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Palladium-*N*-heterocyclic carbene an efficient catalytic system for the carbonylative cross-coupling of pyridine halides with boronic acids

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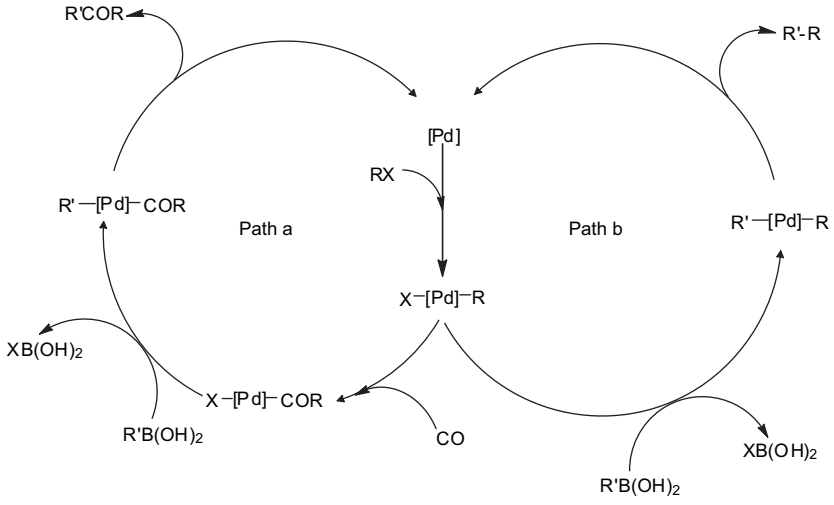
Abstract—Carbonylative cross-coupling of different pyridyl halides with various boronic acids was studied using catalytic systems constituted of *N*-heterocyclic carbene type ligands and palladium. These systems easily obtained in situ from the corresponding imidazolium salt and palladium acetate appear more efficient toward bromopyridines than catalysts based on hindered and basic alkylphosphines such as tricyclohexylphosphine. Their higher efficiency was also evidenced by coupling using chloro- or dichloropyridines and chloroquinolines, which practically do not react with catalytic systems based on phosphines.

1. Introduction

Different methodologies have been described to synthesize α-aryl pyridyl ketone derivatives that are useful intermediates in the syntheses of various natural products and drugs.[1] However, many of them have the disadvantage of using expensive or unfriendly reagents,[2] giving poor or moderate yields[3] or being only effective with specific substrates. In this context, we have recently reported that the palladium catalyzed three component cross-coupling of pyridine halides, carbon monoxide, and boronic acid (carbonylative Suzuki reaction) provides a straightforward access to this class of compounds.[4]

The main drawback of this approach is the direct coupling reaction (i.e., without carbon monoxide insertion) giving biaryl products in particular with electron deficient aryl halides such as pyridyl halides.[5] Actually, from a mechanistic point of view, the first step of the catalytic cycle is the oxidative addition of the substrate on a Pd^0 species leading to the formation of a palladium aryl complex (Scheme 1). This one can insert a CO molecule (path a) or react directly



Scheme 1.

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with boronic acid by transmetalation (path b). In the first case the expected ketone is obtained via transmetalation and reductive elimination whereas in the second case a biaryl compound is formed. As the two paths (a and b) are in competition, the electronic properties of the substrate, ligand of the palladium as well as the reaction conditions can have a great influence on the selectivity of the reaction.

In this context, we have shown that a proper choice of the reaction conditions (CO pressure, palladium precursor, ligand, solvent,…) allowed us to obtain high selectivity for the desired pyridyl ketone.[4] Another limitation of this reaction arises from the fact that whilst iodides and bromides are efficiently coupled under carbonylative conditions, chlorides suffer from a lack of reactivity.

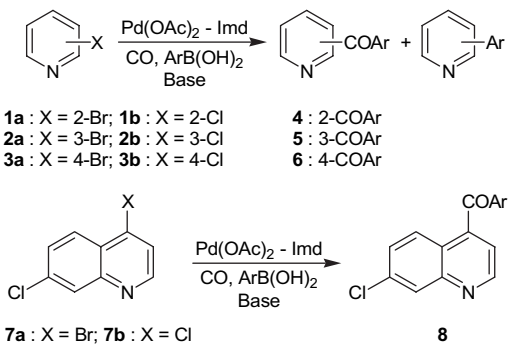
Direct coupling of aryl chlorides, which are much cheaper and more readily available compounds than their iodide or bromide counterparts remained a challenge for a long time. However, recently, remarkable progress has been achieved in this field[6] and different ligands (generally bulky electron rich phosphanes or bulky carbenes associated to palladium on the form of co-ordinatively unsaturated complexes) have been reported as efficient catalysts for the direct coupling (Suzuki, Stille, Heck…reactions) of even deactivated chlorides under relatively mild conditions. Nevertheless there are very few examples of activation of aryl chlorides under CO conditions.[7]

We have previously reported that the use of a palladium-catalyst based on *N*-heterocyclic carbene ligands allowed the effective carbonylative coupling of different chloropyridines with phenylboronic acid.[8] As a part of an ongoing project on the carbonylation of pyridyl halides, we have studied the behavior of this class of carbene as a ligand in the carbonylative cross-coupling of different haloazines with different boronic acids and compared their efficiency in these reactions with the use of tricyclohexylphosphine previously found to be the most effective ligand for this reaction.[4]

2. Results and discussion

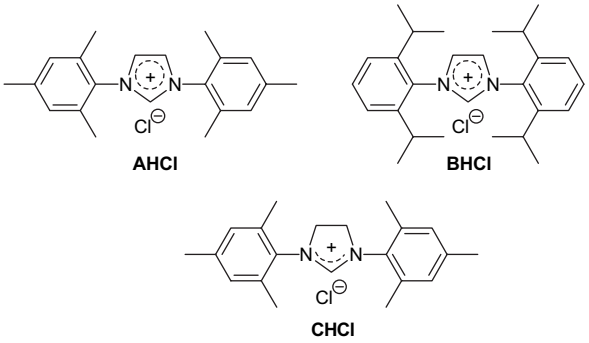
2.1. Carbonylative cross-coupling of bromopyridines

As the use of carbene ligand in carbonylation reaction was not well documented at the beginning of these works, we first explored the reaction with 2-bromopyridine, **1a**, and phenylboronic acid (see Scheme 2). Various solvents, bases,



Scheme 2.

and CO pressures were tested in combination with various palladium precursors and 2 equiv of 1,3-bis(2,4,6-trimethylphenyl)-imidazolium chloride (**AHCl**) in order to find the best reaction conditions (Scheme 3).



