

Pd-Catalyzed Heck Reactions of Aryl Bromides with 1,2-Diarylethenes

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Um sistema catalítico composto por Pd(OAc)₂ e P(*o*-tol)₃ foi aplicado na reação de Heck entre brometos de arila e diariletenos. Utilizando-se K₂CO₃ como base e DMF como solvente, olefinas triarilsustituídas foram obtidas com rendimentos de bons a excelentes. Brometos de arila com substituintes eletroretiradores foram menos ativos para a reação de acoplamento Heck e levaram à formação de produto de homoacoplamento em quantidades substanciais, indicando que a adição oxidativa não deve ser a etapa lenta da reação. A presença de substituintes no diarileteno afetou drasticamente a seletividade da reação. Realizou-se também a dupla arilação do estireno, levando diretamente à olefina triarilsustituída, com rendimento de 73%.

A catalytic system composed of Pd(OAc)₂ and P(*o*-tol)₃ was found to be effective for the Heck reaction of aryl bromides with diarylethylenes. Using K₂CO₃ as a base and DMF as a solvent, trisubstituted olefins were obtained in good to excellent yields. Aryl bromides containing an electron-withdrawing group in *para* position were less reactive for the Heck coupling reaction and gave substantial amount of homocoupling by-product suggesting that oxidative addition is not the rate-determining step. Electron withdrawing group substituent in the *para* position of stilbene affects the regioselectivity of the reaction. In this case, the phenyl group from the Ph-Pd complex migrates preferentially to the same carbon of the double bond to which the phenyl is bonded. Finally, a one pot sequential double Heck arylation of styrene was performed, giving trisubstituted olefin with an overall yield of 73%.

Keywords: Heck reaction, palladium, trisubstituted olefins, double arylation

Introduction

Palladium-catalyzed Heck cross-coupling reactions are one of the most efficient methods for the construction of C–C bonds and have found widespread use in organic synthesis.¹ Most Heck reactions involves arylation of monosubstituted alkenes (especially acrylates and styrene derivatives) to allow synthesis of disubstituted olefins with regio and stereoselective control. In contrast, fewer studies have been conducted on the arylation of disubstituted olefins or double arylation of mono-substituted olefins, to yield trisubstituted products. Stereocontrol during the synthesis of highly substituted double bonds is a significant challenge in organic synthesis,² and the Heck reaction remains an important alternative. In this context, some examples of regio and stereoselective syntheses of trisubstituted α,β -unsaturated compounds, such as nitriles,^{3,4} cinnamates⁵⁻¹⁰ and aldehydes,¹¹ through either

monoarylation of disubstituted olefins or direct diarylation of monosubstituted olefins, have been reported. Arylation of disubstituted alkenes without an electron-withdrawing group conjugated to the C=C double bond (*e.g.*, α - or β -methylstyrene,^{10,12} 1,1-diphenylethene and *trans*-stilbene)¹³⁻¹⁵ has also been investigated. However, to the best of our knowledge, no example using substituted stilbenes has been described. Recently, we reported the Heck arylation of *trans*-stilbene using Pd(OAc)₂/P(*o*-tol)₃ and K₂CO₃ as a base.¹⁶ Using this methodology, we were able to obtain a triarylolefin intermediate for tamoxifen synthesis at 98% of yield with 87% of stereoselectivity for the *Z* isomer. Here we describe the Heck reaction of *trans*-stilbene derivatives and 1,1-diphenylethene with aryl halides in order to obtain substituted triarylethenes. We also report our findings concerning the influence of halide or olefin electro-donating and withdrawing groups on activity, regio and stereoselectivity.

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Experimental

Procedure for Heck reaction coupling of stilbenes and aryl bromides

An oven-dried resealable Schlenk flask was charged with *trans*-stilbene (0.5 mmol), Pd(OAc)₂ (2.2 mg, 0.01 mmol), P(*o*-tol)₃ (6.1 mg, 0.02 mmol), evacuated and black-filled with argon. Then, DMF (3 mL), aryl bromide (0.75 mmol) and K₂CO₃ (138 mg, 1.0 mmol) were added. The reaction mixture was stirred at 130 °C for the desired time. Conversion, regio and diastereoselectivity were determined by the techniques: gas chromatography (GC), gas chromatography-mass spectrometry (GC-MS) and ¹H and ¹³C nuclear magnetic resonance (NMR). Coupling products were compared with authentic standards obtained from Suzuki coupling of *E*-bromostilbenes with aryl boronic acids (triphenylethene and 1-aryl-1,2-diphenylethenes)¹⁷ or from Heck coupling of aryl bromides with 1,1-diphenylethene (1-aryl-2,2-diphenylethenes). The GC yields were obtained using 0.5 mmol of olefin while the isolated yields were obtained using higher scale (1.5 mmol of olefin).

Procedure for competitive Heck reaction coupling of *trans*-stilbene and aryl halides

An oven-dried resealable Schlenk flask was charged with *trans*-stilbene (0.5 mmol), Pd(OAc)₂ (2.2 mg, 0.01 mmol) and P(*o*-tol)₃ (6.1 mg, 0.02 mmol), evacuated and black-filled with argon. Then, DMF (3 mL), two aryl halides (0.25 mmol each) and K₂CO₃ (138 mg, 1.0 mmol) were added. The reaction mixture was stirred at 130 °C for 5 h and conversion, regio and diastereoselectivity were determined by GC and GC-MS analysis.

Procedure for competitive Heck reaction coupling of *trans*-stilbene, 1-nitro-4-styrylbenzene and 1-(4-methoxystyryl)benzene with bromobenzene

An oven-dried resealable Schlenk flask was charged with two olefins (0.25 mmol + 0.25 mmol), Pd(OAc)₂ (2.2 mg, 0.01 mmol), and P(*o*-tol)₃ (6.1 mg, 0.02 mmol), evacuated and black-filled with argon. Then, DMF (3 mL), bromobenzene (0.5 mmol, 78 mg) and K₂CO₃ (138 mg, 1.0 mmol) were added. The reaction mixture was stirred at 130 °C for 5 h and conversion, regio- and diastereoselectivity were determined by GC and GC-MS analysis.

Procedure for competitive Heck reaction coupling of *trans*-stilbene and 1,1-diphenylethene with bromoanisole

An oven-dried resealable Schlenk flask was charged with *trans*-stilbene (0.25 mmol, 45 mg), 1,1-diphenylethene (0.25 mmol, 45 mg), Pd(OAc)₂ (2.2 mg, 0.01 mmol), and

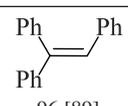
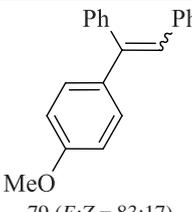
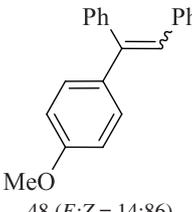
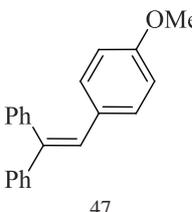
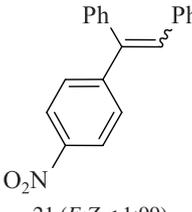
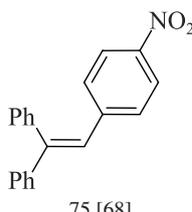
P(*o*-tol)₃ (6.1 mg, 0.02 mmol), evacuated and black-filled with argon. Then, DMF (3 mL), bromoanisole (0.5 mmol, 94 mg) and K₂CO₃ (138 mg, 1.0 mmol) were added. The reaction mixture was stirred at 130 °C for 5 h and conversion, regio- and diastereoselectivity were determined by GC and GC-MS analysis.

Results and Discussion

Recently, we reported the Heck arylation of *trans*-stilbene to obtain a tamoxifen intermediate.¹⁶ In that report, the catalyst system was composed of Pd(OAc)₂ and P(*o*-tol)₃. Classical bases for the Heck reaction, such as Et₃N or NaOAc, gave only moderate yields and selectivities, and the best results were obtained using K₂CO₃ as a base. Due to high steric demands, coupling of *trans*-stilbene with aryl bromides required higher temperature (130 °C) and reaction time (48 h) than those necessary for coupling with styrene. Using these optimized conditions, triphenylethene was obtained at 89% yield from coupling phenyl bromide and *trans*-stilbene (Table 1, entry 1).

Coupling of 4-bromoanisole with *trans*-stilbene resulted in 1,2-diphenyl-1-(4-methoxyphenyl)ethene at 79% yield with an *E:Z* ratio of 83:17 (Table 1, entry 2). This stereoselectivity is higher than previously reported for the arylation of *trans*-stilbene with 4-bromoanisole in the presence of 0.2% catalyst [Pd(C₃H₅)Cl]₂ and *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphanylmethyl)cyclopentane (Tedicyp) as the phosphine ligand (75% yield and *E:Z* = 61:39).¹³ It is important to point out that in the presence of phosphine-free nanoparticles, coupling of phenyl chloride with *trans*-stilbene gave only the *E*-isomer.¹⁸ Depending on the experimental conditions, the Heck reaction is believed to use a neutral or cationic (or polar) mechanism.^{19,20} In Scheme 1, a simplified catalytic cycle for the Heck reaction is shown, based on the neutral mechanism proposed by Heck with Pd(OAc)₂ associated with monophosphine ligands as the precursor,^{21,22} and adapted by us for the particular case of *trans*-stilbene derivatives as alkenes. As shown in Scheme 1, stereoselectivity of the Heck reaction is defined by *syn*-elimination. In the case of coupling 4-bromoanisole with *trans*-stilbene (Ar = 4-MeOC₆H₄ and Ar₁ = Ph in Scheme 1), *syn*-elimination leads to a trisubstituted alkene with both phenyl groups of the stilbene derivative on the same side, even though only the *E* stereoisomer is expected. The presence of the *Z* isomer can be explained by a Pd-H catalyzed isomerization process that may be due to (i) isomerization of the starting alkene; (ii) postreaction isomerization of the trisubstituted alkene product; (iii) isomerization of the coordinated alkene to the Pd-H

Table 1. Pd-catalyzed Heck reaction of *trans*-stilbene derivatives with aryl bromides^a

entry	Ar	Ar'	Yield / % ^b
1	Ph	Ph	 96 [89]
2	Ph	4-MeO-C ₆ H ₄	 79 (<i>E</i> : <i>Z</i> = 83:17)
3	4-MeO-C ₆ H ₄	Ph	 48 (<i>E</i> : <i>Z</i> = 14:86)  47
4	4-NO ₂ -C ₆ H ₄	Ph	 21 (<i>E</i> : <i>Z</i> < 1:99)  75 [68]

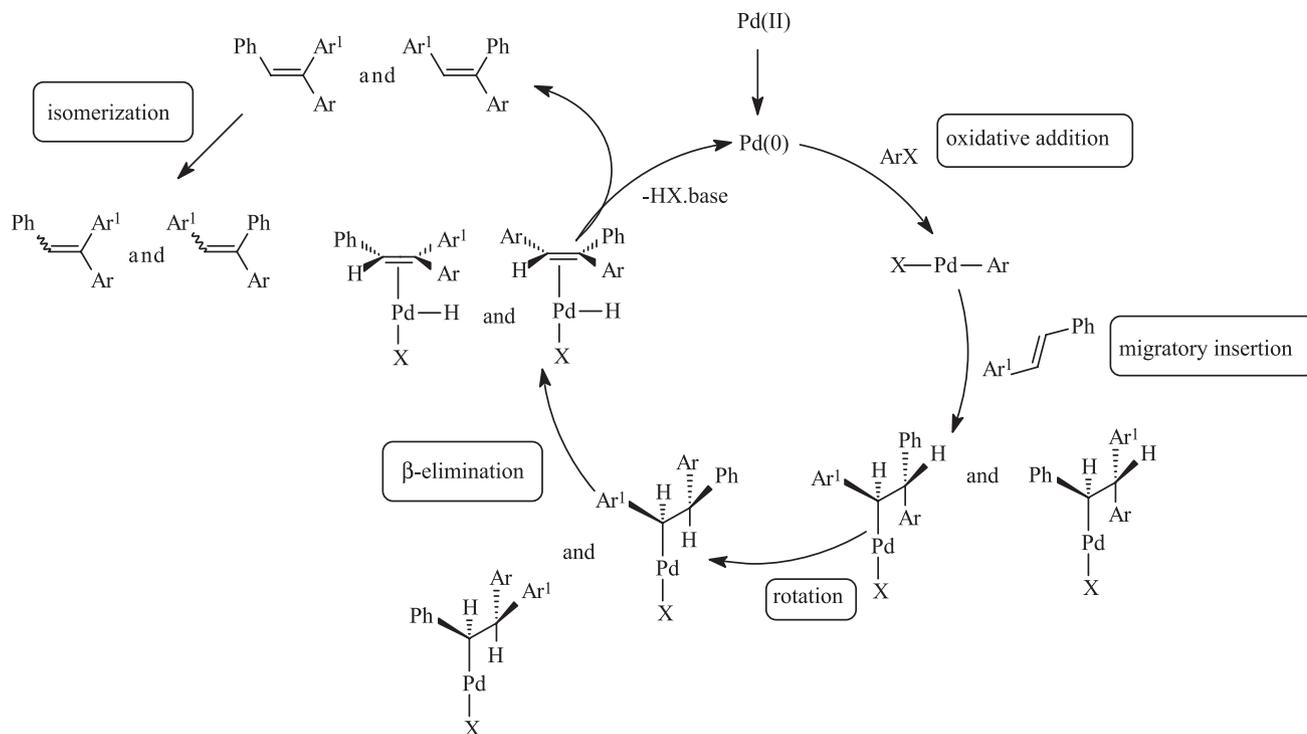
^aReaction conditions for GC analysis: stilbene (0.5 mmol), aryl bromide (0.75 mmol), K₂CO₃ (1 mmol), Pd(OAc)₂ (2 mol %), P(*o*-tol)₃ (4 mol %), DMF (3 mL), 130 °C, 48 h; reaction conditions for isolated yields: stilbene (1.5 mmol), aryl bromide (2.25 mmol), K₂CO₃ (3 mmol), Pd(OAc)₂ (2 mol %), P(*o*-tol)₃ (4 mol %), DMF (9 mL), 130 °C, 48 h; ^byields refer to GC yields (with undecane as an internal standard) and values in square brackets refer to yields of isolated products.

complex before alkene dissociation. Regardless of the isomerization process, an approximately equal mixture of *E* and *Z* isomers is expected if the isomerization reaction is under thermodynamic control.

Next, the coupling of bromobenzene with substituted *trans*-stilbenes was examined (Table 1, entries 3 and 4). When an aryl group different than phenyl is used for coupling with *trans*-stilbene (Ar₁ ≠ Ph in Scheme 1), two *syn* insertion approaches are possible, and, thus, two regioisomers can be formed. No significant effects on regioselectivity in terms of steric effects are expected for substituents at the *para* position. Therefore, assuming the same mechanism for both alkenes, the regioisomer distribution basically depends on the electronic effects of the group present on the *trans*-stilbene derivative. In the case of 4-methoxystilbene, the two regioisomers are obtained at almost the same proportion (Table 1, entry 3), indicating the

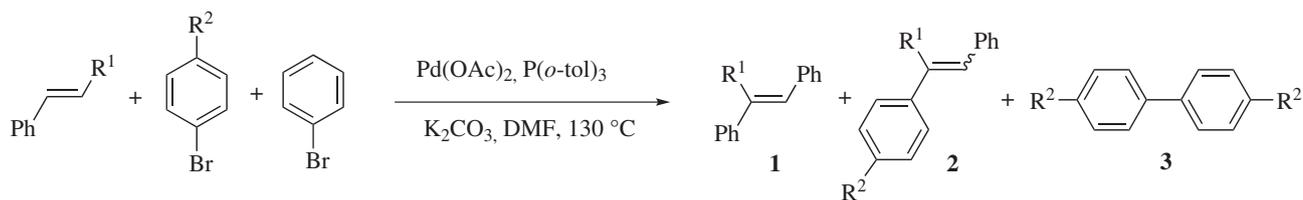
methoxy group had no influence on the olefin insertion step. However, an effect on regioselectivity was observed when *trans*-stilbene containing a strong electron-withdrawing group was used (Table 1, entry 4). In this case, the phenyl group from the Ph-Pd complex migrates preferentially to the same carbon of the double bond to which the phenyl is bonded. This result can be explained by the fact that the major pathway for *syn* insertion is the selective migration of the aryl moiety onto the more charge-deficient carbon of the alkene, which is the β-carbon in the case of an aryl with a nitro group in the *para* position.

In order to evaluate the reactivity of different aryl halides, competition experiments were carried out (Table 2). A mixture of aryl bromide and bromobenzene were subjected to the Heck reaction protocol with *trans*-stilbene and activity was evaluated at low conversions (< 20%), to compare initial rates. Similar reactivity was



Scheme 1. Simplified catalytic cycle for the Heck reaction with *trans*-stilbene derivatives (tri-*o*-tolylphosphine ligands are omitted for clarity).

Table 2. Pd-catalyzed competitive Heck reaction of *trans*-stilbene with different aryl bromides^a



entry	R ¹	R ²	Selectivity 1:2	Selectivity 2:3
1	Ph	OMe	49:51	96:4
2	Ph	COMe	59:41	54:46
3	Ph	CN	69:31	16:84
4	Ph	CF ₃	58:42	39:61
5	H	COMe	34:66	100:0

^aAverage of 2 runs; reaction conditions: stilbene (0.5 mmol), bromobenzene (0.25 mmol), aryl bromide (0.25 mmol), K₂CO₃ (1 mmol), Pd(OAc)₂ (2 mol %), P(*o*-tol)₃ (4 mol %), DMF (3 mL), 130 °C, 5 h, all reactions were performed up to 20% conversion.

observed for coupling *trans*-stilbene with 4-bromoanisole or bromobenzene (Table 2, entry 1). However, the coupling product obtained from the reaction with bromobenzene is preferentially formed over those obtained from aryl bromides containing an electron-withdrawing group (Table 2, entries 2-4). It is worthwhile to mention that when aryl bromides containing an electron-withdrawing group was used, a significant amount of homocoupling product is formed. Oxidative addition has been also postulated as the first step in the catalytic cycle for the homocoupling of aryl halides.²³ Therefore, as expected for the aryl

bromides containing an electron-withdrawing group, the oxidative addition is faster but homocoupling of aryl bromide is the major reaction (Table 2, entries 3 and 4). For purpose of comparison, the competitive reaction of 4-bromoacetophenone with bromobenzene using styrene as olefin partner instead of stilbene was carried out (Table 2, entries 5 and 6). In the presence of styrene, no homocoupling product was observed, and the Heck coupling product obtained from the activated aryl halide was the major product (Table 2, entry 5). These results clearly indicate that oxidative addition is not the rate

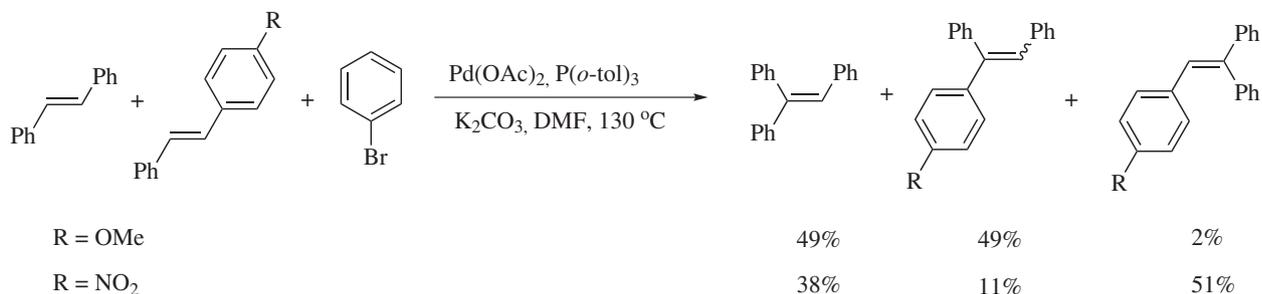
limiting step, which is more likely due to steric effects from the diarylalkene in the coordination and/or migratory insertion steps. In order to confirm this conclusion, the Heck reaction of bromobenzene with iodobenzene was compared. The reaction of the aryl halides with stilbene was carried out separately and analyzed at the same reaction time (6 h). Indeed, bromobenzene gave a two times faster reaction rate for the formation of the Heck coupling product. Again, we were able to confirm the tendency of activated halides to form homocoupling products. For the bromobenzene, the Heck coupling:homocoupling ratio observed was 93:7 and for the iodobenzene was 43:57.

The effect of a substituent group on the stilbene derivative was also evaluated (Scheme 2). A mixture of *trans*-1-aryl-2-phenylethene and *trans*-stilbene was each subjected to the Heck reaction protocol with bromobenzene, and the activity was evaluated at low conversions (< 20%), to compare initial rates. Similar reactivity was observed for coupling bromobenzene with *trans*-4-metoxystilbene or *trans*-stilbene (51:49). However, the coupling product

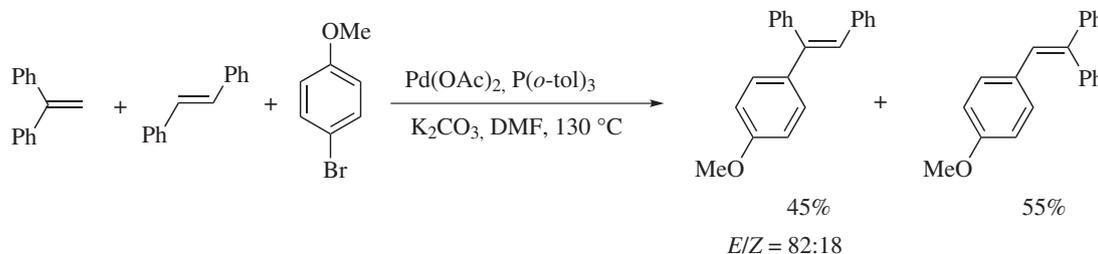
obtained from the reaction, *trans*-1-aryl-2-phenylethene containing a nitro group, is slightly preferred over those obtained from *trans*-stilbene (62:38).

In addition, we compared 1,1- and 1,2-diphenylethene (Scheme 3). A mixture of 1,1-diphenylethene and *trans*-stilbene was each subjected to the Heck reaction protocol with 4-bromoanisole. No significant difference was observed and similar reactivity was obtained for the two olefins, as indicated by the fact that 1,2-diphenyl-1-arylethene and 1,1-diphenyl-2-arylethene were obtained at a ratio of 45:55.

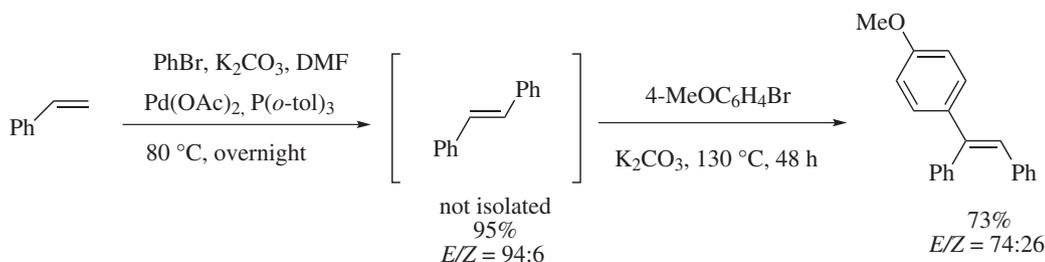
We have recently described a sequential and selective Pd-catalyzed double-Heck arylation of ethylene that results in non-symmetrical nitro-stilbene analogues of *trans*-resveratrol at excellent yields.²⁴ A catalytic system consisting of Pd(OAc)₂ and P(*o*-tol)₃ became possible to carry out two consecutive Heck arylations without losing activity from the first to the second Heck reaction. This approach is also used in the present work to obtain a trisubstituted olefin from styrene in a one pot protocol (Scheme 4). Arylation of styrene was carried out at 80 °C to



Scheme 2. Pd-catalyzed competitive Heck reaction of bromobenzene with different *trans*-stilbene derivatives.



Scheme 3. Pd-catalyzed competitive Heck reaction of 1,1-diphenylethene and stilbene with *p*-bromoanisole.



Scheme 4. Pd-catalyzed Heck double-arylation of styrene.

give the stilbene. After the first Heck arylation, no isolation or additional catalyst loading is required for the second Heck arylation reaction. For the second Heck reaction, the only difference was the addition of 4-bromoanisole and base and the raising of the temperature to 130 °C, resulting in the trisubstituted olefin at 73% yield. Because the stilbene was obtained at an *E:Z* ratio of 94:6, regioselectivity obtained for this trisubstituted olefin (74:26) was lower than that obtained using pure *trans*-stilbene (83:17, Table 1, entry 2). The main by-product obtained was a triphenylethene generated from the coupling of stilbene with unreacted bromobenzene.

Conclusions

In summary, the Heck arylation of diarylethylenes giving triarylolefins with good to excellent yields with a simple Pd(OAc)₂/P(*o*-tol)₃ catalytic system is described. The electron withdrawing group substituent in the *para* position of stilbene affect the regioselectivity of the reaction is also described. In this case, the phenyl group from the Ph-Pd complex migrates preferentially to the same carbon of the double bond to which the phenyl is bonded. Through competitive Heck reactions, it was possible to determine that (i) oxidative addition is not involved in the rate-determining step; and (ii) electron-withdrawing groups in the olefin slightly increase the reaction rate. Finally, a one-pot Heck double arylation of styrene, resulting in 1,2-diphenyl-1-(4-methoxyphenyl)ethene at 73% yield is described.

Supplementary Information

Supplementary data is available free of charge at <http://jbcs.sbc.org.br> as a pdf file.

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