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tricyclohexylphosphine tetrafluoroborate enhances reactivity.

# Suzuki–Miyaura cross-coupling of alkenyl tosylates with alkenyl MIDA boronates

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## ARTICLE INFO

## ABSTRACT

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Suzuki-Miyaura coupling reactions are an invaluable weapon for the synthetic chemist in natural product and drug discovery programmes.<sup>1</sup> Although the majority of the early studies concentrated on the use of aryl and vinyl halides as the electrophilic coupling partners, there has been increasing interest in the coupling reactions of aryl and vinyl sulfonate esters.<sup>2</sup> This approach is particularly valuable with sulfonate esters derived from enolisable carbonyl compounds, and there are many elegant examples from the pharmaceutical industry and in natural product synthesis.<sup>3–5</sup> Most of these examples employ carbonyl-derived vinyl triflates (and this method was the cornerstone of our recent synthesis of dictyosphaeric acid A<sup>5</sup>). However, vinyl triflates are rather reactive compounds and in recent years there have been considerable advances in the design of improved catalyst/ligand systems which facilitate the Suzuki coupling reactions of the more tractable tosyl-ate and mesylate analogues.<sup>6-13</sup> Notable highlights of this methodology in drug research are the Suzuki coupling reactions of thymidine mesitylenesulfonates<sup>14</sup> and of carbapenem-derived vinyl tosylates.<sup>15</sup> However, vinyl tosylates are still relatively little exploited, despite the fact that they are attractive coupling partners-they are often crystalline and they are significantly more stable towards moisture and air than triflates and mesylates (and the sulfonylating agents, TsCl and Ts<sub>2</sub>O, are relatively inexpensive).

As part of a natural product synthesis, we therefore chose as the cornerstone the cross-coupling of alkenyl tosylates with alkenyl boronates. Wishing both coupling partners to be bench-stable,

we opted to employ *N*-methyliminodiacetic acid (MIDA) boronates, developed by Burke,<sup>16</sup> as the nucleophilic partners (Scheme 1). Not only are MIDA boronates stable on silica and upon common bench storage, their use in a slow-release Suzuki protocol<sup>17</sup> was anticipated to be advantageous in terms of suppressing

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A practical procedure for the palladium-catalysed Suzuki-Miyaura coupling of various alkenyl tosylates

with alkenyl MIDA boronates has been developed. Commercially available trans-bromo[N-succinimidyl-

bis(triphenylphosphine)]palladium(II) [Pd(PPh<sub>3</sub>)<sub>2</sub>NBS] is an effective catalyst under the slow release

conditions of MIDA boronates; with less activated alkenyl tosylates addition of the cheap, air-stable

we opted to employ *N*-methyliminodiacetic acid (MIDA) boronates, developed by Burke,<sup>16</sup> as the nucleophilic partners (Scheme 1). Not only are MIDA boronates stable on silica and upon common bench storage, their use in a slow-release Suzuki protocol<sup>17</sup> was anticipated to be advantageous in terms of suppressing undesired side-reactions during reactions with less reactive alkenyl tosylates. Published examples involving the cross-coupling of alkenyl tosylates and alkenyl boronates are rather scarce,<sup>18,19</sup> and to the best of our knowledge, there are no reported examples of the Suzuki coupling of alkenyl sulfonates with MIDA boronates.<sup>20</sup>

Herein we demonstrate the successful cross-coupling of alkenyl tosylates and alkenyl MIDA boronates under slow-release Suzuki– Miyaura reaction conditions. We further show that alkenyl tosylates can outperform the more labile alkenyl triflates in comparable coupling processes.