Scheme 3. Imidazolium salt (Imd) precursors of carbenes **A**, **B**, and **C**.

Selected results are shown in Table 1. In polar aprotic solvents such as DMF or NMP and with $Pd(OAc)_2$ as palladium source, no reaction took place (entries 4 and 5). Ethereal solvents were more convenient and among them 1,4-dioxane was the best solvent, which enabled complete conversion of **1a**, within reasonable reaction time and with high selectivity, into 2-benzoylpyridine **4** (entry 2). With other ethers such as anisole and THF, both the reactivity and selectivity were slightly lower (entries 1 and 3). As in direct Suzuki coupling reactions (without CO), the base used also greatly affected the efficiency of the process,[9] the best results were obtained with alkaline carbonates and more specifically with Cs_2CO_3 although with K_2CO_3 the conversion was only slightly lower (compare entries 2 and 6). The use of KF, which is also an effective base for direct coupling,[10] led to low conversion and the main product obtained was biphenyl, which resulted from direct homocoupling. Finally, although alkoxide anions are known to reduce imidazolium salts into their corresponding carbenes,[11] $Mg(OEt)_2$ or *t*-BuOK proved to be totally ineffective (entries 9 and 10).

The CO pressure had little effect on the reaction since only a slight decrease in the selectivity occurred on lowering the pressure from 50 to 5 bar whereas the activity remained unchanged (compare entries 2, 11, and 12).

On the other hand, activity and selectivity were greatly influenced by the nature of the catalytic precursor; using $[Pd(allyl)Cl]_2$ as precursor resulted in a remarkable enhancement of the activity but to the slight detriment of the selectivity. In contrast $PdCl_2$ was less efficient than $Pd(OAc)_2$.

Taking into account the catalytic performances of the Pd-carbene ligand system, slightly better than those obtained with PCy_3 (compare Table 1, entries 3 and 15), we have tested its behavior toward various bromoazines and different boronic acids under the conditions previously optimized for **1a** with the aim to delimit the scope and limitation of the process and also for synthetic purpose.

Comparative results between the use of ligand **A** and PCy_3 are summarized in Table 2. Starting with 2-bromopyridine

Table 1. Palladium–imidazolium-catalyzed carbonylative coupling of 2-bromopyridine (**1a**) with phenylboronic acid

Entry	Catalyst precursor	Solvent	Base	*P* (CO) (bar)	Time (h)[a]	Conversion of **1a** (%)	Selectivity of **4**[b] (%)
1	$Pd(OAc)_2$	Anisole	Cs_2CO_3	50	24	83	93
2	$Pd(OAc)_2$	1,4-Dioxane	Cs_2CO_3	50	21	100	95
3	$Pd(OAc)_2$	THF	Cs_2CO_3	50	22	88	89
4	$Pd(OAc)_2$	DMF	Cs_2CO_3	50	22	0	—
5	$Pd(OAc)_2$	NMP	Cs_2CO_3	50	21	0	—
6	$Pd(OAc)_2$	1,4-Dioxane	K_2CO_3	50	22	95	95
7	$Pd(OAc)_2$	1,4-Dioxane	KF	50	22	35	0
8	$Pd(OAc)_2$	1,4-Dioxane	K_2CO_3/CsCl	50	22	67	94
9	$Pd(OAc)_2$	1,4-Dioxane	$Mg(OEt)_2$	50	22	7	0
10	$Pd(OAc)_2$	1,4-Dioxane	*t*-BuOK	50	22	0	—
11	$Pd(OAc)_2$	1,4-Dioxane	Cs_2CO_3	5	21	100	91
12	$Pd(OAc)_2$	1,4-Dioxane	Cs_2CO_3	10	21	100	94
13	$PdCl_2$	1,4-Dioxane	Cs_2CO_3	50	30	68	96
14	$[Pd(allyl)Cl]_2$	1,4-Dioxane	Cs_2CO_3	50	5.5	99	90
15	$PdCl_2(PCy_3)_2$[c]	THF	K_2CO_3	5	20	74	90

General conditions: **1a**=2.1 mmol, $PhB(OH)_2$=2.2 mmol, base=4.0 mmol, [Pd]=0.06 mmol, **AHCl**=0.12 mmol, solvent=15 mL, and *T*=100 °C.
[a] Reaction time was not necessarily optimized.
[b] Selectivity for carbonylated product **4**; 2-phenylpyridine accounts for the balance.
[c] Without **AHCl**.

and *p*-tolylboronic acid, high conversions were achieved with both ligands. However, the results remained similar to those obtained with phenylboronic acid with a slightly better activity and selectivity for ligand **A**. In contrast, a remarkable enhancement of the activity was observed with *o*-tolylboronic acid using a catalyst based on ligand **A**. Actually, the reaction went almost to completion only after 6 h while more than 20 h were needed with PCy_3 (or with **A** in the case of phenylboronic acid). In the same way, the sterically hindered 1-naphthylboronic acid led to a better activity than $PhB(OH)_2$. Other boronic acids such as *p*-methoxyphenyl, *p*- and *m*-chlorophenylboronic acids exhibited a reactivity similar or lower to the one observed with $PhB(OH)_2$.

