Reactivity and Regioselectivity in the Heck Reaction: Hammett Study of 4-Substituted Styrenes

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Received July 21, 2004

The regioselectivity in the cationic Heck reaction of 4-substituted styrenes was addressed by a Hammett study. In this branching reaction, plots based on the substrate reactivity did not give meaningful data, whereas the product distribution was variable due to differing preferences for further substitution under the reaction conditions and, thus, unsuitable for Hammett plots. Mechanistically meaningful graphs were obtained by combination of the measured initial branching ratio with the approximately constant substrate reactivity. For the α-substitution a clear Hammett relation is observed, whereas *β*-substitution does not depend on electronic effects. This implies that, for α-substitution, the slow step of the addition is an electrophilic attack by Pd(II) on the double bond, followed by a rapid migratory insertion.

Introduction

The Heck reaction, palladium-catalyzed cross-coupling of olefins with aryl halides or triflates, is an indispensable tool for modern organic synthesis.[1] This robust process, in either its inter- or intramolecular version, is simple to perform and is in general tolerant of functional groups, making it an attractive tactic for multistep target-oriented synthesis.[2] The development of chiral ligands for palladium has taken the Heck reaction into the realm of asymmetric synthesis,[3] and it can now even be used for the enantioselective construction of quaternary stereogenic centers.[4]

As with most synthetically useful transition-metal-catalyzed organic transformations, the Heck reaction has been subjected to much empirical fine tuning of the reaction conditions in order to extend the scope and to increase yields, turnover numbers, and selectivities, sometimes with spectacular success.[5] In contrast, major developments based on detailed mechanistic insight[6] have largely been lacking, since the Heck process is subject to a myriad of solvent, additive, and catalyst-precursor effects. Furthermore, it is now apparent that the Heck reaction[7] (in common with related Pd-catalyzed cross-couplings)[8] is mechanistically more complex than the "textbook" depiction (vide infra), which usually consists of a catalytic cycle based on a Pd(0)/Pd(II) couple (Scheme 1). As part of a general program aimed at studying the kinetics, mechanism, and selectivity of palladium-catalyzed organic reactions, we have now turned our attention to the Heck reaction and in this paper we present a study of reactivity and regioselectivity[9] based on a Hammett study of the cross-coupling between some 4-substituted styrenes and phenyl triflate. The present investigation therefore complements an earlier Hammett study on the Heck reaction,[10] which was focused on the nature of the rate-limiting step (suggested to be the oxidative addition) and employed a range of 4-substituted aryl iodides as substrates in the arylation of but-3-en-2-ol. Competition experiments involving the cross-coupling of various

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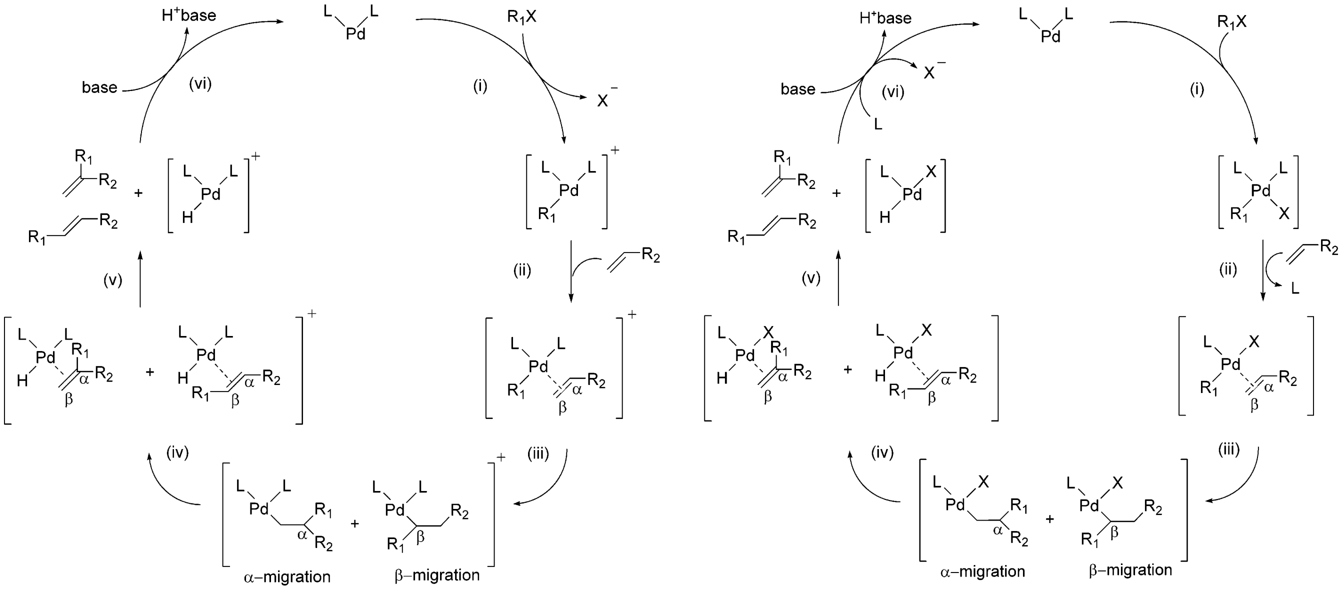
10.1021/om0494521 CCC: $27.50

