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Palladium-Assisted Intramolecular Formation of N-Heterocycles by sp^2 N Nucleophilic Attack on η^3–allyl-Pd Complexes Generated by Allene Insertion into σ Pd-C Bond.

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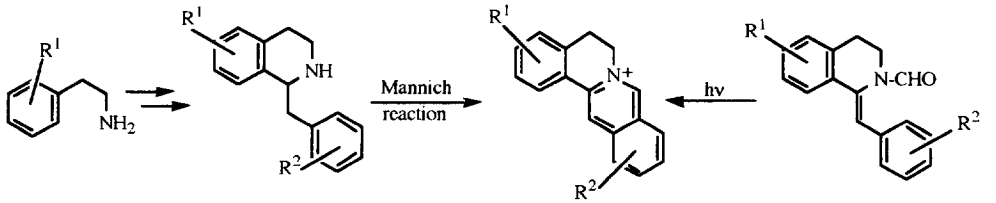
Abstract: 1,1-dimethylallene inserts into the σ Pd-C bond of a series of cyclopalladated pyridine derivatives leading to stable or unstable η^3–allyl-Pd complexes. The demetallation of the latter leads to pyridinium derivatives with good yields. Copyright © 1996 Elsevier Science Ltd

Molecules containing pyridinium with the nitrogen atom shared between two rings are not frequent in the literature and many of them display interesting biological activities. [1] Those containing the benzo(a)quinolizinium skeleton have long been known for their pharmacological activities. [2] The most common ones are the protoberberine alkaloids used for their antibacterial, antimalarial and antipyretic properties. [3] Scheme I below shows two ways of synthesizing this class of alkaloids. [4]

Scheme I



Furthermore, protoberberine derivatives have recently been used as starting materials for the synthesis of other pharmacologically potent alkaloids. [5] We wish to report a novel route of selective synthesis of benzo(a)quinolizinium derivatives and related analogues via a strategy based upon a palladium-mediated process.

Indeed, pyridine derivatives, substituted at the ortho position by an aryl ring, can be easily cyclometallated by palladium; [6] the process we are working on consists of the substitution of Pd by a C_2 unit (e. g. internal alkynes) between the palladated nitrogen and carbon atoms. [7] We show herein that allenes can be an elegant alternate solution to the use of alkynes to achieve this heterocyclisation. Indeed, insertion of allenes into Pd-C bonds is well-known to afford η^3-allyl Pd compounds. [8] With our starting material this reaction may be followed by the intramolecular nucleophilic addition of the sp^2 N atom of the pyridines on the thus generated allyl unit akin to the recently reported work on Pd mediated allene reaction with secundary o-iodoarylamines. [9]

The novel process is summarised in Scheme II and the various examples with which the reaction was successful are reported in Table I.

Scheme II

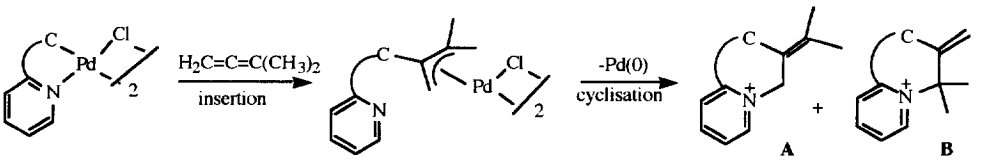
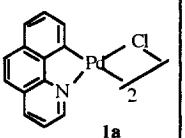
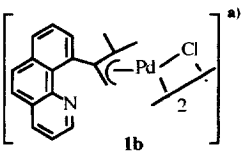
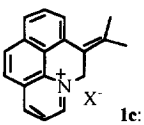
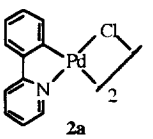
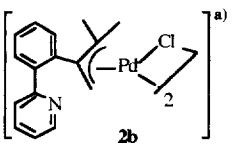
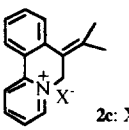
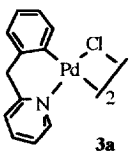
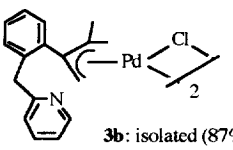
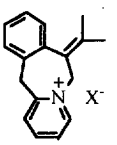
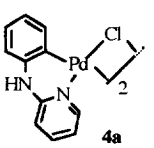
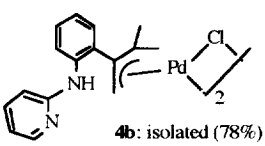
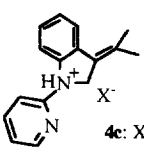


Table I: Heterocycle formation via 1,1-dimethylallene insertion into Pd-C bond.

Entry	Reactants	Insertion products	Heterocycles formed
1	 **1a**	 [a] **1b**	 [b] **1c**: X= PF_6 (75%)
2	 **2a**	 [a] **2b**	 [b,c] **2c**: X= PF_6 (51%)
3	 **3a**	 **3b**: isolated (87%)	 [d] **3c**: X= Cl (53%)
4	 **4a**	 **4b**: isolated (78%)	 [d] **4c**: X= Cl (63%)

[a] Reaction intermediate observed by ^{1}H NMR.

[b] The yields of the products are higher when they are isolated as their PF_6 anions

[c] A mixture of the two regioisomers **A** and **B** in a 2:1 ratio (^{1}H NMR) is obtained after 2 hours reaction if CH_2Cl_2 is used as solvent instead of MeOH.

[d] The products were formed by the reaction of the isolated η^3–allyl palladium complexes with 4 eq. of PPh_3 in methanol at room temperature

Typically 1,1-dimethylallene was added to a suspension of the cyclopalladated derivative and the reaction mixture was allowed to stir at room temperature. Dichloromethane was used as solvent throughout the study except for entry 2 where methanol gave regioisomer **A** with a high regioselectivity (Scheme II).

For the benzo(h)quinoline and the phenylpyridine cyclopalladated derivatives (entries 1 and 2), the heterogeneous solution turned black on standing and the cyclized products **1c** and **2c** were obtained directly. However, a kinetic proton NMR study unambiguously showed the formation of the corresponding unstable η^3-allyl Pd intermediate shown in Table I above.

In the case of entries 3 and 4, the heterogeneous mixture gradually tends to a homogeneous one (without blackening) indicating that the insertion reaction is complete. The η^3-allyl-Pd complexes **3b** and **4b**

were isolated and characterized. Owing to their stability in solution, an activation by PPh_3 [10, 11a] was needed to induce their demetallation, thereby yielding the cyclized organic products **3c** and **4c**.

Considering entry 4, the formation of the five-membered heterocycle rather than the seven-membered one may be assigned to a significant difference in nucleophilicity between an sp^3 nitrogen atom (secondary amine) and an sp^2 one (pyridine) in addition to the fact that the formation of a five- *vs* a seven-membered ring is thermodynamically more favourable. [12]

It is important to note that in the final products the N-C bond formation has occured with the sterically less hindered carbon atom of the allylic unit. [13] However, a cautious examination of the reaction observed with compound **2a** showed that, in CH_2Cl_2, the product formed at early stages of the reaction is the isomer **B** (*ca.* after 20 mn) i.e. in accord with Akermark's study. He showed that 1,1 dialkyl substituted π-allyl complexes react preferentially at the more substituted position. [14] A ^1H NMR study showed that the isomerisation to the thermodynamically stable regioisomer **A** was complete within 12 h. We have observed that in the absence of palladium the isomerisation did not take place, thus showing that the formation of the product **A** is under thermodynamic control.

Conclusion

The reaction of an allene with cyclopalladated compounds can lead to the regioselective formation of new stable pyridinium containing heterocycles having an exocyclic C-C double bond adjacent to an aromatic ring, via an intermediate containing a η^3-allyl-Pd unit. It was shown recently that pyridine may reversibly add in an intermolecular reaction to such allyl group. [15] We have now shown here that as for tertiary amines [11] this reaction when performed intramolecularly may lead to stable N-C bond formation.

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Experimental:

a) Synthesis of **1c** (entry 1, Table I): A mixture of the cyclopalladated derivative **1a** [6a] (320 mg; 0.5 mmol) and 2.5 eq. of 1,1-dimethylallene (85 mg; 1.25 mmol) in CH_2Cl_2 (25 ml) was stirred at room temperature for *ca.* 3/4 h. The black heterogeneous mixture obtained was filtered over celite to remove Pd(0). After concentration of the filtrate, hexane was added slowly to precipitate the heterocycle as a pale yellow solid. Anion exchange using KPF_6 in MeOH or H_2O yielded a white powder corresponding to the pure product (yield: 106 mg, 75%).

Data for **1c** (X=PF_6): Anal. calc. for $C_{18}H_{16}NPF_6$: C, 55.24; H, 4.09; N, 3.58 Found C, 55.59; H, 3.80; N, 3.43. ^{1}H-NMR ($(CD_3)_2CO$): δ 9.90 (d, 1H, Ar, ^3J = 6.3); 9.35 (d, 1H, Ar, ^3J = 8.1) ; 8.46-8.41 (m, 2H, Ar); 8.38-8.30 (m, 3H, Ar); 8.15 (t, 1H, Ar, ^3J = 7.8); 6.14 (s, 2H, NCH_2); 2.16 (s, 6H, $=C(CH_3)_2$). ^{13}C-NMR (CD_3OD): δ 147.0; 142.9; 136.9; 135.2; 133.9; 132.6; 132.2; 130.8; 130.4; 126.7; 126.2; 125.5; 119.5; 119.3 and 118.9 (Ar, C=C); 72.0 (NCH_2); 27.6 (2C, $=C(CH_3)_2$). (Brucker AX 300, 293 K, δ in ppm, *J* in Hz). m/z (without PF_6): 246 (M^+), 244 (M^+- 2H).

b) Synthesis of **3b** (entry 3, Table I): To a suspension of the cyclopalladated compound **3a** [6c] (624 mg; 1 mmol) in CH_2Cl_2 (25 ml) was added 2.5 eq. of 1,1-dimethylallene (171 mg; 2.5 mmol). After 2h stirring at room temperature, a homogeneous mixture was obtained. After filtration on celite (if some decomposition has occured), concentration of the filtrate and precipitation using hexane, a pale yellow solid was obtained (yield: 657 mg, 87%). Anal. Calc. for ($C_{34}H_{36}N_2Pd_2Cl_2$ + 1/4 C_6H_{14}): C, 54.81; H, 5.08; N, 3.60 Found C, 55.18; H, 5.14; N, 3.40(the presence of n-hexane was checked by NMR). ^{1}H-NMR ($CDCl_3$ + pyridine-d_5): δ 8.48

(d, 1H, Ar, ^3J = 4.6); 7.92 (d, 1H, Ar, ^3J = 6.7); 7.51 (td, 1H, Ar, ^3J = 8.4, ^4J = 1.5); 7.29-7.19 (m, 3H, Ar); 7.06 (t, 1H, Ar, ^3J = 5.2); 6.93 (d, 1H, Ar, ^3J = 7.7); 4.25, 4.12 (2d, 2H, CH_2 bridge, J_{AB} = 15.6); 3.46, 3.42 (2 broad s, 2H, allylic CH_2); 1.34, 1.04 (2 broad s, 6H, $2CH_3$). (Bruker AX 300, 293 K, δ in ppm, J in Hz).No convenient ^{13}C-NMR was obtained for this allyl-Pd complex due to its fluxional behaviour in solution.

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