Articles

Pd Nanoparticle Catalyzed Heck Arylation of 1,1-Disubstituted Alkenes in Ionic Liquids. Study on Factors Affecting the Regioselectivity of the Coupling Process

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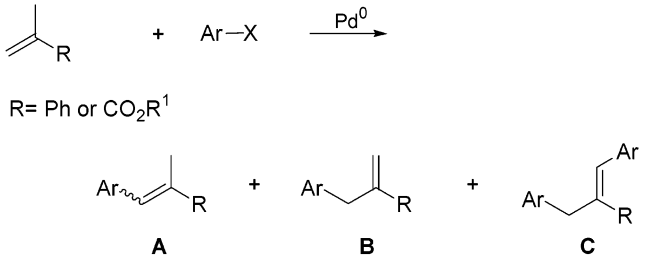
The Heck reaction of neutral or electron-rich aryl bromides with the 1,1-disubstituted olefins butyl methacrylate and α-methylstyrene catalyzed by Pd nanoparticles in tetrabutylammonium bromide as solvent and tetrabutylammonium acetate as base leads to a prevalent formation of the terminal olefin. In contrast, reaction of *p*-bromoacetophenone leads to the internal olefin. Whereas the solvent stabilizes the metal nanoclusters, the base is responsible for a fast neutralization of the PdH impeding the hydride readdition to reaction products and avoiding the olefin interconversion. The terminal olefins are efficiently converted into the more stable internal *E* isomers by using tetrabutylammonium pivalate as catalyst.

The Heck reaction and related chemistry occupy a special place among basic types of palladium-catalyzed reactions.[1−3] In this context relatively few Heck arylations of 1,1- and 1,2-disubstituted alkenes have been reported.[4−12] In the arylation of 1,1-disubstituted olefins as methacrylates and α-methylstyrene there are two possible pathways, one leading to the 1,1-disubstituted terminal olefin **B**, which is susceptible to further arylation to **C**, and another that leads to the internal regioisomer **A**, for which there is an *E*/*Z* stereochemical issue (Scheme 1).

Scheme 1



In this case, the ratio found for the two regioisomeric olefins could be explained either by the Curtin−Hammett kinetic control principle,[13] the terminal and internal isomer ratio reflecting the relative energy of the respective transition states, or by base-catalyzed isomerization of products leading to the accumulation of the

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more thermodynamically favorable internal isomer[8,10,11] as well as by readdition of PdH to the reaction products[2c] if the base does not neutralize the hydride very quickly. 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 regio- and stereochemistry.[14−18] As Heck reactions of aryl halides with methacrylates and α-methylstyrene lead to medicinally interesting products,[19] the search in controlling the regiochemistry of this process was targeted by some authors. Beller[6] reported that, in the Heck arylation of these olefins, catalyzed by Herrmann's palladacycle,[20] the control of the regioselectivity depended on the choice of the base. Inorganic bases as sodium acetate led to the formation of a mixture of the two regioisomers, whereas the internal olefin was favored by organic bases represented by sterically hindered tertiary amines. Good regioisomeric control with these amines was also found by Buchwald et al.[8] and Fu et al.,[11] though with different Pd catalysts. In contrast, Jensen et al.[9] reported that in these reactions, catalyzed by a phosphinito Pd complex in DMF at 180 °C, both inorganic and organic bases were equally effective in giving the internal olefin. From these data it is difficult to see which of the two regioisomers is the kinetically favored one or whether, in contrast, the observed ratio between the two olefins is due to PdH equilibration and/or to base-catalyzed isomerization of the reaction products.

Recently, palladium nanoparticles of different origin have been utilized in the Heck arylation of unsubstituted acrylates[21−30] and styrene with variable degrees of success, but to our knowledge none of these catalysts was applied to a selective synthesis of 1,1-disubstituted and trisubstituted olefins. In this context, we[31] and Cacchi[12] reported the Pd nanoparticle catalyzed stereospecific Heck arylation of cinnamates in the ionic liquid[32] tetrabutylammonium bromide (TBAB) and by using tetrabutylammonium acetate (TBAA) as base. We justified the control of the stereoselectivity in this case as due to a very fast neutralization of PdH by this base.

This paper reports the influence exerted on the regiochemistry by TBAA as base and TBAB as solvent in the arylation, catalyzed by palladium nanoparticles, of butyl methacrylate and α-methylstyrene.