Table 2. Carbonylative coupling of various bromoazines with different aryl boronic acids

Entry	Azine	Boronic acid Ar	Ligand	Solvent	Time (h)	Conversion (%)	Selectivity[c] (%)
1[a]	**1a**	*o*-Tolyl	**A**	Dioxane	6	97	96
2[b]	**1a**	*o*-Tolyl	PCy_3	THF	22	83	95
3[a]	**1a**	*p*-Tolyl	**A**	Dioxane	24	99	97
4[b]	**1a**	*p*-Tolyl	PCy_3	THF	40	100	82.5
5[a]	**1a**	*m*-ClPh	**A**	Dioxane	30	74	93
6[b]	**1a**	*m*-ClPh	PCy_3	THF	62	100	50
7[a]	**1a**	*p*-ClPh	**A**	Dioxane	21	100	95
8[a]	**1a**	*p*-MeOPh	A	Dioxane	45	87	96
9[a]	**1a**	Naphthyl	**A**	Dioxane	15	100	75
10[a]	**1a**	$NaB(Ph)_4$	**A**	Dioxane	22	100	82
11[a]	**2a**	Ph	**A**	Dioxane	46	70	88
12[b]	**2a**		PCy_3	THF	62	100	67
13[a]	**2a**	*o*-Tolyl	**A**	Dioxane	30	86	86
14[b]	**2a**	*o*-Tolyl	PCy_3	THF	30	45	49
15[a]	**2a**	*p*-Tolyl	**A**	Dioxane	30	83	85
16[b]	**2a**	*p*-Tolyl	PCy_3	THF	30	48	51
17[a]	**2a**	*m*-ClPh	**A**	Dioxane	30	70	92
18[b]	**2a**	*m*-ClPh	PCy_3	THF	30	12	71
19[a]	**7a**	Ph	**A**	Dioxane	4.5	75	72
20[b]	**7a**	Ph	PCy_3	Dioxane	4.5	86	47
21[a]	**7a**	*o*-Tolyl	**A**	Dioxane	4	96	90
22[b]	**7a**	*o*-Tolyl	PCy_3	Dioxane	4	96	76

General conditions: substrate=2.1 mmol, boronic acid=2.2 mmol except entry 9: $NaB(Ph)_4$=0.55 mmol, P_{CO}=50 bar, *T*=120 °C, solvent=15 mL.
[a] $Pd(OAc)_2$=0.06 mmol, **AHCl**=0.12 mmol, and Cs_2CO_3=4 mmol.
[b] $PdCl_2(PCy_3)_2$=0.06 mmol and K_2CO_3=4 mmol.
[c] Selectivity for the carbonylated product.

However, it is difficult to connect the activity with the electronic properties of the substituent of the aryl moiety of the boronic acid. It is also noteworthy that in the test carried out with *m*-chlorophenylboronic acid and carbene **A** (entry 5), a large amount of chlorobenzene was found in the reaction medium resulting from the decomposition of the boronic acid (boronic acids bearing withdrawing groups are prone to deboronation). Thus the modest conversion obtained in this case was probably due to the lack of reagent. Finally, sodium tetraphenylborate reacted in the same way as $PhB(OH)_2$ and provided a high yield of the corresponding ketone even using 0.25 equiv of $NaB(Ph)_4$ perbromopyridine (entry 10).[12]

Under the same conditions as those used with 2-bromopyridine, 3-bromopyridine was found to react much more slowly with both ligands whichever boronic acid was used. This observation is not surprising since the carbon–halogen bond in the 3-position of the pyridine ring is known to be deactivated toward the nucleophilic substitution[1a] and hence toward the oxidative addition onto the palladium in contrast with the 2-position. However, carbene **A** led to much better results than PCy_3 both in terms of conversion, particularly in the case of *m*-chlorophenylboronic acid, and selectivity with *o*- or *p*-tolylboronic acids.

Finally 4-bromo-7-chloroquinoline reacted very easily even with the hindered *o*-tolylboronic acid since in this case the reaction went almost to completion within only 4 h with the two ligands (entries 21 and 22) but once again with a better selectivity when using the carbene ligand. This example evidences the enhanced reactivity of the halogen in 4-position of the pyridinic ring toward this reaction and is in accordance with results previously reported with iodopyridines.[4]

2.2. Carbonylative cross-coupling of chloropyridines

Having demonstrated the effectiveness of the ligand **A** in the palladium catalyzed carbonylative cross-coupling of bromopyridines with boronic acids, the applicability of this system toward various chloropyridines was next examined (Table 3) under the conditions optimized for bromopyridines (i.e., using 1,4-dioxane as solvent and Cs_2CO_3 as base).

Table 3. Carbonylative cross-coupling of 2-chloropyridine

Entry	Ligand[a]	Temp (°C)	Time (h)	Conversion (%)	Selectivity of **4**[b] (%)
1[c]	**A** (2)	140	1	100	—[g]
2	**A** (2)	100	40	35	86
3	**A** (2)	120	40	63	93
4	**A** (2)	140	22	72	90
5	**A** (2)	150	24	60	87
6	**A** (1)	140	30	32	84
7	**A** (1.5)	140	22	67	89
8	**A** (4)	140	30	49	87
9	**A** (2) preformed	140	30	30	92
10[d]	**A** (2)	140	22	88	91
11[e]	**A** (2)	140	60	40	92
12	**A** (1)+PCy_3(1)	140	22	72	92
13	**B** (2)	140	30	48	89
14	**C** (2)	140	30	39	90
15[f]	**A** (2)	140	22	73	91

Conditions: **1b**=2.1 mmol, $PhB(OH)_2$=2.2 mmol, Cs_2CO_3=4.0 mmol, [Pd]=0.06 mmol, dioxane=15 mL, and P_{CO}=50 bar.
[a] The number inside brackets refers to the ligand to Pd ratio.
[b] Selectivity for carbonylated product **4**.
[c] Without CO.
[d] Percolated dioxane.
[e] Addition of 0.2 mL of water.
[f] $PhB(OH)_2$=4 mmol.
[g] 100% selectivity for 2-phenylpyridine.

