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Low Pressure Vinylation of Aryl and Vinyl Halides via Heck-Mizoroki Reactions Using Ethylene

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Abstract

Aryl bromides and iodides in the presence of catalytic amounts of a palladacycle derived from acetophenone oxime and 2 equivalents of potassium acetate react with ethylene under ambient pressure (15–30 psi) to give the corresponding vinylarenes. The reactions work with both electron-deficient and electron-rich aryl compounds and tolerate wide variety of common functional groups. Vinyl bromides lead to 1,3-dienes in moderate yields.

Introduction

Vinylarenes are important intermediates in fine chemical synthesis. Not only have they been employed in such well known reactions as Heck reactions¹ and olefin metathesis,² but also in selective transformations which introduce benzylic functionality to these simple starting materials.³ Ortho-substituted styrenes also serve as precursors for the synthesis of a wide variety of benzo-fused heterocycles. In the development of new reactions, vinylarenes are among the first substrates often tested, and many of the resultant products have significant utility in the syntheses of medicinally important compounds. In our recent work, we disclosed several new protocols for highly selective hydrovinylation (addition of ethylene) of functionalized vinylarenes and 1,3-dienes.⁴ When fully developed, we hope, many of these reactions, which are characterized by very high yield (>95%) enantioselectivity (>95%), and turnovers in the Ni(II)-catalyst, might add to our repertoire of ‘green’ manufacturing methods. As an extension of this work we sought a general, broadly applicable route to various substituted vinylarenes by expanding the scope of Heck arylation of ethylene, and this paper summarizes the results of such a study.

Transition-metal-mediated cross-coupling reactions provide efficient routes to vinylarenes that compliment more traditional methods, such as dehydration or Hofmann elimination,⁵ both of which have proven to be incompatible with sensitive functional groups. These reactions involve the use of vinyl -boron,⁶ -silicon,⁷ -tin,⁸ or -magnesium⁹ reagents that couple with the appropriate aryl electrophiles to afford substituted styrenes.

The Suzuki-Miyaura reaction provides a versatile method for the vinylation of aryl halides, but is plagued by a number of problems. Matteson^{6a} demonstrated that vinylboronic acid

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Supporting Information Available

Full experimental details, copies of all NMR spectra (¹H and ¹³C), and chromatograms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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polymerizes rapidly, and cannot be isolated. This problem can be circumvented via the use of three equivalents of 2,4,6-trivinylcyclotriboroxane-pyridine complex,^{6b} which affords vinylboronic acid in situ for use in coupling reactions. Vinyl boronate esters also participate in Suzuki cross-coupling reactions,^{6g} but the reagent needs to be prepared first, like the recently introduced potassium trifluoroborate salts.⁶ⁱ

Vinylpolysiloxanes^{7a-c} offer an inexpensive method for the vinylation of aryl bromides and iodides in moderate to good yields. Vinyltrimethylsilanes^{7d} have seen use in palladium-catalyzed vinylation reactions of aryl iodides in good yields when tris-diethylaminosulfonium trifluorosiliconate was used as an activator.

The Stille reaction of vinyltributyltin with aryl halides to access styrene derivatives is arguably the most advanced of the palladium-catalyzed vinylation processes. Fu *et al.*^{8a} have developed conditions that couple even deactivated aryl chlorides with vinyltributyltin in good yields when a fluoride activator is present. As with any tin-based reagents, toxicity, expense, lack of atom economy, and separation of byproducts are occasional detractors of this otherwise useful method.

Although the Pd-mediated reaction of aryl halides with ethylene was an early example of a Heck reaction,^{10a} high pressures traditionally required for the reactions and the propensity of further reaction of the primary product to yield stilbenes made this process less attractive.^{10,11} Recently, a number of advances in this field of Heck chemistry, including the advent of palladacycle-mediated couplings,^{12,13,14} have allowed greater control of selectivity and efficiency compared to the more traditional protocols that use Pd-salts. Though there are numerous palladacycles,¹² those with nitrogen,¹⁵ oxygen,¹⁶ phosphorous,¹⁷ and sulfur¹⁸ - containing donor ligands are the most commonly studied. Palladacycles tend to be more stable than the classical palladium phosphine complexes and are active at higher temperatures (100–160 °C), leading to increased reaction rates and higher turnover numbers (TONs). Among these, the oxime palladacycles used by Nájera *et al* in classical Heck reactions of iodo- and bromoarenes (TON up to 10¹⁰) are particularly noteworthy.¹⁴ We decided to examine the use of these complexes in Heck arylation of ethylene. We find that many of the problems associated with Heck reactions carried out at high pressures of ethylene can be circumvented by employing these highly active palladacycle catalysts at lower pressures. The Heck coupling of aryl and vinyl bromides and iodides with ethylene can be carried out using one of the oxime-palladacycles¹⁹ at 15 psi (balloon pressure) in the case of electron-deficient substrates and at 30 psi (Fisher-Porter tube) in the case of electron-rich substrates. In a paper that appeared after our work was completed,^{13d} vinylation of 6-methoxy-2-bromonaphthalene was reported to give the expected product with 73 % selectivity at 35 psi and with >98 % selectivity at 290 psi using a palladacycle derived from 2-phenylpyridine. However the scope and generality of this catalyst has not been reported.

