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Palladium-Mediated Functionalization of Heteroaromatic Cations: Comparative Study on Quinolizinium Cations

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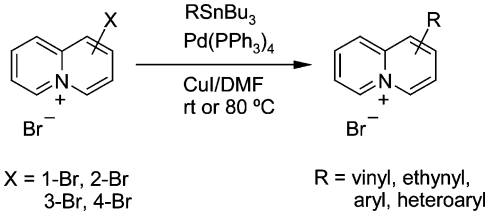

An efficient palladium-catalyzed cross-coupling reaction on heteroaromatic cations is described. A comparative study of the Stille and Suzuki reactions shows that only the Stille reaction is able to produce an efficient C−C bond formation between any of the four isomeric bromoquinolizinium bromides and a variety of stannanes. In the presence of the catalysts $Pd(PPh_3)_4$ or $Pd_2(dba)_3P(o\text{-Tol})_3$, vinyl, ethynyl, aryl, and heteroaryl groups are successfully incorporated into the quinolizinium system in satisfactory yields under mild reaction conditions. This procedure represents a marked improvement on the functionalization of this class of heteroaromatic cation.

Introduction

Heteroaromatic cations are considered as a kind of heterocyclic compounds that are structurally classified as azinium/azolium- and quinolizium-type cations depending on the nature of the quaternary nitrogen and aromatic heterocycle.[1] Thus, in azinium and azolium salts a nitrogen of an azine or azole is quaternized, whereas in quinolizinium-type salts a bridgehead quaternary nitrogen is the common feature of the charged system (Figure 1).

These compounds have attracted attention in fields as diverse as natural products,[2] fluorescent dyes,[3] antitumoral compounds,[4] DNA intercalators,[5] topoisomerase[6] and telomerase[7] inhibitors, and, more recently, NLO materials[8] and ionic liquids.[9] Recently,

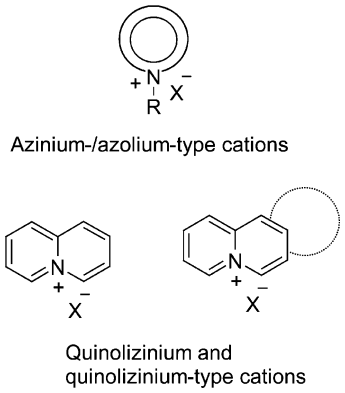

FIGURE 1. General structures for heteraromatic cations.

we faced a problem associated with the functionalization and/or introduction of substituents on some antiproliferative cations

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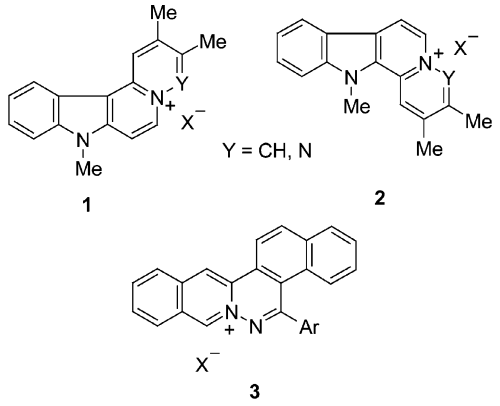

FIGURE 2. DNA intercalators based on a quinolizinium and an aza−quinolizinium core.

such as **1**−**3**, which are based on a quinolizinium and an aza−quinolizium core and behave as a new class of DNA intercalators and Topo I inhibitors[5c,10] (Figure 2).

As an example, introduction of substituents in systems **1**−**3** in order to improve their DNA binding properties and/or antiproliferative activity cannot easily be achieved using classical methods in heterocyclic chemistry. In this respect, electrophilic substitution is not a useful strategy for a positively charged heterocycle; nucleophiles usually react to give addition reactions that in many cases yield ring-opening products, and furthermore, metalation is a process with poor selectivity and is restricted to the use of non-nucleophilic bases. On the other hand, the traditional strategy of using appropriately substituted starting materials[11] is limited by either the tolerance of such substituents to the reaction conditions or their negative influence on the reactivity of such substrates.

The lack of a general methodology to achieve substitution—particularly on quinolizium-type cations—and our interest in this field led us to study a promising approach involving a palladium-catalyzed cross-coupling methodology. This approach has

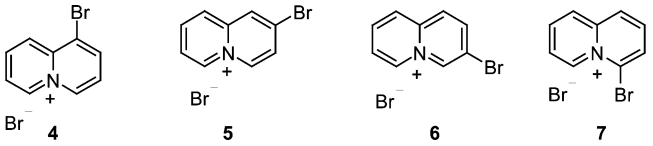

FIGURE 3. Isomeric bromoquinolizinium bromides.

proven to be extremely useful to build carbon−carbon[12] or carbon−heteroatom[13] bonds. Although the methodology has been applied to a variety of heterocycles,[14] to the best of our knowledge, only Zoltewicz[15] has reported an example involving a cationic heteroaromatic stannane. Our initial results demonstrated that both haloquinolizinium[16] and haloazinium cations[17] are appropriate partners in the Stille reaction. We report here our full investigations in a comparative study and discuss the scope of the functionalization of quinolizinium salts using Stille and Suzuki reactions.

