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The synthesis of non-symmetrical stilbene analogs of *trans*-resveratrol using the same Pd catalyst in a sequential double-Heck arylation of ethylene

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We have developed a sequential and selective Pd-catalyzed double-Heck arylation of ethylene that results in non-symmetrical nitro-stilbene analogs of *trans*-resveratrol at excellent yields. A catalytic system consisting of $Pd(OAc)_2$ and $P(o\text{-tolyl})_3$ permitted us to carry out the two consecutive Heck arylations without losing activity from the first to the second Heck reaction. After the first Heck arylation of ethylene, no isolation or additional catalyst loading is required for the second Heck arylation reaction. This protocol was applied to the synthesis of methylated *trans*-resveratrol, which was obtained at a 65% overall yield.

Keywords: Heck reaction; palladium; *trans*-resveratrol; stilbene

Introduction

Hydroxylated stilbenes, such as resveratrol,[1] pterostilbene[2] and pinosylvin[3], are natural compounds that exhibit many biological activities. Resveratrol is a phytoalexin toxin that is produced by plants in response to infection or stress (phytoalexin) and has received considerable attention since Jang and colleagues published a seminal article demonstrating its anti-carcinogenic effects.[4] In addition, resveratrol exhibits anti-inflammatory, antioxidant and platelet antiaggregatory activity, as well as potential benefits to lifespan extension.[5] For these reasons, several analogs of resveratrol have been synthesized and their activities investigated. For example, trimethylated resveratrol was found to be a potent and selective human cytochrome P450 1B1 inhibitor,[6] and it has shown more activity against several human cancer cell lines in comparison to resveratrol.[7] Several synthetic routes based on Wittig-type reactions have been used to prepare resveratrol and its analogs.[6–16] Most of these approaches require relatively long synthetic routes and have variable diastereoselectivities. Therefore, Pd-catalyzed cross-coupling reactions are very effective alternatives due to their synthetic versatility and efficiency.[17] Suzuki reactions between β-halostyrenes and arylboronic acids,[18–20] decarbonylative Heck reactions between resorcylic acid chlorides and styrenes,[21,22] and Heck reactions between aryl halides and styrene derivatives regioselectively furnish the *trans*-stilbene coupling products in one step;[23–32] however, in all of these cases, a styrene derivative substrate is required. Although some styrene derivatives are commercially available, most need to be prepared by elimination reactions, partial alkyne reductions, carbonyl olefination methods or, more recently, via Pd-catalyzed cross-coupling reactions.[33] In addition, styrenes can polymerize under a wide range of conditions, and finding protocols that produce styrene derivatives *in situ* not only overcomes these problems but also simplifies the associated workup and purification procedures. In this context, selective one-pot procedures for the construction of symmetric and non-symmetric *trans*-stilbene derivatives have been reported based on two sequential Heck-type reactions using vinyltrimethylsilane as an ethylene equivalent,[24] along with consecutive palladium-catalyzed Hiyama–Heck reactions starting from vinyltriethoxysilane.[34] Copper-catalyzed methylenation reactions have been used to produce terminal alkenes that can be directly submitted without isolation to further Heck reactions so as to produce stilbene derivatives. The copper catalyst from the first step is a cocatalyst for the subsequent palladium-catalyzed cross-coupling reaction.[29] Ethylene has also been used for the preparation of non-symmetrically substituted stilbenes using a one-pot, two-step double Heck strategy;[35] however, in this protocol, two different Pd catalysts were used for the two Heck reactions. Herein, we wish to present our results on the synthesis of non-symmetrical stilbene analogs of *trans*-resveratrol using the same Pd catalyst in a sequential double-Heck arylation of ethylene.

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Experimental Section

Catalytic reactions that involved ethylene were carried out in a 100 ml stainless steel autoclave. The catalytic reactions that involved the synthesis of stilbenes were carried out under an argon atmosphere in Schlenk tubes. Chemicals were purchased from commercial sources and were used without further purification. 1-iodo-3,5-dinitrobenzene[36] and 1-bromo-3,5-dinitrobenzene[37] were obtained using procedures that have been described in the literature. Elemental analyses were performed by the Analytical Central Service of IQ-UFRGS. NMR spectra were recorded on a Varian XL300 spectrometer. Infrared spectra were acquired on a Varian 640-IR FT-IR. Mass spectra were obtained on a Shimadzu QP-5050 gas chromatograph/mass spectrometer (GC/MS; EI, 70 eV). Gas chromatography (GC) analyses were performed on a Hewlett-Packard-5890 gas chromatograph with a flame ionization detector (FID) and a 30-m capillary column with a dimethylpolysiloxane stationary phase. Tetradecane was used as internal standard and the conversions were calculated based on the consumption of the limited reagent (aryl halide).

