Insights into the catalytic activity of [Pd(NHC)(cin)Cl] (NHC = IPr, IPrCl, IPrBr) complexes in the Suzuki-Miyaura reaction

Frédéric Izquierdo,[+[a],[b]] Caroline Zinser,[+[b]] Yury Minenkov,[[c]] David B. Cordes,[[b]] Alexandra M. Z. Slawin,[[b]] Luigi Cavallo,[[c]] Fady Nahra,[[d]] Catherine S. J. Cazin*[[d]] and Steven P. Nolan*[[d],[e]]

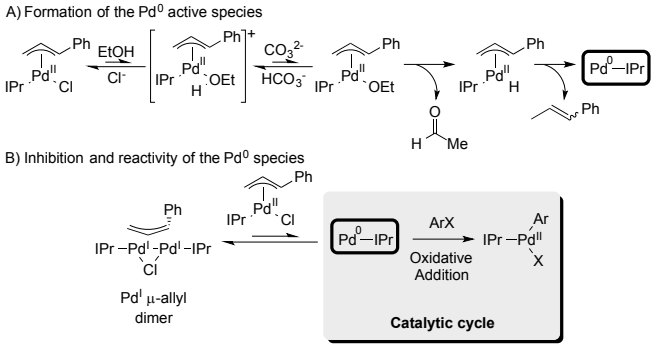
Dedicated to the memory of Professor István E. Markó

Abstract: The influence of $C^{4,5}$-halogenation on palladium N-heterocyclic carbene complexes and their activity in the Suzuki-Miyaura reaction have been investigated. Two [Pd(NHC)(cin)Cl] complexes bearing IPr^{Cl} and IPr^{Br} ligands were synthesized. After determining electronic and steric properties of these ligands, their properties were compared to those of [Pd(IPr)(cin)Cl]. The three palladium complexes were studied using DFT calculations to delineate their behaviour in the activation step leading to the putative 12-electron active catalyst. Experimentally, their catalytic activity in the Suzuki-Miyaura reaction involving a wide range of coupling partners (30 entries) at low catalyst loading was studied.

Introduction

Nowadays, palladium-catalyzed cross-coupling reactions have become an essential tool in organic and organometallic chemistry.[1] Since the first report in 1979,[2] the Suzuki-Miyaura reaction[1a, 3] has evolved to become the most popular method amongst the numerous palladium cross-coupling reactions.[1d, 4] For its ease of use, this reaction has been widely studied over the last decade and has found numerous applications in fields as varied as pharmaceuticals, agrochemicals and electronics.[3c, 5] Early on, tertiary phosphine ligands were prominent as catalyst modifiers in this transformation, in view of their stabilizing effects.[6] The use of bulky, electron-rich phosphine ligands such as dialkylbiaryl-[7] and trialkylphosphines was much later found to be beneficial for cross-coupling reactions.[8]

Regarding the development of other protocols, *N*-heterocyclic carbene (NHC)-based systems have shown notable catalytic performances,[9] in a number of palladium transformations but especially in the Suzuki-Miyaura reaction.[7c, 10] Among the plethora of Pd-(NHC) complexes,[9d-f, 10f, 11] the [Pd(NHC)(R-allyl)Cl] family has been shown to be highly active in the Suzuki-Miyaura coupling. However, the use of a strong base (*e.g.*, KO^{t}Bu) was thought required to generate the catalytically active species, a fact that limited the functional group tolerance of the protocol.[10a, 10b, 12] The first description of the activation of Pd-(allyl) complexes, using an alternate weak base (K_2CO_3), was described by Colacot and co-workers[13] and was followed by similar reports.[14] In the course of the preparation of the dinuclear Pd^I complex [Pd_2(IPr)$_2$-(η^3-cin)Cl] [IPr: 1,3-*bis*(2,6-di*iso*propyl-phenyl)imidazol-2-ylidene], Hazari and co-workers[14c] proposed an equilibrium between the Pd^I-dimer and the catalytically active Pd^0-NHC intermediate by a comproportionation/disproportionation reaction with unreactive [Pd(IPr)(cin)Cl].[14d-g] In this context, this study suggested the activation pathway of [Pd(NHC)(R-allyl)Cl] to proceed as depicted in Scheme 1. Based on these studies, Nolan and co-workers described the preparation of a wide range of organic compounds using 0.5 mol% [Pd(IPr)(cin)Cl] activated by K_2CO_3 in a 1:1 mixture of ethanol/water.[15]



Scheme 1: Activation pathway of [Pd(NHC)(R-allyl)Cl].

Further investigations continue to be carried out with the aim of designing ever more efficient catalytic system. Recently, Hazari and co-workers[14d] have prepared a variety of [Pd(IPr)(2-R-allyl)Cl] and compared their activity in the Suzuki-Miyaura reaction. What was examined in this report, both experimentally and computationally, were the effects of allyl group substitution on the Pd^0/Pd^I dimer interconversion.[14d] Subsequent reports from Hazari[14e, 14f] and Colacot,[16] highlighted the observation that the incorporation of very sterically hindered ligands should disfavor the comproportionation with unreactive pre-catalyst,

[a] Dr F. Izquierdo
Concept Life Sciences,
Discovery Park, Ramsgate Road,
Sandwich CT13 9FF (UK)

[b] C. Zinser, Prof. A.M. Z. Slawin, Dr D. B. Cordes
EaStCHEM School of Chemistry
University of St Andrews, St Andrews, KY16 9ST (UK)

[c] Dr Y. Minenkov, Prof. L. Cavallo
Department KAUST Catalysis Centre (KCC),
King Abdullah University of Science and Technology,
Thuwal-23955-6900, Saudi Arabia

[d] Dr Fady Nahra, Prof. Dr. S. P. Nolan, Prof. Dr C. S. J. Cazin
Department of Chemistry, Ghent University, Campus Sterre, Bldg S3, Krijgslaan 281, 9000 Ghent, Belgium
Phone: +32(0)92644458
E-mail: Steven.Nolan@UGent.be; Catherine.Cazin@Ugent.be

[e] Prof. Dr. Steven P. Nolan
Chemistry Department, College of Science, King Saud University,
Riyadh 11451, Saudi Arabia

[+] These authors contributed equally to this work.

Supporting information for this article is given via a link at the end of the document.

thereby providing highly active Pd^0 species. As a result, biarylphosphines[16-17] or bipyrazolylphosphines[16-17] have been combined with the π-allylpalladium platform (Figure 1, A) or the η^3- 1- ^{t}Bu-indenyl ligand has been used as a modified π-allyl moiety in conjunction with phosphine or NHC ligands[14f] (Figure 1, B) to generate longer-living catalytic species.

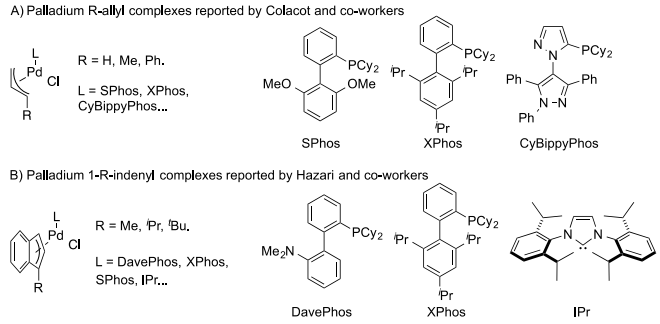


Figure 1: Recent Pd-complexes reported by Colacot and Hazari.

To contribute to this field of interest, the use $C^{4,5}$-halogenated NHCs was considered (Figure 2, **1** and **8**). Modified-backbone NHCs have gained notable significance, allowing the tuning of either electronic and/or steric properties.[9f, 18] Numerous highly efficient palladium pre-catalysts,[19] bearing ligands such as quinone-[19j, 20] and acenaphthylene-annelated[19p, 21] imidazol-2-ylidenes respectively **2** and **5** (Figure 2), alkyl-[19g, 19h, 22] (**3** and **4)** and chloro-disubstituted[19a, 19i, 22-23] carbenes (**1** and **6**) as well as *bis*(dimethylamino) carbene **7**[19b, 24] have shown remarkable activity in cross-coupling reactions.

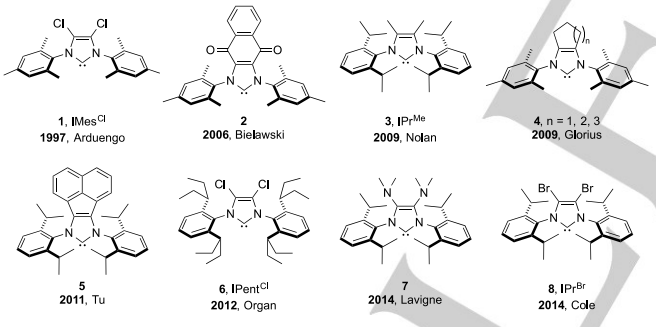


Figure 2: NHCs of interest presenting a modified backbone.

