# Solid-Phase Suzuki Coupling for C−C Bond Formation

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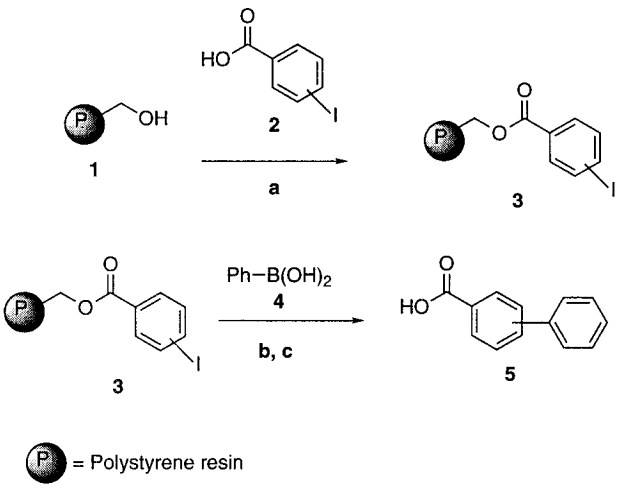
## Introduction

Methods describing the use of polymer supports for performing chemical reactions in a heterogeneous medium are enjoying a pronounced resurgence.[1,2] This renewed interest has been sparked by the combinatorial synthesis of pharmaceutically interesting compounds.[3] Newly emerging solid phase synthesis techniques for the formation of nonpeptidic C−C bonds include 1,3-cycloadditions,[4] palladium-catalyzed couplings,[5] Mitsonubu coupling,[6] enolate alkylation,[7] and reductive amination.[8] Optimization of these reactions is central for performing multiple simultaneous syntheses in the generation of compound libraries. Additionally, performing chemistry in an automated fashion may place restrictions on temperature and pressure. Palladium-catalyzed coupling via Stille or Suzuki reactions are powerful methods for C−C bond formation.[9] These reactions generally result in excellent yields when performed at temperatures of 50−80 °C. Adapting these powerful C−C coupling reactions to a resin mounted procedure is of interest.[5a,c,7,10] Reported herein are the results from our study on the generality of the solid-phase Suzuki reaction.

## Discussion

The central objective for performing our chemistry on a solid support was to identify a general set of conditions that allows for complete conversion to product, over a wide range of substrates. Commercially available resins (SASRIN[11] or Wang[12] ) **1** were coupled with an iodobenzoic acid such as **2** via standard protocol with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, EDCI, and 1-hydroxybenzotriazole, HOBT, to provide resin **3** (Scheme 1).

**Scheme 1**




[a](a) EDCI, $Et_3N$, HOBT, $CH_2Cl_2$, 20h, RT (b) Pd(0) cat., DMF, RT (c) TFA/$CH_2Cl_2$, RT, 30 min

**Table 1. Polymer Bound Biphenyl Coupling at Room Temperature**

| entry | ArI | catalyst[a] | time (h) | conversion[b] (% yield[c]) of biphenyl |
|---|---|---|---|---|
| 1 | 3-I | $PdCl_2$(dppf) | 18 | 0 |
| 2 | 3-I | $NiCl_2$(dppp) | 18 | 0 |
| 3 | 3-I | $Pd_2(dba)_3$ | 20 | 100 (84) |
| 4 | 4-I | $Pd_2(dba)_3$ | 18 | 100 (72) |
| 5 | 3-I | $Pd(PPh_3)_4$ | 18 | 100 (56)[d] |
| 6 | 2-I | $Pd(PPh_3)_4$ | 18 | 57 (N.A.) |
| 7 | 3-I | $Pd_2(dba)_3$ | 2 | 20 (N.A.) |
| 8 | 3-I | $Pd_2(dba)_3$ | 6 | 72 (N.A.) |

[a] 5−10 mol %, 2 equiv of $K_2CO_3$ in DMF. [b] Conversion estimated from $^1$H NMR and HPLC. [c] Isolated yield based on loading of iodobenzoic acid (mmol/g resin). [d] 2% $H_2O$−DMF.

