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$PdCl_2(P(OPh)_3)_2$ catalyzed coupling and carbonylative coupling of phenylacetylenes with aryl iodides in organic solvents and in ionic liquids

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Efficient cross-coupling and carbonylative coupling of terminal alkynes with aryl iodides catalyzed by $PdCl_2(P(OPh)_3)_2$ in the presence of NEt_3 in toluene and in ionic liquids is described. In imidazolium ionic liquids, $[bmim]PF_6$ or $[mokt]PF_6$ (bmim = 1-butyl-3-methyl imidazolium cation, mokt = 1-methyl-3-octyl imidazolium cation) catalyst was recycled and used in four concecutive catalytic cycles with high activity. In the absence of aryl iodide the same catalytic system catalyzed head-to-tail dimerization of phenylacetylene to the 1,3-diphenyl enyne, *trans*-$PhC \equiv C{-}C(Ph){=}CH_2$, with a yield of 85%.

KEY WORDS: Sonogashira coupling; carbonylative Sonogashira coupling; phenylacetylene dimerization; palladium catalyst; ionic liquids.

1. Introduction

The high catalytic activity of $PdCl_2(P(OPh)_3)_2$ precursor in methoxycarbonylation of benzyl bromide and iodobenzene demonstrated by us earlier [1–3] warranted the expectation that it would also be active in other reactions of aryl halides. The mechanistic studies shown that $PdCl_2(P(OPh)_3)_2$ reacted with NEt_3 at the presence of trace amount of water forming Pd(0) complexes of $Pd(P(OPh)_3)_x(NEt_3)_{4-x}$ type and $Pd(P(OPh)_3)_4$ was identified as the main form [4]:

$$PdCl_2(P(OPh)_3)_2 + NEt_3 + H_2O \rightarrow Pd(P(OPh)_3)_x (NEt_3)_{4-x} + CH_3CHO + HNEt_2 + 2HCl \quad x = 0\text{–}4$$

Pd(0) complexes containing $P(OPh)_3$ ligand, formed in above reaction, activate aryl or benzyl halides *via* oxidative addition which initiates catalytic methoxycarbonylation reaction [4]:

$$Pd(P(OPh)_3)_x(NEt_3)_{4-x} + PhCH_2X \rightarrow [XPd(P(OPh)_3)_y (NEt_3)_{y-2}(CH_2Ph)] \quad x = 0\text{–}4, y = 0\text{–}2.$$

This makes $PdCl_2(P(OPh)_3)_2$ a very good precursor of catalyst for different reactions of aryl halides and we selected Sonogashira coupling as a test. To our best knowledge this palladium catalyst precursor, containing π-acceptor ligand, has never been tested in this reaction.

The typical catalytic system designed for the Sonogashira coupling contains a palladium complex with coordinated phosphorus ligands, in most cases bulky and of high basicity, and CuI (or other copper halide) as co-catalyst [5,6]. However, the presence of CuI in the catalytic system has a negative side-effect – the formation of homo-coupling products (diphenyldiacetylenes) through oxidative isomerization in the so-called Glaser reaction [7]. This fact provides strong motivation for searching for palladium catalysts active without CuI additives and examples of copper-free Sonogashira coupling reactions have been reported recently [8–12]. Also recently, not only copper-free but also ligandless Pd catalysts, including Pd nanoparticles, have been described [13–15].

The application of ionic liquids as reaction media instead of organic solvents makes it possible to construct recyclable catalytic systems. Some examples of such methodology applied for Sonogashira coupling have been reported recently with (bisimidazole) PdCl(Me) as catalyst [16] and with $Pd(OAc)_2$ under ultrasonic irradiation [17]. The classic Sonogashira catalytic system containing $Pd(OAc)_2/PPh_3/CuI$ has been tested in $[bmim]PF_6$ demonstrating good stability in five runs [18]. The procedure for the synthesis of arylalkynes *via* Pd/C mediated cross-coupling in water was reported [19].