Results and Discussion

For our investigation we chose the quinolizinium cation as the simplest model that offers four possible positions to explore substitution on quinolizium-type cations by palladium-mediated cross-coupling processes. The four isomeric bromoquinolizinium cations **4**−**7** (Figure 3) appeared to be the most appropriate models to study the scope of substitution on these charged heterocycles since they exhibit markedly different behavior from an electronic point of view at the C1/C3 and C2/C4 positions. Moreover, one would also expect a different steric effect on C1/C4 and C2/C3.

These four cations can be prepared according to previously reported procedures,[18] but their syntheses were not particularly efficient, mainly for 1-bromoquinolizinium bromide (**4**), which is obtained by bromination of quinolizinium bromide. This is a difficult reaction that was carried out at 200 °C and afforded only 10% yield of this bromo derivative (1.5% overall yield).[18a] We were able to improve the syntheses of **4** and **6**[18a] using a new approach to the quinolizinium system. This approach is based on a ring-closing metathesis (RCM) reaction on 1-butenyl-

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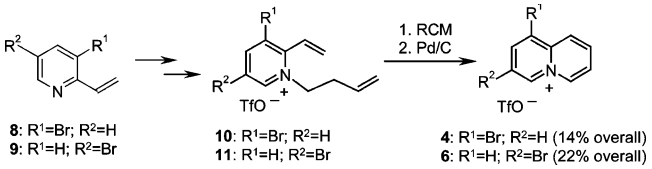
(18) For the synthesis of 1-bromo-(**4**), 3-bromo-(**6**), and 4-bromoquinolizinium (**7**), see: (a) Sanders, G. M.; van Dijk, M.; van der Plas, H. C. *Heterocycles* **1981**, *15*, 213. For the synthesis of 2-bromoquinolizinium (**5**), see: (b) Fozard, A.; Jones, G. *J. Chem. Soc.* **1963**, 2203.

SCHEME 1



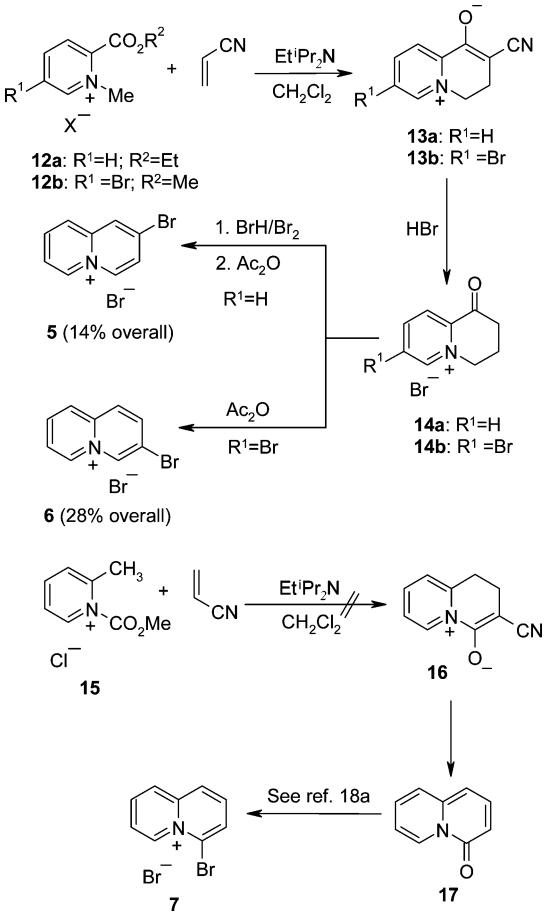
2-vinylpyridinium salts followed by oxidation of the resulting 3,4-dihydroquinolizinium[19] (Scheme 1).

However, this straightforward and efficient methodology could not be applied to the other two isomeric bromoquinolizinium cations.[20] For **5** and **7** a new approach to the previously reported precursor ketones **14a**[21] and **17**[22] was attempted, but our method, which is based on the reaction of pyridinium carboxylates with propenenitrile (Scheme 2), gave similar yields to that previously reported for the pyridinium salt **14a** and failed to produce the bicyclic ketone **17**. However, this approach also led to an improvement in the preparation of **6** from **12b** when compared with the classical method[18a] (28% vs 17%).

