Organometallic methods for the synthesis and functionalization of azaindoles

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Azaindoles (also called pyrrolopyridines) constitute essential subunits in many pharmaceutically important compounds. The synthesis of azaindoles has been a great synthetic challenge for chemists. Many classical methods for indole synthesis (such as Fischer and Madelung cyclizations) often cannot be effectively applied to the synthesis of the corresponding azaindoles. In recent years, advances in organometallic chemistry have enabled a number of novel and efficient methodologies for azaindole formation as well as for the further functionalization of azaindole templates. In this *tutorial review*, we have surveyed the recent development of organometallic chemistry-based methods for azaindole synthesis.

1. Introduction

The indole nucleus is arguably one of the most important heterocycles and is a key structural element for a vast number of biologically active molecules. The widespread utility of indoles in life sciences has stimulated the development of numerous methodologies for its synthesis.[1] Replacing one of the carbon atoms at positions 4–7 in the indole template with a nitrogen atom gives the so-called 4-, 5-, 6-, or 7-azaindoles (or pyrrolopyridines, Fig. 1), respectively. Current interests in azaindoles originated primarily from their medicinal relevance and they are frequently exploited as indole bioisosteres in the design of biologically interesting molecules.[2–5] In addition, azaindoles have also found applications in material synthesis and coordination chemistry. Most azaindole derivatives are synthetic products, although some azaindole-containing compounds do exist in nature. For example, 7-azaindole was isolated from coal tar in 1943. Other well-known 7-azaindole-containing natural products are the Variolins which were isolated from marine sponge *Kirkpatrickia varialosa*. Variolins, particularly Variolin B, have exhibited notable anti-cancer properties.[6,7]

From a synthetic point of view, azaindoles present a unique challenge. The frequently employed strategy for azadindole synthesis is to start with substituted pyridines and build up a

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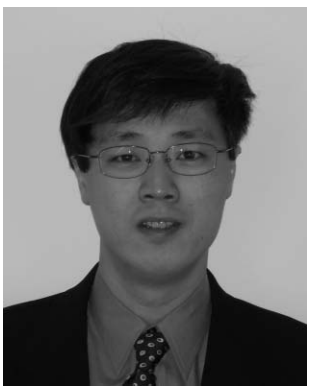

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Dr Jinhua Jeff Song received his undergraduate education at Nankai University in Tianjin, China (1989 to 1992). After a brief stay at Rice University in Houston, TX, he moved to Massachusetts Institute of Technology in 1993 and obtained his PhD degree in 1998 under the supervision of Prof. Satoru Masamune. Subsequently, he joined the Department of Chemical Development at Boehringer Ingelheim Pharmaceuticals in Ridgefield, CT, where he is currently a Senior Principal Scientist. Dr Song's research interests concern the discovery of new synthetic methodologies and their applications to the development of practical and economical synthesis of biologically active compounds. He has published in the areas of natural product synthesis, asymmetric synthesis of chiral drug substances, efficient methodologies for heterocycle synthesis, and more recently, organocatalysis using N-heterocyclic carbenes as novel catalysts.

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pyrrole ring. The electron-deficient nature of the pyridine ring alters the electronics of the π-system in such a way that many classical indole formation methods either do not work or are not as efficient when directly applied to the synthesis of azaindole analogues. For example, Fischer cyclization, which has been a reliable and general method for indole formation, often gives poor results when pyridinyl hydrazines are used. Furthermore, reactions involving pyridinyl hydrazines require more drastic reaction conditions and have a rather limited substrate scope.[2,3]

Very few comprehensive reviews on azaindole chemistry have been published in the literature.[2–5] This is partly due to the fact that, for quite a long period of time before 1990, little progress had been made in new method development for azaindole synthesis. However, over the past 15 years, thanks to the development of the field of organometallic chemistry,

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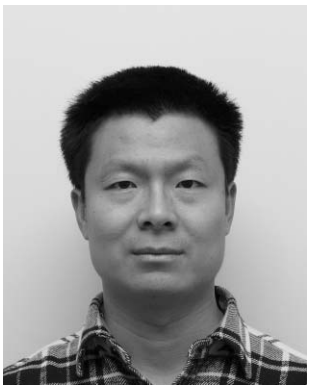

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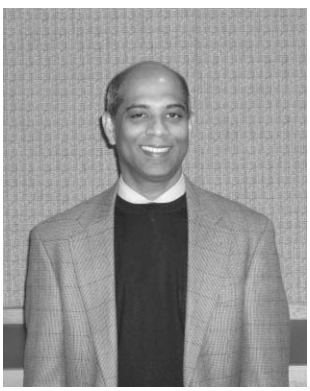


Chris H. Senanayake

Dr Chris H. Senanayake was born in Sri Lanka and received a BS degree (First Class) in Sri Lanka. After coming to the United States, he completed his MS at Bowling Green State University. He obtained his PhD at Wayne State University in 1987 where he worked on the total synthesis of complex natural products such as, ophiobolanes, and completed the first total synthesis of grosshemin in the guaianolide family. He then undertook a postdoctoral fellow with Professor Carl R. Johnson and worked on the total synthesis of polyol systems such as amphotericin B and compactin analogous, and the synthesis of C-nucleoside precursors. In 1989 he joined Dow Chemical Co. as a Senior Research Chemist in the Department of Process Development. After a brief stay at Dow Chemical, he joined the Merck Process Research Group in 1990 as a Senior Research Chemist. In 1996, he joined Sepracor, Inc. as Director of Chemical Process Research. He was promoted to Senior Director of Chemical Process Research in 1998, and Executive Director of Chemical Process Research in 2001. In 2002, he joined Boehringer Ingelheim Pharmaceuticals, Inc. as Director of Chemical Process Research. In 2004, he was named as Director, Chemical Development at Boehringer Ingelheim Pharmaceuticals, Inc. In 2005, he was appointed as VP, Chemical Development. He currently leads a group of scientists and engineers located in labs at Ridgefield, CT and Richmond Virginia. Dr Senanayake's research interests focus on the development of new asymmetric methods for the synthesis of bioactive molecules and heterocycles and on catalytic, enzymatic, and mechanistic studies. He has published and lectured in the area of practical asymmetric synthesis and many disciplines of organic chemistry on how to develop drugs in an economical and practical manner in large-scale operation. He is the author about 100 papers and 65 patents and applications in many areas of synthetic organic chemistry and design of improved chemical entities.

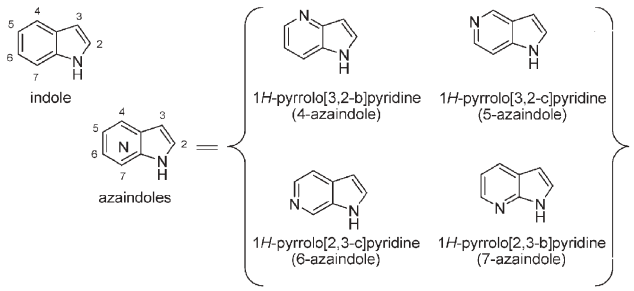


Fig. 1

particularly transition-metal catalysis and lithiation chemistry, a number of new synthetic methodologies were invented for azaindole formation. These methods proved to have much broader substrate scope and offer better synthetic efficiencies. In this review article, we intend to highlight the impact of modern organometallic chemistry on azaindole synthesis by summarizing the new advances over the past 15 years. While the emphasis of this review is on methods for the construction of azaindole ring systems, as the second part of this article, we will also reference a few useful and representative organometallic chemistry-based methods for functionalization of azaindole templates.

