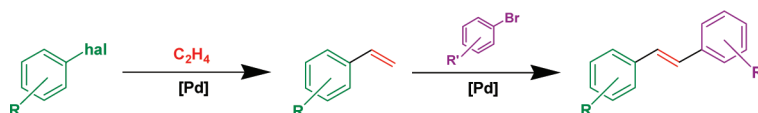# Preparation of Nonsymmetrically Substituted Stilbenes in a One-Pot Two-Step Heck Strategy Using Ethene As a Reagent

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We present here a strategy for the preparation of nonsymmetrically substituted stilbenes using a one-pot two-step double Heck strategy. First a protocol is developed for the selective preparation of a range of styrenes using ethene as the alkene coupling partner. Then conditions are found for the effective coupling of the styrenes with aryl halides using a 1:1 stoichiometric ratio of the two components. The use of the microwave apparatus to perform the reactions offers a convenient method for synthesis as well as for safely, easily, and accurately loading vessels with gaseous reagents.

Introduction

The palladium-catalyzed C−C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base is well-known now as the Heck reaction.[1,2] There have been a number of recent reviews of the scope and versatility of the reaction.[3–7] It finds wide applications from natural product to fine chemicals synthesis as well as in the preparation of functional polymers and their precursors.[8–11] When looking in the literature, the vast majority of the publications citing the Heck reaction involve the reaction of aryl halides with monosubstituted alkenes such as styrene and butyl acrylate. Generally the alkene coupling partner is used in a stoichiometric excess relative to the aryl halide component and a wide range of catalyst systems have been developed for obtaining the Heck products in good yields. An alkene that has received relatively little attention is ethene; indeed, there are very few research papers published using ethene as a substrate. This is despite the fact that it is the simplest alkene coupling partner that could be

imagined in a Heck reaction. Also, the styrene and stilbene products formed have a rich variety of chemical and biological properties and so their synthesis is of interest in the organic chemistry community.[12]

The reason behind the sparcity of reports using ethene as a reagent in the Heck reaction is that it is fraught with difficulties. The main problem is over-reaction with the aryl halide coupling partner to give the symmetric stilbene product rather than the monosubstituted alkene. It is therefore necessary to control precisely the amount of gas used; this usually implies a complex experimental setup. Another problem is that under the high temperature/long reaction time conditions often used, polymerization of the desired monosubstituted alkene product can occur. To circumvent these problems, liquid vinyltrialkylsilanes and vinyltrialkoxysilanes have been used as ethene substitutes. For example, a selective procedure for the construction of symmetric and nonsymmetric *trans*-stilbene derivatives has been reported based on two sequential Heck-type reactions using vinyltrimethylsilane as ethene equivalent.[13] More recently, symmetric and nonsymmetric (*E*)-1,2-diarylethenes have been prepared in consecutive palladium-catalyzed Hiyama−Heck reactions.[14]

In our laboratory, we have had success performing Heck reactions using water as a solvent in conjunction with microwave heating.[15,16] We also have the capability to perform microwave-

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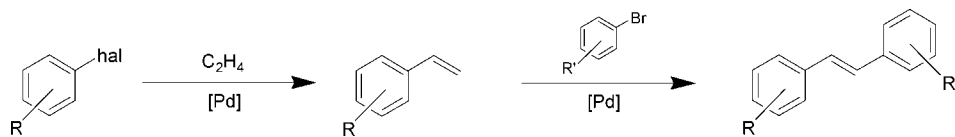(14) Gordillo, A.; de Jesús, E.; López-Mardomingo, C. *Chem. Commun.* **2007**, 4056–4058.

FIGURE 1. Proposed one-pot two-step protocol for the preparation of nonsymmetric substituted stilbenes.

promoted reactions in the presence of a reactive gas.[17–19] We therefore wanted to take steps to address the problems of using ethene in Heck coupling reactions and, in so doing, develop a selective one-pot two-step protocol for the preparation of nonsymmetric substituted stilbenes (Figure 1). We present our results here.