Scheme 1 Two Different "Textbook" Mechanisms for the Heck Reaction: (left) Cationic Intermediates, Involved When Chelating Diphosphines Are Used in Conjunction with Weakly Coordinating Anions (e.g. X = Triflate); (right) Use of Monophosphines along with Coordinating Anions (e.g. X = Halides), Giving Neutral Intermediates in the Catalytic Cycle



4-substituted aryl iodides with methyl acrylate in the presence of a PCP-type Pd(II) catalyst[11] gave a Hammett correlation which suggested that olefin insertion may have been the rate-limiting step. More recently, a Hammett correlation for 4-substituted aryl bromides in the Heck reaction with *n*-butyl acrylate was used as part of an important study on the question of possible Pd(IV) intermediates when a phosphapalladacycle was employed as the catalyst.[12]

Results and Discussion

The simplified "textbook" mechanism for the Heck reaction[7] is shown in Scheme 1 and involves (i) oxidative addition to a coordinatively unsaturated Pd(0) complex, (ii) ligand exchange (halide/triflate for olefinic double bond), (iii) regiodetermining formation of a Pd−C single bond via migratory insertion, and (iv) β-hydride elimination, which generates the product and a Pd(II) hydride. A base-induced reductive elimination of HX then furnishes the catalytically active Pd(0) species. As shown in Scheme 1, a neutral or a cationic pathway[13,14] is possible,[1] depending on the reaction conditions. In the present study, we have chosen reaction parameters (phenyl triflate as reactant and a bidentate phosphine as ligand) which favor the cationic version, and we reasoned that by using electronically different olefins, information regarding the charge distribution in the regiodetermining step (iii) could be obtained. Our experiments were designed to probe the net effect of alkene binding and insertion, i.e., the selectivity-determining steps; we are not at present concerned with the nature of the overall rate-limiting step.[10] We thus performed a Hammett study of the 4-substituted styrenes shown in Table 1, with a range of σ values between −0.87 and 0.54. (4-Nitrostyrene, which would have extended the span of σ values even further, unfortunately proved intractable in the competition studies.)

Table 1. Selected 4-Substituted Styrenes and Associated σ Values[15]

compd	substituent (X)	σ
1a	NMe_2	−0.87
1b	OMe	−0.27
1c	Me	−0.17
1d	H	0
1e	Cl	0.23
1f	COOMe	0.45
1g	CF_3	0.54

All the styrenes could be separated using GC (for retention times, see the Supporting Information), allowing determination of the relative concentrations at various levels of conversion in competition experiments. With the concentrations of styrene and the relevant 4-substituted styrene in hand, the relative reactivities of the two substrates could then easily be determined, assuming a first-order reaction in each styrene and identical reaction orders in other reactants (eq 1; *A* and *B* are the concentrations of the two competing substrates, with the subscript "0" indicating the initial concentration).

$$\ln\left(\frac{A_0}{A}\right) = k_{\mathrm{rel}} \ln\left(\frac{B_0}{B}\right) \tag{1}$$

Prior to the competition experiments, pure reference materials were generated by the individual preparative-scale coupling (60−80% overall yield) of each styrene with phenyl triflate (Scheme 2).

