

# *N*-Vinylpyridinium and -ammonium Tetrafluoroborate Salts: New Electrophilic Coupling Partners for Pd(0)-Catalyzed Suzuki Cross-Coupling Reactions

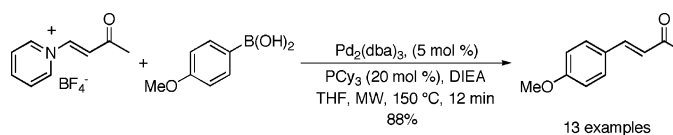
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## ABSTRACT



*N*-Vinylpyridinium and -trialkylammonium tetrafluoroborate salts represent a new class of electrophilic coupling partner for Pd(0)-catalyzed Suzuki cross-coupling reactions and give very good to excellent yields of products with a wide range of boronic acids. The salts are easily prepared from activated acetylenes and pyridinium or trialkylammonium tetrafluoroborates to form crystalline, air-stable, and nonhygroscopic crystals.

The Suzuki reaction is a powerful member of the important and versatile suite of palladium catalyzed carbon–carbon bond-forming reactions.<sup>1</sup> The versatility is enhanced by the coupling of aryl, vinyl, and alkyl<sup>1f–h</sup> halides or their corresponding triflates with literally hundreds of commercially available boronic acids and is thus ubiquitous in

organic synthesis. Suzuki coupling additionally plays a major role in the production of diverse compound libraries in combinatorial chemistry employing either parallel or solid-phase methods.<sup>2</sup> Notwithstanding these advantages, the requisite vinyl halides and triflates can be unstable or rely on expensive or toxic reagents for their preparation.<sup>3</sup> As part of an ongoing program to build novel natural product-like libraries that rely on Suzuki cross-coupling protocols, we searched for a robust and reliable vinyl halide or triflate equivalent. We now report that the readily available *N*-vinylpyridinium and ammonium tetrafluoroborate salts<sup>4</sup> such as **1** and **2** (Figure 1) represent new and excellent electrophilic coupling partners for the Suzuki reaction.

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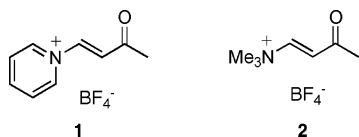
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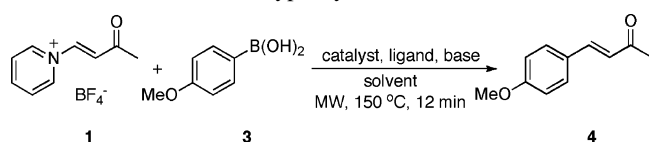


**Figure 1.** Examples of vinylpyridinium and -ammonium salts.

The synthesis of these salts was first reported by Jung and Buszek,<sup>4</sup> and they were employed as dienophiles by these workers in Diels–Alder cycloadditions. However, no other synthetic applications are found in the literature. This paper describes the first example of oxidative insertion of Pd(0) into vinylpyridinium and -ammonium bonds. Although a recent report by MacMillan shows that aryltrimethylammonium triflate salts undergo nickel-catalyzed Suzuki coupling,<sup>5</sup> it was noted that these same reactions fail with palladium catalysts. The MacMillan case more closely resembles the nickel-catalyzed Suzuki, Stille, and Kumada coupling of aryldiazonium salts, which have been known for some time.<sup>6</sup> There are no examples in the literature of *any* metal-mediated vinylpyridinium or vinyltrialkylammonium salt carbon–carbon bond formation,<sup>7</sup> and furthermore, the corresponding vinyldiazonium salts are unknown. Accordingly, these salts represent a completely new and useful class of palladium-catalyzed electrophilic coupling partner. The salts have the distinct advantage of being easily prepared almost quantitatively in one step from activated acetylenes and either pyridinium or trialkylammonium tetrafluoroborates. Additionally, they possess the highly desirable properties of being crystalline, nonhygroscopic, and indefinitely air-stable.

We initially examined the coupling of the (*E*)-1-(3-oxobut-1-enyl)pyridinium tetrafluoroborate **1** with *p*-methoxyphenylboronic acid **3** (Scheme 1) and surveyed a range of

**Scheme 1.** Coupling of Pyridinium Salt **1** with 4-Methoxyphenylboronic Acid



parameters to optimize the reactions conditions for this class of substrate (Table 1).

