*e.g.*, Suzuki-Miyaura, Heck, Negishi, *etc.*), the underlying principles remain consistent.

[Insert Figure 11 here]

Scheme 11. General reaction mechanism of a cross coupling reaction between and organic halide (R-X) and a coupling partner (R'-M'), the formal oxidation state of the metal catalyst is given between parentheses.

Following the sequence shown in Scheme 11, the first key stage is the oxidative addition process; in this reaction step the carbon-halogen bond of the organic halide (or pseudohalide, R-X) is cleaved onto the transition metal catalyst [M] to form new M-X and M-R bonds. During this process, the metal transfers two electrons to the antibonding R-X orbital to promote its breaking; therefore, after the oxidative addition the coordination number and the formal oxidation state of the metal have both increased by two units. Usually, low-valent (electron-rich) transition metal catalysts are employed to facilitate this process *e.g.* Pd(0), Ni(0), Rh(I), *etc.*; nonetheless, oxidative addition has been reported to proceed through many different -occasionally more unusual- transition metals and oxidation states, for instance: from Pt(II),[80] W(II),[81] V(III),[82] *etc*. Other factors can play a role on the oxidative addition, which should be favored by electron-rich ligands and electron-deficient organic halides for promoting the electron transfer from the metal catalyst to the organic reactant. The second key stage within the cross-coupling mechanism is the transmetalation; in this step the halide (X) group onto the catalytic species is exchanged by the organic part of the nucleophilic coupling partner (R'-M') generating a new organometallic M-R' bond. During this stage the formal oxidation state of the transition metal catalyst remains unaffected. This process is usually more complex than represented in Scheme 11 since different reaction pathways (either associative or dissociative) may be operating. In general, the transmetalation step tends to be less energy-demanding than the oxidative addition or the reductive elimination; however, this tendency may change for systems bearing large ligands or for electron-poor R'-M' coupling partners. The last stage in the reaction mechanism is the reductive elimination; during which the newly formed R-R' bond is generated. This step involves the simultaneous cleavage of the M-R and M-R' bonds, resulting in the formation of the desired product and regeneration of the active catalytic species. Typically, the leaving organic groups should be in *cis* arrangement to each other for this process to take place. This stage, which can be seen as the reversal of the oxidative addition, entails that two electrons are transferred back to the metal. Therefore, after the reductive elimination the catalyst recovers its original coordination number and oxidation state. In general, higher oxidation states of the transition metal catalyst, *e.g*. from Au(III), Pd(IV) or Ir(V), produce more favored reductive elimination processes. Furthermore, electron-poor and/or bulky ligands, and electron-rich organic substituents (either R or R') tend to promote faster eliminations.

Studied metal-catalyzed Suzuki-Miyaura reactions

The Suzuki-Miyaura coupling, described above (Scheme 6), is one of the most widely employed cross-coupling reactions for the formation of new carbon-carbon bonds. Typically, the coupling partners are an organic halide and an organoborane species (boronic acids or boronate esters). The whole system is completed by adding a transition metal catalyst (palladium phosphanes in the classical version) and an additional base, often considered to be the activator of the organoborane substrate by formation of borate analogues. This reaction has a vast range of applications in organic synthesis and has been extensively explored from both experimental[83-89] and computational[90-95] points of view. One of the critical points when studying transition metal systems as catalysts for the Suzuki-Miyaura coupling is the nature of the active species. Frequently, two equivalents of phosphane ligand are either present in the catalyst precursor or added in the mixture, and, at first glance, it seems reasonable to assume that they remain

attached to the metal throughout the whole reaction. However, other systems with bulky electron-rich ligands tend to increase the reaction rate in a 1:1 ligand to catalyst ratio, and it has been proposed that monophosphane species may act as catalysts as well.[96-99] More recently, phosphane ligands have been replaced by N-heterocyclic carbene ligands in Suzuki-Miyaura couplings; in these cases, the metal-to-ligand ratio tends to be 1:1 by default to avoid undesired steric hindrance problems on the catalyst.[100-104] In this work, density functional theory (DFT) calculations on the full catalytic cycle of the Suzuki–Miyaura coupling between bromobenzene (PhBr) and phenylboronate ($PhB(OH)_3^-$) are reported for different transition metal catalysts. The reaction is studied using different monoligated catalytic species of three transition metals: Pd(0), Ni(0) and Cu(I), derived from either P-ligands: trimethylphosphane (PMe_3) and tris(trifluoromethyl)phosphane ($P(CF_3)_3$), or N-heterocyclic carbenes: 1,3-bis(methyl)imidazol-2-ylidene (NHC) and 1,3-bis(trifluoromethyl)imidazol-2-ylidene (NHC-CF_3) (Scheme 12). These ligands reflect the electronic features of both ligand families while keeping relatively small steric effects. To get comparable results for all the studied systems, the origin of the computed relative Gibbs energies is set to be the first species within the catalytic cycle. Obviously, all the explored systems contain off-cycle bisligated transition metal species, for instance [$Pd^0(L_2)$], [$Ni^0(L_2)$] and [$Cu^IBr(L_2)$], should be taken into consideration and have been computed. However, for the sake of simplicity and comparison, these complexes have not been included as relevant into the discussion. Finally, the boronic acid (phenylboronic acid) and the additional base (in this case the hydroxyl anion) have not been computed separately and have been introduced directly as a phenylboronate substrate. The solvent of choice for studying the Suzuki-Miyaura coupling is 1,4-dioxane, which is one often employed in experimental studies; given the non-polar nature of this solvent, the reaction pathways that involve charge separation, in the shape of separated cationic and anionic intermediate species, have not been computed.