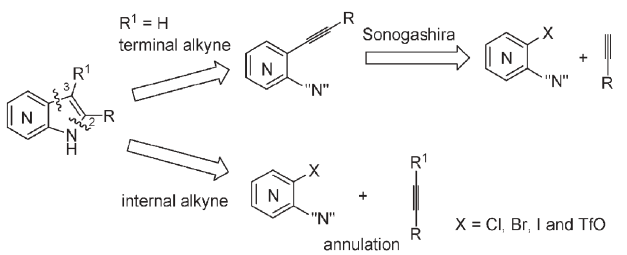
2. Organometallic chemistry-based methods for construction of azaindole ring systems

In this section, transition metal-mediated and organolithium-based methods for azaindole synthesis will be discussed.

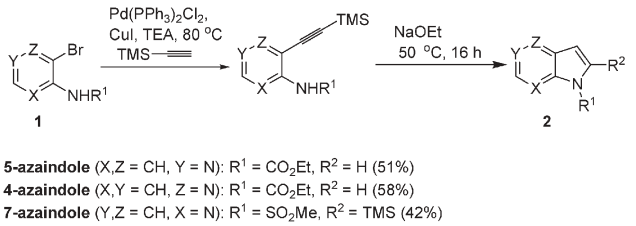
2.1 Construction of azaindoles *via* transition-metal mediated processes

Palladium catalysis has been extensively employed for indole synthesis.[1] This strategy has also been applied with success to the preparation of azaindoles. Most of these methods model after the corresponding indole synthesis by cross-coupling aryl halides with either terminal or internal alkynes (Scheme 1). It is believed that reactions with terminal alkynes proceed *via* the initial Sonogashira reaction followed by intramolecular cyclization, whereas reactions with internal alkynes proceed through the annulation pathway proposed by Larock.[8]

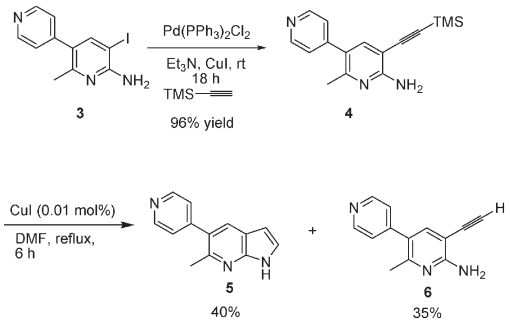
2.1.1 Azaindole formation from terminal alkynes. *ortho*-Aminohalopyridines can be coupled with a terminal alkyne by Sonogashira reaction in fairly high yields. Subsequent cyclization into azaindoles can be achieved using a variety of



Scheme 1



Scheme 2

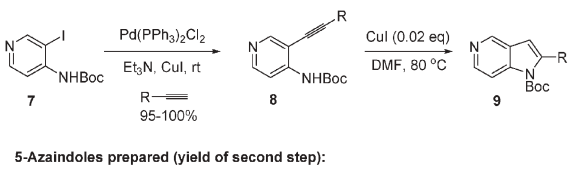


Scheme 3

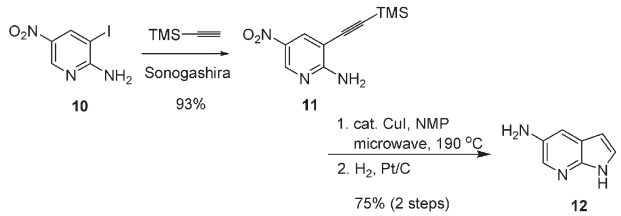
methods. Early examples for this ring-forming strategy came from the Yamanaka group.[9] A few 4-, 5- and 7-azaindoles (**2**, Scheme 2) were prepared in moderate yields starting with *N*-protected aminobromopyridines (**1**). The cyclization was accomplished by treatment with NaOEt.

Subsequently Kumar *et al.* reported that a fairly complex, *unprotected* amino pyridyl iodide (**3**, Scheme 3) underwent Sonogashira coupling with trimethylsilylacetylene to give alkyne **4**.[10] Cyclization was effected by heating in DMF in the presence of a catalytic amount of CuI to afford 7-azaindole product **5** in 40% yield. It should be noted that the TMS group is lost either during the reaction or during the workup. Also 35% of desilylated starting material **6** was recovered. To improve the yield, the authors developed an alternative method based on a Suzuki coupling strategy, which will be discussed later in Section 2.1.4.

Xu and co-workers expanded upon these initial results and reported the synthesis of a variety of 2-substituted-5-azaindoles starting with Boc-protected aminoiodopyridines (Scheme 4).[11] The two-step process involved a Sonogashira coupling of alkynes with *N*-Boc-4-amino-3-iodopyridine (**7**) to give alkynylpyridines **8**, followed by CuI-catalyzed cyclization in DMF at 80 °C to Boc-protected 5-azaindoles **9**. Unlike in Kumar's case, the TMS group on the terminal alkyne could be tolerated under the reaction conditions and was retained in the



Scheme 4



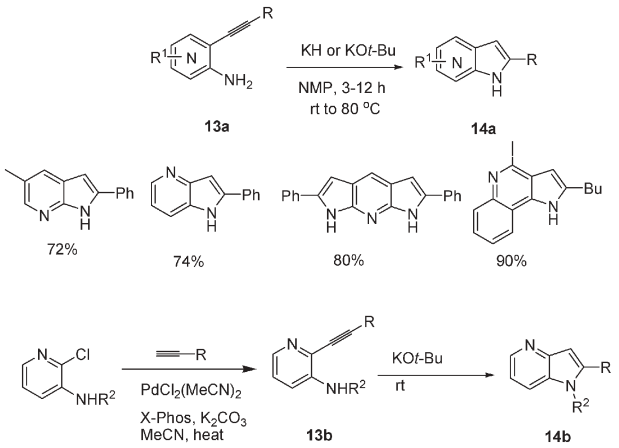
Scheme 5

azaindole product (90% yield). It is interesting to note that TBS protected terminal alkyne gave no desired cyclized azaindole product. The authors have found that the entire process could be performed in one pot by heating the Sonogashira coupling reaction for a longer time, but variable yields were obtained. Therefore, the two-step protocol is recommended. The use of Boc as the protecting group is critical for the cyclization. It was observed that *N*-acetyl, *N*-tosyl or *N*-unprotected substrates gave no reaction in the CuI-catalyzed cyclization reactions.

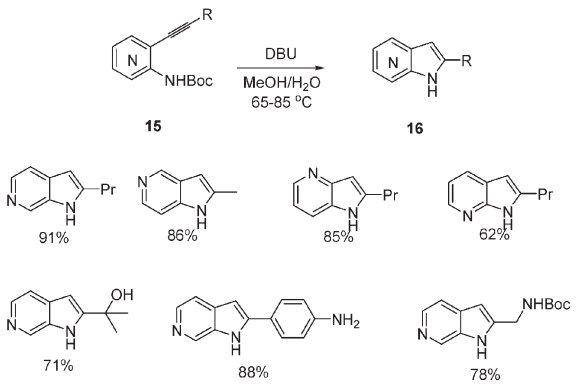
Pearson *et al.* have investigated the microwave-assisted CuI-catalyzed cyclization of aminoalkyne **11** in their synthesis of 5-amino-7-azaindole. Compound **11** was derived from Sonogashira coupling of unprotected amino iodide **10** with trimethylsilylacetylene (Scheme 5).[12] CuI-catalyzed cyclizations of **11** under Kumar's original thermal conditions (16 h in refluxing DMF) or under microwave irradiation (190 °C) were both tried and it was found that the microwave-promoted process provided a faster reaction (30 min at 190 °C in NMP). Subsequent hydrogenation of the nitro group gave the target 5-amino-7-azaindole **12** in 75% yield over two steps.