Dichlorinated imidazol-2-ylidenes at the $C^{4,5}$-positions **1** were first reported by Arduengo and co-workers in 1997.[19i, 19n] These ligands have showed predicted lower relative σ-donicity compared to their non-halogenated analogues.[18b] The IPr^{Cl} ligand (**1**) was involved in alkene metathesis transformations by Nolan and co-workers,[22] while $IPent^{Cl}$ (**6**) was used by Organ and co-workers in Stille cross-coupling[19a, 23b] and Pd-catalyzed amination.[23a, 23c] More recently, Cole and co-workers[19d] have reported on a series of metal complexes bearing IPr^{Br} (**8**) along with [Pd(IPr^{Br})(cin)Cl] (Figure 3, **9c**) which was briefly studied in the Suzuki-Miyaura cross coupling.[19d]

Results and Discussion

Preparation and characterization of [Pd(IPr^X)(cin)Cl] (X = Cl, Br).

In a desire to improve the catalytic activity of existing systems in the Suzuki-Miyaura cross-coupling, and comparing the influence of halogen substituents in the $C^{4,5}$-positions of imidazol-2-ylidene ring, [Pd(NHC)(cin)Cl] complexes bearing IPr (Figure 2, **9a**), IPr^{Cl} (**9b**) and IPr^{Br} (**9c**) were prepared.

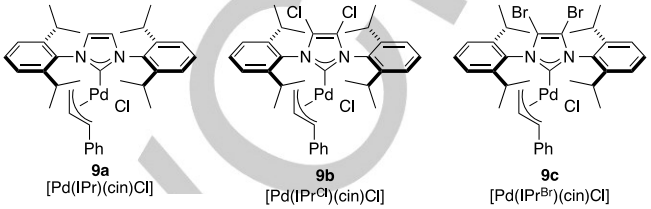
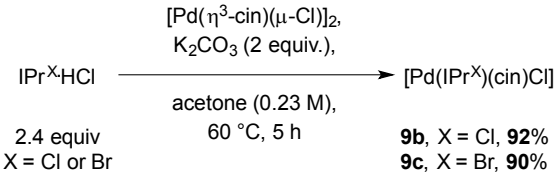


Figure 3: [Pd(NHC)(cin)Cl] involved in this study.

A friendly and efficient procedure was described by Nolan and co-workers[25] to prepare [Pd(NHC)(R-allyl)Cl] pre-catalysts including [Pd(IPr)(cin)Cl]. Hereafter, this family of complexes can be prepared under air, starting from their respective imidazolium salt, in acetone in the presence of a weak base (K_2CO_3) avoiding the preparation of the free carbene or its formation *in-situ* by action of a strong base (*e.g.*, KO^{t}Bu).[25] Their corresponding salts were obtained in quantitative yields as previously reported.[19a, 19d] Under inert atmosphere, IPr reacted with either CCl_4 or CBr_4 for three hours, generates the $C^{4,5}$-haloganed carbene and one equivalent of haloform (CHX_3, with X = Cl or Br).[19i] The free carbene was finally quenched with HCl in diethylether to afford the desired salt. Subsequently, the salt was reacted with 0.5 equivalent of [Pd(η^3-cin)(μ-Cl)]$_2$ using K_2CO_3 at 60 °C in acetone (Scheme 2). Conditions were optimized for each complex to reach completion. Complex **9b** was isolated in excellent yield (92%) after five hours, using 1.2 equivalents of the salt, whereas **9c** was obtained in 90% yield using only one equivalent of the salt but a slight excess of the base.

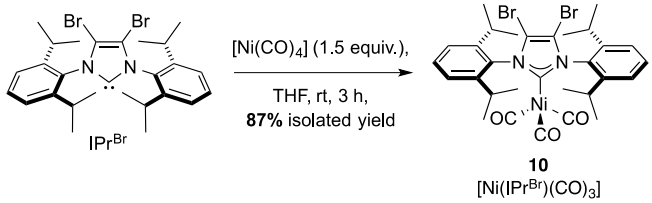


Scheme 2: Preparation of [Pd(IPr^X)(cin)Cl] where X = Cl and Br.

As reported by Cole and co-workers, [Pd(IPr^{Br})(cin)Cl] (**9c**) can be prepared in good yield using the free carbene route.[19d] We also prepared [Pd(IPr^{Cl})(cin)Cl] (**9b**) from free IPr^{Cl}. The latter reacted with 0.5 equivalent of [Pd(η^3-cin)(μ-Cl)]$_2$ under inert atmosphere to deliver **9b** in 89 % isolated yield after overnight reaction at room temperature.[26]

Aiming to fully compare the influence of these ligands, the synthesis of [Ni(IPr^{Br})(CO)$_3$] was achieved (Scheme 3, **10**) to determine the Tolman Electronic Parameter[18b-d] (TEP). This

parameter was developed to obtain the electron-donor ability of two electron ligands by measuring the IR carbonyl stretching frequencies of the related $[Ni(L)(CO)_3]$ complexes. The A_1 stretching frequency of the CO ligands, ν_{CO} (A_1) in cm^{-1} is referred to as the TEP. In that manner, the more electron density donated by the NHC to the metal center the stronger the metal-carbon bond (π-back-donation); thus resulting in a weaker C-O bond (more π^*-back-donation) and a lower IR stretching frequency (ν_{CO}).[18b-d] The corresponding Ni-complex was prepared under inert atmosphere by reacting the required free IPr^{Br} in the presence of 1.5 equivalents of $[Ni(CO)_4]$. The desired complex **12** was obtained in a 87 % isolated yield.[27]



Scheme 3: Preparation of $[Ni(IPr^{Br})(CO)_3]$.

In addition to NMR spectroscopy and elemental analysis, suitable X-ray diffraction quality crystals of complexes **9b** and **9c** were grown,[26] (Figure 4) allowing further insight into the properties of these pre-catalysts. In some cases, electronic properties are not sufficient to rationalize differences in catalytic activity between NHC ligands. The steric hindrance was determined by calculating the percent buried volume ($\%V_{Bur}$) using the Samb*V*ca application,[28].[18f, 18g, 29] This concept defines the percentage of volume of a sphere occupied by the ligand bond to the metal centre.[29a] In terms of reactivity, sterically demanding ligands have been proven to help stabilize low-valent, 12-electrons Pd^0-intermediates.[30] Both steric and electronic properties of complexes **9b** and **9c** are summarized in Table 1.

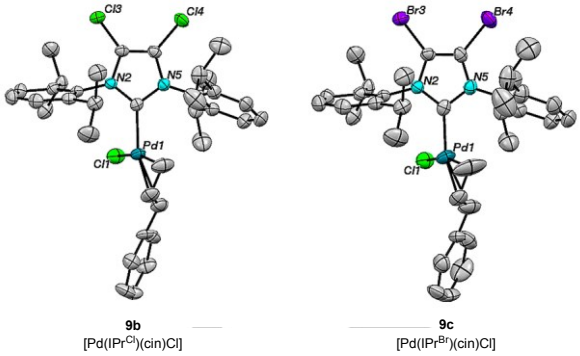


Figure 4: ORTEP diagrams of molecular structures of **9b** and **9c** showing 50% probability ellipsoids. Hydrogen atoms and disordered cinnamyl moeity have been omitted for clarity.

