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PALLADIUM-CATALYZED CARBON- CARBON BOND FORMATION ON A SOLID PHASE UTILIZING HYPERVALENT IODONIUM SALTS

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Abstract: Palladium-catalyzed cross-coupling of hypervalent iodonium salts with polymer bound alkene, alkyne, and boronate was achieved under mild conditions.

Recently, advantages of solid phase organic chemistry for the discovery and optimization of pharmaceutical lead compounds are well recognized in combinatorial synthesis.[1] In particular, palladium-catalyzed coupling carbon-carbon bond formations have been developed as suitable methods for generation of libraries of diverse compounds. Recently, several groups have described intermolecular palladium cross-coupling reactions on solid support *via* Stille,[2] Suzuki,[3] and Heck[4] reactions, etc.[5]

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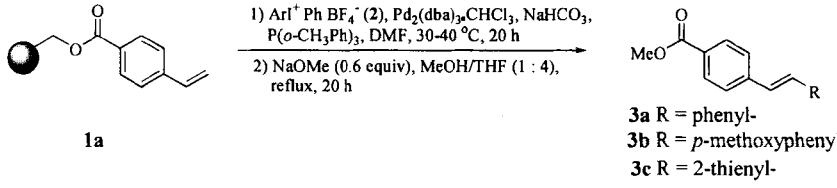


1a

3a R = phenyl-
3b R = *p*-methoxyphenyl-
3c R = 2-thienyl-

Scheme 1

In connection with our programs to utilize nontoxic hypervalent iodine compounds,[6] we wish to report here the palladium-catalyzed cross-coupling of hypervalent iodine compounds with polymer bound alkene, alkyne, and boronate under mild conditions.

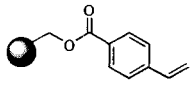
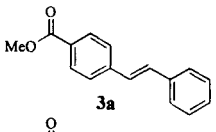
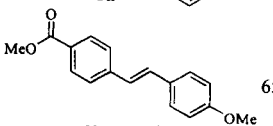
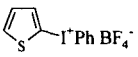
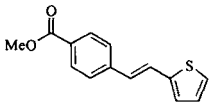
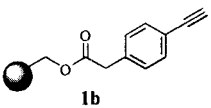
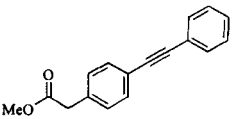
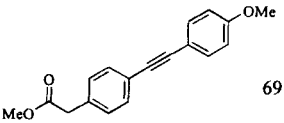
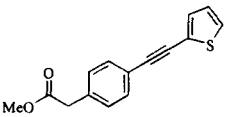
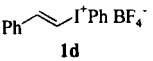
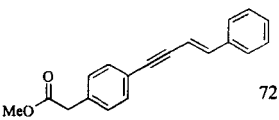
Our experiments began by studying the coupling of iodonium salts with resin-bound styrene derivative **1a** (Scheme 1).

The resin-bound **1a**[7] was treated with diphenyliodonium tetrafluoroborate (**2a**)(1.5 equiv) in the presence of $Pd_2(dba)_3$•$CHCl_3$ (5 mol %) and $(o\text{-Tol})_3P$ with $NaHCO_3$ (2 equiv) as base at 40 °C for 20 h followed by transesterification with NaOMe to afford the phenyl-substituted styrene derivative **3a**[8] in 80% yield (entry 1 in Table 1). With *p*-methoxyphenyl(phenyl)iodonium tetrafluoroborate (**2b**), the coupled product **3b**[9] (71%) along with **3a** (25%) was obtained after transesterification (entry 2). When 2-thienyl(phenyl)iodonium tetrafluoroborate (**2c**) was treated with **1a** under the same conditions followed by transesterification to give 2-thienyl-substituted product **3c**[8] (55%) together with **3a** (44%)(entry 3).

We have extended this protocol to Sonogashira reaction and studied the cross-coupling of resin-bound alkyne with iodonium salts (Scheme 2).

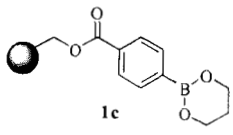
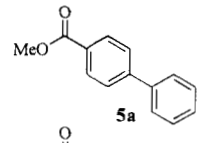
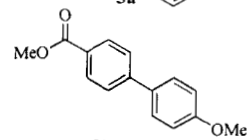
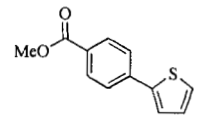
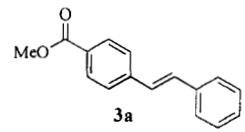
Reaction of resin-bound **1b**[10] with diphenyliodonium tetrafluoroborate (**2a**) in the presence of $Pd(PPh_3)_4$(5 mol %) and CuI (10 mol %) with $NaHCO_3$ (2 equiv) as base in DMF at 40 °C for 20 h followed by transesterification with NaOMe (0.6