2. Results and discussion

The presented catalytic system contains $PdCl_2(P(OPh)_3)_2$ precursor and NEt_3. Triethylamine plays double role – first, it reduces Pd(II) to Pd(0) and second, it neutralizes HX, side product of the catalytic process. The

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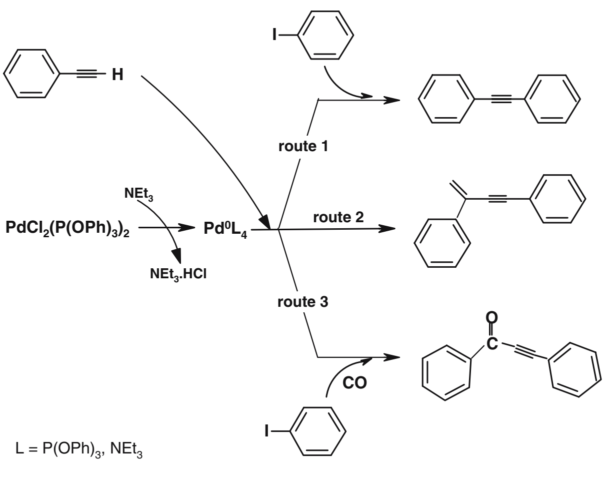
main advantage of this catalytic system is its versatility in phenylacetylenes transformations, as illustrated on scheme 1. Depending on the reaction conditions, three different products can be selectively obtained: diphenylacetylenes (scheme 1, route 1), enynes (scheme 1, route 2) and acetylene ketones (scheme 1, route 3).

2.1. *Sonogashira coupling (scheme 1, route 1)*

Sonogashira coupling of aryl iodides with phenylacetylenes, leading to diphenyl acetylenes (scheme 1, route 1), can be performed already at room temperature with a yield of *ca.* 35% after 1 h. For further studies the temperature of 80 °C was selected to obtain higher yields of products in 0.5–2 h. Under these conditions the reaction proceeds smoothly and 82% and 100% of diphenylacetylene was obtained after 30 min with 1 and 2 mol% of the catalyst, respectively (table 1). Good to excellent results were also obtained with other substrates, substituted iodobenzenes and substituted phenylacetylenes (table 1). The results show that reaction yield is influenced mostly by iodobenzene substituents (entry 7), whereas the presence of methyl groups in phenylacetylene practically does not change the high productivity of the system (entries 4–6). *p*-Tolylacetylene appeared to be less reactive than *m*-tolylacetylene (entries 4, 5). The lowest yield, only 12% of the coupling product, was obtained with 2-iodotiophene (entry 10). Instead, *ca.* 50% of phenylacetylene was converted to a homocoupling product,$PhC \equiv C{-}C \equiv CPh$, in this reaction. Formation of homocoupling product was observed only when iodotiophene was employed. This can be explained by modification of the catalyst by coordination of this substrate to palladium, probably *via* S-atom.

The C–C coupling product was also obtained with benzyl bromide and phenylacetylene as substrates, despite of higher energy of C–Br bond compared with the C–I bond (table 1, entries 11, 12).

A catalytic system for Sonogashira coupling of iodobenzene with phenylacetylene was also used in ionic liquids, instead of organic solvent. Reaction yields in ionic liquids were similar to these obtained in toluene or in DMF, however the presence of ionic liquid facilitate easy recovering of the catalyst. In ionic liquids containing imidazolium cation and non-coordinating anion, [bmim]BF_4 and [bmim]PF_6, the catalyst was easily recovered and used with only a small decrease in yield in subsequent runs (entries 15, 16). Similar results were reported for other palladium systems [16,18]. In contrast the strong inhibiting effect of imidazolium chloride, [mokt]Cl, illustrated by the lack of catalytic activity, was observed (entry 17). It is interesting that negative influence of imidazolium halides we observed earlier also in methoxycarbonylation reaction catalyzed by Pd(0) colloid [20] (table 2).



Scheme 1. Reactions of phenylacetylene catalyzed by $PdCl_2(P(OPh)_3)_2$ precursor.

