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Grau de Química

Treball Final de Grau

Bibliographic search of transition metal based catalysts for carbon-carbon coupling reactions.

Recerca bibliogràfica de catalitzadors basats en metalls de transició per a reaccions d'acoblament carboni-carboni.

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June 2023

Universitat de Barcelona

B:KC Barcelona Knowledge Campus
Campus d'Excel·lència Internacional

No ganes el mundo y pierdas tu alma; la sabiduría es mejor que el oro o la plata.

Bob Marley

Voldria agrair a la meva família, per donar-me amor i suport moral en tot moment, i als meus amics i companys de carrera ja que hem compartit molts bons moments i m'han motivat a seguir progressant. També voldria apreciar tots els coneixements que m'han transmès els professors durant aquests anys i la dedicació dels meus tutors del TFG per poder guiar-me en aquest treball.

REPORT

IDENTIFICATION AND REFLECTION ON THE SUSTAINABLE DEVELOPMENT GOALS (SDG)

Carbon-carbon coupling reactions can have an impact on the area of *People* of the SDGs, more specifically on the number 3: *Good Health and Well-Being*. These type of reactions can contribute to the synthesis of pharmaceutical compounds, facilitating the production of more effective and accessible drugs for the treatment of diseases. In addition, by enabling the synthesis of useful organic molecules, these reactions can drive research and development of new drugs to address global health challenges.

Additionally, the project is related to SDG 9 of the *Prosperity* cluster. This goal is named *Industries, Innovation and Infrastructure*. These catalytic reactions allow the synthesis of organic compounds used in various industrial sectors and, therefore, a catalytic system that gives a high yield with the least amount of metal possible, allows the use of fewer reagents and a more sustainable process.

On the other hand, Stille and Sonogashira coupling reactions could have an impact on SDG 12: *Responsible Consumption and Production*, in the area of *Planet*. These reactions can employ a room-temperature ionic liquid (RTIL) as a solvent instead of using an organic solvent. This allows for the use of the same solvent and catalyst for multiple consecutive catalytic cycles. Furthermore, solvents composed of water/surfactant and the biomass-derived solvent Cyrene do not create toxic or mutagenic waste, making the coupling process environmentally friendly.

CONTENTS

1. SUMMARY

The reactions that link a carbon of one organic molecule with the carbon of another, resulting in the bonding of the two compounds, are known as carbon-carbon cross-coupling reactions and are carried out with the assistance of a catalyst composed of a transition metal complex. The most common reaction mechanism is a catalytic cycle in which the metallic palladium species serves as the initiator of the process. The conditions surrounding the palladium complex are crucial for the future of the reaction, as evidenced by an exhaustive earch of Stille and Sonogashira reactions in the Reaxys database to understand which ligands, solvents, substrates, and experimental conditions enhance the reaction yield. Special attention has been given to the turnover number (TON), which refers to the number of times the catalyst can react with the substrate within a given period of time. The aim has been to identify catalytic systems with a higher TON value, as palladium is an expensive metal and minimizing its usage in catalytic cycles is desirable.

Keywords: carbon-carbon cross-coupling, catalyst, catalytic cycle, complex, palladium, Sonogashira reaction, Stille reaction, TON, transition metal.

2. RESUM

Les reaccions que enllacen un carboni d'una molècula orgànica amb el carboni d'una altra, amb la conseqüent unió dels dos compostos, són conegudes com a reaccions d'acoblament creuat carboni-carboni i són dutes a terme amb l'ajuda d'un catalitzador format per un complex de metall de transició. El mecansime de reacció més freqüent és un cicle catalític en el qual l'espècie de pal·ladi metàl·lic és l'iniciador del procés. Les condicions que envolten el complex de pal·ladi son crucials per al futur de la reacció, tal com s'ha pogut comprovar a la base de dades de Reaxys, on s'ha fet una cerca exhaustiva de reaccions de Stille i Sonogashira per poder entendre quins lligands, dissolvents, substrats i condicions experimentals fan augmentar el rendiment de la reacció. S'ha atorgat especial importància al nombre de cicles catalítics (TON) que fa referència al nombre de vegades que el catalitzador pot reaccionar amb el substrat en un període de temps determinat. S'ha buscat identificar els sistemes catalítics amb un valor de TON més elevat, ja que el pal·ladi és un metall car i interessa emprar la mínima quantitat possible en el cicles catalítics.

Paraules clau: acoblament creuat carboni-carboni, catalitzador, cicle catalític, complex, metall de transició, pal·ladi, reacció de Sonogashira, reacció de Stille, TON.

3. INTRODUCTION

Metal-catalyzed carbon-carbon coupling reactions are highly valuable in contemporary organic synthesis due to their versatility and ability to selectively produce desired compounds under mild conditions. However, these reactions involve numerous steps where transient intermediates species have a short lifespan. Besides, there are alternative reaction pathways with similar activation energies, which adds complexity to their mechanism. [1]

These reactions are characterized by the formation of carbon-carbon bonds by the interaction of an organic electrophile (R^1-X) and an organometallic nucleophile (R^2-m) in the presence of a catalyst. They are known as C-C cross-coupling reactions and they are classified according to the metal or semimetal found in the nucleophile. For instance, Suzuki reaction uses a boronic acid, Stille reaction employs an organostannane, Negishi reaction utilizes an organozinc compound, Hiyama reaction applies an organosilane and Kumada reaction is carried out by a Grignard reagent as nucleophile. On the other hand, there are cross-coupling reactions that use a base instead of an organometallic such as the Sonogashira reaction and Heck reaction.[2]

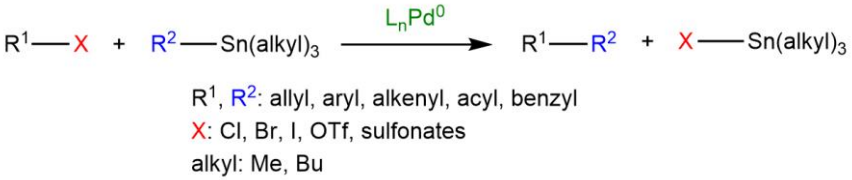
Among the catalysts used, transition metal complexes of groups 8-10, especially palladium complexes, are the most commonly used. A key advantage of palladium catalysts is their compatibility with a wide range of functional groups and their ability to facilitate rapid bond formation between carbon atoms. This ability greatly expands synthetic possibilities and allows the construction of complex molecules with fast reaction rates and high yields, making palladium-catalyzed cross-coupling reactions more efficient and time-saving compared to alternative catalysts.

In this work we will focus on the Stille and Sonogashira reactions as the main object of the investigation. Following this, the general mechanism of the C-C cross-coupling reactions will be explained and then the mechanism of the Suzuki and Sonogashira reactions will be explained in detail. Furthermore, an extensive bibliographic search of the catalysts and conditions used in a variety of reactions will be carried out in order to discuss which catalytic systems are the most efficient for this type of reactions.