[Insert Figure 12 here]

Scheme 12. Studied Suzuki-Miyaura coupling between bromobenzene and phenylboronate catalyzed by different transition metal catalysts.

In this section, the catalytic cycles of all the studied systems will be described and the general reactivity trends, comparing between different metal/ligand combinations will be carried out. In all cases, the results account for the most favored monoligated catalytic system; obviously, this does not mean that the most favored pathway out of all the possible combinations of metal and ligand has been found, which should be much more complicated than intended in this work.

In theory, the studied Suzuki-Miyaura reactions should be expected to proceed following the catalytic cycle shown in Scheme 11. In practice, the palladium and nickel catalysts agree with that reaction sequence; however, the monovalent nature of copper(I) introduces a significant change in the reactivity of its active species and a swap in the order of elemental steps is observed, in which transmetalation happens prior to oxidative addition.

Palladium-catalyzed reactions

The most favored computed catalytic cycle for monoligated palladium species is shown in Scheme 13.

[Insert Figure 13 here]

Scheme 13. Computed Suzuki-Miyaura catalytic cycle for coupling bromobenzene and phenylboronate with monoligated transition metal catalysts (M = Pd or Ni).

As mentioned above, the reaction starts with an off-cycle bisligated palladium(0) species (**A0**) which undergoes an exchange between one of the monodentate ligands and phenyl bromide. This replacement generates the first monoligated palladium(0) species within the catalytic cycle of the reaction (**A1**). In previous studies, this exchange process has been proposed to proceed through a concerted associative displacement transition state,[91] which has not been computed in this work. After the generation of **A1**, the oxidative addition of the C-Br bond takes onto palladium to produce the organometallic complex **A2**, in which the new Pd-C and Pd-Br bonds have been formed, and the metal has been formally oxidized to palladium(II). This process could generate two different analogues of **A2**, depending on the spatial arrangement of both incoming groups (*cis* vs. *trans*) regarding the ancillary ligand. In all cases, the **A2** isomer displaying the ligand and the phenyl group in *cis* is energetically favored, in agreement with the *trans* influence of the three groups present in these intermediates (Ph^- > L > Br^-). In this line, the transition states leading to both **A2** complexes (*cis* and *trans*) were computed for PMe_3 and NHC ligands and found to preferentially produce the most stable palladium(II) **A2** intermediate. The reaction proceeds by the replacement of the bromide ligand by phenylboronate to produce intermediate **A3**. This reaction stage is thermodynamically favored in all cases and the corresponding transition state has not been computed, although it should be expected to be lower than other bond activation steps such as oxidative addition or reductive elimination. Complex **A3** shows a chelated boronate ligand, in which two hydroxyl groups appear bound to the palladium center. The next step in the reaction sequence is the transmetalation, in which the phenyl group of the boronate is transferred to the palladium to produce intermediate **A4**. This process is governed by the corresponding transmetalation transition state (**TMTS**) and generates boric acid as a byproduct. During the transmetalation one of the hydroxyl groups bound to palladium in **A3** is released to create a free position on the metal for the incoming organic group. The preferred ligand arrangement on **A4** shows that the new incoming phenyl ring ends up in a *trans* arrangement to the ancillary ligand, therefore both organic rings lie in *cis* to each other, in an ideal position to generate the final product by reductive elimination. The transmetalation transition state leading to the isomeric **A4** intermediate, in which both phenyl rings are placed *trans* to each other, was found to be energetically less favored for PMe_3 and NHC ligands. Finally, the reductive elimination process, through the associated transition state (**RETS**), generates the biphenyl product, which remains bound to the palladium(0)/ligand fragment (**A5**). At this point, the formation of the C-C bond liberates a large amount of energy (*ca*. 60 kcal mol^{-1}, see below). The catalytic cycle is closed by replacement of the organic product by phenyl bromide, which regenerates the starting active species (**A1**).

The computed Gibbs energies of all the studied palladium systems as catalysts for the Suzuki-Miyaura coupling between phenyl bromide and phenylboronate, following the mechanism in Scheme 13, can be found in Table 2, and are represented in Scheme 14.