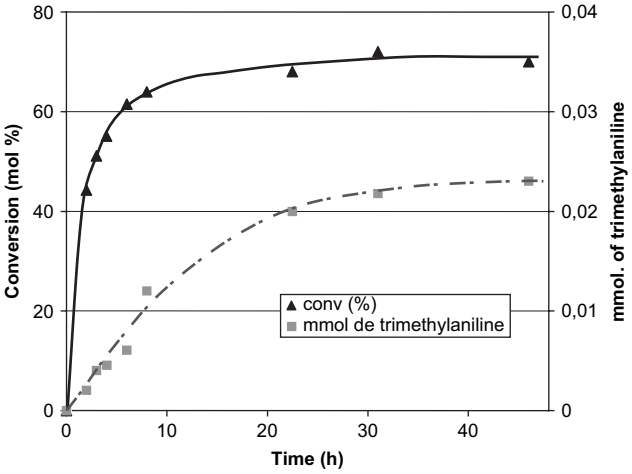


Figure 1. Carbonylative coupling of 2-chloropyridine; conversion and decomposition of the catalytic system versus time. *Conditions*: See Table 3, entry 4.

At the same temperature (100 °C) to that one used with **1a**, the carbonylative cross-coupling of 2-chloropyridine with phenylboronic acid was very slow (only 30% conversion after 40 h, see Table 3, entry 2). Increasing the temperature led, as expected, to a great increase in the activity with practically no effect on the selectivity. However, 140 °C seems to be optimal, leading to 72% conversion after 16 h. At 150 °C both the overall conversion and the selectivity decreased slightly, at this temperature the catalytic system probably reached its stability limit.

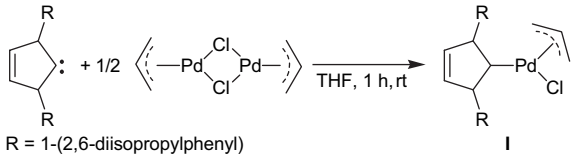
The influence of the palladium on ligand molar ratio was also studied (with various amounts of imidazolium salt). For a 1:1 ratio low conversion was observed whereas it is noteworthy that this ratio was reported as leading to the best results in the case of the direct Suzuki coupling of aryl chlorides without CO.[13] Ratios ranging between 1:1.5 and 1:2 led to the best activities. With a higher amount of ligand the conversion markedly decreased. The latter observation is probably related to the fact that when higher quantities of ligand are used, the coordination sphere of the palladium center is too hindered to allow easy oxidative addition and therefore good activity. On the contrary with low amounts of ligand the lack of efficiency of the catalyst is probably due to the fact that, on one hand, CO can act as a ligand with poor sigma donor character and good π acceptor properties, thus the electronic density of the metal decreases and consequently the oxidative addition is more difficult. This influence of the CO on the reaction rate is perfectly highlighted by an experiment carried out in the absence of CO but under the same conditions to those giving the best conversion with CO. In this case, total conversion into the coupling Suzuki type product was obtained in only 1 h even with a **A**/Pd ratio of 2 (entry 1). On the other hand, it is also possible that the system with low amount of ligand **A** is not stable enough over a long period. Actually, Figure 1 shows that at the beginning of the reaction the system exhibited high activity (about 50% conversion after 4 h), but after several hours this dramatically dropped. In parallel, GC–MS analyses of the reaction medium showed the appearance of trimethylaniline during the course of the reaction. The formation of this compound can only be explained by the total decomposition of the carbene **A** (or its imidazolium salt precursor). However, determination of the quantity of trimethylaniline formed proved that only a minor part of the carbene was retrieved in this form (about 10%) and that the rate of formation of the aniline decreased with the reaction rate.

The decomposition of the boronic acid under the drastic conditions used was also envisioned to explain the decrease of the reaction rate, therefore, a run was carried out with a higher quantity (2 equiv $PhB(OH)_2$/chloropyridine) but unfortunately no increase in the conversion was observed (entry 15).

In order to enhance the stability of the catalyst the use of a mixture of carbene **A** and tricyclohexylphosphine,[14] was also checked but provided no improvement in the conversion in comparison with **A** alone. In the same way, pre-formation of the free carbene **A** in a separate vessel by action of a base on the imidazolium salt and addition to the reaction medium just before introduction of CO has a detrimental effect on the conversion. Finally, bulky carbene **B** (with isopropyl substituents on the phenyl groups) or **C** (the saturated counterpart of **A**) formed in situ from the corresponding imidazolium salts, was also tested but were found to be much less efficient than **A**.

Taking into account these different results, we have been endeavoring to improve the long term stability of the catalyst. In this context, we have studied the influence of the purity of the solvent. Much better results in terms of conversion (88% after 22 h) were obtained when dioxane was percolated just before use through freshly activated alumina (entry 10). In contrast addition of a small quantity of water (0.2 mL in 15 mL of solvent) had a very detrimental effect since the conversion dropped to 40% after 60 h (entry 11). Better defined palladium species than the one obtained in situ

from $Pd(OAc)_2$ and the imidazolium salts were also tested. For this purpose, complexes **I** and **II** in which the metal is coordinated to one or two carbenes **B**, were synthesized according to literature methods[15,16] (see Schemes 4 and 5).



Scheme 4.