3.1. STILLE AND SONOGASHIRA REACTION MECHANISMS

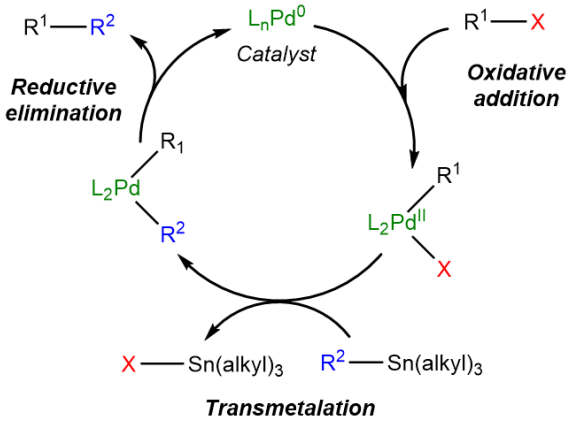
The C-C cross-coupling reactions follow a catalytic cycle comprising three main stages: oxidative addition, transmetalation and reductive elimination. The Stille and Sonogashira reactions comply with the general rule but have small distinctions between themselves.

Stille reaction involves a carbon-carbon coupling of an electrophilic organic group R^1, which has a leaving group X, and of a nucleophilic organic group R^2 linked to a trialkyltin $Sn(alkyl)_3$, according to the general reaction depicted in Scheme 1.[3]



Scheme 1. Stille general reaction.

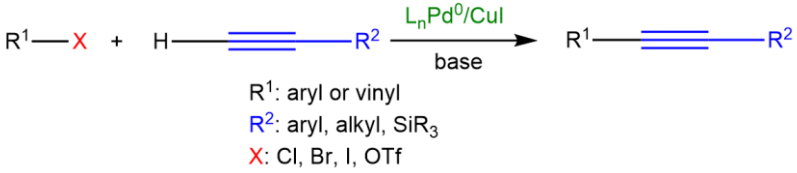
The Stille reaction proceeds through a catalytic cycle as shown in Scheme 2.[3]



Scheme 2. Catalytic cycle of Stille reaction.

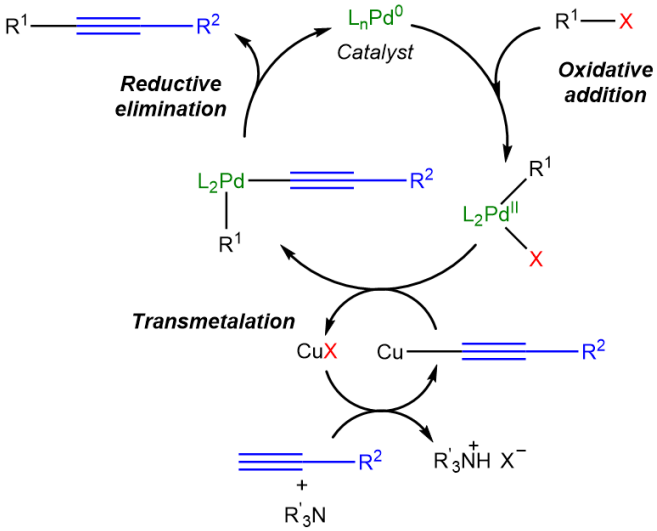
Although the effective catalyst is the Pd(0) complex, a Pd(II) complex is commonly used as the initial catalyst because it is more stable and yields the same results. In fact, before entering the catalytic cycle, the Pd(II) complex undergoes an on-site reduction, generating the catalytically active Pd(0) species.[4]

In the case of Sonogashira reaction, occurs a coupling between a terminal alkyne and an aryl or vinyl halide/triflate (Scheme 3). In addition, the reaction commonly employs a Cu(I) co-catalyst, typically CuI, and an equimolar amount of a base, with Et_3N being the most frequently used base.[5]



Scheme 3. Sonogashira general reaction.

The inclusion of a Cu(I) salt is commonly understood to enhance the transfer of the alkynyl group to the Pd catalyst through the on-site formation of a copper acetylide species. This species then undergoes transmetalation to transfer the alkynyl group to the Pd catalyst. The catalytic cycle of Sonogashira reaction can be seen in Scheme 4.[6]



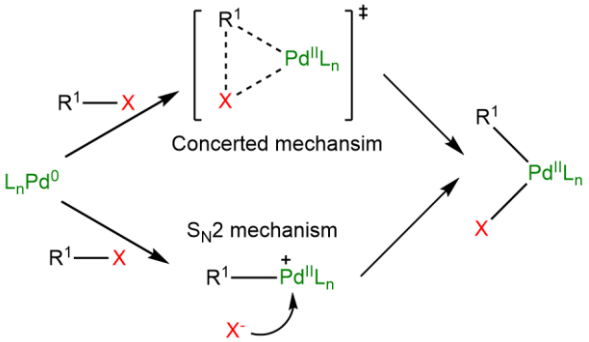
Scheme 4. Catalytic cycle for the copper co-catalysed Sonogashira reaction.

In past few years, considerable efforts have been dedicated to the development of reaction methodologies that can be conducted without the use of copper salts. These innovative strategies are commonly known as copper-free Sonogashira reactions.[1]

3.1.1. Oxidative addition

The catalytic cycle begins with the oxidative addition. The bond between organic R^1 group and the X halide/pseudohalide dissociates and both form a new linkage to the palladium(0) center, forming a Pd(II)-complex. This process could be reversible but the oxidation is favored when the ligands are electron-donating because they stabilize high oxidation states.[1]

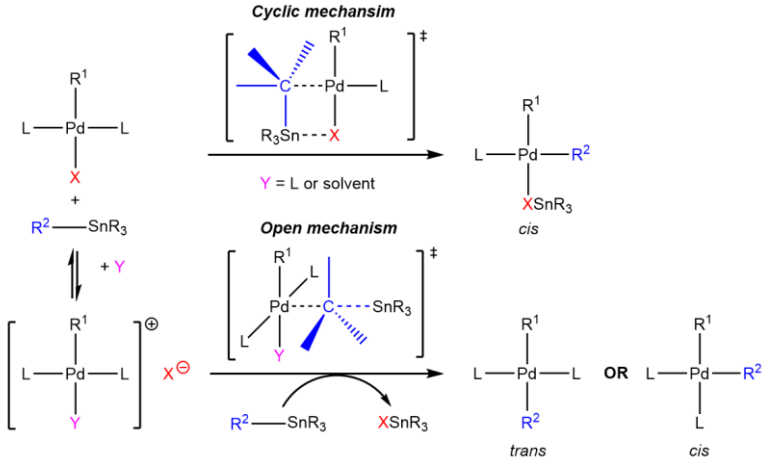
Scheme 5 illustrates two primary mechanisms proposed for this step. The first mechanism, known as the concerted pathway, involves the simultaneous formation of both the Pd-C and Pd-X bonds in the transition state. The second mechanism is an S_N2 substitution. The metal acts as a nucleophile and attacks the electrophile carbon, leading to the expulsion of the X^- anion and the formation of a cationic species. In the subsequent step, these charged species combine to produce the final product.[1,3] Nevertheless, even though a *cis*-intermediate is typically formed through an oxidative addition, it quickly reaches an equilibrium with its *trans*-isomer.[7]



Scheme 5. Two mechanisms for the oxidative addition.