General Procedure for the Heck Coupling Reaction of Ethylene with 1-Halo-3,5-dinitrobenzene

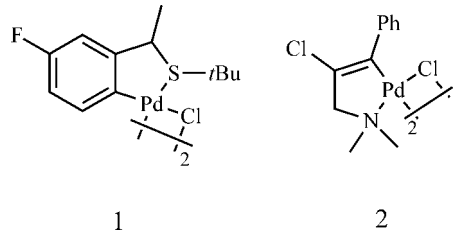
1-Iodo-3,5-dinitrobenzene or 1-bromo-3,5-dinitrobenzene (1 mmol), $Pd(OAc)_2$ (0.01 mmol, 2.24 mg), P(*o*-tol)$_3$ (0.04 mmol, 12.16 mg), NaOAc (1.1 mmol, 90.2 mg) and DMF (10 ml) were added to a 100 ml stainless steel autoclave under argon. The reactor was pressurized with 10 atm of ethylene and the reaction mixture was stirred at 90 °C for the desired time. After cooling and releasing the excess ethylene, the reaction mixture was analyzed by GC and GC-MS. For the isolation of 3,5-dinitrostyrene, the reaction mixture was taken up in ether (30 ml), washed with H_2O, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography so as to produce 3,5-dinitrostyrene as a slightly yellow solid. This compound was characterized by comparing their m.p., ^1H, ^{13}C NMR spectra with those published in the literature.[37]

General Procedure for the Synthesis of Non-symmetrical Stilbenes

3,5-Dinitro-1-iodobenzene or 1-bromo-3,5-dinitrobenzene (1 mmol), $Pd(OAc)_2$ (0.01 mmol, 2.24 mg), P(*o*-tol)$_3$ (0.04 mmol, 12.16 mg), NaOAc (1.1 mmol, 90.2 mg) and DMF (10 ml) were added to a 100 ml stainless steel autoclave under argon. The reactor was pressurized with 10 atm of ethylene and the reaction mixture was stirred at 90 °C for the desired time. After cooling and releasing the excess ethylene, the reaction mixture was transferred under argon to a Schlenk tube. Next, aryl halide (1 mmol) and NaOAc (1.1 mmol, 90.2 mg) were added and the mixture was stirred at 130 °C for 16 h. After cooling to room temperature, the solution was taken up in ether (30 ml), washed with H_2O, dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. The residue was purified by column chromatography or recrystallization so as to produce the corresponding *trans*-stilbene. These known compounds were characterized by comparing their mp, ^1H, ^{13}C NMR spectra with those published in the literature.[6,38–40]