(1)

Results and Discussion

Our work in this area started with the modest goal of finding a reliable and practical source for 4-vinyl-2-fluorobiphenyl (2), a precursor to (*S*)-flurbiprofen, which we have synthesized

in >97% ee via asymmetric hydrovinylation of **2**.^{4c,20} We wondered whether 4-bromo-2-fluorobiphenyl (**1**) would react with ethylene in the presence of the palladacycle **3** under ambient pressure (Eq 1).¹³ In an initial set of experiments the vinylation reaction was optimized by examining the product distribution as a function of temperature (Figure 1, Table 1).²¹ Our initial findings revealed that this process displays a high dependence upon reaction temperature, as the catalyst is not active below 85 °C, but is highly active at 110 °C, leading to undesired dimerization and polymerization products. Within a narrow range of 100–105 °C, the reaction appears to be highly selective for the formation of the desired product.

The effect of a variety of bases [Na₂CO₃, K₂CO₃, Cs₂CO₃, Na₂SO₄, KH₂PO₄, K₂HPO₄, CsF, NaOAc, KOAc, CsOAc, pyridine, Hünig's base] on the distribution of products was investigated under the modified reaction conditions using two prototypical palladacycles **3** and **4** and the results are shown in Table 2. As can be seen there CsOAc and amine bases tend to produce more of the dehalogenated product, **7**.

The reaction proceeded most effectively using 3 mol% **4** with phenothiazine as a radical inhibitor in *N,N*-dimethylacetamide in the presence of 2.2 equivalents of potassium acetate as the base at 105 °C to furnish **2** in 91% isolated yield of the product (entry 15). Through the optimization process, it was noted that these reactions could also be successfully conducted in *N*-methyl-2-pyrrolidone (NMP), but DMF and dioxane did not offer acceptable results. Palladacycle **4** appears to offer definite advantages over **3**, as **4** required lower catalyst loadings, shorter reaction times, and is both air and moisture stable. In the absence of phenothiazine, significant amount of polymerization was observed (entry 20).

More active catalytic species led to significant by-product formation when employed under our optimized conditions. For example, reaction of **1** with ethylene in the presence of the oxime-palladacycle **5** (Figure 1), the most reactive oxime-palladacycle reported to date,¹⁴ led to tandem Heck processes (i.e. stilbene formation) and polymerizations. Acetylene led to polymerization under our optimized conditions, while propylene afforded a 3:1:1 mixture of the desired isopropenyl substituted product to the *E*- and *Z*-*n*-propenyl adducts.

We next turned our attention to the scope of the leaving group. As outlined in Table 3, iodide, triflate, bromide, and chloride were all surveyed as leaving groups. Only iodide and bromide offered satisfactory results, the iodide being more active than bromide. The discovery that triflates are inert under these reaction conditions reactions is of some utility. It offers two distinct advantages, first, this method offers the ability to perform tandem cross-coupling reactions without contamination from divinylated materials as seen with the Stille reaction.²² Besides, generally unreactive phenols or other deactivated electron-rich substrates can be transformed into highly activated electron-deficient triflated or tosylated aryl halides.

With optimized conditions in hand, we explored the scope of the reaction in the presence of a number of common functionalities. As shown in Tables 4 and 5, the reaction proceeds with moderate to excellent yields in the presence of a large variety of functional groups including nitriles, ketones, esters, aldehydes, carboxylic acids, triflates, and nitro groups. Furthermore, both electron-deficient and electron-rich aryl halides react with ethylene to afford the desired products; even though, as expected, the rate of reaction of electron-deficient aryl halides is higher. Although reaction times for each specific halide might need further optimization, the general protocol was to run the reactions for either 18 h (electron-deficient substrates) or 24 h (electron-rich substrates). Notice that for several selected substrates (entries 2, 3, 4, 6 in Table 4; entries 1, 2 Table 5), shorter times were sufficient.

Our investigations revealed that the reactions of electron-rich aryl halides never went to completion at 15 psi even at high catalyst loadings (i.e. 10 mol% palladacycle dimer). Increasing the pressure by running the reactions in Fisher-Porter tubes to maintain an ethylene pressure of 30 psi, all other conditions being identical, gave complete conversion and moderate to good isolated yields for these substrates. *The only product formed other than the vinylarene is high molecular weight material (i.e. undefined polymers) which are easily removed upon column chromatography.* Functional groups such as free phenols, amines, thiols, and primary amides were incompatible even with the optimized conditions reported here. Noteworthy transformations include those of **10h**, **10i**, and **20d**, which were problematic under the Suzuki-Miyaura conditions with potassium vinyltrifluoroborate.⁶ⁱ

Having demonstrated the utility of the reaction primarily for para-substituted electrophiles, we decided to compare these yields with those for the ortho and meta substituted analogs and these results are shown in Table 6. The methyl-substituted aryl bromide represents an electron-rich bromide, whereas the chloro-, acetyl- and nitrile-substituted bromides were chosen as examples of electron-deficient bromides. In all cases, the functional groups were well tolerated as the desired products were formed in comparable yields for the three congeners. Acetyl or methoxy group at the ortho position of a bromide significantly reduces its reactivity (entry 10). 2-Iodoanisole also gave a low yield of the expected product.

