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# Optimised conditions for styrene syntheses using Suzuki–Miyaura couplings and catalyst-ligand-base pre-mixes

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#### ARTICLE INFO

# ABSTRACT

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Keywords: Suzuki-Miyaura Styrenes Vinylboronic acids Optimised Microwave Optimised conditions are reported for Suzuki–Miyaura couplings between *N*-tosyl-2-bromo-benzylamines and -phenethylamines with vinylboronic acids, using pre-mixes of catalyst, ligand and base, leading to the corresponding 2-tosylaminomethyl- and 2-tosylaminoethyl-styrenes in generally excellent yields, using microwave excitation at 100 °C.

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In connection with another project (see following Letter), we recently required a representative series of the 2-tosylaminoalkyl styrenes 1 and 2 (Scheme 1). Amongst the many possibilities, such as aldehyde olefinations (Wittig, Julia, etc.) and dehydration reactions, use of one of the ubiquitous palladium-catalysed coupling reactions, which have all now reached a high level of sophistication in terms of both the range of experimental conditions and the choice of ligands which are available, seemed to offer the greatest flexibility and practicality. Amongst these options, the Suzuki-Miyaura method<sup>1</sup> featuring couplings between an aryl bromide **3** and a vinylboronic acid **4** appeared especially attractive, particularly in view of the wide variety of experimental parameters now regularly employed for such couplings.<sup>2</sup> Further, we wished to explore the practicality of employing pre-formed mixtures of suitable phosphine ligands, bases and catalysts, as these are especially convenient reagent combinations for general combinatorial synthesis. This is especially so when their deployment obviates the rather tiresome and time-consuming necessity of weighing small amounts of both ligand and metal source, which are usually only required in such quantities for the synthesis of such libraries of related compounds. A range of these types of pre-mixes were readily available as these are in regular use in the Lilly Research Laboratories,<sup>3</sup> which presented us with an ideal opportunity to attempt to define optimum conditions for their application in the desired styrene synthesis at least, as well as, hopefully, for many other applications.

\* Corresponding author. E-mail address: knightdw@cf.ac.uk (D.W. Knight). Further, the required coupling partners were also readily available in appropriate quantities. Sulfonamide **3a** was obtained in one step from commercially available 2-bromobenzylamine by direct tosylation [TsCl (1.0 equiv), DMAP (cat.), Et<sub>3</sub>N (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0–20 °C, 16 h; 87%; mp 78–80 °C<sup>4</sup>], while the homologous sulfonamide **3b** was obtained from a Mitsunobu coupling between 2-bromophenethanol and TsNHBoc<sup>5</sup> [Ph<sub>3</sub>P then DIAD, 0 °C, THF, 15 min. then alcohol (1.0 equiv), 20 min then TsNHBoc (1.01 equiv) then 20 °C, 16 h (94%), followed by deprotection using 20% TFA–CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 2 h; 99%; mp 62–63 °C<sup>6</sup>]. All the vinylboronic acids **4** employed in this study were obtained by hydroboration of the corresponding aryl alkynes using catecholborane.<sup>7</sup>

The necessity for this type of study was revealed immediately when an attempted Suzuki–Miyaura coupling between sulfonamide **3a** and (*E*)-2-phenylboronic acid **5** using relatively routine microwave-assisted conditions<sup>1,2c</sup> led to essentially none of the desired product **6** (Scheme 2) on the first attempt. In a subsequent reaction, a small amount of product **6** was detected by <sup>1</sup>H NMR analysis of the crude product when wet DMF was used as the solvent. As such polar solvent systems, especially water,<sup>2d</sup> generally favour these types of couplings, we chose to standardise upon 1:1 aqueous DMF in subsequent studies, then systematically to evaluate the various combinations of palladium source, phosphine ligand and base, with a view to securing a successful version of the coupling shown in Scheme 2. In particular, the use of a rather more sterically hindered phosphine ligand seemed especially likely to be productive.<sup>2f</sup>

Although perhaps rather counter-intuitive, such sterically hindered species, whose likely positive contribution was suggested many years ago by Heck, have subsequently made many significant

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Scheme 1. The key Suzuki-Miyaura disconnection.