Considering the TEP (Table 1), *N*-alkyl substituted ICy showed a low ν_{CO} stretching frequency (2049.6 cm^{-1}) compared to its *N*-aryl counterparts.[18e] The saturated analogue of IPr (SIPr) has slightly lower donating abilities than IPr (2052.2 compared to 2051.5 cm^{-1}).[18e] Then going from IPr to its halogenated derivatives (IPr^{Cl} and IPr^{Br}), a more important increase of the ν_{CO} frequency was observed. The TEP of IPr^{Cl} (2055.1 cm^{-1}) was obtained after re-evaluating the correlation between the nickel and iridium systems.[18b] The $[Ni(IPr^{Br})(CO)_3]$ presented a ν_{CO} of 2052.3 cm^{-1} in dichloromethane. The brominated IPr is showed to be more donating than the chlorinated congener. Similar results were observed for the halogenated analogues of IMes (1,3-*bis*(2,4,6-trimethylphenyl)imidazol-2-ylidene); i.e., $IMes^{Br}$ (2051.7 cm^{-1}, 1,3-*bis*(2,4,6-trimethylphenyl)-4,5-dibromoimidazol-2-ylidene) is more donating than $IMes^{Cl}$ (2052.6 cm^{-1}, 1,3-*bis*(2,4,6-trimethylphenyl)-4,5-dichloroimidazol-2-ylidene).[18b] Finally, the following σ-donating trend was observed: IPr > IPr^{Br} > IPr^{Cl}. In term of steric properties, as reported in Table 1, IPr was found to feature the smallest percent buried volume in the [Pd(NHC)(cin)Cl] family whereas IPr* presented the largest.[12c] By saturating the IPr backbone (SIPr), the $\%V_{Bur}$ was increased by 0.3% (37% for SIPr compared to 36.7% for IPr). With IPr^{Cl}, the TEP was predicted higher than IPr and we expected its bulk to be higher. As expected, a $\%V_{Bur}$ of 37.3% was observed, presumably due to the chlorides pushing the aromatic rings towards the metal centre. Surprisingly, IPr^{Br} presented a lower $\%V_{Bur}$ (37.0%) than IPr^{Cl} (37.3%) in the same system when a higher value might have been expected tin view of the presence of the bulkier bromide atoms. This outcome, to a certain extent, can be explained comparing the geometries of IPr^{Cl}/IPr^{Br} crystal structures. The aromatic rings of IPr^{Br} are more bent towards the Pd-centre than in IPr^{Cl}, which is clear when comparing the angle formed with the imidazolylidene ring (C^{Br}-N-C^{Ar}: 123.4 *vs* 122.8 °). Additionally, the aromatic rings are more tilted in the case of IPr^{Br} decreasing the steric hindrance. It appears that the IPr^{Br} ligand accommodates bulk by distorting more significantly leading to a $\%V_{Bur}$ similar to SIPr (37.0%).

Table 1. Steric and electronic properties of NHC ligands.

NHC	TEP_{DCM}(cm^{-1})	$\%V_{Bur}$ (%)[c]
ICy	2049.6[a]	-
IPr	2051.5[a]	36.7[d]
SIPr	2052.2[a]	37.0[d]
$IMes^{Cl}$	2052.6[b]	-
IPr^{Cl}	2055.1[b]	37.3
$IMes^{Br}$	2051.7	-
IPr^{Br}	2052.3	37.0
IPr*	2052.7[b]	44.6[d]

[a]Reference [20e]. [b]Reference [20b]. [c]Calculation parameters: sphere radius, 3.50 Å; distances for the metal–ligand bond, 2.00 Å; hydrogen atoms were omitted; scaled Bondi radii were used as recommended by Cavallo. [d]Reference [29].

To complete this study, a three-dimensional steric map was developed by determining the $\%V_{Bur}$ in four quadrants around the metal center (Figure 5).[10f, 29a, 31]. Looking along the z-axis, the calculation provides more information on how the ligand adapts its shape to the metal environment. Usually, two

quadrants are more sterically congested with the catalytic pocket assuming almost C_2-symmetry. This shape of the steric map is a consequence of the opposite rotation around the N-aryl bonds, which results in a staggering of the *i*Pr substituents facing each other on the two aryl rings on opposite sides of the NHC ring. Of course, rotation around the *N*-aryl bonds would invert the bulk in the quadrants of the steric maps of Figure 5. The less sterically crowded areas can be thought of as the preferential approach for substrate leading to the formation of the intermediate involved in oxidative addition.[10f, 29a, 31] As observed with the overall percent buried volume, both halogenated ligands showed similar behavior in the cinnamyl platform.

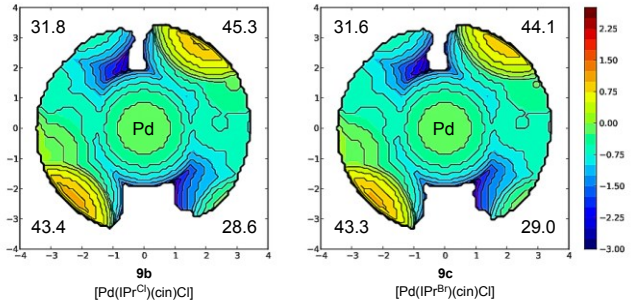
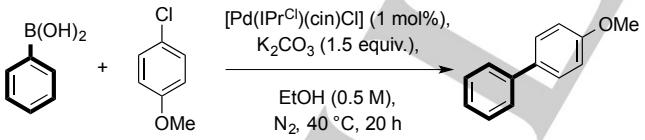


Figure 5: Steric map of Pd-complexes **9b** and **9c**.

With the aim of comparing these three palladium complexes (**9a-c**), we decided to optimize the reaction conditions using the newly designed [Pd(IPr^{Cl})(cin)Cl] (**9b**) as benchmark catalyst.

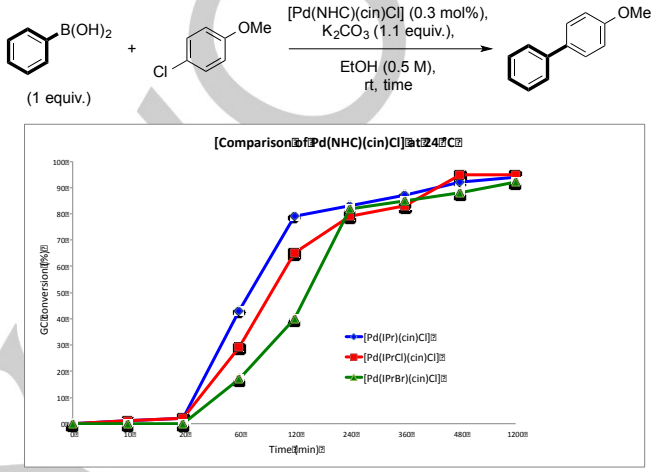
Study of [Pd(NHC)(cin)Cl] (NHC = IPr, IPr^{Cl} and IPr^{Br}) in the Suzuki-Miyaura cross-coupling reaction.

We began our study by deploying reaction conditions close to the ones previously described by Nolan and co-workers.[15] The optimization was carried out with phenylboronic acid and the less reactive *p*-chloroanisole to gauge the viability of our system. The preliminary conditions depicted in Scheme 4 gave complete conversion toward the desired coupling compound.



Scheme 4: Preliminary conditions used in the optimization.

During the optimization of parameters such as the catalyst loading, the temperature, etc., certain aspects are noteworthy .[26] Indeed, increasing the temperature to 80 °C was found to be detrimental to the catalytic activity leading to lowering of the conversion. We were delighted to observe complete conversion at room temperature (ca. 24 °C) with 0.2 mol% of [Pd(IPr^{Cl})(cin)Cl]. Finally, in order to conduct the reaction with a stoichiometric amount of boronic acid and a slight excess of K_2CO_3 (1.1 equiv.), the catalyst loading had to be increased to 0.3 mol%. The use of other alcohol solvents or bases was shown to be detrimental.[26] In order to gain better understanding of the activation of the pre-catalysts, additional experiments were conducted before testing efficiency. At first, the reaction was conducted with the three different pre-catalysts **9a-c** using the optimized conditions and conversions were reported for different time intervals (Scheme 5). To confirm these results, two sets of data were acquired for each pre-catalyst and compared to the final conversion of a third reaction. The data presented in the following reaction profiling are an average of GC conversions composed of the two runs.

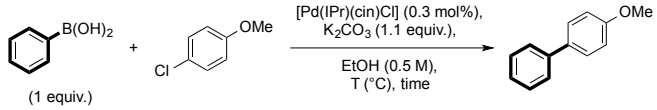


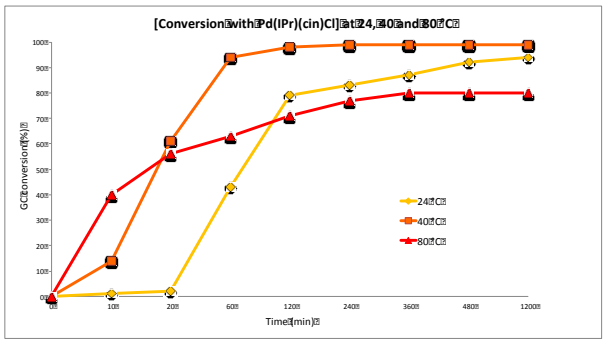
Scheme 5: Comparison of the Pd pre-catalyst with benchmark conditions.

All three pre-catalysts gave similar conversions after 20 hours (IPr: 94%, IPr^{Cl}: 95% and IPr^{Br}: 92%). They also showed the same activation time of 20 minutes to form the active Pd^0-species. After the activation step, each pre-catalyst displayed a different behavior. With IPr^{Cl}, the conversion increased more in a linear fashion over time; whereas IPr and IPr^{Br} exhibited a rapid rise in conversion (IPr: 77% after 100 min; IPr^{Br}: 82% after 200 min). Interestingly, the rate of conversion with [Pd(IPr^{Cl})(cin)Cl] pre-catalysts slowed between 60 and 120 min, then reached maximum conversion linearly.

