SCIENTIFIC LETTER 18

Upcoming Webinar

Edito

Compte tenu de leur importance en chimie médicinale, la chimie des azaindoles suscite toujours autant d'intérêt pour le développement de nouvelles stratégies de synthèse ou pour leur fonctionnalisation. Pour cette 18ème lettre scientifique, nous avons souhaité vous faire partager cette chimie très riche.

Chez AtlanChim Pharma notre expertise scientifique nous permet au quotidien de relever les challenges de vos projets de synthèse chimique, de molécules marquées à froid ou de travaux d'isolement d'impuretés, mais pour nous notre collaboration ne s'arrête pas là. En effet dans cette période de tension sur les matières premières (prix, délai, disponibilité) notre objectif reste et restera de mener à bien tous les projets confiés et de tenir nos engagements de qualité et de livraison dans les délais demandés. Nous pouvons le réaliser grâce à une communication transparente avec vous et en restant flexible et réactif face aux différentes situations rencontrées.

Pour initier vos projets l'équipe commerciale d'AtlanChim Pharma s'étoffe avec l'arrivée d'Héléna CHENOT qui vous sollicitera prochainement afin de vous rencontrer et d'étudier avec vous vos demandes de prestation en synthèse de petites molécules du milligramme à la dizaine de grammes. Nous sommes ravis de l'avoir à nos côtés pour vous accompagner dans vos projets.

Dans le cadre de notre veille scientifique un webinaire est également au programme en cette fin d'année (vous pouvez retrouver tous nos webinaires sous ce lien) . Le Mardi 13 décembre vous pourrez retrouver à 15h Jacques Lebreton sur la thématique des réactions d'oxydation via quelques exemples.

Dans l'attente de ce nouveau rendez-vous je vous souhaite une très bonne lecture !

Aurélie MOREAU

Editorial

Given their importance in medicinal chemistry, the chemistry of azaindoles always arouses as much interest in the development of new synthesis strategies or for their functionalization. For this 18th scientific letter, we wanted to share with you, insights with this very rich chemistry.

At AtlanChim Pharma, our scientific expertise enables us to meet the challenges of your chemical synthesis projects, cold-labelled molecules or impurity isolation work daily, but for us our collaboration does not stop there. Indeed, in this period of stress on raw materials (price, times, availability) our objective remains and will remain to carry out all the projects and to meet our quality and delivery commitments within the requested deadlines. We can achieve this through transparent communication with you and by remaining flexible and responsive in all situations.

To initiate your projects, AtlanChim Pharma's sales team is expanding with the arrival of Héléna CHENOT who will soon be asking you to meet you and study with you your requests for services in small molecule synthesis from milligram to ten grams. We are delighted to have her within our team to support you in your projects.

As part of our scientific monitoring, a webinar is also scheduled at the end of the year (you can find all our webinars under this link). On Tuesday 13th December at 3pm, Jacques LEBRETON will hold a webinar on the theme of oxidation reactions via some examples.

We are looking forward to seeing you then. Enjoy the reading!

Some Examples of Azaindole Synthesis and Functionalization

Jacques Lebreton

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The azaindoles, considered as effective bioisosteres of indole or purine moiety, are a very important family of drug-like heteroaromatic structures that exhibit a broad spectrum of biological activities. The azaindole core is present in some natural products, such as variolin, grossularine 2 and neocryptolepine and in a large number of synthetic products with various pharmacological properties[1], such as antiviral[2] and anticancer[3] activities (see Figure 1).

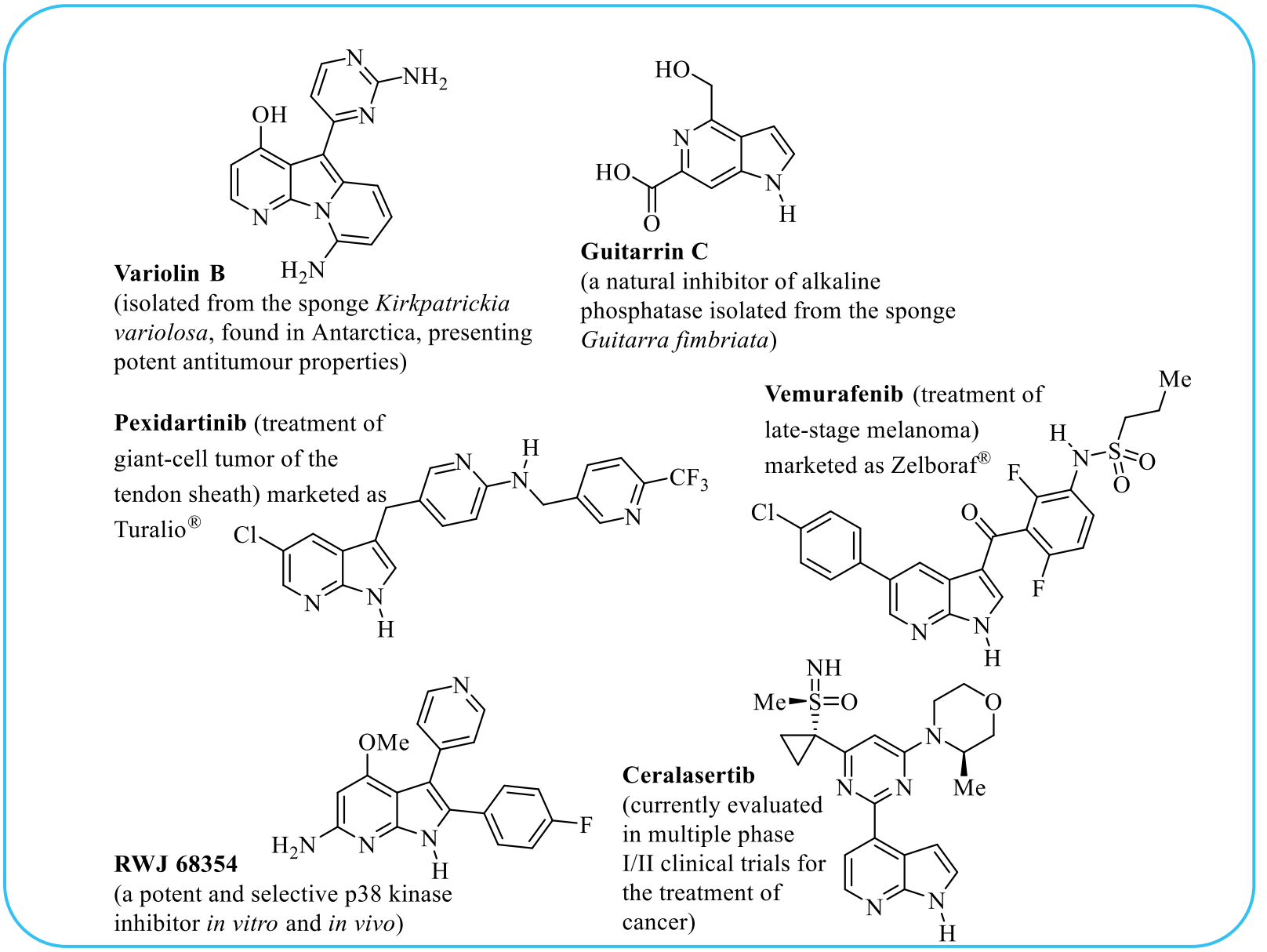


Figure 1. Some presentative azaindole natural products and bioactive compounds.

