Influence of Ionic Liquids on Pd-Catalyzed Carbon–Carbon Bond Formation

Vincenzo Calò and Angelo Nacci

Centro CNR "MISO", Dipartimento di Chimica, Università di Bari, via Amendola,
173-70126 Bari-Italy

Reprint requests to Prof. V. C.; Fax: +39-80-544-2924; E-mail: calo@chimica.uniba.it

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Rates of Heck-type reactions, catalysed by a Pd-catalyst with benzothiazole carbene as ligands, are strongly influenced by tetrabutylammonium bromide utilized as solvent.

Key words: Ionic Liquids; Heck Reaction; Palladium; Carbenes; Aryl Acrylates.

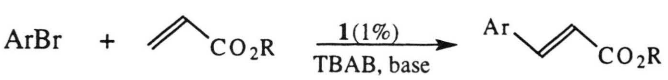
In today's environmentally conscious world, a problem with homogenous catalysts has emerged, *viz.* many of the solvents traditionally used in transition metal catalysis, such as chlorinated hydrocarbons, acetonitrile, DMF, to name but a few, are currently on the 'environmental blacklist'. Furthermore, toxic and air sensitive phosphanes have been used as ligands in many such metal complexes. For these reasons most of the industrial organic syntheses needs rethinking.

An approach to resolve these drawbacks may be the replacement of traditional solvents with ionic liquids together with the discovery of new ligands for metals. The advantages of ionic liquids will be manifold: in addition to facilitated catalyst recovery, they may exhibit low viscosity, high thermal and air stability, low vapour pressure, and they will readily solubilise the reagents and catalysts [1].

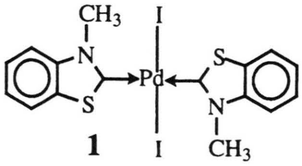
The objective of our research was to find phosphane-free new catalysts and their application, in an ionic liquid as solvent, for the carbon–carbon coupling reactions. The replacement of phosphanes as ligands was achieved by us through the synthesis of some catalysts with benzothiazole carbenes as ligands [2]. For example, the palladium catalyst **1** (Fig. 1), which proved to be very stable to high temperature, air and moisture, was utilized for a very efficient synthesis of cinnamates [3], largely utilized as UV screening agents (Scheme 1).

An astonishing increase of the reaction rate was observed by performing the reactions in tetrabutylammonium bromide (TBAB) in the presence of sodium formate as reducing agent for **1** with bromobenzene being converted into butyl cinnamate within 10 min (Table 1, run 2), whereas the same reaction in dimethylformamide required at least 24 h. Furthermore, less activated bromoaromatics reacted easily with high conversion rates and *p*-nitrochlorobenzene gave the nitrocinnamic ester in 95% yield in 1 h (Table 1, run 9).

Arylation of β-substituted, α,β-unsaturated esters requires harsh reaction conditions, cyclopalladated phosphanes [4, 5] or palladium acetate as catalysts, sterically hindered tertiary amines as bases and quaternary ammonium salts as phase-transfer agents in DMF or DMA as solvents [6]. These pharmaceutically important compounds were easily synthesized in TBAB [7] (Scheme 2 and Table 2).



Scheme 1



1

Fig. 1. Bis(2,3-dihydro-3-methylbenzothiazole-2-ylidene) palladium(II) Diiodide

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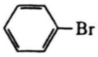
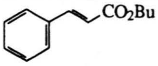
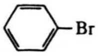
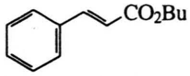
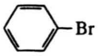
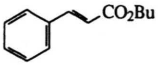
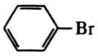
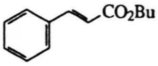
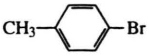
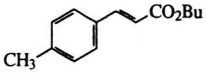
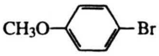
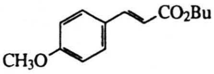
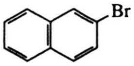
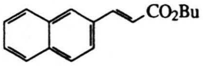
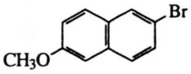
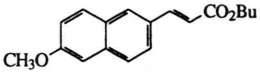
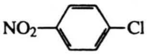
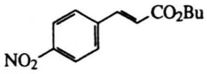
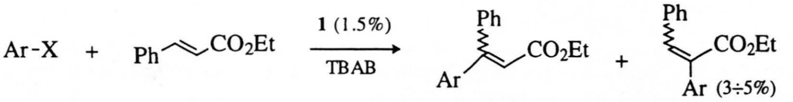
Table 1. Arylation of butyl acrylate catalysed by complex **1**.[a]

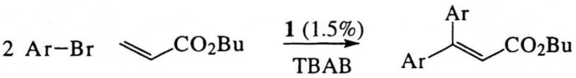
Entry	Aryl halide	Base	Product	Yield (5)[b]	Time
1		NaOAc		90	4 h
2		Na_2CO_3		94	10 min
3[c]		Na_2CO_3		78	1 h
4		$NaHCO_3$		94	1 h
5		$NaHCO_3$		95	2 h
6		$NaHCO_3$		85	5 h
7[d]		$NaHCO_3$		90	3 h
8		$NaHCO_3$		93	1 h 15 min
9		$NaHCO_3$		95	1 h

[a] Reaction conditions: aryl halide:butyl acrylate:Base 1:1:2 and 1 mol% of the catalyst at 130°C. [b] Isolated products. [c] 0.1 mol% of catalyst. [d] Reaction performed at 110°C.

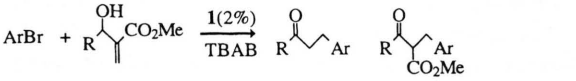


Ar = p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$, p-$CH_3COC_6H_4$, α-naphthyl, p-$O_2NC_6H_4$, p-NCC_6H_4; X = Cl, Br

Scheme 2



Scheme 3



Ar = H, p-MePh, p-MeOPh, p-AcPh, α-naphthyl; R = Ph, Me, i-propyl, n-propyl, n-octyl

Scheme 4

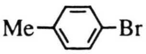
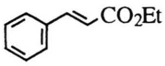
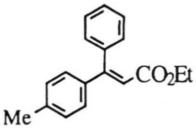
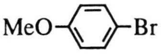
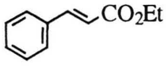
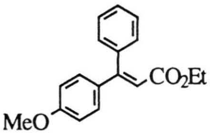
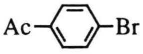
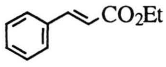
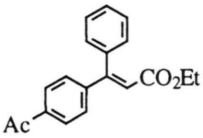
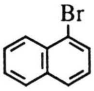
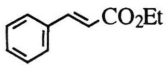
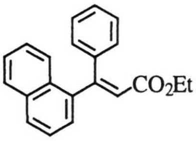
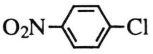
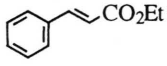
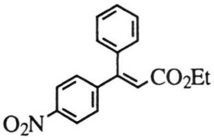
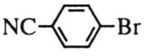
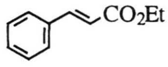
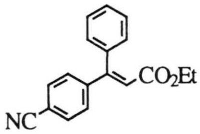
An extension of this process [7] was applied to one-step synthesis of β,β-diarylacrylates by reaction of butyl acrylate with an excess of an aryl halide (Scheme 3).

Catalyst **1** was stable in TBAB melt and efficiently allowed the reaction [8] of various p-substituted bromoaromatics with hydroxymethylenealkanoates **2** to give β-arylketones **3** but not the expected Heck product, β-oxoalkanoate **4** [9] (Scheme 4).

Table 3 reports some relevant results.

In all C–C-coupling reactions reported in this paper, the role exerted by both the anion and the cation was essential. Indeed, reactions performed in different ionic liquids as N-butylpyridinium tosylate or [Bmim] BF_4, [7, 8], gave poor results. Furthermore, TBAB as solvent makes the recycling of the catalyst feasible. But, despite the observed beneficial effects exerted by quaternary ammonium salts on the Heck reaction [10], the exact na-

Table 2. Synthesis of β,β-diaryl acrylates in TBAB, catalyzed by Pd-benzothiazole carbene complex **1**.[a]

Entry	Aryl halide	Olefin	Product	E:Z Ratio	Time [h]	Yield [%][b]
1				59:41	8	91
2				61:39	17	84
3				60:40	7	97
4				64:36	4	76
5				60:40	40	78
6				58:42	18	70

[a] Conditions: 130 °C, TBAB (3 g), $NaHCO_2$ 3 mol%; ratio haloarene/olefin/$NaHCO_3$ 1.5:1:2.5; 1.5 mol% of **1** with the exception of entry 5 (2.5 mol% of **1**); [b] Yields refer to chromatographic isolated product.

ture of this influence cannot be ascribed to a single effect such as the high polarity or phase-transfer ability [11], but rather to a superposition of several factors. For example, Reetz et al. [12] found that reduction of a Pd salt in THF and in the presence of tetrabutylammonium acetate or formate gave Pd-nanoparticles stabilized by the large ammonium cation. Furthermore, Neghishi et al. [13] and Amatore and Jutand [14] demonstrated that $Pd(0)(PPh_3)_2$, the proposed catalyst in the Heck reaction, was unstable in the absence of halide or acetate ions which transform this complex into a more stable and catalytically active 16-electron anionic complex as $[Pd(PPh_3)_2X]^{(-)}$. The stabilization of catalytic systems by halide salts was also demonstrated by extension of the lifetime of the Herrmann palladacycle [15]. To explain some ionic liquid effects, we propose some considerations that could explain our results. The addition of sodium formate does reduce **1** to the underligated $L_2Pd(0)$ complex [12], which, by reaction with TBAB, would afford an anionic and catalytically active 16-electron complex $[L_2Pd\,Br]^{(-)}\,NR_4^{(+)}$. This would be not surprising, since in TBAB the bromide ion, being poorly solvated, should be a good nucleophile for palladium. On the contrary, ionic liquids, bearing less nucleophilic anions such as tosylate or tetrafluoroborate, should not stabilize the 14-electron complex $L_2Pd(0)$, like halides can. Evidence for this was provided by the inefficacy of **1** in catalyzing the reaction in butylpyridinium tosylate

Table 3. Synthesis of β-arylketones in TBAB, catalyzed by Pd-carbene complex **1**.[a]

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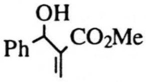
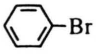
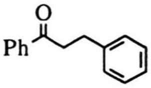
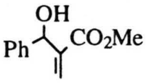
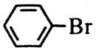
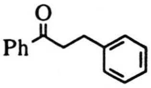
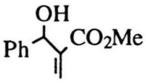
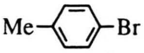
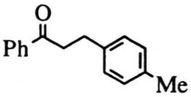
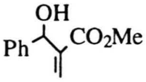
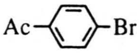
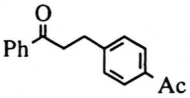
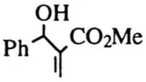
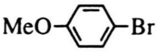
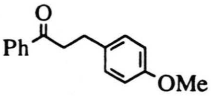
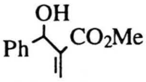
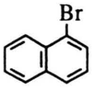
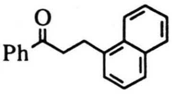
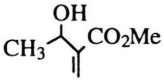
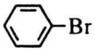
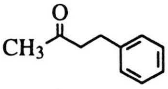
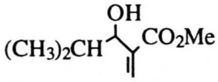
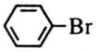
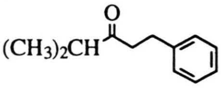
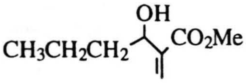
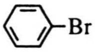
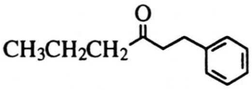
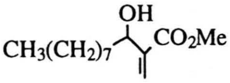
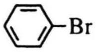
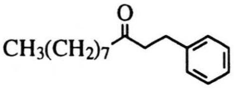
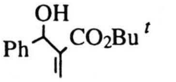
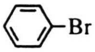
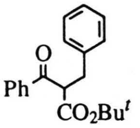
1				20	77
2[c]				24	n.r.
3				22	66
4				14	78
5				14	82
6				15	80
7				6	79
8				4	71
9				20	77
10				8	79
11				14	66[d]

[a] Reaction conditions: TBAB (3 g), catalyst (0.38 mmol, 2 mol%), sodium formate (0,76 mmol), bromoarene (19 mmol), sodium bicarbonate (40 mmol) and hydroxymethylene alkanoate (27 mmol) stirred at 130 °C. [b] Determined by glc integrated with diethylene glycol dibutyl ether as internal standard. [c] Performed in *N*-butylpyridinium tosylate as solvent. [d] Total yield as sum of β-oxoalkanoate and the corresponding β-arylketone.

or [bmim] BF_4. Furthermore, the same anion effect was observed [16] in other ionic liquids such as imidazolium hexafuorophosphate. The stabilizing effect was exerted not only by the bromide ion, which is likely to enter the co-ordination shell of underligated $L_2Pd(0)$ to give the anionic complex, but also by the large tetrabutylammonium cation. Indeed, the formation of a large $[L_2Pd\,Br]^{(-)}\,NR_4^{(+)}$ complex, by imposing a Coulombic barrier for collision, should impede the formation of clusters growing further into metal particles. Besides this effect, interaction of the tetrabutylammonium cation with the bromide or iodide ligated to the palladium center gives rise to the formation of ion pairs with a naked $L_2Pd(0)-Br^{(-)}-NR_4^{(+)}$ which does afford a more reactive palladium(0) complex [13, 14]. Furthermore, the ammonium cation could electrostatically assist the polarization or decomplexation of the bromide ion from the anionic Pd(II) pentacoordinated complex $[L_2PdArBr_2]^{(-)}\,NR_4^{(+)}$ deriving from oxidative addition with aryl bromides, and this would render the Pd(II)-complex more electrophilic for a fast olefin insertion. This is conceivable since it was calculated, for analogous Pd-complexes with imidazolidene carbenes ligands, that the removal of bromide from the oxidative addition complex of aryl bromides was a strongly endothermic process [17].

In conclusion, while some aspects of the catalytic cycle involving Pd-carbene complexes in ionic liquids are not well understood, our results show that ionic liquids cannot be considered as simple high polarity solvents, but their efficacy is due to several factors which are studied by us.

Acknowledgements

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