In the competition experiments, the amount of phenyl triflate was increased to ensure a rapid coupling process, a small amount of naphthalene being used as internal standard. The procedure for the kinetic studies is shown schematically in Scheme 3.

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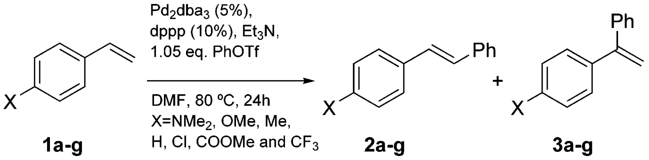
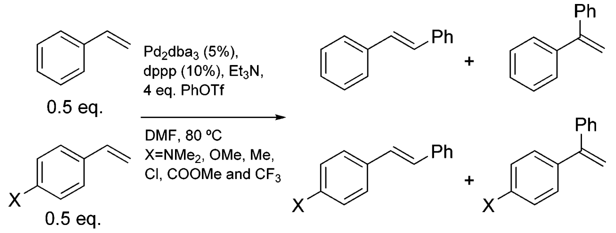
Scheme 2 Preparative Reactions Used to Generate Reference Compounds



Scheme 3 Competitive Reaction Procedure Used to Measure the Reactivity of the 4-Substituted Styrenes Relative to Styrene



The data from the kinetic experiments were plotted according to eq 1, yielding a straight line for each competition experiment, as expected (Figure 1). Final conversions were between 44% ($\ln(C_0/C) = 0.62$) and 87% ($\ln(C_0/C) = 2.01$).

The slope of each line gives the relative reactivity of the 4-substituted styrene compared to styrene itself, and the r^2 value was close to unity in all cases. 4-(Dimethylamino)styrene is more than 3 times as reactive as styrene, while all the other 4-substituted styrenes had relative reactivities in the range 0.79 (4-chlorostyrene) to 1.21 (4-methoxystyrene) (see Table 2).

The resulting Hammett plot is shown in Figure 2.

The left part of the Hammett plot shows linear behavior up to and including the relatively weakly electron-withdrawing 4-chloro substituent. This line has a small negative slope (−0.53), which indicates that the aryl ring is donating electron density to the reaction center in the selectivity-determining step, in agreement with the assumed electrophilic attack of Pd(II) upon the double bond. Cabri et al. also observed a higher reactivity of electron-rich alkenes in the cationic Heck reaction (butyl vinyl ether was more reactive than methyl acrylate).[13,16] However, with the more strongly electron-withdrawing substituents the plot does not follow a linear relationship but flattens out and even shows a slight rate increase compared to the chloro-substituted styrene.

A nonlinear Hammett plot is usually interpreted as a shift to another type of reaction mechanism.[17] A plot with a reactivity maximum indicates a change of rate-determining step in a multistep reaction, whereas a plot with a reactivity minimum is interpreted as a competition between two different mechanisms, one favored by electron-withdrawing substituents and the other by electron donation. In this regard it should be noted that we measure only *relative* rates in a competition situation, not absolute rates. We thus do not know if the electron-poor styrenes react faster than 4-chlorostyrene, just that they are better able to compete with styrene. However, the nonlinearity of the Hammett plot is still a strong indication that the selectivity-determining step is not the same at low and high σ values.