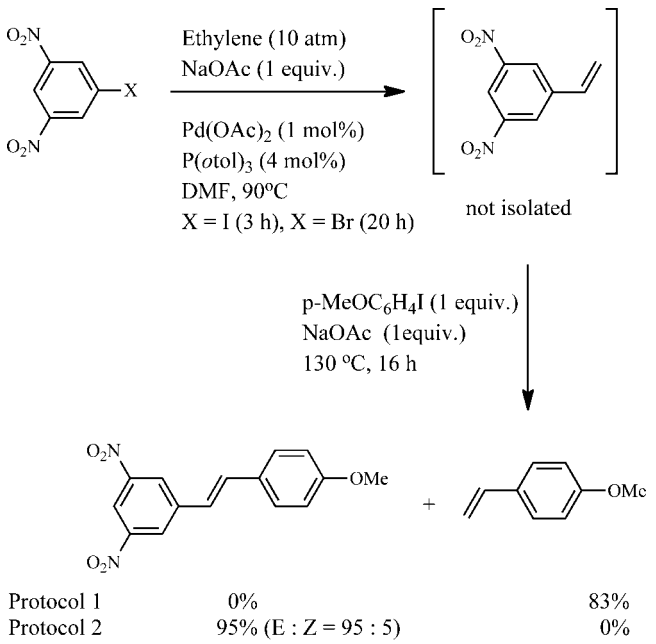
Results and Discussion

To obtain a sequential double-Heck arylation of ethylene without the isolation of the intermediate using the same Pd catalyst, we used the model substrates 1-iodo-3,5-dinitrobenzene and 1-bromo-3,5-dinitrobenzene for the first arylation and 1-iodo-4-methoxybenzene for the second arylation. The 1-halo-3,5-dinitrobenzenes were selected because they are easily obtained from a cheap starting material, *m*-dinitrobenzene. In addition, they possess the 3,5-substitution pattern of the resveratrol motif and facilitate the preparation of resveratrol nitrogen analogs. We performed an extensive optimization of the reaction conditions using S- and N-containing palladacycles[41,42] (Fig. 1), phosphine-free $Pd(OAc)_2$ and phosphine-based $Pd(OAc)_2$ catalysts for each arylation reaction, and then a one-pot procedure. S-containing palladacycle **1** and phosphine free $Pd(OAc)_2$ gave low conversions (<10%) for the coupling of 1-iodo-3,5-dinitrobenzene with ethylene under the conditions used (DMF or DMA as solvent, 90–130 °C, NaOAc or Et_3N as base). On the other hand both N-containing palladacycle 2 and $Pd(OAc)_2$ associated with P(*o*-tolyl)$_3$ gave complete conversion for the arylation of the ethylene. However, only the phosphine-containing palladium catalyst $Pd(OAc)_2$+P(*o*-tolyl)$_3$ allowed us to carry out the two consecutive Heck arylations without losing activity from the first to the second Heck reaction (Scheme 1). For the N-containing palladacycle 2 we observed formation of black palladium after the first arylation and low conversions were obtained for the second arylation. Therefore the presence of the phosphine ligand is crucial to keep the catalyst active for the second arylation reaction. Thus,



1 2

Figure 1. S- and N-containing palladacycles tested.

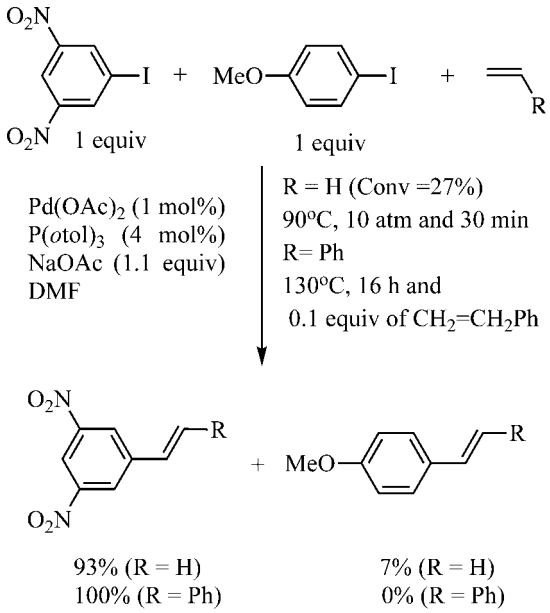


Scheme 1. The sequential double-Heck arylation of ethylene using the same Pd catalyst (GC yields).

the coupling reaction between 1-iodo-3,5-dinitrobenzene and ethylene (10 atm) using $Pd(OAc)_2$ + P(*o*-tolyl)$_3$ as a catalyst, NaOAc as base, and DMF as the solvent at 90 °C produced 3,5-dinitrostyrene at an turnover number of 98 according to GC, and the coupling product was isolated at an 85% yield. As judged by GC-MS, the only by-product of the process was the symmetric stilbene that was formed by the arylation of the 3,5-dinitrostyrene (1–2%). Our first approach to performing the second arylation was to cool the reactor and release the excess ethylene, followed by the addition of 4-iodoanisol (1 equiv.) and more base (1.1 equiv.) to the autoclave (protocol 1). Using this protocol, we obtained 83% of 4-methoxystyrene without the formation of the stilbene product. These results indicate that the 4-iodoanisol instead of 3,5-dinitrostyrene reacted with the ethylene that remained in the solvent. To overcome this problem, we decided to transfer the reaction mixture under argon to a Schlenk tube, wherein we performed the second arylation under an argon atmosphere at reflux (protocol 2). Using this procedure, the 3,5-dinitro-4′-methoxystilbene was obtained at a 95% yield with a regioselectivity of $E:Z = 95:5$ (Scheme 1). Purification of the crude material by column chromatography resulted in pure (*E*)-3,5-dinitro-4′-methoxystilbene at an 88% overall yield.