As shown in the above examples, CuI-catalyzed cyclization of *ortho*-amino alkynylarenes has been an effective method to prepare azaindoles, but it requires quite harsh conditions (80–190 °C in a polar solvent). In efforts to identify milder alternatives, several new conditions have been developed for cyclization of *ortho*-amino alkynylarenes (derived from Sonogashira coupling) to aza- and diazaindoles. In 2000, Knochel and co-workers reported the utility of potassium or caesium bases for cyclization of unprotected *ortho*-amino alkynylpyridines and pyrimidines (Scheme 6).[13] The use of 1–2 eq. of KO*t*-Bu, CsO*t*-Bu or KH in NMP gave good yields of 4-, 5- and 7-azaindoles (**14a**) from the corresponding aminoalkynes **13a**. Additionally, one example for the synthesis of a 4,6-diazaindole (78%) and one for a 5,7-diazaindole (61%) were provided. This protocol was recently applied to *N*-alkyl *ortho*-amino alkynylpyridines.[14] Compounds **13b** were prepared from 3-amino-2-chloropyridines by using Pd-catalyzed cross coupling reactions and subsequent treatment with 50 mol% of KO*t*-Bu in THF led to the formation of 4-azaindoles in very good overall yields.

More recently, Riether and co-workers described a very mild DBU-mediated cyclization of *ortho*-(*N*-Boc-amino)alkynylarenes to give a broad range of *N*-deprotected 4-, 5-, 6- or 7-azaindoles as well as diazaindoles (Scheme 7).[15] The reaction was carried out in MeOH/H_2O (3 : 1) at 65–85 °C with 5 eq. of DBU. It is important to note that substrates lacking the Boc group (*i.e.* unprotected amino alkynes) gave no reaction under these conditions, and it is reasonable to assume that the Boc



Scheme 6



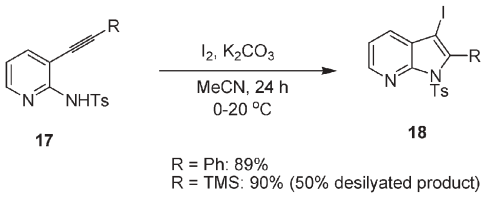
Scheme 7

group is lost only after cyclization occurs. This is in contrast to Knochel's method described above where the unprotected aminoalkynes were efficiently cyclized under the influence of KH or KO*t*-Bu. This type of protecting group effect has been a general observation for this class of reactions.

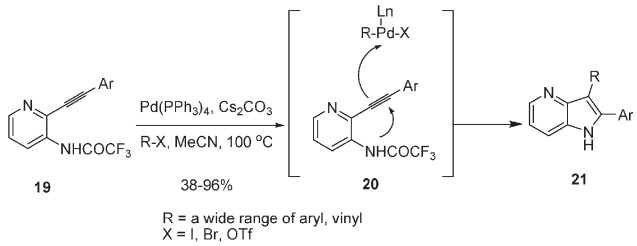
The paper also listed four examples for diazaindole formation using this method (86–98%). It was demonstrated that the mild reaction conditions allowed greater functional group compatibility than previously existing procedures. As can be seen in Scheme 7, substrates with a tertiary alcohol, a free amino group as well as a Boc-amino group were tolerated.

Knight and Amjad described an iodocyclization procedure to convert Sonogashira products such as **17** into 3-iodo-7-azaindoles.[16] Thus, treatment of *ortho*-(tosylamino)alkynylpyridine **17** with iodine and K_2CO_3 in acetonitrile gave *N*-tosyl-iodoazaindole **18** in ~90% yield (Scheme 8). One obvious benefit of this protocol is that the iodide provides a convenient handle for further functionalization. It was noticed that the TMS group on the terminal alkyne was partially lost during the reaction.

Cacchi and co-workers have reported an aminopalladation–reductive elimination reaction for the synthesis of a wide range of 2,3-disubstituted 4- and 7-azaindoles.[17] In this process, *ortho*-(trifluoroacetamido)alkynylpyridines (**19**) and aryl



Scheme 8

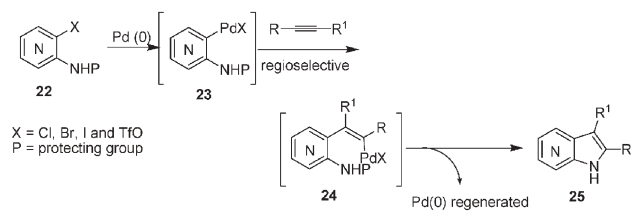


Scheme 9

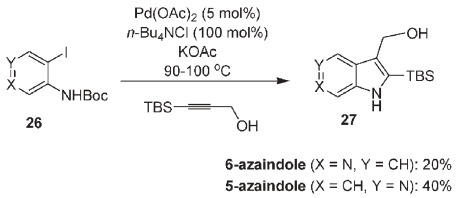
iodides, bromides or triflates (or vinyl triflates) are combined to give 2,3-disubstituted azaindole products in a highly convergent manner (Scheme 9). The use of the *N*-trifluoroacetamide group was shown to be essential for this reaction (by modulating the proper pK_a of the N–H group). Substrates with an unprotected amino group or an acetyl-protected amino group gave poor results. An added benefit of using the *N*-trifluoroacetamide is that it is readily cleaved under the reaction conditions to give *N*-deprotected azaindole products directly. Overall this method provides a completely regio-controlled synthesis of 2,3-diarylazaindoles. This is a main advantage over the Pd-catalyzed heteroannulation method (see Section 2.1.2), where the control of the regioselectivity on diaryl alkynes could be challenging, especially when the two substituents on alkynes have similar sizes and electronic properties.

2.1.2 Azaindole formation *via* heteroannulation using internal alkynes. The palladium-catalyzed heteroannulation of internal alkynes, originally reported by Larock[8] in 1991 for indole synthesis, has been applied to the construction of 5-, 6- and 7-azaindoles. The following is the currently accepted mechanism for this reaction (Scheme 10). Two general empirical observations were made for this process: 1) the regioselectivity relative to the alkyne is usually high if R and R^1 are adequately different; and 2) the protecting group on the amino nitrogen has a major influence on the reaction outcome.

Gronowitz and co-workers investigated the possibility of utilizing Larock's indole formation method for azaindole



Scheme 10

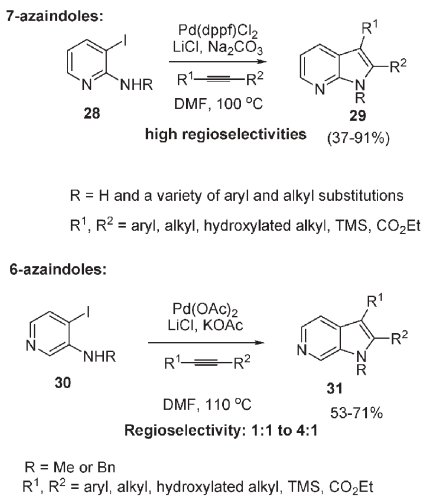


Scheme 11

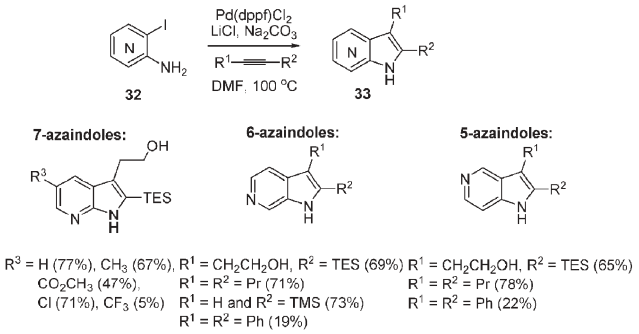
synthesis in the early 90's (Scheme 11).[18] They found that reaction with trimethylsilylacetylene generally gave complex reaction mixtures. On the other hand, using the more stable TBS protection allowed the isolation of desired products in low to modest yields. Excellent regioselectivities were observed for this reaction, with the bulky TBS group being attached at the C(2) position.