3.1.2. Transmetalation

The mechanism for the transmetalation step is expected to show variations depending on the specific cross-coupling reactions, since they use different nucleophiles. Sonogashira transmetalation is performed by the copper salt depicted in Scheme 4. In Stille reaction, the organotin reagent, usually an aryl-, alkenyl- or allyl-trialkylstannane (R^2-Sn(alkyl)$_3$), coordinates with the Pd(II)-halide complex through one of its double bonds. Subsequently, ligand detachment occurs, restoring a square planar complex.[3] This transfer requires breaking the R^2-Sn bond, while the X group coordinated with the palladium must leave along with the tin, completing the transmetalation. Two main mechanisms could explain this stage: cyclic mechanism and open mechanism (Scheme 6).



Scheme 6. Mechanisms for the transmetalation stage in the Stille reaction.

In the open mechanism, both ancillary ligands (often phosphines or arsines) remain attached to palladium during the key transition state. On the other hand, the cyclic mechanism occurs when one of the ligands is released during the process. The dominance of either mechanism is influenced by certain factors.

The cyclic mechanism is favored when phosphine dissociation is promoted. This can be achieved by using bulky phosphines. Conversely, the open mechanism is favored when the dissociation of the X group (leaving group) is encouraged. This is because dissociation of group X removes electron density from the complex and impedes ligand dissociation. Factors that promote X group dissociation include the presence of good leaving groups, such as triflate, or the use of polar solvents.[1]

3.1.3. Reductive elimination

Following transmetalation, reductive elimination occurs. During this step, the palladium catalyst undergoes a rearrangement, resulting in the formation of a new carbon-carbon bond. The newly formed sigma bond, between the organic groups R^1 and R^2 in *cis*-position, coordinates to the palladium center and, ultimately, dissociation occurs, leading to the formation of the coupled product and simultaneosly reducing Pd(II) to Pd(0). It has been demonstrated that C_{sp^2}-C_{sp^2} elimination is the most favorable.[8] At this stage, the catalyst is regenerated and can undergo further catalytic cycles to facilitate additional Stille coupling reactions.

4. OBJECTIVES

The main objectives of this work dealing with the carbon-carbon coupling reactions are the following:

1. A search of bibliography of both Stille and Sonogashira reactions using the Reaxys database. Important information about each experimental process, such as catalysts, substrates and conditions, is also retrieved.
2. A classification of the obtained information for these two reactions. In this point, the study is focused on the catalysts species and the conditions of reaction (yield, time, temperature, solvent…).
3. A discussion containing the detailed analysis of these results in order to understand the factors that control the performance of each member of the two families.
4. A guide of the activity for an ideal catalyst, in order to provide more efficient process.

5. METHODS

The Reaxys platform was launched in 2009 by Elsevier. It is a web-accessed tool to provide chemical information such as physical and chemical properties as well as reaction conditions from the original publications, covering all organic, organometallic, and inorganic chemistry. As the successor of the Cross-Fire database, it includes information found in Beilstein (organic chemistry) and Gmelin (organometallic and inorganic chemistry). Overall, it currently contains more than 267 million substances and 62 million reactions from 143 million documents including patents.

Reaxys was accessed from the *Centre de Recursos per l'Aprenentatge i la Investigació* (CRAI) of the *Universitat de Barcelona*. A quick search by type for reactions was made in all cases, and posteriorly the results were refined by reaction yield and similarity. All chemical information available in the database relative to the reactions was downloaded together with the bibliographic references. In some cases, original references were consulted to clarify or to search additional information, in order to complete the values of TON and TOF parameters.

6. RESULTS AND DISCUSSION

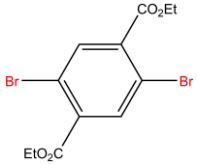
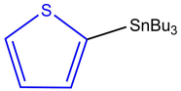
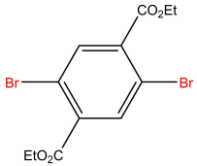
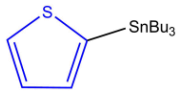
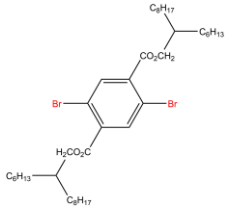
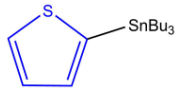
A multitude of papers have been found presenting Stille and Sonogashira reactions using different catalysts and carried out under different experimental conditions. Thus, the yield and the turnover number (TON) of each reaction have allowed to understand which catalysts are the most efficient for each type of carbon-carbon coupling mechanism.

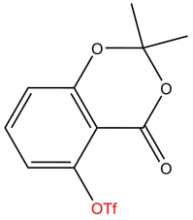
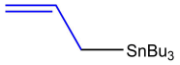
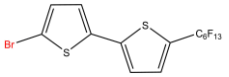
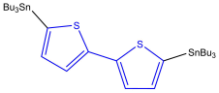
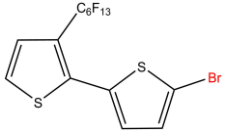
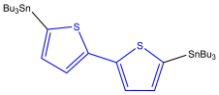
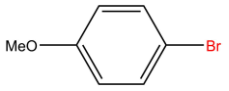
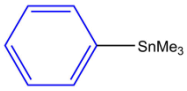
The turnover number of the catalyst is the number of moles of substrate that a mole of catalyst is able to convert before becoming inactivated. This value has been calculated by dividing the moles of product obtained by the moles of catalyst used.[9] Furthermore, the turnover frequency (TOF) was also calculated by dividing the TON by the reaction time in hours.

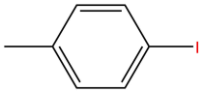
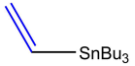
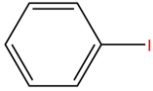
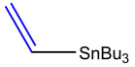
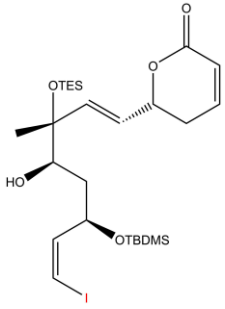
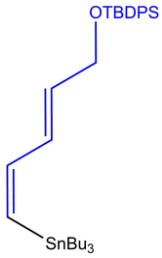
Table 1 illustrates the compilation of Stille reactions, while Table 2 presents the Sonogashira reactions. After each table, a discussion of the results will be provided. The entries of the tables, to make it easier to compare the reactions, have a letter following the number in case the substrates A (electrophilic group; leaving group in red color) and B (nucleophilic group in blue color) are identical or similar. In the case where there are subgroups within the reaction comparisons, a numerical subindex has been placed after the letter.

