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Tetrahedron Letters 49 (2008) 2506–2509
Tetrahedron Letters

Copper-free Sonogashira cross coupling in ionic liquids

Paulo Galdino de Lima, O. A. C. Antunes *

Instituto de Química, Universidade Federal do Rio de Janeiro, Av. Athos da Silveira Ramos 149, CT Bloco A 641,
Cidade Universitária, Rio de Janeiro, RJ 21941-909, Brazil

Received 26 January 2008; revised 16 February 2008; accepted 19 February 2008
Available online 23 February 2008

Abstract

In the present Letter the use of ionic liquids based on butylpyridinium salts (C_4PyPF_6, C_4PyBF_4, and C_4PyNO_3) is described in the Sonogashira reaction. Aiming the development of recyclable catalytic system using Pd(II) salts as precursors, the importance of the induction period prior to the addition of substrates was established. A new methodology that can be performed under Cu(I)-free and at mild conditions was established. Good conversions were obtained and good recyclability was observed.

Sonogashira reaction[1] is a powerful method for the formation of Csp^2–Csp bonds with aryl or vinylhalides and terminal acetylenes. This palladium catalyzed cross-coupling reaction has been widely utilized in the synthesis of natural products[2] and nonlinear optical electronic devices,[3] for example. The typical procedures make use of Cu_2I_2 as co-catalyst, phosphine ligands (like Ph_3P), and strong bases (amines and carbonates) in organic solvents.

The increasing demand for environmental friendly and low cost process has lead to the development of recyclable catalytic systems, where ionic liquids have been recognized as promising alternative solvents.[4] Most of the ionic liquids employed in Sonogashira and other palladium catalyzed cross-coupling reactions are dialkylimidazolium molten salts, which can form palladium–NHC, N-heterocyclic carbenes, as active catalytic species depending on the anion.[5]

Ryu and co-workers disclosed the use of $[PdCl_2(PPh_3)_2]$ (5 mol %) as good catalyst precursor for copper-free Sonogashira coupling in *bmim*PF_6 at 60 °C.[6] The same research group performed a screening study in a 24-array parallel reactor to establish *bmim*PF_6 as a suitable solvent to immobilize the carbenoid catalyst [*bmim*Pd$(PPh_3)Cl_2$].[7] Alper and Park developed a copper- and phosphine-free Sonogashira reaction with aryl iodides employing the carbenoid species [(bismethylimidazole)PdClMe] in *bmim*BF_4 at 120 °C.[8] Hierso et al. developed a catalytic system from $[Pd(allyl)Cl]_2/Ph_3P$ in *bmim*BF_4 for coupling of deactivated aryl bromides at 120 °C.[9] In the latter case, however, reduced products were obtained with long time reactions with activated substrates.[10] Moreover, simple palladium sources have been used in imidazolium salt-ionic liquids, such as $Pd(OAc)_2/Ph_3P$ in the presence of Cu_2I_2 at 80 °C[11] and $PdCl_2$/*bbim* under ultrasound irradiation at 30 °C.[12] In the latter, it was proposed that Pd(0)-nanoparticles would be the active catalyst species, although [(*bbim*)$_2$Pd$(BF_4)_2$] carbene complex was extracted from the ionic phase with chloroform.

The alternative ionic liquids *N*-alkylpyridinium salts, as for example, the *N*-butyl derivatives C_4Py, are not supposed to be able to form palladium carbenoid complexes, although this can be possible under strong base conditions with pyridinium cations bearing chelating groups.[13] This feature lead to the expectation that their use would provide different activities than those observed with dialkylimidazolium salts in Sonogashira cross-coupling reaction.

Therefore, our goal was to study the Sonogashira cross coupling under mild conditions employing alkylpyridinium ionic liquids as reaction solvents and simple palladium

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* Corresponding author. Tel.: +55 21 2562 7248; fax: +55 21 2562 7559. *E-mail address:* octavio@iq.ufrj.br (O. A. C. Antunes).