With complex **II** at 140 °C no reaction occurred until 20 h after which a very low activity was observed (12% conversion after 45 h) with concomitant formation of 2,6-diisopropylaniline. In contrast, complex **I** was a much more active catalytic precursor even at a lower temperature (120 °C) since the conversion reached 85% after 22 h and interestingly after that period the catalyst remained still active to give an almost total conversion after 30 h. On the other hand, Figure 2 shows that when the reaction was carried out with complex **I**, low activity was observed in the early stage of the reaction (lower activity than the one obtained with the catalyst formed in situ from $Pd(OAc)_2$+ **AHCl** at the same temperature). However, after this induction period, which probably corresponds to the time needed to reduce the complex **I** into the catalytic species, the activity greatly increased and started to decrease after about 5–6 h. This decrease was however, much lower than the case of catalyst formed in situ and thus the reaction can go to completion.

The high efficiency of complex **I** in comparison with the one of complex **II** indicates that the catalytic species contains only one carbene ligand. The fact that diisopropylaniline was found in the reaction medium when the reaction starts to take place with complex **II**, is in accordance with this hypothesis. Complex **II** becomes active only after losing one carbene (the low activity observed under these conditions probably results from the low concentration of the active species due to a very high stability of complex **II** versus its dissociation into a monocarbene palladium species).

2.3. Carbonylative cross-coupling of dichloropyridines

The reactivity of various dihalopyridines was also tested with a catalyst formed in situ from $Pd(OAc)_2$ and the imidazolium salt precursor of carbene **A**.

As it can be seen (Scheme 6) 2,3-dichloropyridine was found to be much more reactive than 2-chloropyridine since 90% conversion was obtained only after 4 h. This higher activity of the Cl in the 2-position is probably due to the withdrawing effect of its counterpart in the 3-position. On the other hand, the influence of the 2-Cl (or 2-COPh) on the reactivity of the 3-position is limited since no coupling product at this position was observed. Nevertheless a substantial amount of reduction product i.e. 2-benzoylpyridine was also obtained.

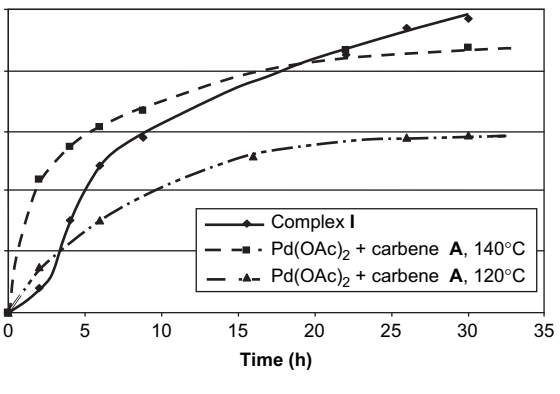
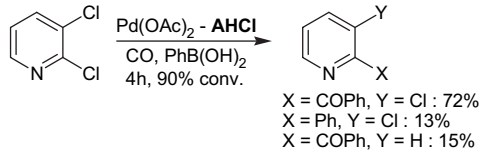
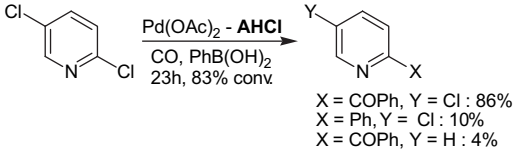


Figure 2. Carbonylative coupling of 2-chloropyridine catalyzed by complex **I** and systems formed in situ from $Pd(OAc)_2$ and **AHCl**. *Conditions*: [Pd]=0.06 mmol, **1b**=2.1 mmol, $PhB(OH)_2$=2.2 mmol, Cs_2CO_3=4.0 mmol, [Pd]=0.06 mmol, dioxane=15 mL, P_{CO}=50 bar. Addition of **AHCl** in the runs carried out with $Pd(OAc)_2$.

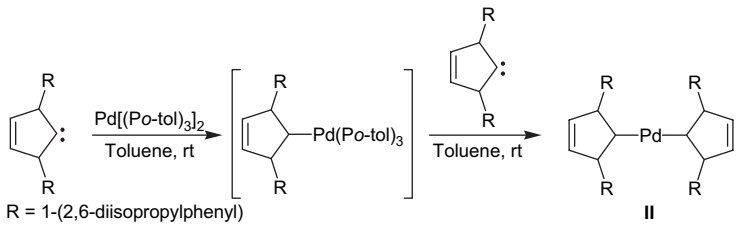


Scheme 6.

Consistent with the above results, in the case of the 2,5-dichloropyridine, only the 2-position of this substrate reacted to give the corresponding 2-aroyl derivative (Scheme 7). However, in this case the influence on the reactivity of the halogen in the 5-position was very low and the conversion is very close to that observed with 2-chloropyridine moreover as in the above case the reduction product was also observed.

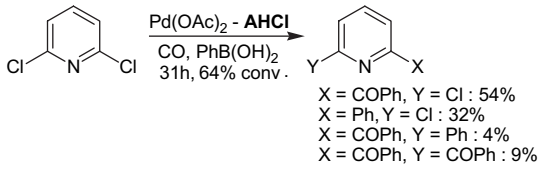


Scheme 7.



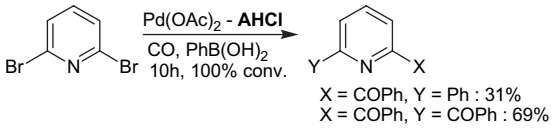
Scheme 5.

Although the two halogen atoms of 2,6-dichloropyridine are activated this substrate exhibited a low reactivity (only 64% conversion after 31 h) and the reaction products resulted mainly from mono coupling with a low ketone versus direct coupling product ratio (Scheme 8).