[Pd(IPr^{Br})(cin)Cl] (**9c**) showed interesting reactivity with intermediate activity compared to its IPr and IPr^{Cl} counterparts. Finally, we studied the impact of the temperature on the catalytic system with [Pd(IPr)(cin)Cl] (**9a**) by plotting the conversion over time. Three different reaction temperatures were used: room temperature (24 °C), 40 °C and 80 °C (Scheme 6). First and as expected, the increase of the temperature shortened the activation period, going from 20 minutes at 24 °C to immediate release of the active species at 80 °C. Even though higher temperature accelerated the reaction, the effect on the final conversion was deleterious with a drop of 20% compared to 40 °C. The lower conversion at high temperature (80 °C) could be explained by degradation of the active palladium(0) species, as well as of the competition with side reactions favored by elevated temperature, such as reduction of the aryl chloride/boronic acid, homocoupling and comproportionation of Pd^0 with unreactive pre-catalysts. The intermediate temperature

(40 °C) was found to be optimum leading to the highest conversion (99%) and shortest induction period.



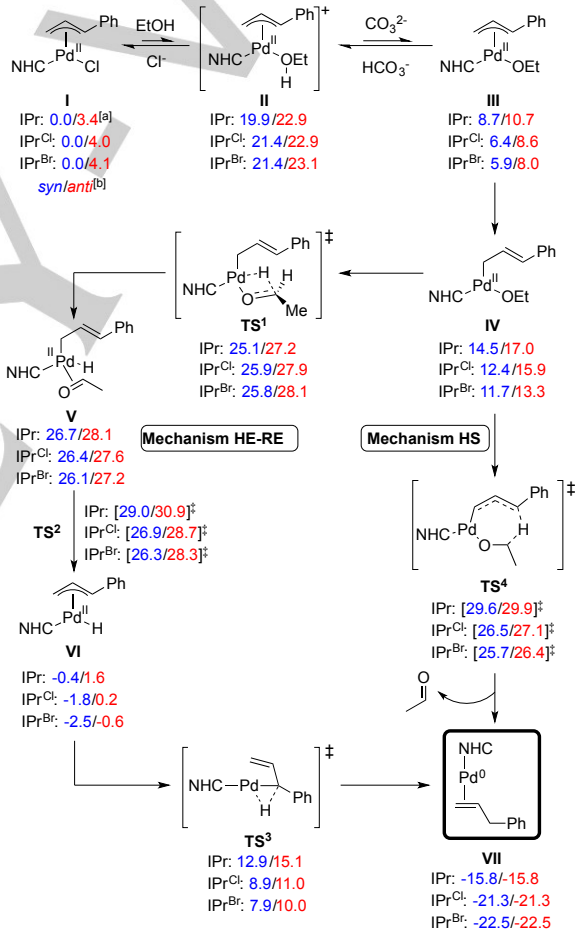


Scheme 6: Influence of temperature on our catalytic system.

Computational studies of the activation pathway of [Pd(NHC)(cin)Cl] (NHC = IPr, IPr^{Cl}, IPr^{Br}).

DFT calculations were performed with the aim to explore the influence of halogenated backbone on the formation of the active species (NHC-Pd^0) (Scheme 7) and the effect on the disproportionation/comproportionation pathway (Scheme 8). In order to carry our investigation, we used the mechanism proposed by Hazari and co-workers.[14c] We extended this study, exploring as well the formation of the Pd^0 from the stable [Pd(NHC)(cin)Cl] complexes. The calculations were carried out using the well-defined NHCs (IPr, IPr^{Cl} and IPr^{Br}). To identify the important rate-limiting steps in the mechanism, the complete reaction profile has been explored only for reference complex [Pd(IPr^{Cl})(cin)Cl] (**9b**). For the monomers [Pd(NHC)(cin)Cl] and dimers [Pd$_2$(NHC)$_2$(cin)Cl], both *syn* and *anti* conformations of the η^3-cin or μ-cin ligand were modeled. In accordance with our calculations the *syn* conformation of the η^3-cin ligand is the most stable for [Pd(NHC)(η^3-cin)(μ-Cl)], while the *anti* conformations of the μ-cin ligand is the most stable for the Pd-dimers which matches the previous findings of Hazari and co-workers.[14c, 14e] Only the formation of the terminal olefin has been considered since only this product has been experimentally observed under similar conditions.[17b]

The reaction starts with conversion of neutral species **I** to the positively charged species **II** *via* dissociative substitution of Cl$^-$ by EtOH. The free energy change associated with this process is 21.4 kcal/mol, indicating this step is achievable at room temperature. The following deprotonation of the coordinated EtOH to form **III** is thermodynamically favored by 15 kcal/mol. To proceed further, a change in allyl coordination from η^3 to κ^1 (**IV**) is needed, and this transformation is endergonic by 6 kcal/mol. Then, to arrive at the Pd^0 olefin complex (**VII**), two competitive mechanisms are possible. In the first mechanism, HE-RE in Scheme 7, species **IV** undergoes a *β*-hydride elimination step. This transformation occurs *via* transition state (**TS^1**) and leads to intermediate **V**, which represents the palladium hydride coordinated to an acetaldehyde molecule. This step requires a barrier of 13.7 kcal/mol (or 25.9 for barrier **I** to **TS^1**) and the resulting intermediate **V**, at 26.4 kcal/mol, is marginally more stable than transition state **TS^1**. Nevertheless, de-coordination of acetaldehyde from **V** is a substantially barrierless process and the system collapses into the stable palladium hydride **VI** at -1.8 kcal/mol. This step is exergonic by 28.4 kcal/mol and requires only 0.5 kcal/mol of energy (the overall barrier **I** to **TS^2** is 26.9) kcal/mol. Next, the reductive elimination between the hydride and the cinnamyl ligand occurs *via* transition state **TS^3** with a relatively small free energy barrier of 10.7 kcal/mol, indicating this step as very fast. When following the imaginary frequency in **TS^3**, intermediate **VII** was formed by stabilization of the Pd^0 species with the olefin. The transformation from **VI** to **VII** was found very exergonic and the associated free energy change turned out to be 19.5 kcal/mol.

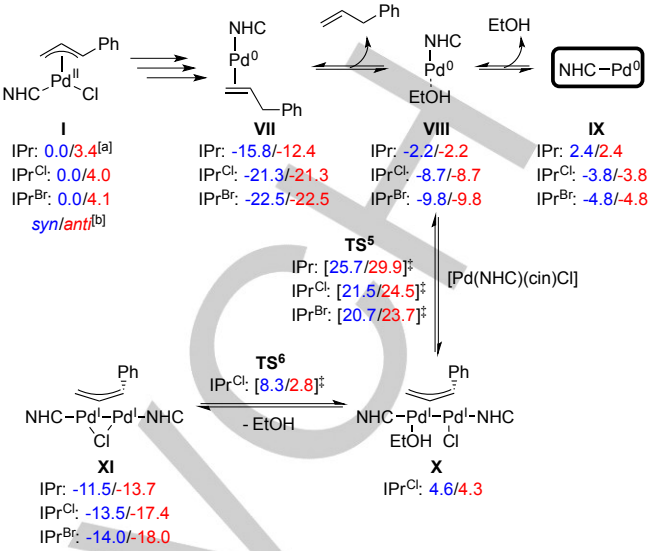


Scheme 7: Computational study of the formation of Pd^0 and disproportionation/comproportionation pathway. [a]Energies are in kcal.mol^{-1}. [b]*Syn*/*anti* refers to the isomers of the cinnamyl ligand.