Our initial strategy to achieve the functionalization of these quinolizinium cations was to convert the bromoquinolizinium derivatives into the heteroaryltin **18**, heteroarylboronic acid **19**, and heteroaryl zinc **20** derivatives in order to test the well-known Stille, Suzuki, and Negishi reactions with a variety of commercially available alkyl, alkenyl, alkynyl, aryl, and heteroaryl halides.

As stated earlier, the only precedent found for a metalated heteroaromatic cation was reported by Zoltewicz et al.[15] They described the preparation of a pyridinium trialkylstannane by quaternization of the corresponding pyridylstannane with methyl iodide. This approach cannot be applied to the quinolizinium system, but this precedent did demonstrate the feasibility of preparing stable metalated heteroaromatic cations. For this reason, preparation of stannane **18** initially seemed a viable goal since other heteroarylstannanes have previously been prepared by reaction of the corresponding lithiated heterocycle with trialkyltin chlorides or by a palladium-mediated coupling reaction between a haloheterocycle and a hexaalkyldistannane.[23] We envisaged that the first approach to our target would be associated with several disadvantages (low solubility of the salts in the appropriate solvents for organolithium reagents, sensitivity of the substrate to nucleophilic attack, and poor selectivity of the lithiation reaction, inter alia) when compared with the cross-coupling reaction. For this reason, this latter approach was chosen as the most suitable to prepare **18**. Using 2-bromoquinolizinium bromide (**5**) as a model, all our attempts to isolate **18** by reaction with hexamethyldistannane or hexabutyldistannane in *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMAC) were unsuccessful. We tested three different catalytic systems [$Pd(PPh_3)_4$/CuI, $Pd_2(dba)_3$/P(*o*-Tol)$_3$, and $Pd_2(dba)_3$/BINAP] at different temperatures with standard and inverse slow addition of **5** and with addition of 1.2 equiv of KF when $Pd_2(dba)_3$/P(*o*-Tol)$_3$ was used as the catalytic system. The results obtained in all of these attempts to obtain **18** were variable, and inseparable mixtures of the homocoupling compound **21**, debrominated quinolizinium **22**, and starting material were obtained. Decomposition products were also detected in most of the attempted reactions.

SCHEME 2



The one-step procedure reported by Miyaura[24] for the preparation of arylboronic esters, based on a palladium-catalyzed coupling reaction between the pinacol ester of diboron and **5**, also failed using the same palladium sources and phosphines in DMF and DMSO at room temperature and at 70 °C in the presence of K_2CO_3 and Et(*i*-Pr)$_2$N as bases. As expected, attempts to synthesize heteroarylboronic acid **19** using either trimethoxyborane or the more selective triisopropoxyborane as reagents (via the lithiated heterocycle) were also unsuccessful, with extensive decomposition of the heterocycle being observed (Scheme 3).

Finally, we studied formation of the organozinc **20**[25] using 1,2-dibromomethane[26] and ultrasound[27] as methods for activation of the Zn with DMAC being used as the solvent in both cases. Under these conditions the presumably formed organozinc **20** was reacted with 4-iodotoluene in the presence of $Pd(PPh_3)_4$ at room temperature. Although we were able to detect by NMR formation of the cross-coupling compound **24**, formation of **21** and **22** was also observed. The best result afforded **24** in about

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(20) The RCM reaction for **5** required the use of 2,4-dibromopyridine as the starting heterocycle. This compound could not be *N*-alkylated with the 3-butenyl triflate. The RCM for **7** required the use of 2,6-dibromopyridine, which could not be selectively transformed into the 2-bromo-6-vinylpyridine, the appropriate precursor of the *N*-butenylpyridinium salt.

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(25) Boudier, A.; Bromm, L.O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414.

SCHEME 3

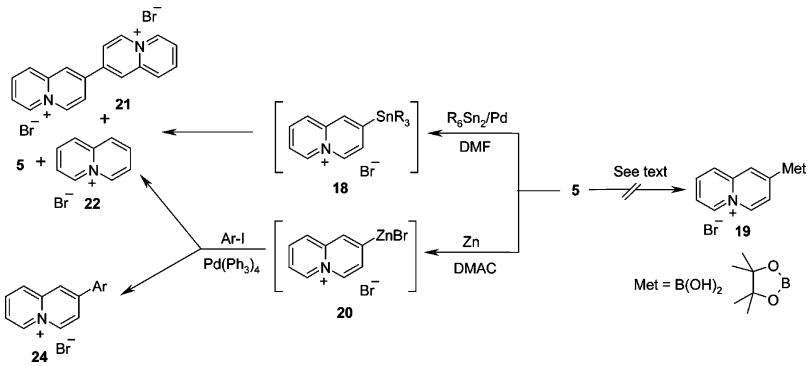
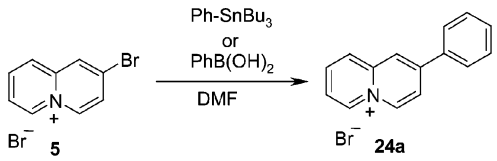