Since our initial objective was to employ these salts in library synthesis, we elected to use microwave heating

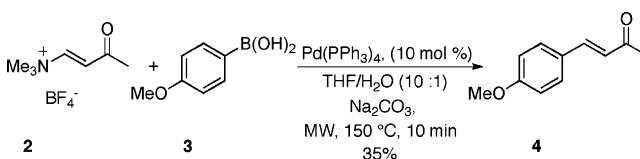
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**Table 1.** Optimization for the Suzuki Reaction

entry	catalyst (mol %)	ligand (mol %)	base	solvent	yield (%)
1	Pd(PPh <sub>3</sub> ) <sub>4</sub> (30)	none	Py	THF	34
2	Pd(PPh <sub>3</sub> ) <sub>4</sub> (30)	none	DIEA	THF	69
3	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	PPh <sub>3</sub> (20)	DIEA	THF	18
4	PdCl <sub>2</sub> [P( <i>o</i> -tolyl) <sub>3</sub> ] <sub>2</sub> (10)	none	DIEA	THF	20
5	PdCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (10)	none	DIEA	THF	55
6	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	P( <i>p</i> -tolyl) <sub>3</sub> (20)	DIEA	THF	20
7	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	PBn <sub>3</sub> (20)	DIEA	THF	80
8	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	PCy <sub>3</sub> (20)	DIEA	THF	88

(150 °C) under pressure for brief periods of time (10–12 min). Microwave-assisted chemistry is widely employed as a powerful tool in library development and organic synthesis in general for its ability to substantially reduce reaction times and increase throughput.<sup>8</sup> The use of tetrakis(triphenylphosphine)palladium(0) gave reasonable yields of the desired product but only with a high (30%) catalyst loading (entry 2). It was eventually found that Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol %) with 20 mol % of PCy<sub>3</sub> gave superior results (entry 8). Although the present unoptimized catalyst loads are relatively high, especially when compared to those recently reported by Buchwald in the parts per million range with certain hindered phosphine ligands,<sup>9</sup> they are not atypical for many Suzuki cross-coupling applications. We assume an oxidative insertion of Pd(0) into the C–N bond consistent with the accepted mechanism for conventional substrates.<sup>10</sup> The yields drop markedly with arylphosphine either as an initial or added ligand (entries 3, 4, and 6). Although a different set of conditions was needed for use with the corresponding class of vinyltrimethylammonium salts (Scheme 2), the yields are

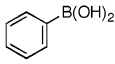
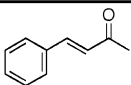
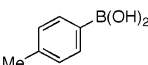
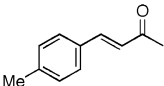
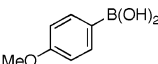
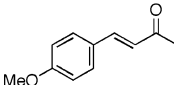
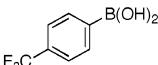
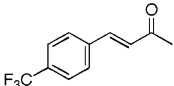
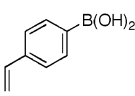
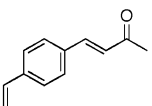
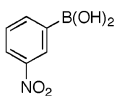
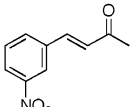
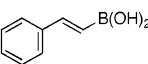
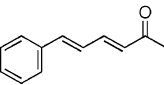
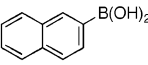
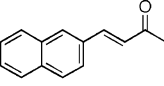
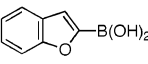
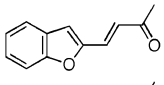
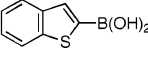
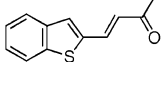
**Scheme 2.** Coupling of Ammonium Salt **2** with 4-Methoxyphenylboronic Acid



modest (35%) with this system and similarly remain unoptimized. The reasons for this difference are not yet clear.

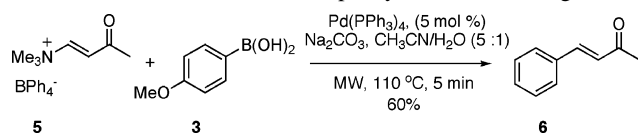
- (7) Nitrile-functionalized pyridinium ligands for palladium have been reported to enhance catalytic activity in ionic liquids, but no examples of oxidative insertion of Pd(0) into vinyl pyridinium salts are known: Zhao, D.; Fei, Z.; Geldbach, T. J.; Scopelliti, R.; Dyson, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 15876–15882. (8) (a) Lidström, P.; Tierney, J.; Watney, B.; Westmeier, J. *Tetrahedron* **2001**, *57*, 9225–9283. (b) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314–320. (9) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696. (10) (a) Tamao, K.; Hiyama, T.; Negishi, E. *J. Organomet. Chem.* **2002**, *653*, 1. (b) Miyura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (c) Miyaura, N. In *Metal Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diedrich, F., Eds.; John Wiley and Sons: New York, 2004; Chapter 2, pp 41–123.

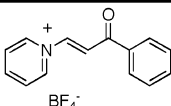
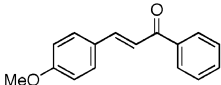
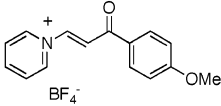
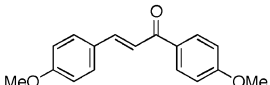
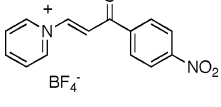
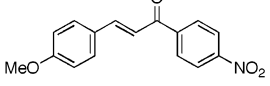
**Table 2.** Suzuki Coupling of Various Boronic Acids with Pyridinium Salt **1**<sup>a</sup>

entry	boronic acid	product	yield (%)
1			72
2			74
3			88
4			68
5			88
6			71
7			67
8			92
9			81
10			76

<sup>a</sup> Conditions: Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol %), PCy<sub>3</sub> (20 mol %), DIEA (2 equiv), THF, MW (150 °C), 12 min.

With the preferred conditions for the pyridinium salts in hand, we next examined the coupling of **1** with several representative aryl- and vinylboronic acids (Table 2). The yields (67–92%) are uniformly very good to excellent across the range of acids and are generally consistent and comparable to those found with conventional electrophiles. No clear trend emerged with respect to the effect of electron-donating and electron-withdrawing groups, except that yields were noticeably higher with strong electron donors (entry 3). The reaction of pyridinium salts of aryl ketones were likewise examined (Table 3) and, gratifyingly, showed similar behavior.

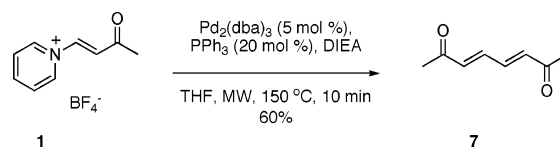
**Scheme 3.** Transfer of Tetraphenylborate Anion Ligand**Table 3.** Suzuki Coupling of *N*-Vinylpyridinium Vinyl Aryl Ketones with 4-Methoxyphenylboronic Acid<sup>a</sup>

entry	salt	product	yield (%)
1			81
2			60
3			71

<sup>a</sup> Conditions: Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol %), PCy<sub>3</sub> (20 mol %), DIEA (2 equiv), THF, MW (150 °C), 12 min.

In an effort to improve solubility of the salts in various solvents at ambient temperatures, we substituted the tetrafluoroborate anion with tetraphenylborate (Scheme 3) and found it gave with either vinylpyridinium or vinyltrimethylammonium substrates mainly the product **6** from the competitive transfer of the counterion ligand. No cross-coupling products were detected. Although the use of tetraphenyl borate as a reagent for the Suzuki reaction is preceded, the mechanism for this process is not fully understood.<sup>11</sup>

Finally, we discovered that vinylpyridinium salts can be made to undergo dimerization, presumably via reductive coupling,<sup>12</sup> by substituting 20 mol % triphenylphosphine as the added ligand for tricyclohexylphosphine, resulting in the formation of the 1,6-dioxo-2,4-diene **7** in 60% unoptimized yield (Scheme 4). We are continuing to explore the mech-

**Scheme 4.** Homocoupling To Give Dienedione **7**

anism and generality of this process, as there are only a few methods for the preparation of this useful class of compound.<sup>13</sup>

In conclusion, we have discovered a new class of palladium-catalyzed cross-coupling partners involving *N*-vinylpyridinium and related salts. The ease of preparation of

(11) Suzuki reactions with tetraarylborates have been observed: Lu, G.; Franzen, R.; Zhang, Q.; Xu, Y. *Tetrahedron Lett.* **2005**, *46*, 4255–4259 and references cited therein.

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(13) Ong, C. W.; Chen, C. M.; Wang, L. H.; Jan, J. J.; Shieh, P. C. *J. Org. Chem.* **1998**, *63*, 9131–9134 and references cited therein.

these salts in one step, the ready availability of the catalyst and ligands, and the simple and rapid reaction conditions make this method especially attractive. This system offers the added flexibility of introducing further functionality into the molecule, in this case, with ketones. Further investigations into the utility of these salts in other metal-mediated processes are underway and will be reported in due course.

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**Supporting Information Available:**  $^1\text{H}$  NMR data for all compounds reported in Tables 2 and 3 and experimental details for the cross-coupling reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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