

Pd Nanoparticles Catalyzed Stereospecific Synthesis of β -Aryl Cinnamic Esters in Ionic Liquids

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Reaction of the catalyst **1** or Pd(OAc)₂ with tetrabutylammonium acetate, dissolved in tetrabutylammonium bromide, leads to a fast formation of Pd nanoparticles which efficiently catalyze the stereospecific reaction of cinnamates with aryl halides to give β -aryl-substituted cinnamic esters. The role of tetrabutylammonium acetate is crucial in determining the formation of nanoparticles and stereospecificity of the C–C coupling process.

The Heck reaction and related chemistry occupy a special place among basic types of palladium-catalyzed reactions.^{1–3} In the last 10 years ionic liquids (IL) have attracted a great deal of attention as a possible replacement of conventional solvents for catalytic and organic reactions.⁴ Quaternary ammonium salts,^{5,6} pyridinium,⁷ and imidazolium salts^{7–9} have been used as solvents for Heck reactions of monosubstituted alkenes with aryl halides, mainly iodides, to increase yields and reaction rates. Relatively few Heck arylations of 1,1- and 1,2-disubstituted alkene have been reported.^{10–16} In particular, arylation of cinnamic esters, which requires harsh reaction conditions particularly for aryl bromides, was experimented with by Moreno-Mañas et al.¹³ and Buchwald et al.¹⁴ by using a phosphane-free procedure, in

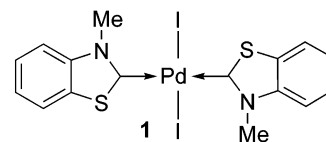
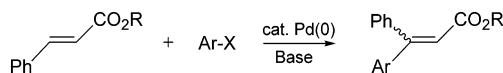


FIGURE 1.

DMF or DMA with variable results in controlling the stereochemistry of this process. As some β -aryl cinnamic acids are useful intermediates for the synthesis of medicinal products,^{17–19} the development of an efficient and stereoselective synthetic method for these compounds would be of significant utility (Scheme 1).

SCHEME 1



The search for alternative media and palladium catalysts for Heck chemistry was targeted by us for development of highly productive, environmentally safe, recyclable techniques which can be promoted to large-scale applications. For this purpose, recently we reported²⁰ the synthesis of a Pd catalyst **1** with benzothiazole carbenes as ligands and its application for an efficient Heck synthesis of *trans*-cinnamates in molten tetrabutylammonium bromide (TBAB) as solvent and sodium hydrogencarbonate as base.²¹

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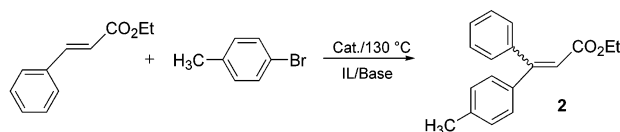
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TABLE 1. Base Effect on the Reaction of 4-Bromotoluene with *trans*-Ethyl Cinnamate^a

run	base	catalyst	solvent	<i>t</i> (h)	conversion (%)	yields ^b (%)	<i>E/Z</i> ratio ^b
1	NaHCO ₃	1	TBAB	7	100	97	59:41
2	K ₃ PO ₄	1	TBAB	4	75	95	61:39
3	Sparteine	1	TBAB	3	95	96	60:40
4	DABCO	1	TBAB	5	85	95	62:38
5	Na ₂ CO ₃	1	TBAB	9	74	95	59:41
6	Bu ₃ N	1	TBAB	8	94	96	60:40
7	NaOAc	1	TBAB	8	92	97	64:36
8	NaHCO ₃	1	[bmim] Br	24	22	94	65:35
9	NaHCO ₃	Pd(OAc) ₂ /PPh ₃	TBAB	15	100	95	58:42

^a Reaction conditions: TBAB (3 g), haloarene (5.68 mmol), cinnamate (5.68 mmol), catalyst (1.5 mol %), *T* = 130 °C. ^b Determined by GLC.

Under these conditions, **1** also efficiently catalyzed the reaction of *trans*-cinnamic esters with aryl bromides and chlorides.²² A procedure employing the catalyst **1** (1.5%), sodium formate (3%) as reducing agent, and sodium bicarbonate as base in TBAB at 130 °C was very effective in coupling *trans*-cinnamates with both electron-rich and electron-poor aryl halides. The stability of this catalyst makes the recycling process feasible. Indeed, in only 3 g of TBAB, after three cycles, 8 g of bromobenzene was processed with a total TON of around 1720, thus making the whole process economically viable. However, in every case the coupling process was devoid of stereoselectivity. This finding is of considerable interest since the generally accepted mechanism for the Heck arylation of disubstituted alkenes predicts that the trisubstituted alkenes should be formed in a stereospecific manner. This lack of stereoselectivity may be explained either as base-catalyzed isomerization of products leading to the accumulation of the more thermodynamically favorable isomer¹⁴ or by readdition of PdH to the reaction products if the hydride is not scavenged fast by base. This latter process is well-known as it leads to the isomerization of alkenes, which results in the formation of isomeric Heck products with the wrong stereochemistry.^{23–25} Recently, palladium nanoparticles of different origin have been utilized in the Heck arylation of unsubstituted acrylates^{26–34} and styrene with variable degrees of success,

but, to our knowledge, none of these catalysts were applied to a stereoselective synthesis of trisubstituted olefins.