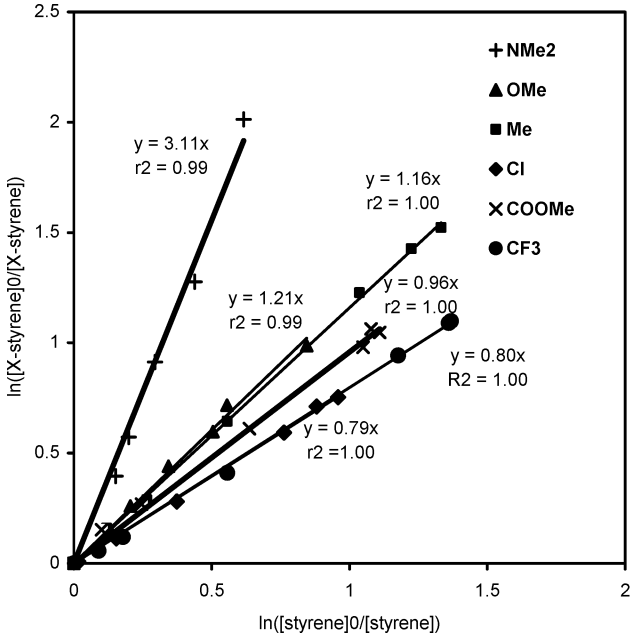


Figure 1. Plot of the kinetic data obtained from the competitive Heck reactions.

Table 2. Data from the Competive Reactions, Relative Rates Compared to Styrene (k_{rel}), with 90% Confidence Intervals, and the Initial Ratio (r) of Product 3 to 2

entry	substituent (X)	k_{rel}	r
1	NMe_2	3.11 ± 0.17	1.27
2	OMe	1.21 ± 0.05	0.81
3	Me	1.16 ± 0.02	0.89
4	H	1	0.78
5	Cl	0.79 ± 0.01	0.58
6	COOMe	0.96 ± 0.03	0.23
7	CF_3	0.80 ± 0.02	0.23

To elucidate the source of the nonlinearity, we realized that it is necessary to account for the differences in reactivity at the branching point of the mechanism, which is the migratory insertion to either the α - or β-position. The overall rate of product formation is the sum of the rates of formation of the *gem* and *trans* products (formation of the *cis* product was negligible in all cases) (eq 2).

$$k_{rel} = k_{gem} + k_{trans} \tag{2}$$

For each substrate, the two products were formed in the ratio *r*. The product ratio showed a curved dependence on the conversion, attributed to a difference in stability of the two products to further reaction under the conditions employed. We have therefore used only the initial *r* value, since this should correspond best to the relative rates of formation (eq 3). It is not a priori certain that the GC sensitivity is equal for all products. The ratio *r* was therefore corrected for differences in burn ratios of the different products, obtained from comparison of GC ratios to relative concentrations determined by high-resolution ^{1}H NMR for standard

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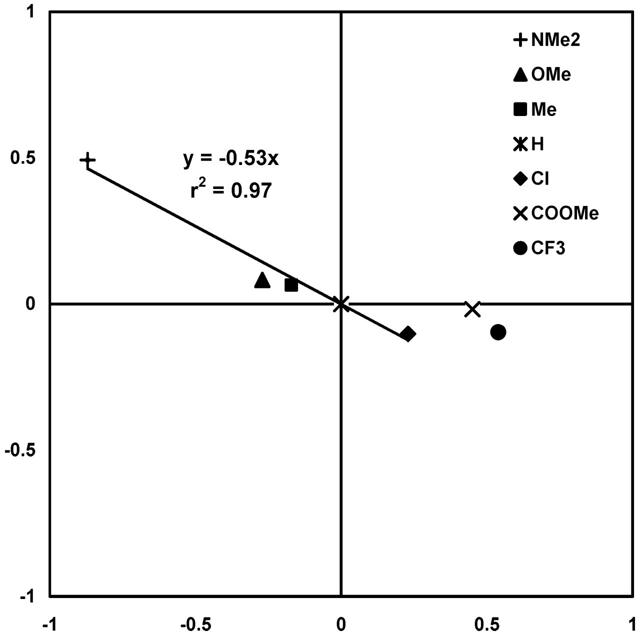


Figure 2. Hammett plot based on kinetic data and σ values.