[1]For an excellent review on azaindole as therapeutic agents, see: D. Reddy Motati, R. Amaradhi, T. Ganesh, *Bioorg. Med. Chem*. **2020**, *28*, 115830.
[2]K. Chen, C. Risatti, M. Bultman, M. Soumeillant, J. Simpson, B. Zheng, D. Fanfair, M. Mahoney, B. Mudryk, R. J. Fox, Y. Hsaio, S. Murugesan, D. A. Conlon, F. G. Buono M. D. Eastgate, *J. Org. Chem*. **2014**, *79*, 8757-8767.
[3]Y. Han, W. Dong, Q. Guo, X. Li, L. Huang, *Eur. J. Med. Chem.* **2020**, *203*, 112506.

The azaindole core with a pyridine and a pyrrole ring, fused together give rise to four structural regioisomers, known as 4-, 5-, 6- and 7-azaindoles (see Figure 2).

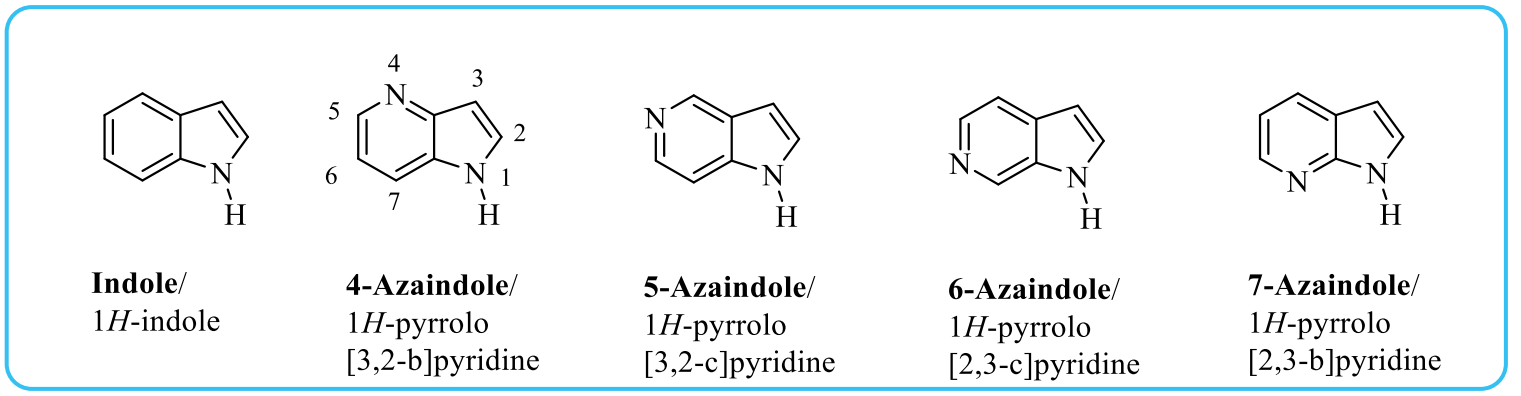


Figure 2. Indole and regioisomeric azaindole structures.

Interestingly, these different regioisomers show distinct physicochemical and pharmacological properties depending on the position of the nitrogen atom in the pyridine ring. Also, it is not surprising that since more than two decades, azaindoles have emerged as privileged pharmacophores in Medicinal Chemistry and serve as key intermediates in the identification of lead compounds in drug discovery. It should be pointed out that the 7-azaindole is the most attractive regioisomer with sp^2-hybridized nitrogen in the C-7 position of indole ring providing a scaffold containing a hydrogen-bond donor and acceptor in a rigid three-atom arrangement.[4]

Nevertheless, the preparation of these substituted azaindole scaffolds can be challenging and greatly depend on the targeted regioisomer.[5]

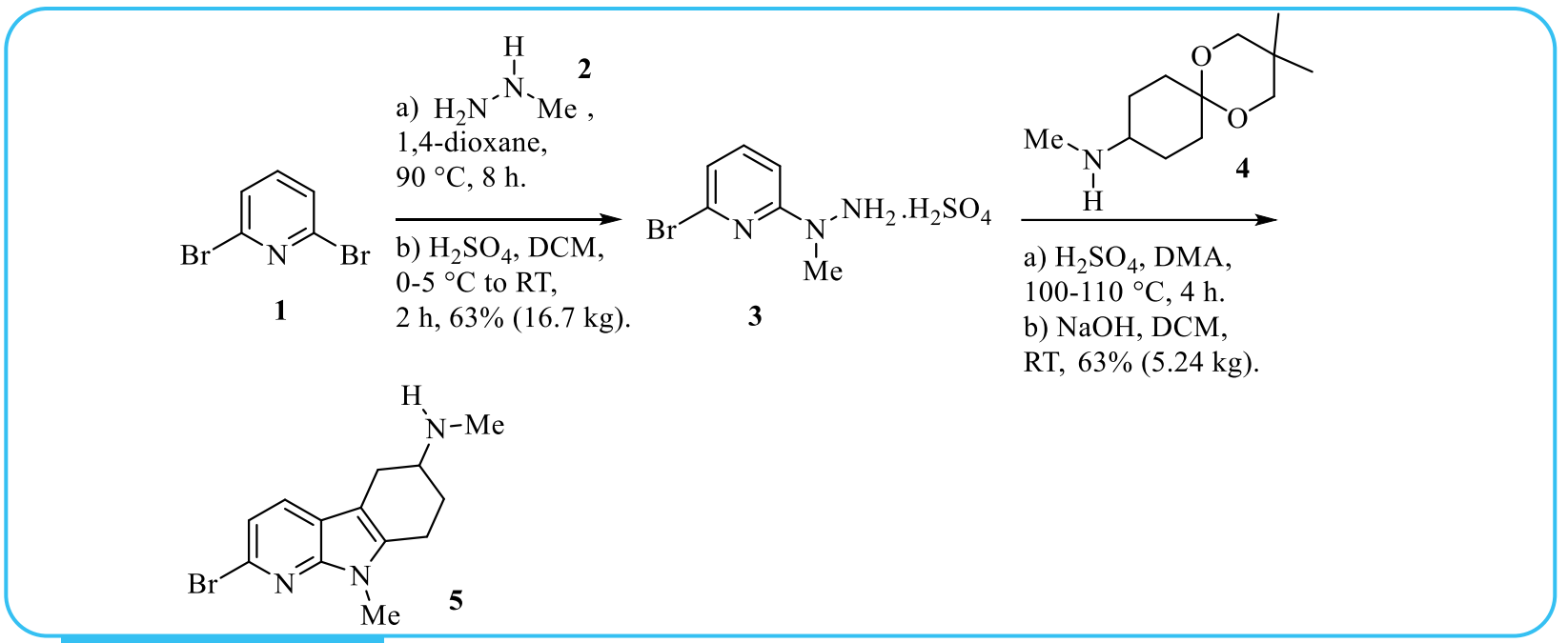
The objective of this new scientific letter is to present, through some interesting and recent work on the synthesis of azaindoles from the literature, the chemistry that we have achieved in this field for our customers, over the past 18 years.