This study commenced with the Suzuki coupling of the known dimedone-derived triflate, tosylate and mesylate  $1a-c^{21-23}$  and the known MIDA boronate  $2^{24}$  to give the previously reported product  $3^{25}$  (Table 1). Initial studies were carried out using Burke's slow-release coupling protocol [3 mol % Pd(OAc)<sub>2</sub>, 6 mol % SPhos, aq K<sub>3</sub>PO<sub>4</sub>] in 1,4-dioxane/water (5:1) at 60 °C in a sealed tube under argon. Using these conditions, neither triflate 1a nor tosylate **1b** underwent efficient coupling, with the less stable but more reactive triflate being slightly superior to the tosylate (entries 1 and 2). Surprisingly, in both cases, complete decomposition of the unreacted alkenyl sulfonate was observed.

We therefore went on to investigate the use of  $Pd(PPh_3)_2NBS^{26,27}$  as catalyst as it has recently been used successfully for the Suzuki coupling of an alkenyl iodide with a MIDA bor-





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Scheme 1. Suzuki-Miyaura coupling of alkenyl tosylates and MIDA boronates.

onate in our laboratory.<sup>5</sup> Pleasingly, using this catalyst, successful coupling was achieved with all three sulfonates (entries 3-6). The reaction with triflate **1a** afforded the coupled product **3** in 71% yield (entry 3) whereas the crystalline tosylate 1b (which was much easier to handle) furnished 3 in excellent (>90%) yield in either aqueous K<sub>3</sub>PO<sub>4</sub>/1,4-dioxane or the more commonly employed aqueous Na<sub>2</sub>CO<sub>3</sub>/THF (entries 4 and 5). The reaction was essentially complete after 6 h but overnight heating could be employed without loss of yield. Mesylate 1c also underwent coupling but decomposition was observed and product 3 was obtained in only moderate (48%) yield (entry 6).

The reaction temperature was investigated next using tosylate **1b**, MIDA boronate **2** and catalytic Pd(PPh<sub>3</sub>)<sub>2</sub>NBS in THF/Na<sub>2</sub>CO<sub>3</sub>. In accordance with Burke's kinetic studies on the release of boronic acid from MIDA boronates (1 h at 100 °C, 4-6 h at 60 °C and 24 h at rt),<sup>17</sup> the overnight reaction at 40 °C revealed that the release of the free boronic acid from **2** indeed becomes the rate limiting factor. Significant quantities of unreleased 2 (1.07 equiv/sulfonate) could be recovered together with product 3 (68%) and 1b (32%) (entry 7). Carrying out the reaction at 80 °C shortened the time to 5 h without a decrease in efficiency (entry 8). Most importantly, from a practical viewpoint, using a conventional reaction set-up with a reflux condenser gave 3 in almost quantitative isolated yield (96%) after a reaction time of 6 h (entry 9).

With optimised conditions in hand, we went on to examine the scope of the coupling process with a variety of known tosylates (Table 2).<sup>28</sup> The sealed tube method (overnight at 60 °C under argon) was examined in order to give a meaningful comparison.

The cross-coupling with activated tosylate **4**, a lactone analogue of 1b, showed similarly efficient coupling under standard conditions (entry 1). By contrast, the efficiency dropped drastically with less activated, sterically hindered alkenyl tosylate 5. The expected product 15 was only formed in 33% yield and all remaining tosylate 5 (67%) was recovered (entry 2). We tentatively attributed the incomplete reaction to insufficient catalyst reactivity and a screening of simple phosphine ligands as additives with Pd(PPh<sub>3</sub>)<sub>2</sub>NBS confirmed this assumption. With triphenylphosphine, the conversion was doubled and on changing to more electron-donating ligands such as SPhos and tricyclohexylphosphine the reaction was further accelerated. Pleasingly, a quantitative yield was achieved with the inexpensive and air-stable PCy<sub>3</sub>·HBF<sub>4</sub> salt. Similarly, with the pyrone-derived tosylate 6, the use of Pd(PPh<sub>3</sub>)<sub>2</sub>NBS/ PCy<sub>3</sub>·HBF<sub>4</sub> was required for optimum yield (98%, entry 3). Pyrones such as product 16 possess antimicrobial and cytotoxic activities and their synthesis has been studied previously, but with significantly lower yields.<sup>29</sup> Interestingly, the reaction with coumarin-derived tosylate **7** was slightly more efficient without the additional PCv<sub>3</sub>·HBF<sub>4</sub> ligand but incomplete conversion was observed nevertheless (57%, entry 4). This lower reactivity may be explained by the high aromatic character of **7**. In accord with this suggestion. phenyl tosylate (8, entry 5) was inert under both sets of reaction conditions. However, simple unactivated alkenyl tosylates 9-11