Yum *et al.* have carried out more extensive studies on this heteroannulation strategy for synthesis of substituted 7-azaindoles (Scheme 12).[19] They have shown that, consistent with Larock's observation for indole synthesis, the use of LiCl is crucial for getting good yields of azaindoles. Similar to other researchers, they noticed that the efficiency of the reaction greatly depends on the nitrogen protecting group (R) in precursor **28**. When R = Ac, Piv or Boc, either no reaction or low yield of cyclized azaindole product was obtained, whereas when alkyl or aryl groups were used, the cyclized product could be formed in synthetically useful yields. Regioselectivity is high for all alkynes examined, with the sterically demanding group on the alkyne being positioned at the C(2) carbon, except for 1-phenylpropyne. Using this reaction, a variety of 2,3-disubstituted-7-azaindoles were prepared.

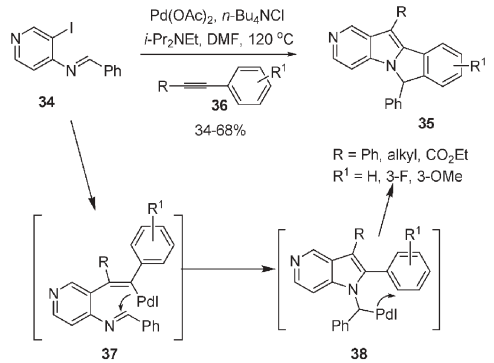
More recently, the same research group extended this protocol to the construction of 6-azaindoles (Scheme 12).[20] Again, it was found that the key to success was to use *N*-alkylated (methyl or benzyl) 3-amino-4-iodopyridines (**30**). The free-NH_2 substrates gave yields <20%. However, the regioselectivities for 6-azaindole formation were unexpectedly low (ranging from 1 : 1 to 4 : 1) compared to the above analogous 7-azaindole formation. The reason for the poor regioselectivities in this case is unclear.



Scheme 12



Scheme 13

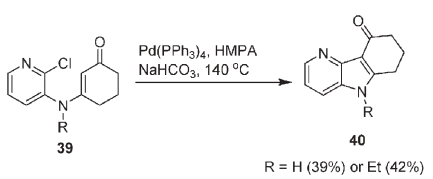


Scheme 14

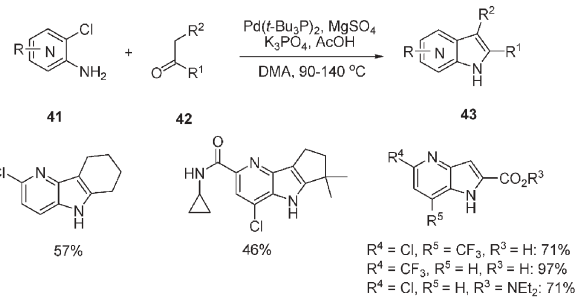
Ujjainwalla *et al.* have provided a method for the heteroannulation reaction with unprotected *ortho*-aminoiodopyridines (**32**) as substrates using a $Pd(dppf)Cl_2$–LiCl–Na_2CO_3 reagent system (Scheme 13).[21] A number of 5-, 6- and 7-azaindoles were regioselectively synthesized from alkyl, silyl and alkyl, alkyl substituted alkynes in good yields.

Yum and co-workers reported a novel cascade heteroannulation reaction to give tetracyclic 5-azaindole analogues using benzylidene as the protecting group in aminoiodopyridine **34** (Scheme 14).[22] Thus, treatment of compound **34** with an aryl-substituted internal alkyne **36** allows heteroannulation to form the 5-azaindole moiety as well as a subsequent C–C bond forming annulation to give tetracyclic products **35** in moderate yields. It was believed that, after initial formation of the normal vinyl Pd intermediate **37**, Pd adds across the imine double bond to give **38** which undergoes C–H insertion onto the *ortho* position of the aromatic ring leading to the tetracyclic product **35**.

2.1.3 Azaindole formation *via* Heck reaction. The application of Heck-type reactions to the construction of the azaindole framework was briefly investigated by Blache and co-workers in 1997 (Scheme 15).[23] Compound **39** which was prepared



Scheme 15

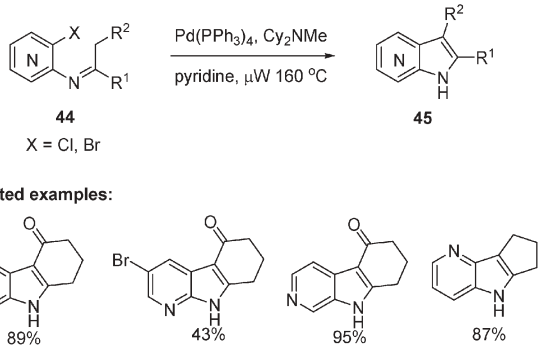


Scheme 16

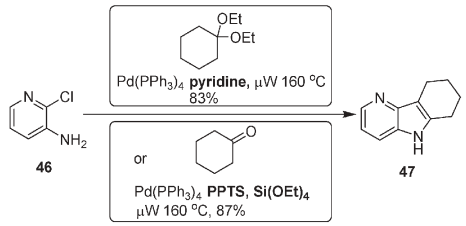
from a 1,3-diketone was subjected to $Pd(PPh_3)_4$ and $NaHCO_3$ in HMPA at 140 °C to provide corresponding azaindoles (**40**) in moderate yields.

Recently, the palladium-catalyzed annulation of amino-chloropyridines with regular ketones has been reported for the synthesis of azaindoles (Scheme 16).[24] The reaction proceeds by initial enamine formation followed by intramolecular Heck reaction. The use of $Pd(t\text{-}Bu_3P)_2$ as catalyst and a K_3PO_4–AcOH base-additive mixture were found to be essential for high yields. The process was used for direct construction of 4- and 7-azaindoles from *ortho*-aminochloropyridines and ketones. When simple cyclic aliphatic ketones were used, azaindoles were obtained in relatively moderate yields. But for α-keto acid derivatives, azaindoles could be synthesized with quite good efficiencies. The major limitation of the enamine-Heck approach to indoles and azaindoles is that the regioselectivity of enamine formation cannot be well controlled if both sides of the ketone are enolizable. As a consequence, only symmetrical ketones or ketones possessing only one enolizable group can be effectively utilized in this reaction.