Table 2. Computed relative Gibbs energies for all the species involved in the coupling between phenyl bromide and phenylboronate catalyzed by palladium/ligand systems.

	PMe_3	**$P(CF_3)_3$**	**NHC**	**NHC-CF_3**
A0	-17.9	-8.5	-21.7	-17.5
A1	0.0	0.0	0.0	0.0
OATS	7.8	12.0	5.1	6.0
A2	-22.1	-4.2	-24.9	-16.6
A3	-27.0	-8.1	-29.8	-21.4
TMTS	-13.3	3.8	-15.8	-7.8
A4	-31.4	-21.4	-34.2	-30.0
RETS	-23.5	-18.4	-26.4	-23.4
A5	-60.6	-61.2	-60.7	-60.1

[Insert Figure 14 here]

Scheme 14. Computed Gibbs energy profiles for palladium/ligand-catalyzed Suzuki-Miyaura coupling between phenyl bromide and phenylboronate.

As may be observed, the bisligated palladium(0) initial linear species (**A0**) is more stable for all the ligands; however, this energy value is not that relevant for this study of monoligated catalysts, which may be obtained directly by the right selection/proportion of starting materials. However, the relative values of **A0** serve as an indication of the donation ability of the ligands, indicating that the best donor seems to be NHC, followed by PMe_3 and NHC-CF_3, and, finally, $P(CF_3)_3$. In addition, the $[Pd^0(P(CF_3)_3)_2]$ complex shows a significant reduction of the P-Pd-P angle to 163º, probably due to the interaction between the fluoride groups of both ligands through dispersion (van der Waals) attraction forces. The electronic effects of the ligands seem to appear again within the oxidative addition barriers. In this case both carbene ligands display slightly lower activation energies than phosphanes. For both ligand families, the fluorinated analogues present higher barriers, in agreement with what is expected in terms of donating ability and electron transfer from the palladium fragment towards phenyl bromide. For instance, the oxidative addition barriers for PMe_3 and $P(CF_3)_3$ are 7.8 and 12.0 kcal mol^{-1}, respectively, while for NHC and NHC-CF_3 those barriers decrease to 5.1 and 6.0 kcal mol^{-1}. In any case, all these values indicate very fast oxidative addition stages, as would be expected for monoligated palladium(0) catalysts. After the oxidative addition, the palladium(II) intermediates (**A2**) become more stable for the PMe_3 and NHC ligands, while their fluorinated counterparts are slightly less stable; this is probably due to the destabilizing

steric effect of fluoride groups on these compact T-shaped palladium(II) intermediates. The replacement of bromide by phenylboronate to form intermediate **A3** shows no difference between the ligands and this process is exergonic by ca. 4.5 kcal mol^{-1} for all the studied systems. The transmetalation stage shows again small differences between the ligands. Again, the fluorinated analogues seem to produce lower barriers. This behavior has been reported previously,[91] and may be attributed to the tendency of electron-poorer ligands to promote the replacement of the bridging hydroxyl group in **A3** by the more basic phenyl group of the boronate. In most cases, the transmetalation process is the most energy-demanding stage of the overall studied palladium-catalyzed reactions; the four ligands show transmetalation barriers of 13.7, 11.9, 14.0 and 13.6 kcal mol^{-1} for PMe_3, $P(CF_3)_3$, NHC and NHC-CF_3, respectively. The only exception is the $P(CF_3)_3$ ligand, for which the oxidative addition process shows a very similar barrier of 12.0 kcal mol^{-1}. After the transmetalation, the corresponding bis-phenyl palladium(II) (**A4**) complexes are obtained. These complexes experience a larger energy stabilization for the fluorinated ligands when compared to the previous intermediates, probably because the incoming phenyl group shows a better donation ability than the previous ligands in **A2** (Br^-) or **A3** ($PhB(OH)_3^-$). Finally, the reductive elimination barriers follow the trend that should be expected, and the electron-withdrawing fluorinated ligands tend to produce faster systems. For instance, the computed reductive elimination barriers are 7.9, 3.0, 7.8 and 6.6 kcal mol^{-1} for PMe_3, $P(CF_3)_3$, NHC and NHC-CF_3, respectively. After the formation of the biphenyl product, the Gibbs energy drastically decreases by ca. 60 kcal mol^{-1}, which clearly correlates with the formation of the new C-C bond. The Gibbs energy of the overall process indicates that the reaction is exergonic by 60.0 kcal mol^{-1}; and the global energy barriers are below 14 kcal mol^{-1} in all cases; which suggests that all the studied palladium/ligand combinations should produce operative catalytic systems.

Nickel-catalyzed reactions

The preferred reaction pathway for the monoligated nickel-catalyzed Suzuki-Miyaura coupling between phenyl bromide and phenylboronate is the same as that found for palladium/ligand systems. Therefore, the reaction steps are equal to those shown in Scheme 13 albeit the associated Gibbs energies are different. The relative Gibbs energies for the nickel/ligand catalytic cycles can be found in Table 3 and are represented graphically in Scheme 15.