Alternative to the HE-RE pathway, formation of the Pd^0 complex **VII** from intermediate **IV** could be achieved *via* 1-step proton migration from OEt ligand to allyl (HS pathway in Scheme 7). This process is exergonic by 33.7 kcal/mol and requires 14.1

kcal/mol of activation energy (or 26.5 kcal/mol for **I** to **TS⁴**). The possible evolution of intermediate **VII** is represented in Scheme 8, and is discussed next. In the **VII** to **VIII** step the replacement of the coordinated olefin by a solvent molecule (EtOH) is endergonic by 12.6 kcal/mol indicating stronger coordination of olefin to Pd^0 compared to the alcohol. However, intermediate **VII** appears to be the species liberating the active Pd^0 (**IX**) and reacting with [Pd(NHC)(cin)Cl] to form the Pd-dimer **X**. The slow formation of complex **VIII** would represent a side equilibrium, generating a small amount of active species (**IX**). After the initial study, ethanol can de-coordinate complex **VIII**, liberating the active catalyst **IX**. At this stage, the active Pd^0 can either enter the catalytic cycle of the Suzuki-Miyaura reaction or can interact with another molecule of the initial pre-catalyst **I** and form the Pd-dimer **XI**. Formation of active Pd^0 species (**IX**) is a one-step process endergonic by 5 kcal/mol. On the contrary, as demonstrated by Hazari and co-workers,[14c] conversion of **VIII** to **XI** is a two-step process and exergonic. The first step corresponds to coordination of one molecule of the pre-catalyst **I** to intermediate **VIII** to form intermediate **X**. This process is endergonic by 13.3 kcal/mol and results from the associative transition state **TS⁵** that corresponds to 30.2 kcal/mol in activation energy starting from **VIII**. Finally, intermediate **X** can give the Pd-dimer **XI** releasing a molecule of EtOH. This process is exergonic by 18.1 kcal/mol and requires only a few kcal/mol of activation energy. Thus, overall the **VIII** to **XI** step is exergonic by 4.8 kcal/mol, indicating that formation of the Pd^I-dimer is thermodynamically possible from species **VIII**. The associated overall activation barrier is rather high and will probably result in negligible amount of Pd^I-dimer at room temperature. All the stationary points have been calculated seperately from the transition state **TS⁶** and intermediate **X** for [Pd(IPr)(cin)Cl] (**9a**) and [Pd(IPr^{Br})(cin)Cl] (**9c**), since these values appeared to be less relevant.

The above characterization of conversion of [Pd(NHC)(cin)Cl] to the active Pd^0 have been calculated for complexes **9a-c**. Extending the analysis to the three complexes confirms **TS⁴** (**9b**, **9c**) or **TS²** (**9a**) to be the highest points on the Gibbs free energy surface, suggesting the energy difference between **TS⁴ (9b, 9c)** or **TS²** (**9a**) and the starting pre-catalyst **I**, in the 26-29 kcal/mol range, as the activation energy necessary to form the active species **IX**. It should be noted that in terms of activation energy the difference between the alternative pathways HE-RE and HS of Scheme 7 is negligible and the preference for one of them is probably sensitive to the electronic structure method and the solvation model used. As a remark, the preference of 5 kcal/mol for the hydrogen shift (HS) mechanism found by Hazari and co-workers[17b] can be related to the small Me group of MeOH, which reduces steric repulsion with the Ph group of the substrate in transition state **TS⁴**. This preference is basically cancelled with the bulkier EtOH used in this study.



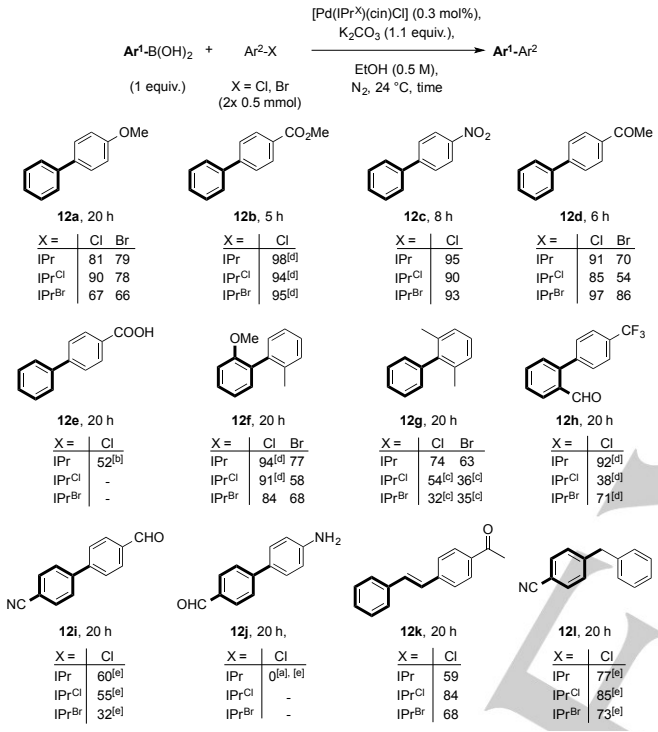
Scheme 8: Computational study of the formation of Pd^0 and disproportionation/comproportionation pathway. [a]Energies are in kcal.mol^{-1}. [b]*Syn*/*anti* refers to the isomers of the cinnamyl ligand.

The energy difference between **TS⁵** and the most stable species **VII**, is about 40 kcal/mol, and represents another important barrier that can be used to estimate the activation needed to form the Pd^I-dimer. We believe the barrier of 40 kcal/mol is rather high and will probably result in negligible amount of Pd^I-dimer at room temperature in the case of the ligands investigated here.

Comparision of the [Pd(NHC)(cin)Cl] (NHC = IPr, IPr^{Cl}, IPr^{Br}) in the Suzuki-Miyaura cross-coupling (Scope and Limitations).

With the optimized reaction conditions in hand, the scope and limitations of the reaction were studied (Scheme 9). The reaction time was also optimized for each entry, based on [Pd(IPr)(cin)Cl] (**9a**) reactivity. We began our investigation by varying both electronic and steric properties of the arylchloride using phenylboronic acid as standard (**12a-e,g**). The benchmark substrate (**12a**) prepared from a deactivated chloride was coupled in excellent isolated yield using the IPr^{Cl} catalyst (90%) whereas IPr and IPr^{Br} congeners gave respectively 81% and 67% conversion. Activated arylchlorides (**12b-c**) bearing electron-withdrawing groups such as ester, nitro and ketone afforded the desired compounds in excellent yields (98-85%). The three complexes led to the formation of the ester **12b** with very similar yields after five hours and we were pleased that no transesterification occurred. Contrary to **12c**, different yields were observed for biphenyl **12d**; with [Pd(IPr^{Br})(cin)Cl] being the most active (97%) and [Pd(IPr^{Cl})(cin)Cl] turned out to be the least effective (85%). Low conversions to **12e** were obtained, using *p*-chlorobenzoic acid, even after increasing both temperature and catalyst loading. This outcome is presumably due to the chelation of the carboxylate to the metal center. Then, we turned our attention to more sterically hindered coupling partners (**12f,g**). Product **12f** was isolated, after work-up, in excellent yield (94%) with the IPr pre-catalyst. When using [Pd(IPr^X)(cin)Cl] (X = Cl, Br), lower yields were obtained and further purification was needed in the case of IPr^{Br}. With bulkier

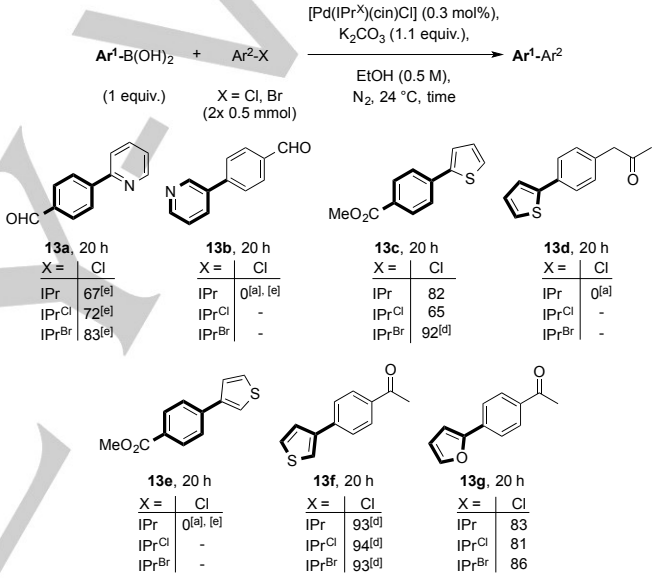
di-*ortho*-substituted chloride (**12g**), poor to good yields were obtained: IPr^{Br} (32%)< IPr^{Cl} (54%) < IPr (74%). The use of the halogenated version of [Pd(IPr)(cin)Cl] seemed to be detrimental in the coupling involving hindered substrates. Next, from compounds **12h** to **12l**, we altered the substitution pattern of both partners. Employing [Pd(IPr)(cin)Cl], the cross-coupling reaction between *o*-formylphenylboronic acid and *p*-chlorobenzotrifluoride gave the Xenalipin intermediate[32] (**12h**) in excellent yield (92%) without further purification. Once again, halogenated analogues were less active and a drastic drop in yield was observed when using the IPr^{Cl} pre-catalyst (38%).



Scheme 9: Scope and comparison. Isolated yields (%) after flash chromatography or recrystallization. [a]GC conversion (%). [b]^{1}H NMR conversion (%). [c]^{1}H NMR yield (%) using mesitylene as internal standard. [d]Isolated yield after work-up, without further purification. [e]Reaction carried out at 40 °C.