2.2. *Carbonylative coupling (scheme 1, route 3)*

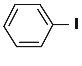
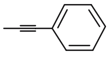
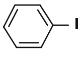
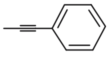
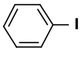
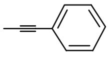
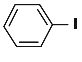
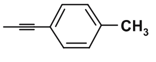
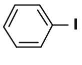
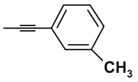
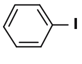
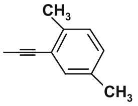
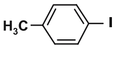
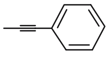
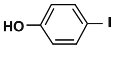
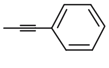
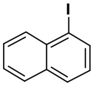
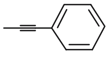
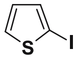
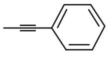
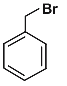
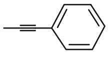
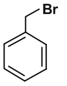
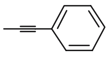
The results of test carbonylative coupling reactions performed under 1 atm of CO are summarized in table 3. Depending on the kind of substrate used, *ca.* 62% of ketones were obtained with the best selectivity in reactions of benzyl bromide (entries 23, 24). In other cases competition between cross-coupling and carbonylative coupling lowered the yield of ketones; however, a quite promising result (76% of ketone) was obtained in reaction of iodobenzene and 4-tolylacetylene (entry 21). The obtained results, although not optimized, present simple one-step pathway to acetylenic ketones. Only a few examples of similar direct synthesis of acetylenic ketones from aryl halide and phenylacetylene under mild conditions have been reported [21]. Very recently the carbonylative Sonogashira coupling was achieved by using $PdCl_2/PPh_3/NEt_3$ system in water as a solvent [22]. The alternative pathway to acetylenic ketones is based on the coupling of acyl halides with terminal alkynes [23].

2.3. *Dimerization of phenylacetylene (scheme 1, route 2)*

From data presented in table 1 one can conclude that selectivity of C–C coupling of benzyl bromide with phenylacetylene was lowered as a result of phenylacetylene head-to-tail dimerization leading to 1,3-diphenyl enyne,$PhC \equiv C{-}C(Ph){=}CH_2$. Dimerization was not observed when iodoaryls were used as substrates (in Sonogashira reaction conditions) because they reacted faster with phenylacetylene. The 1,3-diphenyl enyne was found as the only product with a yield of 85% in the reaction performed with phenylacetylene as the only substrate. The structure of coupling product, a head-to-tail dimer, was identified unequivocally by means of ^1H NMR spectroscopy. The spectrum displayed two doublets at 5.72 and 5.93 ppm with coupling constant J_{H-H} equal 1 Hz.

The high selectivity of phenylacetylene dimerization to head-to-tail product is interesting, because in most of the cases reported in the literature, dimerization of

Table 1
Sonogashira coupling reaction (R--X + ArC ≡ CH → RC ≡ CAr) – studies of substrate effect

Entry	RX	ArC≡CH	Time (h)	Yield of RC≡CAr (% mol)
1			1	89
2[a]			0.5	100
3[b]			1	67
4			1	81
5			2	100
6			2	100
7			2	45
8			2	100
9			2	100
10[c]			2	12
11[d]			4	55
12[e]			4	81

Reaction conditions: 1% mol of $PdCl_2(P(OPh)_3)_2$, 1.0 mmol of RX, 2.0 mmol of ArC ≡ CH, 3 cm^3 toluene, 0.26 cm^3 (1.9 mmol) NEt_3, 80 °C. Reaction yield was calculated from GC in respect to RX.

[a] 2% mol of $PdCl_2(P(OPh)_3)_2$.

[b] 0.5% mol of $PdCl_2(P(OPh)_3)_2$.

[c] 50.2% of phenylacetylene was converted to homocoupling product.

[d] 6% of$H_2C{=}C(Ph){-}C \equiv CPh$ was also formed.