Table 3. Computed relative Gibbs energies for all the species involved in the coupling between phenyl bromide and phenylboronate catalyzed by nickel/ligand systems.

	PMe_3	**$P(CF_3)_3$**	**NHC**	**NHC-CF_3**
A0	-10.1	2.3	-16.1	-15.4
A1	0.0	0.0	0.0	0.0
OATS	11.6	14.9	13.7	14.3
A2	-37.6	-7.9	-36.3	-26.5
A3	-47.4	-21.4	-48.5	-40.1

TMTS	-29.0	-4.7	-27.8	-21.2
A4	-43.1	-24.6	-43.6	-37.3
RETS	-34.0	-23.3	-34.5	-32.5
A5	-60.0	-62.9	-58.7	-59.6

[Insert Figure 15 here]

Scheme 15. Computed Gibbs energy profiles for nickel/ligand-catalyzed Suzuki-Miyaura coupling between phenyl bromide and phenylboronate.

As may be observed, for nickel systems the bisligated linear starting species (**A0**) are slightly less stable than their palladium counterparts; hence, ligand dissociation to generate the active **A1** species is an easier process in all cases. Indeed, for the $[Ni^0(P(CF_3)_3)_2]$ complex, the replacement of one of the phosphanes by the incoming phenyl bromide is exergonic; this behavior is promoted by the geometrical arrangement of both $P(CF_3)_3$ ligands, which forces this bisligated complex to bend producing a P-Ni-P angle of 141º. This is, in principle, the most stable geometry for the **A0** complex for the nickel/$P(CF_3)_3$ system; all the attempts to produce a more linear **A0** intermediate ended up producing the bent structure, even when the empirical dispersion was removed from the optimization procedure. Once the **A1** species has been obtained, the oxidative addition takes place. The energy requirement for this reaction stage is quite similar for all the ligands: 11.6, 14.9, 13.7 and 14.3 kcal mol^{-1} for PMe_3, $P(CF_3)_3$, NHC and NHC-CF_3, respectively. These values are a bit higher than those found for the palladium systems and agree with the expected trend, with the electron-rich ligands displaying lower activation barriers than their fluorinated analogues. In any case, the oxidative addition seems feasible for all the studied systems. The formation of the **A2** nickel(II) complexes entails a large release of energy for all the ligands but for $P(CF_3)_3$; this decrease in the overall Gibbs energy of the system, larger than that found for palladium systems, may be attributed to the higher tendency of nickel to oxidize, which favors the +2 oxidation state. The more oxophillic character, as well as the reduced softness, of nickel when compared to palladium can be observed by the change of energy when replacing the bromide ligand by phenylboronate in the formation of **A3**. These intermediates are 10-14 kcal mol^{-1} more stable than the previous species, and present higher energy releases than their palladium analogous structures. After the obtention of **A3**, the transmetalation takes place to transfer the phenyl group of the boronate onto the nickel center. The activation energies related to this transition state (**TMTS**) are: 18.4, 16.7, 20.7 and 18.9 kcal mol^{-1} for PMe_3, $P(CF_3)_3$, NHC and NHC-CF_3, respectively. These barriers are around 5-7 kcal mol^{-1} higher than those found for palladium/ligand systems, probably because the release of the hydroxyl arm of the boronate to create a vacant position for the incoming phenyl ring requires a larger amount of energy, in fact, the Ni-OH bond should be stronger than its Pd-OH counterpart. On the other hand, and as observed for palladium systems, the electron-poorer ligands $P(CF_3)_3$ and NHC-CF_3, produce lower transmetalation barriers than the non-fluorinated counterparts. The transmetalation stage represents the rate-limiting step of the reaction for all the studied nickel-catalyzed systems. After this step, the $[Ni^{II}L(Ph)_2]$ (**A4**) complexes are obtained; these species are, except for $P(CF_3)_3$, slightly higher in energy than their corresponding

A3 intermediates. In all cases, intermediate **A4** adopts a T-shaped structure, in which both phenyl groups lie *cis* to each other. The reductive elimination barriers are quite low and show two different trends. The electron-poor ligands show the lowest barriers: 1.3 and 4.8 kcal mol^{-1} for $P(CF_3)_3$ and NHC-CF_3, which are also lower than those computed for their palladium analogues. On the other hand, the electron-rich ligands PMe_3 and NHC have higher reductive elimination barriers (9.1 kcal mol^{-1} in both cases), which are slightly higher than those obtained for their palladium equivalents. The general trend observed for the reductive eliminations of these nickel complexes agrees with the expected reactivity, which states that electron-poorer ligands may enhance the elimination. On the other hand, the increase or decrease of these barriers in respect to palladium may be related to the intrinsic bond between the nickel and the ligands; in the case of harder ligands ($P(CF_3)_3$ and NHC-CF_3) the nickel-ligand distance is shorter and the transition state (**RETS**) is stabilized. On the other hand, the longer distance found for softer ligands (PMe_3 and NHC) in **RETS** seems to destabilize the elimination process. In the case of palladium, the transition states show longer distances, and the effect of the overlapping palladium-ligand interaction becomes less noticeable. After the reductive elimination the biphenyl product is formed and retained through π-coordination to the nickel(0) species (**A5**). At this point, the relative Gibbs energy decreases to *ca*. -60 kcal mol^{-1} due to the formation of the C-C bond, as observed previously for the palladium/ligand systems. Again, the Gibbs energy change of the whole coupling reaction is exergonic by 60.0 kcal mol^{-1}. The overall energy barriers for the explored nickel/ligand catalysts are in the range 16.7-20.7 kcal mol^{-1}, slightly higher than those found for palladium-based systems, but still affordable under the experimental, room temperature, reaction conditions.

Copper-catalyzed reactions

As mentioned above, the intrinsic monovalent nature of copper(I) in copper/ligand catalysts for promoting Suzuki-Miyaura couplings induces a drastic change in the overall reactivity of the system. If the original cross-coupling catalytic cycle (Scheme 11) was to be followed, the first elemental bond activation should be the oxidative addition of the carbon-halide bond onto the copper center. This would generate a copper(III) intermediate in which the transmetalation and reductive elimination steps should take place. However, copper(III) intermediates tend to appear at much higher Gibbs energies than their initial copper(I) starting materials, and therefore the transmetalation and reductive elimination stages are located at even higher energies, which indicates that the classical catalytic cycle cannot be operative. This does not mean that copper(III) is unattainable by experimental of computational means. On the contrary, copper(III) has been successfully identified in anionic species in solid state,[105] especially as oxocuprates[106-107] or fluorocuprates.[108-110] Moreover, copper(III) has also been recognized in several molecular complexes within binuclear[111-113] $[Cu^{III}_2O_2]^{2+}$ or mononuclear[114-116] $[Cu^{III}O_2]^{+}$ cores stabilized by different structural motifs, often present as isomeric structures between peroxo and bisoxo forms related to models for the oxyhemocyanin and tyrosinases. More recently, other mononuclear complexes containing one copper(III) center have been well characterized[117-120] and its reactivity in oxidation reactions has been explored.[121-122] On the other hand, several organometallic compounds have been the subject of discussion such as the

tetrakis(trifluoromethyl)cuprate(III) ($[Cu^{III}(CF_3)_4]^-$) anion.[123] The main discussion on the nature of these compounds is focused on the discrepancies between the assignation of the atomic charge of copper (generated from different population analyses) and its formal oxidation state. Although the geometry around the metal is close to square-planar, several studies have assigned this metal center as a copper(I) d^{10} ion.[124-125] However, in basis of the coordination stereochemistry, the copper center should formally be assigned as a copper(III) d^8 ion bearing an important inversion of the ligand field.[126-128] In any case, copper(III) species is often summoned as a viable -albeit mostly transient- intermediate in copper-catalyzed cross-coupling reactions.[129-136] Following this line, the classical catalytic cycle has been modified to accommodate the plausible copper(III) intermediates in a more sensible reaction sequence (Scheme 16).

[Insert Figure 16 here]

Scheme 16. Computed Suzuki-Miyaura catalytic cycle for coupling bromobenzene and phenylboronate with monoligated copper(I) catalysts.

Although the nature of the copper species may allow many different reaction pathways, the calculations seem to indicate that all the non-neutral pathways, *i.e.* those in which cationic or anionic copper species may be formed, are energetically unsuitable to promote the studied Suzuki-Miyaura coupling. This should be attributed to the non-polar nature of the 1,4-dioxane solvent, which may penalize the formation of charged compounds. Therefore, the most favored reaction sequence for copper catalysts accounts for a pathway in which all the copper species remain neutrally charged. Similarly to palladium and nickel, the monoligated catalytic pathway requires that the initial off-cycle copper(I) complex $[Cu^{I}Br(L_2)]$ (**B0**) releases one of the monodentate ligands to form the active species **B1**. After that, in contrast to the other studied transition metals, the copper catalyst must undergo transmetalation to exchange the bromide ligand by the phenyl group of the organic boronate, forming **B2** and then the organometallic complex $[Cu^{I}L(Ph)]$ (**B3**). As stated above, all the attempts to oxidatively add phenyl bromide prior to transmetalation produced much higher overall energy barriers, mainly because the transmetalation onto a hypothetical $[Cu^{III}Br_2L(Ph)]$ would require an additional amount of energy besides that needed to break the C-Br bond on **B1** (see below). Therefore, the reaction sequence shows that, in first place, bromide is replaced by phenylboronate to form the trigonal **B2** complex. As observed before, the incoming substrate acts as a chelate ligand to the copper center through two of its hydroxyl groups. The transmetalation takes place, following the corresponding transition state (**TMTS**), to produce the linear compound **B3** while releasing boric acid to the reaction mixture. Intermediate **B3** reacts with phenyl bromide to produce the **B4** compound, in which a weak interaction is established between both reactants. The reaction should proceed by the oxidative addition of phenyl bromide to form the corresponding copper(III) intermediate that may, afterwards, produce the final biphenyl product by reductive elimination. In practice, the first part of this sequence seems to work as proposed and the oxidative addition transition state (**OATS**) can be located and characterized without any problem. However, all the attempts to compute the hypothetical copper(III) intermediate: $[Cu^{III}BrL(Ph)_2]$ have been unsuccessful. In all cases, the geometry optimization of this species leads to the automatic reductive elimination of the product, indicating that this process seems to be almost barrierless.