TABLE 1. Palladium-Catalyzed Cross-Coupling Reactions of 2-Bromoquinolizinum Bromide (5) under Suzuki and Stille Conditions



entry	stannane/boronic	conditions	yield[a] (%)
1	$PhSnBu_3$	$Pd(PPh_3)_4$, CuI/r.t., 15 h	NR
2	$PhSnBu_3$	$Pd(PPh_3)_2Cl_2$, CuI/r.t., 12 h	NR
3	$PhSnBu_3$	$Pd(PPh_3)_2Cl_2$, LiCl/r.t., 12 h	NR
4	$PhSnBu_3$	$Pd(PPh_3)_2Cl_2$, LiCl/80 °C, 12 h	dec.
5	$PhSnBu_3$	$Pd(PPh_3)_4$, 85 °C, 17 h	60
6	$PhSnBu_3$	$Pd_2(dba)_3P(o\text{-}Tol)_3$, 80 °C, 16 h	60
7	$PhB(OH)_2$	$Pd(PPh_3)_4/K_2CO_3$, r.t, 18 h	NR
8	$PhB(OH)_2$	$Pd(PPh_3)_4/K_2CO_3$, 80 °C, 2 h	traces
9	$PhB(OH)_2$	$Pd(PPh_3)_4/(i\text{-}Pr)_2EtN$, r,t., 18 h	NR
10	$PhB(OH)_2$	$Pd(PPh_3)_4/(i\text{-}Pr)_2EtN$, 90 °C, 5 h	NR
11	$PhB(OH)_2$	$Pd_2(dba)_3/P(o\text{-}Tol)_3$, K_2CO_3, r.t., 16 h	47

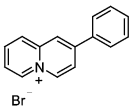
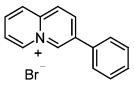
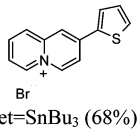
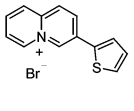
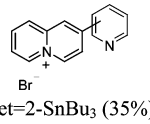
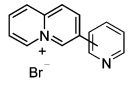
[a] Isolated yield. NR: no reaction; dec.: decomposition.

35% yield, but this compound could not be isolated from the reaction mixture.

The failure of this approach led us to explore reaction of the bromoquinolizinium derivatives as electrophilic partners with aryl- and heteroarylboronic acids and stannanes. Initially, optimization of the reaction conditions for Stille and Suzuki reactions was carried out with 2-bromoquinolizium salt **5** in order to compare the efficiency of these reactions on this high electron-deficient position of the quinolizinium system. The comparative study was carried out with tributylphenylstannane and phenylboronic acid. A summary of the reaction conditions and yields is given in Table 1.

The results showed that coupled compound **24a** was formed in both reactions, although yields were higher using Stille conditions when compared with those obtained with the Suzuki reaction. Under Stille conditions the best results were obtained using either palladium tetrakistriphenylphosphine (entry 5, method A) or tri-*ortho*-tolylphosphine/tris(dibenzylideneacetone)dipalladium (entry 6, method B) with heating at 80 °C for 16−17 h in the absence of any additive. In both cases the isolated yield of pure compound **24a** (60%) was clearly lower than that in the reaction itself (about 78% by NMR) due to losses during the isolation and recrystallization of this compound.

TABLE 2. Reactions of 5 and 6 with Aryl and Heteroaryl Boronic Acids and Stannanes[a]

	5	**6**
 Met=$SnBu_3$ Met=$B(OH)_2$	 Met=$SnBu_3$ (60%) Met=$B(OH)_2$ (47%)	 Met=$SnBu_3$ (53%) Met=$B(OH)_2$ (41%)
 Met=$SnBu_3$ Met=$B(OH)_2$	 Met=$SnBu_3$ (68%) Met=$B(OH)_2$ (11%)	 Met=$SnBu_3$ (48%) Met=$B(OH)_2$ (12%)
 Met=$SnBu_3$ Met=$B(OH)_2$	 Met=2-$SnBu_3$ (35%) Met=3-$B(OH)_2$ (0%)	 Met=2-$SnBu_3$ (58%) Met=3-$B(OH)_2$ (0%)

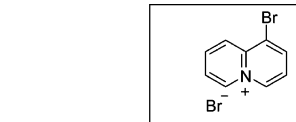
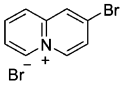
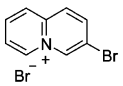
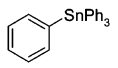
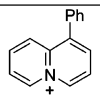
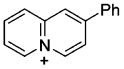
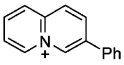
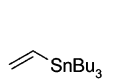
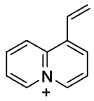
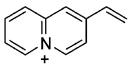
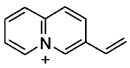
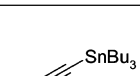
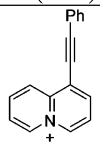
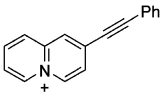
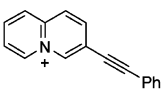
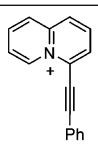
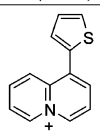
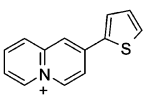
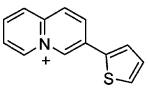
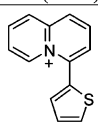
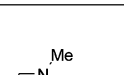
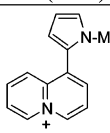
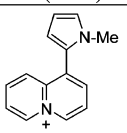
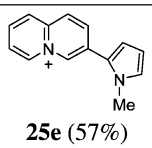
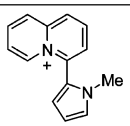
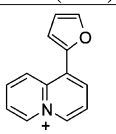
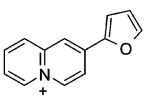
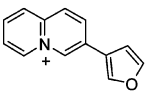
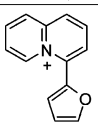
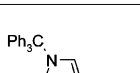
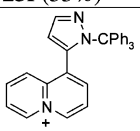
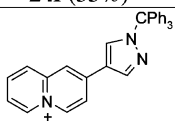
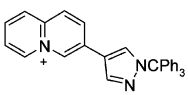
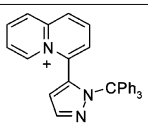
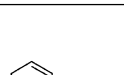
[a] Reactions with stannanes and boronic acids were carried out under the conditions shown in Table 1 (entries 5 and 11, respectively).

The coupling reaction between **5** and phenylboronic acid afforded the coupled compound in only 47% yield when $Pd_2(dba)_3/P(o\text{-}Tol)_3$ or $Pd_2(dba)_3$/(2-biphenyl)di-*tert*-butylphosphine was used in DMF in the presence of K_2CO_3 at room temperature for 16 h (extensive decomposition was observed by heating at 80 °C). In this case the isolated yield was also lower than that of the crude product (about 63%).

These results seem to indicate that the Stille reaction is the most suitable process to study the scope of this palladium-catalyzed cross-coupling reaction as a new methodology for the functionalization of the quinolizinium system. However, despite this we studied further examples to confirm our choice prior to carrying out the reactions of **4**−**7** with a variety of commercially available stannanes. Thus, two other electronically different heteroaromatic stannanes and their corresponding boronic acids were tested under the optimized conditions found for both reactions (Table 1, entries 5 and 11). Moreover, the 3-bromoquinolizinium bromide (**6**) was also subjected to Stille and Suzuki couplings in order to give a broader overview of the reactivity of the C2 and C3 positions of the quinolizinium system, which are electronically very different and similar to C4 and C1, respectively. From Table 2 it is readily apparent that Stille coupling is more expedient

(26) Knochel, P.; Yeh, M. C. P.; Berck, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
(27) Einhorn, C.; Einhorn, J.; Luche, J.-L. *Synthesis* **1990**, 787.

TABLE 3. Stille Reaction on Bromoquinolizinium Bromides 4−7

	 **4**	 **5**	 **6**	 **7**
	 **23a** (34%)[a,d]	 **24a** (60%)[a,c]	 **25a** (53%)	 **26a** (10%)
	 **23b** (55%)[a,c]	 **24b** (10%)[a,c]	 **25b** (22%)	 **26b** (0%)
	 **23c** (58%)[a,c]	 **24c** (91%)[a,c]	 **25c** (55%)	 **26c** (35%)
	 **23d** (68%)[a,c]	 **24d** (68%)[a,c]	 **25d** (48%)	 **26d** (85%)[b]
	 **23e** (77%)[a]	 **24e** (85%)[a]	 **25e** (57%)	 **26e** (70%)
	 **23f** (53%)[a,d]	 **24f** (55%)[a,c]	 **25f** (57%)	 **26f** (52%)
	 **23g** (45%)[a]	 **24g** (96%)[a,c]	 **25g** (71%)	 **26g** (13%)[b]
	**23h** (51%)[d]	**24h** (35%)[a,c]	**25h** (58%)	**26h** (83%)

For all compounds, yields are given for isolated products. [a] Method A: $Pd(PPh_3)_4$ (5 mmol %), CuI (10 mmol %), DMF, r.t. or heating at 80 °C. [b] Method B: $Pd_2(dba)_3/P(o\text{-}Tol)_3$ (5 mmol %), DMF, r.t. or heating at 80 °C. Most of the compounds were isolated as bromides (not shown). [c] Isolated as the picrate. [d] Isolated as the hexafluorophosphate.

than the Suzuki coupling, particularly when performed with electron-rich heteroaryl reagents. When an electron-poor substrate (such as the commercially available 3-pyridineboronic acid) was tested, the reaction failed to give the coupling compound with either 2-bromo- or 3-bromoquinolizinium bromide while the more electron-deficient 2-pyridinestannane afforded the coupled compound in low yield with **5** and in moderate yield with **6**.

