



Triphenylphosphite and ionic liquids: positive effects in the Heck cross-coupling reaction

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ABSTRACT

Configurational pure *trans* and high molecular weights are important for the optoelectronic properties of poly(*p*-phenylenevinylene) derivatives. As a promising approach for obtaining PPVs with these characteristics it was asserted that a simple and inexpensive monodentate phosphite, such as triphenylphosphite, is a good and efficient ligand for the Heck cross-coupling reaction. The catalyst activity is improved by the use of room temperature ionic liquids, obtaining quantitative yields and TONs up to 33,000.

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1. Introduction

Since the discovery of the electroluminescence in polymers by Burroughes et al.,¹ the polymeric and oligomeric systems of extended conjugation have acquired big importance for the study of their chemical and physical properties, as well as for their promissory applications in technology.² Among the most synthesized and studied systems for electroluminescence are the poly(*p*-phenylenevinylene)s (PPV) derivatives that have been obtained by different synthetic routes with high degrees of polymerization. However, the reported procedures show an important limitation: the reactions are not stereoselective toward the formation of *trans* conjugated segments, which is the key for obtaining higher efficiencies in optoelectronic properties.³

A possible solution for the stereoselectivity problem is the cross-coupling Heck reaction,⁴ which allows the formation of configurationally pure *trans* segments. Nevertheless the use of this protocol of synthesis in polymerization reaction is limited due to the low molecular weights and degrees of polymerization obtained.^{4,5} Within the last few years and despite the wrong conviction that only electronically rich phosphites could catalyze the Heck reaction, it was discovered that phosphite ligands (P(OR)₃) are efficient ligands for this type of carbon–carbon coupling.⁶ The ligands derived from phosphites are extremely interesting for

homogeneous catalyst because they are easily synthesizable from alcohols. So far, and the best of our knowledge, only few reports use simple commercial available monodentate phosphites for the Heck reaction with promissory results. Taking into account these outcomes and to improve the Heck reaction's catalyst to use it for the synthesis of PPV derivatives, we report the preliminary results with triphenylphosphite as a simple and inexpensive ligand using ionic liquids (IL)⁷ as additives, co-solvents or solvents, for the palladium-catalyzed coupling of styrene or methyl methacrylate with bromobenzene derivatives. The positive effects of IL are well known for many common organic and catalyzed reactions involving transition metal complexes,⁸ with improved yields, increased selectivities and decreased reaction times.

2. Experimental

2.1. General

All procedures were performed under a nitrogen atmosphere using standard J.T. Young glassware. Reagents were purchased and used as received from Sigma–Aldrich. ILs were purchased from Solvent Innovation and dried in high vacuum for 24 h before use. DMF was dried before use by standing, distilling, and refluxing from BaO. ¹H NMR spectra were measured with a Bruker 300 MHz spectrometer. The chemical shifts are given in ppm relative to tetramethylsilane (TMS, 0.00 ppm) and referenced to the solvent signal. GC analysis was carried out using a Hewlett Packard 5890 with a Zebron capillary GC column (ZB-5, 0.25 mm i.d. × 30 m). Filtrations were carried out on silica gel (MN Kiesengel

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60, 0.063–0.2 mm). GC–MS were carried out in a GC–MS Thermo Finnigan with a Phenomenex ZB-5 (5% Phenyl siloxane, 30 m × 0.25 mm, Program: initial 50 °C × 3 min, rate 8 °C/min, final 250 °C × 20 min).