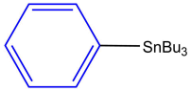
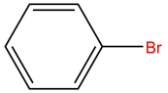
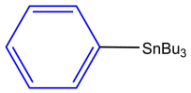
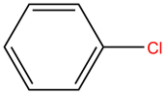
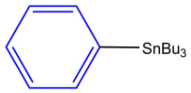
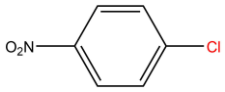
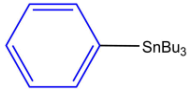
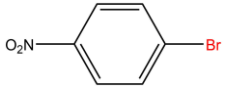
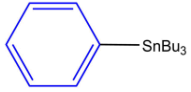
In order to be able to draw conclusions more clearly and to see that the use of certain conditions follows a trend, the number of entries in the tables has been reduced to half of the entries that had been filed earlier in the results search process.

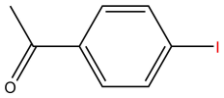
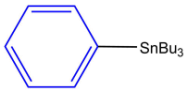
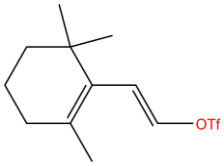
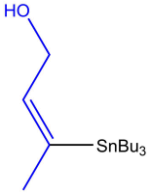
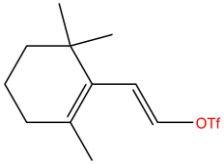
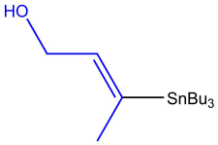
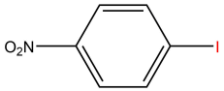
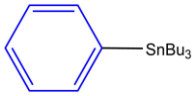
6.1. STILLE CARBON-CARBON COUPLING REACTIONS

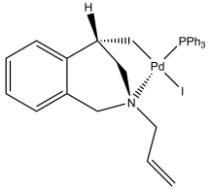
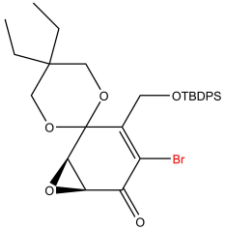
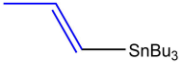
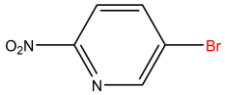
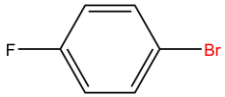
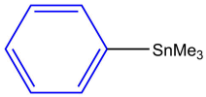
Entry	Stille coupling reaction		Yield	Conditions	Catalyst	TON	TOF [h^{-1}]	*Ref*
	A	B						
1a1			82%	Tol at 110ºC for 24h	$[Pd(PPh_3)_4]$	16	0.7	10
1a2			79%	Tol at 100ºC for 24h	$[Pd(PPh_3)_4]$	16	0.7	11
1b			90%	P(*o*-tol)$_3$ in THF, reflux for 3h	$[Pd_2(dba)_3]$	30	10	12
1c			70%	Tol, reflux for 12h	$[Pd(PPh_3)_4]$	41	3.4	13

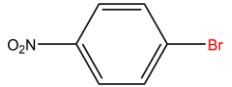
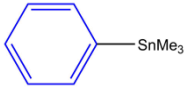
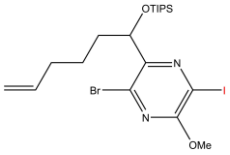
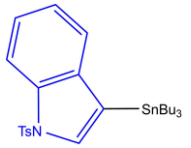
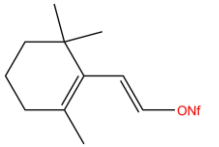
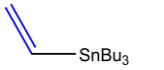
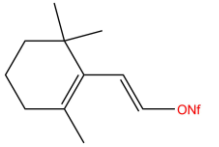
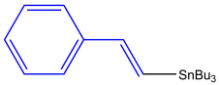
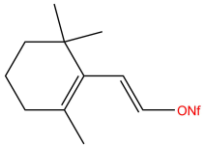
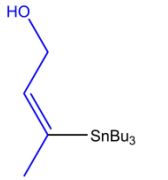
2a			99%	LiCl in THF, reflux for 48h	$[Pd(PPh_3)_4]$	51	1.1	14
2b			87%	TFP, LiCl in NMP, reflux for 44h	$[Pd_2(dba)_3]$	89	2	15
3a			95%	DMF at 80ºC for 7h	$[Pd(PPh_3)_4]$	42	6	16
3b			90%	DMF at 90ºC for 12h	$[Pd(PPh_3)_4]$	40	3.3	17
4a			92%	IPr·HCl, Bu_4NF in THF/1,4-dioxane at 80ºC for 2h	$[Pd(OAc)_2]$	31	16	18
4b			91%	K_2CO_3 in H_2O at 100ºC for 1h	$LaCo_{0.38}Fe_{0.57}O_3Pd_{0.05}$	1820	1820	19
4c			88%	Bu_4NOAc in ^{i}PrOH/Tol (1:1) at 90ºC	$[Pd(OAc)_2]$ encapsulated in polyurea	35	-	20

5a$_1$			100%	NMP at 130ºC for 8h	[$PdCl_2$(4,4'-R_2-bpy)]	13	1.6	21
5a$_2$			88%	NMP at 100ºC for 8h	nano Pt LDH-supported	88	11	22
5b			92%	NMP at 100ºC for 6h	nano Pt LDH-supported	92	15	22
6a			88%	DMF at 0ºC for 24h	[$PdCl_2$(MeCN)$_2$]	18	0.8	23
6b			85%	DMF at 20ºC for 5h	[$PdCl_2$(MeCN)$_2$]	0.6	0.1	24

7a$_1$			99%	CsF in DMSO at 120ºC for 5h	$[PdCl_2(pol\text{-}tz)]$	239	48	25
7a$_2$			95%	CuI, $AsPh_3$ in BMIM-BF_4 at 80ºC for 18h	$[PdCl_2(PhCN)_2]$	19	1.1	26
7a$_3$			84%	CsF in 1,4-dioxane at 110ºC for 14h	Pd@Fe_3O_4 nanowires	168	12	27
7a$_4$			61%	KF, mesitylene in DMF at 80ºC for 6h	$[Pd(OAc)_2]$ supported	122	20	28
7b			75%	CsF in DMSO at 120ºC for 10h	$[PdCl_2(pol\text{-}tz)]$	181	18	25
7c			35%	CsF in DMSO at 120ºC for 24h	$[PdCl_2(pol\text{-}tz)]$	85	3.5	25
7d			95%	CsF in DMSO at 120ºC for 5h	$[PdCl_2(pol\text{-}tz)]$	229	46	25
7e			95%	CsF in DMSO at 120ºC for 8h	$[PdCl_2(pol\text{-}tz)]$	229	29	25

8a			98%	$NaHCO_3$ in H_2O at 110°C for 3h	$[PdCl_2(NH_3)_2]$ + L	9800	3267	29
8b			82%	$NaHCO_3$ in H_2O at 110°C for 48h	$[PdCl_2(NH_3)_2]$ + L	8.2 $\cdot 10^5$	1.7 $\cdot 10^4$	29
9a$_1$			87%	DMF at 20°C for 2h	$[Pd(PPh_3)_4]$	9	5	30
9a$_2$			87%	$AsPh_3$ in DMF at 20°C for 2h	$[Pd_2(dba)_3]$	35	18	31
9b			76%	$AsPh_3$ in DMF at 20°C for 2h	$[Pd_2(dba)_3]$	15	8	32
10a			100%	DABCO, Bu_4NF in 1,4-dioxane at 100°C for 8h	$[Pd(OAc)_2]$	33	4.1	33
10b			100%	Orotic acid, CsF in 1,4-dioxane at 100°C for 18h	$[Pd(OAc)_2]$	33	1.8	34