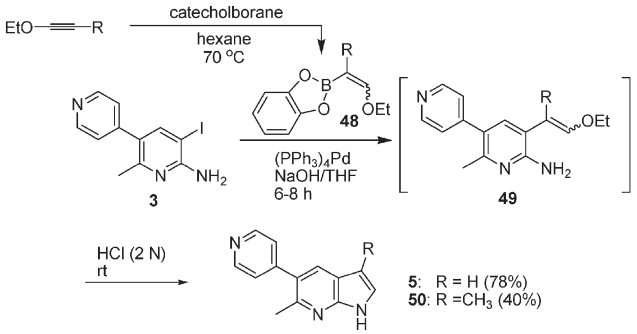
Another variation of this procedure, reported by Lachance and co-workers, employed microwave irradiation to assist in the Heck reaction process (Scheme 17).[25] Treatment of imines **44** (or enamines) with $Pd(PPh_3)_4$ and Cy_2NMe under microwave conditions afforded good yields of some azaindoles (**45**). It was also noted that microwave conditions gave significantly higher yield for certain substrates compared to reactions run under normal thermal conditions. The generality of the process was shown to be excellent, as 4-, 5-, 6- and 7-azaindoles were all prepared using the methodology. The imine/enamine formation and Heck reaction could also be performed in a one-pot fashion using ketones or ketals as illustrated in Scheme 18.



Scheme 17



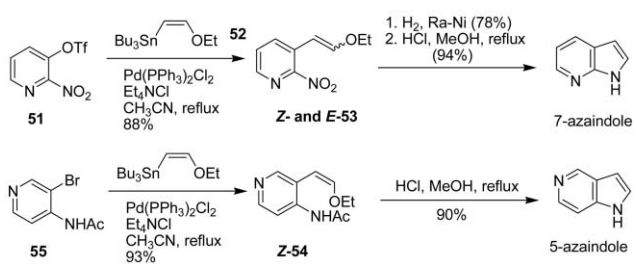
Scheme 18



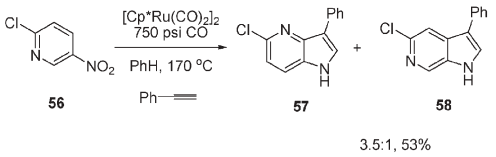
Scheme 19

2.1.4 Azaindole formation *via* other transition-metal catalyzed reactions. Kumar *et al.* have developed a more efficient sequence to compound **5** based on a Suzuki coupling strategy (Scheme 19).[10] Compound **5** was previously prepared in 40% yield *via* coupling of iodide **3** and trimethylsilylacetylene (Section 2.1.1). Alternatively, the authors carried out a Suzuki reaction between iodide **3** and vinyl borate **48** which was formed by reaction of ethoxyacetylene with catecholborane in hexane at 70 °C. The Suzuki product **49** was then subjected to acid hydrolysis to give azaindole **5**. The yield of this new sequence is 78% and can be carried out as a through process. In a similar manner, the 3-methyl substituted analogue **50** was prepared in 40% yield from ethoxypropyne.

Yamanaka *et al.*[26] have utilized a Stille coupling to attach the ethoxyvinyl group (an aldehyde equivalent) to triflate **51** in 88% yield (as a mixture of *Z* and *E* isomers, Scheme 20). Selective hydrogenation of the nitro group furnished the amino intermediate which was treated with HCl in reluxing MeOH to complete the 7-azaindole formation (73% overall yield). Alternatively, *N*-acetyl-aminobromopyridine **55** was cross-coupled with vinyl stannane **52** to give, in this case, selectively the *Z*-isomer of **54** in 93% yield. Subsequent acid hydrolysis and ring closure furnished 5-azaindole in 90% yield.



Scheme 20



Scheme 21

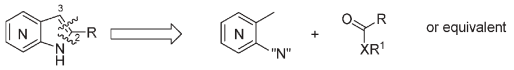
Nicholas and Penoni have discovered a novel indole synthesis *via* the ruthenium-catalyzed reductive annulation of alkynes with nitroaromatics.[27] A single example using nitropyridine **56** and phenylacetylene provided 4- and 6-azaindoles **57** and **58** as a 3.5 : 1 mixture in 53% yield (Scheme 21). However, the regioselectivity relative to the alkyne was high with the phenyl group being located at the C(3) position of the azaindole ring.

2.2 Construction of azaindoles *via* organolithium intermediates

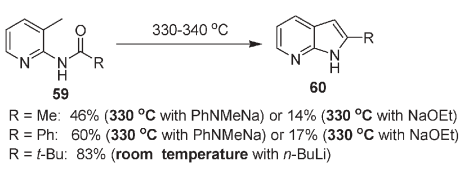
Azaindoles can also be constructed by forming C(2)–C(3) and C(2)–N(1) bonds, as indicated in the following retrosynthetic analysis (Scheme 22). This disconnection leads back to two readily available building blocks, *i.e. ortho*-alkylaminopyridines and carboxylic acid derivatives (*e.g.* amides, esters or nitriles). A number of lithiation methods have been recently reported based on this retrosynthesis.

Two potential bond-forming sequences can be envisioned. The first approach involves the initial C(2)–N(1) bond formation followed by intramolecular C(2)–C(3) bond formation. This represents the traditional Madelung synthesis, which has a very limited scope and often gives azaindoles in disappointing yields (Scheme 23).[2] For example, heating *N*-acetyl-2-amino-3-picoline with a strong base at 330–340 °C gave low yields (14–46%) of the corresponding azaindoles. When the *N*-acyl group does not have enolizable groups (*e.g.* Ph), the yield is slightly higher. It is interesting to note a remarkable example where the 2-*t*-Bu-7-azaindole can be prepared in 83% yield by treating *N*-Piv-2-amino-3-picoline with *n*-BuLi at room temperature for 4 h.[28] However, the Madelung method generally requires very harsh conditions and the yields are particularly substrate-dependent.

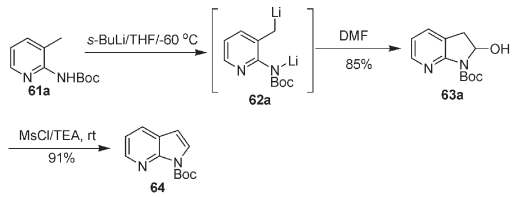
Alternatively, the C(2)–C(3) bond can be formed first, followed by intramolecular C(2)–N(1) bond formation. This strategy has been used for building indoles and briefly examined for azaindole synthesis by Clark (Scheme 24).[29] *N*-Boc-2-amino-3-picoline **61a** was dilithiated with *s*-BuLi at



Scheme 22



Scheme 23



Scheme 24

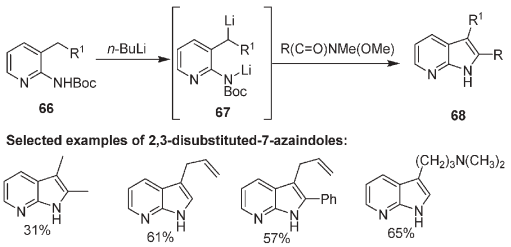
−60 °C to generate dianion **62a**, which was quenched with DMF to give compound **63a**. Subsequent dehydration by MsCl–TEA furnished the *N*-Boc-7-azaindole **64** in 91% yield.

Hands and co-workers[30] have built on this preliminary result and demonstrated that treating dianions **62** with DMF or Weinreb amides furnished intermediates **63** (Scheme 25). Subsequent acidic Boc deprotection–cyclization gave several? 5-, 6-, and 7-azaindoles in moderate to good yields. This protocol was also extended to other 3-alkyl-2-aminopyridines to afford a series of 2,3-disubstituted-7-azaindoles as shown in Scheme 26.