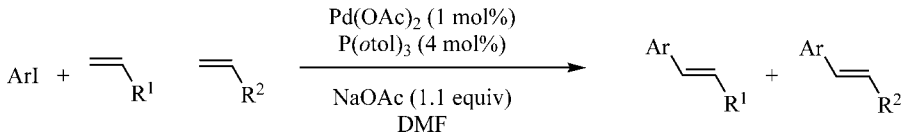
To explain the selectivity, additional competition experiments were carried out (Table 1 and Scheme 2). The reaction of aryl iodides (1 equiv.) with a mixture of ethylene (5 atm) and styrene (18.5 equiv.) demonstrated that ethylene reacts faster than styrene, even when styrene is present in a large excess (Table 1, entries 1 and 2). On the other hand, 3,5-dinitrostyrene (18.5 equiv.) was more reactive than 4-methoxystyrene (18.5 equiv.) in the Heck reaction with iodobenzene (1 equiv.). Finally, we evaluated the relative reactivities of two different aryl iodides (1-iodo-3,5-dinitrobenzene and 4-iodoanisol) in coupling reactions with olefins (Scheme 2). As expected, the aryl iodide that contained electron-withdrawing groups was more reactive than that with electron-donating groups. Using ethylene, 93% of the coupling product resulted from the reaction with 1-iodo-3,5-dinitrobenzene at low conversions, whereas only 1-iodo-3,5-dinitrobenzene coupled with styrene as the limiting reagent (0.1 equiv.). These competition experiments demonstrate that by choosing 1-iodo-3,5-dinitrobenzene in the first step and 4-iodoanisol in the second step, non-symmetrical stilbene could be obtained at an excellent yield and with a high selectivity.

Under the optimized conditions, the second Heck reaction proceeded without any isolation of the first Heck product using the same Pd catalyst so as to provide pure (*E*)-3,5-dinitro-4′-methoxystilbene at an 88% total yield for the two steps (Table 2, entry 1). When we tried to reverse the aryl iodide order by adding 4-iodoanisol to the first Heck reaction and then 1-iodo-3,5-dinitrobenzene to the second, a mixture of stilbene (63%) and *m*-dinitrobenzene (27%) was obtained (Table 2, entry 2). The by-product was formed by reduction of the 1-iodo-3,5-dinitrobenzene. We next tried some other combinations in order to expand the scope of the reaction. When using 1-iodo-4-nitrobenzene in the first Heck reaction, the stilbene coupling product (*E*)-4-methoxy-4′-nitrostilbene was obtained at an excellent yield (Table 2, entry 3). When we tried to reverse the aryl iodide order by adding 4-iodoanisol to the first Heck reaction and then 1-iodo-4-nitrobenzene to the second, the yield of the stilbene decreased to 70% and the selectivity was lower (Table 2, entry 4). A regioselectivity of 70:30 for the (*E*)- and (*Z*)-4-methoxy-4′-nitrostilbene was observed. We have also tested a very activated aryl bromide for the second arylation but the conversion was not complete (70%) and the stilbene product was formed in 60% yield (Table 2, entry 5). 4-Iodoanisol gave better results as the first arylation agent when we used a aryl iodide with an electron donating group in *para* position for the second arylation (Table 2, entry 6). These results indicate that the first



Scheme 2. Heck reaction: competitive reaction between aryl iodides.