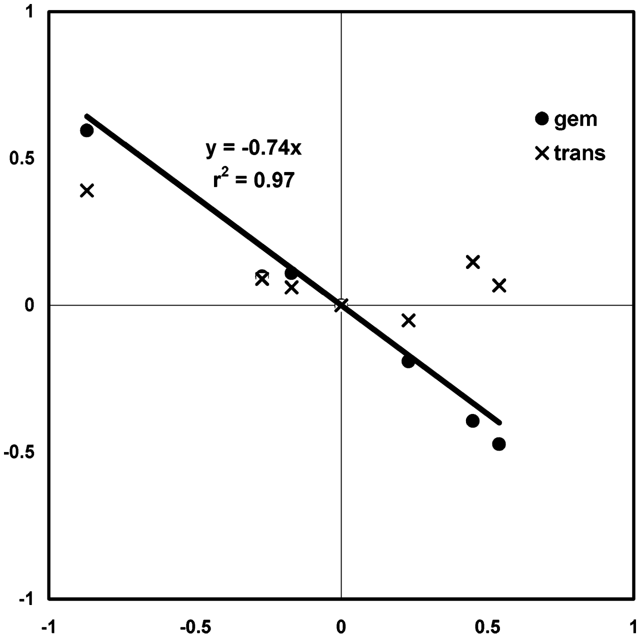


Figure 3. Hammett plots taking into account the branching of the Heck reaction to give either **2** or **3**.

samples. The separate reactivities could then be obtained from eqs 4 and 5.

$$r = k_{gem}/k_{trans} \quad (3)$$

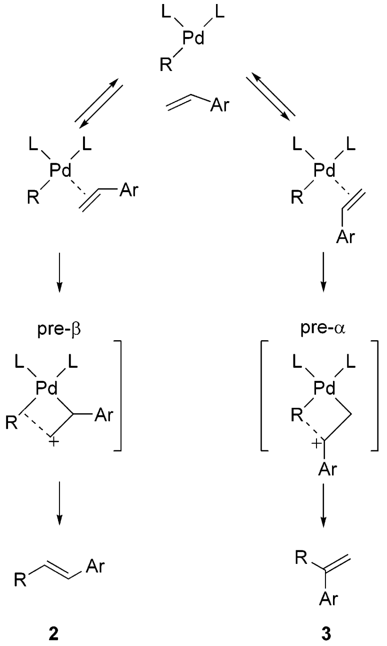
$$k_{trans} = k_{\mathrm{rel}}/(1 + r) \quad (4)$$

$$k_{gem} = rk_{trans} \quad (5)$$

The separated rates are plotted in Figure 3.

Note that the formation of the internal substitution product (*gem*) follows a Hammett correlation over the entire spectrum of σ values. The ρ value of -0.74 clearly indicates the importance of stabilization of positive charge at the benzylic position, indicating an initial electrophilic attack of Pd(II) preceding the migratory insertion. In contrast, the formation of the *trans* substitution product does *not* show a linear dependence on the electronic polarization of the double bond. Only 4-(dimethylamino)styrene shows a significant ability to outcompete styrene, and this might well be due to a preferential coordination of this substrate to palladium.

Scheme 4. Insertion of Pd into the Double Bond, Yielding Two Different Regioisomers[a]



[a] Only in the pre-α transition state can the 4-substituted aryl group interact with the developing positive charge.

These observations can be rationalized by consideration of the different cationic transition states possible after Pd insertion into the double bond (Scheme 4): only in the pre-α transition state can the 4-substituted aryl group interact directly with the neighboring positive charge.

Conclusion

The results of a Hammett study indicate that, in the cationic Heck reaction of 4-substituted styrenes, the formation of linear product (*trans* isomer) is insensitive to electronic substituent effects, whereas geminal substitution is strongly favored by electron-donating substituents, indicating accumulation of cationic charge at the conjugated position in the selectivity-determining step. We suggest that, for α-substitution, the slow step of the addition is an electrophilic attack by Pd(II) on the double bond, followed by a rapid migratory insertion. The current study also serves to underline the necessity of careful consideration of possible mechanistic branching points in relative rate studies.