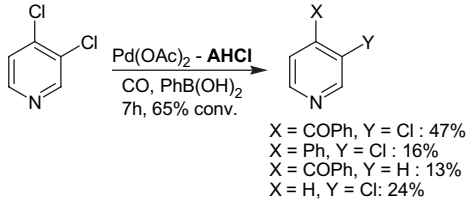
Scheme 8.

In contrast with its chloro-homologue, Scheme 9 shows that 2,6-dibromopyridine was more reactive than 2-bromopyridine since total conversion occurred in only 10 h instead of 22 h with 2-bromopyridine. On the other hand, the diketone was obtained in only moderate yield (69%) plus a notable quantity of the monocarbonylative-direct coupling product. This selectivity for the dicarbonylative coupling product seems modest but results from two consecutive reactions thus one can think that the selectivity of each coupling to give ketone is about 83%, which is slightly lower than that observed with 2-bromopyridine but is in accordance with the fact that a withdrawing effect (Br or COPh) promotes the oxidative addition but is detrimental to the CO insertion (Scheme 9).[4]



Scheme 9.

Finally with 3,4-dichloropyridine, once again the activated Cl (i.e., the Cl in the 4-position) reacted more rapidly than in the case of its homologue 4-chloropyridine to give the corresponding coupling products but once again with a modest selectivity for the ketone over the direct coupling product. As in the case of the other dichloropyridines some reduction occurred even before coupling since a large amount of 3-chloropyridine was obtained (Scheme 10).



Scheme 10.

3. Conclusion

In summary, we have shown that imidazolium salts, precursors of *N*-heterocyclic ligands, in combination with palladium acetate provide efficient catalytic systems for carbonylative cross-coupling reactions of pyridyl bromides with different aryl boronic acids leading to a variety of pyridyl aryl ketones with high selectivities. Moreover, the use of these catalytic systems allowed us to extend the scope of the reaction to the economically attractive but poorly reactive chloro- or dichlorazines even if, with this class of compounds, the reaction takes place only with substrates in which the C–Cl bond is activated by the heteroatom. It also appears that the nature of the imidazolium salt and its ratio versus Pd is crucial with chloroderivatives to obtain good results. In this way, the best results were observed with well defined catalyst precursor Pd(allyl)**B**Cl possessing one carbene (1,3-di(2,6-diisopropylphenyl)imidazolin-2-ylidene) perpalladium. This catalyst in comparison with catalytic systems obtained in situ from imidazolium salts is active at a lower temperature, remains active during all the reaction time and leads to a higher selectivity. Nevertheless, carbonylative cross-coupling of chloroderivatives appears to be much more difficult than simple coupling without CO and is still a challenge in the case of non-activated or deactivated chloroaryls.

4. Experimental

4.1. General remarks

NMR spectra were recorded on a AC-300 Bruker spectrometer at 23 °C in $CDCl_3$; chemical shifts are reported in parts per million downfield from TMS and were determined with reference to the residual ^1H (δ=7.25) and ^{13}C (δ=77.0) solvent peaks. All coupling constants are reported in Hertz. GLC analyses were performed on a Chrompack CP 9001 apparatus equipped with a flame ionization detector and a CPSil 5CB (25 m×0.32 mm ID, Chrompack) column. MS and HRMS were performed on a JMS-700m Station mass spectrometer (JEOL) with either electron impact (70 eV) or chemical (CH_4) ionization mode. Melting points are uncorrected. All the carbonylative cross-coupling products described hereafter gave similar IR spectra (KBr pellets) with ν(C=O) in the range 1690–1640 cm^{-1} and ν(CN) in the range 1590–1550 cm^{-1}.

The commercially available $Pd(OAc)_2$ (Acros), Cs_2CO_3 (Acros), PCy_3 (Acros), *N*-heterocyclic imidazolium salts (**AHCl** and **BHCl** from Strem, **CHCl** from Acros), $PhB(OH)_2$ (Acros), $NaBPh_4$ (Acros), and dihalopyridines (except 3,4-dichloropyridine) were used as received. Monohalopyridines were generally distilled in presence of KOH and kept under a nitrogen atmosphere in a Schlenk tube. 1,4-Dioxane was percolated on activated alumina before being degassed and conserved in Schlenk tube. The substrates: 3,4-dichloropyridine,[17] 4-bromo-7-chloroquinoline,[18] and substituted aryl boronic acids[19] and the complexes $[Pd(allyl)Cl]_2$,[20] [Pd(allyl)**B**Cl],[15] and Pd$\mathbf{B}_2$[16] were prepared according to literature procedures.

4.2. Typical procedure for carbonylative coupling

In a typical experiment (Table 3, entry 4), a 60-mL stainless steel autoclave equipped with a magnetic stirring bar was charged with all of the solid reagents i.e. Cs_2CO_3 (1.3 g, 4.0 mmol), $Pd(OAc)_2$ (13.5 mg, 0.06 mmol), the imidazolium salt (0.12 mmol), and $PhB(OH)_2$ (268 mg, 2.2 mmol). After flushing the atmosphere with N_2, a solution of **1b**

(200 μL, 2.1 mmol) in 1,4-dioxane (15 mL) was added under N_2. The autoclave was flushed with CO, pressurized to 50 bar and heated to 140 °C. The reaction was monitored by GC using dodecane as an internal standard. At the end of the reaction, after cooling to room temperature, CH_2Cl_2 (15 mL) was added to the reaction mixture, the solution was then filtered and the precipitate was washed with CH_2Cl_2. The different filtrates were combined and the solvent removed under vacuum. The residue was then purified by silica gel chromatography to give analytically pure (^1H, ^{13}C NMR, and MS) ketone products.