[e] 5% mol of $PdCl_2(P(OPh)_3)_2$, 20% of$H_2C{=}C(Ph){-}C \equiv CPh$ was also formed.

phenylacetylenes led to a mixture of products formed by head-to head or head-to-tail coupling, the former type dominating [24]. Higher selectivity of dimerization was observed for $Pd(OAc)_2$ used with an electron-rich ligand, tris(2,6-dimethoxyphenyl)phosphine [25], and for μ-methylene ruthenium complex [26].

3. Experimental

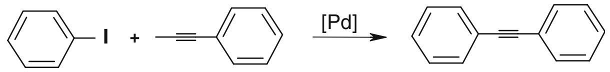
All catalytic reactions have been performed under N_2 atmosphere. Extraction of organic products have been made in air.

$PdCl_2(P(OPh)_3)_2$ [27] and $Pd(P(OPh)_3)_4$ [4] were obtained according to literature methods.

3.1. Catalytic reactions

The Sonogashira reactions were carried out in a Schlenk tube with magnetic stirring. Reagents: 0.26 cm^3 (1.9 mmol) of Et_3N, 1 mmol of aryl halide, 2 mmol of acetylene, 3 cm^3 of toluene (or 3 cm^3 of ionic liquid) and catalyst weighted in small teflon vessel were introduced to the Schlenk in an N_2 atmosphere. Next Schlenk was sealed with a rubber tap and introduced into the oil bath

Table 2
Recyclable Sonogashira coupling in ionic liquids



Entry	Solvent	Time (h)	Catalyst % mol	Cycle No/ Yield % mol
13	DMF	1	1	1/100
14	[bmim]PF_6	4	1	1/83
15	[bmim]PF_6	4^{a}	2	1/100; 2/95; 3/81; 4/67
16	[mokt]PF_6	4^{a}	2	1/94; 2/94; 3/82; 4/56
17	[mokt]Cl	4	1	1/0

Reaction conditions: 1.0 mmol of PhI, 2.0 mmol of PhC ≡ CH, 3 cm^3 of ionic liquid, 0.26 cm^3 (1.9 mmol) NEt_3, 80 °C.
[a] Each run was performed in 4 h, after extraction of products with diethyl ether new portions of PhI, PhC ≡ CH and NEt_3 were added.
DMF, dimethylformamide; bmim, 1-methyl-3-butyl imidazolium cation; mokt, 1-methyl-3-octyl imidazolium cation.

pre-heated to 80 °C. The reaction was carried out at 80 °C for 0.5–4 h and after that time the Schlenk was cooled down and organic products were separated by extraction with diethyl ether (3 times with 10 cm^3) or with the same amount of hexane when reaction was performed in ionic liquid. Extracts were GC-FID analyzed (Hewlett Packard 8452A) with 0.05 cm^3 of mesitylene as internal standard. Products have been identified by GC-MS (Hewlett Packard 8452A).

Carbonylative coupling reactions have been performed in a similar way, but after introduction of all reactants N_2 was removed from the Schlenk and CO was introduced from the balloon, which was kept connected to the Schlenk during the all reaction time.

Acknowledgments

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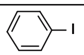
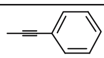
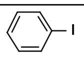
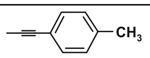
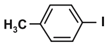
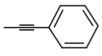
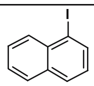
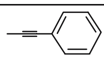
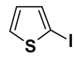
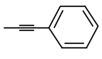
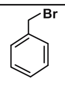
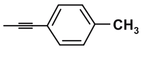
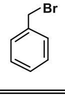
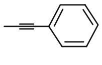
Table 3
Carbonylative Sonogashira coupling under CO atmosphere (1 atm) – formation of acetylenic ketones $R\text{--}X + ArC \equiv CH + CO \rightarrow Ar(CO)\underset{A}{C} \equiv CR + RC \equiv \underset{B}{C}Ar$

R - X	ArC CH	Time (h)	Catalyst % mol	Yield of A Ar(CO)C≡CR % mol	Yield of B RC≡CAr % mol
		0.5	2	29	71
		1	1	76	7
		2	1	47	22^{a}
		2	1	24	76
		1	1	24	-^{b}
		2	1	62	-
		4	1	62	-

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