Experimental Section

General Considerations. Ethyl acetate and hexane for chromatography were distilled under nitrogen. Ether was distilled from Na/benzophenone under nitrogen. DMF was vacuum-distilled and kept over molecular sieves. Purification of crude products was done by flash column chromatography on Matrex 60 Å silica gel. All reactions were performed in flame-dried glassware under argon. ^{1}H NMR spectra were obtained using a Varian Mercury 500 operating at 500 MHz.

Gas chromatography was performed on a Perkin-Elmer Autosystem 1020 equipped with a 25 m × 0.25 mm Chrompack CP-SIL 8CB column. Helium was used as carrier gas to avoid hydrogenation of the unsaturated compounds in the injector. General temperature program: 100 °C for 5 min, then 15 °C/min to 300 °C, which was maintained for 10 min. The general temperature program was able to separate all compounds, except for phenyl triflate/4-methylstyrene (retention time 6.88 min) and *trans*-stilbene/α-phenylchlorostyrene (retention time 16.23 min). Retention times for all compounds obtained with the general temperature program are included in the Supporting Information.

The phenyl triflate/4-methylstyrene mixture was separated using the following temperature program: 70 °C for 20 min, then 15 °C/min to 300 °C, which was maintained for 10 min. The peaks from phenyl triflate (retention time 18.2 min) and 4-methylstyrene (17.4 min) were now baseline-separated. The interference between *trans*-stilbene and α-phenylchlorostyrene was circumvented by using 4-methylstyrene instead of styrene as reference in the arylation of 4-chlorostyrene.

Styrene, 4-methoxystyrene, 4-methylstyrene, 4-chlorostyrene, and 4-(trifluoromethyl)styrene were purchased from Aldrich and used without further purification. $Pd_2(dba)_3$ was purchased from Lancaster and used without further purification. 4-(Dimethylamino)styrene was synthesized using a procedure similar to that described for the 2-isomer,[18] and 4-(((trifluoromethyl)sulfonyl)oxy)benzoic acid methyl ester was synthesized according to literature procedures.[19]

General Procedure for Preparative Heck Reactions. A 30 mL Schlenk tube was charged with $Pd_2(dba)_3$ (46 mg, 0.05 mmol) and 1,3-bis(diphenylphosphino)propane (42 mg, 0.1 mmol). The mixture was degassed twice with an argon purge, dissolved in DMF (1 mL), and stirred for 10 min. A solution of phenyl triflate (238 mg, 1.05 mmol), the 4-substituted styrene (1.0 mmol), and triethylamine (121 mg, 1.2 mmol) in DMF (1 mL) was then transferred via syringe, using DMF (1 mL) to rinse. The reaction mixture was heated to 80 °C and stirred overnight. The reaction mixture was then subjected directly to flash column chromatography on silica gel (5% ethyl acetate in hexanes). The collected fractions were evaporated and analyzed by a combination of GC analysis and ^1H NMR spectroscopy (500 MHz) using a delay time of 10 s. Integration of the vinylic protons gave highly accurate ratios of the two products. By comparison to the ratio for the same mixture obtained by GC, it was possible to obtain an accurate value for the slight difference in "burn ratio" (i.e., the sensitivity of the GC detector) for the two different products. This value was used to correct the product ratio used to construct Figure 3.

General Procedure for Competitive Heck Reactions. A 30 mL Schlenk tube was charged with $Pd_2(dba)_3$ (44 mg, 0.048 mmol) and 1,3-bis(diphenylphosphino)propane (40 mg, 0.096 mmol). The mixture was degassed twice with an argon purge, dissolved in DMF (1 mL), and stirred for 10 min. A solution of phenyl triflate (435 mg, 1.92 mmol), styrene (50 mg, 0.048 mmol), the 4-substituted styrene (0.048 mmol), triethylamine (115 mg, 1.14 mmol), and naphthalene as internal standard (31 mg, 0.24 mmol) in DMF (1 mL) was then added, and the reaction mixture was heated to 80 °C and stirred overnight. A sample (0.05 mL) was taken before and immediately after the addition of the reagents to the preformed palladium catalyst. Subsequent samples (each 0.05 mL) were taken after 15, 30, 60, 120, 240, and 480 min. Each sample was filtered through a plug of cotton wool, which was then flushed with dichloromethane (0.1 mL). Reaction progress was measured by GC, which determined the amounts of unreacted styrenes and allowed construction of Figure 1. In the construction of this plot, all concentrations were measured only in relation to the initial concentration of the same compound and, thus, were not sensitive to differences in burn ratio in the GC detector. The product ratios were also determined by GC and corrected by high-resolution ^1H NMR as described previously. The corrected initial ratios of the two products from each reactant were used according to eqs 3−5 in the construction of Figure 3.