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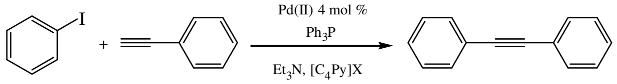
doi:10.1016/j.tetlet.2008.02.110

catalyst precursors. To the best of our knowledge, concerning the palladium catalyzed cross-coupling reactions, pyridinium salts were tested as solvent in Heck cross coupling between arylhalides and acrylate esters,[14] and have been used as nitrile functionalized ionic liquids in Suzuki and Stille cross-coupling reactions.[15]

In the present Letter the unprecedented use of *N*-butylpyridinium ionic liquids[16] C_4PyX (PF_6^-, BF_4^-, and NO_3^-) as solvents in Sonogashira reaction is described. The reaction model studied in the present Letter was the formation of diphenylacetylene from iodobenzene (1 mmol) and phenylacetylene (1 mmol), Scheme 1.

The initial reaction conditions were set up based on the Sonogashira cross-coupling procedure in the imidazolinium ionic liquids reported by Toma et al.[11] Therefore, the catalytic system was produced from $Pd(OAc)_2$ (4 mol %) in the presence of Ph_3P (8 mol %) and 1 g C_4PyPF_6 at 80 °C for 1 h, prior to the addition of Cu_2I_2 (8 mol %), iodobenzene, phenylacetylene, and Et_3N (1.5 mmol) (Table 1).

These conditions yielded moderate conversion (entry 1) and the absence of both PPh_3 and CuI was not deleterious for the formation of diphenylacetylene (entry 2). Unexpectedly, it was obtained a markedly shift of activity on the second runs using EtOH as co-solvent. Since no changes on the reaction profile were observed after 2 h of reaction time, these results may be related to the low concentration of Pd active species in the first run. In order to force Pd(0) formation via reduction of the Pd(II) precursor, EtOH was included to induction period and removed before coupling reaction and no copper salt was added to reaction to avoid Glaser-type homocoupling of the phenylacetylene.[17] This procedure afforded a catalytic system that exhibited high conversion and good recyclability (entry 3). A good conversion was kept even in the absence of Cu_2I_2 and Ph_3P, but in the second run a lower but still reasonable yield was observed (entry 4). These results indicate that although Ph_3P is important to the stabilization of the Pd soluble species formed via oxidative addition on nanoparticles, which have been previously claimed to be the active catalysts,[18,19] it is possible to have a good catalytic system in its absence. Perhaps Pd(0/II) formed via oxidative additions and eliminative reduction, when in low concentrations, turn down the use of phosphines and do not form black Pd(0) at these concentrations.



(1) (2) (3)

Scheme 1. Reaction model for catalytic system development.

Table 1
Conversion[20] of PhI (**1**) in diphenylacetylene (**3**) with C_4PyPF_6 as solvent

Entry	Induction period	Cross coupling	1 Run (%)	2 Run (%)
1	$[C_4Py]PF_6$, $Pd(OAc)_2$, Ph_3P, 80 °C, 1 h	Cu_2I_2, 80 °C, 2 h	61	49[a]
2	Without Ph_3P	80 °C, 2 h	56	87[a]
3	$[C_4Py]PF_6$, $Pd(OAc)_2$, EtOH, Ph_3P, 80 °C, 1 h	80 °C, 2 h	97	82
4	Without Ph_3P	80 °C, 2 h	88	60

[a] EtOH was used as co-solvent on the cross-coupling step.

Once C_4PyPF_6 melts only at about 80 °C, which restrict the extraction step to temperatures about 50–60 °C, that could cause catalyst removing to organic phase, this solvent was substituted to the room temperature ionic liquid C_4PyBF_4, which would allow the extension of our research to milder reaction conditions (Table 2).

The catalyst precursor $Pd(OAc)_2$ (4 mol %) rendered a catalytic system suitable to accomplish Sonogashira cross coupling at 75 °C (entry 1), however, with low activity at room temperature (entry 2). In contrast, $PdCl_2$ promoted moderate conversion at 75 °C with maintenance of activity on the second run (entry 3) and showed an excellent performance at room temperature (entry 4).