On the basis of these results the Stille cross-coupling reaction was chosen for functionalization of the quinolizinium system to positions C1 and C4 using a variety of stannanes to form Csp^2-Csp, Csp^2-Csp^2, and Csp^2-Csp^3 bonds. First, the other possibility of forming a Csp^2-Csp^2 bond was studied by testing the reaction between **5** and tributylvinylstannane under the optimized conditions found for the coupling reaction with **5** and tributylphenyltin. Both catalytic systems shown in Table 1 (entries 5 and 6) afforded the same yield, and so the cheaper catalyst and less toxic phosphine (PPh_3) were chosen to carry out the coupling process. However, all experiments with the 1-bromoquinolizinium bromide (**4**) produced either decomposi-

tion of the substrate or recovery of large amounts of the starting material. In addition, the same procedure was tested in the presence of an additive such LiCl[28] (3 equiv) in DMF, but the reaction mixture contained only starting material. After further experiments the desired coupling reaction was reproducibly achieved in the presence of 10 mol % of copper(I) iodide.[29] The reaction was complete in 17 h and produced 1-vinylquinolizinium bromide (**23b**) (Table 3) in 55% yield.

Attempted coupling of 2-bromoquinolizinium (**5**), 3-bromoquinolizinium (**6**), and 4-bromoquinolizinium (**7**) with tributylvinylstannane under the optimized conditions found for **4** yielded the expected coupling product only with substrate **5** (Table 3, compound **24b**), albeit in only 10% yield. Further attempts on **5** and **6** with the experiment carried out at higher temperatures produced extensive decomposition in the case of **5**, but at 80 °C compound **6** gave the 3-vinylquinolizinium **25b** in 22% yield. In the case of substrate **7** the coupling proved unsuccessful under these conditions. Alternatives to produce coupling of tributylvinylstannane and **7** were tested in the presence of tri-*ortho*-tolylphosphine (5 mmol %) and tris-(dibenzylideneacetone)dipalladium [P(*o*-Tol)$_3$/Pd$_2$(dba)$_3$] (5 mmol %) at room temperature and heating in DMF. However, all of these attempts were also unsuccessful. These latter conditions were also tested for **4**−**6** in order to improve the yields of the coupling products. However, lower yields were obtained than under the original conditions. The failure of the coupling reaction with **7** and the low yield obtained for **24b** are probably related to the high electron deficiency of these two positions of the quinolizinium system, a situation that favors nucleophilic attack instead of the usual substitution mechanism and can even lead to polymerization of the coupled product.

In contrast to tributylvinylstannane, reaction of phenylethynyltributylstannane was successful at room temperature with all four bromoquinolizinium salts, although marked differences in the reaction yields were observed. The 2-bromoquinolizinium **5** in this case produced an excellent yield (91%) of the coupling product **24c**, whereas the other three isomeric cations reacted to give the coupling products (**23c**, **25c**, and **26c**) in moderate yields (35−58%). These yields could not be improved in the presence of [P(*o*-Tol)$_3$/Pd$_2$(dba)$_3$].

Phenyl- and different heteroaryl groups on tin were also successfully transferred to the four quinolizium cations with significant differences in rates and yields, which in some cases were large and dependent on the position of the bromo substituent on the quinolizinium salt and the nature of the stannane. For example, phenyl tributylstannane clearly afforded lower yields in the coupling reaction with **4** and **7** (compounds **23a** and **26a**) when compared with stannanes on electron-rich five-membered heterocycles such as pyrrole, furan, and thiophene (compounds **23d**−**f** and **26d**−**f**). In contrast, yields of the coupling products are more comparable on **5** and **6**, particularly for tributyl-2-furanyl- (**24a**, **24d**, **24f)** and tributyl-2-thienylstannanes (**25a**, **25d**, **25f)**. Reactions of phenyltributylstannane (or Ph_4Sn) are very slow at room temperature, and heating at 80 °C and long reaction times (17−31 h) were necessary to achieve moderate yields of the coupling products. Similar reaction times were also required to obtain the coupled compounds with the heteroarylstannanes if the reaction was conducted at room temperature. Heating at 60−80 °C considerably reduced the reaction times, and some processes were completed within a few hours (3.30 h) for 1-bromoquinolizinium **4**. However, such temperatures could not be generally used for the other isomers due to formation of side products by transfer of *n*-butyl groups. With the exception of the 2-thienyl derivative **26d**, which was obtained using method A in 23% yield and method B in 85% yield, method A was found to be superior in all of the other examples tested.