Preparation of azaindoles using classical indole synthesis methods

The preparation of azaindoles according to classical methods for the synthesis of indoles can prove to be difficult in some cases, affording poor results or requiring the use of protecting groups. Nevertheless, some typical preparations of azaindoles are based on the classical indole formation methods such as the Fischer indole synthesis.[6]

[4]F. Popowycz, S. Routier, B. Joseph, J.-Y. Mérour, *Tetrahedron* **2007**, *63*, 1031-1064.
[5]For excellent review comprehensive reviews on the synthesis and functionalization of azaindoles, see: (a) J.-Y. Mérour, S. Routier, F. Suzenet, B. Joseph, *Tetrahedron* **2013**, *69*, 4767-4834. (b) D. Reddy Motati, R. Amaradhi, T. Ganesh, *Org. Chem. Front*. **2021**, *8*, 466-513 and cited literature.
[6]M. Jeanty, J. Blu, F. Suzenet, G. Guillaumet, *Org. Lett*. **2009**, *11*, 5142-5145.

For example, this versatile Fischer indole synthesis has been applied to the large-scale preparation of the compound **5**, as outlined in Scheme 1.[7] It should be pointed out that due to unfavorable electron deficient character of the pyridine ring in the starting material, the key [3,3]-sigmatropic rearrangement to provide the imine intermediate is less efficient. Reaction of 2,6-dibromopyridine **1** with an excess of *N*-methylhydrazine **2** afforded by mono-nucleophilic substitution reaction the corresponding 2-bromo-6-hydrazinylpyridine which was directly treated with sulfuric acid to give the corresponding salt **3** in 63%. The latter sulfate salt **3** was engaged in Fischer indole synthesis with the *N*-methyl amine partner **4** in DMA (*N*,*N*-dimethylacetamide) at 100-110 °C in the presence of sulfuric acid to afford after basic treatment the required racemic building block **5** as free amine in 63% yield.

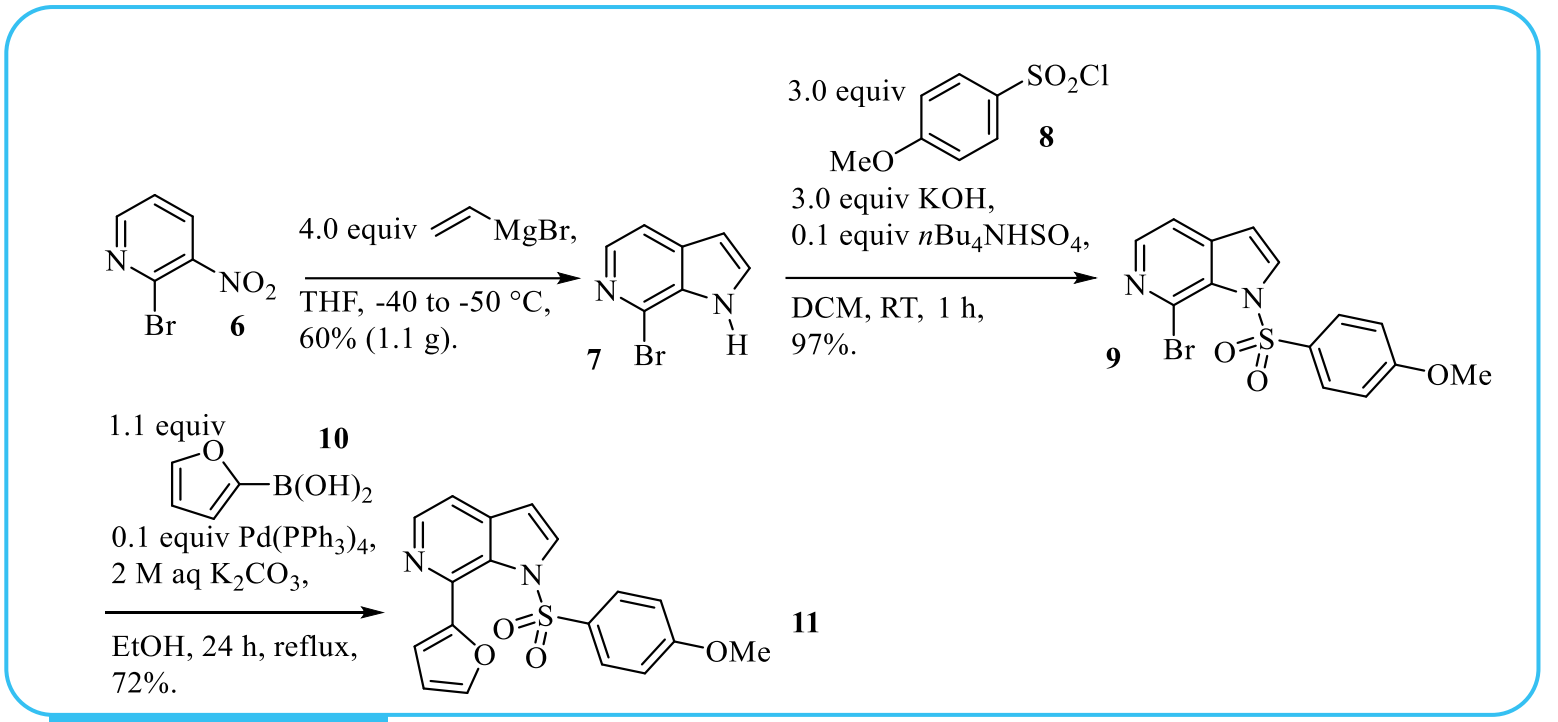


SCHEME 1

A series of 7-aryl-6-azaindole-1-benzenesulfonamides were synthetized from the 7-bromo-6-azaindole **7**, among which furanylazaindole **11** (see Scheme 2) exhibited the most potent anticancer activity against KB, HT29, MKN45, and H460 cancer cell lines with IC_{50} values of 21.1, 32.0, 27.5, and 40.0 nM, respectively.[8] Bartoli indole synthesis has been used to the preparation of the key 7-bromo-6-azaindole **7** in 60% yield on gram scale, by treatment of 2-bromo-3-nitropyridine **6** at low temperature with 4 equivalents of vinylmagnesium bromide. Then, *N*-tosylation of the previous 6-azaindole derivative **7** with the 4-methoxybenzenesulfonyl chloride **8** followed by Pd-catalyzed Suzuki coupling reaction of the resulting sulfonamide **9** with 2-furanylboronic acid **10** led to the targeted furanylazaindole **11** in around 70% overall yield.