#### Table 1

Investigation and optimisation of reaction conditions<sup>a</sup>

BMIDA CeHas 2 (1.1 equiv.) Pd-catalyst (3 mol%) A: Pd(OAc)<sub>2</sub>/SPhos  $1a(SO_2R = Tf)$ B: Pd(PPh<sub>3</sub>)<sub>2</sub>NBS 1b (SO<sub>2</sub>R = Ts) base (7.5 equiv) 1c (SO<sub>2</sub>R = Ms) solvent/water (5:1) ∆, 5-17 h

C <sub>6</sub> H	H <sub>13</sub>

Entry	<b>1</b> (SO <sub>2</sub> R)	Catalyst	Base	Solvent	Temp <sup>b</sup> (°C)	Time (h)	Yield <sup>c</sup> (%)
1	<b>a</b> (Tf)	Α	K <sub>3</sub> PO <sub>4</sub>	1,4-Dioxane	60	15	22
2	<b>b</b> (Ts)	Α	K <sub>3</sub> PO <sub>4</sub>	1,4-Dioxane	60	6	8
3	<b>a</b> (Tf)	В	K <sub>3</sub> PO <sub>4</sub>	1,4-Dioxane	60	15	71
4	<b>b</b> (Ts)	В	K <sub>3</sub> PO <sub>4</sub>	1,4-Dioxane	60	6	94 <sup>d</sup>
5	<b>b</b> (Ts)	В	$Na_2CO_3$	THF	60	6	93 <sup>e</sup>
6	<b>c</b> (Ms)	В	$Na_2CO_3$	THF	60	17	48
7	<b>b</b> (Ts)	В	$Na_2CO_3$	THF	40	17	68 <sup>f</sup>
8	<b>b</b> (Ts)	В	$Na_2CO_3$	THF	80	5	96
9	<b>b</b> (Ts)	В	Na <sub>2</sub> CO <sub>3</sub>	THF	67 <sup>g</sup>	6	96

SPhos = 2-Dicyclohexylphosphino-2,6-dimethoxybiphenyl; Pd(PPh<sub>3</sub>)<sub>2</sub>NBS = trans-bromo[N-succinimidyl-bis(triphenylphosphine)]palladium(II); BMIDA-see Scheme 1. b Oil bath temperature except for entry 9.

Isolated yield.

d

Overnight heating gave 91% isolated vield.

Overnight heating gave 95% isolated yield.

Yield based on recovered sulfone was 100%.

g Reflux under N2.

### Table 2

Suzuki–Miyaura coupling of various tosylates with MIDA boronate  $\mathbf{2}^{a}$ 

