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Improved Sonogashira C–C coupling through clay supported palladium complexes with tridentate pincer bis-carbene ligands

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Abstract—Highly active recyclable Pd catalysts modified with a rigid C,N,C-tridentate pincer carbene ligand were successfully applied to the coupling of aryl halides with terminal acetylenes. The immobilization of Pd(II) complexes onto clays has beneficial effects on the recyclability of the catalytic activity over consecutive runs and also on the catalyst's stability, preventing it from Pd(0) formation.

Nucleophilic *N*-heterocyclic carbenes have attracted considerable attention as possible alternatives for the widely used phosphine ligands in organotransition-metal catalysis. The main advantages of these ligands are that they do not readily dissociate from the metal center, they have a strong σ-donor character and they are considered to be of low toxicity.[1] All these beneficial effects, together with the fact that they are synthesized more readily than many conventional phosphine ligands mean that they have become versatile ligands in catalyzed organic transformations.[2]

Ever since the first applications of palladium complexes with heterocyclic carbene ligands in cross-coupling reactions,[3] a considerable effort has been made to show that they are efficient at coupling aryl halides with amines,[4] amides[5] and alkenes[6] (Heck reaction). The coupling of aryl halides with terminal acetylenes to produce aryl alkynes, (Sonogashira reaction),[7] has been extensively studied because it is frequently used as a key step in the synthesis of antimycotics,[8] antibiotics,[9] liquid crystals, polymers and optical or electronic materials.[10] However, the use of nucleophilic carbenes in Sonogashira coupling has been studied much less,[6b,d,11] although recent results with palladium complexes modified with carbamoyl imidazolium salts under mild conditions[12] and imidazolium chloride assisted coupling of aryl bromides with alkynylsilanes, have been promising.[13]

The commercial success of this C–C coupling[14] depends on two main objectives: (i) a wide variety of cheaply available starting materials such as aryl bromides and aryl chlorides that can be used as the aryl halide source, and (ii) the use of an extremely active and/or recyclable palladium catalyst that can compensate for the cost of the transition metal. As far as the first objective is concerned, it has been reported that palladium systems modified with a bulky and electron rich-phosphine ligand, can be used to provide unusually high activity in the Sonogashira coupling of aryl bromides, at room temperature.[15] But even more significant are the results achieved by Eberhard et al.[16] and Plenio et al.[17] in the coupling of aryl chlorides. They described high-yielding palladium catalytic systems modified with phosponito pincer ligands and bis-adamantylbenzylphosphine ligands, respectively. As far as the second objective is concerned, numerous studies have dealt with the problem of catalyst recovery in homogeneous processes,[18] but very few have been reported to allow this goal in the case of Sonogashira reaction. As far as we know, there are only five purposes in the literature dated from last year and concerned to immobilize the catalytic palladium system in: an aqueous film supported on a mesoporous silica,[19] a fluorous reversed-phase silica gel (FRPSG),[20] soluble polymers,[21] ionic liquids in a microflow system[22] and finally by using layered double hydroxide supported nanopalladium catalysts.[23] All these solutions succeed in separating the palladium catalytic system from the products, but the recyclability

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Keywords: Sonogashira coupling; aryl halides; acetylenes; palladium; tridenatate pincer bis-carabene ligands; clays; immobilization.

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is strongly dependent on the nature of the immobilization. Thus, it seems that best prevention from leaching comes from covalent attachment of the catalyst onto the support, although multistep synthetic pathways are then required. In this context, our group has made a systematic study of immobilizing organotransition metal complexes onto clays through adsorptive and electrostatic interactions, using a simple synthetic protocol that prevents the catalytic system from leaching. This methodology has already been successfully applied in the hydrogenation of imines[24a–c] or the reductive alkylation of amines,[24d] and the asymmetric hydroboration of vinylarenes.[25] More recently, we immobilized palladium complexes modified with tridentate pincer bis-carbene ligands onto clays for the first time, and then applied them in the Heck C–C coupling showing a recycling capacity of at least ten consecutive runs.[26]

Encouraged by the interesting recovering and the possibility of reusing the catalytic system, we now describe the study of the same Pd(II) catalysts in the Sonogashira coupling. Our work involved selecting an optimized palladium catalyst modified with a C,N,C-pincer bis-carbene ligand (Fig. 1) both in homogeneous and heterogenized versions. Once we had established the methodology with model substrates, we extended it to include more attractive starting materials.