10c			99%	DMF at 80ºC for 24h		9900	413	35
11			98%	$AsPh_3$ in Tol at 110ºC for 2h	$[Pd_2(dba)_3]$	20	10	36
12			55%	1,4-dioxane, reflux for 6h	$[Pd(PPh_3)_4]$	14	2.3	37
13a			93%	K_2CO_3 in H_2O at 100ºC for 1h	$LaCo_{0.38}Fe_{0.57}O_3Pd_{0.05}$	1860	1860	19
13b			82%	Bu_4NOAc in ^{i}PrOH/Tol (1:1) at 90ºC	$[Pd(OAc)_2]$ encapsulated in polyurea	33	-	20

14			99%	Bu_4NOAc in $^{i}PrOH$/Tol (1:1) at 90ºC for 3h	$[Pd(OAc)_2]$ encapsulated in polyurea	40	13	20
15			85%	CuCl, LiCl in DMSO at 20ºC for 0.5h	$[Pd(PPh_3)_4]$	9	18	38
16			100%	$AsPh_3$ in DMF at 20ºC for 3h	$[Pd_2(dba)_3]$	40	13	39
17			91%	$AsPh_3$ in DMF at 20ºC for 0.5h	$[Pd_2(dba)_3]$	36	72	39
18			92%	$AsPh_3$ in DMF at 20ºC for 2h	$[Pd_2(dba)_3]$	37	18	39

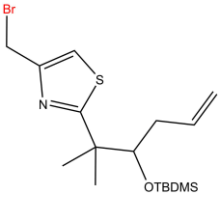
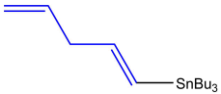
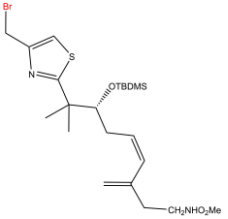
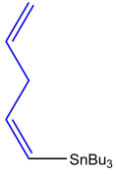
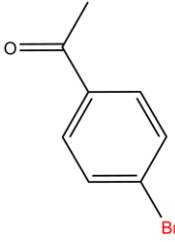
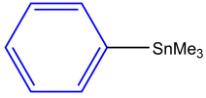
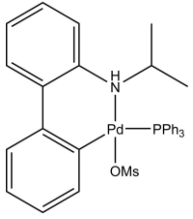
19a			95%	NMP at 20ºC for 0.5h	$[PdCl_2(MeCN)_2]$	8	16	40
19b			94%	CuI, CsF in DMF at 20ºC for 0.83h	$[Pd(PPh_3)_4]$	18	22	41
20			88%	KF, CuI, Bu_4NCl, Brij-30/H_2O at 55ºC for 24h		880	37	42

Table 1. Stille carbon-carbon coupling reactions.

Reactions **1a$_1$** and **1a$_2$** have the same conditions except that the former has been carried out at 10 degrees higher temperature and hence it has a slightly higher yield. Reaction **1b** has a higher yield and has double the TON of reaction **1a** with a reaction time 21 hours shorter. THF has been used as solvent instead of toluene and [$Pd_2(dba)_3$] as catalyst instead of [$Pd(PPh_3)_4$]. It should also be noted that the dimethyl ester of **1b** has less steric hindrance than the diethyl ester of **1a**. On the other hand, in reaction **1c** the same conditions as in **1a** have been used but with half the time and the mixture at reflux. It has suffered more steric hindrance because of the 2-hexyldecyl ester and for that reason the yield is lower despite having a TON value of almost three times more than **1a**.

In entry **2b** it is observed that the [$Pd_2(dba)_3$] catalyst together with the TFP ligand and using NMP as solvent significantly improves the TON of **2a**, which uses [$Pd(PPh_3)_4$] and THF. In THF solvent, LiCl is necessary to make coupling possible because the initial product formed is not effective in catalyzing the reaction. By replacing a ligand with chloride, LiCl forms a more reactive species. However, in highly polar solvents such as NMP, LiCl is usually not necessary and might even be an inhibitor of the coupling.[43] For that reason, **2b** achieves a lower yield than **2a.**

3a achieves a better yield than **3b** because it has less steric hindrance since the two perfluorohexyl groups of the product will remain in *trans*.

4b has used a palladium containing perovskite-like composite oxide as a catalyst for this reaction in the same way as in reaction **13a**. The two reactions differ in the *para*-substituent of the aryl. **13a** has a slightly higher yield since the fluoride is an electron-withdrawing group and increases the electrophilicity of the aryl halide. It is shown that this catalytic system achieves an enormous TON. For each mole of palladium yields 1820 moles of product.

In entry **5**, the bidentate ligand complex of palladium enhances reactivity in the oxidative addition of the aryl iodide.[2] Therefore, **5a$_1$** achieves a higher yield than the rest of the reactions **5**. In contrast, the reactions catalyzed by nano Pt supported in LDH, use less amount of metal (more TON) than **5a$_1$**. It can be deduced that **5a$_2$** have a lower yield than **5b** because the methyl of the aryl iodide is an electron-donating group and decreases his electrophilicity.

The LDHs (layered double hydroxide) consists on alternating cationic $M(II)_{1-x}M(III)_x(OH)_2^{x+}$ and anionic $A^{n-}\cdot zH_2O$ layers. Small hexagonal LDH crystals with $Mg(II)_{1x}Al(III)_x(OH)_2(Cl)_x\cdot zH_2O$ were synthesized (x = 0.25). The positive charged layers contain edge-shared metal M(II) and M(III) hydroxide octahedra, with charges neutralized by A^{n-} anions located in the interlayer

spacing. Hexachloroplatinate was exchanged onto LDH to obtain a light yellow colored LDH-Pt(IV) and subsequently reduced with hydrazine hydrate to give air-stable black LDH-Pt(0) catalyst.[22]

The reaction **6a** obtains more percentage of net product than **6b** due to the longer reaction time spent.

