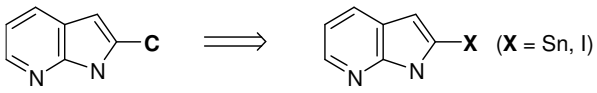
Palladium-catalyzed couplings to 7-azaindoles with formation of C-C bonds

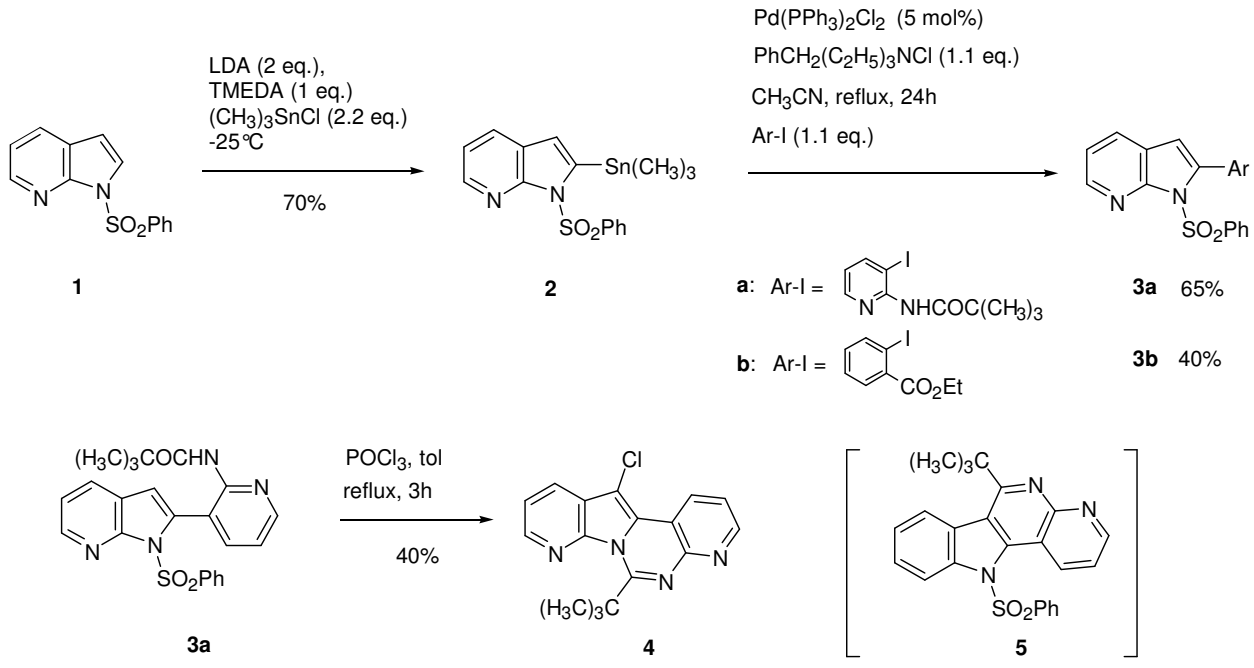
Introduction

In recent years, compounds with the 1*H*-pyrrolo[2,3-*b*]pyridine moiety (more commonly named 7-azaindole; Mérour and Joseph, 2001) have been shown to display significant biological activities. Following these observations, the synthesis of variously substituted 7-azaindole derivatives has become a subject of major concern for medicinal chemists. As a continuation of our precedent review (AtlanChim newsletter N°3), we present herein known examples of palladium-catalyzed carbon-carbon bond formation at carbons C_2, C_3, C_4, C_5 and C_6 of the 7-azaindole nucleus.
NB : Patent literature is not included in this review.