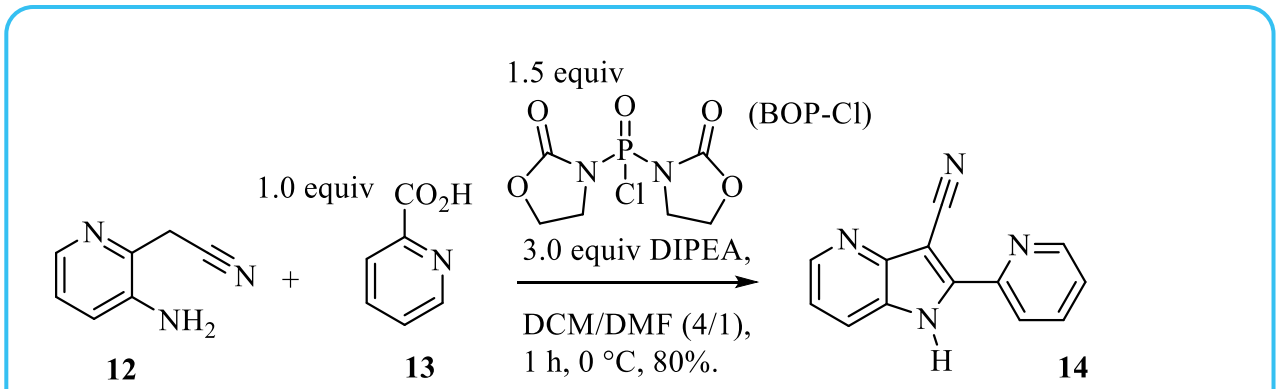
[7] N. Sreenivasachary, H. Kroth, P. Benderitter, W. Barth, A. Pfeifer, A. Muhs, *Org. Process Res. Dev.* **2019**, *23*, 2521-2526

[8] J.-P. Liou *et al*, *J. Med. Chem.* **2013**, *56*, 8008-8018.



SCHEME 2

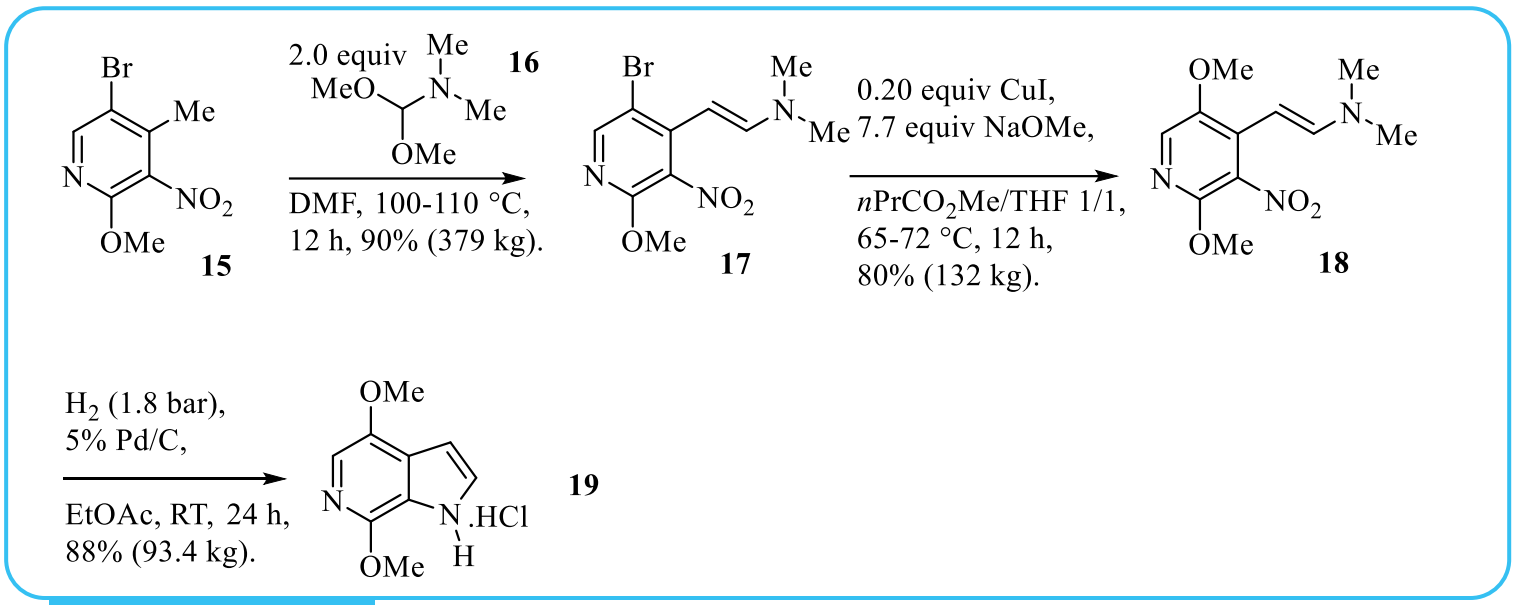
The preparation of various 2-substituted 3-cyano-4-azaindoles using a modified Madelung synthesis has been published by Jadhav *and Coll*. (see Scheme 3).[9] A mixture of (3-aminopyridin-2-yl)acetonitrile **12** and picolinic acid **13** was stirred with BOP-Cl (*bis*(2-oxo-3-oxazolidinyl)phosphonic chloride) and DIPEA (*N*,*N*-diisopropylethylamine, also known as Hünig′s base) leading to the isolation of the 3-cyano-2-pyridine-4-azaindole derivative **14** in 80% yield. As pointed out by the authors, BOP-Cl displays a crucial role by acting as acid-amine coupling agent as well as promoter for the dehydration step.



SCHEME 3

For the preparation of BMS-663068, an HIV attachment inhibitor, the Leimgruber-Batcho indole synthesis has been successfully applied on large scale to the *ortho*-nitropyridine **15**, leading to the key dimethoxy azaindole **19** (See Scheme 4).[10] Treatment of *ortho*-nitropyridine **15** with DMF-DMA (*N*,*N*-dimethylformamide dimethylacetal) **16** afforded the corresponding enamine intermediate **17** which was directly engaged into a copper-catalyzed methoxylation to give the compound **18** in 72% overall yield on 132 kg. Then, from this latter adduct **18**, the reductive cyclization was accomplished in the presence of a catalytic amount of Pd/C under high pressure of hydrogen (1.8 bar) giving the key dimethoxy azaindole **19** in 88% yield on 93.4 kg scale.