This paper reports that Pd nanoparticles, in TBAB as solvent, are very efficient in controlling the stereospecificity in the reaction of *trans*-cinnamates with aryl halides.

Results

Since it was known^{12,14,16,26} that a subtle difference in basicity of bases can have a dramatic effect on regio- and stereoselectivity in the arylation of disubstituted olefins, we first examined the influence of bases on the reaction between 4-bromotoluene and *trans*-ethyl cinnamate catalyzed by **1** in TBAB or butylmethylimidazolium bromide, [bmim]Br, as solvents. The results are reported in Table 1.

The reaction rate or stereoselectivity depends on the choice of bases and solvents, with [bmim]Br being much less efficient than TBAB (run 8). As previously reported,²² however, whatever the base, these reactions were devoid of stereoselectivity. The utilization of Pd(OAc)₂ and triphenyl phosphane as catalyst in place of **1** (run 9) did not increase the rate and stereoselectivity. In this solvent, the addition of inorganic or organic bases to either stereoisomers to verify postreaction isomerization of products did not change the *E/Z* ratio. This was verified by heating at 130 °C one stereoisomer, dissolved in TBAB, in the presence of **1** and base. Therefore, these results can be explained either by the Curtin–Hammett kinetic control principle,³⁵ the *E*- and *Z*-isomers ratio reflecting the relative energy of the respective transition states, or by PdH isomerization of postreaction products. The latter assumption implies that, if bases are not able to neutralize rapidly the PdH, isomerization of the reaction products to a thermodynamically controlled mixture of isomers should occur. Since the addition of amines or sodium acetate and other inorganic bases, the

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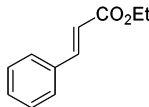
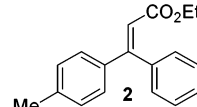
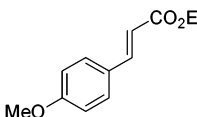
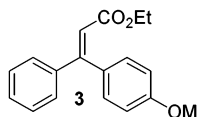
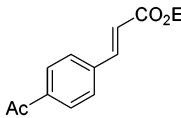
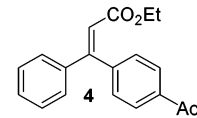
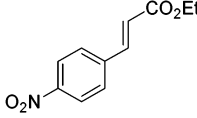
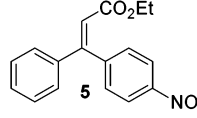
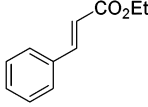
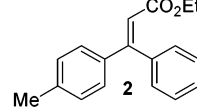
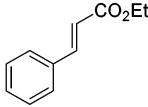
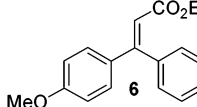
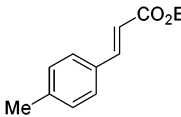
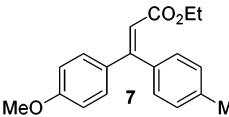
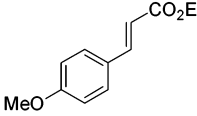
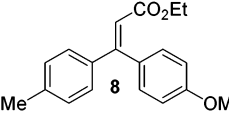
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TABLE 2. Arylation of *trans*-Cinnamates in TBAB Catalyzed by Pd Nanoparticles^a

Run	Cinnamate	Aryl bromide	Product	[TBAA] ^b	Source of Pd nanopart.	t (h)	Yields (%) ^c	E/Z ratio ^d
1		4-MeC ₆ H ₄		1	1	4.2	90	98 : 2
2	“ ”	“ ”	“ ”	2.5	1	3.8	95	>99 : 1
3		C ₆ H ₅		1	1	5.5	86	12 : 88
4		C ₆ H ₅		1.5	1	4.8	95	<1 : 99
5		C ₆ H ₅		1.5	1	4.5	95	12 : 88
6		4-MeC ₆ H ₄		2.5	Pd(OAc) ₂	1	95	>99 : 1
7	“ ”	“ ”	“ ”	0.05 ^e	Pd(OAc) ₂	5.8	85	60 : 40
8	“ ”	“ ”	“ ”	2.5 ^f	Pd(OAc) ₂	3	50	>99 : 1
9		4-MeOC ₆ H ₄		2.5	1	4	95	>99 : 1
10		4-MeOC ₆ H ₄		2	Pd(OAc) ₂	11	86 ^g	>99 : 1
11		4-MeC ₆ H ₄		2	Pd(OAc) ₂	15	82 ^g	<1 : 99