The biphenyl **12i** bearing a nitrile group was prepared with moderate to low yields (IPr: 60% > IPr^{Cl}: 55% > IPr^{Br}: 32%) at 40 °C. As no conversion was observed at 24° C, elevated temperature was employed to presumably reverse nitrile (or aldehyde) coordination with the active Pd^0 species. As expected, the more chelating amino substituent, in *p*-chloroaniline, prevented the coupling with *p*-formylphenylboronic acid (**12j**), even at higher temperature. The cinnamylboronic acid treated with *p*-chloroacetophenone afforded the desired compound **12k** from 84% with [Pd(IPr^{Cl})(cinCl] to 59% with the IPr-complex. Using the same conditions as with **12i**, the cyano-functionalized boronic acid reacted with benzyl chloride to undergo a sp^2-sp^3 coupling and gave **12l** in very good yields. Like the previous entry (**12k**), [Pd(IPr^{Cl})(cinCl] showed the best result with 85% followed by [Pd(IPr)(cinCl] with 77% isolated yield. Finally, using bromides as coupling partners (**12a,d,f,g)** led to lower yields than when their chloride relatives were used but the same relative trend in catalyst activity remains unchanged.

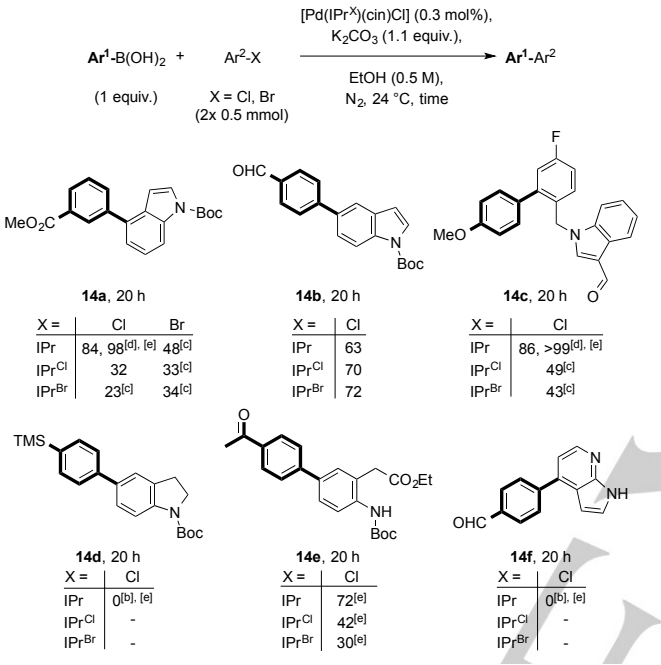
For the second part of the reaction scope, the reactivity of heteroaryls was explored (Scheme 10). Initially, the compatibility with the pyridine moiety (**13a,b**) was examined. Reacting 2-chloropyridine with *p*-formylphenylboronic acid at 40 °C yielded the expected product (**13a**) in moderate (IPr: 67%) to very good yield (IPr^{Br}: 83%). Compound **13b** was not observed by GC using pyridine-3-boronic acid and *p*-chlorobenzaldehyde as starting material. Next, we examined furan and thiophene derivatives (**13c-g**). The *p*-methoxycarbonylphenylboronic acid in combination with 2-chlorothiophene gave the coupling product **13c** in very good yield. Among the Pd-complexes tested, [Pd(IPr^{Br})(cin)Cl] led to the best activity with 92%. When the functionalization of the coupling partners was inverted, no conversion was observed with 2-thiopheneboronic acid (**13d**).



Scheme 10: Scope and comparison involving heterocyclic substrates. Isolated yields (%) after flash chromatography or recrystallization. [a]GC conversion (%). [b]^{1}H NMR conversion (%). [c]^{1}H NMR yield (%) using mesitylene as internal standard. [d]Isolated yield after work-up, without further purification. [e]Reaction carried out at 40 °C.

Having the chloride at the 3-position of the thiophene ring was detrimental and no GC conversion was recorded even at elevated temperature **13e**. On the other hand, the reactivity was restored when using 3-thiopheneboronic acid. With *p*-choloacetophenone, the latter gave the desired product **13f** with excellent yields (93%) and without extensive purification. As previously observed with pyridine partners, certain reactions can be achieved by inversion of the coupling partners. When the 2-choropyridine was a suitable partner, its boronic acid equivalent did not allow the coupling presumably due to poor transmetallation or reduction/homocoupling. Finally, the same chloride was engaged in the coupling with 2-furanboronic acid. The expected compound (**13g**) was obtained in very good yield and [Pd(IPr^{Br})(cin)Cl] was found to be the most effective pre-catalyst (86%).

The last portion of our reaction scope involved indoles and their derivatives (Scheme 11). In the first entry, *m*-methoxy-carbonylphenylboronic acid was coupled with the Boc-protected 4-chloroindole (Boc = ^{t}butyloxycarbonyl). The reaction with [Pd(IPr)(cin)Cl] afforded the desired indole (**14a**) in very good yield. However, an important decrease of the yield was observed with both halogenated Pd-complexes. We were delighted to see that heating at 40 °C with [Pd(IPr)(cin)Cl] led to quantitative yield without further purification. The cross-coupling reaction was also conducted using 5-chloroindole (**14b**).



14a, 20 h		
X =	Cl	Br
IPr	84, 98[d], [e]	48[c]
IPr^{Cl}	32	33[c]
IPr^{Br}	23[c]	34[c]

14b, 20 h	
X =	Cl
IPr	63
IPr^{Cl}	70
IPr^{Br}	72

14c, 20 h	
X =	Cl
IPr	86, >99[d], [e]
IPr^{Cl}	49[c]
IPr^{Br}	43[c]

14d, 20 h	
X =	Cl
IPr	0[b], [e]
IPr^{Cl}	-
IPr^{Br}	-

14e, 20 h	
X =	Cl
IPr	72[e]
IPr^{Cl}	42[e]
IPr^{Br}	30[e]

14f, 20 h	
X =	Cl
IPr	0[b], [e]
IPr^{Cl}	-
IPr^{Br}	-

Scheme 11: Scope and comparison part. III. Isolated yields (%) after flash chromatography or recrystallization. [a]GC conversion (%). [b]^{1}H NMR conversion (%). [c]^{1}H NMR yield (%) using mesitylene as internal standard. [d]Isolated yield after work-up, without further purification. [e]Reaction carried out at 40 °C.

Moving the chloride in the 5-position was found to have a drastic effect on the reactivity with the boronic acid. [Pd(IPr)(cin)Cl] gave the lowest yield with 63% while [Pd(IPr^{Br})(cin)Cl] led to the best result with 72% isolated yield. Compound **14c**, bearing an indole substituent, was prepared in very good yield with the IPr-complex at 40 °C. The workup of the quantitative reaction required only simple extraction. Next, we moved to the indoline ring; the Boc-protected 5-chloroindoline in the presence of *p*-trimethylsilyl-phenylboronic acid did not deliver **14d** even at elevated temperature. Next, 5-chlorooxindole was engaged with *p*-acetylphenylboronic acid at 40 °C. Surprisingly, our conditions led to the ring opening and the formation of the tri-functionalized biphenyl **14e**. This protected amino-ester was prepared in very good yield (72%) with [Pd(IPr)(cin)Cl] (IPr^{Cl}: 42% > IPr^{Br}: 30%). This reaction was conducted under the same conditions in the absence of pre-catalyst and the ring-opened starting material was recovered in 82% isolated yield.[26] Finally, we investigated the challenging unprotected 4-chloro-7-azaindole at 40 °C (**14f**). As might have been expected no conversion was observed in this instance. Compound **14b** was also prepared starting from a bromide, and in keeping with our previous results, a decrease of the reactivity was observed compared to its chloride analogue. The use of the different complexes at low catalyst loading led to very good yields in most cases using our very mild conditions.

The original [Pd(IPr)(cin)Cl] (**9a**) was found to be most effective on average and most reactive with hindered coupling partners. Moreover, [Pd(IPr^{Br})(cin)Cl] was most active in the preparation of thiophene or furan derivatives. The [Pd(IPr^{Cl})(cin)Cl] gave variable results throughout our study of the scope. From the various motifs examined in the course of the exploration of the reaction scope we can state that the use of the three palladium pre-catalysts **9a-c** are substrate dependent for the Suzuki-Miyaura cross-coupling under our reaction conditions. However, we have demonstrated a generality of this room temperature procedure with [Pd(IPr)(cin)Cl] **9a**.