[9] J. Jadhav, S. Khanapaure, R. Kurane, R. Salunkhe, G. Rashinkar, Tetrahedron Lett. 2013, 54, 6858-6863.
[10] Richard J. Fox *et al*., *Org. Process Res. Dev.* **2017**, *21*, 1095-1109.

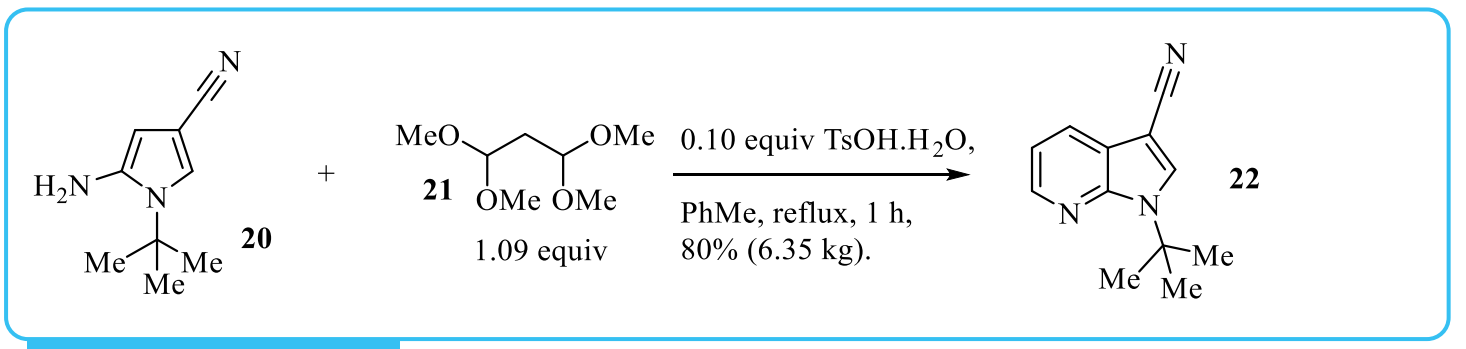


SCHEME 4

Synthesis of azaindoles from pyrroles

An alternative strategy to construct azaindole framework involving formation of the six-membered pyridine ring starting from pyrrole derivatives has been less exploited. In this regard, a convenient synthetic approach to various substituted azaindoles is based on regioselective cyclocondensation of *N*-protected 2-aminopyrroles with 1,3-dicarbonyl compounds or equivalents as reported in the following examples.

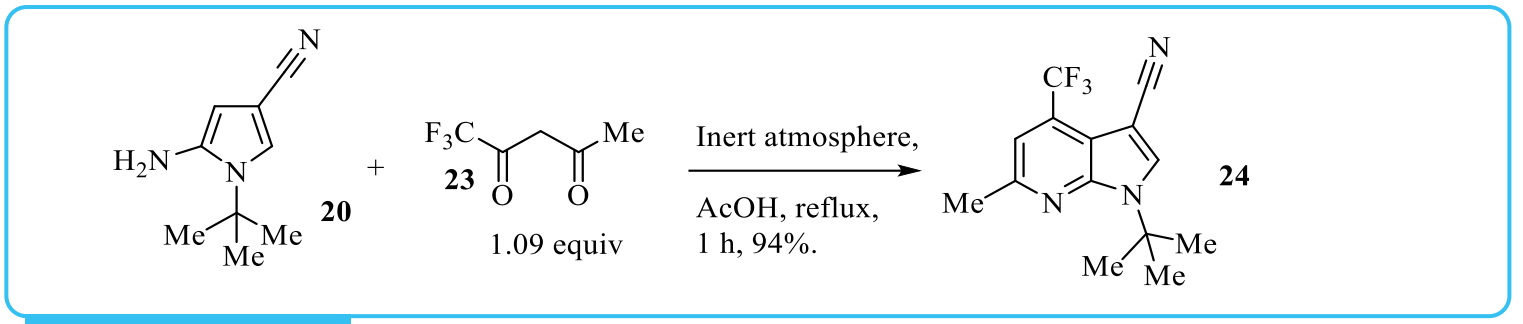
Condensation of *N-tert*-butyl-2-amino-4-cyanopyrrole **20** with 1,1,3,3-tetramethoxypropane **21** in refluxing toluene in the presence of catalytic amount of TsOH (*para*-toluenesulfonic acid) gave the 7-azaindole derivative **22** in 80% yield on multi-kilogram scale, as outlined in Scheme 5.[11]



SCHEME 5

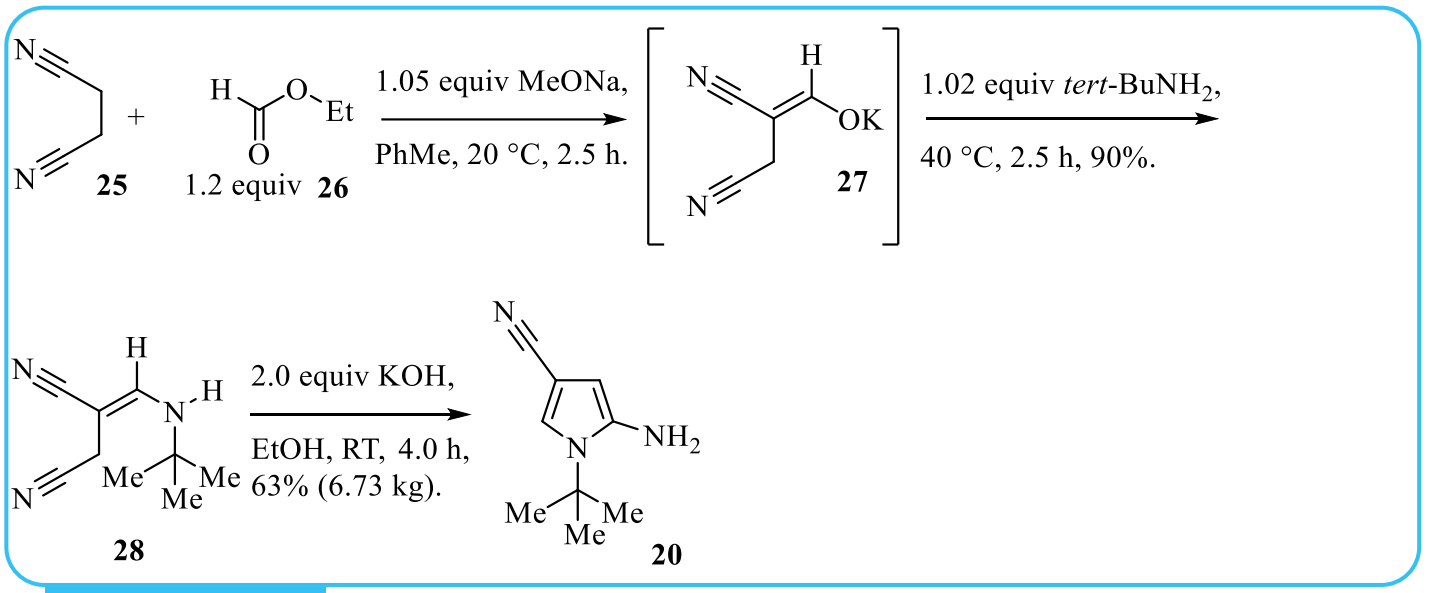
[11] M. Allegretti, R. Anacardio, M. C. Cesta, R. Curti, M. Mantovanini, G. Nano, A. Topai, G. Zampella, *Org. Process Res. Dev.* **2003**, *7*, 209-213.