It has been found that pincer-heterocyclic-carbene ligands are very efficient at C–X activation and extremely stable at high temperatures,[6a,b] which made it possible for them to be used in the C–C coupling of the test substrates phenylacetylene and phenyliodide at the refluxing temperature of pyrrolidine, 87°C (which acts both as a solvent and as a base to intercept the HI formed). Of all the known solutions described to date for suppressing the side reaction of oxidative homocoupling (Glaser coupling) of the alkyne to the corresponding symmetrical diyne,[13,27] we decided to perform the reaction under nitrogen and by slow addition of the alkyne, keeping its concentration in the reaction mixture low. Under these homogeneous reaction conditions, the catalyst [PdBr(CNC-Bu$_2$)]Br proved to be highly efficient, affording the desired product in a 99% yield in 45 min (Fig. 2).

As has been previously described for the Sonogashira reaction, the presence of the co-catalyst CuI seems to be necessary because otherwise conversions are only moderate (38% yield in 1 h, Fig. 2). However, the addition of CuI to other palladium catalytic systems modified with carbene ligands,[6d] surprisingly resulted in almost complete deactivation of the catalyst, probably due to the fact that carbene ligands could be transferred to Cu.[28] A search for the best tridentate pincer bis-carbene ligand showed the influence of the wingtip groups (R = methyl, butyl and benzyl) in the catalytic activity. Whereas the solubility in non-polar solvents increases from C,N,C pincer bis-carbene with R = Me to R = Bu or Bn, the C–C coupling reaction was substantially affected by the difference in the nature of the substituents, affording the highest activity (99% yield in 30 min) when the catalytic system was [PdBr(CNC-Me$_2$)]Br (Fig. 2). Similar increases in activity have been observed in the literature when non-hindered substituents on imidazolium chlorides modify the palladium catalytic system Pd(OAc)$_2$.[13] The reaction rates were also significantly influenced by the identity of the counterion in the catalytic system [PdBr(CNC-Bu$_2$)]X. The C–C coupling proceeded more rapidly when the counterion was X = Br than when it was X = BF$_4$ (Fig. 2). We did not observe the formation of Pd-black during the reaction, but the black deposit started to form some time after all the substrate had been consumed if the solution was maintained at the refluxing temperature of the solvent.

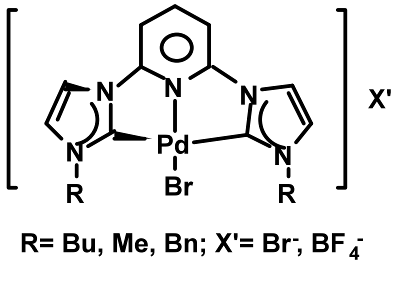


Figure 1.

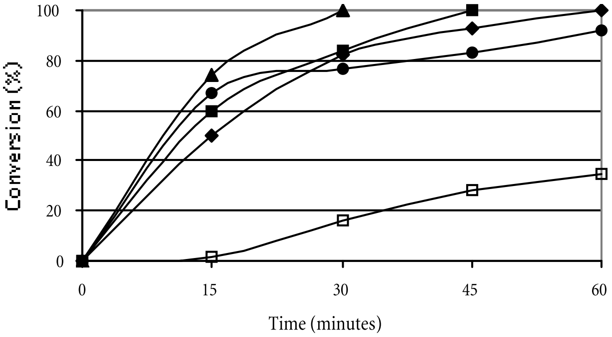


Figure 2. Reaction profiles for Sonogashira coupling of $(C_6H_5)CCH$ and $(C_6H_5)I$ with [PdBr(CNC-R$_2$]X, (▲) R = Me, X = Br; (■) R = Bu, X = Br; (◆) R = Bn, X = Br; (●) R = Bu, X = BF$_4$; (□) R = Bu, X = Br, without CuI.