Results

Arylation of Butyl Methacrylate. A suspension of Pd nanoparticles (1.5%, 1.5−6 nm size), prepared as previously reported,[31,33] catalyzes with high rate, generally less than 15 min, at 120 °C in TBAB as solvent and an excess of TBAA as base, the reaction of aryl bromides with butyl methacrylate. Under these conditions (Table 1), in the reaction of bromobenzene, a sample taken at low conversion value (1 min, entry 1) reveals a ratio of 74:26 in favor of the terminal isomer and no double-arylated product. Furthermore, until the conclusion of the coupling process (6 min), the quantity of the internal isomer remains almost constant, whereas that of the terminal isomer decreases in favor of the double-arylated product (entry 2). After the entire conversion of bromobenzene, catalyzed by TBAA, a gradual isomerization of the terminal isomer into the internal one occurs (entry 3). Similar results (entry 4) are observed when TBAA is used both as base and solvent. A reaction performed using 0.5 equiv of methacrylate/mmol of bromobenzene (entry 5) affords prevalently the bis-arylated product, suggesting that the bis-arylation of the terminal olefin is a faster process than the isomerization into the internal isomer. Almost the same ratio reported in entry 2 is observed in the reaction of *p*-bromotoluene, *p*-bromoanisole, and iodobenzene (entries 6−8).

In contrast, *p*-bromoacetophenone (entry 9) reacted to give almost exclusively the internal isomer with complete conversion in less than 15 min and without the double-arylated product. To explain this differing regiochemical course, the reaction was repeated with 0.1% of the catalyst to decrease the reaction rate and the isomeric ratio was monitored at low conversion

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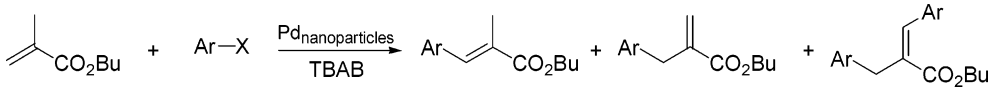
Table 1. Pd Nanoparticle Catalyzed Heck Arylation of *n*-Butyl Methacrylate in TBAB as Solvent[a]



entry	Ar−X	base	*t* (min)	conversn of aryl halide (%)[b]	amt (%) terminal olefin[c]	amt (%) internal olefin[c]	amt (%) double arylated[c]
1	C_6H_5Br	TBAA	1	10	74	26	
2	C_6H_5Br	TBAA	6	>99	65	26	9
3	C_6H_5Br	TBAA	30	>99	46	45	9
4[d]	C_6H_5Br	TBAA	15	>99	66	23	11
5[e]	C_6H_5Br	TBAA	15	>99	8	24	68
6	4-$CH_3C_6H_4Br$	TBAA	15	>99	59	30	11
7	4-$CH_3OC_6H_4Br$	TBAA	15	>99	63	30	7
8	C_6H_5I	TBAA	5	>99	61	26	13
9	4-$CH_3COC_6H_4Br$	TBAA	15	>99	4	96	
10	4-$CH_3COC_6H_4Br$	TBAA	1	45	28	72	
11[f]	C_6H_5Br	TBAP	15	59	36	64	
12	C_6H_5Br	NaOAc	60	>99	44	49	7
13	C_6H_5Br	Bu_3N	60	>99	15	80	5
14[g]	C_6H_5Br	TBAA	18 h		n.r.		

[a] Reaction conditions: 3 mmol of aryl halide with 15 mmol of butyl methacrylate in the presence of 8 mmol of base and 1.5 mol % of $Pd(OAc)_2$ in 3 g of TBAB; $T = 120$ °C. [b] Conversion of aryl halide determined by GLC (internal standard diethylene glycol dibutyl ether). [c] Determined by GLC. The quantity of the *Z* isomer is generally less than 3%. [d] Using TBAA as base and solvent. [e] With 0.5 equiv of methacrylate. [f] With tetrabutylammonium pivalate (8 mmol) as base. After 2 h the conversion reached completion with a ratio of 82:18 in favor of the internal olefin. [g] [bmim]Br as solvent.

values. In a sample taken after 1 min (entry 10), 28% of terminal olefin was detected, but after only 4 min it was almost completely converted into the internal isomer.[34] In the reaction of bromobenzene, the replacement of TBAA with tetrabutylammonium pivalate as base gave (entry 11), in contrast, a major selectivity in favor of the internal isomer. As far as TBAB is concerned, it does contribute to the stabilization of Pd nanoparticles[25,30,31] but it is not responsible for the regiochemical results. Indeed, the replacement of TBAA with organic bases or sodium acetate, the latter being sparingly soluble in TBAB (entries 12 and 13), leads to the reaction of bromobenzene to almost the same isomeric ratio observed by Beller[6] in organic solvents. As previously found[31] in the arylation of cinnamates, no Heck reaction of methacrylates is observed in butylmethylimidazolium bromide (bmim) Br as solvent (entry 14).

The isomerization of the reaction products indicates that, beside a fast PdH neutralization, the TBAA does isomerize, albeit with slower rate, the two regioisomeric olefins. More isomerization was observed by replacing TBAA with tetrabutylammonium pivalate (TBAP) as base. A mixture of the two isomeric olefins, derived from the reaction of bromobenzene and containing 68% of the terminal isomer **1**, dissolved in TBAB and in the presence of TBAA gradually isomerizes, favoring the internal isomer **2** (Figure 1). As a fast and complete isomerization to the internal olefins may be of synthetic value,[19] we replaced the TBAA with TBAP (1.5 mmol) as base. The latter does catalyze more efficiently than TBAA the isomerization (Figure 1) and in only 4 h converted the terminal regioisomer almost completely into the internal *E* olefin.

Arylation of α-Methylstyrene. An almost parallel situation was observed in the Pd-catalyzed arylation of α-methylstyrene, albeit with reaction rates slower than those observed for methacrylate. Furthermore, these reactions occurred with less stereochemical control (Table 2). The reaction of bromobenzene with an excess of alkene requires 45 min to reach a whole conversion. In this reaction, a sample taken after 4 min (entry 1) reveals (GLC) a ratio of 73:27 in favor of the terminal isomer and no double-arylated product. Until the entire conversion of bromobenzene, the quantity of the internal isomer remains almost constant, whereas that of the terminal isomer principally decreases in favor of the double-arylated product. When the reaction goes to completion, the final solution contains 57%, 28%, 3%, and 12% of the terminal, internal trans, internal cis, and double-arylated olefins, respectively (entry 2). At this point the residual TBAA does catalyze a slow increase of both stereoisomers of the internal olefin. The replacement of TBAA with TBAP (entry 3) favors the internal isomer with an *E*:*Z* ratio of 4.4:1 and no diarylated product. *p*-Bromotoluene (entry 4) behaves similarly with a ratio slightly less favorable for the terminal olefin. The reaction of *p*-bromoacetophenone occurs with both less regioselectivity and less stereoselectivity with respect to that observed for methacrylate (entry 5). Whereas the different ratio may be due to a slower isomerization rate of the two regioisomers by TBAA, the increase of the *Z* isomer could arise plausibly from the acidity of the benzylic hydrogen, which favors the *E*/*Z* interconversion. Reaction products deriving from the latter reaction, subjected to isomerization catalyzed by tetrabutylammonium pivalate (entry 6), are almost completely converted into the internal isomers.

A 70:30 mixture of isomeric olefins **3** and **4** deriving from the reaction of bromobenzene, as can be seen in Figure 2, is slowly isomerized by TBAA with a concurrent slight variation in the *E*:*Z* ratio of the internal olefins.

(34) This fast isomerization could be due to the benzylic hydrogen, whose acidity, by favoring a fast isomerization of the terminal isomer, inhibits further arylation into the double-arylated product.

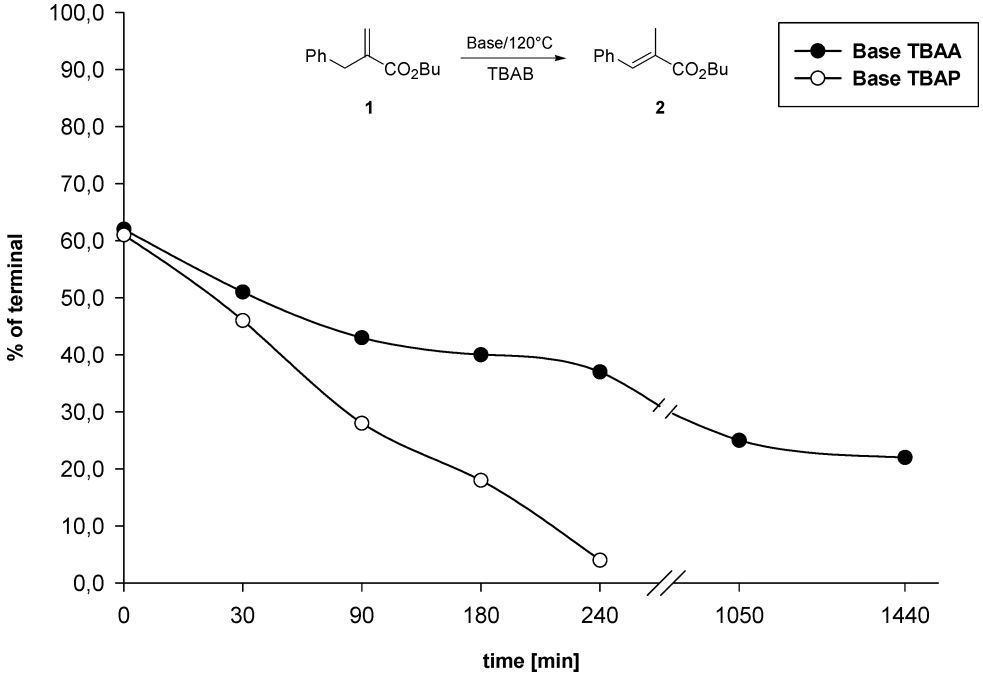
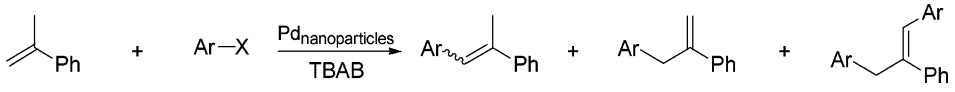


Figure 1. Isomerization of the terminal regioisomer **1** into the internal isomer **2**, catalyzed by TBAA or tetrabutylammonium pivalate (TBAP) in TBAB as solvent.

Table 2. Pd Nanoparticle Catalyzed Heck Arylation of α-Methylstyrene in TBAB as Solvent[a]



entry	Ar−X	*t* (min)	conversn of aryl halide (%)[b]	amt (%) terminal olefin[c]	amt (%) internal olefin[c]	amt (%) double arylated[c]	*E*:*Z*
1	C_6H_5Br	4	5	73	27		30:1
2	C_6H_5Br	45	>99	57	31[d]	12	9.3:1
3[e]	C_6H_5Br	45	>99	25	75		4.4:1
4	4-$CH_3C_6H_4Br$	60	>99	58	34	8	11:1
5	4-$CH_3COC_6H_4Br$	45	>99	36	64		2.6:1
6[f]		360		3	97		2.8:1

[a] Reaction conditions: 3 mmol of haloarene with 12 mmol of butyl methacrylate in the presence of 8 mmol of TBAA and 1.5 mol % of $Pd(OAc)_2$ in 3 g of TBAB; $T = 120$ °C. [b] Conversion of aryl halide determined by GLC (internal standard diethylene glycol dibutyl ether). [c] Determined by GLC. [d] 28 and 3% of *E* and *Z* isomers. [e] TBAP (8 mmol) as base. [f] Isolated mixture of regioisomers (64:36 internal/terminal) deriving from entry 5, heated at 120 °C in TBAB in the presence of tetrabutylammonium pivalate (1.5 mmol).

Discussion

The results reported in Tables 1 and 2 indicate that, for low conversion values, the amount of terminal regioisomer is about 3 times that of the internal isomer. TBAA does exert two effects: (i) it neutralizes very rapidly the PdH species impeding the readdition process responsible for the accumulation of the more thermodynamically stable internal olefin and (ii) it catalyzes also, though with a much lower rate, the 1,3-prototropic rearrangement which leads to the same isomerization process (Figures 1 and 2). This implies that the Heck coupling would be a faster process than a 1,3-prototropic shift. Indeed, the result in entry 5 (Table 1) shows that the further arylation of the terminal isomer leading to **C** (Scheme 1) occurs with higher rate than the isomerization into internal olefin.

The fast neutralization of PdH could be due to an improved basicity of the acetate ion in TBAA. This may be ascribed to the bulkiness of the tetrahedral ammonium ion which, by forcing the acetate away from the cation, should decrease the Coulombic force between the ions, improving both the basicity and the nucleophilicity for palladium of this anion.[35] The latter concept is supported by the better ability of TBAP in isomerizing the regioisomers. Indeed, the pivalate ion, being bulkier than acetate, should be a stronger base. The fast PdH neutralization could be ascribed either to an intermolecular neutralization of PdH, still bound to the olefin,[2c] by an acetate ion or to the same ion as the ligand in the metal coordination shell.[36] Therefore, the 3:1 ratio, measured at low conversion values, indicates that the terminal isomer is the kinetically favored one. This preference for the terminal isomers may be merely statistical, all three hydrogens being equally available for a syn elimination. In contrast, the two hydrogens at internal positions are at least not equal, as the respec-

(35) Surely the pK_a values of acetate and pivalate anions in TBAB cannot be the same as those measured in water. This would not be surprising, since in these solvents the anions, being poorly solvated, should be both good nucleophiles for palladium and stronger bases.

(36) 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. Our data, however, cannot discriminate whether the PdH neutralization by acetate is an intermolecular process or an intramolecular one by acetate ligand in the metal coordination shell.