1. Functionalization at carbon C_2

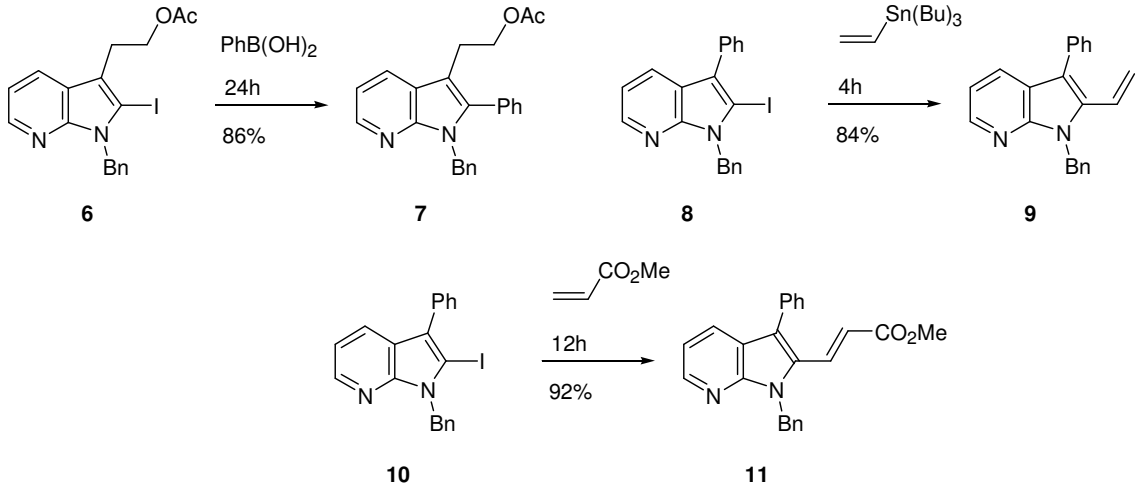


The first reported example was due to Mérour and coll. (1997) who succeeded in coupling the 2-(trimethylstannyl)-7-azaindole **2**, prepared by lithiation of 1-phenylsulfonyl-7-azaindole **1** and subsequent quenching with trimethylstannylchloride, with two aromatic iodo derivatives. Interestingly, compound **3a**, subjected to the conditions of the Bishler-Napieralski reaction, afforded the new heterocyclic pattern **4** in fair yield rather than the expected structure **5** (Scheme 1).



Scheme 1

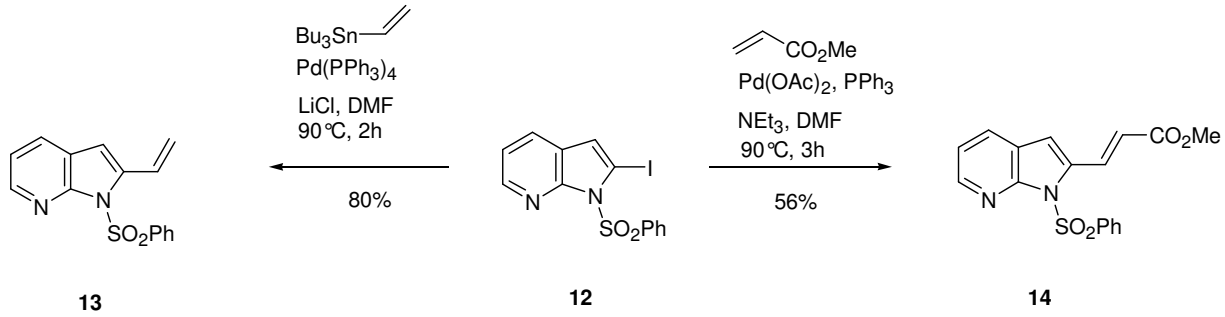
Later on, a general study of the palladium-catalyzed coupling reaction of 3-substituted-2-iodo-7 azaindoles has been reported by Chi et al. (2000). Using 5% $Pd(OAc)_2$, LiCl and KOAc in DMF as standard conditions, aliphatic and aryl substituents could be successfully introduced at carbon C_2 by Suzuki-Miyaura, Stille and Heck reactions. Thus, the reaction of phenylboric acid with several 2-iodo-7-azaindoles provided the corresponding 2-phenyl-7-azaindoles in yields ranging from 60 to 86%. Allyl, vinyl and phenyl substituents were introduced in similar yields from the corresponding tin derivatives. Couplings of methylacrylate, methylvinylketone and but-3-en-2-ol (Heck reaction) were also effected with success. Scheme 2 provides with an illustration of each of these procedures.



Conditions : 5% $Pd(OAc)_2$, 1 eq. LiCl, 2 eq. KOAc, DMF, 110°C.

Scheme 2

Following their pioneering work, Mérour and coll. (2000) also reported the Stille coupling of the 1-phenylsulfonyl-iodo-7-azaindole **12** with vinyltributyltin to give **13** in good yield. Compound **12** also reacted with methylacrylate in the conditions of the Heck coupling to give **14** in fair yield. Compound **13** was subsequently shown to give Diels-Alder adducts in a complete regioselective manner.