The copper(III) intermediate can be accessed by freezing the Ph-Cu-Ph angle at 90º during the geometry optimization procedure; this structure corresponds to a local minimum because all the computed vibrational frequencies are positive. Nevertheless, trying to reoptimize the structure of this intermediate removing the constrained angle produces again the barrierless reductive elimination of the product. Other computational studies have encountered this issue and concluded that all the steps after the oxidative addition should not be taken into consideration, mainly because the energies related to the unstable copper(III) intermediate and the reductive elimination transition state are below the relative energy of the oxidative addition transition state. For this reason, both the copper(III) intermediate and the reductive elimination transition are not relevant to the catalytic cycle of the copper-catalyzed Suzuki-Miyaura studied in this work.

The computed relative Gibbs energies for the copper/ligand studied catalytic cycles are shown in Table 4 and their graphical representation can be found in Scheme 17.

Table 4. Computed relative Gibbs energies for all the species involved in the coupling between phenyl bromide and phenylboronate catalyzed by copper/ligand systems.

	PMe_3	**$P(CF_3)_3$**	**NHC**	**NHC-CF_3**
B0	-8.4	2.9	-8.9	-5.3
B1	0.0	0.0	0.0	0.0
B2	4.4	0.9	6.1	4.4
TMTS	20.7	15.7	22.2	20.6
B3	-2.7	-8.4	-3.2	-5.7
B4	-0.7	-5.8	-1.3	-3.0
OATS	24.3	17.3	29.3	25.8
B5	-59.2	-59.1	-59.9	-58.5

[Insert Figure 17 here]

Scheme 17. Computed Gibbs energy profiles for copper/ligand-catalyzed Suzuki-Miyaura coupling between phenyl bromide and phenylboronate.

As may be observed, the starting bisligated $[Cu^{I}Br(L_2)]$ (**B0**) species are slightly less stable than for palladium and nickel and therefore the formation of **B1** should be even more favored. Again, the $[Cu^{I}Br(P(CF_3)_3)_2]$ complex is the only one showing an energetically favorable ligand release to form the monoligated neutral complex. From **B1**, following the classical reaction mechanism, the next step should be the oxidative addition of phenyl bromide. However, the direct oxidative addition of the organic halide onto **B1** to generate $[Cu^{III}Br_2L(Ph)]$ for the electron-rich ligands, where the barrier should be lower, requires 29.5 and 34.3 kcal mol^{-1} for PMe_3 and NHC, respectively, which is a much higher energy requirement than any other found in the modified catalytic cycle. Hence, the oxidative addition of phenyl bromide onto **B1** can be discarded. Following the pathway proposed in scheme 16, and in contrast to the other two metal centers, the