Despite the result with $PdCl_2$ at room temperature, in general, higher conversions on the two runs were obtained with C_4PyPF_6 as solvent. This can be rationalized from the mechanism proposed by Rothenberg and co-workers, where the Pd species leached from defect sites on the cluster are the active catalyst and the precursors of the new nanoparticles after reductive elimination.[18] Therefore, the lower coordinating ability of the anion PF_6^- would favor the Pd leaching step and the steric stabilization of the re-aggregate by C_4Py^+ cation. Although BF_4^- is considered a noncoordinating anion, it has been identified as a ligand on the Pd carbene complex formed in cross coupling under ultrasound conditions.[12]

To address the difficulties in dealing with C_4PyPF_6 and the conversion decreasing in C_4PyBF_4, the other room temperature ionic liquid C_4PyNO_3 was introduced as a solvent in our model reaction (Table 3).

Employing the induction procedure (C_4PyNO_3, EtOH, Ph_3P, 75 °C), high conversions and good recyclabilities were observed at 75 °C for both palladium sources (entries 1 and 5). However, only $PdCl_2$ based catalyst showed to be suitable to accomplish Sonogashira cross coupling at room temperature (entries 3 and 7), even the addition of Et_3N on the induction step, to favor Pd(II) reduction through Pd-ethanoate formation, did not improve the activity of the $Pd(OAc)_2$ based catalyst (entry 4). To open the green appeal in this protocol, excluding Ph_3P from both catalytic systems resulted in moderate conversions at 75 °C (entries 2 and 6).

Table 2
Conversion[20] of PhI (**1**) in diphenylacetylene (**3**) with C_4PyBF_4 as solvent

Entry	Pd source	Cross coupling	1 Run (%)	2 Run (%)
1	$Pd(OAc)_2$	75 °C, 2 h	86	6
2		rt, 24 h	12	
3	$PdCl_2$	75 °C, 2 h	56	60
4		rt, 24 h	96	65

Table 3
Conversion[20] of PhI (**1**) in diphenylacetylene (**3**) with C_4PyNO_3 as solvent

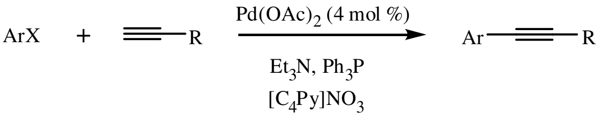
Entry	Pd source	Cross coupling	1 Run (%)	2 Run (%)
1	$Pd(OAc)_2$	75 °C, 2 h	95	79
2[a]		75 °C, 2 h	59	52
3		rt, 24 h	15	
4[b]		rt, 24 h	2	
5	$PdCl_2$	75 °C, 2 h	82	76
6[a]		75 °C, 2 h	42	55
7		rt, 24 h	71	73

[a] Absence of Ph_3P.
[b] Et_3N was added on the induction step.

The results indicated that catalytic activity depends on the nature of the anion of the ionic liquid, temperature, and of the nature of Pd(II) source, the first and last related to the ability of the anions to complex with Pd(II). For cross coupling at warmer conditions, it is supposed that the corresponding anion in each case plays an important role on the reaction profile, since the less coordinating ionic liquids C_4PyPF_6 and C_4PyNO_3 provided active and recyclable catalytic systems from both palladium precursors.

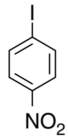
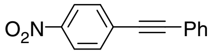
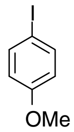
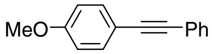
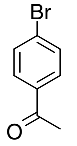
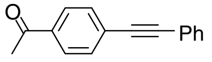
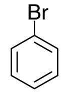
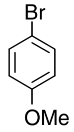
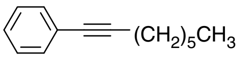
Therefore, to go further, C_4PyNO_3 was employed as solvent to the Sonogashira cross-coupling reaction with other aryl halides, keeping $Pd(OAc)_2$ as palladium source (Scheme 2). These results are disclosed in Table 4.

The catalytic system formed after the induction period, in the absence of Ph_3P, converted the reactive iodoarene **4** and phenylacetylene (**2**) in 4-nitrodiphenylacetylene (**5**), but it failed on the reaction with the deactivated aryl iodide **6** (entries 1 and 2). However, our usual catalyst afforded product **7** with high conversion (entry 3) and showed to be efficient for aryl bromides **8** and **10**, affording the corresponding diphenylacetylenes **9** and **1** (entries 3–5). The catalytic activity decreased for the deactivated substrate 4-methoxybromobenzene (**11**) and for 1-octine (entries 6 and 7). The formation of the disubstituted acetylene **15** was possible only with the addition of Cu_2I_2 on the cross-coupling step (entry 8).



