Published in final edited form as:

Org Lett. 2007 February 15; 9(4): 707–710. doi:10.1021/ol063027h.

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

Keith R. Buszek^{*,†,‡,§} and Neil Brown^{‡,§}

Department of Chemistry, Kansas State University, 111 Willard Hall, Manhattan, Kansas 66506, Center for Chemical Methods and Library Design, University of Kansas, 1501 Wakarusa Drive Lawrence, Kansas 66047, and Department of Chemistry, University of Missouri, 205 Spencer Chemical Laboratories, 5100 Rockhill Road, Kansas City, Missouri 64110

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.¹ The versatility is enhanced by the coupling of aryl, vinyl, and alkyl^{1f–h} 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.² Notwithstanding these advantages, the requisite vinyl halides and triflates can be unstable or rely on expensive or toxic reagents for their preparation.³ 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 salts⁴ such as **1** and **2** (Figure 1) represent new and excellent electrophilic coupling partners for the Suzuki reaction.

The synthesis of these salts was first reported by Jung and Buszek,⁴ 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

© 2007 American Chemical Society

* To whom correspondence should be addressed. Current address: University of Missouri–Kansas City. buszekk@umkc.edu.

[†]Kansas State University.

[‡]University of Kansas.

[§]University of Missouri–Kansas City.

Supporting Information Available: ¹H 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>.

MacMillan shows that aryltrimethylammonium triflate salts undergo nickel-catalyzed Suzuki coupling,⁵ 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.⁶ There are no examples in the literature of *any* metal-mediated vinylpyridinium or vinyltrialkylammonium salt carbon–carbon bond formation,⁷ 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 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 (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.⁸ 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 Pd₂(dba)₃ (5 mol %) with 20 mol % of PCy₃ 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,⁹ 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.¹⁰ 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 modest (35%) with this system and similarly remain unoptimized. The reasons for this difference are not yet clear.

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.

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 precedented, the mechanism for this process is not fully understood.¹¹

Finally, we discovered that vinylpyridinium salts can be made to undergo dimerization, presumably via reductive coupling,¹² 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 mechanism and generality of this process, as there are only a few methods for the preparation of this useful class of compound.¹³

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 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.

Acknowledgment

We acknowledge support of this work by the National Institutes of Health (The University of Kansas Chemical Methodology and Library Development Center of Excellence), P50 GM069663. We wish to thank Mr. Benjamin Neuenswander from the KU-CMLD Library Design and Analysis Core for performing the LC-MS work. We thank Professor Zhonghua Peng (UMKC) for helpful discussions during the preparation of this manuscript. This paper is warmly dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

References

1. a Miyaura N, Suzuki A. *Chem. Rev* 1995;95:2457–2483. b Stanforth SP. *Tetrahedron* 1998;54:263–303. Miyaura, N. *Advances in Metal-Organic Chemistry*. Liebeskind, LS., editor. Vol. 6. JAI; London: 1998. p. 187–243. Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*. Diederich, F.; Stang, PJ., editors. Wiley-VCH; New York: 1998. Chapter 2 e Suzuki A. *J. Organomet. Chem* 1999;576:147–168. f González-Bobes F, Fu GC. *J. Am. Chem. Soc* 2006;128:5360–5361. [PubMed: 16620105] g Zhou J, Fu GC. *J. Am. Chem. Soc* 2004;126:1340–1341. [PubMed: 14759182] h Netherton MR, Fu GC. *Angew. Chem., Int. Ed* 2002;41:3910–3912.
2. a Lorscheid BA, Kurth MJ. *Chem. Rev* 1999;99:1549–1581. [PubMed: 11849002] b Dolle RE. *J. Comb. Chem* 2005;7:739–798. [PubMed: 16283784]
3. a Pillot J-P, Dunogues J, Calas R. *Synth. Commun* 1979;9:395–406. b Ritter K. *Synthesis* 1993:735–762.
4. a Jung ME, Buszek KR. *J. Org. Chem* 1985;50:5440–5441. b Jung ME, Buszek KR. *Tetrahedron Lett* 1986;27:6165–6168. c Jung ME, Buszek KR. *J. Am. Chem. Soc* 1988;110:3965–3969. d Jung ME, Vaccaro WD, Buszek KR. *Tetrahedron Lett* 1989;30:1893–1896.
5. Blakey SB, MacMillan DWC. *J. Am. Chem. Soc* 2003;125:6046–6047. [PubMed: 12785821]
6. a Darres S, Jeffrey JP, Genet JP, Brayer JL, Demoute JP. *Tetrahedron Lett* 1996;37:3857. b Kikukawa K, Kono K, Wada F, Matsuda T. *J. Org. Chem* 1983;48:1333–1336.
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 TJ, Scopelliti R, Dyson PJ. *J. Am. Chem. Soc* 2004;126:15876–15882. [PubMed: 15571412].
8. a Lidström P, Tierney J, Watney B, Westmeir J. *Tetrahedron* 2001;57:9225–9283. b Kappe CO. *Curr. Opin. Chem. Biol* 2002;6:314–320. [PubMed: 12023111]
9. Barder TE, Walker SD, Martinelli JR, Buchwald SL. *J. Am. Chem. Soc* 2005;127:4685–4696. [PubMed: 15796535]
10. a Tamao K, Hiyama T, Negishi E. *J. Organomet. Chem* 2002;653:1. b Miyura N. *Top. Curr. Chem* 2002;219:11. Miyaura, N. *Metal Catalyzed Cross-Coupling Reactions*. de Meijere, A.; Diederich, F., editors. John Wiley and Sons; New York: 2004. p. 41–123. Chapter 2
11. Suzuki reactions with tetraarylborates have been observed: Lu G, Franzen R, Zhang Q, Xu Y. *Tetrahedron Lett* 2005;46:4255–4259. 4259 and references cited therein..
12. Kuroboshi M, Waki Y, Tanaka H. *J. Org. Chem* 2003;68:3938–3942. [PubMed: 12737575]
13. Ong CW, Chen CM, Wang LH, Jan JJ, Shieh PC. *J. Org. Chem* 1998;63:9131–9134. and references cited therein

Figure 1.
Examples of vinylpyridinium and -ammonium salts.

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

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

Scheme 3.
Transfer of Tetraphenylborate Anion Ligand

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

Table 1

Optimization for the Suzuki Reaction

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

Table 2
Suzuki Coupling of Various Boronic Acids with Pyridinium Salt **1**^a

entry	boronic acid
1
2

entry

boronic acid

3

4

5

entry

boronic acid

6

7

entry

boronic acid

8

9

entry

boronic acid

10

^a Conditions: $\text{Pd}_2(\text{dba})_3$ (5 mol %), PCy_3 (20 mol %), DIEA (2 equiv), THF, MW (150 °C), 12 min.

Table 3Suzuki Coupling of *N*-Vinylpyridinium Vinyl Aryl Ketones with 4-Methoxyphenylboronic Acid^a

entry	salt
1
2

entry	salt
-------	------

3

^aConditions: $\text{Pd}_2(\text{dba})_3$ (5 mol %), PCy_3 (20 mol %), DIEA (2 equiv), THF, MW (150 °C), 12 min.