Scheme 3

In the course of a medicinal effort aimed at finding new potent gonadotropin-releasing hormone (GnRH) antagonists, Ujjainwalla and Walsh (2002) reported the preparation of the 7-azaindole **17**. The 2,4-dimethylphenyl substituent at carbon C_2 was introduced by recourse to an efficient Suzuki-Miyaura coupling as shown in Scheme 4 (**15** → **16**). Relatively to its indole analogue, **17** was

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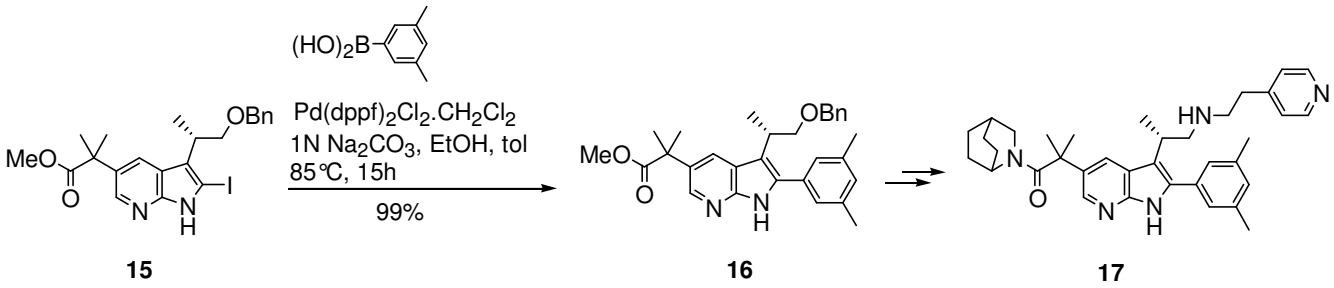
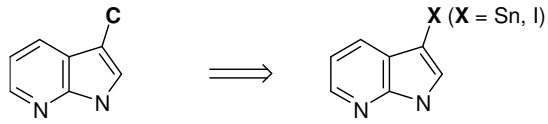
found to be a very potent GnRH antagonist. Following a very similar route, the 6-azaindole analogue was also synthesized. Its biological activity was not reported however.

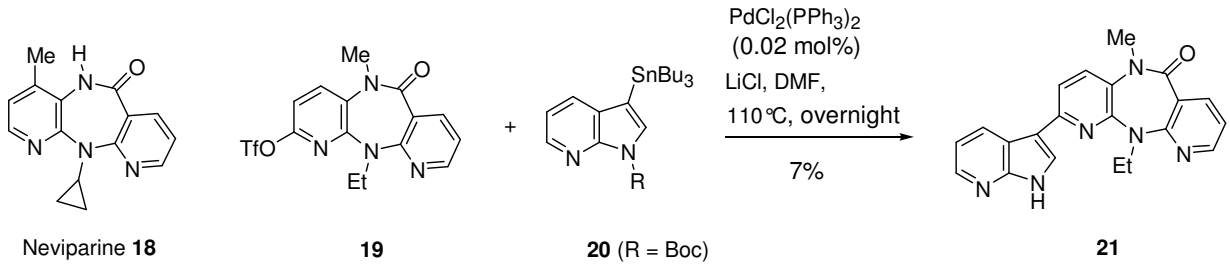


Scheme 4

2. Functionalization at carbon C_3



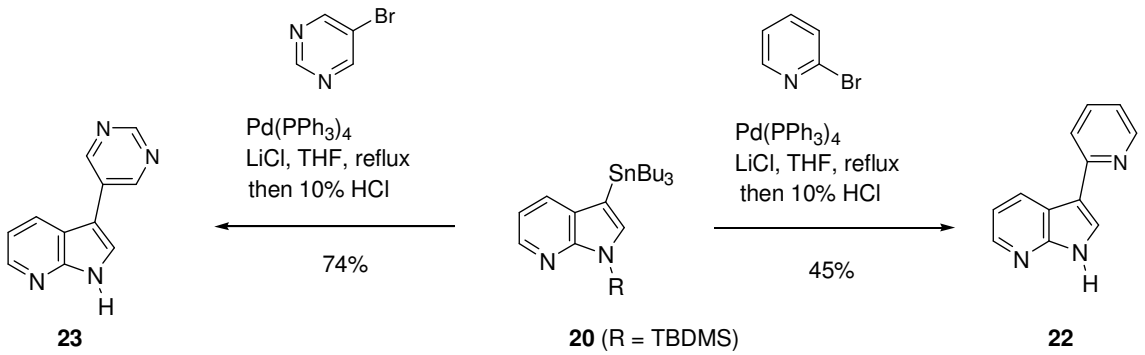
In a research program aimed at discovering analogues of neviparine **18**, a non-nucleoside reverse transcriptase inhibitor, Kelly and coll. (1997) explored the effect of anchoring diversely substituted indole and azaindole rings at carbon C_3 of a closely related neviparine skeleton. This was achieved, albeit in a very low yield, through the intermediacy of a Stille reaction as shown for compound **21** taken as an example (**19** + **20** → **21**, scheme 5). Note that 4-, 5- and 6-azaindolyl motifs were also coupled to **19** following an identical procedure.



