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The preparation of a stable 2-pyridylboronate and its reactivity in the Suzuki–Miyaura cross-coupling reaction

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Abstract—The preparation and reactivity of a 2-pyridylboronate stabilised by *N*-phenyldiethanolamine is described. In Suzuki–Miyaura cross-coupling reactions employing this boronate, significant aryl–aryl exchange from the phosphine ligand was observed with some combinations of ligand and substrates. The amount of the exchange by-product can be minimised by appropriate choice of phosphine ligand.

A recent review[1] highlighted the limited number of examples of pyridyl derivatives serving as the nucleophile source in Suzuki–Miyaura cross-coupling reactions.[2,3] Although there is literature precedence for the preparation of 3- and 4-pyridylboronic acids[4,5] and dialkyl(3- and 4-pyridyl)boranes,[6] there is sparse literature relating to the preparation of 2-pyridylboron species. This includes the synthesis of diethyl(2-pyridyl)borane as an unreactive dimer[7] and the dimeric dimethyl(2-pyridyl)borane.[8] Methods exist for the preparation of dimethyl 2-pyridylboronate[9] and lithium tri-*n*-propyl 2-pyridylboronate,[10] the laboratory scale use of 2-pyridylboronic acid glycol ester has also been described.[11]

Our initial experiments in this area confirmed literature reports that 2-pyridylboronates readily hydrolyse[12] thus making medium and long-term storage challenging. Herein, we describe the reactivity of a stable 2-pyridylboronate that is amenable to large laboratory scale preparation.[13]

As there is literature precedent for diol and thiol derivatives stabilising boronic acids,[14] a screen was conducted using lithium triisopropyl 2-pyridylboronate as the starting material. In terms of the physical form, reactivity and stability of the resulting boronate, the optimum results were obtained when *N*-phenyldiethanolamine was employed (Scheme 1).

A one-pot process was developed to prepare the *N*-phenyldiethanolamine 2-pyridylboronate,[†] in which 2-lithiopyridine formed by reaction of *n*-butyllithium and 2-bromopyridine at −70 °C, was trapped in situ by triisopropyl borate. The intermediate boronate was then reacted with *N*-phenyldiethanolamine to give the prod-

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Keywords: 2-Pyridylboronate; *N*-Phenyldiethanolamine; Suzuki–Miyaura cross-coupling; Tris(*o*-tolyl)phosphine; Palladium(II)acetate.

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[†] Typical procedure: Under nitrogen, a stirred solution of 2-bromopyridine (843 g, 5.33 mol) and triisopropylborate (1.20 kg, 6.40 mol) in THF (6.74 L) was cooled to 75 °C. A 1.6 M solution of *n*-BuLi in hexanes (4.00 L, 6.40 mol) was added at such a rate that the temperature did not exceed −67 °C. After completion of the addition, the reaction was allowed to warm to room temperature and stirred at this temperature for 16 h. After this time, a solution of *N*-phenyldiethanolamine (966 g, 5.33 mol) in THF (966 mL) was added and the resulting mixture heated at reflux for 4 h. The mixture was distilled and replaced with isopropanol until the head temperature reached 76 °C (distilling 11.3 L and adding in 8.4 L of isopropanol during the process). The mixture was cooled to room temperature and stirred for 12 h. After this time the mixture was filtered, the solid washed with isopropanol (1.7 L) and dried in vacuo overnight at 40 °C to give 1605 g of the *N*-phenyldiethanolamine 2-pyridylboronate. ^{1}H NMR (CD_3OD, 300 MHz), δ (ppm) 1.14 (d, $J = 6.14$ Hz, 9.3H (6×1.55)), 3.33 (t, $J = 6.07$ Hz, 5H (4×1.25)), 3.52 (t, $J = 6.07$ Hz, 5H (4×1.25)), 3.72 (sept, $J = 6.14$ Hz, 1.55H), 6.60 (t, $J = 7.23$ Hz, 1.25H), 6.76 (d, $J = 8.90$ Hz, 2.5H (2×1.25)), 7.10 (m, 1H), 7.20 (dd, $J = 7.23$, 8.90 Hz, 2.5H (2×1.25)), 7.4–7.6 (m, 2H), 8.39 (m, 1H). Hence the effective molecular weight[‡] was calculated as 404 g/mol giving a yield of approximately 75%.

