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

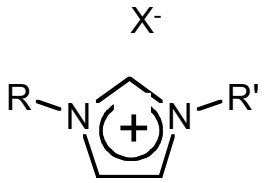
Domingo Garcia-Cuadrado, Ana M. Cuadro, Bernado M. Barchin, Ana Nunez, Tatiana Caneque, Julio Alvarez-Builla, and Juan J. Vaquero

J. Org. Chem. **2006**, *71*, 7989-7995

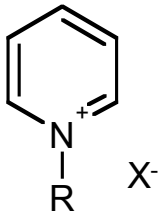
David Arnold: 10/28/06

Nitrogen Containing Heteroaromatic Cations

- Azinium / azolium type cations:



N,N'-dialkylimidazolium cations



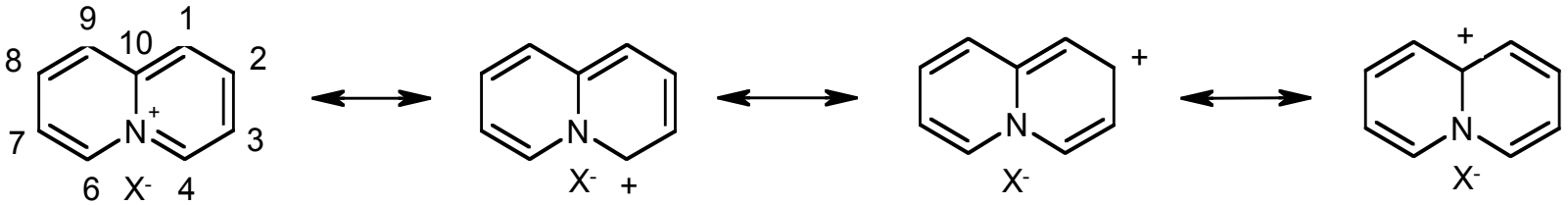
N-alkylpyridiniumcations

Usually X^- = halogen, PF_6, BF_4, etc.

- Studied extensively under a class of compounds known as room temperature Ionic liquids

Chem. Rev. **1999**, *99*, 2071.

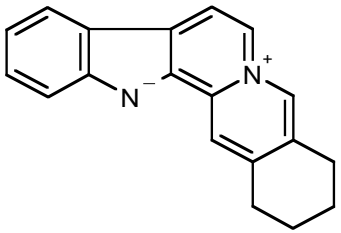
- Quinolizinium type cations: Bridgehead quaternary nitrogen atom



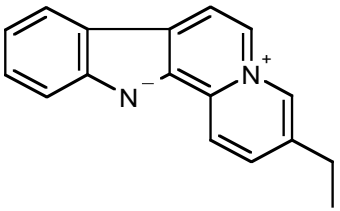
-Resonance analysis shows carbons 2,4,6,8 and 10 to be more electron deficient than carbons 1,3,7 and 9.

Biological Importance of Quinolizinium Cations

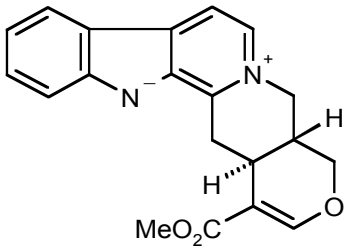
- Many biologically active natural products contain a quinolizinium core



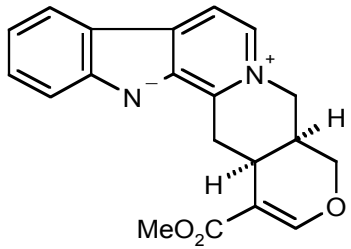
Sempervine isolated in 1916 from Gelsentium sempervirens



Flavopereirine



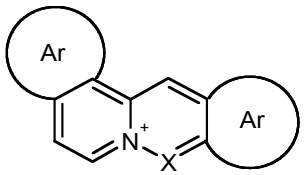
Serpentine



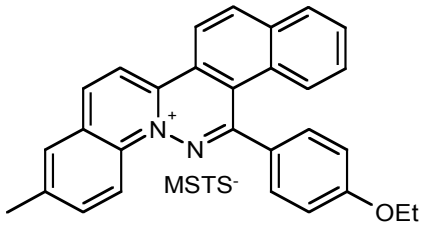
Alstonine

- The family of sempervirine indolo[2,3-α]quinolizine alkaloids represent a class of compounds displaying anti-HIV, immunostimulant, sedative and antipsychotic biological activities.

- Cancer research: DNA intercalation and topoisomerase inhibitors.



X = CH, N
General structure of quinolizinium and aza-quinolizinium type DNA inhibitors

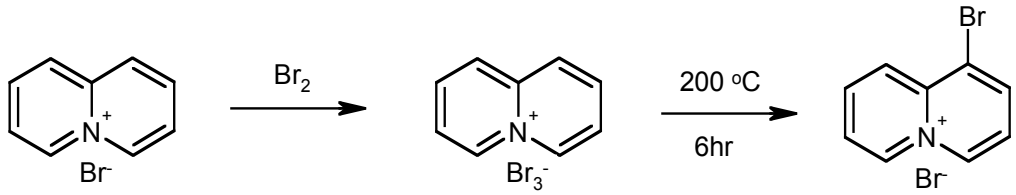


Known DNA intercalator and topoisomerase I inhibitor

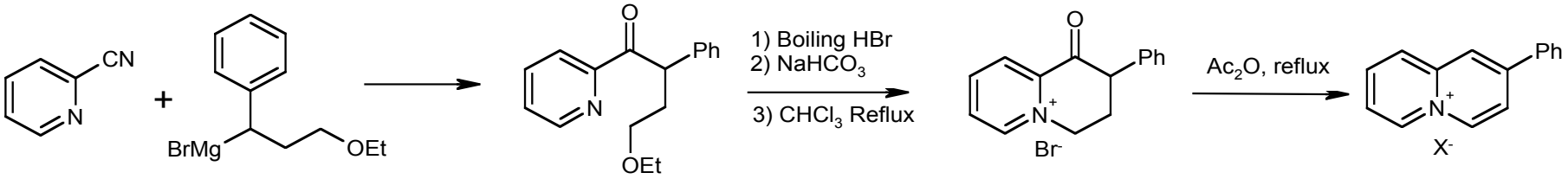
Tetrahedron Letters, **2002**, *43*, 9565; *J. Med. Chem.* **2004**, *47*, 1136

Some Examples of Traditional Routes to Functionalized Quinolizinium Bromides

1) Traditional synthesis of 1-bromoquinolizinium bromide



2) Traditional synthesis of a 2-phenylquinolizinium salt

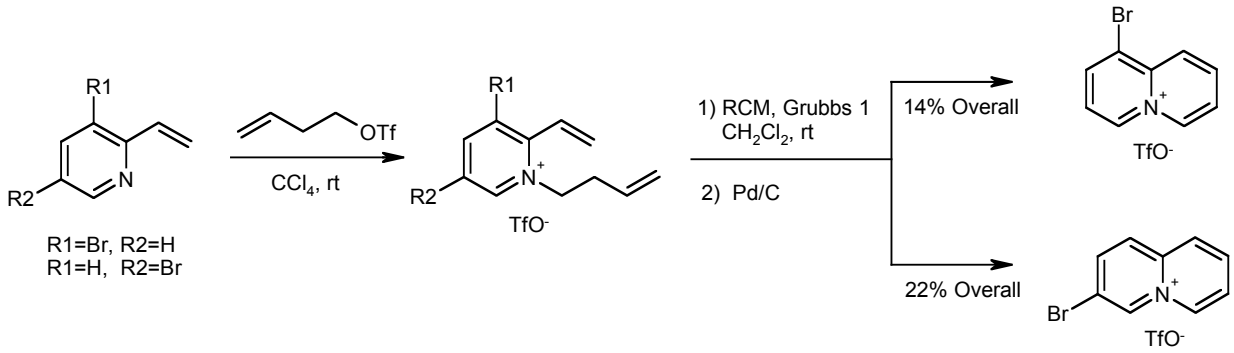


- These two examples show that traditional routes incorporate functionality into the quinolizinium cation mainly through the initial starting materials and often contain harsh reaction conditions.