replacement of bromide by phenylboronate onto the **B1** copper complex is endergonic for all the ligands. This behavior may be attributed to the relatively soft nature of the copper(I) ion, which interacts more strongly with the larger bromide ligand than with the hydroxylic groups of phenylboronate,[137] albeit the interaction with the latter produces a 4-membered chelate structure. Therefore, species **B2** is, in all cases, a bit higher in energy than its **B1** counterpart. The **B2** complexes show similar relative energies, although the intermediate with $P(CF_3)_3$ is more stable by ca. 3-5 kcal mol^{-1} than the rest. This trend is transmitted to the transmetalation transition state (**TMTS**) that shows a lower energy requirement for the fluorinated phosphane. Again, in this transition state one of the hydroxylic arms of the boronate is released to generate a free position for transferring the phenyl group. The isolated transmetalation barriers, computed as the Gibbs energy difference between **TMTS** and **B2**, are very similar: 16.3, 14.7, 16.1 and 16.2 kcal mol^{-1} for PMe_3, $P(CF_3)_3$, NHC and NHC-CF_3, respectively. However, the overall energy investment up to this point of the process is higher because intermediate **B2** is always higher in energy than **B1**, which should be considered the resting state in this part of the catalytic cycle. Therefore, the overall transmetalation barrier should include the energy difference between the two first intermediates: 20.7, 15.7, 22.2 and 20.6 kcal mol^{-1} for the four ligands in the same order as before. It is remarkable that $P(CF_3)_3$ displays a much lower barrier than the rest of the ligands; as before, the electron-poor phosphane and carbene ligands have lower transmetalation barriers than their electron-rich analogues, probably because a more electron-withdrawing ligand facilitates the electron density transfer from the boronate to the metal center. After the transmetalation intermediate **B3** is obtained; this linear complex is the lowest energy species along the reaction coordinate for all ligands and is most stable for the electron-poor ligands. From there, the reaction proceeds by coordination of phenyl bromide to generate intermediate **B4**; this compound is quite different to those formed with palladium and nickel (**A1** complexes), in which a η^2-π-coordinated system is formed. In contrast, **B4** presents a weak coordination between the **B3** and phenyl bromide fragments that remain together mostly from non-bonded interactions; the shortest distances found between them are *ca*. 2.5-2.7 Å for H-H and H-F contacts while the metal sits at longer distances from the incoming organic halide (between 2.8-3.2 Å). From **B4**, the oxidative addition takes place to activate the C-Br bond onto the copper center through the corresponding transition state (**OATS**). This saddle point constitutes the highest energy stage within the reaction coordinate produces overall barriers of 27.0, 25.7, 32.5 and 31.5 kcal mol^{-1} for PMe_3, $P(CF_3)_3$, NHC and NHC-CF_3, respectively. In all cases, the barrier is computed as the energy difference between **B3** and **OATS**. As should be expected, the oxidative addition barriers for palladium and nickel systems are lower than those for copper catalysts, probably because for the former the oxidation states involved (0 and +2) are more easily achievable and, in addition, their starting valence (0) is lower than for copper (+1). On the other hand, the copper systems present a strange behavior towards oxidative addition *i.e.* electron-poor ligands produce lower C-Br activation barriers. In principle, the more electron-donating ligands should provide lower activation barriers due to their ability to donate electron density to the metal, which can further promote it onto the organic halide to cleave the carbon-bromide bond. However, for both phosphane and carbene ligands, the copper(I) catalysts show an inverse trend, which is not easily attributable to any simple feature of the intermediate or transition state structures related to the oxidative addition process. For instance, the computed NBO charges for the **B3** and **B4** complexes indicate that the metal center is slightly more oxidized in the

intermediates bearing electron-poor ligands, which should prevent these species to promote easier oxidative additions. In the same line, the systems with the PMe_3 and the NHC ligands produce higher HOMO energies, suggesting that they should participate in electron transfer processes more easily. In any case, there should be an underlying, albeit more complicated and difficult to ascertain, process driving the observed trend of the computed oxidative addition barriers for copper(I) catalysts. As mentioned before, the isolation of the stable copper(III) intermediates could not be achieved for any ligand and, after the oxidative addition, the reaction evolves directly to the final biphenyl product, again weakly bound to the copper center as in intermediate **B4**, in species **B5**. At this point of the reaction coordinate the relative Gibbs energy largely decreases (*ca*. -60 kcal mol^{-1}) due to the formation of the new carbon-carbon bond. The overall barriers found for copper/ligand systems are larger than those found for palladium and nickel, and their values indicate that only phosphane ligands should be contemplated to furnish operative catalytic systems, although they would probably require increasing the reaction temperature.

Conclusions and outlook

The reaction mechanism of the Suzuki-Miyaura coupling between phenyl bromide and phenylboronate has been explored for different monoligated catalytic systems, in which palladium(0), nickel(0) and copper(I) compounds with different monodentate phosphane and N-heterocyclic carbene ligands have been employed.

The catalytic cycles of palladium and nickel species agree with the classical description of cross-coupling reactions and follow the oxidative addition/transmetalation/reductive elimination sequence. The computed palladium-catalyzed Suzuki-Miyaura coupling produces very low overall activation barriers, typically below 14 kcal mol^{-1}, for all the studied systems. In this case, the highest energy barrier corresponds to the transmetalation step, which is more demanding for the electron-rich ligands. The nickel-catalyzed processes show the same trends as palladium, although the transmetalation process, again the highest energy point within the reaction coordinate, shows slightly larger energy barriers, between 16.7 and 20.7 kcal mol^{-1}.