In 2009, Groth *and Coll*. reported the preparation of fluorinated 7-azaindoles applying the previous acidic conditions in refluxing acetic acid with fluorine containing 1,3-dicarbonyl compounds or equivalents, as described in Scheme 6.[12] It is worth noticing that the cyclocondensation of the substituted pyrrole **20** with the fluoroalkyl-1,3-diketone **23** proceeds regioselectively to provide the desired regioisomer **24** in 94% yield, bearing a CF_3 moiety at C4 position, as sole regioisomer.



SCHEME 6

It should be pointed out that the key 2-amino-1-*tert*-butyl-1*H*-pyrrole-4-carbonitrile **20** was prepared following a three-step sequence on multi-kilogram scale from inexpensive starting materials, as reported in Scheme 7.[11] Succinonitrile **25** and ethylformate **26** were condensed in the presence of sodium methoxide to provide the corresponding salt of 2-hydroxymethylenebutyronitrile **27**. Then the latter reaction mixture was treated with *tert*-butylamine to afford the corresponding enaminonitrile **28** in 90% crude yield as a mixture of (*E*/*Z*) isomers in a 2/1 ratio. Finally, the latter intermediate **28** was submitted to KOH-catalyzed intramolecular condensation to give the targeted pyrrole derivative **20** in 63% crude yield (6.73 kg).



SCHEME 7

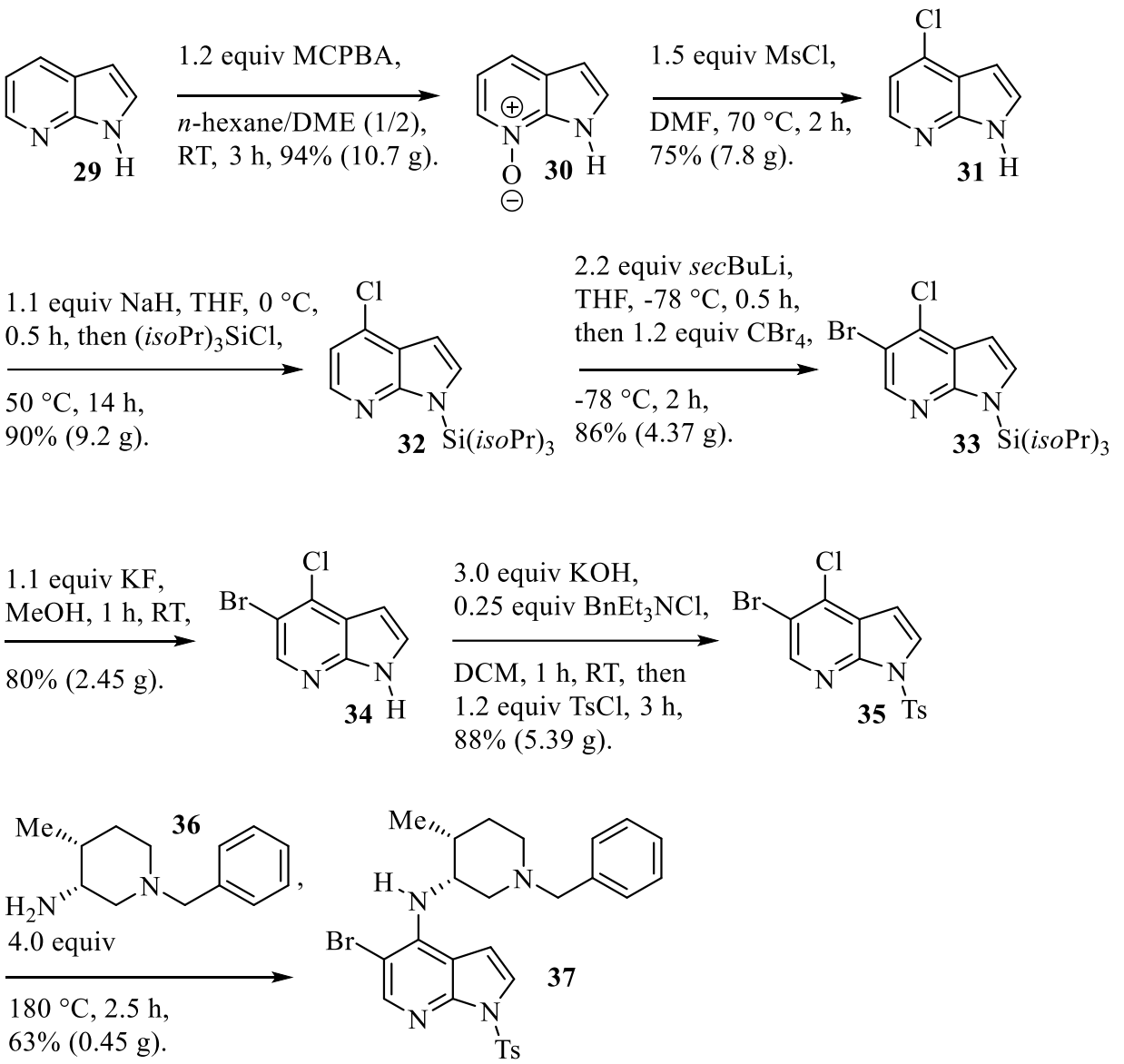
[12] U. Groth, V. O. Iaroshenko, Y. Wang, T. Wesch, *Synlett* **2009**, 456-460.

Preparation of substituted azaindoles based on classical pyridine and pyrrole chemistry

Preparation of azaindole derivatives bearing various substituents in different positions on either pyrrole or pyridine moieties could be done using well-established chemistry of these aromatic heterocycles. Also to facilitate the diversification, the strategy based on regioselective halogenation followed by Pd-catalyzed cross-coupling reactions have been largely described as reported in the following examples.

Treatment of 7-azaindole **29** with a slight excess of mCPBA (*meta*-chloroperoxybenzoic acid) provided the corresponding *N*-oxide **30** which was directly engaged in a high regioselective chlorination at C-4 position over the C-6, by using MsCl (methanesulfonyl chloride (mesyl chloride)) in DMF leading to the desired 4-chloro-7-azaindole **31** in 70% overall yield on gram-scale (see Scheme 8).[13] Protection of the N-1 position of 6-bromo-indole **8** with TIPS-Cl ((*iso*-Pr)$_3$SiCl) in the presence of sodium hydride as base provided intermediate **32** . Then, treatment of the latter compound **32** with *sec*-BuLi gave exclusive deprotonation of the C6-position[14] and after trapping with carbon tetrabromide, 5-bromo-4-chloro-7-azaindole **33** was isolated in 86% yield. After removal of the TIPS group in compound **33** with KF, the resulting 7-azaindole **34** was submitted to *N*-tosyl protection providing the intermediate **35** in 70% yield over the two steps. Finally, nucleophilic aromatic substitution of the chlorine atom at C-4 position in the latter compound **35** with the secondary amine **36** without solvent at 180 °C under microwave activation, gave the desired 7-azaindole derivative **37** in 63% yield. This transformation failed in organic solvents under forcing conditions using various solvents and bases. Also, palladium-catalyzed arylamination under various conditions resulted in poor conversion and sluggish reactions.

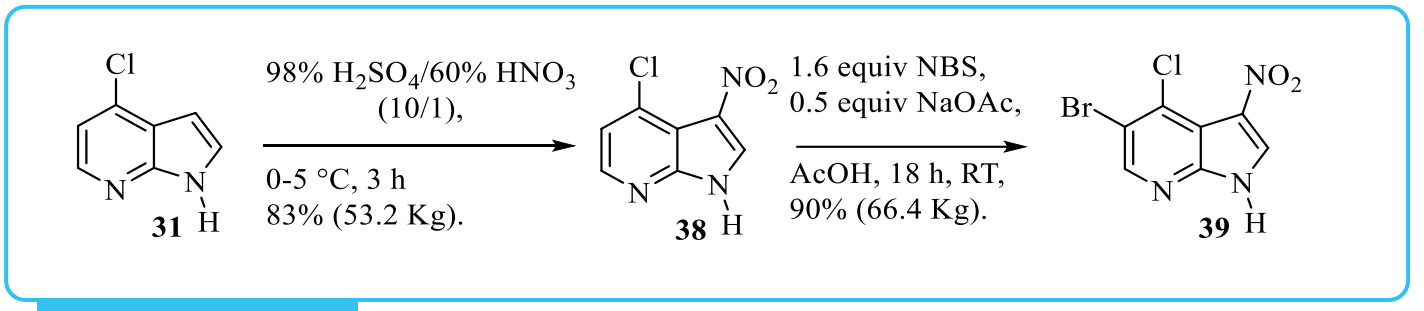
[13] M. Gehringer, E. Pfaffenrot, S. Bauer, S. A. Laufer, *ChemMedChem* **2014**, *9*, 277-281.
[14] M. Schlosser, A. Ginanneschi, F. Leroux, *Eur. J. Org. Chem*. **2006**, 2956-2969.



SCHEME 8

As shown in Scheme 9, F. Gosselin *and Coll*. from Genentech developed an efficient route on >50 kg scale to 5-bromo-4-chloro-3-nitro-7-azaindole **39**, a useful building block for the preparation of a series of 3,4,5-substituted-7-azaindole derivatives.[15] It should be pointed out that the preparation of 4-chloro-7-azaindole **31** from the parent 7-azaindole **29**, previously presented in Scheme 8, was carried out following the same conditions on 65.3 kg scale in 61% yield for the two steps. As in indole chemistry, C-3 electrophilic nitration of the 4-chloro-7-azaindole **31** was conducted under classical conditions by treatment in a mixture 65% HNO_3, and 98% H_2SO_4 to give the 4-chloro-3-nitro-7-azaindole derivate **38** in 83% yield. Finally, bromination step was accomplished with NBS (*N*-bromosuccinimide) in acetic acid in the presence of 0.5 equivalent of NaOAc, as weakly basic additive, to afford the targeted 5-bromo-4-chloro-3-nitro-7-azaindole **39** in 90% yield on 66.4 kg scale. It is noteworthy to mention that since the most reactive C-3 position toward electrophiles was occupied, the electrophilic bromination occurred at C-5.

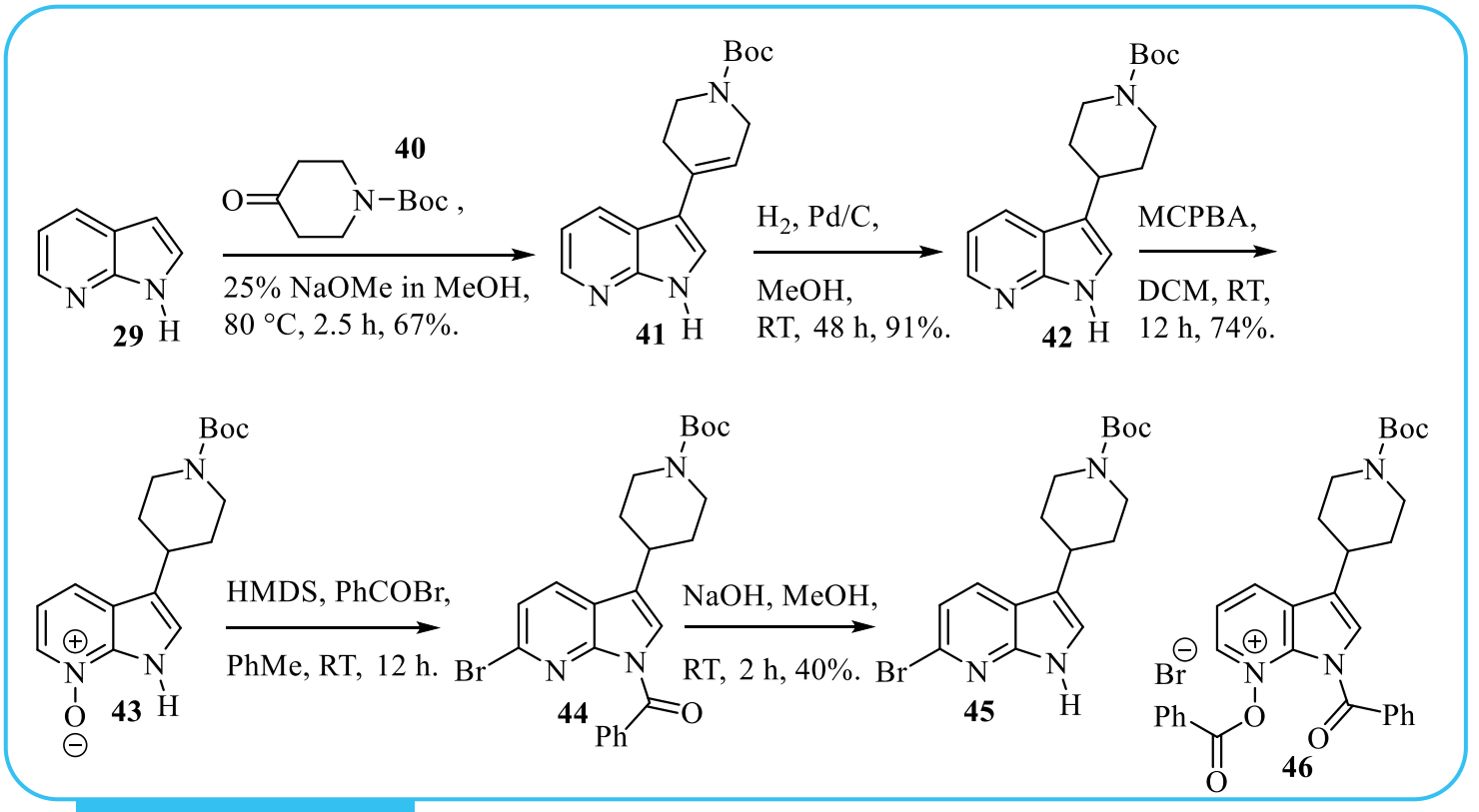
[15] C. Han, K. Green, E. Pfeifer, F. Gosselin, *Org. Process Res. Dev.* **2017**, *21*, 664-668.