To test the long-term stability of the catalyst and its recovery and reuse in consecutive runs, we initiated the immobilization of [PdBr(CNC-Me$_2$)]Br in smectite clays. We used the solvent-impregnation method[29] to immobilize the ionic palladium complex in three types of solids: montmorillonite K10 (MK10, BET surface area = 221 m^2/g), bentonite A (BA, BET surface area = 53 m^2/g) and bentonite B (BB, BET surface area = 150 m^2/g). All these solids are identified by their X-ray pattern as montmorillonite clay, but their structural features show that bentonites are more crystalline than montmorillonite K10.[30] This is in agreement with the fact that montmorillonite K10 is prepared by treating bentonite with acid, which partially destroys the bentonite layer structure and gives a disordered and increased surface area. However, the difference in surface area between bentonite A (BA) and B (BB) is rather attributed to the higher amount of interlamellar cations in BB than in BA, attending to the chemical analyses of the solids (Table 1).

Thus, coloured solutions of the ionic complex [PdBr(CNC-Me$_2$)]Br in anhydrous dichloromethane, were stirred with the clay support for 24 h at room temperature, under nitrogen. The scanning electron microscopy analyses of MK10-[Pd]Br, BA-[Pd]Br and BB-[Pd]Br (Table 1), provide the percentages of palladium complex which agree with the expected amount of metal in the solid catalytic system, (0.6–0.7%). The different ways for grafting complex [PdBr(CNC-Me$_2$)]Br onto the clays, mainly through adsorptive interactions onto the external surface area of MK10 and cation exchange into the layers of bentonites A and B,[25b] may lead to differences in their catalytic behaviour when used as catalysts in the Sonogashira reaction.

Initial experiments with the heterogenized catalytic system [PdBr(CNC-Me$_2$)]Br/clay, (catalyst loading of 1.7 mol% in MK10-[Pd]Br, and 1.8 mol% in BA-[Pd]Br and BB-[Pd]Br), were carried out using the previously optimized conditions for the homogeneous Sonogashira coupling between phenylacetylene and phenyliodide. The three supported catalysts proved to be highly efficient affording a 92–94% yield of the product between 0.5 and 1 h (Table 2, entries 1–3). Therefore, the different structural nature of the clay and the different grafting of the palladium complex, did not make a significant difference to the catalytic activity of the solid system. The coupling reaction of more challenging substrates, such as the activated arylbromides with [PdBr(CNC-Me$_2$)]Br/MK10, was almost complete within 0.5 h for *p*-nitrobromobenzene, and quantitative within 2.5 h for *p*-bromobenzaldehyde and *p*-bromoacetophenone (Table 2, entries 4–7).

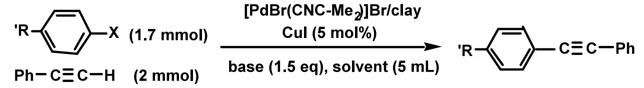
These results indicate that the activity of the catalytic system is higher that that of previously reported Pd-carbene catalysts[6d,12] or Pd-immobilized catalytic systems,[20,21] for the coupling of the same substrates. We also viewed the role of pyrrolidine, piperidine and

Table 1. Chemical analyses of solids and immobilized catalytic systems [PdBr(CNC-Me$_2$)]Br/clay[a]

	MK10[b]	MK10-[Pd]Br	BA[b]	BA-[Pd]Br	BB[b]	BB-[Pd]Br
Si	32.3	31.9	28.7	26.3	25.2	23.9
Al	7.3	7.7	9.4	9.9	3.2	3.6
O	53.6	48.6	51.8	44.9	48.2	41.1
Mg	0.6	0.9	1.7	1.8	14.3	13.4
Na	0.2	0.2	2.0	1.9	–	–
K	1.3	0.8	0.8	0.9	0.7	0.4
Ca	0.2	0.3	1.3	0.7	0.3	0.1
Fe	1.5	2.1	1.9	2.5	1.5	1.1
Pd	–	0.6	–	0.7	–	0.7

[a] Percentages calculated as (% by weight) from scanning electron microanalyser analysis.
[b] MK10: montmorillonite K-10, BA: bentonite A, BB: bentonite B.