***p*-(((Trifluoromethyl)sulfonyl)oxy)benzoic Acid Methyl Ester.** To a stirred solution of *p*-hydroxybenzoic acid methyl ester (0.2 g, 1.31 mmol) and pyridine (0.218 g, 2.76 mmol) in dichloromethane (4 mL) at 0 °C was added dropwise a solution of triflic anhydride (0.890 g, 5.52 mmol) in dichloromethane (4 mL). The reaction mixture was stirred for 4 h. The reaction mixture was then diluted with dichloromethane (30 mL) and washed at 0 °C with water (3 × 15 mL), 5% aqueous HCl (5 × 15 mL), and water (3 × 15 mL). The organic phase was then dried over $MgSO_4$ and rotary evaporated to give an oil which was subjected to flash column chromatography on silica gel (10% ethyl acetate in hexanes), yielding the title compound as a colorless oil (0.363 g, 97%).

4-(Methoxycarbonyl)styrene. A 30 mL Schlenk tube was charged with lithium chloride (596 mg, 14.076 mmol) and flame-dried under vacuum. After the mixture was cooled, $Pd_2(dba)_3 \cdot CHCl_3$ (185 mg, 0.176 mmol), PPh_3 (93 mg, 0.353 mmol), and CuI (68 mg, 0.132 mmol) were added and the mixture was degassed twice with an argon purge. DMF (2 mL) was added, and the mixture was stirred for 10 min. Then a solution of 4-(((trifluoromethyl)sulfonyl)oxy)benzoic acid methyl ester (1 g, 3.519 mmol) and vinyltributylstannane (1.172 g, 3.695 mmol) in DMF (4 mL) was added and the reaction mixture was heated to 110 °C overnight. The reaction mixture was diluted with dichloromethane (100 mL) and filtered through a pad of Celite. The filtrate was washed with a saturated aqueous solution of KF (30 mL), water (30 mL), and brine (30 mL). The organic phase was then dried over $MgSO_4$ and rotary evaporated to give a yellow oil, which was subjected to flash column chromatography on silica gel (10% ethyl acetate in hexanes). Traces of Sn were removed by dissolution of the oil in ether (20 mL) followed by addition of tetra-*n*-butylammonium diphenylphosphinate (2.483 g, 10.557 mmol). The mixture was stirred for 1 h, and the precipitated salts were removed by filtration. The filtrate was rotary-evaporated, and the remaining oil was subjected to flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield the title compound as a white solid (240 mg, 42%). Mp: 35 °C (lit.[20] mp: 34.5−35 °C). ^1H NMR data were identical with literature values.[21]

4-(Dimethylamino)styrene. A solution of triphenylmethylphosphonium bromide (5.747 g, 16.09 mmol) in ether (32 mL) was treated dropwise with *n*-BuLi (1.6 M solution in hexanes, 10.05 mL, 16.09 mmol) and stirred for 5 h. A solution of (dimethylamino)benzaldehyde (2 g, 13.41 mmol) in ether (12 mL) was then added dropwise, causing the precipitation of a white solid. The reaction mixture was then heated under reflux overnight, and after the mixture was cooled, the precipitate was filtered off. The filtrate was rotary-evaporated to give an oil which was subjected to flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield the title compound as a yellow oil (0.809 g, 41%). ^1H NMR data were identical with literature values.[22]

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Acknowledgment. Maria Vinther Juhl and Anne Pernille B. Tofteng are gratefully acknowledged for preliminary kinetic experiments.

Supporting Information Available: A table giving retention times for all compounds in this study and text giving NMR data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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