Scheme 2. Cross coupling with others aryl halides and acetylenes.

Table 4
Conversion[20] of aryl halides in diphenyacetylenes via Scheme 2

Entry	ArX	$\equiv$R	Product	Conversion (%)
1[a]	 (**4**)	(**2**)	 (**5**)	77
2[a]	 (**6**)		 (**7**)	22
3			(*m*/*z*) 208, 193, 165	98
4	 (**8**)		 (**9**) (*m*/*z*) 220, 205, 176	91
5	 (**10**)		(**1**) (*m*/*z*) 178	89
6	 (**11**)		(**7**)	28
7	(**1**)	1-Octine	 (**15**)	0
8[b]			(*m*/*z*) 186, 143, 115	82

[a] Absence of Ph_3P.
[b] Addition of Cu_2I_2 on the cross coupling step.

In conclusion, the use of C_4Py based ionic liquids requires an induction period in EtOH that we hypothesized as to assure the Pd(0) species formation.[21] It has been made possible to avoid the addition of both Cu(I) and Ph_3P when using C_4PyPF_6 as solvent and C_4PyNO_3 in reactions between phenylacetylene (**2**) and iodoarenes bearing electron-withdrawing groups. The catalytic system $Pd(OAc)_2/Ph_3P/C_4PyNO_3$, in the absence of Cu(I), proved to be suitable to our purpose of obtaining a recyclable catalyst for Sonogashira reaction at 75 °C.[22,23] This methodology was successfully applied to other less reactive aryl halides. The presence of the co-catalyst Cu_2I_2 was necessary for aliphatic acetylenes, which can be considered less acidic than aromatic ones. The conversions obtained for diphenylacetylene products in this study were similar to those reported on *bmim* salts.[11]

Acknowledgments

Financial support from FINEP, CNPq, CAPES, and FAPERJ, Brazilian Governmental Financing Agencies, is gratefully acknowledged.

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20. GC analyses were performed on HP 5890 equipped with FID detector using STB-1 capillary column (30 m × 0.32 mm × 0.25 μm) of Supelco. Hydrogen was used as the carrier gas and the injection split ratio was 1:100. The temperature program was 10 °C/min from 150 to 250 °C and finally 5 min at 250 °C. Injector and detector temperatures were 250 °C. The conversions were determined via external standard method using the response factors of the aryl halide and of the diphenylacetylene.
21. *General procedure for the induction period*: In a 10 mL reaction flask, under argon atmosphere, 21 mg of Ph_3P (0.08 mmol) was dissolved in 1 mL of EtOH and 1 mL of C_4PyNO_3 at 75 °C. Then, 8 mg of $Pd(OAc)_2$ (0.04 mmol) was added and the resulting suspension was stirred for 1 h at 75 °C. After that volatile components were eliminated in rotatory evaporator (10 min, 40 °C) and then under high-vacuo (10 min). The yellow suspension was stored under argon atmosphere.
22. *General procedure for Sonogashira reaction*: To the previously prepared catalytic system, were added 110 μL of iodobenzene (**1**, 1 mmol), 110 μL of phenylacetylene (**2**, 1 mmol) and 0.2 mL of Et_3N (1.5 mmol). After 2 h at 75 °C, the reaction medium was extracted exhaustively (five times) with hexane. The organic layer was analyzed by GC, GC–MS, ^{1}H RMN. Diphenylacetylene (**3**)—^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31–7.38 (m, 6H), 7.51–7.56 (m, 4H); GC–MS: *m*/*z* 178.
23. *General procedure for second run*: The ionic phase in the reaction flask was concentrated in a rotatory evaporator (10 min, 40 °C) and then under high-vacuo (10 min). The resulted suspension was carried out in argon atmosphere and charged with 110 μL of iodobenzene (**1**, 1 mmol), 110 μL of phenylacetylene (**2**, 1 mmol) and 0.2 mL of Et_3N (1.5 mmol). The reaction medium was carried out in cross-coupling conditions and the extraction procedure was employed in the first run.