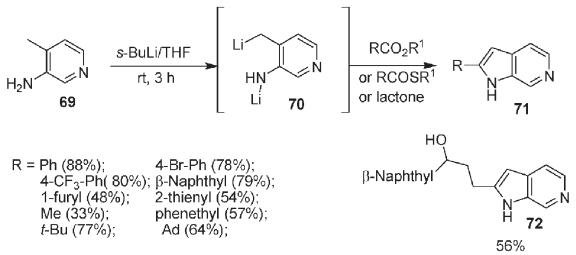
As shown above, Hands' method is quite versatile for constructing a variety of azaindoles. However, for 2-substituted azaindoles, it does require the use of Weinreb amides which need to be prepared in an additional step from esters. Recently, we have reported a method that allowed the synthesis of 2-substituted-6-azaindoles directly from carboxylic esters in one step (Scheme 27).[31] In this study, we investigated the dilithiation of unprotected 3-amino-4-picoline **69** and found that the dianion of 3-amino-4-picoline could be obtained in 70% yield with *s*-BuLi.

Reaction of dianion **70** with esters provided corresponding 6-azaindoles in good to excellent yields in a single operation. Presumably, a series of transformations occurred in this one-step reaction. Addition of the C-anion to the ester furnished a tetrahedral intermediate that collapsed into the ketone which in turn was immediately trapped by the neighboring N–Li. Due to this fast trapping of the putative ketone intermediate by the nitrogen, secondary side reactions with the ketone were prevented. As a result, it is not necessary to use Weinreb amides for the present methodology. This one-step method has been applied to a range of esters, including aromatic, bromoaromatic, enolizable and sterically demanding esters as well as a lactone and a thioester substrate. The commercial availability of the 3-amino-4-picoline and the ready availability of esters (compared to Weinreb amides) render this method truly practical.

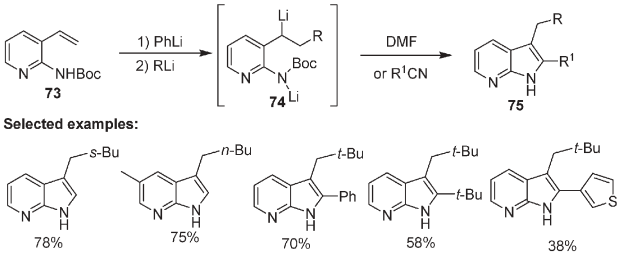
O'Shea *et al.* have described a new method for 7-azaindole synthesis *via* carbolithiation of vinyl pyridines (Scheme 28).[32]



Scheme 26



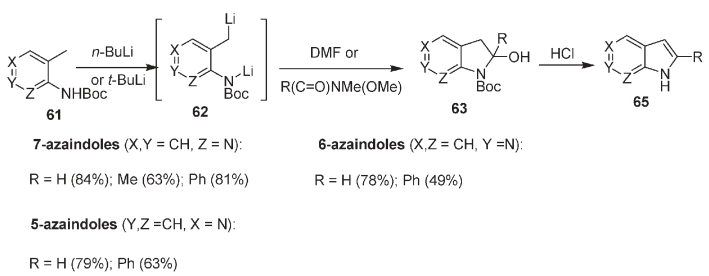
Scheme 27



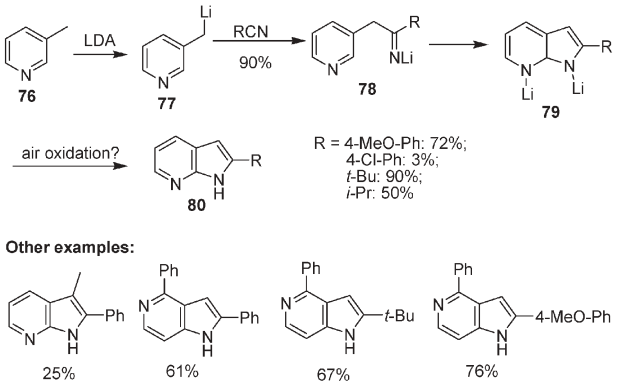
Scheme 28

When vinyl pyridine **73** was treated with 1 eq. of PhLi, the NH deprotonation occurred. Subsequent carbolithiation of the double bond with 1 eq. alkyl lithium (RLi, *e.g.* *t*-BuLi, *n*-BuLi and *s*-BuLi) formed a lithiated species **74** which was allowed to condense with electrophiles such as DMF or nitriles (R^1CN) to give substituted 7-azaindole products. Vinyl pyridines were readily prepared from the corresponding bromopyridines by Suzuki coupling reactions.

Wakefield and co-workers[33] have found that reacting the lithium anion of 3-picoline with nitriles gave intermediate **78** (Scheme 29). The cyclization onto the pyridine ring could be promoted by heating (100 °C for 36 h). But later it was found that in the presence of an excess of strong base (LDA), cyclization occurred more readily at ~60 °C to give



Scheme 25

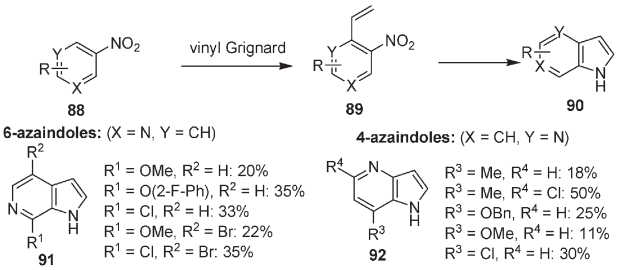


Scheme 29

intermediate **79** which was oxidized (possibly by air) to afford 7-azaindoles. The cyclization is highly regioselective for the C(2) position of the pyridine. The isomeric azaindole resulting from the ring closure onto the C(4) position was observed as a minor by-product in trace amounts. However, when the C(2) carbon of the pyridine ring is substituted (with *e.g.* Ph), cyclization occurs at the C(4) position to furnish 5-azaindoles. This method was also extended to some methyl substituted quinoline, pyrazine, quinoxaline and pyrimidines, although with less efficiencies (12–62% yields).

Schirok[34] reported a reaction sequence for making 7-azaindoles starting with the directed-lithiation of 2,6-dichloropyridine (Scheme 30). Treatment of compound **81** with LDA formed the lithiopyridine **82** which was allowed to couple with a ketone to give the tertiary alcohol **83**. Heating compound **83** with acetic acid and sulfuric acid (3 : 1) at 130 °C for 30 min led to the formation of the olefin intermediate **84**. The double bond was epoxidized with MCPBA to give compound **86**. Finally epoxide opening and displacement of the 2-chloro substituent with an amine (RNH_2) at 100–120 °C provided 7-azaindoles. A range of amines have been successfully used in this sequence.