Results and Discussion

As a starting point, we decided to probe the Heck reaction between iodobenzene and ethene using the conditions optimized in our laboratory for other Heck couplings. This involved using water (2 mL) as the solvent, tetrabutylammonium bromide (1 equiv) as a phase-transfer agent, potassium carbonate (3.7 equiv) as base, heating the reaction mixture to 170 °C using microwave irradiation, and holding it at this temperature for 10 min. We knew from our previous studies that this protocol was quick, used very low levels of a ligand-free palladium catalyst, and was applicable to a range of substrates. Working on the 1 mmol scale, we loaded all the reagents, with the exception of the ethene, into a 10 mL microwave tube and then sealed the vessel and placed it into our microwave unit. Using the gas-loading accessory, we loaded 50 psi of ethene into the vessel. We then attempted to heat the reaction mixture to the target temperature of 170 °C. However, we found that when we reached a temperature of just 120 °C we were already at the pressure limits of the glass vessel (250 psi). Holding the reaction mixture at this temperature for 10 min led, upon cooling and workup, to a low yield of stilbene and only a trace of the desired styrene. We knew from our previous studies that the Heck reaction under these conditions was very temperature dependent, so in order to be able to heat the reaction mixture to the desired temperature of 170 °C, we decided to dose the reaction vessel with a much lower ethene loading of 15 psi. Analysis of the product mixture at the end of this reaction again showed a very low yield of stilbene.

We turned our attention to the use of dimethylformamide (DMF) as a solvent for the reaction. DMF has found use as a solvent for Heck couplings before and its higher boiling point meant that theoretically we could work at higher pressures of ethene. Using palladium acetate as a catalyst and screening a range of reaction conditions, we were unable to obtain significant conversions to styrenes when using aryl bromides as substrates. We therefore turned to the more reactive aryl iodides. As a starting point, we used iodobenzene as substrate, 1 mol% Pd(OAc)$_2$ as catalyst, tributylamine as a base, and an initial loading of 100 psi of ethene. Heating this reaction mixture to 175 °C and holding at this temperature for 10 min resulted in consumption of starting material but formation of significant quantities of stilbene rather than the desired styrene.

To address this problem, we moved from palladium acetate as a catalyst to palladium on carbon. This is known to discharge small quantities of palladium into solution during the course of a reaction. By dosing the reaction mixture with low levels of palladium, we hoped to control the reaction and stop at the styrene rather than over-react to form the stilbene. The result from this was promising, giving a 10:64:26 ratio of unreacted starting material, styrene, and stilbene, respectively. We moved to using an ICP palladium standard as our catalyst source because in previous studies we found that this is a very convenient way of adding very small quantities of ligandless palladium to reaction mixtures. Using 100 μL of a 1000 ppm ICP standard allowed us to perform the reaction at a catalyst loading of 0.1 mol%.

Keeping all other conditions the same, we obtained a 10:69:21 ratio of unreacted starting material, styrene, and stilbene, respectively. To increase further the selectivity of the reaction toward formation of styrene, we turned our attention to the reaction temperature and time. We postulated that if we slowed the reaction down by reducing the temperature and extending the time, we could favor formation of the styrene. Also, by working at lower temperatures we could increase the initial loading of ethene because the autogenic pressure generated during the course of the reaction would be less. This would also favor formation of the styrene product. Performing the reaction at 125 °C for 1 h using 0.1 mol% palladium from the ICP standard as catalyst and an ethene loading of 150 psi we saw complete conversion of iodobenzene and obtained an 82:18 ratio of styrene to stilbene respectively. Interestingly, the reaction can be followed by monitoring the pressure. At the start of the reaction the pressure increases to approximately 155 psi as the mixture is heated to the target temperature. It then drops over time, indicating the consumption of ethene. In further optimization studies we found that the catalyst loading could be reduced to 0.02 mol% without a deleterious effect on product yield. It was also possible to reduce the quantity of tributylamine used in the reaction by adding a stoichiometric equivalent of potassium carbonate. Although this modification is not essential, it does make the subsequent step in the protocol easier (conversion of styrenes to stilbenes). Using our optimal conditions, we screened three further aryl iodides as representitive examples as shown in Table 1.

We next needed to develop a protocol for preparing stilbenes from styrenes. Generally, the alkene coupling partner is used in excess relative to the aryl halide component in Heck couplings. Because the styrenes in our studies were themselves prepared from aryl halides in a Heck coupling, to make a one-pot strategy successful, a challenge that faced us was to develop a method for the stoichiometric conversion of these styrenes to stilbenes. The first step of the protocol restricted us to using DMF or DMF/cosolvent mixtures. Using a 1:1 stoichiometric ratio of 4-bromoanisole and styrene as test coupling partners, we screened a range of reaction conditions. It became clear that using ligandless palladium sources as catalysts for the preparation of stilbenes from the stoichiometric combination of aryl

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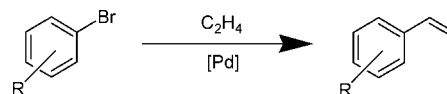(19) Kormos, C. M.; Leadbeater, N. E. *Synlett* **2006**, 1663–1666.