Finally a brief investigation of the synthesis of 1,3-dienes from vinyl bromides was undertaken. As shown in Table 7, the process affords the desired products in moderate to good yields without any attendant Diels-Alder by-products. Although detailed studies were not carried out, electron-deficient vinyl halides appear to react faster than electron-rich vinyl halides. In all cases studied, the reactions went to completion with no greater than 5 mol% of the oxime-palladacycle catalyst **4**.

Conclusions

The Mizoroki-Heck reactions of aryl bromides and iodides with ethylene under low pressures (15–30 psi) provide an efficient and highly selective route to functionalized styrenes and 1,3-dienes. Conditions that avoid polymerization and tandem Heck processes that plague traditional high pressure versions of this reaction are reported. The reaction proceeds readily in the presence of a wide variety of functional groups including triflates.

Experimental Section

General methods

All substrates were used as received without further purification. The palladacycle (**3**),^{13a} oxime palladacycles^{15a} (**4** and **5**) and vinyl bromides **36b**,²³ **36c**,²⁴ and **36d**²⁵ were prepared according to literature. *N,N*-Dimethylacetamide was distilled under reduced pressure from CaH₂ before use and stored under nitrogen. Ethylene (99.5%) was purchased from Praxair Inc., and dried before use by passing through a column (0.5" × 4") of Drierite®. Analytical TLC was performed on E. Merck precoated (0.25 mm) silica gel 60 F254 plates. Flash column chromatography²⁶ was carried out on silica gel 40 (Scientific Adsorbents Incorporated, Microns Flash). Both conversion and selectivity were determined by gas chromatographic analyses, which were performed on a Hewlett-Packard 5890 equipped with a [poly(dimethylsiloxane)] (25 m × 0.20 mm, 0.33 mm film thickness) capillary GC column purchased from Sigma-Aldrich® (Supelco® Analytical) and a FID detector connected to a HP 3396 integrator.

General Procedure for Heck Reaction with Electron-deficient Aryl (Vinyl) Halides

In a fumehood, a 25 mL three-necked round-bottomed flask equipped with a magnetic stirring bar, two glass stoppers, and a three-way flow-controlled stopcock was greased, assembled, evacuated, flame-dried, and purged with nitrogen. The flask was then charged with substrate (0.5 mmol), catalyst (8.2 mg, 0.015 mmol), phenothiazine (6.0 mg, 0.03 mmol), anhydrous potassium acetate (108 mg, 1.1 mmol), and *N,N*-dimethylacetamide (4.0 mL) under a strong stream of nitrogen. The vessel was then closed to nitrogen and the nitrogen line was removed. Two balloons of ethylene were then placed on the flow-controlled adapter to create a positive pressure of ethylene in the system when opened to the balloons. Upon opening the system to the two ethylene balloons, the flask was placed into a pre-heated 105 °C silicone oil bath and the reaction was maintained for 16 h. Upon completion of reaction, the vessel was removed from the oil bath and cooled to ambient temperature at which time the system was opened to air and filtered through a plug of Celite® (1" × 0.5") to remove salts and palladium metal. The filtrate was then poured into a 100 mL separatory funnel containing 10% H₂SO₄ (v:v, 30 mL). The mixture was then extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were then combined, dried with MgSO₄ (1.0 g), decolorized with activated charcoal (0.5 g), filtered, and reduced via rotary evaporation. The yellow-brown oil was then purified by flash column chromatography.²⁷ The appropriate fractions were collected and the product was isolated. All relevant analytical data were collected for each product and is located below.

General Procedure for Heck Reaction with Electron-rich Aryl (Vinyl) Halides

A dry Fisher-Porter tube was charged with substrate (0.5 mmol), catalyst (16.4 mg, 0.03 mmol), phenothiazine (12.0 mg, 0.06 mmol), anhydrous potassium acetate (108 mg, 1.1 mmol), and *N,N*-dimethylacetamide (4.0 mL) under a strong stream of nitrogen. The vessel was then closed and the nitrogen line was removed. After the tube was connected to an ethylene line, the line was evacuated 3 times, and then ethylene gas was introduced to the tube, and pressurized to 30 psi. Upon charging the system with ethylene, the Fisher-Porter tube was placed into a pre-heated 105 °C silicone oil bath, with an associated pressure increase to 32–35 psi, and the reaction was maintained for 24 h. The remainder of the procedure (i.e. workup and isolation) is identical to that described above for electron-deficient substrates.

3-Fluoro-4-Phenylstyrene (2)

Clear liquid. ¹H NMR (400 MHz, CDCl₃): δ 7.60–7.58 (m, 2H), 7.50–7.46 (m, 2H), 7.43–7.38 (m, 2H), 7.29–7.23 (m, 2H), 6.74 (dd, *J* = 17.60, 10.80 Hz, 1H), 5.83 (d, *J* = 17.60 Hz, 1H), 5.36 (d, *J* = 10.80 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 159.9 (d, *J*_{C-F} = 159.9 Hz), 138.9 (d, *J*_{C-F} = 3.2 Hz), 135.6, 135.5, 130.7, 128.9, 128.4, 128.3 (d, *J*_{C-F} = 5.6 Hz), 127.7, 122.4, 115.2, 113.5, 113.3. HRMS-ESI: *m/z* [M + Na]⁺ calcd for C₁₂H₁₁F + Na: 197.0737; found: 197.0734. *R*_f = 0.52 (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 5 min at 100 °C, 5 °C/min, 5 min at 200 °C; retention time (min): 22.10.