The copper(I) catalytic processes show significant differences to the other two transition metal-catalyzed reactions. Most remarkably, the monovalent nature of the active catalyst produces a preferred pathway in which the transmetalation stage occurs prior to oxidative addition and reductive elimination. This sequence should entail the formation of copper(III) intermediates after the oxidative addition; however, these high-valent complexes could not be properly computed because they automatically In all cases, the rate-determining step of the reaction corresponds to the oxidative addition step, in agreement to the relatively lower tendency of a monovalent transition metal to give electrons away to the incoming bromide substrate. The computed overall barriers of the copper-catalyzed reactions range between 25.7 and 32.5 kcal mol^{-1}. These values indicate that copper(I)/ligand systems would behave poorly towards the studied C-C coupling when compared to palladium and nickel, which display lower activation energies. Finally, the oxidative addition barriers for the copper(I) catalysts show an inverted trend in the expected reactivity, with electron-poor ligands displaying the lowest values. This strange behavior could not be attributed to a simple underlying feature *i.e.* charge distribution or frontier orbital energies, of the involved species during the

activation process. Probably, a more complex mechanistic process, which compensates the lack of electron-donating power of the monodentate ligands within the oxidative addition, is helping to promote this transformation.

Looking to the future, copper(I) catalysts for promoting the Suzuki-Miyaura coupling with phosphane and carbene ligands need further studies to produce new and improved systems. Although these systems may appear less attractive than their palladium and nickel counterparts they could be potentially interesting due to several reasons, including lower prices, better availability and more affordable reaction conditions since, in contrast to nickel(0) catalysts, they would not require the usage of a glovebox. Given that electron-poor ligands seem to successfully reduce the energy requirements for the desired carbon-carbon couplings, it would be desirable to explore the reactivity of chelating bidentate phosphane ligands bearing electron-withdrawing substituents *e.g.* trifluoromethyl or pentafluorophenyl functional groups. In the same line, other electron-poor N-heterocyclic ligands, including fluorinated substituents or other electron-withdrawing groups should be tested. Computational tools are well suited for undertaking these developments at a low cost in terms of time, and they should be employed to guide the experimental design of new ligands to construct improved catalytic platforms.

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Computational data

All systems have been fully optimized in 1,4-dioxane using the Gaussian16 program[138] along with the B3LYP functional.[139-142] In the geometry optimization process, the 6-31G* basis set[143-145] has been used to describe all atoms except Ni, Cu and Pd, for which the Stuttgart double zeta basis set (SDD),[146-149] including their associated ECPs, has been employed. Ultrafine integration grids were used to ensure satisfactory convergence. In all cases, the solvation energies in 1,4-dioxane have been computed within the SMD version[150] of the IEF-PCM continuum dielectric solvation model.[151-152] Dispersion correction terms have been included using the D3 method of Grimme[153] as implemented in Gaussian16. These computational settings are referred to as scheme BS1. After geometry optimization, frequency calculations have been performed to ensure the nature of the stationary points and transition states; all the local minima and transition states display zero and one imaginary frequencies, respectively.

Additional single-point calculations, including the same solvation and dispersion corrections as in scheme BS1, have been employed in the optimized geometries to obtain improved Gibbs energy values with larger basis sets (BS2 scheme). In these calculations, the B3LYP functional has been retained and the def2-TZVPPD all-electron basis set[154] has been employed to describe all atoms. This computational methodology has been successfully employed for studying similar metal-catalyzed coupling reactions.[155-159]

The final computed Gibbs energies at room temperature (298.15 K= 25°C) have been corrected to use a standard state corresponding to species in solution with a standard 1 M concentration. Therefore, the Gibbs energies at a given temperature, based on the rigid rotor/harmonic oscillator approach of statistical mechanics, have been obtained with the following formula:

$$G_T^\circ = E_{BS2} + H_{corr,BS1} - TS_{BS1} + RT \ln (\mathrm{C}^\circ/\mathrm{C}^{1atm})$$

where E_{BS2} is the electronic energy, including solvent and dispersion terms, obtained with the BS2 scheme. $H_{corr,BS1}$ is the thermal correction to the enthalpy and contains the zero-point energy plus the vibrational, rotational and translational energies calculated with the BS1 scheme. Finally, TS_{BS1} represents the entropic correction obtained from the BS1 scheme. The Gibbs energies obtained from Gaussian16 refer to a standard ideal gas state (P = 1 atm). These values have been corrected to use a standard state in which the species in solution have a concentration of 1 M. This procedure has been carried out by adding an additional term to the calculated Gibbs energy of each species. This term is calculated as $RT\ln(C^\circ/C^{1atm})$, where C° is the concentration of the standard reference state (1 M), and C^{1atm} is the concentration of an ideal gas at the standard conditions of P = 1 atm at a given temperature. Therefore, for an ideal gas at 1 atm and at 298.15°C: $C^{1atm} = 1/V_m = P/RT = 0.030$ M; numerically, this correction term is equal to 2.80 kcal mol^{-1} per molecule.

Unless otherwise stated, all the reported Gibbs energy values correspond to those obtained with the abovementioned equation, in the 1 M standard state and at 25ºC (298.15 K).

All the computed structures (Gaussian16 input and output files) have been uploaded to the ioChem-BD database and can be retrieved in the following link: https://doi.org/10.19061/iochem-bd-1-321. The relative Gibbs energy values, along with other computed terms, can be found in the following link: https://shorturl.at/htzAJ.

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