TABLE 1. Conversion of Aryl Iodides to Styrenes Using a Heck Reaction with Ethene as the Alkene Coupling Partner[a]
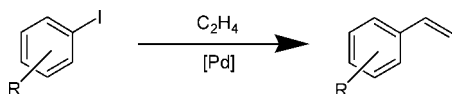
entry	aryl iodide	conversion to styrene (%)[b]
1		82
2	COMe	88
3		91
4	OMe	91

[a] Initial microwave irradiation of 50 W was used, the temperature being ramped from rt to 125 °C where it was then held for 60 min. Reactions were run using 1 mmol aryl iodide, 150 psi ethene, 1.5 mL DMF, and 0.25 mL tributylamine. ICP palladium standard was used as catalyst (0.02 mol%). [b] Crude conversions were calculated by comparing the integrations of styrene protons versus the total aromatic integration in d_6-DMSO.

TABLE 2. Conversion of Aryl Bromides to Styrenes Using a Heck Reaction with Ethene as the Alkene Coupling Partner[a]

entry	aryl iodide	conversion to styrene (%)[b]	styrene isolated yield (%)[c]
1	COMe / Br	73	36
2	Br	73	-
3	OMe / Br	81	67
4	NH₂ / Br	78	44
5	Br / OMe	83	69
6	Br	95	-
7	Br	-	66
8	Cl	5	-

[a] Initial microwave irradiation of 50 W was used, the temperature being ramped from r.t. to 125 °C where it was then held for 60 min. Reactions were run using 1 mmol aryl bromide, 150 psi ethene, 1.5 mL DMF and 0.25 mL tributylamine. CataCXium C was used as catalyst (0.5 mol%) [b] Crude conversions were calculated by comparing the integrations of styrene protons versus the total aromatic integration in d_6-DMSO. [c] Substituted styrene products were isolated by silica gel chromatography following aqueous/organic work-up using diethyl ether.

halide and alkene was not going to be possible. However, the palladium complex *trans*-bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (called Herrmann's catalyst and marketed under the name CataCXium C) was catalytically active under our conditions. We obtained complete conversion within 15 min at 175 °C in the coupling of 4-bromoanisole and styrene. The reaction could be performed either in DMF or a 1:1 DMF/water mix as solvent. Putting this in context, CataCXium C has been used previously in Heck reactions with success, but when using an excess of the alkene coupling partner.[20–23]

Before performing a screening of aryl halides for the synthesis of stilbenes, we wanted to revisit the preparation of styrenes using aryl bromides as coupling partners in conjunction with CataCXium C as the catalyst. This would then allow us to use both iodo- and bromo-arenes in the first step of the process. We found that we could indeed achieve this but that the reaction temperature had to be increased from 125 °C, as was used in the case of the ligandless palladium catalyzed coupling of aryl iodides with ethene, to 150 °C. This was successful for a range of aryl bromides as shown in Table 2. Of note is that while product conversions are generally high, small-scale isolation of styrenes from the DMF solution is difficult. Also, with activated substrates such as 4-bromoacetophenone, the high reaction temperature required (150 °C) resulted in polymerization of the styrene product. We also screened 4-chlorotoluene and 4-chlo-

roanisole as representative aryl chloride substrates in the reaction but found that product conversions were very low (<5%) indicating the limitations of the methodology.

With routes for all the desired steps in hand, we screened different pairs of aryl halides in the one-pot two-step synthesis of nonsymmetrical stilbenes. Results are gathered in Table 3. We present data for isolated product yields as well as product purity. As with any synthetic protocol, product purity is important and especially when considering the one-pot two-step approach used here. The product mixtures from our reactions in some cases contained up to 10 mol% of the symmetrically substituted stilbene arising from reaction of a second equivalent of the first aryl halide with the styrene product. We find that the easiest method for product isolation is recrystallization from ethanol/water, this allowing for separation of the stilbenes from other constituents in the product mixture such as unreacted aryl halide and remaining amine base and DMF. As a strategy for increasing the product yield while limiting competitive formation of the undesired symmetric stilbene we find that its is prudent to use the less reactive aryl halide in the first (styrene forming) step. That way, the first step of the process results in a high styrene to symmetric stilbene