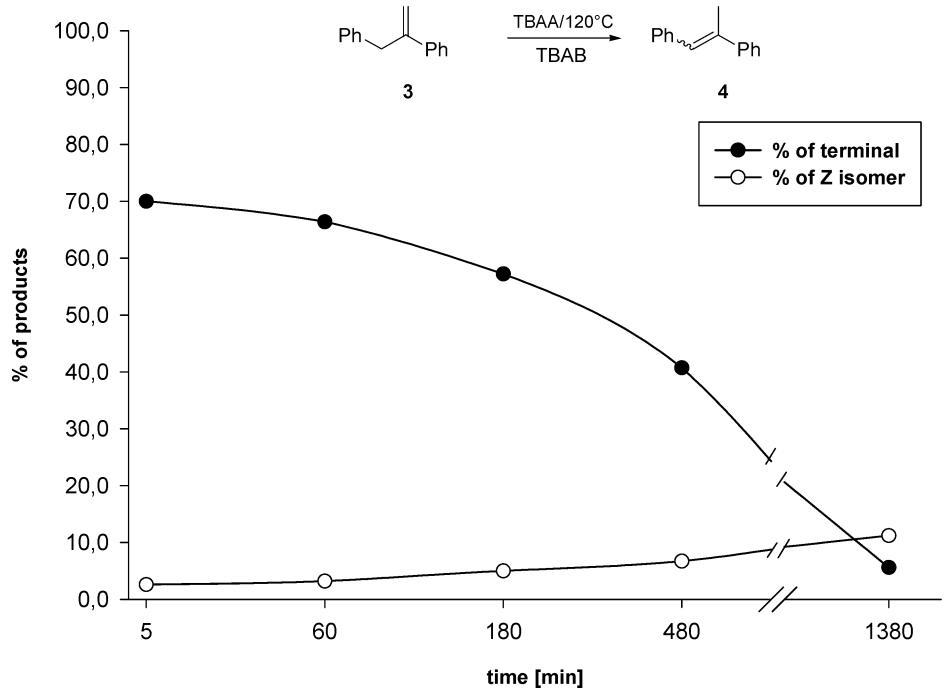
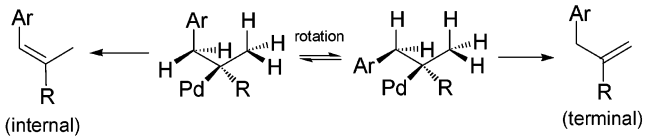


Figure 2. Isomerization of the terminal regioisomer **3** into the internal isomer **4**, catalyzed by TBAA in TBAB as solvent, and variation of the *Z* isomer.

Scheme 2



tive conformations are different in energy due to Pd−Ar, Ar−R, and Ar−Me eclipsing (Scheme 2).[37] Furthermore, the internal hydrogens might be inaccessible for a PdH syn conformation due to the π-bonding secondary interaction of Pd−Ar, which fixes a conformation that cannot lead to internal products.

In addition to the stabilizing effect exerted by the ionic liquid[25,30,31] on the Pd nanoparticles and the control of the regioselectivity in the coupling process, another advantage in using TBAA lies in overcoming the drawback commonly found in the Heck reaction: namely, the gradual catalyst deactivation due to an increase of inorganic salt or ammonium halide concentrations derived from PdH neutralization by inorganic or organic bases as tertiary amines.[27,38] Indeed, the neutralization of PdH by TBAA affords, in addition to acetic acid, tetrabutylammonium cation, which behaves as a sequestering agent for the bromide ion to give tetrabutylammonium bromide.

Conclusions

The Heck reaction of aryl bromides with butyl methacrylate and α-methylstyrene, in the ionic liquid tetrabutylammonium bromide as solvent and in the presence of tetrabutylammonium acetate as base, occurs under kinetic control. The 3:1 ratio found in favor of the terminal olefins may be explained by a fast neutralization of PdH, still bound to the coupled products, by TBAA, which impedes isomerization of the regioisomeric olefins. This implies that the C−C coupling process should be faster than the isomerization. TBAA and, more efficiently, tetrabutylammonium pivalate catalyze the 1,3-prototropic shift between the regioisomeric olefins, favoring a conversion into the thermodynamically more stable internal isomers.

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(37) Due to predominant formation of *E* product from the less sterically hindered conformer, statistical weights of the two routes leading to *E* and *Z* internal olefins are not equal, as the route leading to the *Z* diastereomer can be neglected.

(38) Bouquillon, S.; Ganchegui, B.; Strine, B.; Henin, F.; Muzart, J. *J. Organomet. Chem*. **2001**, *634*, 153−156.