**Scheme 2.** Reagents and conditions: (i) 1 equiv each of **3a** and **5** in DMF, 5 mol % Pd(PPh\_3)\_4, NaHCO\_3, 100 W, 100  $^\circ$ C, 0.5 h.

advances to the viability of a diversity of palladium-catalysed coupling chemistry.<sup>8</sup> Such sterically hindered species often work well in combination with milder bases such as potassium carbonate or potassium phosphate.<sup>9</sup> The results of some of these optimisation experiments are presented in Table 1.

Evidently, the highly hindered phosphine ligand dtbpf [1,1'bis(di-*tert*-butylphosphino)ferrocene] (entries 3 and 4) was effective, as was the use of potassium phosphate<sup>9</sup> and the change to aqueous DMF. In the quest for an even higher yielding and more efficient process, we chose to use the catalyst combination employed in entry 3 as the basis of a solvent study, the outcomes of which are shown in Table 2.

Although all three of the mixed solvent systems (entries 1–3) gave very similar yields, for reasons of convenience, volatility and lack of toxicity, we chose to use 1:1 aqueous ethanol in subsequent reactions. Although, all three aqueous solvent mixtures delivered essentially the same isolated yields, this particular combination gave the cleanest 'crude' product **6**, which contained no starting material **3a** according to <sup>1</sup>H NMR analysis immediately after isolation.

This optimised procedure<sup>10</sup> was then applied to the synthesis of a selection of substituted styrenes from the 2-bromosulfonamide **3a** and also one-carbon homologues from the phenethyl sulfonamide **3b**. The structures of all products are collected below, together with the associated isolated yields in Table 3.

In general, yields were excellent and were not noticeably affected by the nature of the boronic acid, whether this was carrying an aromatic or an alkenyl substituent. Unsurprisingly, there was also very little change in the yields of styrenes when boronates were used, specifically 4,4,5,5,-tetramethyl-1,3,2-dioxaborolanes,

#### Table 1

Optimisation of couplings between 3a and 5 (Scheme 2)<sup>a</sup>

Entry	Cat./ligand/base	Solvent	% Yield
1	$Pd(PPh_3)_4 - NaHCO_3$	DMF	0
2	$Pd(OAc)_2 - PCy_3 - K_3PO_4$	1:1 DMF-H <sub>2</sub> O	61
3	$Pd(OAc)_2$ - $dtbpf$ - $K_3PO_4$	1:1 DMF-H <sub>2</sub> O	63
4	Pd(dba)2-dtbpf-K3PO4	1:1 DMF-H <sub>2</sub> O	43
5	$Pd(Q^b)_2 - K_2CO_3$	1:1 DMF-H <sub>2</sub> O	58
6	Pd(PPh <sub>3</sub> ) <sub>4</sub> -NaOH	1:1 DMF-H <sub>2</sub> O	47
7	$Pd(OAc)_2 - K_2CO_3$	H <sub>2</sub> O	37

<sup>a</sup> All reactions run at 100 °C, 100 W for 0.5 h.

<sup>b</sup> Q = quinoline-8-carboxylate.

#### Table 2

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Solvent	ontimication	or commings	nerween <b>s</b>	1 2 m / 1 5	licino		_arnnt_k_Pi	1.4
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Entry	Solvent	% Yield
1	1,4-Dioxane-H <sub>2</sub> O	92
2	1:1 Toluene–H <sub>2</sub> O	89
3	1:1 Ethanol-H <sub>2</sub> O	90
4	H <sub>2</sub> O	72

<sup>a</sup> All reactions run at 100 °C, 100 W for 0.5 h.