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TABLE 3.   One-Pot Two-Step Synthesis of Nonsymmetrical Stilbenes[a]
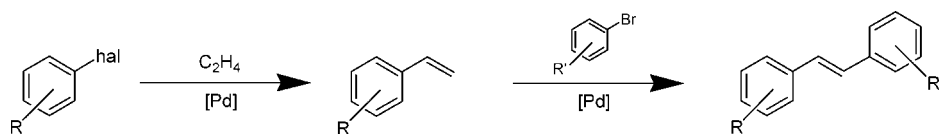
entry	aryl halide for preparation of styrene	aryl halide for preparation of stilbene	stilbene isolated yield (%)	stilbene purity (%)[b]
1	I—C6H4—OMe	Br—C6H4—COMe	41	89
2	I—C6H4—OMe	Br—C6H4—CH3	57	92
3	I—C6H4—OMe	1-bromonaphthalene	45	88
4	I—C6H4—CH3	Br—C6H4—OMe	35	92
5	I—C6H4—COMe	Br—C6H4—OMe	38	93
6	Br—C6H4—OMe	Br—C6H4—COMe	64	89
7	Br—C6H4—OMe	Br—C6H4—CH3	55	91
8	Br—C6H4—OMe	2-Br—C6H4—OMe	59	88
9	Br—C6H4—CH3	Br—C6H4—COMe	72	91
10	Br—C6H4—CH3	Br—C6H4—OMe	61	91
11	Br—C6H4—COMe	Br—C6H4—OMe	6	75
12	Br—C6H4—COMe	Br—C6H4—CH3	13	95[c]
13	Br—C6H4—NH2	Br—C6H4—OMe	34	95[d]
14	2-Br—C6H4—OMe	Br—C6H4—OMe	19	95[c]

[a] If an aryl iodide is used in the styrene-forming step, ICP palladium standard is employed as the catalyst, DMF as solvent and potassium carbonate, and tributylamine as bases. The reaction is heated to 125 °C using an initial microwave power of 50 W and held at that temperature for 60 min. If an aryl bromide is used in the styrene forming step, CataCXium C is employed as the catalyst, DMF as the solvent, and tributylamine as the base. The reaction is heated to 125 °C using an initial microwave power of 50 W and held at that temperature for 60 min. In both cases, the reaction vessel is prepressurized with 150 psi of ethene. In the stilbene-forming step, potassium carbonate, CataCXium C, and the second aryl halide coupling parner are added to the styrene-containing reaction mixture, and this is heated to 175 °C using an initial microwave power of 5–25 W and held at that temperature for 15 min to give the desired product. [b] Stilbene products were isolated directly by recrystallization from ethanol/water. [c] Required silica gel chromatography (5–10% ethyl acetate in hexanes as eluent). [d] Required silica gel chromatography (100% dichloromethane as eluent).

ratio and then in the second step when the more reactive aryl halide is added, the formation of the desired nonsymmetrical stilbene is favored. Conversely, if the more reactive aryl halide is used, it tends to over-react in the first stage yielding symmetric

stilbene and then any remaining aryl halide reacts competitively in the second step giving a double-hit to the yield of the desired product. The difference between the two strategies is clearly seen in the case of the 4-bromoacetophenone and 4-bromoanisole as the two aryl halide components for the preparation of 4-acetyl-4′-methoxystilbene (Table 3, entries 6 and 11).

In summary, we present here a strategy for the preparation of nonsymmetrical stilbenes using a one-pot two-step double Heck strategy. Several significant obstacles were overcome. First, a protocol was developed for the selective preparation of a range of styrenes using ethene as the alkene coupling partner. Then conditions were found for the effective coupling of the styrenes with aryl halides using a 1:1 stoichiometric ratio of the two components unlike the majority of cases in the literature where an excess of the alkene component is used. Our optimal conditions involve starting with the less reactive aryl halide to form the styrene. In this step, if an aryl iodide is used, ICP palladium standard is employed as the catalyst, DMF as solvent and potassium carbonate and tributylamine as bases. The reaction is run at 125 °C for 60 min. If an aryl bromide is used in the styrene forming step, *trans*-bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (called Herrmann's catalyst and marketed under the name CataCXium C) is employed as the catalyst, DMF as the solvent and potassium carbonate and tributylamine as bases. The reaction is run at 125 °C for 60 min. In both cases, the reaction vessel is prepressurized with 150 psi of ethene. In the stilbene-forming step, potassium carbonate, CataCXium C, and the second aryl halide coupling parner are added to the styrene-containing reaction mixture and this heated to 175 °C for 15 min to give the desired product. Microwave heating was used as a tool for performing the reaction. As well as the inherent advantages of rate acceleration, the use of the microwave apparatus offers a convenient method for safely, easily, and accurately loading vessels with gaseous reagents and monitoring the progress of reactions.