The coupling reaction with 4-tributylstannyl-1-trityl-1*H*pyrazole (compounds **23g**−**26g**) yielded analogous results to that found for tributylphenylstannane with yields in the range 13−96% depending on the bromoquinolizinium cation. Finally, coupling of **4**−**7** with electron-deficient stannanes such as pyridin-2-yl tributylstannane gave the coupling products **23h**−**26h** with an unexpectedly high yield (83%) for the coupling product on **7** (**26h**).

The methodology described above, however, cannot be applied to the transfer of alkyl groups, and all experiments with tetramethylstannane were unsuccessful. It is generally accepted that an sp^3 carbon directly attached to the metal is less reactive in Pd-catalyzed reactions than carbons with lower hybridization,[23] and this could explain the lack of reactivity observed.

In relation to the reactivity of the different bromoquinolizíniums and yields of the coupling products, it is not easy to establish a correlation between the halogenated position on the quinolizinium and the efficiency of the Stille process. On the basis of the isolated compounds the transfer of groups with different electrodonicity does not have a large effect on the yields of the coupled compounds in reactions involving the less electrophilic C1 and C3 positions. However, the most activated 2-bromo- and 4-bromoquinolizinium cations seem to be much more sensitive to the electronic effect on the ligands on tin, and position C2 usually gave better yields than the C4 position. One remarkable exception to this trend is **26h**, which was obtained in much better yield than **24h** (83% vs 35%). These results were confirmed in repetitive experiments, and this large difference in yield cannot be attributed to experimental difficulties encountered in the isolation of **24h**.

In summary, it has been shown that Stille coupling is the most efficient procedure among other palladium-catalyzed cross-coupling reactions such as the Suzuki and Negishi reactions to produce acceptable yields of substituted quinolizinium cations. Although we were not able to isolate the corresponding trialkylquinolizinium stannanes, we developed a general method for functionalization of the quinolizinium cation by reactions between the four isomeric bromoquinolizinium bromides and different vinyl-, ethynyl-, aryl-, and heteroarylstannanes using Pd(PPh$_3$)$_4$ (5 mmol %), CuI (10 mmol %), and Pd$_2$(dba)$_3$/P(*o*-Tol)$_3$ (5 mmol %) as catalytic systems in DMF at room temperature or heating at 80 °C. This procedure allows convenient quinolizinium substitution under mild conditions and

(28) Although there are few reports on LiCl/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) Echavarren, 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.

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eliminates inherent limitations associated with the lack of reactivity of this heteroaromatic cation.

Experimental Section

General. Literature procedures were used to prepare pyridinium salts **12a**,[30] **12b**,[31] and **15**.[32] 4-Bromoquinolizinium bromide (**7**) was prepared according to the method described in ref 18a. 1-Bromo- and 3-bromoquinolizinium bromides **4** and **6** were prepared by the method developed by us and reported in ref 19 (Scheme 1). 2-Bromoquinolizinium bromide **5** was obtained according to the procedure reported in ref 18b. Compounds **5** and **6** were also obtained by the method detailed in Scheme 2.

3,4-Dihydro-2-cyano-1-olate Quinolizinium (13a). To a solution of **12a** (3.5 g, 0.012 mol) in CH_2Cl_2 (40 mL) was slowly added *N*,*N*-ethyldiisopropylamine (4.16 mL, 0.024 mol), and the reaction mixture was stirred at room temperature for 10 min. Propenenitrile (7.86 mL, 1.2 mol) was added, and the mixture was heated under reflux for 20 h. The resulting precipitate was filtered off, washed with cold CH_2Cl_2, and recrystallized from CH_3CN to afford **13a** (1.20 g, 58%) as an orange solid. Mp 259−260 °C. IR (KBr) υ_{max} 2153, 1580, 1551, 1160 cm^{-1}.^{1}H NMR (CD_3OD, 300 MHz) δ 8.75 (d, 1H, $J = 6.1$ Hz), 8.56 (t, 1H, $J = 7.9$ Hz), 8.43 (d, 1H, $J = 7.9$ Hz), 7.92 (dd, 1H, $J = 7.6$, 1.5 Hz), 4.71 (t, 2H, $J = 6.9$ Hz), 2.84 (t, 2H, $J = 6.9$ Hz). ^{13}C NMR (CD_3OD, 75 MHz): δ 163.7, 151.6, 146.8, 145.1, 127.2, 125.1, 122.3, 76.0, 56.5, 23.7. MS (ESI^+) *m*/*z* 172 (M^+). Anal. Calcd for $C_{10}H_8N_2O$ (172.19): C, 69.76; H, 4.68; N, 16.27. Found: C, 69.85; H, 4.65; N, 16.37.