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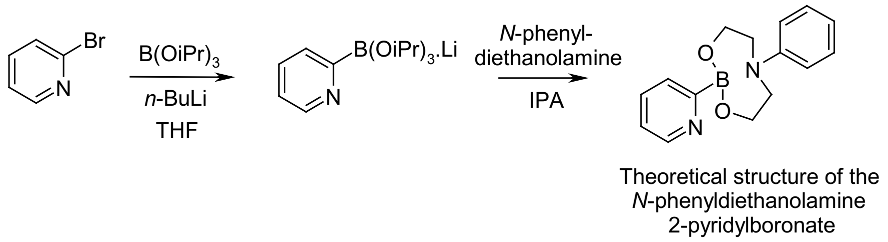
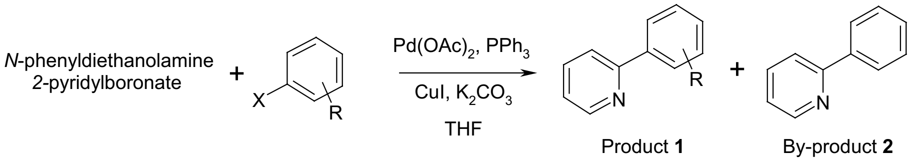


Scheme 1.

Table 1. Reactivity of *N*-phenyldiethanolamine 2-pyridylboronate with selected aryl halides



Entry	R	X	1^a (%)	2^a (%)
1	3-CN	I	84	2
2	4-NO_2	I	82	Trace
3	2-CH_3	I	88	2
4	2,6-$(CH_3)_2$	I	89	Trace
5	4-OMe	I	47	24
6	4-NH_2	I	54	14
7	4-CH_3	I	74	26
8^b	4-CH_3	Br	10	1.5
9	4-NO_2	Br	70	Trace

[a] Isolated yield.

[b] With 4-bromotoluene the reaction was heated at 100 °C to achieve complete reaction.

uct boronate in approximately 75% yield on a 4 molar scale. The exact structure was not determined but NMR showed the presence of both isopropyl and *N*-phenyldiethanolamine groups in the product, while the presence of a stoichiometric level of lithium was determined by ICP-AES. As the stoichiometry of the stabilising groups varies with the reaction conditions, the effective molecular weight of the *N*-phenyldiethanolamine 2-pyridylboronate was calculated following analysis by ^{1}H NMR[‡] prior to further reaction. It was shown that the first stage of the reaction can also be performed at −10 °C giving rise to a product containing higher levels of both isopropyl and *N*-phenyldiethanolamine.

The reactivity of the *N*-phenyldiethanolamine 2-pyridylboronate was then studied. Several aryl halides were screened (Table 1)[§] and in some cases a significant quantity of 2-phenylpyridine was isolated. Good yields of the desired product were obtained with aryl iodides substituted with electron withdrawing groups (Table 1, entries 1 and 2). With electron donating groups on the aryl iodide the reaction produced two major products, the anticipated 2-arylpyridine **1** and the corresponding phenyl by-product **2** (Table 1, entries 5–7). For aryl

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[‡] The boronate was analysed by ^{1}H NMR in CD_3OD, measuring the number of *N*-phenyl groups (x) and the number of isopropyl groups (y) relative to the number of pyridyl groups. For use in further reactions the effective molecular weight of the *N*-phenyldiethanolamine 2-pyridylboronate was calculated using the following formula:

$$(\text{MW of 2-pyridylboron}) + (\text{MW of } N\text{-phenyldiethanolamine} - 2) \times x + (\text{MW of isopropanol} - 1) \times y.$$

