

Use of the Stille Coupling Reaction on Heteroaromatic Cations: Synthesis of Substituted Quinolizinium Salts

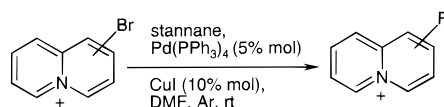
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Received April 30, 1999

ABSTRACT

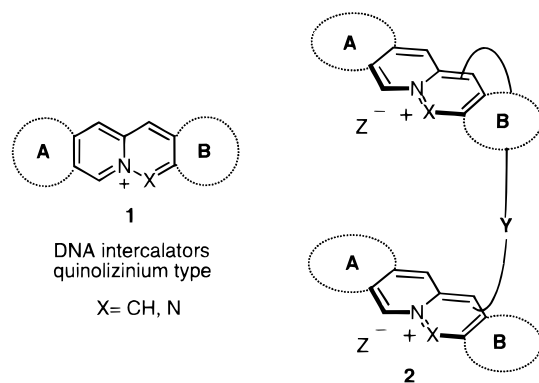


We describe the first efficient application of the Stille coupling reaction on heteroaromatic cations. In the presence of Pd(0)/CuI, the reaction of bromoquinolizinium salts and various tributylstannyl compounds proceeds in satisfactory yield under mild reaction conditions, affording different substituted quinolizinium salts.

The palladium-catalyzed cross-coupling reaction of organostannanes with organic electrophiles (usually halides or triflates), known as the Stille reaction,¹ has emerged as an extremely powerful tool for C–C bond formation.² Although this methodology has been applied to a variety of heterocyclic substrates,³ a cross-coupling route involving heteroaromatic cations such as azinium or quinolizinium salts has not been previously described.

As part of a project focused on the development of a novel class of DNA intercalators based on quinolizinium and azaquinolizinium-type systems **1**,⁴ and subsequent transforma-

tion into bis-intercalators **2** with chromophores linked by chains with different length, rigidity, and functionality (see below), we examined the feasibility of using a palladium-



mediated catalyzed coupling reaction as a means of introducing different aryl/heteroaryl substituents and aliphatic side chains in **1** in order to improve their intercalating properties

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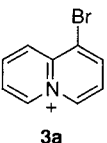
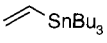
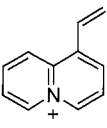
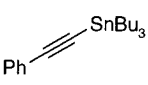
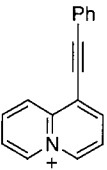
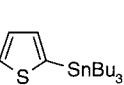
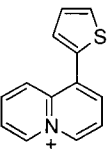
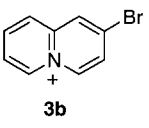
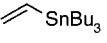
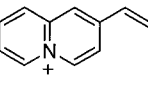

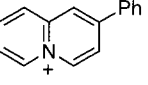
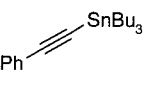
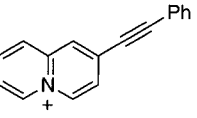
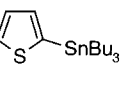
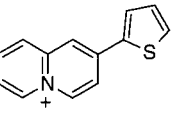
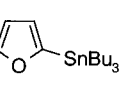
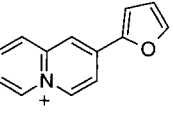
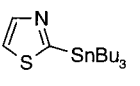
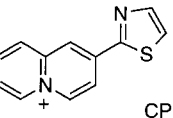
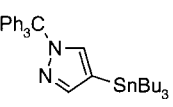
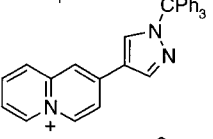
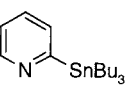
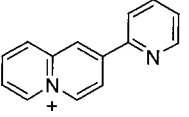
(2) (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons: Chichester, 1995; Chapter 4, p 125. (b) Farina, F. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, Chapter 3.4, p 161.

(3) (a) Undheim, K.; Benneche, T. *Adv. Heterocycl. Chem.* **1995**, *62*, 330. (b) Kalinin, V. N. *Synthesis* **1992**, 413.

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Table 1. Palladium-Catalyzed Cross-Coupling Reaction between Bromoquinolizinium Salts and Stannanes

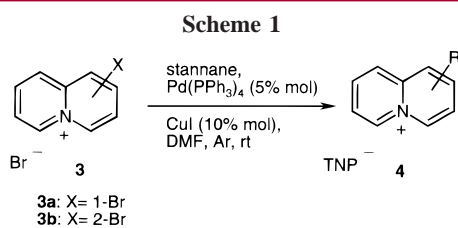
entry	quinolizinium salts (3)	stannane	coupling product (4)	yield (%)
1				4a 55
2				4b 58
3				4c 60
4				4d 10
5				4e 60
6				4f 91
7				4g 68
8				4h 55
9				4i 53
10				4j 96
11				4k 20

as well as their antitumor activity. In this Letter, we report our initial results on the transformation of some quinolizinium salts **3**, as simple models, into substituted quinolizinium derivatives **4** (Scheme 1) via the Stille coupling reaction.

Our efforts to achieve a cross-coupling route to quinolizinium derivatives focused on the 1- and 2-bromoquinoliz-

inium salts. The bromo derivatives **3**, being accessible substrates to study the reactivity of the 1- and 2-bromoquinolizinium salts in various coupling processes, were prepared in several steps by standard procedures.⁵

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We initially examined the coupling process with 1-bromoquinolinizinium salt **3a** and tributylvinylstannane to establish the best reaction conditions in the presence of 5 mol % of $\text{PdCl}_2(\text{PPh}_3)_2$ as the catalyst and in dimethylformamide (DMF) or tetrahydrofuran (THF) as the solvents at different temperatures. In all experiments, however, we found only extensive decomposition of the substrate. In addition, under the above conditions, the same procedure was tested in the presence of 3 equiv of LiCl ⁶ in DMF, a solvent that can both solubilize lithium chloride and act as a ligand for palladium. The reaction products, however, contained only starting material. In the presence of 3 equiv of LiCl in DMF, the use of tetraphenylstannane instead of tributylvinylstannane produced homo-coupling of the heterocycle^{7,8} in a 44% yield after 12 h of heating at 85 °C.

After further experiments, the desired coupling reaction was reproducibly obtained from **3a** and tributylvinylstannane in the presence of 5 mol % of $\text{Pd}(\text{PPh}_3)_4$, in DMF at room temperature, and with the addition of 10 mol % of copper(I) iodide as a cocatalyst. The reaction was completed in 17 h, producing 1-vinylquinolinizinium (Table 1, entry 1) in a 55% yield, with CuI being essential for success of the reaction. The beneficial effect of the $\text{Cu}(\text{I})$ salts in cross-coupling reactions has been previously observed.⁹ Although the exact role of copper is not clear, transmetalation of the R groups has been suggested.^{9c}

Starting with **3a**, alkenyl, alkynyl, and heteroaryl groups on tin were all transferred in high yield (entries 1–3). By

(6) Although there are a few reports on $\text{LiCl}/\text{Pd}(0)$ -promoted cross-coupling reactions, the salt effects have been examined with different electrophiles. (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (b) Echavarran, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478. (c) Tsuji, Y.; Kajita, S.; Isobe, S.; Funato, M. *J. Org. Chem.* **1993**, *58*, 3607. (d) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434. (e) Cummins, C. H. *Tetrahedron Lett.* **1994**, *35*, 857. (f) Fujita, M.; Oka, H.; Ogura, K. *Tetrahedron Lett.* **1995**, *36*, 5247.

(7) Homocoupling products derived from the stannane have been observed, with the homocoupling of the electrophile being less common. (a) Dubois, E.; Beau, J.-M. *Tetrahedron Lett.* **1990**, *31*, 5165. (b) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 2572. (c) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243. (d) Reference 6d. (e) van Asselt, R.; Elsevier, C. *J. Organometallics* **1994**, *13*, 1972, and references therein. (f) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583. (g) Jutand, A.; Mosleh, A. *J. Org. Chem.* **1997**, *62*, 261. (h) Danieli, B.; Lesma, G.; Martinelli, M.; Passarella, D.; Peretto, I.; Silvani, A. *Tetrahedron* **1998**, *54*, 14081.

(8) The homocoupling product [1,1']biquinolinizinium dipicrate has been characterized (see Supporting Information).

comparison, the same coupling of 2-bromoquinolinizinium **3b** with tributylvinylstannane under optimized conditions¹⁰ produced the desired substituted compound, although in poor yield (entry 4). Similarly, coupling of **3b** with phenylethynyltributylstannane and 2-thiophenyl- and 2-furanyltributylstannane produced yields ranging from good (entry 6) to moderate (entries 7 and 8). On the other hand, heating (85 °C) was required in the coupling with tetraphenylstannane to obtain the 2-phenylquinolinizinium salt (entry 5) in a 60% yield.

The method was further extended to tributylstannylpyridine, -thiazole, and -pyrazole, which were prepared according to previously reported procedures.¹¹ The results of the cross-coupling with 2-bromoquinolinizinium was successful for the thiazole and pyrazole derivatives (entries 9 and 10) and, as anticipated, resulted in a lower yield with the more electron-deficient pyridine (entry 11).

The above methodology, however, is limited to the transfer of alkyl groups. Our experiments with tetramethylstannane were unsuccessful and it is generally accepted that an sp^3 carbon directly attached to the metal is less reactive than carbons with lower hybridization in Pd-catalyzed reactions,^{1d} which likely accounts for the lack of reactivity observed.

In summary, a new and simple route to substituted heteroaromatic cations, with a bridgehead quaternary nitrogen, was developed involving palladium-catalyzed cross-coupling between bromoquinolinizinium and various aryl, heteroaryl, vinyl, and ethynyl stannanes. This method expands the scope of the Stille reaction and provides a good alternative for substitution of quinolinizinium derivatives, which are usually very unstable when in contact with nucleophilic species.

Acknowledgment. We wish to express our thanks for financial support to the Comisión Interministerial de Ciencia y Tecnología (CICYT, Project SAF98-0093).

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(9) For leading references, see: (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. (b) Gronowitz, S.; Björk, P.; Malm, J.; Hörnfeldt, A.-B. *J. Organomet. Chem.* **1993**, *460*, 127. (c) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905. (d) Roht, G. P.; Farina, V.; Liebeskind, L. S.; Peña-Cabrera, E. *Tetrahedron Lett.* **1995**, *36*, 2191. (d) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

(10) **Typical Procedure is as follows:** A flame-dried two-neck flask was charged under argon with 50 mg (0.173 mmol) of bromoquinolinizinium salt in 2 mL of dry DMF, then 10 mol % of CuI (0.0173 mmol, 3 mg) and 5 mol % of $\text{Pd}(\text{PPh}_3)_4$ (0.0086 mmol, 10 mg) were slowly added, and then 0.225 mmol of the corresponding stannane was added. After stirring at room temperature for 15–20 h, the solution was filtered through a small pad of Celite and washed with methanol. The solution was concentrated and the solid isolated by filtration. All compounds were isolated as picrates (TNP) by treatment of the crude bromide with a slight excess of sodium picrate in refluxing ethanol for 1 h.

(11) (a) 2-Tributylstannylpyridine: Lee, A. S.-Y.; Dai, W.-C. *Tetrahedron* **1997**, *53*, 859. (b) 2-Tributylstannylthiazole: Dondoni, A.; Mastellari, A. R.; Medici, A.; Negrini, E.; Pedrini, P. *Synthesis* **1986**, 757. (c) 4-Tributylstannyl-1-trityl-1H-pyrazole: Elguero, J.; Jaramillo, C.; Pardo, C. *Synthesis* **1997**, 563.