2.2. Catalysis in DMF

In a J.T. Young tube, 0.75 mmol of olefinic compound, 0.5 mmol of aryl halide, 0.6 mmol of potassium carbonate, 0.005 mmol of triphenylphosphite, 0.0005 mmol of Pd(dba)₂ or the respective palladium source, and 0.1 mmol of *trans*-stilbene (as internal standard) were dissolved in 1 mL of DMF under nitrogen atmosphere. The tube was sealed and before putting it into a 100 °C hot bath of silicon oil, it was purged three times carrying out cycles of vacuum/nitrogen. After 20 h of continuous stirring the mixture was cooled to room temperature and 0.5 mL of 2 M HCl and 0.5 mL of dichloromethane were added. The organic phase was analyzed by GC. The products were crystallized from methanol/dichloromethane cold mixtures and characterized by ¹H NMR, GC–MS, IR, and mp and compared with the reported spectra.

2.3. Catalysis with IL as additives

Under similar experimental conditions and reagent amounts in 2.2., the mixture was dissolved in 0.02 mL of IL and 1 mL of DMF. The organic phase was passed through silica gel in order to retain

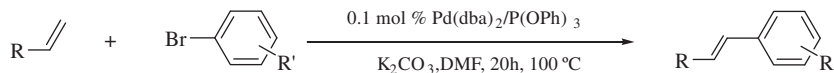
Table 1
Effect of P-ligands on the Heck reaction between bromobenzene and styrene catalyzed by different Pd-sources^a

Entry	Catalyst	Yield ^b (%)	TON
1	PdCl ₂ /PPh ₃	9	90
2	Pd(NO ₃) ₂ ·2H ₂ O/PPh ₃	19	190
3	Pd(AcO) ₂ /PPh ₃	34	340
4	Pd(dba) ₂ /PPh ₃	34	340
5	PdCl ₂ /P(OPh) ₃	0	0
6	Pd(NO ₃) ₂ ·2H ₂ O/P(OPh) ₃	0	0
7	Pd(AcO) ₂ /P(OPh) ₃	14	140
8	Pd(dba) ₂ /P(OPh) ₃	43	430

^a Bromobenzene (0.5 mmol), styrene (0.75 mmol), Pd-source (0.0005 mmol, 0.1 mol %), phosphite or phosphine (0.005 mmol, P/Pd = 10), and K₂CO₃ (0.6 mmol) in DMF (1.0 mL) at 100 °C for 20 h.

^b Yields are for isolated products.

Table 2
Electronic effect on the aryl bromides coupled with styrene or MMA, catalyzed by Pd(dba)₂/P(OPh)₃^a



Entry	Olefin	R'	Yield (%)	TON
9	Styrene	4-OMe	78 ^b	780
10	Styrene	4-Me	58 ^b	580
11	Styrene	4- <i>t</i> Bu	82 ^b	820
12	Styrene	4-NO ₂	43 ^b	430
13	Styrene	4-CF ₃	98 ^b	980
14	Styrene	4-Cl	61 ^b	610
15	Styrene	3-Cl	29 ^b	290
16	Styrene	2-Cl	14 ^b	140
17	MMA	4-Me	92 ^c	920
18	MMA	4- <i>t</i> Bu	93 ^c	930
19	MMA	4-NO ₂	92 ^c	920
20	MMA	4-CF ₃	94 ^c	940
21	MMA	4-Cl	92 ^c	920
22	MMA	3-Cl	92 ^c	920
23	MMA	2-Cl	92 ^c	920

^a Bromobenzene (0.5 mmol), olefin (0.75 mmol), Pd(dba)₂ (0.0005 mmol, 0.1 mol %), triphenylphosphite (0.005 mmol, P/Pd = 10), and K₂CO₃ (0.6 mmol) in DMF (1.0 mL) at 100 °C for 20 h.

^b Yields are for isolated products.

^c Yields determined by GC with *trans*-stilbene as internal standard.

the IL and analyzed by GC and the isolated products characterized by ¹H NMR, GC–MS, IR, and mp.

2.4. Catalysis with IL as co-solvent

Under similar experimental conditions and reagent amounts in 2.2., the mixture was dissolved in 0.5 mL of IL and 0.5 mL of DMF. The products of reaction were extracted from the IL/DMF mixture with ethyl ether and the organic phase was analyzed by GC and the isolated products characterized by ¹H NMR, GC–MS, IR, and mp.

2.5. Catalysis with IL as solvent

Under similar experimental conditions and reagent amounts in 2.2., the mixture was dissolved in 1 mL of IL under nitrogen atmosphere. The products of reaction were extracted from the IL with ethyl ether and the organic phase was analyzed by GC and the isolated products were characterized by ¹H NMR, GC–MS, IR, and mp.

3. Results and discussion

Some preliminary catalyses were carried out to select the best source of palladium and to corroborate that in general phosphites are as good as or better ligands than phosphines (Table 1). As it was expected, the best catalytic system for the coupling of styrene and bromobenzene in DMF is Pd(dba)₂ as a catalyst precursor⁹ in the presence of P(OPh)₃ as a ligand (P/Pd = 10:1, entry 8). It is important to notice that triphenylphosphite is not able to reduce other Pd-sources in a significant amount, showing zero or very low yields (entries 5–7). Triphenylphosphite proved to be a better ligand than triphenylphosphine (entries 4 and 8) due probably to the stability provided by the phosphite to the palladium(0); triphenylphosphite is a better π-acceptor than triphenylphosphine and stabilizes the Pd(0)-catalyst, avoiding the aggregation and precipitation of black Pd.

The selected catalytic system (0.1 mol % of Pd(dba)₂ with 1 mol % of P(OPh)₃ as a ligand) was probed with a range of substrates, evaluating the electronic effects of the substituents in the aryl halide and using styrene or methyl methacrylate (MMA) as the olefin. In a general overview (Table 2) it is clear that reactions carried out with MMA show better yields (always more than 90%).

The substituent electronic effect on the aryl halide is observed clearly in the cross-couplings with styrene. Electron donating groups like alkyl and alkoxy substituents (entries 9–11) allow good yields of the corresponding products (58–82%); this can be attributed to the more basic phenyl-fragment coordinated to the Pd-complex, which improves the migratory insertion to the olefin in the second step of the proposed catalytic cycle.¹⁰ On the other hand, electron withdrawing groups, such as the trifluoromethyl substituent (entry 13) enhance also the reactivity, showing excellent yields (98%). In this case we suppose that the oxidative addition (first step in the catalytic cycle) is the key to understand the electronic effect.¹¹ The position of the substituent also was evaluated (entries 14–16) using 2-chlorobromobenzene, 3-chlorobromobenzene and 4-chlorobromobenzene. The *ortho* substituent (entry 16) presents the worst yield because of its steric hindrance that practically avoids the formation of the aryl-coordinated intermediate. *meta* and *para* substituents do not present a really strong steric effect but the yield of the isolated product is not better than 61% (entries 14 and 15). Formations of the corresponding bromide products were not detected. The catalytic assays using MMA as olefin (entries 17–23) allowed excellent yields, with TONs up to 940. The more electron withdrawing MMA improves the migratory insertion of aryl compounds, without the significance of the aryl substituents.

Nevertheless, this simple catalytic system also tolerates deactivated aryl bromides, overcoming one of the limitations of the cross-coupling reactions.¹² Moreover, the catalytic activity in the Heck reaction is susceptible to the solvent and additives effects.¹³ As we are interested in the positive effect of IL in homogeneous catalytic reactions, we also test a range of imidazolium and picolinium derivatives in this reaction with one of the worst aryl bromides as substrate (Tables 3 and 4): the coupling of 3-chlorobromobenzene (29% yield in DMF, entry 15) was tried with styrene and MMA. The IL were used as additive (approx. 20 mol % related to the aryl halide), co-solvent (DMF/IL = 1:1) or solvent (without DMF). For all the cross-couplings with styrene (Table 3) better

yields were obtained related to results shown in DMF (Table 2). When the IL was added as additive an important increase in the yield was observed (Table 3, entries 24–27, 30–31, 34–35). It is interesting to note that larger amounts of IL, going from additive to solvent, make a positive effect in this coupling with styrene (Table 3, entries 31–33).

These results should indicate that the possible rate determining step (the migratory insertion) follows an ionic mechanism,^{10,11,13,14} or the IL inhibit the formation of black Pd.¹⁵ Deeper studies on the single steps in order to understand the role of the ionic liquids in the mechanism are in progress. Conversely, as the phosphite–palladium bond is stronger than the one with phosphine, the ligand dissociation is less probable than the halide dissociation, constraining the cationic mechanism of the migratory insertion.^{10,11,16}

On the other hand, moderate increments in yield were only found for MMA when IL was used as additive (Table 4, entries 36–39, 41, 44, 45). And more surprisingly, larger amounts of IL in the coupling of 3-chlorobromobenzene with MMA decrease the yield of this reaction (entries 41–43), probably due to solubility problems of MMA into the solvent-IL and solo-IL, confirmed by the decreased yield with increased amount of IL. Also in the case of the coupling of 3-chlorobromobenzene with MMA in [OPIC]PF₆ it is possible to achieve high TON and reasonable turnover frequencies, with the catalysis carried out with only 0.001 mol % of Pd(dba)₂ (TON up to 33,000 and TOF up to 1650 h⁻¹, entry 40). This result is even better than previously reported with monodentate phosphites.^{6,17} This scenario opened the possibility to exploit phosphites as ligands and IL as additives or solvents in the synthesis of more complicated products, such as PPVs derivatives.

In general, it is not straightforward to establish a relationship between the nature of the IL and its effectiveness in a catalytic reaction. In this case, the nature of the cation (imidazolium or picolinium) seems to be unimportant for the coupling of 3-chlorobromobenzene with styrene. In both cases, if the anion is PF₆⁻, it is possible to reach quantitative yields (Table 3, entries 27 and 30). Since the reaction with [OPIC]PF₆ allows one of the higher

Table 3
Coupling of 3-chlorobromobenzene with styrene in the presence of IL catalyzed by Pd(dba)₂/P(OPh)₃^a

Entry	Olefin	IL	Yield ^b (%)	TON	TOF (h ⁻¹)
24	Styrene	[BPIC]BF ₄	94	940	47
25	Styrene	[OPIC]BF ₄	89	890	44.5
26	Styrene	[BMIM]BF ₄	84	840	42
27	Styrene	[OPIC]PF ₆	>99	1000	50
28	Styrene	[OPIC]PF ₆ ^{c,d}	33	3300	165
29	Styrene	[OPIC]PF ₆ ^{d,e}	27	27,000	1350
30	Styrene	[BMIM]PF ₆	>99	1000	50
31	Styrene	[EMIM][TFMS]	69	690	34.5
32	Styrene	[EMIM][TFMS] ^f	76	760	38
33	Styrene	[EMIM][TFMS] ^d	98	980	49
34	Styrene	[BMIM][TFMS]	96	960	48
35	Styrene	[EMIM][ETS]	89	890	44.5

^a 3-Chlorobromobenzene (0.5 mmol), olefin (0.75 mmol), Pd(dba)₂ (0.000005–0.0005 mmol, 0.001–0.1 mol %), P(OPh)₃/Pd = 10, and K₂CO₃ (0.6 mmol) in DMF (1.0 mL) with 0.02 mL of IL at 100 °C for 20 h. [BMIM] = 1-butyl-3-ethylimidazolium; [EMIM] = 1-ethyl-3-methylimidazolium; [BPIC] = *N*-butylpicolinium; [OPIC] = *N*-octylpicolinium; [ETS] = ethylsulfate; [TFMS] = trifluoromethanesulfonate; [TFMSI] = bis(trifluoromethylsulfonyl)imide.

^b Yields (average of at least 2 runs) determined by GC with *trans*-stilbene as internal standard.

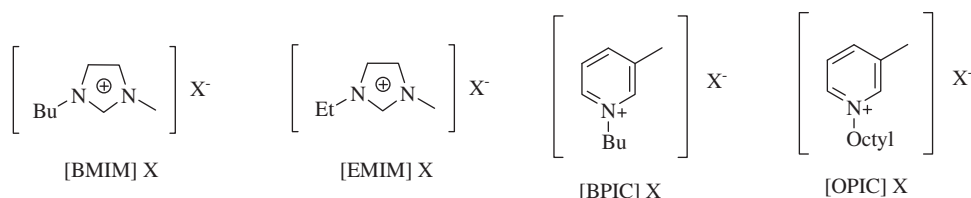
^c With 0.01 mol % Pd(dba)₂.

^d Only 1 mL of IL, without DMF.

^e With 0.001 mol % Pd(dba)₂.

^f Solvent DMF/IL = 1:1.

Table 4
Coupling of 3-chlorobromobenzene with methyl methacrylate (MMA) in the presence of IL catalyzed by Pd(dba)₂/P(OPh)₃^a



Entry	Olefin	IL	Yield ^b (%)	TON	TOF (h ⁻¹)
36	MMA	[BPIC]BF ₄	>99	1000	50
37	MMA	[OPIC]BF ₄	99	990	49.5
38	MMA	[BMIM]BF ₄	95	950	47.5
39	MMA	[OPIC]PF ₆	93	930	46.5
40	MMA	[OPIC]PF ₆ ^{c,d}	33	33,000	1650
41	MMA	[EMIM][TFMSI]	93	930	46.5
42	MMA	[EMIM][TFMSI] ^e	84	840	42
43	MMA	[EMIM][TFMSI] ^c	76	760	38
44	MMA	[BMIM][TFMS]	>99	1000	50
45	MMA	[EMIM][ETS]	97	970	48.5

^a 3-Chlorobromobenzene (0.5 mmol), olefin (0.75 mmol), Pd(dba)₂ (0.000005–0.0005 mmol, 0.001–0.1 mol %), P(OPh)₃/Pd = 10, and K₂CO₃ (0.6 mmol) in DMF (1.0 mL) with 0.02 mL of IL at 100 °C for 20 h. [BMIM] = 1-butyl-3-ethylimidazolium; [EMIM] = 1-ethyl-3-methylimidazolium; [BPIC] = *N*-butylpicolinium; [OPIC] = *N*-octylpicolinium; [ETS] = ethylsulfate; [TFMS] = trifluoromethanesulfonate; [TFMSI] = bis(trifluoromethylsulfonyl)imide.

^b Yields (average of at least 2 runs) determined by GC with *trans*-stilbene as internal standard.

^c Only 1 mL of IL, without DMF.

^d With 0.001 mol % Pd(dba)₂.

^e Solvent DMF/IL = 1:1.

TONs (entry 27), it has reduced the amount of catalyst for this catalytic system (Table 3, entry 29) obtaining a considerable increase in TON (up to 27,000), values comparable to those reported previously.^{6,17} But in our case using a non-activated aryl halide and milder reaction conditions. Furthermore, with the coupling with MMA (Table 4) the benefits of the reaction with IL are different.

4. Conclusions

In summary, it can be asserted that the simple and inexpensive monodentate triphenylphosphite is a good and efficient ligand for the Heck cross-coupling reaction and the catalyst activity is improved by using room temperature IL.

A better efficiency in the Heck reaction opens the way to the effective synthesis of conjugated polymers with high stereoselectivities and high molecular weights. Moreover, the possibility that the polar mechanism in the insertion step is preferred using IL and phosphite ligands enhances the control of the formation of configurationally pure *trans* segments.

Although the positive influences of the IL and phosphite are evident, kinetic and theoretical studies of this Heck cross-coupling are under investigation as a means to have a better understanding of this Pd-catalyzed reaction.

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