Table 2. Sonogashira reaction catalyzed by [PdBr(CNC-Me$_2$)]Br/clay[a]



Entry	X	R′	Clay[b]	Base[c]	Solv.	*T* (°C)	*t* (h)	Yield (%)[d]
1	I	H	MK10	Pyrr	Pyrr	87	0.5	92
2	I	H	BA	Pyrr	Pyrr	87	1	94
3	I	H	BB	Pyrr	Pyrr	87	1	92
4	Br	NO_2	MK10	Pyrr	Pyrr	87	0.5	99
5	Br	CHO	MK10	Pyrr	Pyrr	87	2.5	77
6	Br	MeCO	MK10	Pyrr	Pyrr	87	2.5	73
7	I	H	MK10	Pip	Pip	106	0.5	99
8	I	H	MK10	Pip	DMA	100	1	86
9	I	H	MK10	Cs_2CO_3	DMA	100	1	64
10	I	H	BA	Pip	DMA	100	1	97
11	I	H	BB	Pip	DMA	100	1	93.5
12	Br	NO_2	MK10	Pip	DMA	100	0.5	99
13	Br	CHO	MK10	Pip	DMA	100	2	98
14	Br	MeCO	MK10	Pip	DMA	100	2	72

[a] 0.029 mmol [Pd]Br in 0.5 of MK10; 0.032 mmol [Pd]Br in 0.5 of BA and BB.
[b] MK10: montmorillonite K-10, BA: bentonite A, BB: bentonite B.
[c] Pyrr: pyrrolidine, Pip: piperidine.
[d] Conversion of the arylalkynes determined by GC.

Cs_2CO_3 as the base, and we conclude that activity was highest with piperidine[13] (Table 2, entries 1, 7 and 9). Before validating the concept of effective catalyst recycling, we selected an appropriate solvent to simplify the protocol of washing the solid catalyst system after it has been separated from the products via filtration. Therefore, we demonstrated that the use of DMA (*N*,*N*-dimethylacetamide) as solvent could be a convenient medium for efficient catalyses and for removing all the products and ammonium salts involved in the reaction, from [PdBr(CNC-Me_2)]Br/clay (Table 2, entries 8–14). Catalyst recycling studies were carried out after [PdBr(CNC-Me_2)]Br/clay had been recovered, and washed with DMA and CH_2Cl_2. Pd-black deposit was not observed in the washed solid, confirming the great stability of the catalyst when is immobilized. The resulted recovered solids could be successfully reused showing the same activity as for the first run in the coupling of phenylacetylene and phenyliodide (Fig. 3, a: [PdBr(CNC-Me_2)]Br/MK10, b: [PdBr(CNC-Me_2)]Br/BA and c: [PdBr-(CNC-Me_2)]Br/BB).

Encouraged by the satisfactory recycling capacity of these systems, we extended our study of the reusability of [PdBr(CNC-Me_2)]Br/MK10 to the consecutive coupling of phenylacetylene with *p*-nitrobromobenzene and *p*-bromobenzaldehyde, (Fig. 2(d) and (e), respectively). Reaction rates were similar for the first and second consecutive runs in both cases. We are currently in the process of extending this study to the coupling of arylchlorides with alkynes, and of exploring the recyclability limit of the supported catalysts.

In conclusion, a suitable palladium phosphine-free catalytic system has significant advantages in the Sonogashira coupling of alkynes with aryliodides and bromides. Not only does it catalyze the reaction successfully, it is also easily recovered and reused when it is immobilized on clays, because of its great stability.

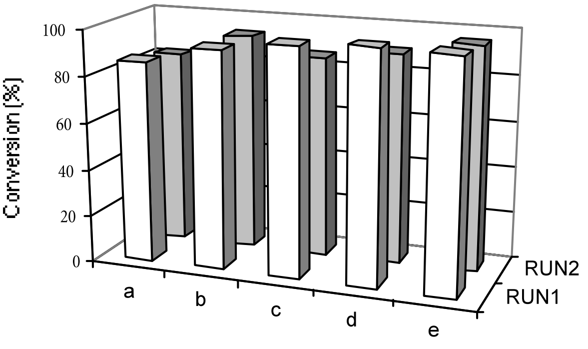


Figure 3. Reusability of [PdBr(CNC-Me_2]Br/clay in the coupling of phenylacetylene and R′-C_6H_4-X: (a) R′=H, X=I; clay=MK10; (b) R′=H, X=I; clay=BA; (c) R′=H, X=I; clay=BB; (d) R′=NO_2, X=Br; clay=MK10; (e) R′=CHO, X=Br; clay=MK10.

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