Experimental Section

General Experimental Details. All materials were obtained from commercial suppliers and used without further purification. All reactions were carried out in air. Reactions were conducted using a scientific microwave unit. The machine consists of a continuously focused microwave power delivery system with operator selectable power output from 0 to 300 W (CEM Discover). Reactions were performed in thick-walled glass vessels (capacity 10 mL, maximum working volume 5 mL). The vessel was sealed with a septum with ports for pressure and temperature measurement devices. The pressure is measured by a load cell connected directly to the vessel. The pressure limit was set to 200 psi for all reactions, beyond which the apparatus shuts down. The temperature of the contents of the vessel was monitored using a calibrated fiber-optic probe inserted into the reaction vessel by means of a sapphire immersion well. In all cases, the contents of the vessel were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Gas loading is achieved through a manifold coupled with the pressure sensor. The manifold allows isolation of the reaction vessel, loading of gas, purging to vacuum, and a vent option that opens the vessel to a vent line in the back of the manifold. A built-in analog pressure gauge conveniently indicates the pressure inside the vessel, even during loading. Once a reaction method has been started, switching the manifold off the Run position to the Fill position pauses the microwave heating but maintains reaction stirring. This can be used to stir a reaction under an open source of gas, allowing gas to

saturate the solvent before heating. The switch must be reset to Run before the microwave heating can be resumed. This capability was generally found not to be necessary for this methodology (see Supporting Information).

Representative Procedure 1. Preparation of Styrenes from Aryl Iodides: 4-Methoxystyrene from 4-Iodoanisole. In a 10 mL microwave tube were placed 4-iodoanisole (1 mmol, 234 mg), anhydrous potassium carbonate (1 mmol, 138 mg), dimethylformamide (1.5 mL), and tributylamine (0.25 mL). The mixture was stirred with a magnetic stir bar as palladium ICP standard (20 uL of a 1000 ppm solution in 5% HCl, 0.02 mol% Pd) was added. Using the gas-loading manifold, a pressure of 150 psi ethene as set at the cylinder regulator was introduced into the vessel by slowly turning the switch from "Run" to "Load", then back to "Run", isolating the reaction vessel. A second brief switch back to "Load" was sometimes necessary for the manifold analog pressure gauge to read 150 psi. The reaction mixture was heated to 125 °C with stirring using an initial microwave power of 50 W and held at that temperature for 60 min. The reaction mixture was cooled to 40 °C, and the remaining pressure was carefully vented. This crude mixture was carried on directly to a stilbene synthesis (procedure 3).

Representative Procedure 2. Preparation of Styrenes from Aryl Bromides: 4-Methoxystyrene from 4-Bromoanisole. In a 10 mL microwave tube were placed 4-bromoanisole (1.00 mmol, 187 mg), anhydrous potassium carbonate (1.00 mmol, 138 mg), CataCXium C (2.3 mg, 0.50 mol% Pd), dimethylformamide (1.5 mL), and tributylamine (0.25 mL, 1.05 mmol). The mixture was stirred briefly, then the vessel was sealed and loaded with ethylene gas (150 psi) using the method outlined in procedure 1. The reaction mixture was heated to 150 °C using an initial microwave power of 50 W and held at that temperature for 60 min. The reaction mixture was cooled to 40 °C, and the remaining pressure was carefully vented. This crude mixture can be carried on directly to a stilbene synthesis (procedure 3). Otherwise, the reaction was poured into diethyl ether (50 mL) and water (25 mL). The organic layer was washed with 2 M HCl (15 mL). The evaporated organic residue was purified by silica gel chromatography (40 g, 5% ethyl acetate in hexanes) to isolate 4-methoxystyrene (90 mg, 67% yield) as a clear, colorless oil.

Representative Procedure 3. Preparation of Stilbenes from Styrenes: 4-Methoxy-4′-Methylstilbene from Crude 4-Methoxystyrene. To the crude, cooled mixture from procedure 1 or 2 was added anhydrous potassium carbonate (1.00 mmol, 138 mg), CataCXium C (2.3 mg, 0.50 mol% Pd), and 4-bromotoluene (1.00 mmol, 171 mg). The reaction mixture was heated to 175 °C with stirring using an initial microwave power of 5–25 W and held at that temperature for 15 min. The presence of iodide greatly increased the microwave absorptivity of the sample, so when the styrene was prepared from an aryl iodide, careful monitoring was required to prevent overheating. The reaction mixture was cooled to 40 °C and poured into diethyl ether (50 mL) and water (25 mL). The organic layer was washed with 2 M HCl (2 × 15 mL). The evaporated organic layer yields a solid which can be recrystallized from ethanol and water to yield 4-methoxy-4′-methylstilbene (55–57% yield, >90% purity).

Supporting Information Available: Photographs of the gas loading apparatus and NMR spectral data for the styrene and stilbene products. This material is available free of charge via the Internet at http://pubs.acs.org.

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