In entry **7**, CsF is used to activate the stannane by fluoride coordination affording a pentacoordinated tin species with a better reactivity in transmetalation step.[3] For this reason, **7a**$_1$, **7a**$_3$, **7b-e** reactions present a great TON. It is noted that **7c** gives a poor yield because the chlorobenzene is less electrophilic because of chloride is worse leaving group than other halides. **7a**$_2$ employs BMIM-BF4, a room-temperature ionic liquid (RTIL), as a solvent allowing the recycling of the solvent and catalyst system, which can be used at least five times with little loss in activity making the process more cost-effective. In the coupling of aryl iodides, [$PdCl_2(PhCN)_2$] catalyst system gives food yields but, on the other hand, [$Pd(PPh_3)_4$] offers very low product percentages. In the case of aryl bromide coupling, the opposite happens.[26]

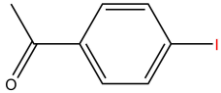
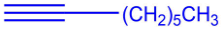
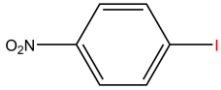
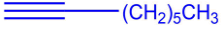
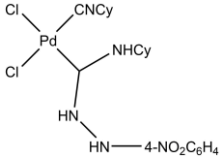
The reactions in entry **8**, reach a remarkably high TON with the use of [5,5'-$(Me_3NCH_2)_2$bpy] bidentate ligand. Also, reactions **10c** and **20**, using a bidentate ligand in the catalyst showed both in Table 1, have TON values around 10^4 and 10^3, respectively. The second one uses Brij-30, as a surfactant, and water to replace the commonly used organic solvent.

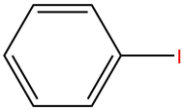
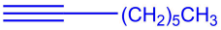
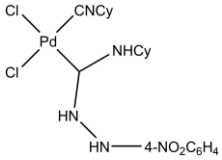
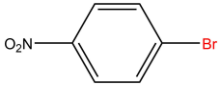
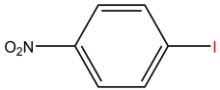
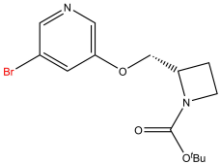
9a$_2$, using [$Pd_2(dba)_3$] gives a higher TON than **9a**$_1$, which use [$Pd(PPh_3)_4$], under exactly the same conditions. The mixing of [$Pd_2(dba)_3$] and $AsPh_3$ forms monomeric [$Pd(dba)(AsPh_3)_2$]. This combination gives excellent results in **11** and **16-18**. On the other hand, **9b**, because of the steric hindrance of the alkene isomer *Z*, obtains less quantity of product and less TON (half) than **9a**. Moreover, **18** turns out to give a better yield than the other reactions **9** since the nonaflate (ONf) is a better leaving group than the triflate (OTf).

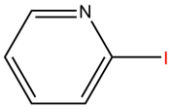
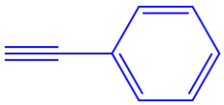
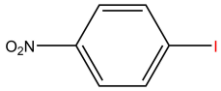
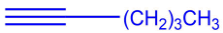
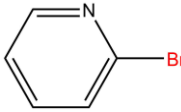
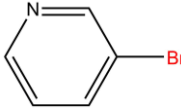
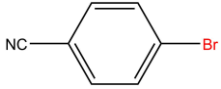
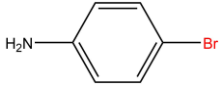
14 improves the yield of **13b** since the nitro group is more electron-withdrawing than fluoride.

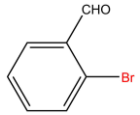
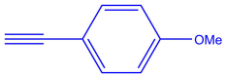
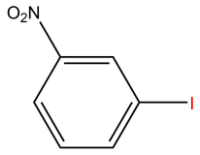
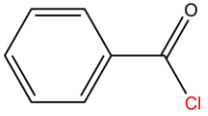
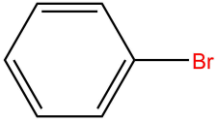
The copper salt employed in **15**, as well as **19b**, has the function of favoring the dissociation of two ligands of the catalyst precursor [PdL_4]. On the contrary, **12** does not use a copper salt and its performance falls drastically, also due to the fact that the nucleophilic organic group is not presenting a C_{2p}[2].

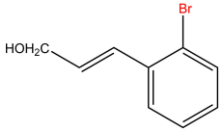
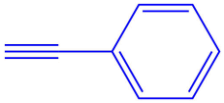
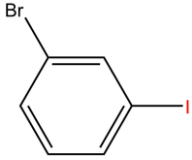
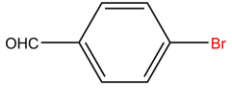
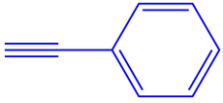
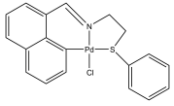
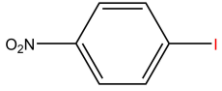
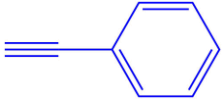
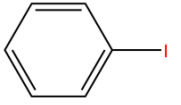
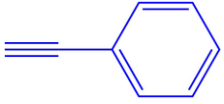
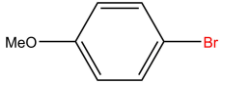
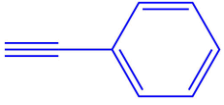
6.2 SONOGASHIRA CARBON-CARBON COUPLING REACTIONS

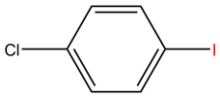
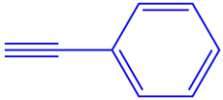
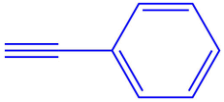
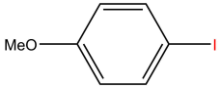
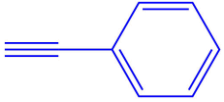
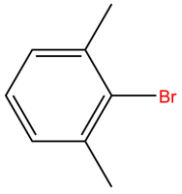
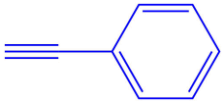
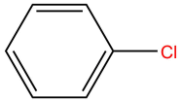
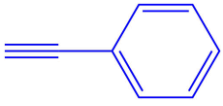
Entry	Sonogashira coupling reaction		Yield	Conditions	Catalyst	TON	TOF	*Ref*
	A	B						
1a			96%	piperidine, CuI, SDS in H_2O at 40ºC for 5h	$[PdCl_2(PPh_3)_2]$	48	9.6	44
1b			61%	piperidine, SDS in H_2O at 40ºC for 5h	$[PdCl_2(PPh_3)_2]$	31	6.2	44
$2a_1$			97%	K_2CO_3 in EtOH at 80ºC for 2h		1940	970	45
$2a_2$			96%	Bu_4NOAc in DMF at 20ºC for 3h	$[Pd(OAc)_2]$	96	32	46

2b			89%	K_2CO_3 in EtOH at 80ºC for 2h		1780	890	45
3a$_1$			92%	Bu_4NOAc in DMF at 20ºC for 5h	$[Pd_2(dba)_3]$	46	9.2	46
3a$_2$			86%	Bu_4NHSO_4, Et_3N, PPh_3 in H_2O/MeCN (1:10) at 25ºC for 1.5h	$[Pd(OAc)_2]$	9	6	47
3b			98%	Bu_4NOAc in DMF at 20ºC for 3h	$[Pd(OAc)_2]$	98	33	46
4			81%	$^{i}PrNH_2$, CuI, $P(^{t}Bu)_3$ in hexane at 80ºC for 36h	$[PdCl_2(PPh_3)_2]$	16	0.4	48