Neviparine **18** **19** **20** (R = Boc) **21**

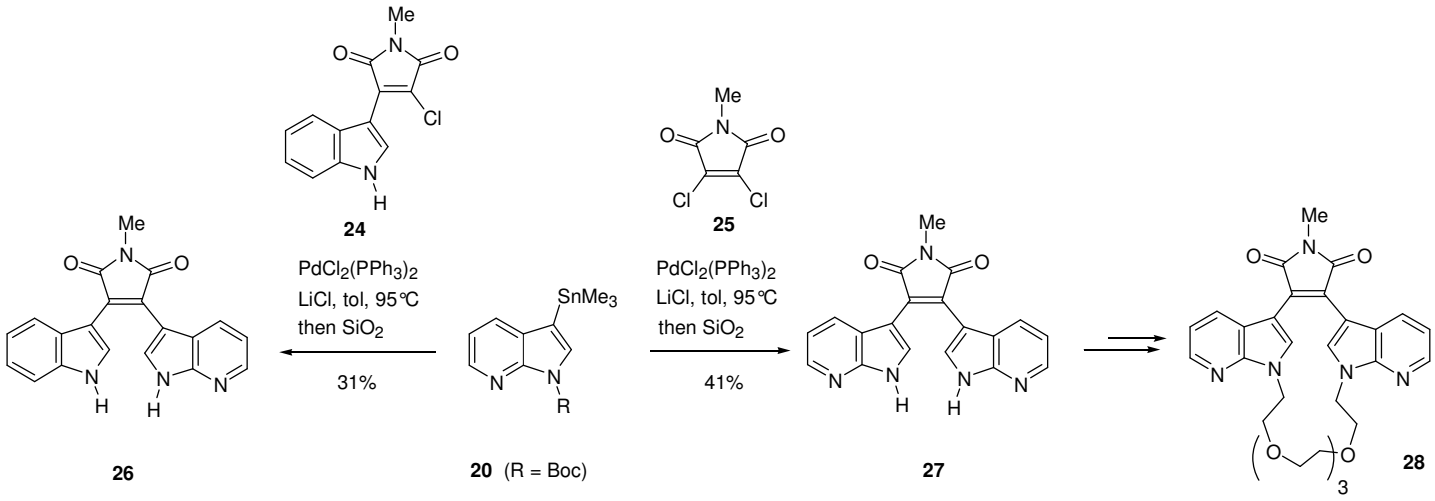
Scheme 5

Two years later, Alvarez and coll. (1999) reported their results dealing with the preparation of 7-azaindoles substituted at carbon C_3 with pyridin-2-yl and pyrimidin-5-yl moieties. A Stille reaction between the 1-protected 3-trimethylstannyl-7-azaindole **20** (R=TBDMS) and the appropriately chosen heteroaryl bromide was put into practice to reach the targeted compounds. It was shown that the nature of the protecting group at C_1 of **20** (e.g. TBDMS, MEM, Boc, Ts) has a little influence on the yield of the reaction whereas the attachment of a pyrimidin-5-yl substituent is significantly more efficient than a pyridin-2-yl substituent (scheme 6, TBDMS is the protecting group).



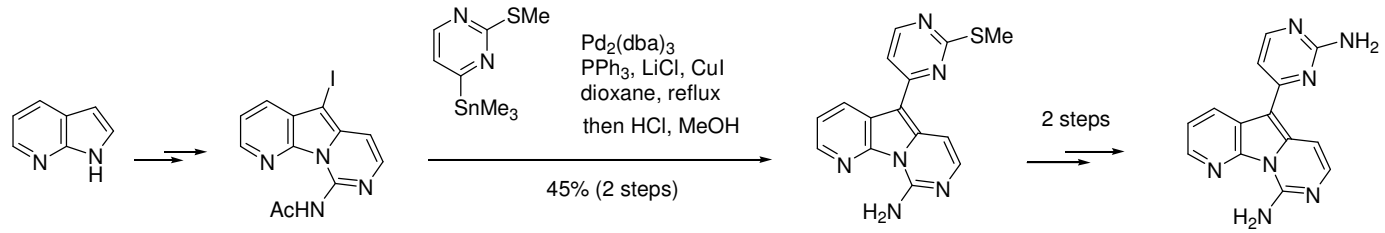
Scheme 6

Kuo and coll. (2003, 2004) reported the synthesis of macrocyclic maleimides exhibiting potent and selective inhibition towards glycogen synthase kinase-3β (GSK-3β), (e.g. **28**). As shown in Scheme 7, a palladium-catalyzed Stille reaction between the 3-trimethylstannyl-7-azaindole **20** (R=Boc) and the chloroindolylmaleimide derivative **24**, or the 2,3-dichloro-N-methylmaleimide **25**, was effective to prepare the key synthetic intermediates **26** or **27**, respectively.