4.2.1. 2-Benzoylpyridine. White solid, mp=42 °C. ^1H NMR ($CDCl_3$) δ=8.70 (d, 1H, J=4.4 Hz, H-6), 8.04 (d, 1H, J=7.6 Hz, H-3), 8.01 (d, 2H, J=7.5 Hz, H-9), 7.86 (td, 1H, J=7.6 and 1.7 Hz, H-4), 7.56 (t, 1H, J=7.6 Hz, H-11), 7.44–7.49 (m, 3H, H-5 and H-10). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=193.9 (CO), 155.3, 148.6, 137.1, 136.2, 132.9, 131.0, 128.2, 126.2, 124.6. MS (EI): m/z=183 (M^+, 38), 182 (62), 155 (M^+-CO, 92), 154 (42), 127 (6), 106 (M^+-Ph, 10), 105 (M^+-Py, 90), 78 (Py^+, 28), 77 (Ph^+, 100), 52 (18), 51 ($C_4H_3^+$, 76), 50 (28).

4.2.2. *o*-Tolyl-2-pyridylmethanone. Pale yellow solid, mp=67–68 °C. ^1H NMR ($CDCl_3$) δ=8.67 (d, 1H, J=4.2 Hz, H-6), 8.05 (d, 1H, J=7.8 Hz, H-3), 7.84 (td, 1H, J=7.8 and 1.5 Hz, H-4), 7.21–7.45 (m, 5H, H-5, H-10, H-11, H-12, and H-13), 2.37 (s, 3H, H-14). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=197.3 (CO), 154.9, 149.1, 137.7, 137.3, 136.9, 131.0, 130.9, 129.9, 126.4, 125.0, 124.0, 20.4. MS (EI): m/z=197 (M^+, 9), 182 (M^+-CH_3, 13), 168 (100), 119 (M^+-Py, 8), 91 (Tol^+, 22), 78 (Py^+, 2), 51 ($C_4H_3^+$, 3).

4.2.3. *p*-Tolyl-2-pyridylmethanone. Yellow solid, mp=43–44 °C. ^1H NMR ($CDCl_3$) δ=8.68 (d, 1H, J=3.0 Hz, H-6), 7.81–7.98 (m, 4H, H-3, H-9, H-4, and H-13), 7.40 (t, 1H, J=7.2 Hz, H-5), 7.24 (d, 2H, J=11.9 Hz, H-10 and H-12), 2.40 (s, 3H, H-14). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=193.4, 152.2, 148.3, 143.6, 136.8, 133.4, 130.9, 128.7, 125.8, 124.3, 21.6. MS (EI): m/z=197 (M^+, 29), 182 (M^+-CH_3, 46), 169 (M^+-CO, 100), 119 (44), 91 (Tol^+, 65), 78 (Py^+, 3), 51 ($C_4H_3^+$, 6).

4.2.4. *m*-Chlorophenyl-2-pyridylmethanone. Yellow oil, ^1H NMR ($CDCl_3$) δ=8.70 (d, 1H, J=4.2 Hz, H-6), 8.03–8.06 (m, 2H, H-3 and H-9), 7.85–7.97 (m, 2H, H-4 and H-13), 7.48–7.56 (m, 2H, H-5, H-11), 7.41 (t, 1H, J=7.8 Hz, H-12). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=192.3, 154.3, 148.6, 137.8, 137.2, 134.2, 132.7, 130.9, 129.4, 129.1, 126.5, 124.7. MS (EI): m/z=217 (M^+, 24), 189 (M^+-CO, 100), 182 (M^+-Cl, 31), 154 ($M^+-CO-Cl$, 75), 139 (M^+-Py, 31), 111 ($PhCl^+$, 45), 78 (Py^+, 5), 77 (Ph^+, 3), 75 (32), 51 ($C_4H_3^+$, 10).

4.2.5. *p*-Methoxyphenyl-2-pyridylmethanone. Pale yellow oil, ^1H NMR ($CDCl_3$) δ=8.70 (d, 1H, J=4.4 Hz, H-6), 8.12 (d, 1H, J=8.8 Hz, H-9), 7.98 (d, 1H, H-3, J=7.8 Hz), 7.88 (m, 1H, H-4), 7.46 (m, 1H, H-5), 6.98 (d, 1H, H-10), 3.88 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=192.2, 163.5, 155.7, 148.3, 136.9, 133.4, 128.9, 125.8, 124.5, 113.4, 55.4.

4.2.6. *p*-Chlorophenyl-2-pyridylmethanone.[21] Pale yellow solid, mp=60–61 °C. ^1H NMR ($CDCl_3$) δ=8.70 (d, 1H, J=4.2 Hz, H-6), 8.05 (d, 2H, H-9 and H-3), 7.90 (t, 1H, J=7.5 Hz, H-4), 7.40–7.50 (m, 2H, H-5 and H-10). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=192.3, 154.6, 148.5, 139.3, 139.1, 134.5, 132.4, 128.4, 126.4, 124.6.

4.2.7. 1-Naphthyl-2-pyridylmethanone. White solid, mp=43–44 °C. ^1H NMR ($CDCl_3$) δ=8.70 (d, 1H, J=4.4 Hz, H-6), 8.25 (m, 1H, H-15), 8.17 (d, 1H, J=7.9 Hz, H-3), 8.03 (d, 1H, J=8.2 Hz), 7.84–7.94 (m, 2H), 7.72 (d, J=7.0 Hz), 7.45–7.60 (m, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=196.5, 155.4, 149.1, 137.0, 134.7, 133.8, 132.2, 131.2, 129.9, 128.4, 127.4, 126.5, 126.3, 125.6, 124.6, 124.1.