^a Reaction conditions: TBAB (3 g), haloarene (5.68 mmol), cinnamate (5.68 mmol), source of palladium (1.5 mol % of Pd), $T = 130\text{ }^{\circ}\text{C}$.
^b Equivalents of TBAA with respect to substrates. ^c Determined by GLC. ^d Determined by GLC. ^e NaHCO₃ (2.5 equiv) as base. ^f TBAA used both as base and solvent (conversion 60%). ^g Isolated yields.

latter being almost insoluble in TBAB, did not improve the stereoselectivity of this reaction (run 7), we added tetrabutylammonium acetate (TBAA) as base, which proved to be very soluble in TBAB. The red color of the solution faded rapidly to give, in addition to a dark

suspension, a contemporary increase of both reaction rate and stereoselectivity as well the decomposition of the catalyst **1** (Table 2, run 1). The TBAA effect on the stability of **1** was verified by adding an excess of TBAA to **1** dissolved in TBAB at $130\text{ }^{\circ}\text{C}$. In addition to the

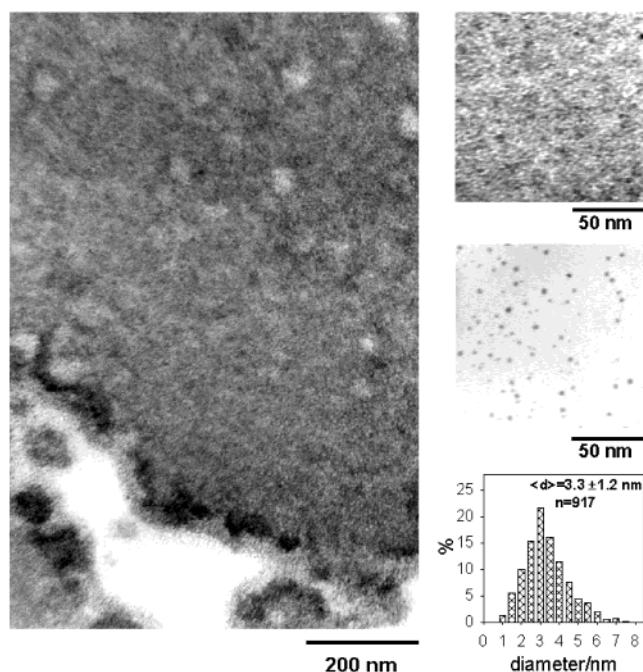
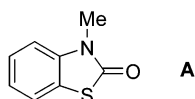


FIGURE 2. TEM image (left) of a typical sample of a Pd colloid formed in the reaction of **1** with TBAA. The size distribution of the nanoparticles (right) appears unsymmetrical because the TEM instrument does not detect particles smaller than 1 nm. Left image (bottom): high magnification view of the typical morphologies observed for the nanocolloids embedded in tetraalkylammonium salt.

formation of a black suspension, we isolated 2-oxo-3-methylbenzothiazole **A** arising from deligation of the benzothiazolyldiene ligands in **1**.



A reaction sample, deposited on carbon film coated TEM grids, revealed the presence of Pd nanoparticles 2–6 nm in size (Figure 2). As Reetz et al.³⁶ found that, by heating a Pd salt in THF and in the presence of tetraalkylammonium alkanoates, Pd nanoparticles were formed, we replaced **1** with Pd(OAc)₂ dissolved in TBAB followed by the addition of TBAA.

These conditions did afford more rapidly a dark suspension of nanoparticles, which proved to be even more catalytically active, allowing the stereospecific preparation of either (*Z*)- or (*E*)- β,β -diarylacrylates (Table 2). For example, under these conditions, 4-bromotoluene reacted with *trans*-ethyl cinnamate in only 1 h with complete stereospecificity (run 6).

By using nanoparticles prepared starting from **1** or Pd(OAc)₂, we observed that the stereoselectivity of the coupling process increased with the amount of TBAA. As an example, by adding to 1.5% of Pd(OAc)₂ only 5% of TBAA to prepare these nanoparticles, and by using sodium bicarbonate as base, the stereoselectivity dramatically decreased (run 7). In addition to the observed stereoselectivity, in this reaction, the use of TBAA as base

can overcome the drawback commonly found in the Heck reaction, namely the gradual catalyst deactivation due to an increase of inorganic salts or ammonium halides concentrations deriving from PdH neutralization by inorganic or organic bases as tertiary amines.^{32,37} Indeed, the neutralization of PdH by TBAA gives, in addition to acetic acid, tetrabutylammonium cation, which behaves as a sequestering agent for the bromide ion.

