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

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Received December 19, 2002

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. 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. Quaternary ammonium salts, pyridinium, and imidazolium salts 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 arylation of 1,1- and 1,2-halides, mainly iodides, to increase yields and reaction rates. Relatively few Heck arylation of 1,1- and 1,2-disubstituted alkenes have been reported.

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 reported 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 hydrogen carbonate as base.

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, the development of an efficient and stereoselective synthetic method for these compounds would be of significant utility (Scheme 1).

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lates, palladium nanoparticles of different origin have been isomerized or by readdition of PdH to the reaction products. The cumulation of the more thermodynamically favorable isomer14 or by isomerization of postreaction products. This latter assumption implies that, if bases are not able to neutralize rapidly the PdH, isomerization of the 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–Hammet 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 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 triphenylphosphine 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, 1, L = OAc or PPh3.

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 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 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 known24,16,26 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.

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### Table 1. Base Effect on the Reaction of 4-Bromotoluene with trans-Ethyl Cinnamate

| run | base          | catalyst | solvent | t (h) | conversion (%) | yields (%) | E/Z ratio |
|-----|---------------|----------|---------|-------|---------------|------------|-----------|
| 1   | NaHCO₃        | 1        | TBAB    | 7     | 100           | 97         | 59:41     |
| 2   | K₃PO₄        | 1        | TBAB    | 4     | 75            | 95         | 61:39     |
| 3   | Spartein      | 1        | TBAB    | 3     | 95            | 96         | 60:40     |
| 4   | DABCO        | 1        | TBAB    | 5     | 85            | 95         | 62:38     |
| 5   | Na₂CO₃       | 1        | TBAB    | 9     | 74            | 95         | 59:41     |
| 6   | BuNa         | 1        | TBAB    | 8     | 94            | 96         | 60:40     |
| 7   | NaOAc        | 1        | TBAB    | 8     | 92            | 97         | 64:36     |
| 8   | NaHCO₃       | 1        | [bmim] Br | 24   | 22            | 94         | 65:35     |
| 9   | NaHCO₃       | 1        | TBAB    | 15    | 100           | 95         | 58:42     |

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

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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
Table 2. Arylation of trans-Cinnamates in TBAB Catalyzed by Pd Nanoparticles

| Run | Cinnamate | Aryl bromide | Product | [TBAA] | Source of Pd nanopart. | t (h) | Yields (%) | E/Z ratio |
|-----|-----------|--------------|---------|--------|-----------------------|------|------------|-----------|
| 1   |           | 4-MeC₆H₄    | 2       | 1      | 4.2                   | 90   | 98 : 2     |
| 2   |           | *           | *       | 2.5    | 3.8                   | 95   | >99 : 1    |
| 3   | MeO       | C₆H₅        | 3       | 1      | 5.5                   | 86   | 12 : 88    |
| 4   | Ac        | C₆H₅        | 4       | 1.5    | 4.8                   | 95   | <1 : 99    |
| 5   | O₂N       | C₆H₅        | 5       | 1.5    | 4.5                   | 95   | 12 : 88    |
| 6   |           | 4-MeC₆H₄    | 2       | 2.5    | Pd(OAc)₂              | 1    | 95         | >99 : 1   |
| 7   |           | *           | *       | 0.05   | Pd(OAc)₂              | 5.8  | 85         | 60 : 40   |
| 8   |           | *           | *       | 2.5    | Pd(OAc)₂              | 3    | 50         | >99 : 1   |
| 9   |           | 4-MeOC₆H₄   | 6       | 2.5    | 4                     | 95   | >99 : 1    |
| 10  | MeO       | 4-MeOC₆H₄   | 7       | 2      | 11                    | 86   | >99 : 1    |
| 11  | MeO       |           |         | 2      | 15                    | 82   | <1 : 99    |

* Reaction conditions: TBAB (3 g), haloarene (5.68 mmol), cinnamate (5.68 mmol), source of palladium (1.5 mol % of Pd), T = 130 °C.
* Equivalents of TBAA with respect to substrates. * Determined by GLC. * Determined by GLC. * NaHCO₃ (2.5 equiv) as base. * TBAA used both as base and solvent (conversion 60%). * Isolated yields.

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formed, we replaced tetralkylammonium alkanoates, Pd nanoparticles were by heating a Pd salt in THF and in the presence of (OAc)₂, we observed that the stereoselectivity of the complete stereospecificity (run 6). In addition to the observed stereoselectivity, in this reaction, the use of TBAA as base matically decreased (run 7). In addition to the observed stereoselectivity, the use 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. 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.³⁶,³⁸ 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 in the Heck reaction, 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, Negishi et al.⁴¹ and Amatore and Jutand³ demonstrated that Pd(0)[PPh₃]₂Br, 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 [ArPdX]⁺⁻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 tetrahydro ammonium ion, by forcing the bromide or acetate anions away from the cation, renders these anions more nucleophilic than the planar [bmim]⁺ ion. Indeed, the planar structure of [bmim]Br, by binding the bromide ion tightly,² would decrease its availability for the formation of a stable 16-electrons complex, [ArPdX]⁺⁻2NR₄⁺. This stabilizing effect was exerted by the bromide as well as by acetate ions which are likely to enter the coordination sphere of Pd.³⁴ The observed stereoselectivity in the formation of a black suspension, we isolated 2-oxo-3-methylbenzothiazole A arising from deligation of the benzothiazolylidene ligands in 1.

![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.](image)

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 tetralkylammonium 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 stereoselectivity (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...
The 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 stereoselectivity 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 stereoselectivity could be explained by an intramolecular neutralization of PdH, still ligated to the olefin, by an acetate ion in the metal coordination shell through a five-membered transition state as depicted in Scheme 2.

Acknowledgment. This work was financially supported by Ministero dell’Università e della Ricerca Scientifica e Tecnologica, Rome and the University of Bari (National Project: “Stereoselezione in Sintesi Organica: “Metodologie ed Applicazioni”).

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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