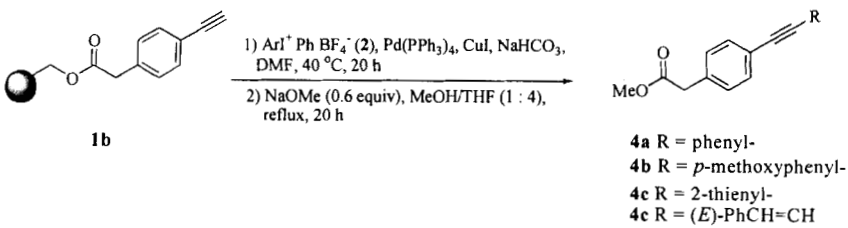
Table 1. Palladium-Catalyzed of Polymer Bound Alkene, Alkyne, and Boronate with Hypervalent Iodonium Salts

Entry	Polymer Bound Substrate	Iodonium Salt	Product	Yield(%)
1	 **1a**	$Ph_2I^+ BF_4^-$ **2a**	 **3a**	80
2	**1a**	p-$MeOC_6H_4I^+Ph\ BF_4^-$ **2b**	 **3b** + **3a** (25%)	65
3	**1a**	 **2c**	 **3c** + **3a** (44%)	55
4	 **1b**	**2a**	 **4a**	75
5	**1b**	**2b**	 **4b** + **4a** (29%)	69
6	**1b**	**2c**	 **4c** + **4a** (38%)	50
7	**1b**	 **1d**	 **4d**	72

(continued)

Table 1. Continued.

8	 **1c**	**2a**	 **5a**	86
9	**1c**	**2b**	 **5b** + **5a** (20%)	75
10	**1c**	**2c**	 **5c** +**5a** (30%)	60
11	**1c**	**2d**	 **3a**	75

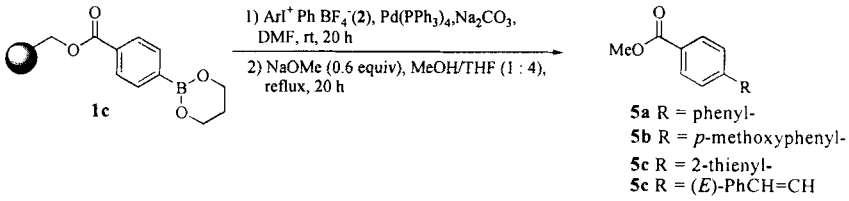


1b

4a R = phenyl-
4b R = *p*-methoxyphenyl-
4c R = 2-thienyl-
4c R = (*E*)-PhCH=CH

Scheme 2

equiv) in MeOH/THF (1 : 4) at reflux for 20 h gave the phenyl-substituted product **4a** in 75% yield (entry 4 in Table 1). For the iodonium salt **2b** treatment with **1b** under the same conditions, gave the coupled product **4b** in 69% yield with 4a (29%) as a minor product (entry 5). When the same reaction was conducted with **2c**, the 2-thienyl- substituted product **4c** as a major product (entry 6). It is notable



Scheme 3

that β-styryl(phenyl)iodonium tetrafluorobrate (**2d**) afford the coupled ester **4d** as the sole product in 72% yield (entry 7).

Accordingly, we examined the Suzuki coupling reaction of **1c** with iodonium salts, which is shown in Scheme 3.

The diphenyliodonium tetrafluoroborate (**2a**) was reacted with **1c**[11] in the presence of $Pd(PPh_3)_4$(5 mol %) with Na_2CO_3 (3 equiv) as base in DMF at room temperature followed by treatment of NaOMe (0.6 equiv) in MeOH/THF (1 : 4) at reflux for 20 h to provide the coupled ester **5a**[12] in 86% yield (entry 8). The resin-bound **1c** underwent facile coupling with iodonium salt **2b** under the same conditions, to afford the ester **5b**[13] (75%) as a major product as a separable component (entry 9). Treatment of **1c** with iodonium salt **2c** gave the 2-thienylsubstituted **5c**[14] in 60% yield (entry 10). Finally, for the β-(*E*)-styryl(phenyl)iodonium tetrafluoroborate (**2d**) the coupled ester **3a** was afforded as the sole product in 75% yield (entry 11).

Experimental Section

Typical procedure: Preparation of methyl (*E*)-4-(2-phenylethenyl)benzoate (**3a**)[8]

To a degassed suspension of polymer bound styrene **1a** in anhydrous DMF (3 mL) was added $Pd_2(dba)_3$•$CHCl_3$ (17.3 mg, 5 mol %), P(*o*-$CH_3C_6H_4)_3$ (10.2 mg,

10 mol %), and $NaHCO_3$ (56.3 mg, 0.67 mmol). And then diphenyliodonium tetrafluoroborate (**2a**)(185 mg, 0.50 mmol) in DMF (7 mL) was slowly added *via* syringe pump for 4 h at 40 °C. The reaction mixture was allowed to stir at 40 °C for 20 h and then transferred to a glass filter and thoroughly washed with CH_2Cl_2, MeOH, DMF, MeOH, CH_2Cl_2. Cleavage of the product from resin was achieved readily by transesterification by treating NaOMe (17.8 mg, 0.6 equiv) in MeOH/THF (1 : 4, 5 mL) at reflux for 20 h to provide the methyl 4-(2-phenylethenyl)benzoate (**3a**) TLC; SiO_2, EtOAc/ hexanes = 1 : 10, R_f = 0.32. ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.11 (d, 1H J = 16 Hz), 7.21 (m, 1H), 7.32 (d, 1H J = 16 Hz), 7.38 (m, 2H), 7.53 (m, 4H), 8.02(m, 2H). IR (KBr) 2945, 1717, 1281, 1109, 965 cm^{-1}. MS (EI): m/e (relative intensity) = 238 (M^+, 69), 207 (47), 179 (93) 178 (100), 89 (54), 76 (26).

Methyl (*E*)-4-[2-(4-methoxyphenyl)ethenyl]benzoate (**3b**)[9]

TLC; SiO_2, EtOAc/hexanes = 1 : 10, R_f = 0.28. ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.92 (s, 3H), 6.91 (m, 2H), 6.97 (d, 1H J = 16 Hz), 7.16 (d, 1H J = 16 Hz), 7.47 (m, 2H), 7.53 (m, 2H), 8.00(m, 2H). IR (KBr) 2960, 1716, 1600, 1408, 1266 cm^{-1}. MS (EI): m/e (relative intensity) = 268 (M^+, 100), 165 (81), 119 (39), 59 (52).

Methyl (*E*)-4-[2-(2'-thienyl)ethenyl]benzoate (**3c**)[8]

TLC; SiO_2, EtOAc/hexanes = 1 : 10, R_f = 0.31. ^1H NMR (400 MHz, CDCl3) δ 3.92 (s, 3H), 6.92 (d, 1H J = 16 Hz), 7.02 (m, 1H), 7.12 (m, 1H), 7.20 (d, 1H J = 16 Hz), 7.25 (m, 1H), 7.35 (m, 2H), 8.00(m, 2H). IR (KBr) 3262, 1717, 1284, 1268, 1110 cm^{-1}. MS (EI): m/e (relative intensity) = 244 (M^+, 100), 213 (43), 184 (78), 152 (36), 92 (65).

Typical procedure: Preparation of methyl 4-(2-phenylethynyl)phenylacetate (**4a**)

To a degassed suspension of polymer bound phenylacetylene **1b** in anhydrous DMF (3 mL) was added $Pd(PPh_3)_4$(19.4 mg, 5 mol %), CuI (6.4 mg, 10 mol %), and $NaHCO_3$ (56.3 mg, 0.67 mmol). And then diphenyliodonium tetrafluoroborate (**2a**)(185 mg, 0.50 mmol) in DMF (7 mL) was slowly added *via* syringe pump for 4 h at 40 °C. The reaction mixture was allowed to stir at 40 °C for 20 h and then transferred to a glass filter and thoroughly washed with CH_2Cl_2, MeOH, DMF, MeOH, CH_2Cl_2. Cleavage of the product from resin was achieved readily by transesterification by treating NaOMe (17.8 mg, 0.6 equiv) in MeOH/THF (1 : 4, 5 mL) at reflux for 20 h to provide the 4-(2-phenylethynyl)phenylaceticacid methylester (**4a**) TLC; SiO_2, EtOAc/hexanes = 1 : 10, R_f = 0.34. ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 2H), 3.70 (s, 3H), 7.23 (m, 2H), 7.33 (m, 1H), 7.35 (m, 2H), 7.45 (m, 4H). IR (KBr) 2927, 1739, 1512, 1437, 1160 cm^{-1}. MS (EI): m/e (relative intensity) = 250 (M^+, 81)), 191 (100), 189 (22), 95 (170, 83 (15). HRMS (EI) calcd for $C_{17}H_{14}O_2$ (M^+) 250.0142, found 250.0152.