Numerous catalysts were investigated to effect the coupling of **3** with phenylboronic acid **4**, at room temperature (Table 1). Commercial Pd(0) sources, tris(dibenzylideneacetone)dipalladium {$Pd_2(dba)_3$} or tetrakis(triphenylphosphine)palladium {$Pd(PPh_3)_4$} were found to be very effective catalysts. Whereas, Pd(II) or Ni(II) catatlysts such as [1,1′-bis(diphenylphosphino)ferrocene]palladium chloride, {$PdCl_2$(dppf)} and [1,1′-bis(diphenylphosphino)propane]nickel chloride {$NiCl_2$(dppp)} were ineffective. At room temperature the couplings were found to proceed at a modest rate, requiring approximately 18 h for completion (entry 3 vs 7, 8). The coupling of *o*-iodobenzoate was noticeably slower than its meta or para congeners, perhaps as a response to steric crowding (entry 6). The bromo-substituted benzoate analogs were found to be completely unreactive under similar reaction conditions. The benzoate is cleaved from the polymer support with dilute trifluoroacetic acid in 30 min providing the biaryl acid product **5**. The purity of the cleaved biaryl products was verified by HPLC and $^1$H NMR and routinely found to be >95%. The isolated yields were

(1) (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149. (b) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327.
(2) (a) DeWitt, S. H.; Kiely, J. S; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909. (b) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997. (c) Moon, H.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6088. (d) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055. (e) Ahlberg R. L. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661.
(3) (a) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84. (b) Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (c) Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.
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(5) (a) Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613. (b) Yu, K.-L., Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1994**, *35*, 8919. (c) Sucholeiki, I.; Forman, F. W. *J. Org. Chem.* **1995**, *60*, 523. (d) Plunkett M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306. (e) Hiroshige, M.; Hauske, J. R.; Zhou, P. *Tetrahedron Lett.* **1995**, *36*, 4567. (f) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5748.
(6) Krchnak, V.; Flegelova, Z.; Weichsel, S. A.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6193.
(7) Ellman, J. A.; Backes, B. J. *J. Am. Chem. Soc.* **1994**, *116*, 11171.
(8) Steele, J.; Gordon, D. W.; *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47. Bray, A. M.; Chiefari, D. S.; Valerio, R. M.; Maeji, N. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 5081.
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(10) (a) Reference 7. (b) Friesen, R. W.; Frenette, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177.
(11) Mergler, M.; Tanner, R.; Gosteli, J.; Grogg, P. *Tetrahedron Lett.* **1988**, *29*, 4005.
(12) Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.

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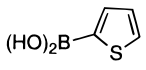
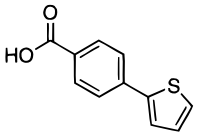
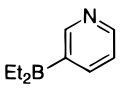
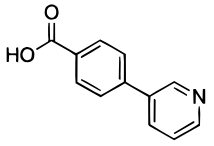
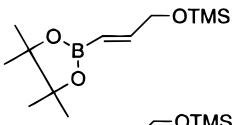
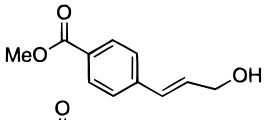
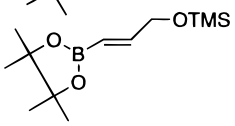
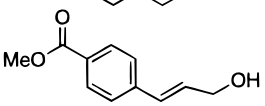
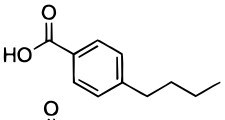
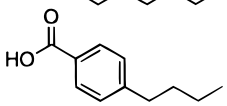
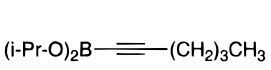
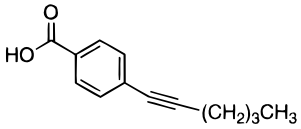
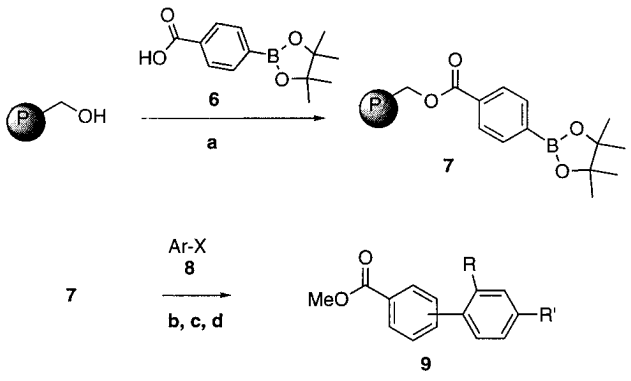
**Table 2. Coupling of Polymer Bound Aryl Iodide with Boron Reagents**

| Entry | Boron Reagent | Catalyst[a] | Product | Conversion ( % Yield)[b] |
|---|---|---|---|---|
| 1 |  | $Pd_2(dba)_3$ |  | 100(91) |
| 2 |  | $Pd_2(dba)_3$ |  | 100(73)[c] |
| 3 |  | $Pd(PPh_3)_4$ |  | 100(50)[d] |
| 4 |  | $PdCl_2(dppf)$ |  | 100(68)[d] |
| 5 | $B(n\text{-}Bu)_3$ | $Pd(PPh_3)_4$ |  | 100(56) |
| 6 | $B(n\text{-}Bu)_3$ | $PdCl_2(dppf)$ |  | 100(55) |
| 7 |  | $PdCl_2(dppf)$ |  | 100(91) |

[a] 5−10 mol % catalyst, 2 equiv of $K_2CO_3$ in DMF at rt. [b] Conversion estimated from $^1H$ NMR and HPLC. [c] Reaction required heating at 70 °C. [d] TMS removal with TBAF/THF, followed by cleavage with MeOH/MeONa (3.0 equiv)/THF, 1 h.

**Scheme 2**



[a](a) EDCI, $Et_3N$, HOBT, $CH_2Cl_2$, 20h (b) $Pd(PPh_3)_4$ cat., $K_2CO_3$, DMF (c) 50% TFA/$CH_2Cl_2$, 30 min (d) $TMSCHN_2$, $CHCl_3$/MeOH

somewhat variable, but routinely >56% based upon loading of the iodobenzene (mequiv/g resin).

This method was next investigated for the formation of a variety of other C−C bonds onto an aromatic ring. A diverse scope of boronic coupling agents (heteroaryl, alkyl, alkenyl, and alkynyl) were chosen. This wide array of coupling partners was optimized under conditions similar to those used for the phenylboronic acid coupling (Table 2). The optimal Pd catalyst was found to vary depending upon the boronic coupling partner. The aryl or heterobiarylboronic acids exhibited excellent conversion with $Pd_2(dba)_3$. The $PdCl_2(dppf)$ catalyst worked best for reactions involving the alkenylborane, in sharp contrast to its complete lack of activity in the biphenyl coupling.

**Table 3. Coupling of Polymer Bound Aryl Boronate 7**

| entry[a] | ArX[b] | R, R′ | reaction time, h | %conversion to 9[c] |
|---|---|---|---|---|
| 1 | I | H, H | 24 | 43 |
| 2 | I | H, H | 48 | 60 |
| 3 | I | $NO_2$, H | 24 | 59 |
| 4 | Br | H, OMe | 48 | 62[d] |
| 5 | Br | CN, H | 24 | 77[d] (100)[e] |

[a] 5 mol % $Pd(PPh_3)_4$, 6 equiv of $K_2CO_3$, 10% $H_2O$ added to all reactions. [b] 6 equiv of ArX added to all reactions. [c] GC/MS analysis. [d] Reaction heated to 55 °C. [e] Resin submitted to two couplings.

The irreversible immobilization of an aryl boronic acid and subsequent Suzuki coupling has been described previously.[13] The resin bound aryl boronic acid reagent **7**, prepared by standard coupling procedures, has been found to couple with a variety of substituted bromo- or iodobenzenes **8** (Scheme 2). Initial studies have shown that the resin-bound boronate couplings proceed at a slower rate than the resin-bound aryl iodides, (Table 3). In general, the couplings proceed to within 40−77% of completion after 24 or 48 h, with the balance as unreacted boronate. The reactions may be driven to completion

(13) Wulff, G.; Schmidt, H.; Witt, H.; Zentel, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 188.

upon resubmission to the reaction conditions (entry 5). Where aryl bromides were employed the reaction proceeded only upon heating.

In conclusion, procedures for resin bound Suzuki coupling at both ambient and elevated temperatures to form a wide array of substituted benzoates has been described. The mild reaction conditions are viewed as being well suited for robotic synthesis and the generation of combinatorial or traditional libraries. A more thorough examination of the resin-bound boronate coupling and its application are under investigation.

## Experimental Section

High and low resolution mass spectra were recorded using desorption chemical ionization and electrospray ionization. Analytical reversed-phase HPLC was carried out on a YMC ODS-A C-18 column with gradient elution ($CH_3CN/H_2O$/0.1%TFA) and UV detection at 254 and 280 nM. $^1H$ NMR spectra were recorded at 300 MHz. All compounds exhibited $^1H$ NMR and mass spectral data in agreement with those previously reported.