4'-Vinylacetophenone (9)

mp 33–34 °C. ^1H NMR (500 MHz, CDCl_3): δ 7.92 (d, $J = 8.00$ Hz, 2H), 7.48 (d, $J = 8.00$ Hz, 2H), 6.76 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.87 (d, $J = 17.50$ Hz, 1H), 5.39 (d, $J = 11.00$ Hz, 1H), 2.60 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 197.6, 142.1, 136.3, 135.9, 128.7, 126.3, 116.7, 26.6. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_{10}\text{O} + \text{Na}$: 169.0624; found: 169.0620. $R_f = 0.33$ (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane) conditions: 30 min at 135 °C; retention time (min): 13.57.

3-Vinylbenzophenone (11)

mp 38–41 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.84–7.80 (m, 3H), 7.68–7.62 (m, 2H), 7.60–7.55 (m, 1H), 7.49 (t, $J = 8.00$ Hz, 2H), 7.44 (t, $J = 8.00$ Hz, 1H), 6.76 (dd, $J = 17.60$, 10.80 Hz, 1H), 5.81 (d, $J = 17.60$ Hz, 1H), 5.33 (d, $J = 10.80$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 196.6, 137.9, 137.8, 137.5, 136.0, 132.5, 130.0, 129.9, 129.4, 128.4, 128.3, 127.7, 115.3. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{12}\text{O} + \text{Na}$: 231.0780; found: 231.0786. $R_f = 0.22$ (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane) conditions: 5 min at 100 °C, 5 °C/min, 5 min at 250 °C; retention time (min): 27.48.

3-Chlorostyrene (12)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.43 (s, 1H), 7.31–7.25 (m, 3H), 6.68 (dd, $J = 17.50$, 11.00 Hz, 1H), 5.79 (d, $J = 17.50$ Hz, 1H), 5.33 (d, $J = 11.00$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 139.4, 135.6, 134.5, 129.8, 127.8, 126.2, 124.5, 115.3. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_8\text{H}_7\text{Cl} + \text{Na}$: 161.0128; found: 161.0123. $R_f = 0.83$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 100 °C; retention time (min): 13.45.

4-Vinylmethylbenzoate (13)

mp 33–34 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.99 (dd, *J* = 7.50, 1.50 Hz, 2H), 7.45 (d, *J* = 7.00 Hz, 2H), 6.75 (dd, *J* = 17.50, 11.00 Hz, 1H), 5.86 (d, *J* = 17.50 Hz, 1H), 5.37 (d, *J* = 11.00 Hz, 1H), 3.91 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 166.8, 141.9, 136.0, 129.9, 129.3, 126.1, 116.4, 52.0. HRMS-ESI: *m/z* [M + Na]⁺ calcd for C₁₀H₁₀O₂ + Na: 185.0573; found: 185.0570. *R_f* = 0.39 (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane) conditions: 30 min at 135 °C; retention time (min): 15.44.

4-Vinylbenzaldehyde (14)

Clear liquid. ¹H NMR (500 MHz, CDCl₃): δ 10.00 (s, 1H), 7.84 (d, *J* = 7.50 Hz, 2H), 7.53 (d, *J* = 7.50 Hz, 2H), 6.77 (dd, *J* = 17.50, 11.00 Hz, 1H), 5.89 (d, *J* = 17.50 Hz, 1H), 5.43 (d, *J* = 11.00 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 191.7, 143.4, 135.9, 135.7, 130.1, 126.7, 117.4. HRMS-ESI: *m/z* [M + Na]⁺ calcd for C₉H₈O + Na: 155.0467; found: 155.0463. *R_f* = 0.24 (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane) conditions: 30 min at 110 °C; retention time (min): 18.15.

4-Vinylbenzonitrile (15)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.60 (d, J = 8.50 Hz, 2H), 7.47 (d, J = 8.50 Hz, 2H), 6.72 (dd, J = 17.50, 11.00 Hz, 1H), 5.87 (d, J = 17.50 Hz, 1H), 5.44 (d, J = 11.00 Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 141.9, 135.3, 132.3, 126.7, 118.8, 117.7, 111.1.

HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_7\text{N} + \text{Na}$: 152.0471; found: 152.0476. R_f = 0.27 (hexanes-EtOAc, 19:1). GC [poly(dimethylsiloxane)] conditions: 30 min at 135 $^\circ\text{C}$; retention time (min): 9.09.

4-Nitrostyrene (16)

Clear oil. ^1H NMR (500 MHz, CDCl_3): δ 8.18 (dt, J = 9.00, 2.00 Hz, 2H), 7.53 (dd, J = 9.00, 2.00 Hz, 2H), 6.78 (dd, J = 17.50, 11.00 Hz, 1H), 5.93 (d, J = 17.50 Hz, 1H), 5.50 (d, J = 11.00 Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 147.2, 143.8, 135.0, 126.8, 123.9, 118.6.

HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_8\text{H}_7\text{NO}_2 + \text{Na}$: 172.0369; found: 172.0361. R_f = 0.39 (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane)] conditions: 30 min at 120 $^\circ\text{C}$; retention time (min): 23.69.