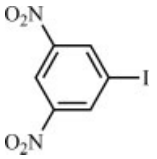
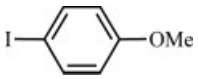
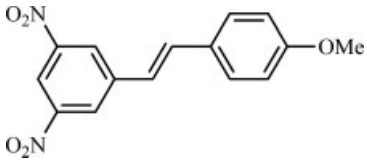
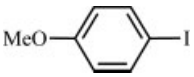
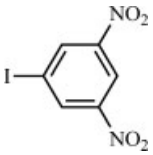
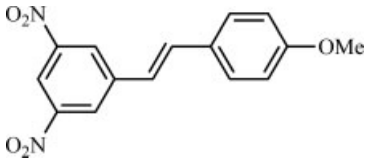
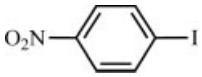
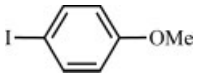
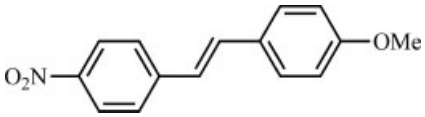
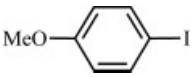
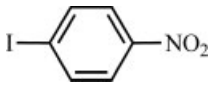
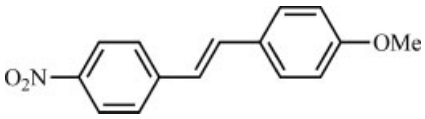
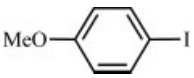
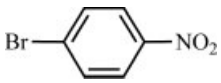
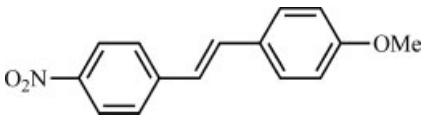
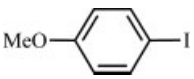
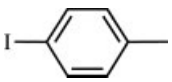
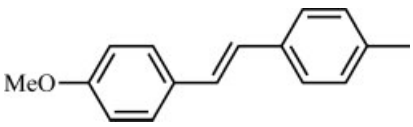
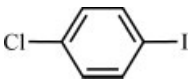
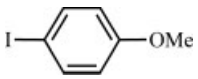
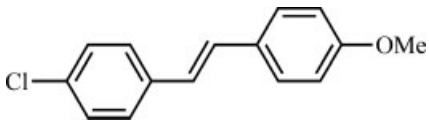
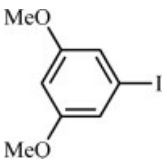
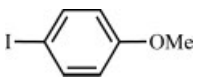
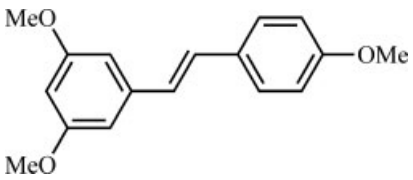
Table 1. Heck reaction: competitive reaction between olefins[a]



Entry	Ar	R^1	R^2	$ArCH{=}CHR^1$ (%)	$ArCH{=}CHR^2$ (%)
1	3,5-$(NO_2)_2C_6H_3$	H	Ph	85	15
2	4-$MeOC_6H_4$	H	Ph	84	16
3	Ph	3,5-$(NO_2)_2C_6H_3$	4-$MeOC_6H_4$	74	26

[a] ArI (1 mmol), styrene or substituted styrene (18.5 mmol), ethylene (5 atm), $Pd(OAc)_2$ (0.01 mmol), P(*o*-tol)$_3$ (0.04 mmol), NaOAc (1.1 mmol), and DMF (10 ml).

Table 2. The synthesis of non-symmetrical stilbenes via the sequential double-Heck arylation of ethylene[a]

Entry	Ar^1I	Ar^2I	Stilbene isolated yield (%)
1			 88%
2			 63%[b]
3			 90%
4			 70%
5			 60%[c]
6			 80%
7			 87%
8[d]			 65%

[a] Ar^1I (1 mmol), $Pd(OAc)_2$ (0.01 mmol), P(*o*-tol)$_3$ (0.04 mmol), NaOAc (1.1 mmol), and DMF (10 ml). The reactor was pressurized with 10 atm of ethylene, and the reaction mixture was stirred at 90 °C for 3–4 h. After cooling and releasing the excess ethylene, the reaction mixture was transferred under argon to a Schlenk tube. Next, Ar^2I (1 mmol) and NaOAc (1.1 mmol, 90.2 mg) were added, and the mixture was stirred at 130 °C for 16 h. [b] GC yield. Reduction product *m*-dinitrobenzene was formed in 27% GC yield. [c] GC yield. Only 72% conversion of 1-bromo-4-nitrobenezene. [d] $Pd(OAc)_2$ (0.02 mmol), P(*o*-tol)$_3$ (0.08 mmol).

aryl iodide must preferentially have strong electron-withdrawing groups that are attached to the aryl ring. Finally, the aryl iodide that contained two methoxy groups in the *meta* positions (moderate electron-withdrawing groups) was evaluated (Table 2, Entry 8). The reaction with 3,5-dimethoxy-1-iodobenzene in the first Heck reaction resulted in a 65% yield of the methylated resveratrol, which is known to be as biologically active as resveratrol itself.

Conclusions

In summary, we have developed a sequential and selective double-Heck arylation of ethylene that produces non-symmetrical nitro-stilbene analogs of *trans*-resveratrol at excellent yields. After the first Heck arylation of ethylene, no isolation or additional catalyst loading is required for the second Heck arylation. This protocol was also applied to the synthesis of methylated *trans*-resveratrol, which was obtained at a 65% yield over the two Heck reactions.

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