Conclusions

In summary, in order to improve Pd-complexes activity in the Suzuki-Miyaura cross-coupling, the reactivity of two unexploited [Pd(NHC)(cin)Cl] complexes bearing IPr^{Cl} and IPr^{Br} ligands have been investigated. These complexes were prepared in excellent yields (92% and 90%) using conditions employing a weak base (K_2CO_3) and acetone in air. After determining both electronic and steric properties of these ligands, they were compared with [Pd(IPr)(cin)Cl]. The three palladium complexes were studied using DFT calculations to highlight their behavior in the activation step, and experimentally by measuring their catalytic activity with a wide range of coupling partners. From their properties the IPr^{Br} ligand showed intermediate features (TEP and %V_{Bur}) compared to IPr and IPr^{Cl}. The IPr^{Br} proved more donating than its chlorinated counterpart, while also being less donating than IPr. Conversion over time plots showed three different behaviors, with an increase of the conversion faster from IPr^{Cl} to the IPr complex. The temperature was also of importance with degradation of conversion at higher temperature. From the activation step point of view, based on DFT calculations, overall activation energies do not permit to differentiate between catalysts; [Pd(IPr^{Br})(cin)Cl] was found to be more prone to form the Pd^I-dimer than its counterparts and therefore should be generally the least reactive. Moreover, calculations were found to correlate with the time (20 min) needed to generate the active species at room temperature. Additionally, lower catalytic activity at high temperature could be explained by more comproportionation towards the dimer, as the dimer formation barriers could be overcome with heating. We showed our system was effective with a wide range of coupling partners. The most versatile complex was found to be [Pd(IPr)(cin)Cl] **9a** since best yields were obtained on average. We observed that [Pd(IPr^{Br})(cin)Cl] gave great activity in the preparation of thiophene or furan derivatives. As for [Pd(IPr^{Cl})(cin)Cl], it gave unpredictable results throughout the investigation of the scope of the reaction. We have shown that

for the Suzuki-Miyaura reaction, the use of halogenated NHCs does not generally lead to significant improvement of the catalytic activity and that **9a** represents a good general pre-catalyst.

Experimental Section

Preparation of [Pd(NHC)(cin)Cl] complexes:

Suzuki-Miyaura cross-coupling: A catalyst solution in CH_2Cl_2 was prepared. The corresponding volume of solution was added to a vial and the CH_2Cl_2 was finally removed under vacuum. Under air, in the vial equipped with a stirring bar and sealed with a screw cap fitted with a septum, were added the boronic acid (0.5 mmol, 1 equiv.) and the aryl-, heteroarylchloride (0.5 mmol) when the latter was a solid. In the glovebox, K_2CO_3 (76 mg, 0.55 mmol, 1.1 equiv.) was added. Under inert atmosphere (N_2), were added EtOH (1 mL) and the aryl-, heteroarylchloride (0.5 mmol) when it was a liquid. After reaction at 24 or 40 °C, (except when otherwise mentioned) an equal volume of water and CH_2Cl_2 (10 mL) were added and the aqueous phase was extracted with 3x10 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under vacuum. As a function of the substrate, the desired compound may require further purification by column chromatography but generally does not. Full details are provided in ESI.

Acknowledgements

We gratefully acknowledge the European Commission (EC) for funding through the seventh framework program SYNFLOW, the European Research Council (ERC) (Advanced Investigator Award “FUNCAT” to S. P. N.), The Engineering and Physical Sciences Research Council (EPSRC) and AstraZeneca (Studentship to C. M. Z.). We thank the EPSRC National Mass Spectrometry Service Centre in Swansea for mass spectrometric analyses. We thank King Saud University and King Abdullah University of Science and Technology (*Award No. OSR-2015-CCF-1974-03*.)

Keywords: Catalysis • NHC • Palladium • Ligands• Suzuki-Miyaura• DFT

[1] a) A. de Meijere, F. Diederich, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH Verlag GmbH & Co. KGaA, **2008**; b) T. Colacot, in *New Trends in Cross-Coupling: Theory and Applications*, The Royal Society of Chemistry, **2015**; c) S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1439-1439; d) E. Negishi, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley & Sons, Inc., **2003.**

[2] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437-3440.

[3] a) N. Miyaura, in *Cross-Coupling Reactions*, Springer Berlin Heidelberg, **2002**; b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085; c) J. C. H. Lee, D. G. Hall, in *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH Verlag GmbH & Co. KGaA, **2014**, pp. 65-132.

[4] A. Suzuki, *J. Organomet. Chem.* **2002**, *653*, 83-90.

[5] a) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027-3043; b) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177-2250; c) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633-9695.

[6] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313-348.

[7] a) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461-1473; b) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361; c) I. Maluenda, O. Navarro, *Molecules* **2015**, *20*, 7528-7557.

[8] a) C. A. Fleckenstein, H. Plenio, *Chem. Soc. Rev.* **2010**, *39*, 694-711; b) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555-1564.

[9] a) Y. Fort, C. Comoy, in *N-Heterocyclic Carbenes*, Royal Society of Chemistry, **2011**, pp. 284–316; b) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612-3676; c) G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* **2011**, *40*, 5151-5169; d) N. Marion, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 1440-1449; e) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 3314-3332; f) S. Würtz, F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523-1533.

[10] a) N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101-4111; b) O. Navarro, N. Marion, J. Mei, S. P. Nolan, *Chem. Eur. J.* **2006**, *12*, 5142-5148; c) O. Diebolt, P. Braunstein, S. P. Nolan, C. S. J. Cazin, *Chem. Commun.* **2008**, 3190-3192; d) M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem. Int. Ed.* **2009**, *48*, 2383-2387; e) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743-4748; f) L. Wu, E. Drinkel, F. Gaggia, S. Capolicchio, A. Linden, L. Falivene, L. Cavallo, R. Dorta, *Chem. Eur. J.* **2011**, *17*, 12886-12890; g) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem. Int. Ed.* **2003**, *42*, 3690-3693.

[11] a) V. Lavallo, Y. Canac, C. Präsang, B. Donnadieu, G. Bertrand, *Angew. Chem. Int. Ed.* **2005**, *44*, 5705-5709; b) V. Lavallo, Y. Canac, A. DeHope, B. Donnadieu, G. Bertrand, *Angew. Chem. Int. Ed.* **2005**, *44*, 7236-7239; c) I. Maluenda, M. T. Chen, D. Guest, S. Mark Roe, M. L. Turner, O. Navarro, *Catal. Sci. Tech.* **2015**, *5*, 1447-1451; d) D. Guest, V. H. Menezes da Silva, A. P. de Lima Batista, S. M. Roe, A. A. C. Braga, O. Navarro, *Organometallics* **2015**, *34*, 2463-2470; e) D. Guest, M. T. Chen, G. J. Tizzard, S. J. Coles, M. L. Turner, O. Navarro, *Eur. J. Inorg. Chem.* **2014**, *2014*, 2200-2203; f) C. W. D. Gallop, M. T. Chen, O. Navarro, *Org. Lett.* **2014**, *16*, 3724-3727.

[12] a) A. Chartoire, A. Boreux, A. R. Martin, S. P. Nolan, *RSC Advances* **2013**, *3*, 3840-3843; b) F. Izquierdo, A. Chartoire, S. P. Nolan, *ACS Catal.* **2013**, *3*, 2190-2193; c) A. Chartoire, M. Lesieur, L. Falivene, A. M. Z. Slawin, L. Cavallo, C. S. J. Cazin, S. P. Nolan, *Chem. Eur. J.* **2012**, *18*, 4517-4521; d) A. R. Martin, A. Chartoire, A. M. Z. Slawin, S. P. Nolan, *Beilstein J. Org. Chem.* **2012**, *8*, 1637-1643; e) A. Chartoire, X. Frogneux, S. P. Nolan, *Adv. Synth. Catal.* **2012**, *354*, 1897-1901; f) S. Meiries, G. Le Duc, A. Chartoire, A. Collado, K. Speck, K. S. A. Arachchige, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2013**, *19*, 17358-17368.

[13] C. C. C. Johansson Seechurn, S. B. L. Parisel, T. J. Colacot, *J. Org. Chem.* **2011**, *76*, 7918-7932.

[14] a) Y. Takeda, Y. Ikeda, A. Kuroda, S. Tanaka, S. Minakata, *J. Am. Chem. Soc.* **2014**, *136*, 8544-8547; b) D. Ortiz, M. Blug, X. F. Le Goff, P. Le Floch, N. Mézailles, P. Maître, *Organometallics* **2012**, *31*, 5975-5978; c) D. P. Hruszkewycz, D. Balcells, L. M. Guard, N. Hazari, M. Tilset, *J. Am. Chem. Soc.* **2014**, *136*, 7300-7316; d) D. P. Hruszkewycz, L. M. Guard, D. Balcells, N. Feldman, N. Hazari, M. Tilset, *Organometallics* **2015**, *34*, 381-394; e) P. R. Melvin, D. Balcells, N. Hazari, A. Nova, *ACS Catal.* **2015**, 5596-5606; f) P. R. Melvin, A. Nova, D. Balcells, W. Dai, N. Hazari, D. P. Hruszkewycz, H. P. Shah, M. T. Tudge, *ACS Catal.* **2015**, *5*, 3680-3688; g) N. Hazari, D. P. Hruszkewycz, *Chem. Soc. Rev.* **2016**, *45*, 2871-2899.