Scheme 7

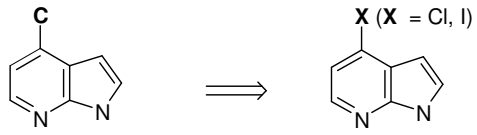
Although not strictly relevant to this review we may cited herein examples of palladium-catalyzed heteroaryl coupling reactions of 5-halogeno-pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine derivatives for the introduction of a pyrimidine substituent at C_3 of the 7-azaindole moiety . These reactions were carried out in the context of the synthesis of the alkaloids of marine origin variolin and deoxyvariolin B, which exhibit cytotoxic activities against the P388 cell line next to being active against *Herpes simplex*. For example, in their synthesis of deoxyvariolin, Alvarez et al. (2001, 2003) described the Stille reaction between the 2-(methylthio)-4-(trimethylstannyl)pyrimidine and the iodo derivative **29** to give an advanced precursor (**30**) of the targeted molecule (Scheme 8). Other closely related examples can be found in recent work done by Molina (2002, 2003) and Vaquero (2004).



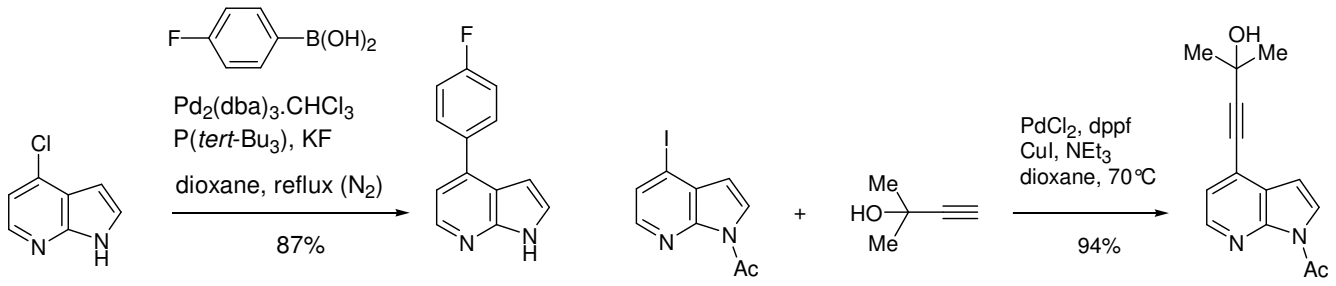
7-azaindole **29** **30** **deoxyvariolin B**