5a			96%	CuI, K_2CO_3 in PEG-400/H_2O (3:2) at 100ºC for 2h	$[NiCl_2(PPh_3)_2]$	19	10	49
5b			96%	Cs_2CO_3 in MeOH at 55ºC for 6h	$[Pd(OAc)_2]$ + Xantphos	19	3.2	50
6			97%	piperidine, CuI at 20ºC for 1.5h	$[Pd(PPh_3)_2]$ supported	194	129	51
7a			100 %	CuI, Et_3N at 70ºC for 3h	$[PdCl_2(PPh_3)_2]$	35	12	52
7b			80%	CuI, Et_3N at 80ºC for 5h	$[PdCl_2(PPh_3)_2]$	28	5.6	52
8a			99%	CuI, Et_3N in THF at 45ºC for 24h	$[Pd(PPh_3)_4]$	99	4.1	53
8b			77%	CuI, Et_3N in THF at 45ºC for 24h	$[Pd(PPh_3)_4]$	77	3.2	53

9			99%	CuI, Et_3N at 50ºC for 6h	$[PdCl_2(PPh_3)_2]$	50	8.3	54
10a			99%	CuI, Et_3N, BMIM-BF_4 at 65ºC for 24h	$[PdCl_2(PPh_3)_2]$	99	4.1	55
10b			98%	piperidine, CuI at 20ºC for 2h	$[Pd(PPh_3)_2]$ supported	196	98	56
11a			98%	CuI, Et_3N in THF at 20ºC for 0.5h	$[PdCl_2(PPh_3)_2]$	49	98	57
11b			97%	$C_{10}F_{21}PPh_2$, Et_3N in Tol at 40ºC for 1.5h	$[PdCl_2(PhCN)_2]$	97	65	58
12a			95%	pyrrolidine, CuI in H_2O at 70ºC for 0.5h	$[Pd(PPh_3)_4]$	19	38	59
12b			93%	piperidine in H_2O at 50ºC for 3h	$[(BeDABCO)_2 Pd_2Cl_6]$	310	103	60
12c			90%	$(^iPr)_2NH$, $(^tBu)_3PHBF_4$, CuI at 80ºC for 12h	$Na_2[PdCl_4]$	9000	750	61

13			96%	CuI, P(^{t}Bu)$_3$, Et$_3$N in Tol at 20ºC for 8h	[PdCl$_2$(PhCN)$_2$]	20	2.5	62
14			92%	CuI, Et$_3$N at 60ºC for 2h	[PdCl$_2$(PPh$_3$)$_2$]	100	50	63
15			99%	K$_2$CO$_3$ in DMF at 90ºC for 1h		1980	1980	64
16a			96%	DABCO, Cs$_2$CO$_3$ in MeCN at 20ºC for 20h	[Pd(OAc)$_2$]	960	48	65
16b			74%	DABCO, Cs$_2$CO$_3$ in MeCN at 20ºC for 24h	[Pd(OAc)$_2$]	740	31	65
17			100 %	CuI, K$_2$CO$_3$ in DMF at 130ºC for 20h	[PdCl(η^3-C$_3$H$_5$)]$_2$ + 1,1'-bis[bis(5-methyl-2-furanyl)phosphino]ferrocene	1000	50	66

18			100 %	Pyrrolidine, Bu_4NBr at 100ºC for 1h	$PdCl_2$ + py_2NMe	1000	1000	67
19			100 %	CuI, K_2CO_3 in 1,4-dioxane/water (3:1), reflux for 4h	$[NiCl_2(PPh_3)_2]$	20	5	68
20			100 %	CuI, Et_3N in Cyrene at 30ºC for 1h	$[PdCl_2(PPh_3)_2]$	50	50	69
21			95%	K_2CO_3 in DMF at 140ºC for 20h	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ + Tedicyp	950	48	70
22			99%	Et_3N in DMF at 25ºC	$[Ni(dmbpy)(H_2O)_4]SeO_4$	83	-	71

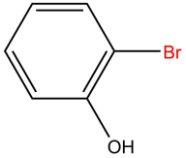
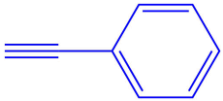
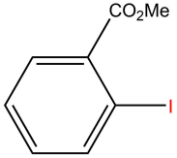
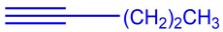
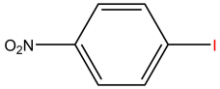
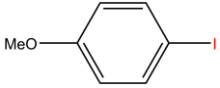
23			92%	$AuCl(PPh_3)$, Et_3N in DMF at 80ºC for 3h	$[PdCl_2(PPh_3)_2]$	46	15	72
24a			99%	CuI, $(^iPr)_2NEt$ in DMF at 20ºC for 24h	$[PdCl_2(PPh_3)_2]$	11	0.5	73
24b			80%	CuI, Et_3N in DMF at 20ºC for 5h	$[PdCl_2(PPh_3)_2]$	27	5.4	74
25			97%	CuI, Et_3N in $CHCl_3$ at 20ºC for 1.25h	$[PdI(Ph)(PPh_3)_2]$	97	78	75
26			99%	CuI, Et_3N in MeCN at 20ºC for 3h	$[PdCl_2(PPh_3)_2]$	99	33	76

Table 2. Sonogashira carbon-carbon coupling reactions.

In reaction **1a**, sodium dodecyl-sulfat (SDS) acts as a surfactant enhancing reactivity in water and thus minimizes the need for organic solvents. CuI 5 mol% works as a co-catalyst and significantly influences the reaction yield. This is seen in reaction **1b** which lacks the co-catalyst. The main advantage of using Cu is its ability to promote the formation of the Pd-acetylide, which occurs through the formation of a Cu-acetylide intermediate.

2a$_1$ did not use copper co-catalyst because it may lead to unwanted side reactions such as the formation of diynes or the subsequent cyclization of the products. The catalyst used belongs to the family of the acyclic diaminocarbenes (ADC) palladium complexes and has been shown to be active in copper-free Sonogashira coupling reaction under mild conditions without air protection. **2a**$_2$ also does not use copper but needs inert atmosphere, so it uses argon. **2b**, under same condition as **2a**$_1$, achieved a lower yield because it does not have the nitro substituent that lowers the electron density of the aryl iodide. However, both, **2a**$_1$ and **2b**, have a great TON value around $2 \cdot 10^3$.

In reaction **3**, it is noted that palladium acetate is used as catalyst for aryl iodides and $[Pd_2(dba)_3]$ for bromides.[46] Moreover, reaction **3b** has a higher yield than **3a**$_1$, mainly because the iodide is a better leaving group than the bromide. **3a**$_2$, containing triphenylphosphine as a ligand for palladium diacetate and without the addition of copper iodide, ends the reaction with less time but achieves worse performance and lower TON.

The product of **4** is a precursor in the synthesis of sazetidine-A, which is a desensitizer of $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors (nAChRs) without first activating them. These receptors are important for our body's normal functions and have been connected to nicotine addiction. They can also be targeted for potential treatments of different conditions like cognitive disorders, neuropathic pain, and Parkinson's disease.

