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C–Cl Activation

Heck Reactions with Palladium Nanoparticles in Ionic Liquids: Coupling of Aryl Chlorides with Deactivated Olefins**

Vincenzo Calò, Angelo Nacci, Antonio Monopoli, and Pietro Cotugno*

The palladium-catalyzed Heck arylation of olefins is one of the most important carbon–carbon bond-forming processes in synthetic organic chemistry.[1] There are at present two main concerns with respect to this reaction: 1) the discovery of catalytic systems that activate the C–Cl bond and 2) the development of phosphane-free palladium catalysts. Chloroarenes are the most readily available and cheapest starting materials; however, they are generally unreactive under the conditions used to couple the corresponding iodides and bromides. In particular, the use of neutral and electron-rich aryl chlorides requires high temperatures (> 140 °C) as well as expensive and air-sensitive phosphane ligands.[2] A further drawback is that complex substituted olefins (cinnamates or other 1,2-disubstitued alkenes) are relatively uncommon substrates as a result of their low reactivity toward typical catalysts. From a synthetic standpoint, all these factors are considerable limitations that need to be addressed.

To date, most of the catalysts that show high activity in Heck reactions of deactivated (electron-rich) chloroarenes require toxic solvents along with air-sensitive bulky alkyl phosphane ligands and the presence of a hindered amine.[3] Other systems are based on either PCP pincer complexes[4] or N-heterocyclic carbene ligands,[5] whereas very few efficient methods have been reported in which benign solvents and ligand-free conditions are used.[6] Moreover, most of these catalyst systems require harsh conditions ($T > 140$ °C), so that a reaction may have broad scope with respect to the aryl chloride substrate but poor generality with respect to the olefin.

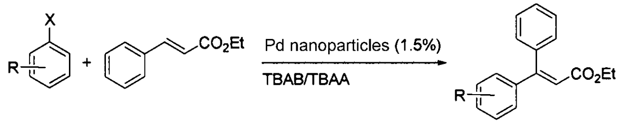
During the past decade, we[7] have demonstrated widely that tetraalkylammonium ionic liquids (ILs)[8] are superior reaction media for the Heck coupling catalyzed by Pd colloids. For instance, we were the first to couple bromoarenes with less reactive 1,2-disubstituted alkenes, such as cinnamates, in a stereospecific manner under ligand-free conditions.[9] In that study, reactions were carried out at 130 °C in a molten mixture of the solvent tetrabutylammonium bromide (TBAB) and the efficient base tetrabutylammonium acetate (TBAA) in an approximately 1:1.5 molar ratio. However, the coupling of chloroarenes proved to be unsatisfactory under these conditions. To extending the scope of that procedure, we decided to investigate the coupling of more challenging deactivated chloroarenes and a wider array of olefins.

With the aim to improve catalyst performance, we examined the use of TBAB and TBAA in various ratios, whereby we took into account our recent findings,[7b,10] which showed a strong dependence of the catalyst activity and selectivity on the composition of the ionic solvent. After a preliminary screening,[11] we found that a reversed TBAB/TBAA ratio of 2:1 increased catalyst efficiency remarkably, with the activation of a wider range of substrates, including chloroarenes. The need for greater amounts of TBAB was in line with our hypothesis that bromide ions, poorly solvated in these reaction media, can provide adequate electron density to the Pd^0 species in place of the electron-rich phosphane ligands to facilitate the oxidative-addition step.[7a,9]

By virtue of the improved catalyst performance, we were able to carry out the reactions under milder conditions, at a lower reaction temperature than that required previously. For example, bromobenzene and 4-bromoanisole were coupled rapidly in high yields at 100 °C (Table 1, entries 1 and 2).

The corresponding aryl chlorides were also activated readily at 120 °C (Table 1, entries 3–10). We found that the catalyst activity was dependent on the olefin/chloroarene

Table 1: Heck arylation of ethyl cinnamate in TBAB/TBAA.[a]



Entry	Aryl halide R	X	Olefin/ArX	T [°C]	t [h]	Yield [%][b,c]
1	H	Br	1:1	100	1	96
2	4-OCH_3	Br	1:1	100	2	90
3	H	Cl	1:1	100	14	–
4	4-OCH_3	Cl	1:1	100	14	–
5	H	Cl	2:1	120	3	45
6	H	Cl	1:1	120	3	63
7	H	Cl	1:2	120	3	95
8	4-CH_3O	Cl	1:1	120	4	50
9	4-CH_3O	Cl	1:2	120	4	72
10	4-CH_3O	Cl	1:3	120	4	90

[a] Reactions were carried out in a mixture of TBAB (1 g) and TBAA (0.45 g). [b] The yield was determined by GC by using diethylene glycol di-*n*-butyl ether as an internal standard. [c] Unless otherwise indicated, the E/Z ratio is > 98:2, as determined by GC–MS.