Scheme 8

3. Functionalization at carbon C_4

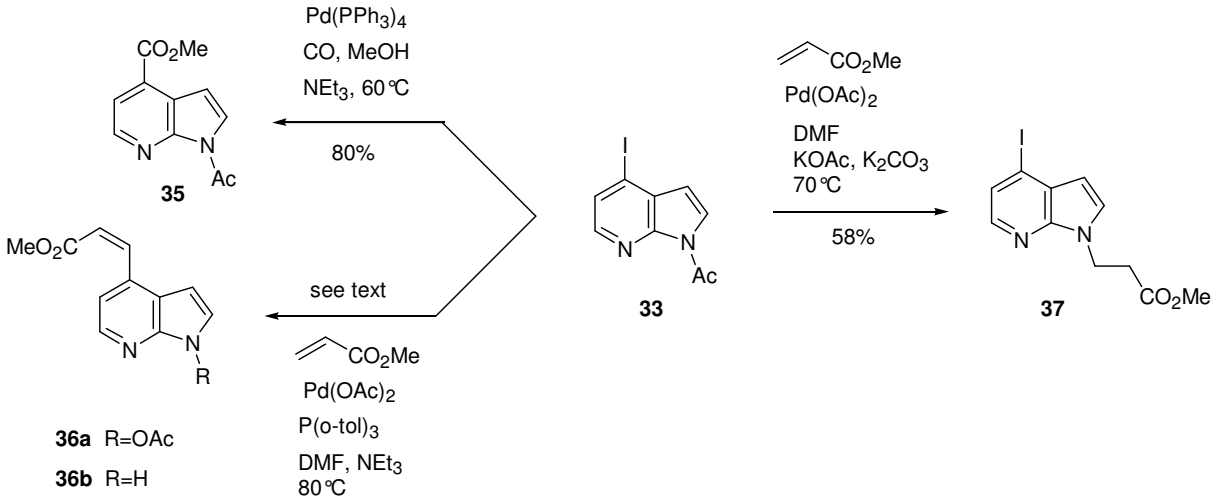


Known examples of such a C-C coupling reaction are scarce. Arcadi and coll. (2001) described the reaction of the 4-chloro-7-azaindole **31** with a series of aromatic and heteroaromatic boronic acids under conditions of the Suzuki coupling (e.g. **31** → **32**). They also reported reactions of the 4-iodo-1-acetyl-7-azaindole **33** with 2-methyl-3-butyn-2-ol under conditions of the Sonogashira coupling to give compound **34** in up to 94% yield (Scheme 9). Examples of Heck coupling reactions were also reported in the same paper (Scheme 10). It is worthnoting that the reaction course of the palladium acetate-catalyzed reaction of **33** with methyl acrylate is controlled by the nature of the base present in the reactional medium. Thus, if NEt_3 led to the formation of the C_4 coupling products **36a** (38%) and **36b** (45%, deprotected form), use of more basic conditions (e.g. K_2CO_3/KOAC) led, by contrast, to the Michael adduct **37** as the sole isolated compound (58%).



31 **32** **33** **34**

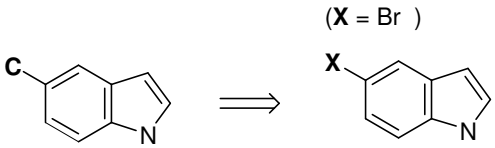
Scheme 9



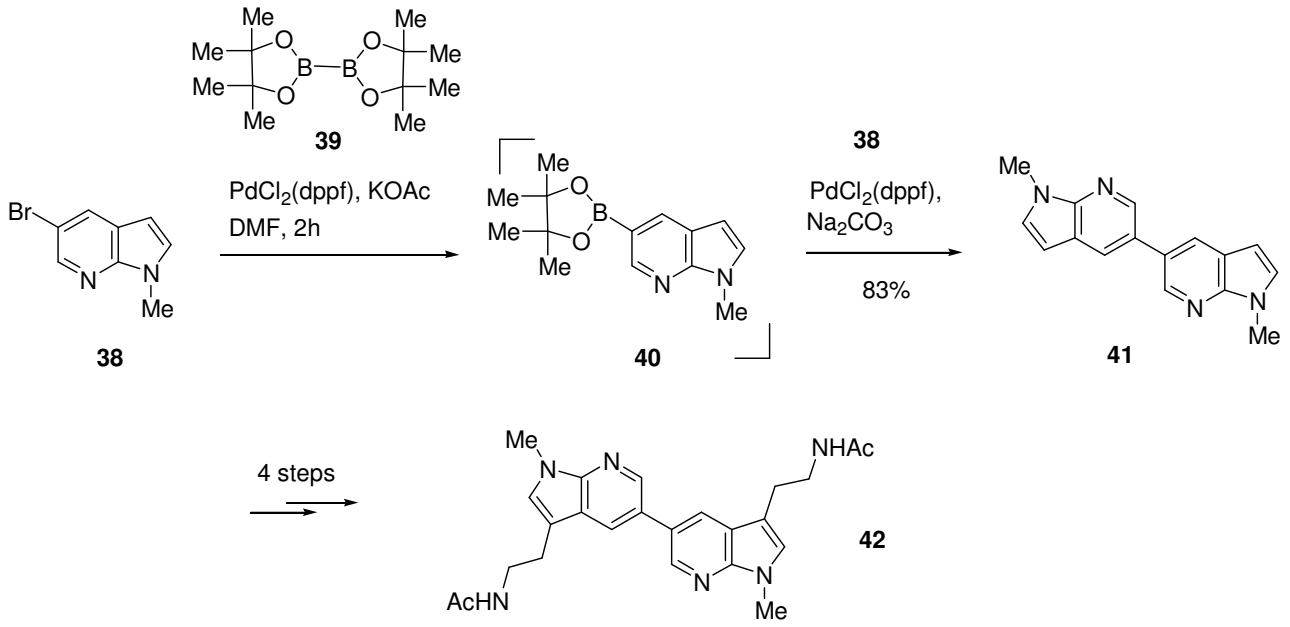
Scheme 10

Note that Thutewohl et al. (2006) recently reported the substitution of 4-chloro-7-azaindoles with anilines and arylphenols via palladium-catalyzed coupling reactions with formation of C-N and C-O bonds, respectively.