In entry **5a**, **19**, and **22** nickel replaces the palladium as a metal center of the catalyst and had an excellent yield and an average TON. It seems to be an inexpensive alternative to palladium catalysts. The price of a kilo of palladium is around 20000 euros as opposed to 10 euros for a kilo of nickel.[77] Reaction **5b** reaches the same yield than **5a** and uses Xantphos as a ligand for palladium diacetate, which undergoes intramolecular reduction to form Pd(0) complex.

In entry **6**, the bis(triphenylphosphine)-palladium(0) is supported in a mesoporous sillica called MCM-41 and the heterogeneous Sonogashira coupling was efficiently catalyzed as it can be seen in his TON value. The catalyst was recycled 10 times without loss of activity.[51]

7b obtained an 80% yield in contrast to the 100% yield of **7a**. This fact is due to the electronegative character of nitrogen. The 2-bromopyridine has the bromide closer to the nitrogen than the 3-bromopyridine, therefore the carbon linked to the bromide will be more electrophilic due to the removal of electron density by the nitrogen.

8b has an amino group as activator of the aromatic ring of the halide. Therefore, it obtained a yield of 77% unlike the case of **8a**, where the aryl bromide has a deactivating group as nitrile, which achieved a quantitative reaction.

In **11b**, the ligand $C_{10}F_{21}PPh_2$ reacts with $[PdCl_2(PhCN)_2]$ to form $[PdCl_2(C_{10}F_{21}PPh_2)_2]$, a catalyst that does not require the presence of CuI.

12b has a quaternary ammonium salt that is effective in inhibiting the aggregation of Pd(0) nonstable species. The phosphonium salt $(^tBu)_3PHBF_4$, in reaction **12c**, is not sensitive to oxidation, but immediately generates $P(^tBu)_3$ ligand in the basic amine solvent, $(^iPr)_2NH$). Of the three reactions **12**, the **12c** has a slightly lower performance than the others but compensates for it with a highly superior TON and TOF. Thus, it would be the most efficient reaction.

In entry **15**, the bidentate ligand palladium complex provides a 1980 TON in a copper-free Sonogashira coupling reaction with potassium carbonate acting as base.

The electron-withdrawing group nitro in **16** significantly increases yield. In addition, these reactions with DABCO as a ligand show a TON around 10^3.

The reaction **17** and **37b** have a great TON (10^3) by using a similar catalytic system but the latter is not using CuI as co-catalyst. Both methods applies a ligand to allylpalladium(II) chloride dimer.

When the reaction **18** was also irradiated with microwaves, the TOF increased to 12000 h^{-1}. Here, the (dipyridin-2-yl)methylamine, coordinated with palladium(II) dichloride complex, enhance the coupling facilitating the oxidative addition because is an electron-donor ligand.

In **20**, is used (1*R*)-7,8-dioxabicyclo[3.2.1]octan-2-one (Cyrene) as solvent. It is an environmentally friendly alternative to DMF and NMP.

23 uses $AuCl(PPh_3)$ as a co-catalyst. Au(I) species have a stronger preference for reacting with alkynes compared to other metals like copper and silver. This means that using cationic gold(I) instead of copper as a co-catalyst in Sonogashira reaction can not only promote the

reaction between aryl halides and alkynes but also avoid the formation of unwanted byproducts commonly seen when copper is used.

In reaction **24**, it can be observed that the base N,N-diisopropylethylamine provides a 19% higher yield compared to using triethylamine.

Reaction **26** exhibits a higher yield compared to reaction **25**, despite having an electron-donating group in the aryl halide. This suggests that the catalyst bis(triphenylphosphine)-palladium(II) dichloride is more efficient than phenylbis(triphenylphosphine)-palladium(II) iodide.

7. CONCLUSIONS

- The catalytic cycle of cross-coupling reactions of carbon-carbon begins with a metal complex in a 0 oxidation state since it needs to be oxidized upon coordination with the organic halide. In many cases, catalyst precursor is a palladium species, as revealed by the Reaxys database search, in a 2 oxidation state for greater stability, which will subsequently be reduced to initiate the oxidative addition step. Ligands and solvents play a significant role in the reaction performance as they can modify the nucleophilic character of the catalyst and influence the behavior of the metal with the reagents, potentially directing the reaction pathway towards different mechanisms.

- In general, precursor catalysts of the [PdL_4] type, such as [$Pd(PPh_3)_4$], are less efficient because the dissociation of two ligands prior to oxidative addition is not as favored as in the case of [$PdCl_2(PPh_3)_2$], where chlorides have a higher affinity to leave.

- Increasing the reaction time, raising the temperature, or even a microwave irradiation are conditions that typically enhance the process's yield. Additionally, the steric effects, the electron-withdrawing/donating nature of the substituent groups on the aryl halide and the leaving group significantly impact the efficiency of the carbon-carbon coupling. It has also been observed that the choice of solvent plays a crucial role, and the base used in the Sonogashira reaction influences the amount of final product obtained.

- In most cases, the use of bidentate ligands significantly increases the catalyst's TON by enhancing reactivity during the oxidative addition step. For the Stille reaction, it has been observed that both palladium-doped perovskites and platinum nanoparticles provide good yields with minimal metal consumption.

- In the Sonogashira reaction, it has been found that the copper(I) co-catalyst can be eliminated if other species facilitate the transmetalation step. In this case, the ligand DABCO offers a high TON without the need for a copper salt. Furthermore, isopropylamines as bases have shown better yields compared to the more popular triethylamine.

- Lastly, the search results indicate that there is currently little competition for palladium as the preferred metal catalyst in Stille and Sonogashira reactions. Nickel may be a more cost-effective and viable substitute for palladium, but palladium affords significantly higher yields and turnover number. Therefore, it is crucial to be able to recycle the catalyst since palladium is a scarce and expensive metal. The use of room-temperature ionic liquids as solvents and mesoporous supports allows for multiple repetitions of the reaction without losing catalytic efficiency.

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12. ACRONYMS

BMIM: 1-butyl-3-methylimidazolium

Brij-30: 2-(dodecyloxy)ethan-1-ol

Cy: isocyanide

DABCO: 1,4-diaza-bicyclo[2.2.2]octane

dba: dibenzylideneacetone

dmbpy: 5,5'-dimethyl-2,2'-bipyridine

IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene

Ms: methanesulfonyl (mesyl)

Nf: nonafluorobutanesulfonyl (nonaflyl)

NMP: 1-methyl-pyrrolidin-2-one

PEG: polyethylene glycol

TBDMS: tert-butyldimethylsilyl

TBDPS: tert-butyldiphenylsilyl

Tedicyp: (1RS,2RS,3SR,4SR)-1,2,3,4-tetrakis((diphenylphosphanyl)methyl)cyclopentane

TES: triethylsilyl

TMS: trimethtlsilyl

Tf: trifluoromethanesulfonyl (triflyl)

TFP: tri(2-furyl)phosphine

TIPS: triisopropylsilyl

Ts: p-toluenesulfonyl (tosyl)

tz: 4-(2-pyridyl)-1,2,3-triazole

Xantphos: (9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane)