



Synthesis of biaryl-styrene monomers by microwave-assisted Suzuki coupling

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ABSTRACT

Biaryl-styrenic monomers are prepared via Suzuki coupling as functional monomers in the synthesis of molecularly imprinted polymers. Traditional thermal Suzuki approaches are hampered by competition between Suzuki, Heck and homo-coupling reactions. Microwave-assisted approaches facilitated rapid access to the desired Suzuki products whilst suppressing both Heck and homo-couplings of 4-vinylboronic acid.

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The preparation of molecularly imprinted polymers (MIPs) for selective recognition of molecules of interest involves a judicious choice of functional monomers that are complementary to, and therefore, capable of selectively binding the target molecule.^{1,2} In order to increase our group's library of functional monomers, we synthesized a number of styrenic monomers **1a–f**, capable of potentially interacting with selected targets by π – π stacking and/or H-bonding interactions (Fig. 1).

Typically, access to such biaryl systems is via Suzuki cross-coupling of aryl bromides and 4-vinylphenylboronic acid **2** (Scheme 1). Whilst the Suzuki protocol has been widely used for aryl–aryl bond formation, its application for the preparation of styrene-based aryl compounds has been very limited. Given the known propensity for tetrakis(triphenylphosphine)palladium ($\text{Pd}(\text{PPh}_3)_4$) to generate unwanted side-products, we commenced our study using $\text{Pd}(\text{DIPHOS})_2$.³ Generally, Suzuki couplings are characterized by the persistence of side-reactions comprising a self-coupling of the boronic acid (**3**) and the equivalent Heck coupling (**4**) (Scheme 1).^{4,5} The presence of the vinylic moiety obviously increases the probability of Heck coupling.

Herein we report the synthesis of the biaryl-styrenic functional monomers **1a–f** via microwave irradiation of the Suzuki coupling mixture under a variety of conditions whilst minimizing the formation of by-products.^{6–9}

Our initial efforts employed traditional thermal Suzuki coupling conditions.⁹ Thus, a mixture of 4-vinylphenylboronic acid **2** (1.0 mmol) and aryl bromide (1.0 mmol), 1 mol % of $\text{Pd}(\text{DIPHOS})_2$ and 2 M K_2CO_3 (2.4 mmol) in THF (4 mL) was heated at reflux

(either under an air or N_2 atmosphere).¹⁰ Contrary to reports by De et al., our styrenic systems are sensitive to air.⁹

Suzuki coupling (air atmosphere) of 4-bromophenol and **2** affords **3** (12%, 18 h reaction time) and none of the desired **1a**. The

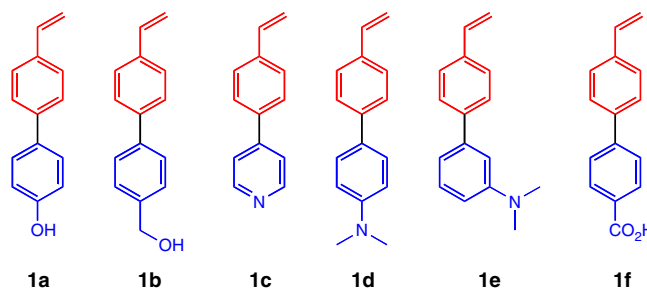
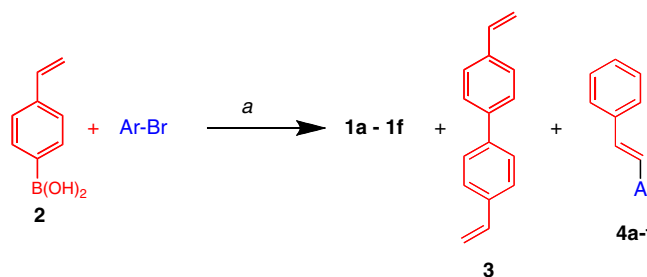


Figure 1. Target styrenyl biaryl functional monomer systems.



Scheme 1. Suzuki coupling (a) $\text{Pd}(\text{DIPHOS})_2$, 2 M K_2CO_3 , THF, Δ , N_2 , 5 d.

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introduction of an N₂ atmosphere, under otherwise identical reaction conditions, gave **1a** (11%) and **3** (3%). Nevertheless, even under N₂, the reactions were still very slow requiring five days to obtain the optimal cross-coupling yields (Table 1). Excellent yields of biaryl products **1b** (86%) and **1c** (78%) were obtained using this modified approach. However, the yields observed for acidic analogues **1a** (13%), **1f** (0%) and basic analogues **1d** (41%) and **1e** (30%) were synthetically unsatisfactory. Additionally, we were unable to directly prepare **1f** from 4-bromobenzoic acid. Carboxylate protection (benzyl ester) was necessary to effect the desired Suzuki coupling. Subsequent saponification afforded **1f**.¹¹ The yield variation is consistent with the expected reactivity of the substituted aryl bromides towards electrophilic substitution. Previous studies have shown that arylboronic acid homo-coupling increases in the presence of oxygen and competes with the Suzuki cross-coupling in open air conditions.⁵ This is consistent with our findings with the degree of homo-coupling reduced, but not eliminated by careful control of the reaction atmosphere. Additionally, we note that the low yield of **1a** (13%) is a function of the acidity of 4-bromophenol.

Given the dual issues of low yields and long reaction times we next turned our attention to the use of microwave heating as a possible means to improve both issues. Microwave-assisted Suzuki couplings have already been reported,^{12–14} but to the best of our knowledge, the method has not yet been applied to cross-coupling of vinylic aryls.

Microwave irradiation of benzyl 4-bromobenzoate in PhCH₃/H₂O (1:1) with Pd(DIPHOS)₂/K₂CO₃ returned an identical yield of **1f** as that observed with the equivalent thermal reaction (Table 1). Given the reduced reaction times, we examined the synthesis of **1a**, a reaction that proceeded very poorly (13%) in the thermal case. Microwave irradiation as per the synthesis of **1f** (THF:H₂O; 30 min, 150 W/100 °C) gave **1a** in 33% yield, a significant improvement over the thermal reaction. Raising the reaction temperature to 150 °C resulted only in a significant loss of solvent with no improvement in reaction outcome. Whilst, importantly, there was no evidence of the homo-coupling product **3**, as one might have anticipated, the major species (at 66%) was the Heck product **4f**. Switching to the less volatile THF/H₂O (1:1) mixed solvent system facilitated control of the reaction temperature at 150 °C (100 W, 30 min) and essentially quantitative conversion to **1a**. Subsequent experimentation showed the same outcome in THF/H₂O (1:1) at 100 °C, and all further synthesis was conducted at this temperature (Table 1).¹⁰ These data clearly demonstrate a highly

efficient conversion into the desired Suzuki product (>98%) in all cases thereby demonstrating the flexibility of our approach.

In this Letter we have demonstrated the ease of synthesis of biaryl-styrenic functional monomers. Careful control of the microwave synthesis conditions facilitates quantitative conversion into the desired coupling product suppressing the potentially competing pathway that leads to the Heck products. This work suggests that the Suzuki coupling in the presence of vinylic moieties is synthetically feasible and opens the way to the synthesis of a wide range of novel monomer systems for molecularly imprinted polymer systems.

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- In a typical synthesis: A mixture of aryl bromide (1.0 mmol), 4-vinylphenylboronic acid (1.0 mmol), Pd(DIPHOS)₂ (1 mol %) and 2 M K₂CO₃ (2.4 mmol) in THF/H₂O (1:1, 6 mL) in a 10-mL microwave vessel with a magnetic stirrer was degassed and purged with nitrogen prior to microwave irradiation. Microwave irradiation was conducted in a CEM Discover microwave. The vessel was placed in the microwave sample cavity and sealed with a pressure lock. The microwave source was turned on and was set to 100 °C using 100 W of power to heat the reaction mixture for 30 min. The reaction mixture was allowed to cool before the addition of EtOAc (10 mL) and was filtered through Celite. The filtrate was evaporated to dryness, after which the residue was dissolved in water, extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over Na₂SO₄ prior to rotary evaporation. The product was purified by silica gel flash chromatography. Compound **1d**: ¹H NMR (300 MHz, CDCl₃) δ 2.96 (s, 6H, N(CH₃)₂), 5.23 (d, *J* = 10.9 Hz, 1H, vinyl H), 5.75 (d, *J* = 17.6 Hz, 1H, vinyl H), 6.72 (ddd, *J* = 9.3, 6.6, 4.6 Hz, 2H, vinyl H and Arom. H), 6.93 (dd, *J* = 8.7, 1.4 Hz, 1H, Arom. H), 7.28 (t, *J* = 7.8 Hz, 2H, Arom. H), 7.44 (d, *J* = 8.4 Hz, 2H, Arom. H), 7.55 (d, *J* = 8.2 Hz, 2H, Arom. H); ¹³C NMR (75 MHz, CDCl₃): δ 40.4, 113.0, 113.8, 125.9, 127.0, 127.3, 130.5, 135.1, 136.7, 140.1, 150.3. IR (ATR) 3080, 2972, 2882, 2843, 2796, 1912, 1881, 1603, 1501, 1352, 1227, 992, 890, 751, 539 cm⁻¹. HRMS: calcd for C₁₆H₁₇N *m/z* = 223.13610; found 223.13615; mp 170 °C (dec). Compound **1e**: ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.94 (s, 6H, N(CH₃)₂), 5.23 (d, *J* = 10.9 Hz, 1H, vinyl H), 5.80 (d, *J* = 17.7 Hz, 1H, vinyl H), 6.74 (dd, *J* = 15.2, 8.5 Hz, 1H, vinyl H), 6.80 (d, *J* = 8.9 Hz, 2H, Arom. H), 7.46–7.58 (m, 6H, Arom. H); ¹³C NMR (75 MHz, CDCl₃): δ 41.2, 111.8, 112.3, 114.1, 116.2, 127.0, 127.9, 129.9, 137.1, 142.2, 142.3 (2C), 151.5. IR (ATR) 3080, 3028, 2983, 2888, 2805, 1918, 1816, 1598, 1563, 1487, 1354, 993, 903, 836, 772, 691, 626 cm⁻¹. HRMS: calcd for C₁₆H₁₇N *m/z* = 223.13610; found 223.13618; mp 44–47 °C.
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Table 1

Conversion (%) of styrenic compounds **1a–f** prepared under thermal conditions and microwave-assisted Suzuki coupling catalyzed by Pd(DIPHOS)₂.

Product	Thermal	Microwave	
	THF ^{a,b}	PhCH ₃ /H ₂ O (1:1) ^{b,c}	THF/H ₂ O (1:1) ^{b,d}
1a	13 ^b	33	>98
1b	86	>98	>98
1c	78	>98	>98
1d	41	80	>98
1e	30	85	>98
1f	>98 ^e	>98	>98

^a THF reflux, N₂, 5 d.

^b GC and ¹H NMR yields.

^c THF/H₂O (1:1) at 100 °C for 30 min (100 W).

^d PhCH₃/H₂O (1:1) at 100 °C for 30 min (100 W).

^e Commenced with benzyl 4-bromobenzoate followed by saponification.