tracted with hexane. (An oily layer, which is probably product, develops.) The hexane layer was backwashed with 1 N NaOH, and the aqueous layers were combined. After acidification (3 N HCl), the aqueous mixture was extracted with ethyl acetate (3×), and the organic layers were filtered through Na_2SO_4. The solvent was removed in vacuo, and the residue was chromatographed on silica gel using a gradient of 100% CH_2Cl_2 to 4% MeOH/CH_2Cl_2 to give 4.13 g (87%) of **10** as a gum: $[\alpha]_D$ −65.9° (*c* 0.9075, EtOH); MS, *m/z* at 349, most intense ions 114, (9999), 70 (7771), 57 (4699), 170 (3531); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.73 (m, 4 H), 2.95–3.47 (m, 6 H), 3.85 (br m, 1 H), 4.11 (dd, 1 H), 6.20 (br, 1 H), 7.25 (s, 5 H). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.20; H, 7.70; N, 3.98.

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Synthesis of Functionalized Styrenes via Palladium-Catalyzed Coupling of Aryl Bromides with Vinyl Tin Reagents

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Highly functionalized styrene derivatives have been synthesized in a single step by the palladium-catalyzed coupling of aryl bromides with tributylethenylstannane. Aryl bromides substituted with electron-withdrawing groups couple rapidly under the reaction conditions while bromides containing electron-donating substituents require further addition of catalyst for complete conversion. 1,4-Dibromobenzene can be coupled in a highly selective fashion with either 1 or 2 equiv of tin reagent to give 4-bromostyrene or diethenylbenzene, respectively.

The recent interest in specialty polymers, particularly in the areas of polymer-bound reagents and catalysts, has created a need for the preparation of styrene monomers or intermediates that contain sensitive functionality on the aromatic ring.[1] Most of the traditional methods for the preparation of styrene derivatives use strong acidic or basic conditions. With many reactive functional groups, these methods would require protection and deprotection steps in order to avoid destruction of the sensitive group.

Transition-metal-catalyzed vinylation reactions have been exploited for the preparation of many styrene derivatives.[2-6] Although most of these methods proceed under neutral reaction conditions, undesirable side reactions are observed in many cases.

The cross coupling of organotin reagents with various electrophiles in the presence of catalytic quantities of palladium has been demonstrated to be a highly efficient method[7] for the preparation of a wide variety of organic compounds. The reaction proceeds under neutral conditions, is generally not particularly sensitive to water or oxygen, and possesses a high degree of selectivity with respect to organic group transfer from unsymmetrical tin reagents. This paper discusses the application of this coupling method to the synthesis of styrene derivatives from the corresponding aryl bromides.[8,9]

$$\underset{}{\mathrm{ArBr}} + \underset{\mathbf{1}}{\mathrm{CH_2{=}CHSnBu_3}} \xrightarrow{\mathrm{Pd}} \mathrm{ArCH{=}CH_2}$$

Table I. Conditions and Percent Conversion for the Coupling of 4-Bromoacetophenone and 1[a]

solvent	catalyst (2 mol %)	temp, °C	% conversion
DMF	$PdCl_2(PPh_3)_2$	24	10
THF	$PdCl_2(PPh_3)_2$	60	50
toluene	$Pd(PPh_3)_4$	110	100

[a] Reactions were carried out until no further conversion was observed by GLC.

Results and Discussion

A number of reaction conditions were tried in order to optimize the conversion to coupled product (Table I). The best conversion was obtained by using $Pd(PPh_3)_4$ catalyst in toluene at reflux. The organotin bromide byproduct was removed by reaction with a pyridinium fluoride solution,[10,11] followed by flash chromatography, which removed residual tin.

The method has been extended to a number of aromatic bromide substrates (Table II). From a synthetic standpoint, the yields obtained are quite good, and in most cases the reaction proceeds rapidly to completion. No significant

(1) Hodge, P.; Sherrinton, D. C. *Polymer-supported Reactions in Organic Synthesis*; Wiley: New York, 1980. Akelah, A.; Sherrington, D. C. *Polymer* **1983**, *24*, 1369.
(2) Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345. Plevyak, J. E.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2454.
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(5) Kikukawa, K.; Ikenaga, K.; Kono, K.; Toritani, K. *J. Organomet. Chem.* **1984**, *270*, 277.
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(8) For coupling of aryl halides with substituted vinyl tin reagents, see: Zimmermann, E. K.; Stille, J. K. *Macromolecules* **1985**, *18*, 321.
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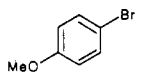
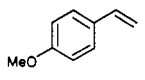
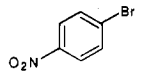
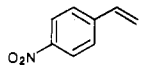
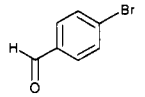
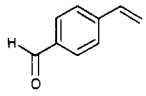
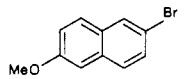
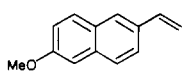
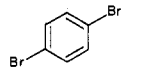
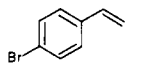
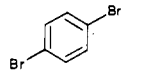
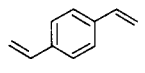
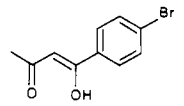
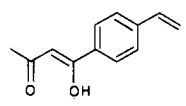
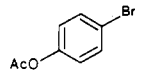
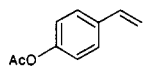
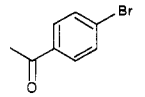
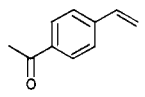
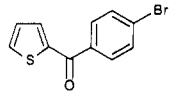
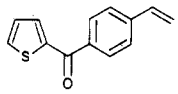
(10) Prepared according to Trost et al.: Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252.
(11) Nearly complete tributyltin bromide removal can be accomplished by pyridinium fluoride treatment followed by washing with a 1:1 NH_4OH/H_2O solution during workup.

0022-3263/87/1952-0422$01.50/0

Table II. Palladium-Catalyzed Coupling of Tributylethenylstannane with Aryl Bromides[a]

entry	aryl bromide	rctn time, h	product	isolated yield	ref[b]
1		24		76	19[c]
2		4		80	20
3		3		78	21
4		1		83	22
5		1[d]		63	19, 23
6		12[e,f]		73	24
7		2		72	*g*
8		8[h]		62	20
9		4		82	18
10		1		85	*g*

[a] The reactions were performed in the presence of 2 mol % of tetrakis(triphenylphosphine)palladium(0). [b] All products had physical properties in agreement with published data, the references for which are given in this column. [c] Structure confirmed by comparison of spectral data with published data. [d] The reaction was performed by using 1.1 equiv of 1. [e] The reaction was performed by using 2.2 equiv of 1. [f] An additional 2 mol % of $Pd(PPh_3)_4$ was added after 5 h. [g] Satisfactory elemental analysis, NMR spectral data, and IR spectral data were obtained for these compounds (see Experimental Section). [h] An additional 1 mol % of $Pd(PPh_3)_4$ was added after 4 h.

side products were observed. The utilization of aromatic bromides (instead of the less readily available iodides) for the coupling reaction makes possible very efficient overall synthetic strategies for the preparation of styrene derivatives.

Coupling of aryl bromides containing electron-withdrawing substituents was very rapid and went to completion with 2 mol % of catalyst. Aryl bromides with electron-donating groups generally reacted more sluggishly and required the incremental addition of catalyst.[12] For example, coupling of 4-bromophenyl acetate (entry 8) was 86% complete after 4 h. Further addition of 1% catalyst and heating brought about complete conversion to product.

The coupling of 1,4-dibromobenzene (entries 5 and 6) showed a high degree of selectivity. Coupling with 2.2 equiv of tin reagent gave 1,4-divinylbenzene in good yield. However, the coupling with 1.1 equiv of 1 gave a reaction mixture consisting of 92% of monocoupled product, 4-bromostyrene, which was isolated in 63% yield (not optimized).

Bromonaphthalene derivatives also can undergo coupling under these conditions (entry 4). Despite the presence of an electron-donating substituent in the other ring, the coupling proceeded rapidly with no need for additional catalyst.

The palladium-catalyzed coupling of vinylstannane 1 with substituted bromobenzenes and bromonaphthalenes offers several advantages for the preparation of styrene derivatives. The reaction gives high yields of styrene derivatives without any major side product and proceeds under neutral reaction conditions, which alleviates the need for functionality protection. The coupling of aryl bromides offers distinct advantages over aryl iodides in terms of their ease of preparation and greater commercial availability. The use of butyltin reagents is desirable because of the lower toxicity of these substances compared to the methyltin compounds. In the single dibromide case that was studied, the reaction exhibited remarkable selectivity.

Experimental Section

General Methods. All melting points were uncorrected. Infrared spectra were recorded on a Beckman Model 4250 infrared spectrometer. Low-field (60-MHz) NMR spectra were run on a Varian Associates Model EM 360 spectrometer. High-field (270-MHz) proton and carbon-13 spectra were taken on an IBM–Bruker WP270-SY spectrometer. NMR spectra were run in deuteriochloroform solution with tetramethylsilane (proton) or deuteriochloroform (carbon) internal standard.

Materials. Toluene was freshly distilled from sodium prior to use. Tributylethenylstannane (1)[13] and tetrakis(triphenylphosphine)palladium(0)[14] were prepared by the literature methods

(12) The coupling reactions of aryl bromides containing *p*-amino substituents did not yield aminostyrenes.

(13) Seyferth, D.; Stone, F. G. A. *J. Am. Chem. Soc.* **1957**, *79*, 515.
(14) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

in 90% and 92% yields, respectively. The aryl bromides 4-bromoanisole, 4-bromonitrobenzene, 4-bromobenzaldehyde, 1,4-dibromobenzene, 2-bromo-6-methoxynaphthalene, and 4-bromoacetophenone were obtained from Aldrich and used without further purification. Other aryl bromides were synthesized by known methods; 4-bromophenyl acetate was prepared in 99% yield by acetylation of 4-bromophenol (Aldrich) with acetic anhydride in the presence of triethylamine and 4-(dimethylamino)pyridine.[15]

1-(4-Bromophenyl)-1,3-butanedione. A mixture of 9.40 g (196 mmol) of a 50% dispersion of sodium hydride and 14.5 g (67.7 mmol) of methyl 4-bromobenzoate[16] in 10 mL of freshly distilled dimethoxyethane (DME) was heated to reflux, and a solution of 6.00 mL (8.17 mmol) of acetone (freshly distilled from anhydrous calcium sulfate) in 5.0 mL of DME was added dropwise over a period of 5 min. The resulting mixture was heated at reflux for an additional 3 h. The mixture was allowed to cool to room temperature, and 2.0 mL of concentrated hydrochloric acid was added. The resulting mixture was partitioned between ether and water. The aqueous phase was removed and extracted once with ether. The combined ethereal phase was extracted with 3 × 50 mL of 5% aqueous sodium hydroxide solution. The combined basic extracts were washed once with pentane and then acidified with concentrated sulfuric acid (with cooling) and saturated with sodium chloride. The mixture was extracted with 3 × 50 mL of ether. The combined ethereal extracts were washed with water and saturated aqueous sodium chloride solution, dried (magnesium sulfate), and concentrated. The crude material was purified by flash chromatography (40% ether/hexane) and recrystallized from aqueous ethanol to give 10.3 g (63%) of 1-(4-bromophenyl)-1,3-butanedione: mp 88–90 °C (lit.[17] 90–93 °C); IR (CCl_4) 2990, 2880, 1530, 1250, 1120, 1080 cm^{-1}; ^1H NMR (270 MHz) δ 10.27 (br s, 1 H), 7.72 (d, J = 8.5 Hz, 2 H), 7.56 (d, J = 8.5 Hz, 2 H), 6.13 (s, 1 H), 2.19 (s, 3 H); ^{13}C NMR (68 MHz) δ 193.6, 182.3, 132.1, 131.9, 128.4, 127.0, 96.5, 25.6.

Typical Coupling Procedure. 1-(4-Ethenylphenyl)-1-ethanone from the Coupling of 4-Bromoacetophenone and Tributylethenylstannane. To a solution of 2.00 g (10.1 mmol) of 4-bromoacetophenone, 0.23 g (0.20 mmol) of $Pd(PPh_3)_4$, and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol in 20 mL of toluene was added 3.50 g (11.0 mmol) of tributylethenylstannane. The resulting solution was heated to reflux for 4 h. GLC analysis indicated complete reaction. The mixture was allowed to cool to room temperature, and 4.4 mL of pyridine was added followed by 9.3 mL of 1.2 N pyridinium fluoride solution.[10] The resulting mixture was stirred for 16 h at room temperature. The mixture was diluted with 200 mL of ether and washed with 50 mL of water, 2 × 50 mL of 10% aqueous hydrochloric acid solution, 50 mL of water, and 50 mL of a saturated aqueous sodium bicarbonate solution. The organic phase was dried (magnesium sulfate) and concentrated. The crude material was purified by flash chromatography (20% ether/hexane) to give 1.20 g (82%) of 4-ethenylacetophenone: bp 102–104 °C (1.5 mm) (lit.[18] 104–106 °C (1.5 mm)); IR (neat) 3100, 3020, 1690, 1610, 1410, 1360, 1270, 845 cm^{-1}; ^1H NMR (270 MHz) δ 7.90 (d, J = 8.4 Hz, 2 H), 7.46 (d, J = 8.2 Hz, 2 H), 6.74 (dd, J = 17.6, 10.9 Hz, 1 H), 5.86 (d, J = 17.6 Hz, 1 H), 5.38 (d, J = 10.7 Hz, 1 H), 2.57 (s, 3 H); ^{13}C NMR (68 MHz) δ 197.1, 142.0, 136.4, 135.9, 128.6, 126.2, 116.5, 26.3.

1-(4-Ethenylphenyl)-1,3-butanedione was synthesized in 72% yield by the same procedure: white solid, mp 66–67 °C; IR (CCl_4) 1610, 1530, 1250, 915 cm^{-1}; ^1H NMR (270 MHz) δ 10.13 (br s, 1 H), 7.83 (d, J = 8.3 Hz, 2 H), 7.45 (d, J = 8.2 Hz, 2 H), 6.73 (dd, J = 17.5, 10.9 Hz, 1 H), 6.16 (s, 1 H), 5.85 (d, J = 17.6 Hz, 1 H), 5.36 (d, J = 10.9 Hz, 1 H), 2.18 (s, 3 H); ^{13}C NMR (68 MHz) δ 193.6, 182.7, 141.4, 136.0, 127.3, 126.5, 126.3, 116.1, 96.5, 25.7. Anal. (Copper complex). Calcd for $C_{24}H_{22}O_4Cu$: C, 65.81; H, 5.06. Found: C, 65.55; H, 5.14.

4-Bromophenyl 2-Thienyl Ketone. A three-neck flask equipped with a mechanical stirrer and a reflux condenser was charged with 3.64 g (0.027 mol) of aluminum trichloride and 12 mL of carbon disulfide. The mixture was cooled to 0 °C, and a solution of 6 g (0.027 mol) of 4-bromobenzoyl chloride and 2.18 g (0.026 mol) of thiophene in 10 mL of carbon disulfide was added dropwise over a period of 3 h. The red mixture was allowed to warm to room temperature and stirred for 3.5 h and then allowed to stand for 10 h. The mixture was heated to reflux for 3 h and then cooled to room temperature, poured on ice, and extracted with diethyl ether. The ether extracts were washed with sodium bicarbonate saturated solution and water and dried over magnesium sulfate. Removal of the solvent under reduced pressure afforded a brown solid, which was recrystallized from ligroin to give 6 g (87%) of white crystals: mp 100–101 °C; ^1H NMR (270 MHz) δ 7.72 (d, J = 8.4 Hz, 2 H), 7.71 (d, J = 4.9 Hz, 1 H), 7.61 (d, J = 8.4 Hz, 2 H), 7.60 (d, J = 4.8 Hz, 1 H), 7.15 (dd, J = 4.8, 4.9 Hz, 1 H); ^{13}C NMR (68 MHz) δ 186.8, 137.2, 134.5, 134.2, 132.0, 131.8, 130.7, 128.0, 127.3. Anal. Calcd for $C_{11}H_7OSBr$: C, 49.44; H, 2.62; S, 11.99; Br, 29.26. Found: C, 49.44; H, 2.67; S, 11.95; Br, 29.85.

4-(2-Thienylcarbonyl)styrene was synthesized in 85% yield by the general procedure described above: white solid; mp 58 °C; ^1H NMR (270 MHz) δ 7.85 (d, J = 8.3 Hz, 2 H), 7.72 (d, J = 6.0 Hz, 1 H), 7.66 (d, J = 4.8 Hz, 1 H), 7.52 (d, J = 8.3 Hz, 2 H), 7.17 (dd, J = 4.8, 6.0 Hz, 1 H), 6.79 (dd, J = 17.6, 10.9 Hz, 1 H), 5.89 (d, J = 17.6 Hz, 1 H), 5.41 (d, J = 10.9 Hz, 1 H); ^{13}C NMR (68 MHz) δ 187.3, 141.6, 137.5, 136.1, 134.2, 133.7, 129.6, 129.2, 127.8, 126.2, 116.3. Anal. Calcd for $C_{13}H_{10}OS$: C, 72.89; H, 4.67; S, 14.95. Found: C, 72.26; H, 4.73; S, 14.74.

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