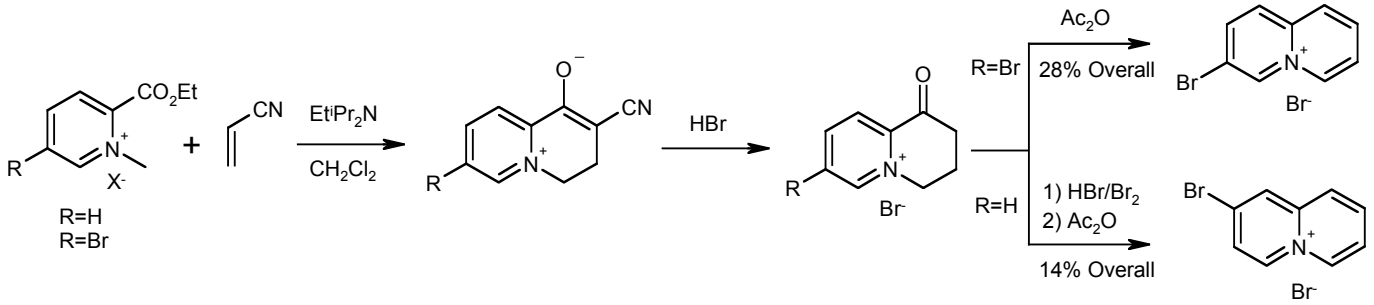
Heterocycles. **1981**, *15*, 213; *J. Am. Chem.Soc*. **1958**, 3021

Preparation of Bromoquinolizinium Bromides for Use in Palladium Catalyzed Cross Coupling Reactions

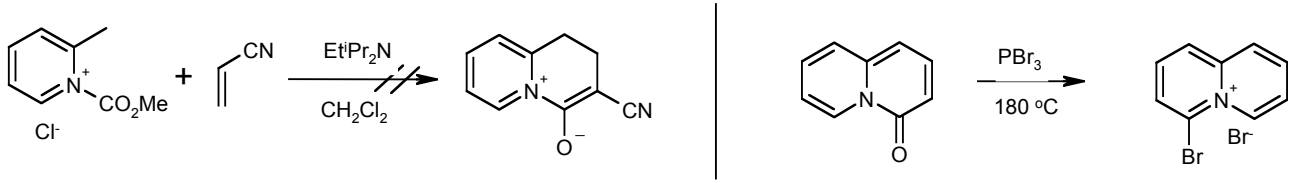
- Preparation of 1-bromo and 3-bromoquinolizinium bromides



- Preparation of 2-bromoquinolizinium bromide



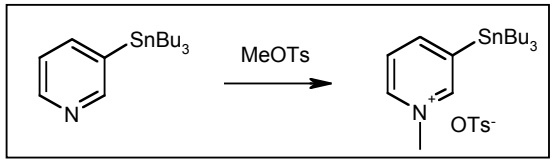
- Preparation of 4-bromoquinolizinium bromide



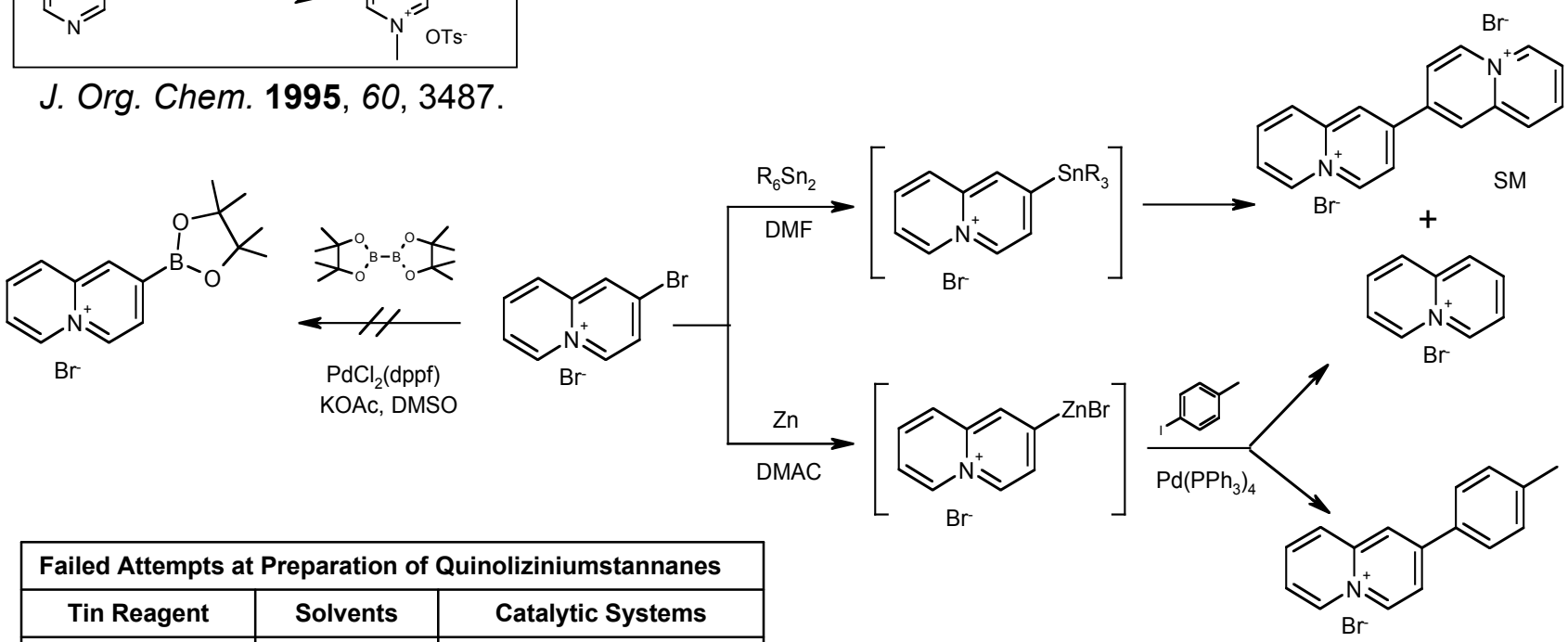
Org. Lett. **2004**, *6*, 4125; *Heterocycles* **1981**, *15*, 213.

Attempted Metalation of the Bromoquinolizinium Bromides for Preparation of Tin, Boronic Acid and Zinc Heteroaryl Derivatives

- Literature precedence for cationic heteroaromatic stannanes; Zoltwicz

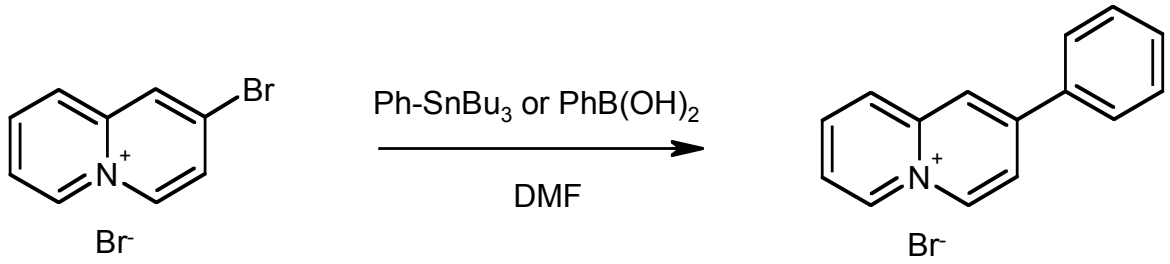


J. Org. Chem. **1995**, *60*, 3487.



Failed Attempts at Preparation of Quinoliziniumstannanes		
Tin Reagent	**Solvents**	**Catalytic Systems**
Me_6Sn_2	DMF	$Pd(PPh_3)_4$/CuI
Bu_6Sn_2	DMAC	$Pd_2(dba)_3$/P(o-tol)$_3$
		$Pd_2(dba)_3$/BINAP

Optimization of Palladium-Catalyzed Cross-Coupling Reactions of 3-bromoquinolizinium Bromide Under Suzuki and Stille Conditions

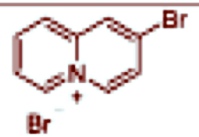
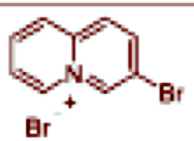
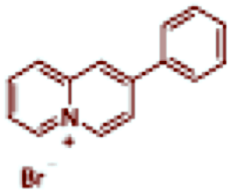
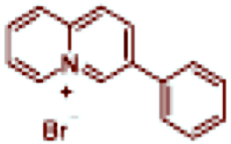
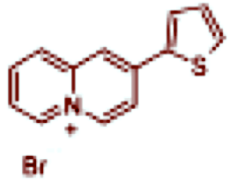
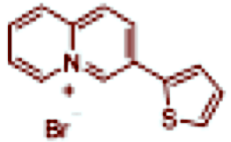
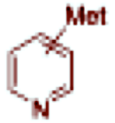
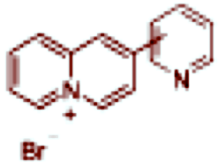
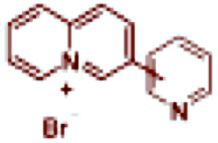