The authors also demonstrated that the epoxide intermediate **86** can be accessed in one step *via* reaction between



Scheme 31

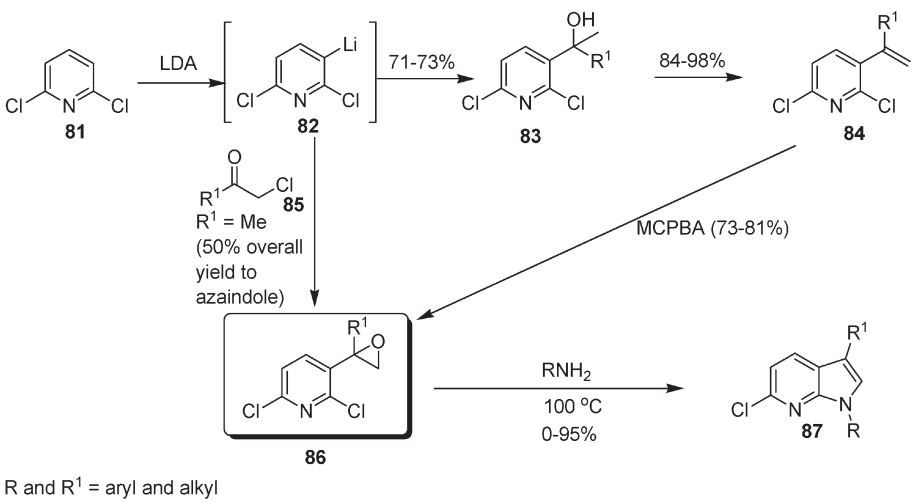
lithiopyridine **82** with α-chloroketone **85** as depicted in Scheme 30. Epoxide prepared from chloroacetone using this protocol is about 60% pure contaminated with unreacted starting material. This crude epoxide was subjected to the subsequent ring-closing step with benzylamine to give product in 50% overall yield from chloroacetone and 2,6-dichloropyridine.

2.3 Construction of azaindoles *via* nucleophilic reactions with electron-deficient pyridines

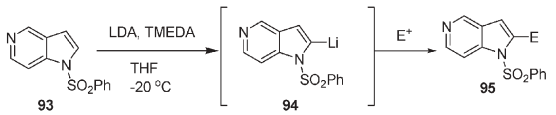
The Bartoli indole synthesis involves the reaction of a Grignard reagent with nitrobenzene derivatives. Wang *et al.* have applied this protocol to the synthesis of azaindoles (Scheme 31).[35] It was found that reaction between nitropyridines **88** and a large excess of vinyl Grignard at −78 to −20 °C produced 4- or 6-azaindoles. It was observed that the presence of a halogen substituent next to the nitrogen atom in the pyridine ring or having a large substituent directly adjacent to the nitro group gave relatively higher yields of azaindole products, although the yields from this method are generally low (11–50%). Further improvements are certainly desired.

3. Functionalization of azaindoles using organometallic reactions

Azaindoles have often exhibited distinctive reactivities in various types of reactions due to the unique electronic



Scheme 30



Scheme 32

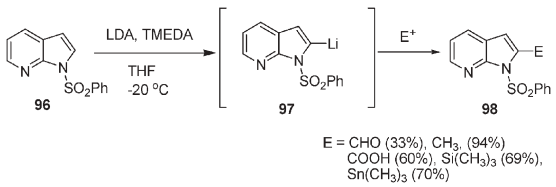
properties imparted by the pyridine moiety. A significant amount of scientific literature was devoted to the development of methods to selectively functionalize azaindole ring systems. Within organometallic chemistry-based methods, directed metalation, lithium–halogen exchange, and transition metal-catalyzed cross-coupling reactions have been the methods of choice for derivatizing azaindoles. Due to the length limit of this review, only a few representative examples for azaindole derivatizations are summarized in this section.

3.1 Functionalization of azaindoles *via* organolithium intermediates

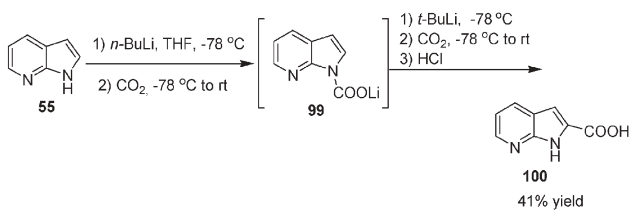
Dormoy and co-workers have described the directed *ortho*-metalation of *N*-protected 5-azaindole to selectively functionalize the C(2) position (Scheme 32).[36] *N*-Benzenesulfonyl-5-azaindole **93** was lithiated with either LDA or TMPLi in the presence of TMEDA to give 2-lithio-species **94** which was quenched with various reagents (Ac_2O, TMSCl, CO_2, formate, aldehydes, ketones, MeI, EtI, $ClCO_2Et$ and Weinreb amides) to give corresponding adducts **95** in moderate to good yields. This reaction also worked well with *N*-Boc-protected 5-azaindole.

Mérour *et al.* have applied this strategy to 7-azaindole systems (Scheme 33).[37] The *N*-benzenesulfonyl-7-azaindole **96** was treated with LDA–TMEDA at −20 °C and coupled with several electrophiles to afford the corresponding 2-substituted-7-azaindoles **98** with reasonable to good efficiencies.

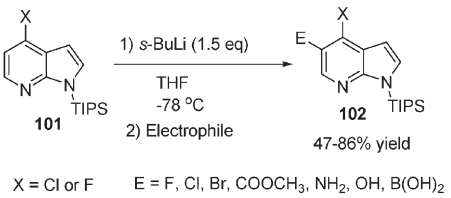
Curtis and co-workers took advantage of an *in situ*-formed carbamate to direct the lithiation at C(2) (Scheme 34).[38]



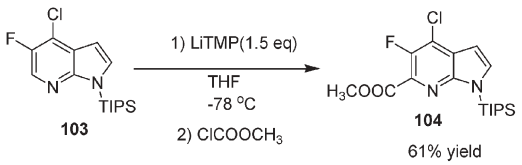
Scheme 33



Scheme 34



Scheme 35



Scheme 36

7-Azaindole was first *in situ* protected as 1-carboxylate-7-azaindole **99** and further lithiated to give the 2-lithio-7-azaindole-1-carboxylate. This intermediate was then quenched with carbon dioxide to provide 7-azaindole-2-carboxylic acid **100** in 41% yield. No other electrophiles have been reported with this approach.

Directed *ortho*-metalation was also used for the C(5)-functionalization of 7-azaindoles. L'Heureux and co-workers used the directing ability of halides in 4-chloro- and 4-fluoro-1-triisopropylsilyl-7-azaindoles to promote the C(5)-lithiation (Scheme 35).[39] The use of a bulky silyl protecting group on N(1) prevented the lithiation at position 2. Chloride, bromide, fluoride, hydroxyl, amine, ester and boronic acids were introduced in good yields without halogen scrambling or competing lithiation at C(2).

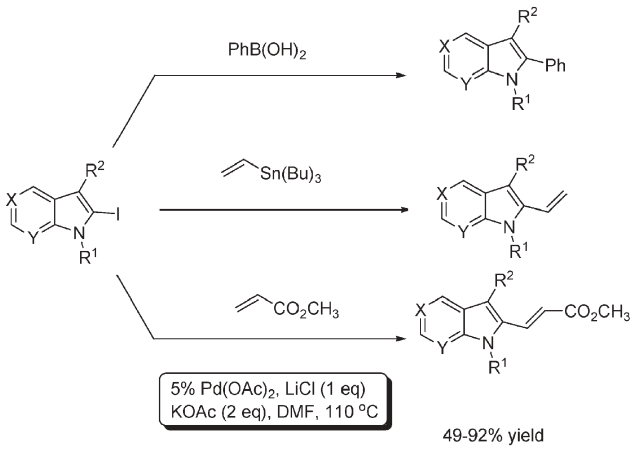
An interesting extension of this methodology showed that iteration of the process could lead to 4,5,6-trisubstituted-7-azaindoles (conversion of **103** to **104**, Scheme 36). The bulkier lithium tetramethylpiperidide in THF at −78 °C must be used in order to avoid aromatic nucleophilic substitution at C(4).