Entry	Tosylate	Product	Additional phosphine (6 mol %)	Recovered tosylate <sup>b</sup> (%)	Yield <sup>b</sup> (%)
1	orts 4	14 C <sub>6</sub> H <sub>13</sub>	None	_	90
2	CO <sub>2</sub> Et OTs	CO <sub>2</sub> Et	None PPh <sub>3</sub> SPhos PCy <sub>3</sub> PCy <sub>3</sub> ·HBF <sub>4</sub>	67 35 28  -	33 65 72 95 <b>99</b> °
3	OTS		None PCy <sub>3</sub> ·HBF <sub>4</sub>	24 _	73 98
4	6 OTs	16 C <sub>6</sub> H <sub>13</sub>	None PCy <sub>3</sub> ·HBF <sub>4</sub>	36 39	<b>57</b> 41
5	7 OTs		None PCy <sub>3</sub> ·HBF <sub>4</sub>	100 <sup>d</sup> 100 <sup>d</sup>	Ξ
6	o OTs 9	<b>19</b> C <sub>6</sub> H <sub>13</sub>	None PCy <sub>3</sub> ·HBF <sub>4</sub>	91 <sup>d</sup>	9 88 <sup>d</sup>
7	BocN OTs	BocN 20 C <sub>6</sub> H <sub>13</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	_	91
8	OTs		PCy <sub>3</sub> ·HBF <sub>4</sub>	_	97
9	11 OTs 12	21 C <sub>6</sub> H <sub>13</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	47	52
10	Ph OTs 13	23 C <sub>6</sub> H <sub>13</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	52	48

<sup>a</sup> Reaction conditions: alkenyl tosylate (0.40 mmol), MIDA boronate 2 (0.44 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>NBS (3 mol %) and additional phosphine (6 mol %) in degassed THF (5 mL), aq Na<sub>2</sub>CO<sub>3</sub> (3 M in degassed H<sub>2</sub>O, 1 mL), heated in sealed tube under argon, at 60 °C overnight (16–21 h). <sup>b</sup> Isolated yield. <sup>c</sup> Average yield over two runs.

<sup>d</sup> Percentage (by NMR) in the substrate/product-ratio of the crude mixture.

were high yielding substrates for the coupling reaction under the PCy<sub>3</sub>·HBF<sub>4</sub> conditions (88–97%, entries 6–8). Some limitations of this methodology were observed with the cyclooctenyl tosylate 12 and with the hindered vinyl tosylate 13, where only moderate conversions were obtained after overnight reactions (entries 9 and 10).



Scheme 2. Scope of MIDA boronates in the Suzuki coupling with tosylate 1b.

The scope of the nucleophilic coupling partner was tested next with the previously employed *cis*-propenyl MIDA boronate **24**,<sup>5</sup> as well as with MIDA boronates **25–27**,<sup>30</sup> using tosylate **1b** with a conventional reflux procedure (Scheme 2). This procedure is of high practical convenience and excellent yields (>90%) were obtained in all cases. The stereochemistry of the alkenyl group in the boronate is retained affording, for example, product **28** as the *Z*-isomer with only minor traces of the *E*-isomer, although acid-catalysed isomerisation was observed to be fairly rapid.

In summary, we have shown that activated and unactivated alkenyl tosylates can undergo efficient coupling with a variety of alkenyl groups derived from MIDA boronates in a practical Suzuki-Miyaura cross-coupling reaction. The process involves air stable and commercially available Pd(PPh<sub>3</sub>)<sub>2</sub>NBS as precatalyst and does not require expensive phosphine ligands. The use of the cheap and easy to handle PCy<sub>3</sub>·HBF<sub>4</sub> salt is sufficient to achieve nearly quantitative yields with less activated substrates. We are confident that this robust and practical procedure will be of general use, for example in the synthesis of synthetic building blocks, as well as for library synthesis. Furthermore, both the use of alkenyl tosylates that are easily derived from carbonyl precursors and MIDA boronates, which are known to be stable to a variety of reaction conditions make this method an attractive tool for total synthesis. We are currently applying this procedure to more complex systems as part of a natural product synthesis programme.

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# Supplementary data

Supplementary data (general procedures and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.091.

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R	catecholborane (1 equiv) neat, 70 °C, 3 h then MIDA (1 equiv) DMSO, 60 °C, 3-16 h	R	<b>2</b> 53% (R = C <sub>6</sub> H <sub>13</sub> ) <b>25</b> 59% (R = C <sub>8</sub> H <sub>17</sub> ) <b>26</b> 74% (R = Ph) <b>27</b> 66% (R = CHCHPh)
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