[15] (a) F. Izquierdo, M. Corpet, S. P. Nolan, *Eur. J. Org. Chem.* **2015**, 1920-1924. (b) for the original synthesis of IPr, see: J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999**, *121*, 9889-9890.

[16] A. J. DeAngelis, P. G. Gildner, R. Chow, T. J. Colacot, *J. Org. Chem.* **2015**, *80*, 6794-6813.

[17] T. J. Colacot, C. J. Seechurn, S. L. Parisel, (Johnson Matthey Public Limited Company), *US20130165660 A1*, **2013**.

[18] a) F. E. Hahn, M. C. Jahnke, *Angew. Chem. Int. Ed.* **2008**, *47*, 3122-3172; b) D. J. Nelson, S. P. Nolan, *Chem. Soc. Rev.* **2013**, *42*, 6723-6753; c) H. Jacobsen, A. Correa, A. Poater, C. Costabile, L. Cavallo, *Coord. Chem. Rev.* **2009**, *253*, 687-703; d) D. G. Gusev, *Organometallics* **2009**, *28*, 6458-6461; e) R. Dorta, E. D. Stevens, N. M. Scott, C. Costabile, L. Cavallo, C. D. Hoff, S. P. Nolan, *J. Am. Chem. Soc.* **2005**, *127*, 2485-2495; f) L. Cavallo, A. Correa, C. Costabile, H. Jacobsen, *J. Organomet. Chem.* **2005**, *690*, 5407-5413; gA. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano, L. Cavallo, *Eur. J. Inorg. Chem.* **2009**, *2009*, 1759-1766.

[19] a) M. Pompeo, R. D. J. Froese, N. Hadei, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, 11354-11357; b) Y. Zhang, V. César, G. Storch, N. Lugan, G. Lavigne, *Angew. Chem. Int. Ed.* **2014**, *53*, 6482-6486; c) V. Cesar, J. C. Tourneux, N. Vujkovic, R. Brousses, N. Lugan, G. Lavigne, *Chem. Commun.* **2012**, *48*, 2349-2351; d) S. K. Furfari, M. R. Gyton, D. Twycross, M. L. Cole, *Chem. Commun.* **2014**; e) B. Hildebrandt, S. Raub, W. Frank, C. Ganter, *Chem. Eur. J.* **2012**, *18*, 6670-6678; f) M. Amini, M. Bagherzadeh, S. Rostamnia, *Chin. Chem. Lett.* **2013**, *24*, 433-436; g) S. Gaillard, X. Bantreil, A. M. Z. Slawin, S. P. Nolan, *Dalton Trans.* **2009**, 6967-6971; h) S. Urban, M. Tursky, R. Frohlich, F. Glorius, *Dalton Trans.* **2009**, 6934-6940; i) A. J. Arduengo, F. Davidson, H. V. R. Dias, J. R. Goerlich, D. Khasnis, W. J. Marshall, T. K. Prakasha, *J. Am. Chem. Soc.* **1997**, *119*, 12742-12749; j) M. D. Sanderson, J. W. Kamplain, C. W. Bielawski, *J. Am. Chem. Soc.* **2006**, *128*, 16514-16515; k) L. Benhamou, N. Vujkovic, V. César, H. Gornitzka, N. I. Lugan, G. Lavigne, *Organometallics* **2010**, *29*, 2616-2630; l) M. Braun, W. Frank, G. J. Reiss, C. Ganter, *Organometallics* **2010**, *29*, 4418-4420; m) V. Karthik, I. A. Bhat, G. Anantharaman, *Organometallics* **2013**, *32*, 7006-7013; n) A. J. Arduengo III, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall, M. Unverzagt, *Tetrahedron* **1999**, *55*, 14523-14534; o) V. César, V. Mallardo, A. Nano, G. Dahm, N. Lugan, G. Lavigne, S. Bellemin-Laponnaz, *Chem. Commun.* **2015**, *51*, 5271-5274; p) T. Tu, W. Fang, J. Jiang, *Chem. Commun.* **2011**, *47*, 12358-12360.

[20] A. G. Tennyson, V. M. Lynch, C. W. Bielawski, *J. Am. Chem. Soc.* **2010**, *132*, 9420-9429.

[21] T. Tu, Z. Sun, W. Fang, M. Xu, Y. Zhou, *Org. Lett.* **2012**, *14*, 4250-4253.

[22] C. A. Urbina-Blanco, X. Bantreil, H. Clavier, A. M. Z. Slawin, S. P. Nolan, *Beilstein J. Org. Chem.* **2010**, *6*, 1120-1126.

[23] a) K. H. Hoi, J. A. Coggan, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 843-845; b) M. Pompeo, R. D. J. Froese, N. Hadei, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 11354-11357; c) S. Sharif, R. P. Rucker, N. Chandrasoma, D. Mitchell, M. J. Rodriguez, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2015**, n/a-n/a.

[24] Y. Zhang, V. César, G. Lavigne, *Eur. J. Org. Chem.* **2015**, *2015*, 2042-2050.

[25] S. P. Nolan, F. Nahra, C. Zinser, M. Brill, C. S. J. Cazin, A. Slawin, D. B. Cordes, R. E. Meadows, *Chem. Commun.* **2017**, *53*, 7990-7993.

[26] *For more details, see the Supporting Information*.

[27] CCDC-1430161 (**9b**) and CCDC-1430090 (**9c**) contain the supplementary crystallographic data for this contribution.

[28] *The SambVca application is available from* http://www.molnac/.*unisa.it/ OMtools/sambvca.php. Calculation parameters: sphere radius, 3.50 Å.; distances for the metal-ligand bond, 2.00 Å.; hydrogen atoms were omitted; scaled Bondi radii were used as recommended by Cavallo.*

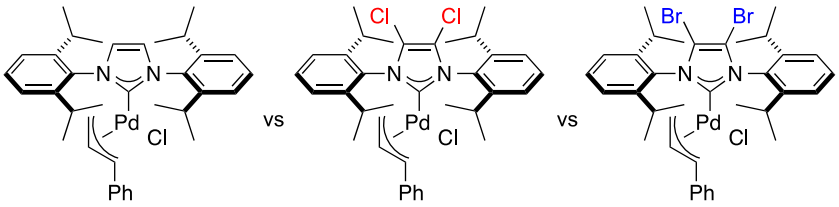
[29] a) H. Clavier, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 841-861; b) A. Poater, F. Ragone, S. Giudice, C. Costabile, R. Dorta, S. P. Nolan, L. Cavallo, *Organometallics* **2008**, *27*, 2679-2681.

[30] F. Izquierdo, S. Manzini, S. P. Nolan, *Chem. Commun.* **2014**, *50*, 14926-14937.

[31] a) A. Poater, F. Ragone, R. Mariz, R. Dorta, L. Cavallo, *Chem. Eur. J.* **2010**, *16*, 14348-14353; b) F. Ragone, A. Poater, L. Cavallo, *J. Am. Chem. Soc.* **2010**, *132*, 4249-4258.

[32] a) C. Dupuis, K. Adiey, L. Charruault, V. Michelet, M. Savignac, J. P. Genêt, *Tetrahedron Lett.* **2001**, *42*, 6523-6526; b) K. Koch, R. J. Chambers, M. S. Biggers, *Synlett* **1994**, 347-348.

FULL PAPER



[Pd(IPr)(cin)Cl] [Pd(IPr^{Cl})(cin)Cl] [Pd(IPr^{Br})(cin)Cl]

The catalytic activity of [Pd(NHC)(cin)Cl] (NHC = IPr, IPr^{Cl}, IPr^{Br}) complexes has been compared in the Suzuki-Miyaura cross-coupling reaction. The activation pathway involving these complexes has been studied using DFT calculations and their activity extensively tested (30 entries) using an operationally simple protocol.

*F. Izquierdo, C. Zinser, Y. Minenkov, D. B. Cordes, A. M. Z. Slawin, L. Cavallo, F. Nahra, C. S. J. Cazin and S. P. Nolan**

Page No. – Page No.

Insights into the catalytic activity of [Pd(NHC)(cin)Cl] (NHC = IPr, IPr^{Cl}, IPr^{Br}) complexes in the Suzuki-Miyaura reaction.