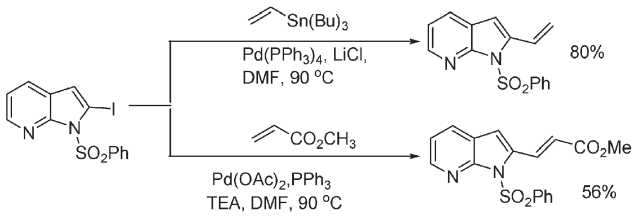
3.2 Further functionalization from halogenated azaindoles

Halogenated azaindoles can undergo a variety of reactions to introduce added molecular complexity. Classical methods include S_NAr and Ullmann coupling reactions which usually require vigorous conditions. In the past few years, thanks to the advances in transition metal chemistry, these transformations can now be achieved under much milder conditions. In addition, haloazaindoles can be subjected to halogen–metal exchange reactions for further functionalizations. A few such examples are shown below.

3.2.1 *Via* Pd-catalyzed C–C bond forming reactions. Highly substituted systems have been prepared from haloazaindoles through cross-coupling reactions. Some examples are listed in Scheme 37[40,41] illustrating the coupling of protected or unprotected 2-iodo-5-azaindoles and 2-iodo-7-azaindoles with boronic acids, stannanes and olefins.

3.2.2 *Via* Pd-catalyzed C–X bond forming reactions. An efficient substitution of 4-chloro-7-azaindoles by anilines and

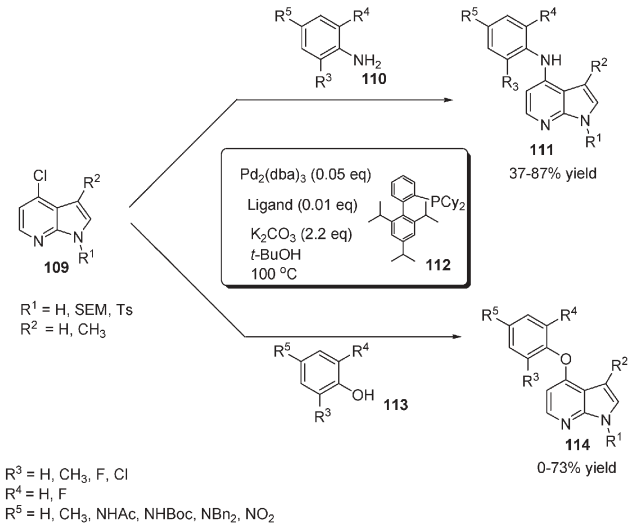




Scheme 37

phenols *via* palladium-catalyzed C–N and C–O bond formation was reported by Thutewohl and co-workers (Scheme 38).[42] A highly active catalytic system containing the bulky and air-stable X-PHOS ligand **112** was developed and allowed for the addition of both electron-poor and electron-rich anilines to 4-chloro-7-azaindole. Reasonably good yields were obtained for C–N bond formation as shown. This catalyst system was also applied to the corresponding ether bond forming reaction. Yields were relatively low for this challenging transformation (due to the more difficult reductive elimination to form the C–O bond), along with long reaction time. Only electron-rich substrates provided good yields for ether bond formation.

3.2.3 *Via* halogen–lithium exchange reactions. Mérour and co-workers reported a C(3)-selective iodination reaction for



Scheme 38

5-azaindoles **116** using I_2 and KOH in DMF (Scheme 39).[43] Lithium–halogen exchange on the 3-iodo-5-azaindole **117** followed by quenching with a variety of electrophiles furnished the C(3)-functionalized azaindoles **118** in reasonable to excellent yields.

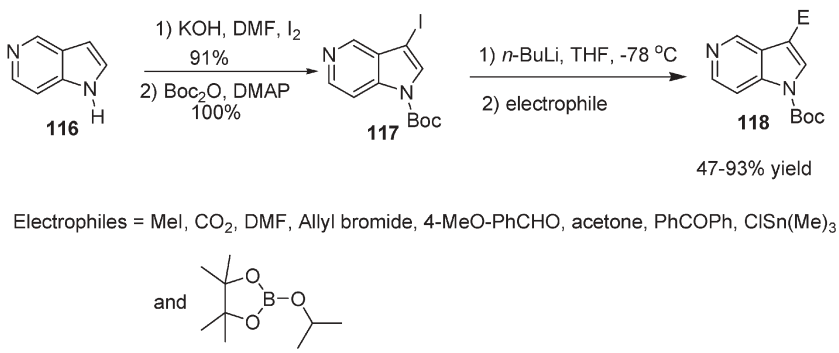
3.3 Cu-mediated method for N(1)-arylation

N(1)-arylation of azaindoles with arylbromides can be accomplished by the Cu-mediated Ullmann coupling reaction. For example, 7-azaindole was coupled with aryl bromides in the presence of $CuSO_4$ and K_2CO_3 or KOH at 180–220 °C (Scheme 40).[44,45]

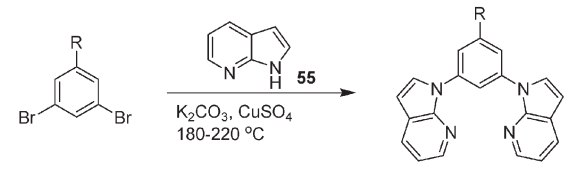
Much milder conditions for N(1)-arylation of nitrogen heterocycles were reported by Buchwald and co-workers (Scheme 41).[46] One single example for coupling of an aryl iodide **119** with 7-azaindole **55** was described using copper(I) iodide, the inexpensive racemic *trans*-1,2-diaminocyclohexane **120** and potassium phosphate to give compound **121** in nearly quantitative yield.

4. Conclusion

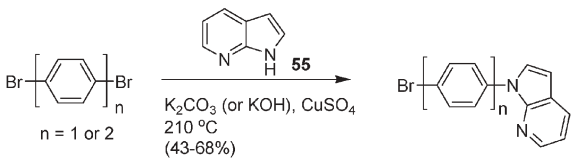
As can be seen from the preceding discussions, the field of azaindole chemistry has enjoyed a significant growth during



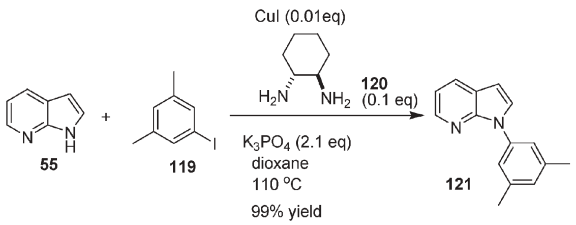
Scheme 39



R = H, F, Cl, Br, CF_3, MeO, 7-azaindolyl (12-85%)



Scheme 40



Scheme 41

the past 15 years. A number of new organometallic-based methods have been invented for azaindole formation with higher yields, milder conditions and wider scopes. So far the most versatile and general method for construction of azaindole frameworks is to use the Pd-catalyzed reactions. But additional steps are necessary to prepare the requisite, properly substituted aminohalopyridine and/or alkyne fragments and often times this is not a trivial task. A few lithiation-based methods were reported and they tend to employ more readily available raw materials and often have shorter sequences. It should be noted, however, that due to the need to use strong bases to achieve the lithiation, functional group tolerance is somewhat more limited than the Pd-mediated processes.

It was also our observation that, despite the impressive progress in the field of azaindole chemistry in recent years, there remains room and need for improvement in terms of substrate scope and overall efficiency of these synthetic methods. It is our hope that this review article serves to highlight the unique synthetic challenges associated with azaindole chemistry and in turn to inspire further development in this area. We believe that the rapid development of organometallic chemistry as well as the popular use of azaindole motifs in medicinal, inorganic and material sciences will continue to drive the chemical research on azaindoles in the years to come.

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