3,4-Dihydro-2-cyano-7-bromo-1-olate Quinolizinium (13b). *N*,*N*-Ethyldiisopropylamine (3.0 mL, 16.63 mmol) was slowly added to a solution of **12b** (3.04 g 9.06 mmol) in CH_3CN (10 mL), and the reaction mixture was stirred at room temperature for 10 min. Propenenitrile (6.3 mL, 95.64 mmol) was added, and the mixture was heated under reflux for 48 h. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (CH_2Cl_2:MeOH 8:2) to afford **13b** (1.22 g, 51%) as a red solid. Mp 196−197 °C. IR (KBr) υ_{max} 2170,1578, 1541, 860 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 9.19 (d, 1H, $J = 1.7$ Hz), 8.68 (dd, 1H, $J = 7.6$, 0.9 Hz), 8.16 (d, 1H, $J = 8.8$ Hz), 4.56 (t, 2H, $J = 7.0$ Hz), 2.64 (t, 2H, $J = 6.7$ Hz). ^{13}C NMR (DMSO, 75 MHz): δ 161.3, 149.1, 146.6, 123.9, 123.4, 118.4, 113.7, 75.4, 54.7, 21.9. HRMS calcd for $C_{10}H_7N_2OBr$ *m*/*z* 250.9820, found 250.9817.

1-Oxo-1,2,3,4-tetrahydroquinolizinium Bromide (14a). A solution of **13a** (1.15 g, 6.7 mmol) in aq. HBr (48%, 24.5 mL) was heated at 120 °C for 21 h. Then the solvent was evaporated under reduced pressure, and the residue was treated with EtOH to give a solid, which was recrystallized from EtOH affording 0.78 g (51%) of a brown solid. The product was a 74:26 mixture of the oxo and hydroxy tautomers. Mp 210−212 °C (lit.[21] 210−211 °C).

7-Bromo-1-oxo-1,2,3,4-tetrahydroquinolizinium Bromide (14b). A solution of **14b** (1.95 g, 7.77 mmol) in aq. HBr (48%, 30 mL) was heated at 120 °C for 24 h. The solvent was evaporated under reduced pressure, and the residue was treated with EtOH to give a solid, which was recrystallized from EtOH to afford a pale yellow solid (2.12 g, 89%). The product was a 75:25 mixture of the oxo and hydroxy tautomers. Mp 260−263 °C (lit.[18a] 261−264 °C).

General Procedures for Substituted Quinolizinium Salts 23−26. (1) Method A. A flame-dried two-necked flask was charged under argon with the corresponding bromoquinolizinium salts **4**−**7** (50 mg, 0.173 mmol) in dry DMF (2 mL). Then 10 mol % CuI (3 mg, 0.0173 mmol), 5 mol % $Pd(PPh_3)_4$ (10 mg, 0.0086 mmol), and the corresponding stannane (0.225 mmol) were slowly 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 was isolated by filtration. Some coupling products obtained from bromoquinolizinium **4** and **5** were isolated as picrates (TNP) by treatment of the crude bromide with a slight excess of sodium picrate in refluxing ethanol for 1 h. Other derivatives were isolated as hexafluorophosphates by treatment with ammonium hexafluorophosphate in water followed by purification by column chromatography on silica gel using CH_2Cl_2/MeOH (9.5:0.5) as the eluent. For the coupling products obtained from 3- and 4-bromoquinolizinium salts **6** and **7**, after washing with methanol, the solvent was removed and the residue triturated with ether and EtOAc. Purification of the crude product by column chromatography on silica gel (reverse phase) using H_2O/AcOH (100:0.5) as the eluent yielded the coupling products **23** and **24**, which were isolated as bromides.

(2) Method B. A dried two-necked flask was charged under argon with the corresponding quinolizinium salt (100 mg, 0.333 mmol) in dry DMF (5 mL). $Pd_2(dba)_3$ (5 mol %, 15.1 mg, 0.0165 mmol), P(*o*-Tol)$_3$ (5 mol %, 5 mg, 0.0165 mmol), and the corresponding stannane (1.3 equiv, 0.429 mmol) were slowly added. The mixture was stirred at room temperature, filtered through a small pad of Celite, and washed with methanol. The solvent was removed, and the residue was triturated with EtOAc. Purification of the crude product by column chromatography on silica gel (reverse phase) using water as the eluent yielded the product, which was isolated as the bromide.

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Supporting Information Available: Complete experimental procedures for the synthesis and analytical and characterization data (^{1}H NMR/^{13}C NMR, IR, MS) of compounds **23**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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