4. Functionalization at carbon C_5

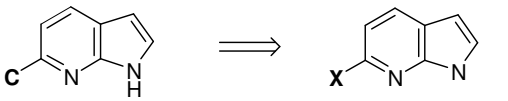


In the search for new melatonine analogues, Viaud-Massuard and coll. (2003) developed a palladium-catalyzed method allowing the access to dimers of 7-azaindole. Thus, in situ formation of borane **40** from 5-bromo-1-methyl-7-azaindole **38** and tetraalkoxydiboron **39**, followed by a Suzuki homocoupling reaction with **38**, afforded the dimer **41** in good overall yield. Subsequent chemical transformations allowed the introduction of the N-ethylacetamide side chain also present in melatonin (→ **42**, scheme 11).



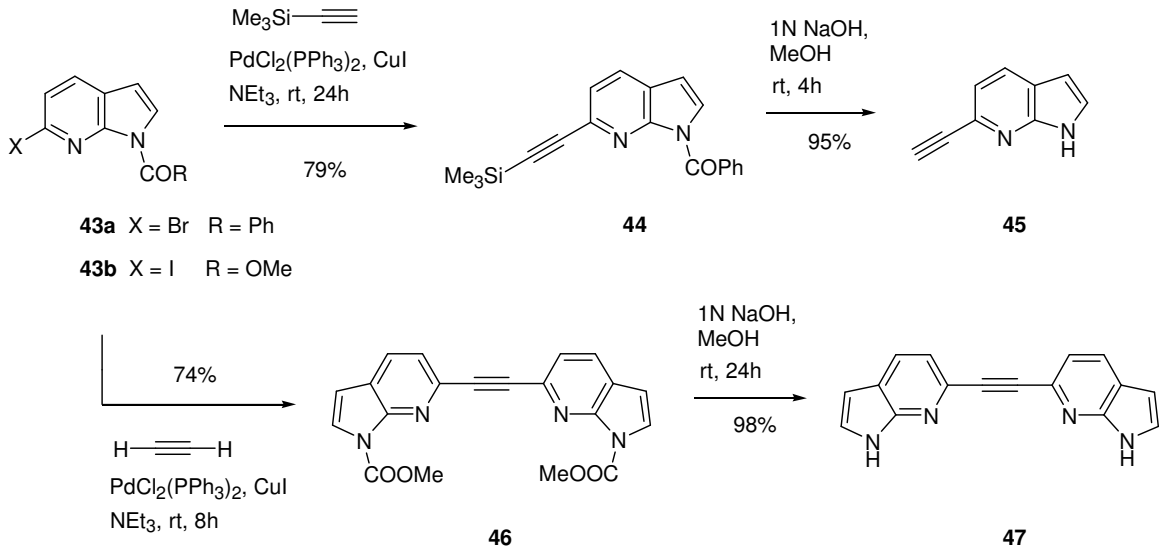
Scheme 11

5. Functionalization at carbon C_6



(**X** = Cl, Br, I, OTf)

The first known examples of such a transformation were reported by Ohshira and coll. (1992). Thus, palladium-catalyzed reaction of 6-bromo-7-azaindole **43a** with trimethylsilylacetylene afforded the coupling product **44** which was subsequently desilylated and debenzoylated to give the 6-ethynyl-7-azaindole **45**. Treatment of the more reactive 6-iodo-7-azaindole **43b** with gaseous acetylene afforded, in the presence of the same catalytic system as above, the bis-coupling product **46,** next N-deprotected into **47** by exposure to the action of a base (Scheme 12).



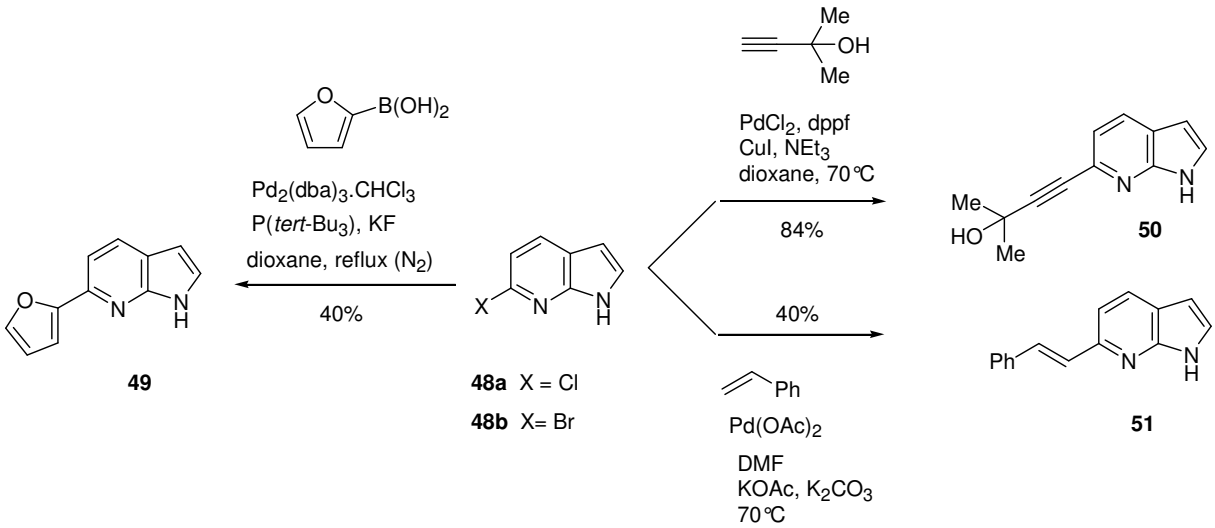
43a X = Br R = Ph

43b X = I R = OMe

44 **45** **46** **47**

Scheme 12

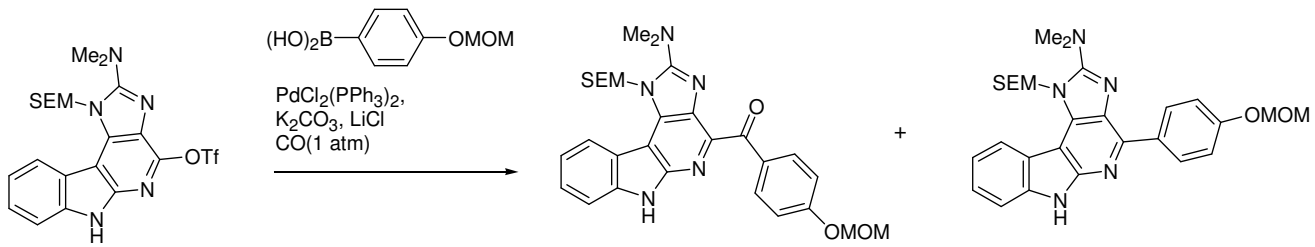
In a paper mentioned above, Arcadi and coll. (2001) also reported examples of preparation of 6-substituted-7-azaindoles through palladium-mediated coupling reactions. Thus, in the presence of a palladium catalyst, the 6-chloro-7-azaindole **48a** reacted with phenyl- and 2-furanyl-boronic acids to give the corresponding coupling products in 76 and 40% yields, respectively, whereas the 6-bromo-7-azaindole **48b** was proned to Sonogashira and Heck couplings (Scheme 13).



49 **48a** X = Cl **48b** X= Br **50** **51**

Scheme 13

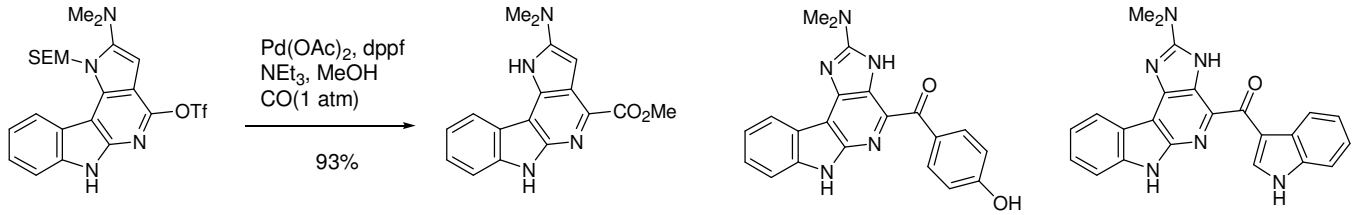
In the course of a total synthesis of the marine cytotoxic agent glossularine, Hibino and coll. (1995) reported the three-component Suzuki coupling reaction between tosylate **52** (embodying the 7-aza-indole skeleton), carbon monoxide and [4-(methoxymethoxy)-phenyl]boronic acid to provide the desired 2-benzoyl-pyrido[2,3-*b*]indole **53**, albeit in low yield (19%), along with compound **54** (58%).



52 **53** **54**

Scheme 14

They also reported the preparation of methyl ester **55** from tosylate **52** in an excellent yield of 93% (Scheme 15). Further manipulations of **55** allowed the improvement of the synthesis of glossularine B and a synthesis of glossularine A.



52 **55** glossularine B glossularine A

Scheme 15

A very similar approach to the analogs of glossularines A and B, lacking the dimethylamino group, was concomitantly reported by Achab et al. (1995) using Stille coupling reactions.

Acknowledgement : I thank Prof. J. Lebreton for helpful comments regarding this review.

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