4-Trifluoromethylstyrene (17)

Clear oil. ^1H NMR (500 MHz, CDCl_3): δ 7.47 (dd, $J = 7.00, 1.50$ Hz, 2H), 7.24 (dd, $J = 7.00, 1.50$ Hz, 2H), 6.72 (dd, $J = 18.00, 11.00$ Hz, 1H), 5.77 (d, $J = 18.00$ Hz, 1H), 5.35 (d, $J = 11.00$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 148.9, 138.0, 135.0, 127.8, 121.4, 118.8 (q, $J_{\text{C-F}} = 255.0$ Hz), 116.0. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_7\text{F}_3\text{O}_3\text{S} + \text{Na}$: 274.9966; found: 274.9961. $R_f = 0.48$ (hexanes-EtOAc, 19:1). GC [poly(dimethylsiloxane)] conditions: 30 min at 140 $^\circ\text{C}$; retention time (min): 7.90.

4-Vinylbenzoic acid (18)

mp 142–144 $^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3): δ 8.08 (d, $J = 8.00$ Hz, 2H), 7.40 (d, $J = 8.00$ Hz, 2H), 6.78 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.90 (d, $J = 17.50$ Hz, 1H), 5.41 (d, $J = 11.00$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 171.9, 142.8, 136.0, 130.6, 128.4, 126.2, 117.0. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_8\text{O}_2 + \text{Na}$: 171.0422; found: 171.0420. $R_f = 0.16$ (hexanes-EtOAc, 2:1).

2, 6-Dichlorostyrene (19)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.31 (d, $J = 8.00$ Hz, 2H), 7.09 (t, $J = 7.00$ Hz, 2H), 6.73 (dd, $J = 18.00, 12.00$ Hz, 1H), 5.81 (dd, $J = 18.00, 1.00$ Hz, 1H), 5.73 (dd, $J = 12.00, 1.00$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 135.0, 134.3, 130.9, 128.4, 128.2, 122.8. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_8\text{H}_6\text{Cl}_2 + \text{Na}$: 194.9744; found: 194.9740. $R_f = 0.92$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 120 °C; retention time (min): 15.16.

4-Isobutylstyrene (21)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.33 (d, J = 8.00 Hz, 2H), 7.11 (d, J = 8.00 Hz, 2H), 6.71 (dd, J = 17.60, 11.00 Hz, 1H), 5.71 (dd, J = 17.60, 0.80 Hz, 1H), 5.20 (dd, J = 11.00, 0.80 Hz, 1H), 2.47 (d, J = 7.20 Hz, 2H), 1.88 (septet, J = 6.80 Hz, 1H), 0.92 (d, J = 6.80 Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3): δ 1141.4, 137.7, 135.0, 129.2, 125.9, 112.7, 45.2, 30.2, 22.3. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{16} + \text{Na}$: 183.1144; found: 183.1141. R_f = 0.68 (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 120 $^\circ\text{C}$; retention time (min): 16.71.

4-Methoxystyrene (22)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.37 (dt, J = 8.50, 2.50 Hz, 2H), 6.89 (dt, J = 8.50, 2.50 Hz, 2H), 6.70 (dd, J = 17.50, 11.00 Hz, 1H), 5.64 (d, J = 17.50 Hz, 1H), 5.16 (d, J = 11.00 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 159.3, 136.2, 130.4, 127.3, 113.9, 111.5, 55.2. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_{10}\text{O} + \text{Na}$: 157.0624; found: 157.0620. R_f = 0.79 (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane) conditions: 30 min at 110 $^\circ\text{C}$; retention time (min): 14.88.

4-Methylstyrene (23)

Clear liquid. ¹H NMR (500 MHz, CDCl₃): δ 7.39 (d, *J* = 8.00 Hz, 2H), 7.2 (d, *J* = 8.00 Hz, 2H), 6.77 (dd, *J* = 17.50, 11.00 Hz, 1H), 5.78 (d, *J* = 17.50 Hz, 1H), 5.26 (d, *J* = 11.00 Hz, 1H), 2.41 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 137.5, 136.7, 134.8, 129.2, 126.1, 112.7, 21.1. HRMS-ESI: *m/z* [M + Na]⁺ calcd for C₉H₁₀ + Na: 141.0675; found: 141.0671. *R_f* = 0.46 (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 80 °C; retention time (min): 15.99.

2,4,6-Trimethylstyrene (24)

Clear liquid. ¹H NMR (500 MHz, CDCl₃): δ 6.90 (s, 2H), 6.71 (dd, *J* = 17.00, 11.00 Hz, 1H), 5.53 (d, *J* = 17.00 Hz, 1H), 5.27 (d, *J* = 11.00 Hz, 1H), 2.32 (s, 6H), 2.30 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 136.1, 135.7, 135.0, 134.8, 128.5, 119.0, 20.9, 20.8. HRMS-ESI: *m/z* [M + Na]⁺ calcd for C₁₁H₁₄ + Na: 169.0988; found: 169.0983. *R_f* = 0.57 (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 120 °C; retention time (min): 12.53.

1-Vinylnaphthalene (25)

mp 63–64 °C. ^1H NMR (500 MHz, CDCl_3): δ 8.17 (d, $J = 8.00$ Hz, 1H), 7.90 (d, $J = 7.50$ Hz, 1H), 7.84 (d, $J = 8.00$ Hz, 1H), 7.68 (d, $J = 7.50$ Hz, 1H), 7.57–7.49 (m, 4H), 5.85 (dd, $J = 17.50, 1.50$ Hz, 1H), 5.53 (dd, $J = 11.00, 1.50$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 135.6, 134.4, 133.6, 131.1, 128.5, 128.1, 126.0, 125.7, 125.6, 123.7, 123.6, 117. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{10} + \text{Na}$: 177.0675; found: 177.0673. $R_f = 0.36$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 150 °C; retention time (min): 14.84.

2-Vinylnaphthalene (26)

mp 64–66 °C. ^1H NMR (500 MHz, CDCl_3): δ 7.83–7.80 (m, 3H), 7.77 (s, 1H), 7.65 (dd, $J = 8.50, 1.50$ Hz, 1H), 7.49–7.44 (m, 2H), 6.89 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.89 (d, $J = 17.50$ Hz, 1H), 5.35 (d, $J = 11.00$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 136.9, 135.0, 133.6, 133.2, 128.1, 128.0, 127.7, 126.3, 126.2, 125.9, 123.2, 114.2. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{10} + \text{Na}$: 177.0675; found: 177.0675. $R_f = 0.33$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 150 °C; retention time (min): 15.91.

2-Methylstyrene (28)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.54-7.52 (m, 1H), 7.24-7.19 (m, 3H), 7.00 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.69 (dd, $J = 17.50, 1.50$ Hz, 1H), 5.34 (dd, $J = 11.00, 1.50$ Hz, 1H), 2.41 (s, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 136.8, 135.4, 134.9, 130.2, 127.6, 126.1, 125.4, 115.1, 19.7. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_{10} + \text{Na}$: 141.0675; found: 141.0671. $R_f = 0.60$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 90 °C; retention time (min): 11.55.

3-Methylstyrene (29)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.28-7.26 (m, 3H), 7.13-7.12 (m, 1H), 6.74 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.78 (d, $J = 17.50$ Hz, 1H), 5.27 (d, $J = 11.00$ Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 138.0, 137.5, 137.0, 128.6, 128.4, 126.9, 123.3, 113.5, 21.4. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_{10} + \text{Na}$: 141.0675; found: 141.0673. $R_f = 0.56$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 80 $^\circ\text{C}$; retention time (min): 15.63.

2-Chlorostyrene (30)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.59 (dd, $J = 7.50, 1.50$ Hz, 1H), 7.38 (dd, $J = 8.00, 1.50$ Hz, 1H), 7.26 (dt, $J = 7.50, 1.50$ Hz, 1H), 7.21 (dt, $J = 7.50, 1.50$ Hz, 1H), 7.15 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.77 (dd, $J = 17.50, 1.00$ Hz, 1H), 5.41 (dd, $J = 11.00, 1.00$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 135.7, 133.2, 133.1, 129.6, 128.8, 126.8, 126.6, 116.5. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_8\text{H}_7\text{Cl} + \text{Na}$: 161.0128; found: 161.0126. $R_f = 0.66$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 90 $^\circ\text{C}$; retention time (min): 17.25.

4-Chlorostyrene (31)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.35-7.29 (m, 4H), 6.68 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.73 (d, $J = 17.50$ Hz, 1H), 5.28 (d, $J = 11.00$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 136.0, 135.7, 133.4, 128.7, 127.4, 114.4. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_8\text{H}_7\text{Cl} + \text{Na}$: 161.0128; found: 161.0123. $R_f = 0.60$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 100 $^\circ\text{C}$; retention time (min): 13.06.

2-Vinylbenzonitrile (32)

Clear oil. ^1H NMR (500 MHz, CDCl_3): δ 7.67 (d, $J = 8.00$ Hz, 1H), 7.62 (dd, $J = 8.00, 1.00$ Hz, 1H), 7.56 (dt, $J = 8.00, 1.00$ Hz, 1H), 7.34 (dt, $J = 8.00, 1.00$ Hz, 1H), 7.08 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.94 (d, $J = 17.50$ Hz, 1H), 5.53 (d, $J = 17.50$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 140.7, 132.9, 132.7, 127.9, 125.4, 118.9, 117.7, 111.2. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_7\text{N} + \text{Na}$: 152.0471; found: 152.0470. $R_f = 0.31$ (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane) conditions: 30 min at 120 $^\circ\text{C}$; retention time (min): 11.92.

3-Vinylbenzonitrile (33)

Pale yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 7.66 (m, 1H), 7.61 (d, $J = 7.50$ Hz, 1H), 7.53 (d, $J = 7.50$ Hz, 1H), 7.43 (d, $J = 8.00$ Hz, 1H), 6.69 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.81 (d, $J = 17.50$ Hz, 1H), 5.39 (d, $J = 11.00$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 138.7, 134.8, 131.0, 130.3, 129.7, 129.3, 118.7, 116.6, 112.8. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_7\text{N} + \text{Na}$: 152.0471; found: 152.0477. $R_f = 0.38$ (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane) conditions: 30 min at 120 $^\circ\text{C}$; retention time (min): 12.60.

2-Vinylacetophenone (34)

Clear oil. ^1H NMR (500 MHz, CDCl_3): δ 7.64-7.60 (m, 1H, + x), 7.56 (d, $J = 8.00$ Hz, 1H), 7.47-7.44 (m, 1H, + x), 7.37-7.32 (m, 1H, + x), 7.20 (dd, $J = 17.50, 11.00$ Hz, 1H), 5.64 (dd, $J = 17.50, 1.00$ Hz, 1H), 5.34 (dd, $J = 11.00, 1.00$ Hz, 1H), 2.58 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 202.0, 137.7, 137.5, 135.9, 131.6, 128.6, 127.6, 127.4, 116.7, 29.8. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_8\text{O} + \text{Na}$: 155.0467; found: 155.0460. $R_f = 0.36$ (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane) conditions: 30 min at 135 $^\circ\text{C}$; retention time (min): 10.47.

3-Vinylacetophenone (35)

Pale yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 7.97 (t, $J = 1.50$ Hz, 1H), 7.83 (dt, $J = 8.00$, 1.50 Hz, 1H), 7.60 (d, $J = 7.00$ Hz, 1H), 7.42 (t, $J = 8.00$ Hz, 1H), 6.75 (dd, $J = 17.50$, 11.00 Hz, 1H), 5.83 (d, $J = 17.50$ Hz, 1H), 5.33 (d, $J = 11.00$ Hz, 1H). 2.61 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 198.0, 138.0, 137.4, 135.9, 130.5, 128.7, 127.6, 126.0, 115.2, 26.6. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_8\text{O} + \text{Na}$: 155.0467; found: 155.0468. $R_f = 0.32$ (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane)] conditions: 30 min at 135 $^\circ\text{C}$; retention time (min): 12.44.

1-Phenyl-1,3-butadiene (37)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.41 (d, $J = 7.50$ Hz, 2H), 7.32 (t, $J = 8.00$ Hz, 2H), 7.23 (t, $J = 7.50$ Hz, 1H), 6.80 (dd, $J = 16.00, 10.00$ Hz, 1H), 6.57 (d, $J = 16.00$ Hz, 1H), 6.54-6.50 (m, 1H), 5.34 (d, $J = 17.00$ Hz, 1H), 5.18 (d, $J = 10.00$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 137.2, 137.1, 132.8, 129.6, 128.6, 127.6, 126.4, 117.6. HRMS-ESI: m/z $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_{10}$: 130.0777; found: 130.0773. $R_f = 0.40$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 100 $^\circ\text{C}$; retention time (min): 20.04.

4-*t*-Butyl-1-vinylcyclohex-1-ene (38)

Clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 6.36 (dd, $J = 17.50, 10.50$ Hz, 1H), 5.76 (t, $J = 3.00$ Hz, 1H), 5.06 (d, $J = 17.50$ Hz, 1H), 4.89 (d, $J = 10.50$ Hz, 1H), 2.36-2.30 (m, 1H), 2.20-2.14 (m, 1H), 2.10-2.02 (m, 1H), 1.94-1.88 (m, 2H), 1.32-1.26 (m, 1H), 1.18 (ddd, $J = 12.00, 8.00, 5.00$ Hz, 1H), 0.89 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ 139.7, 136.0, 130.0, 109.8, 44.3, 32.2, 27.4, 27.2, 25.2, 23.7. HRMS-ESI: m/z $[\text{M}]^+$ calcd for $\text{C}_{12}\text{H}_{20}$: 164.1560; found: 164.1558. $R_f = 0.76$ (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 130 $^\circ\text{C}$; retention time (min): 12.51.

Methyl 2,4-pentadienoate (39)

Clear liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.22 (dd, $J = 15.20, 10.40$ Hz, 1H), 6.41 (dt, $J = 17.20, 10.80$ Hz, 1H), 5.86 (d, $J = 15.20$ Hz, 1H), 5.55 (d, $J = 17.20$ Hz, 1H), 5.44 (d, $J =$

10.00 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 167.1, 144.7, 134.6, 125.5, 121.6, 51.4. HRMS-ESI: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_6\text{H}_8\text{O}_2 + \text{Na}$: 135.0416; found: 135.0411. R_f = 0.32 (hexanes-EtOAc, 9:1). GC [poly(dimethylsiloxane) conditions: 30 min at 70 °C; retention time (min): 7.90 (Z), 8.94 (E); 3:97.

1-Vinylcyclohex-1-ene (40)

Clear liquid. ^1H NMR (400 MHz, CDCl_3): δ 6.35 (dd, J = 17.60, 10.80 Hz, 1H), 5.77 (s, 1H), 5.07 (d, J = 17.60 Hz, 1H), 4.90 (d, J = 10.80 Hz, 1H), 2.14 (d, J = 4.40 Hz, 4H), 1.72-1.60 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 140.2, 136.0, 129.8, 109.5, 25.8, 23.8, 22.5, 22.4. HRMS-ESI: m/z $[\text{M}]^+$ calcd for C_8H_{12} : 108.0935; found: 108.0938. R_f = 0.94 (isocratic *n*-pentane). GC [poly(dimethylsiloxane) conditions: 30 min at 60 °C; retention time (min): 18.10.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Palladacycle Catalysts and Phenothiazine (PTZ), a Radical Inhibitor.

Table 1 Temperature Dependence in the Activation of Palladacycle **3**.^a

temp. (°C)	conv. (%)	selectivity (%)
75	no rxn	n/a
80	no rxn	n/a
85	8	>99
90	36	>99
95	95	>99
100	97	>99
105	100	>99
110	100	89 ^b
115	100	61 ^b

^aSee Eq 1 for reaction conditions.^bBy-products arising from reduction, tandem Heck processes, and polymerization were observed.

Table 2

Effect of Base on Palladacycle-Mediated Heck Reactions with Ethylene

(2)

entry	cat.	mol %	time (h)	base	conv. (%)	selec. ^a (2:7)
1	-	-	48	NaOAc	0	-
2	3	5	48	none	4.6	100:0
3	3	5	48	Na ₂ CO ₃	48	100:0
4	4	2.5	18	Na ₂ CO ₃	3.3	-
5	3	5	48	K ₂ CO ₃	94	93:7
6	3	5	48	Cs ₂ CO ₃	24	98:2
7	3	5	48	Na ₂ SO ₄	9	100:0
8	4	2.5	18	Na ₂ SO ₄	2.7	-
9	3	5	48	KH ₂ PO ₄	28	100:0
10	3	5	48	K ₂ HPO ₄	17	100:0
11	3	5	48	CsF	84	98:2
12	3	5	48	NaOAc	82	97:3
13	3	5	48	KOAc	93	100:0
14	4	2.5	18	KOAc	97.5	100:0
15	4	3	18	KOAc	100	100:0
16	3	5	48	CsOAc	35	92:8
17	4	2.5	18	CsOAc	33.4	91:9
18	3	5	48	pyridine	10	79:21

(2)

entry	cat.	mol %	time (h)	base	conv. (%)	selec. ^a (2:7)
19	3	5	48	EtN(<i>i</i> -Pr) ₂	64	89:11
20	4	2.5	18	KOAc	100	^b

^aRatio of **2**:**7** determined by GC assay of isolated material.

^bWith the exclusion of PTZ from the reaction, compound **2** was isolated only in 58% yield. Polymeric material (as determined by ¹H NMR) accounted for the remainder of the mass balance for the transformation.

Table 3

Effect of the Nature of the Electrophile

entry	no.	ArX	product	yield
1	8a		9	80

entry	no.	ArX	product	yield
2	8b		9	85
3	8c		-	0
4	8d		-	0

Table 4

Heck Vinylation of Electron-Deficient Aryl Halides with Ethylene^a

entry	no.	ArX	time	vinylarene	yield (%)
1	10a		18	11	68

entry	no.	ArX	time	vinylarene	yield (%)
2	10b		4	12	81

entry	no.	ArX	time	vinylarene	yield (%)
3	10c		6	13	91

4 8b

10 9 85

entry	no.	ArX	time	vinylarene	yield (%)
5	10d		18	14	90

6 10e

10 15 92

entry	no.	ArX	time	vinylarene	yield (%)

7 10f

8 10g

18 17 93

9 10h

18 18 95

entry	no.	ArX	time	vinylarene	yield (%)
10	10i		18	19	83

^a See Eq 3 for procedure.

^b 3.2 Equivalents of KOac were used.

Table 5

Heck Vinylation of Electron-Rich Aryl Halides with Ethylene^a

entry	no.	ArX	time	vinylarene	yield (%)
1	20a		16	21	70

entry	no.	ArX	time	vinylarene	yield (%)

2b 20b

53

22

20

3 20c

23

24

86

entry	no.	ArX	time	vinylarene	yield (%)
4	20d		24	24	71

entry	no.	ArX	time	vinylarene	yield (%)
6	20f		24	26	84

^a See Eq. 3 for procedure except 6 mol% catalyst and 30 psi ethylene pressure (Fisher Porter Reactor) was used.

^b 10 mol% catalyst was used.

Table 6

Comparison of Vinylation of *o*-, *m*- and *p*-Substituted Aryl Bromides and Aryl Iodides^a

entry	no.	ArX	mol% 4/pres. (psi)	product	yield (%)
1	27a		6/30	28	81

entry	no.	ArX	mol% 4/pres. (psi)	product	yield (%)
2	27b		6/30	29	84
3	20c		6/30	23	86
4	27c		3/15	30	75

entry	no.	ArX	mol% 4/pres. (psi)	product	yield (%)

5 10b

12 81

6 27e

31 82

3/15

7 27f

32 82

3/15

8 27g

33 88

3/15

entry	no.	ArX	mol% 4/pres. (psi)	product	yield (%)

9 10e

15

92

10 27h^b

34^b

3/15

78

11 27i

35

3/15

97

entry	no.	ArX	mol% 4 /pres. (psi)	product	yield (%)
12	8b		3/15	9	85

^a 3–6 mol% **4**, KOAc (2.2 equiv.) PTZ, ethylene, *N,N*-DMA 105 °C.

^b **34** is contaminated with ~25% **27h** by mass. The two compounds are inseparable by column chromatography.

Table 7

Palladacycle-Catalyzed Reactions of Vinyl Bromides with Ethylene

(4)

entry	no.	vinyl-X	pres. (psi)	product	yield (%)
1	36a		15	37	68

(4)

entry	no.	vinyl-X	pres. (psi)	product	yield (%)
2	36b		30	38	74

3 36c

15

39

63

(4)

entry	no.	vinyl-X	pres. (psi)	product	yield (%)
4	36d		30		48