entry	stannane/boronic	conditions	yield[a] (%)
1	$PhSnBu_3$	$Pd(PPh_3)_4$, CuI/r.t., 15 h	NR
2	$PhSnBu_3$	$Pd(PPh_3)_2Cl_2$, CuI/r.t., 12 h	NR
3	$PhSnBu_3$	$Pd(PPh_3)_2Cl_2$, LiCl/r.t., 12 h	NR
4	$PhSnBu_3$	$Pd(PPh_3)_2Cl_2$, LiCl/80 °C, 12 h	dec.
5	$PhSnBu_3$	$Pd(PPh_3)_4$, 85 °C, 17 h	60
6	$PhSnBu_3$	$Pd_2(dba)_3P(o\text{-}Tol)_3$, 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.

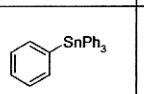
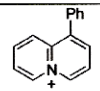
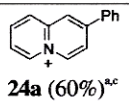
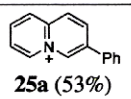
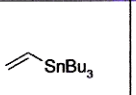
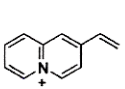
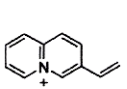
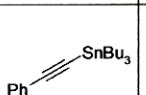
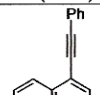
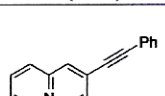
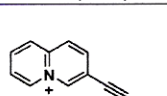
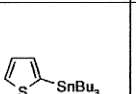
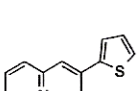
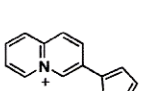
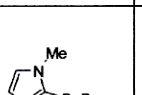
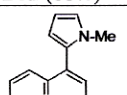
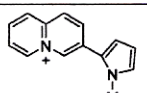
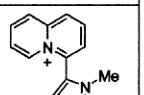
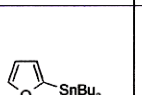
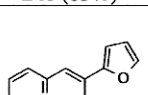
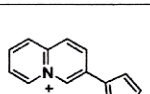
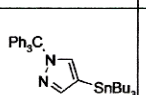
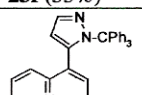
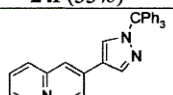
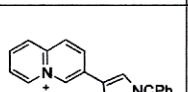
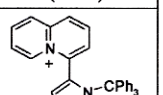
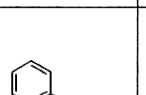
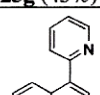
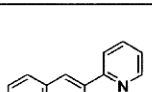
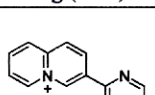
- Under optimized conditions, Stille coupling has been found to be more efficient than Suzuki coupling.

Comparison of the Reactions of 2-bromo and 3-bromoquinolizinum Bromide with Aryl and Heteroaryl Boronic acids and Stannanes Under Optimized Conditions

	 **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 comparison of the reactions with both isomers shows that Stille coupling is still more efficient.
- Suzuki coupling gives poor results with both electron rich and electron deficient aromatic heterocycles.

Stille Reactions of the Four Bromoquinolizinium Bromides

	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%)

- The reactions of 4 and 5 with tributylvinylstannane were further optimized by adding 10 mol% Cu(I)I.
- Much better yields were obtained with the phenylethynyltributylstannane.
- The methodology was not found to be applicable to the transfer of alkyl groups from tetramethylstannane.

Conclusions

- Stille cross coupling reactions with bromoquinolizinium bromides have been shown to be more efficient than Suzuki and Negishi palladium catalyzed cross coupling reactions, affording moderate yields of vinyl, ethynyl, aryl and heteroaryl functionalized quinolizinium cations under mild conditions.

- The new synthetic strategy promotes selective mono functionalization of the quinolizinium ring system under conditions that are not limited exclusively to the starting materials, which provides a profound improvement over many traditional synthetic approaches.