Discussion

The results obtained in TBAB were consistently higher than those obtained by us²⁰ with the same catalyst or by Herrmann et al.^{38,39} in coupling styrene and unsubstituted acrylates with aryl bromides in DMA or DMF solvents. However, despite the observed beneficial effects exerted by quaternary ammonium salts on the Heck reaction,⁴⁰ the exact nature of this influence cannot be ascribed to a single effect such as the high polarity or phase-transfer ability, but rather to a superposition of several factors. For example, Reetz et al.³⁶ found that Pd nanocolloids were stabilized by large ammonium cations. Furthermore, Neghishi et al.⁴¹ and Amatore and Jutand³ demonstrated that Pd(0)(PPh₃)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 such as [Pd(PPh₃)₂X]⁻. To explain the ionic liquid effects, we propose some considerations that could explain our results. The reaction of aryl halides with Pd nanoparticles would afford an unstable 12-electron complex ArPdX, which could be stabilized by interaction with TBAB or TBAA to give an anionic and more stable 16-electron complex [ArPdX₃]²⁻ 2NR₄⁺ (X = Br⁻ and/or AcO⁻). This would not be surprising, since in these solvents the anions, being poorly solvated, should be good nucleophiles for palladium. Furthermore, the ammonium cation could assist electrostatically the polarization or decomplexation of the bromide ion from this anionic Pd(II) complex and this would render the Pd(II) complex more electrophilic for a fast olefin insertion. Evidence supporting this assumption was given by the low reaction rates and stability of nanoparticles in [bmim]Br as solvent. Probably, the bulkiness of the tetrahedral ammonium ion, by forcing the bromide or acetate anions away from the cation, renders these anions more nucleophilic than the planar [bmim]⁺ can. Indeed, the planar structure of [bmim]Br, by binding the bromide ion tightly,⁴² would decrease its availability for the formation of a stable 16-electrons complex, [ArPdX₃]²⁻ 2NR₄⁺. This stabilizing effect was exerted by the bromide as well as by acetate ions which are likely to enter the coordination shell of Pd.^{3,43} The observed stereoselectivity in the

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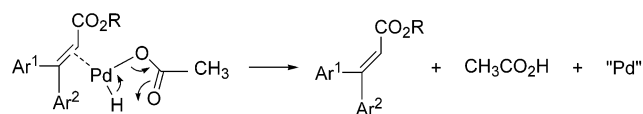
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SCHEME 2



presence of nanoparticles cannot be ascribed only to a better solubility of TBAA in TBAB since other soluble bases such as amines did not increase the stereospecificity of the process (Table 1, runs 3, 4, and 6). We believe that acetate anions might participate in a fast elimination step of PdH. Moreover, we observed that, whereas a fast neutralization of PdH, which inhibits the isomerization of the reaction products, required the presence of TBAA, the reaction rates were influenced by the mixture of these two ionic liquids. Indeed, the reaction performed in TBAA as solvent and base, though stereospecific, occurred with lower reaction rate (Table 2, run 8). Besides the stabilizing effect of Pd nanoparticles by these ionic liquids, we believe that the observed stereospecificity could be explained by an intramolecular neutralization of PdH, still ligated to the olefin, by an acetate ion⁴³ in the metal coordination shell through a five-membered transition state as depicted in Scheme 2.

(43) Evidence for ligation of acetate ion to Pd(0) and Pd(II) intermediates was reported: Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605–5614.

The absence of acetate in the coordination shell would allow the PdH isomerization leading to a thermodynamic mixture of isomeric olefins. The same behavior was observed by us for Heck reactions of 1,1-disubstituted olefins and this will be reported in due course. However, whatever the real effect of TBAA may be,⁴⁴ it remains that both the ionic liquids play an important role in determining the reaction rate and stereospecificity of this C–C coupling process.

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Supporting Information Available: Experimental procedures for arylations of cinnamates with Pd nanoparticles in TBAB melts, and physical and spectral data for compounds **7**, **8**, and **A**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(44) Early blackening of the reaction mixture, upon addition of TBAA, indicated the in situ reduction to palladium(0) with catalytic activity greater than Pd on carbon.⁹ By nature our studies do not address the question of whether the observed 1.5–6 nm sized Pd colloids are the actual catalysts, or whether they function as a "reservoir" or "donor" of smaller and probably more reactive fragments.

(45) Calò, V.; Lopez, L.; Marchese, L.; Pesce, G. *J. Chem. Soc., Chem. Commun.* **1975**, 621–622.