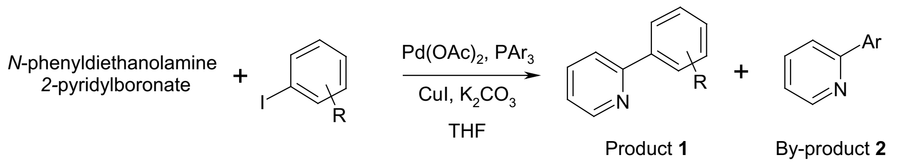
That is,

$$\text{MW} = 89 + (179 \times x) + (59 \times y).$$

As lithium is a minor component of the *N*-phenyldiethanolamine 2-pyridylboronate with respect to molecular weight, lithium was not included in the effective molecular weight calculation.

[§] Procedure for the Suzuki reaction: A suspension of aryl halide (10.8 mmol), the *N*-phenyldiethanolamine 2-pyridylboronate (21.6 mmol), PPh_3 (0.57 g, 2.17 mmol), $Pd(OAc)_2$ (0.12 g, 0.53 mmol), K_2CO_3 (3.99 g, 21.6 mmol) and CuI (0.82 g, 4.30 mmol) in THF (38 mL) was heated to reflux under nitrogen until the reaction was judged complete by HPLC. The reaction was cooled to rt, filtered through a filter agent, evaporated to dryness and purified by column chromatography using ethyl acetate/heptane as eluent. Appropriate fractions were combined, evaporated to dryness and the product(s) identified by ^{1}H NMR, MS and microanalysis. In some cases the ratio of products was obtained by ^{1}H NMR of the combined mixture of product and by-product.

Table 2. Effect of the phosphine ligand on the reaction



Product **1**

By-product **2**

	Ratio of the 2-arylpyridine (**1**)/by-product (**2**)[a]			
Aryl iodide	PPh$_3$	P(*o*-tolyl)$_3$	P(*p*-tolyl)$_3$	P(*p*-anisole)$_3$
4-CH$_3$	82/18	99.9/0.1	N/A	92/8
4-OMe	77/23	>99.9/<0.1	72/28	N/A

N/A: Product and by-product are identical.

[a] Ratio as determined by HPLC.

iodides with *ortho* substitution, the formation of **2** was negligible (Table 1, entries 3 and 4) and the data indicate that with aryl bromides, electron withdrawing groups are required in order to obtain good yields (Table 1, entries 8 and 9).

Aryl–phenyl exchange from the phosphine ligand, resulting in the formation of the by-product **2** is well known[15] and can be rationalised by an aryl–phenyl exchange in the intermediate palladium(II) complex and subsequent coupling with the 2-pyridyl boronate.[16]

To determine whether variation of the phosphine ligand minimised formation of the exchange by-product, four triarylphosphine ligands [PPh$_3$, P(*o*-tolyl)$_3$, P(*p*-tolyl)$_3$, P(*p*-anisyl)$_3$] were investigated in the reaction (Table 2). The best reaction profile was obtained when tris(*o*-tolyl)phosphine was used. In the reaction with 4-iodoanisole, the product was isolated in 85% yield and only a trace of the exchange by-product was observed. Use of trialkyl ligands [P(*n*-Bu)$_3$, P(*t*-Bu)$_3$ or P(cyclohexyl)$_3$] led to a slower reaction rate, but formation of 2-alkylpyridine or 2-phenylpyridine by-products was not observed.

In summary, a scalable process for the formation of a stable[17] 2-pyridylboronate is described along with examples of the reactivity of this material. In cases when a high level of the by-product generated by aryl–phenyl exchange was formed using triphenylphosphine as the ligand, it was shown that using tris(*o*-tolyl)phosphine greatly reduced the level of by-product formation.

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