**Materials.** All solvents were Fisher HPLC grade and used as received. Reagents were obtained from Aldrich with the following exceptions: SASRIN resin obtained from Bachem, Wang resin from Advanced Chemtech, and thiophene-2-boronic acid through Lancaster. The 1-alkenyl and alkynyl boronates were prepared according to literature procedure.[14,15] All reagents were used without further purification.

**General Method for Attachment of Substituted Phenylacetic Acids.** SASRIN resin (9.93 g, 0.89 mmol/g) was first swelled in $CH_2Cl_2$ (200 mL) for approximately 10 min. In sequential order 4-iodobenzoic acid (2.63 g, 10.6 mmol), $Et_3N$ (1.48 mL, 10.6 mmol), EDCI·HCl (2.03 g, 10.6 mmol), and HOBT (0.143 g, 1.60 mmol) are added to the reaction vessel at ambient temperature. The reaction was stirred for 20 h and then filtered and washed with DMF (3×) and $CH_2Cl_2$ (3×) and dried *in vacuo*. Mass recovery was used to determine resin loading after cleavage of an aliquot with 2% TFA/$CH_2Cl_2$. Typically, coupling was achieved with greater than 95% efficiency (the above sequence was repeated for optimal coupling).

**General Method for Resin-Bound Aryl Iodide Coupling.** SASRIN-bound 4-iodobenzoic acid **3** (0.480 g, 0.738 mmol/g theoretical load) was swelled in DMF (10 mL) for 10 min. To this slurry was added, 1-hexynyldiisopropoxyborane (99 mg, 0.47 mmol, prepared by literature procedure from 1-hexyne and triisopropoxyborane[15]), $PdCl_2$(dppf) (17 mg, 0.021 mmol), and $K_2CO_3$ (118 mg, 0.85 mmol). The mixture was stirred or swirled for 20 h under a nitrogen atmosphere. The resin was filtered and washed alternately with DMF/$H_2O$ (4:1), followed by MeOH and $CH_2Cl_2$. The SASRIN-bound product was treated with TFA/$CH_2Cl_2$ (2%, 2 mL) for 30 min, the resin was filtered and washed with $CH_2Cl_2$/MeOH (2 mL), and the filtrate was concentrated *in vacuo*. Alternatively, the Wang-bound product was treated with TFA/$CH_2Cl_2$ (1:1, 4 mL) for 30 min. The filtrate was concentrated *in vacuo* and the product, 4-(1-hexynyl)benzoic acid (65 mg), isolated in 91% overall yield.

**General Method for Resin-Bound Arylboronate Coupling.** The phenyldioxaborinane **6**, prepared via the procedure of Takahashi,[16] was coupled to Wang resin (vida infra) to generate **7**. Resin-bound phenyldioxaborinane **7** (0.100 g, 0.628 mmol/g theoretical load) was swelled in DMF (2 mL) for 10 min. To this slurry were added iodobenzene (51 $\mu$L, 0.45 mmol), $K_2CO_3$ (62 mg, 0.45 mmol), $Pd(PPh_3)_4$ (4 mg, 0.003 mmol), and $H_2O$ (200 $\mu$L). The mixture was swirled for 24 h under a nitrogen atmosphere and then the resin collected on a medium porosity fritted glass funnel. The resin was washed alternately with 50% $MeOH_{(aq)}$ and DMF followed by MeOH and $CH_2Cl_2$. The resin-bound product **9** was treated with TFA/$CH_2Cl_2$ (1:1, 2 mL) for 30 min, the resin was filtered and washed with $CH_2Cl_2$/MeOH (2 mL), and the filtrate was concentrated *in vacuo*. The solid residue was suspended in $CHCl_3$/MeOH (3:1, 3 mL) and chilled in an ice bath, and (trimethylsilyl)diazomethane (2 M in hexanes) was added until a yellow color persisted. After 10 min the ice bath was removed and the sample swirled for approximately 3 h. The sample was concentrated *in vacuo* and analyzed by GC/MS.

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**Supporting Information Available:** Copies of sample HPLC, GC/MS, and NMR spectra (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) (a) Vaultier, M.; Jehanno, E. *Tetrahedron Lett.* **1995**, *36*, 4439. (b) Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, February, 103.

(15) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631.

(16) Matsubara, H.; Seto, K.; Tahara, T.; Takahashi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3896.