# Table 3

Optimised yields from couplings of sulfonamides  ${\bf 3}$  and vinylboronic acids  ${\bf 5}$  using Pd(OAc)\_2–dtbpf–K\_3PO\_4



as these would be rapidly converted into the corresponding boronic acids under the aqueous conditions used in the optimised procedure.

In many examples, after a simple aqueous work-up, the products obtained were pure enough for use in a subsequent synthetic step, in particular if a concentrated ethereal solution was passed through a short pad of silica gel. Although we used the optimised procedure<sup>10</sup> routinely,<sup>11</sup> we have also found that the amount of pre-mix used can be reduced to as little as one tenth of the amount specified herein (i.e., 0.04 g of pre-mix per 0.30 mmol of sulfonamide **3**) given that all reactants and solvents were scrupulously clean. This resulted in no noticeable diminution in the yields.

In summary, we believe this optimised procedure represents a general and practicable approach which should find ready application to the construction of these types of arylalkene.

# Acknowledgment

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- Generaliszed procedure for Suzuki-Miyaura couplings leading to styrenes 7 and 8: Sulfonamide 3 (0.30 mmol, 1 equiv) and a vinylboronic acid 4

(1.3 equiv) were suspended in 1:1 aqueous EtOH (3 ml per 0.30 mmol of sulfonamide **3**). To this suspension was added the Suzuki-Miyaura pre-mix [0.55 wt% Pd(OAc)<sub>2</sub>, 1.05 wt% dtbpf and 98.4 wt% K<sub>3</sub>PO<sub>4</sub>] (0.425 g per 0.30 mmol of sulfonamide **3**) and the resulting mixture placed in a microwave oven and heated using a power of 100 W to 100 °C for 0.5 h. The cooled mixture was then extracted with Et<sub>2</sub>O (3 × 15 ml) and the combined organic extracts washed with saturated NaCl (30 ml) then dried (MgSO<sub>4</sub>), filtered and evaporated. Usually, the crude product was of sufficient purity, especially after filtration of an ethereal solution through a pad of silica gel, for direct use in a subsequent reaction. <sup>11</sup>

11. (E)-4-Methyl-N-(2-(4-methylstyryl)benzyl)benzenesulfonamide (11a): Using the general reaction procedure, between N-(2-bromobenzyl)-4-0.294 mmol), methylbenzenesulfonamide (**3a**) (0.100 g, (E)-2-(4methylphenyl)-vinylboronic acid (0.062 g, 0.384 mmol) and the Pd(OAc)2dtbpf-K<sub>3</sub>PO<sub>4</sub> pre-mix (0.425 g) in 1:1 aqueous EtOH (3 ml) gave the sulfonamide **11a** (0.106 g, 96%) as a yellow oil which showed  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.64 (d, 2H, J 8.3 Hz, 2 × ArH), 7.39 (d, 2H, J 8.3 Hz, 2 × ArH), 7.30-7.11 (m, 6H), 7.10-7.02 (m, 3H), 6.95 (d, 1H, J 15.8 Hz), 4.16 (d, 2H, J 6.6 Hz, CH<sub>2</sub>N), 2.34 (6H, s, 2  $\times$  ArMe);  $\delta_{C}$  (100 MHz, CDCl<sub>3</sub>) 146.5 (s), 136.9 (2  $\times$  s), 135.5 (3 × s), 132.8 (2 × d), 130.5 (2 × d), 129.8 (2 × d), 129.7 (2 × d), 129.6 (2 × d), 127.8 (d), 127.2 (2 × d), 123.5 (d), 41.5 (t), 21.6 (2 × q);  $v_{max}$  (film) 3289, 3021, 2921, 1598, 1512, 1448, 1274 815, 750 cm<sup>-1</sup>; HRMS (EI) m/z 377.1438 (M<sup>+</sup>, 100%); C23H23NO2S requires M, 377.1450.