4.2.8. 3-Benzoylpyridine. White solid, mp=40–41 °C. ^1H NMR ($CDCl_3$) δ=9.01 (d, 1H, J=2.0 Hz, H-2), 8.85 (dd, 1H, J=5.0 and 2.0 Hz, H-6), 8.15 (dt, 1H, J=8.0 and 2.0 Hz, H-4), 7.84 (d, 2H, J=7.5 Hz, H-9), 7.75 (dd, 1H, J=8.0 and 5.0 Hz, H-5), 7.35–7.75 (m, 3H, H-10 and H-11). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=194.8, 152.8, 151.0, 137.1, 136.6, 133.1, 129.9, 128.5, 128.4, 123.3. MS (EI): m/z=183 (M^+, 96), 182 (48), 155 (M^+-CO, 8), 154 (10), 127 (5), 106 (M^+-Ph, 40), 105 (M^+-Py, 100), 78 (Py^+, 56), 77 (Ph^+, 84), 63 (2), 51 ($C_4H_3^+$, 78).

4.2.9. *o*-Tolyl-3-pyridylmethanone. Yellow oil, ^1H NMR ($CDCl_3$) δ=8.89 (s, 1H, H-2), 8.72 (t, 1H, J=3.4 Hz, H-6), 8.05 (d, 1H, J=7.8 Hz, H-4), 7.34–7.39, (m, 2H), 7.18–7.29 (m, 3H), 2.32 (s, 3H, H-14). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=196.4, 152.9, 151.0, 136.9, 136.8, 136.7, 132.9, 131.0, 130.7, 128.6, 125.1, 123.1, 19.8. MS (EI): m/z=197 (M^+, 27), 168 (30), 119 (M^+-Py, 10), 91 (Tol^+, 26), 78 (Py^+, 6), 51 ($C_4H_3^+$, 5).

4.2.10. *p*-Tolyl-3-pyridylmethanone. White solid, mp=76–77 °C. ^1H NMR ($CDCl_3$) δ=8.96 (s, 1H, H-2), 8.78 (d, 1H, J=3.0 Hz, H-6), 8.08 (d, 1H, J=6.7 Hz), 7.69 (d, 2H, J=7.5 Hz), 7.42 (d, 1H, J=4.8 Hz), 7.28 (d, 2H, J=7.3 Hz), 2.43 (s, 3H, H-14). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=194.4, 152.4, 150.6, 144.1, 137.1, 134.0, 130.2, 129.2, 123.3, 21.6. MS (EI): m/z=197 (M^+, 67), 182 (M^+-CH_3, 100), 119 (M^+-Py, 51), 91 (Tol^+, 52), 78 (Py^+, 8), 51 ($C_4H_3^+$, 7).

4.2.11. *m*-Chlorophenyl-3-pyridylmethanone. Yellow oil, ^1H NMR ($CDCl_3$) δ=8.96 (s, 1H, H-2), 8.80 (d, 1H, J=3.7 Hz, H-6), 8.08 (d, 2H, J=7.8 Hz), 7.75 (s, 1H, H-9), 7.51–7.64 (m, 2H), 7.39–7.47 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=193.2, 152.8, 150.5, 138.1, 137.3, 134.9, 133.0, 132.6, 129.9, 129.7, 128.0, 123.5. MS (EI): m/z=217 (M^+, 2), 182 (M^+-Cl, 100), 139 (M^+-Py, 21), 111 ($PhCl^+$, 18), 106 (M^+-PhCl, 6), 78 (Py^+, 10), 51 ($C_4H_3^+$, 7).

4.2.12. 4-Benzoylpyridine. White solid, mp=70–71 °C. ^1H NMR ($CDCl_3$) δ=8.81 (d, 2H, J=3.9 Hz, H-2), 7.78 (d, 2H, J=7.3 Hz, H-7), 7.49–7.67 (m, 5H, J=7.3 Hz, H-3, H-8, and H-9). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=195.1, 150.3, 144.3, 135.8, 133.5, 130.1, 128.6, 122.9. MS (EI): m/z=183 (M^+, 34), 106 (M^+-Ph, 10), 105 (M^+-Py, 100), 78 (Py^+, 12), 77 (Ph^+, 52), 51 ($C_4H_3^+$, 38).

4.2.13. Phenyl-4-(7-chloroquinolyl)methanone. Pale solid, mp=104–105 °C. ^1H NMR ($CDCl_3$) δ=9.01 (d, 1H, J=4.4 Hz, H-2), 8.19 (d, 1H, J=1.95 Hz, H-5), 7.84 (d,

2H, J=7.3 Hz, H-13), 7.82 (s, 1H, H-8), 7.65 (m, 1H, H-15), 7.50 (m, 2H, H-14), 7.47 (m, 1H, H-6), 7.41 (d, 1H, J=4.4 Hz, H-3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=195.5, 150.5, 149.1, 144.2, 136.4, 136.0, 134.3, 130.3, 128.9, 128.8, 128.7, 126.7, 123.3, 119.8. MS (EI): m/z=267 (M^+, 72), 232(M^+-Cl, 100), 105 ($PhCO^+$, 63), 77 (Ph^+, 48), 51 ($C_4H_3^+$, 13).

4.2.14. *o*-Tolyl-4-(7-chloroquinolyl)methanone. White solid, mp=78–79 °C. ^1H NMR ($CDCl_3$) δ=8.95 (dd, 1H, J=3.7 and 2.0 Hz, H-2), 8.80 (d, 1H, J=2.0 Hz, H-5), 8.00–8.10 (m, 3H), 7.70 (d, 1H, J=8.8 Hz), 7.07–7.42 (m, 3H, H-15), 2.51 (s, 3H, H-18). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ=197.5, 151.0, 150.5, 135.6, 132.4, 131.9, 131.6, 128.8, 128.6, 128.5, 128.1, 127.3, 126.6, 125.5, 121.0, 120.6, 21.1. MS (EI): m/z=281 (M^+, 100), 264 (40), 252 (M^+-CO, 72), 246 (M^+-Cl, 45), 217 (35), 151 ($TolCO^+$, 29), 119 ($M^+-TolCO$, 15), 91 (Tol^+, 36).

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