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[*] Prof. V. Calò, Prof. A. Nacci, Dr. A. Monopoli, P. Cotugno
Department of Chemistry
University of Bari
Via Orabona 4, 70126 Bari (Italy)
Fax: (+39) 080-544-2499
E-mail: nacci@chimica.uniba.it
Prof. A. Nacci
CNR–ICCOM, Department of Chemistry, University of Bari
Via Orabona 4, 70126 Bari (Italy)

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ratio. In particular, the β,β-diaryl acrylates were formed in excellent yield when chlorobenzene was used in twofold excess (Table 1, entries 5–7) or 4-chloroanisole was used in threefold excess (Table 1, entries 8–10). These findings, together with our preliminary kinetic observations, which showed that in these cases the reaction rate is zero-order in the olefin, are consistent with the oxidative addition as the turnover-limiting step.

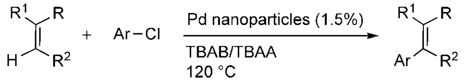
Nevertheless, another explanation for the influence of the aryl chloride on the reaction yield is possible, if one assumes, as also reported by Schmidt and Smirnov[12] for the Heck coupling of bromoarenes under similar conditions, that an increased concentration of the aryl halide would favor partial recovery of the aggregated palladium species into the catalytic cycle through oxidative addition of the aryl chloride. A corresponding increase in the catalyst concentration would be expected to lead to higher yields.

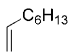
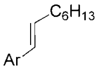
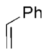
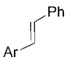
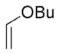
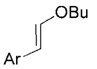
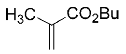
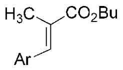
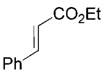
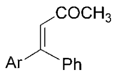
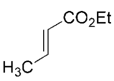
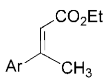
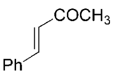
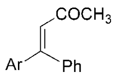
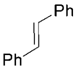
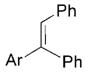
To expand the scope of our procedure, we applied these optimized conditions to a wide array of substrates. The catalytic reactions appeared quite general with respect to the nature of the olefin (Table 2). Alkyl monosubstituted alkenes, such as 1-octene, proved to be extremely reactive; they underwent coupling at 100 °C even with deactivated chloroarenes (Table 2, entries 1–3).[13] Styrene was also coupled smoothly with a wide range of activated and deactivated chloroarenes at 120 °C (Table 2, entries 4–8). Unfortunately, the reaction of less reactive (electron-rich) butyl vinyl ether with unactivated chlorobenzene was unsatisfactory (Table 2, entry 10).

The catalyst also proved to be very active with 1,1-disubstituted alkene substrates. For example, butyl methacrylate was transformed into α-methylcinnamic acid derivatives, which are useful intermediates in the synthesis of pharmaceuticals,[14] in good yields; small amounts of diarylated products were also obtained (Table 2, entries 11 and 12).

Remarkable results were obtained with (generally less reactive) 1,2-disubstituted olefins. β-Substituted α,β-unsaturated esters, which are usually unreactive towards most aryl chlorides, were coupled smoothly with electron-rich chloroarenes at 120 °C (Table 2, entries 13–21). For example, under these conditions, β,β-diaryl acrylates were obtained in excellent yield with excellent stereoselectivity (Table 2, entries 13–17). These compounds are valuable precursors for the synthesis of a variety of medicinally interesting compounds.[15] The 1,2-disubstituted alkenes benzylideneacetone and stilbene were also compatible with the coupling reaction. The corresponding synthetically valuable trisubstituted olefins were obtained in high yield (Table 2, entries 22–27).

Table 2: Heck olefination of chloroarenes in TBAB/TBAA.[a]

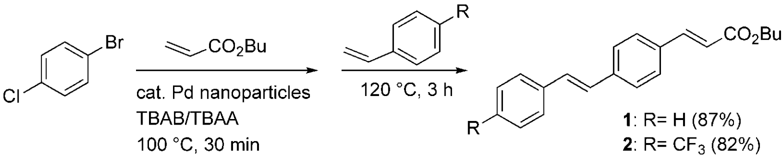


Entry	Olefin	Ar	t [h]	Product	Yield [%][b,c]
1[d]		C_6H_5	2		90[e]
2[d]		4-$CH_3C_6H_4$	1		98[e]
3[d]		4-$CH_3OC_6H_4$	6		88[e]
4		4-$CF_3C_6H_4$	3		95
5		4-$CH_3COC_6H_4$	3		98
6		C_6H_5	3		88
7		4-$CH_3C_6H_4$	3		90
8		4-$CH_3OC_6H_4$	2		95
9		4-$CH_3COC_6H_4$	5		76[f]
10		C_6H_5	8		25[f]
11[g]		C_6H_5	2		67[h]
12		4-$CH_3OC_6H_4$	3		75[h]
13		4-NCC_6H_4	8		72
14		4-$CH_3COC_6H_4$	5		94
15		C_6H_5	5		95
16		4-$CH_3C_6H_4$	5		90
17[i]		4-$CH_3OC_6H_4$	5		90
18		C_6H_5	5		80[j]
19		4-$CH_3C_6H_4$	2		94[j]
20		2-$CH_3C_6H_4$	3		95[j]
21		4-$CH_3OC_6H_4$	5		92
22		4-$CH_3COC_6H_4$	3		98[k]
23		C_6H_5	3		95
24		4-$CH_3C_6H_4$	3		97[k]
25		4-$CH_3OC_6H_4$	3		90
26		C_6H_5	5		78
27		4-$CH_3OC_6H_4$	5		85

[a] TBAB: 1 g, TBAA: 0.45 g, olefin: 0.5 mmol, chloroarene: 1 mmol. [b] The yield was determined by GC by using diethylene glycol di-*n*-butyl ether as an internal standard. [c] Unless otherwise indicated, the *E*/*Z* ratio is >98:2, as determined by GC–MS. [d] The reaction was carried out at 100 °C. [e] The product includes isomers (ca. 40%) of the 1-aryl 1-octene.[13] [f] β/α≈80:20; β-arylated products were formed in an *E*/*Z* ratio of 2:1. [g] Olefin/ArCl substrate ratio: 2:1. [h] Value includes the yield of the diarylated product (15%), which was also formed. [i] Olefin/ArCl substrate ratio: 1:3. [j] *E*/*Z* ratio: 80:20. [k] *E*/*Z* ratio: 70:30.

To highlight the synthetic value of this method, we attempted its application to a synthesis of practical importance for the pharmaceutical and materials industries: the one-pot sequential coupling of aryl dihalides to produce unsymmetrically disubstituted arenes.[16] Most of the reported methods for such transformations suffer from disadvantages, such as the requirement of two different catalysts, the need to isolate the intermediate product, or the use of expensive and not readily available substrates. Moreover, to the best of our knowledge, no examples of the use of cheaper bromochloroarenes as starting materials have been reported until now, because of the difficulty in activating the C−Cl bond. With our catalyst, we were able to couple 1-bromo-4-chlorobenzene with two different olefins in a one-pot sequential manner by activating the C−Br and C−Cl bonds on the aromatic ring at the two different temperatures of 100 and 120 °C. The unsymmetrical substituted arenes **1** and **2** were produced in this way with high reaction rates and in high overall yield (Scheme 1).

In summary, we have developed a general method for the Heck coupling of chloroarenes, including deactivated, electron-rich compounds, with substituted olefins of low reactivity. The reaction conditions are unprecedented: 1) In



Scheme 1. One-pot sequential Heck coupling of 1-bromo-4-chlorobenzene.

contrast to most reported methods,[3] neither toxic, air-sensitive phosphane ligands nor an inert atmosphere is required, 2) an environmentally safer IL medium is employed, 3) unusual combinations of substrates that are not compatible with many traditional catalysts are possible (e.g. chloroanisole and cinnamates), and 4) shorter reaction times (typically in the range of 1–5 h) and milder temperatures are used than in many other procedures.[3c–f,5,6] Furthermore, these findings open the way to the use of bromochloroarenes as starting materials for sequential couplings. For these reasons, as well as its generality, this operationally simple method can compete with the most efficient known procedures. We anticipate that this catalyst system will find wide applicability.

Experimental Section

General procedure: TBAB (1 g), TBAA (0.45 g, 1.5 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol, 1.5 mol %), the olefin (0.5 mmol), the aryl halide (1 mmol), and diethylene glycol di-*n*-butyl ether (internal standard, 50 μL) were placed in a 10 mL vial equipped with a screw cap and a magnetic stirrer bar. The reaction mixture was stirred and heated in air at the temperature and for the time indicated (see Table 1 and Table 2). Product yields were determined by GLC and GC–MS of the reaction mixture. Products were identified by the same techniques and comparison with spectral data reported in the literature.

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Keywords: aryl chlorides · colloids · Heck reaction · ionic liquids · palladium

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[11] The optimal TBAB/TBAA molar ratio of 2:1 was determined on the basis of results with a model reaction between chlorobenzene (0.5 mmol) and ethyl cinnamate (1 mmol) in the presence of the catalyst (1.5 mol %) in the solvent TBAB (1 g) at 120 °C (n.r. = no reaction):

Base	TBAA				NaOAc	Cs$_2$CO$_3$
TBAB/base	1:2	1:1	2:1	[a]	2:1	2:1
yield [%][b]	30	47	95	52	n.r.	35

[a] TBAA was used as the solvent and base.
[b] The yield was determined by GLC.

TBAA clearly plays a key role. Indeed, a generic source of acetate did not have the same effect on catalyst activity. Two plausible explanations can be given for this difference in reactivity: 1) NaOAc (and other inorganic bases) show low solubility in TBAB, and 2) the presence of inorganic cations can lower the basicity of the acetate anion in the IL by forming tight ion pairs.

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