Methyl 4-[2-(4-methoxyphenyl)ethenyl]phenylacetate (**4b**)

TLC; SiO_2, EtOAc/hexanes = 1 : 10, R_f = 0.32. ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 2H), 3.71 (s, 3H), 3.83 (s, 3H), 6.89 (m, 2H), 7.24 (m, 2H), 7.45 (m, 4H). IR (KBr) 2952, 1735, 1519, 1247, 1163 cm^{-1}. MS (EI): m/e (relative intensity) = 280 (M^+, 61), 221 (100), 178 (23), 111 (13). HRMS (EI) calcd for $C_{18}H_{16}O_3$ (M^+) 280.1099, found 280.1099.

Methyl 4-[2-(2-thienyl)ethynyl]phenylacetate (**4c**)

TLC; SiO_2, EtOAc/hexanes = 1 : 10, R_f = 0.35. ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 2H), 3.71 (s, 3H), 7.00 (m, 1H), 7.27 (m, 2H), 7.33 (m, 1H), 7.46 (m,

2H), 7.52 (m, 1H). IR (KBr) 3055, 2987, 1407, 1265 cm^{-1}. MS (EI): m/e (relative intensity) = 256 (M^+, 68), 198 (17), 197 (100), 152 (19), 45 (15). HRMS (EI) calcd for $C_{15}H_{12}O_2S$ (M^+) 256.0558, found 256.0562.

Methyl 4-[2-(styryl)ethynyl]phenylacetate (**4d**)

TLC; SiO_2, EtOAc/hexanes = 1 : 10, R_f = 0.35. ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 2H), 3.71 (s, 3H), 6.36 (d, 1H J = 16 Hz), 7.02 (d, 1H J = 16 Hz), 7.24 (m, 2H), 7.35 (m, 3H), 7.42 (m, 4H). IR (KBr) 3055, 2954, 1737, 1265, 1163 cm^{-1}. MS (EI): m/e (relative intensity) = 276 (M^+, 54), 217 (100), 215 (65), 202 (41). HRMS (EI) calcd for $C_{19}H_{16}O_2$ (M^+) 276.1150, found 276.1146.

Typical procedure: Preparation of methyl 4-phenylbenzoate (**5a**)[12]

To a degassed suspension of polymer bound phenylboronate (**1c**) in anhydrous DMF (3 mL) was added $Pd(PPh_3)_4$ (19.4 mg, 5 mol %), and Na_2CO_3 (57 mg, 1.01 mmol). And then diphenyliodonium salt (**2a**)(185 mg, 0.50 mmol) in DMF (7 mL) was added. The reaction mixture was allowed to stir at room temperature for 20 h and then transferred to a glass filter and thoroughly washed with CH_2Cl_2, MeOH, DMF, MeOH, CH_2Cl_2. Cleavage of the product from resin was achieved readily by transesterification by treating NaOMe (17.8 mg, 0.6 equiv) in MeOH/THF (1 : 4, 5 mL) at reflux for 20 h to provide the methyl 4-phenyl benzoate (**5a**) TLC; SiO_2, EtOAc/hexanes = 1 : 10, R_f = 0.30. ^1H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.40 (m, 1H), 7.47 (m, 2H), 7.62 (m, 4H), 8.10 (m, 2H). IR (KBr) 2952, 1724, 1306, 1246, 1113 cm^{-1}. MS (EI): m/e (relative intensity) = 212 (M^+, 63), 181 (100), 152 (58), 76 (26).

Methyl (4-methoxyphenyl)benzoate (**5b**)[13]

TLC; SiO_2, EtOAc/hexanes = 1 : 10, R_f = 0.27. ^1H NMR (400 MHz, $CDCl_3$)

δ 3.87 (s, 3H), 3.94 (s, 3H), 7.00 (m, 2H), 7.57 (m, 2H), 7.62 (m, 2H), 8.08 (m, 2H). IR (KBr) 3056, 1718, 1403, 1290, 1266 cm^{-1}. MS (EI): m/e (relative intensity) = 242 (M^+, 100), 211 (85), 168 (23), 139 (40), 106 (32).

Methyl (2-thienyl)benzoate (**5c**)[14]

TLC; SiO_2, EtOAc/hexanes = 1 : 10, R_f = 0.31. ^1H NMR (400 MHz, $CDCl_3$)

δ 3.92 (s, 3H), 7.11 (m, 1H), 7.43 (m, 1H), 7.62 (m, 1H), 7.66 (m, 2H), 8.03 (m, 2H). IR (KBr) 3055, 1718, 1704, 1265 cm^{-1}. MS (EI): m/e (relative intensity) = 218 (M^+, 78), 187 (100), 159 (12), 115 (49), 79 (15).

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