SCHEME 9

A series of 7-azaindole derivatives as inhibitors of β-amyloid-42 aggregation for the treatment of Alzheimer's disease has been prepared as outlined in Scheme 10.[16] Condensation reaction of 7-azaindole **29** with *tert*-butyl 4-oxopiperidine-1-carboxylate **40** under basic conditions afforded the corresponding 3-substituted 7-azaindole derivative **41** in 67% yield. Hydrogenation of the double bond in **41** was carried out with palladium on carbon, under hydrogen gas pressure to lead to the intermediate **42** in excellent yield. Next, after the formation of the *N*-oxide **43** by oxidation of **42** with mCPBA, treatment with an excess of benzoyl bromide in anhydrous toluene, in presence of HMDS (hexamethyldisilazane), provided the *N*-benzoyl-6-bromo-7-azaindole **44**. This latter intermediate **44** was then submitted to saponification of the benzoyl group with sodium hydroxide in methanol, affording the desired intermediate **45** in 40% yield for the two steps. It is important to mention that HMDS is used as trapping agent of the resulting HBr formed by benzoylation at N-1 position of the *N*-oxide intermediate **43** to provide the *N*-benzoyloxypyridinium salt **46** after *O*-benzylation which underwent by nucleophilic attack of the bromide at C-6 position followed by elimination of benzoic acid, to yield the *N*-benzoyl 6-bromo-7-azaindole **44**. This transformation is known as the Reissert-Henze-type reaction.[17]

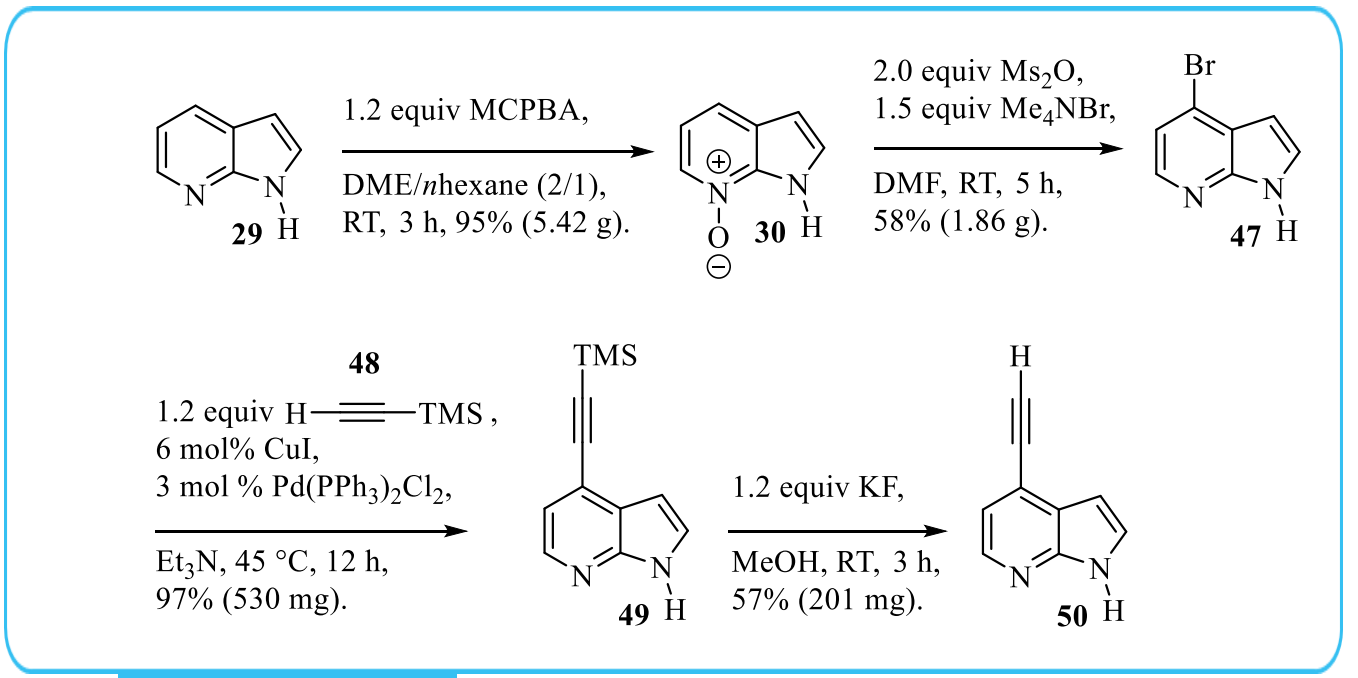
[16] N. Sreenivasachary, H. Kroth, P. Benderitter 1, A. Hamel, Y. Varisco, D. T. Hickman, W. Froestl, A. Pfeifer, A. Muhs, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1405-1411.
[17] H. Asahara, A. Kataoka, S. Hirao, N. Nishiwaki, *Eur. J. Org. Chem*. **2015**, 3994-3999.



SCHEME 10

A solution-phase parallel synthesis of triazole-derived of ruxolitinib analogues were prepared from the key alkyne **50**.[18] In this context, the 4-bromo-7-azaindole **47** (see Scheme 11) was prepared following the same sequence as previously described in Scheme 8 for its 4-chloro homologue **31**, from the *N*-oxide **30** the regioselective bromination step was achieved by treatment with Ms_2O (methanesulfonic anhydride) and tetramethylammonium bromide. Next, Sonogashira coupling reaction of the previous intermediate **47** with trimethylsilylacetylene **48** gave the desired adduct **49** and subsequent TMS deprotection with KF in methanol provided the alkyne **50** in 55% yield for the two steps.

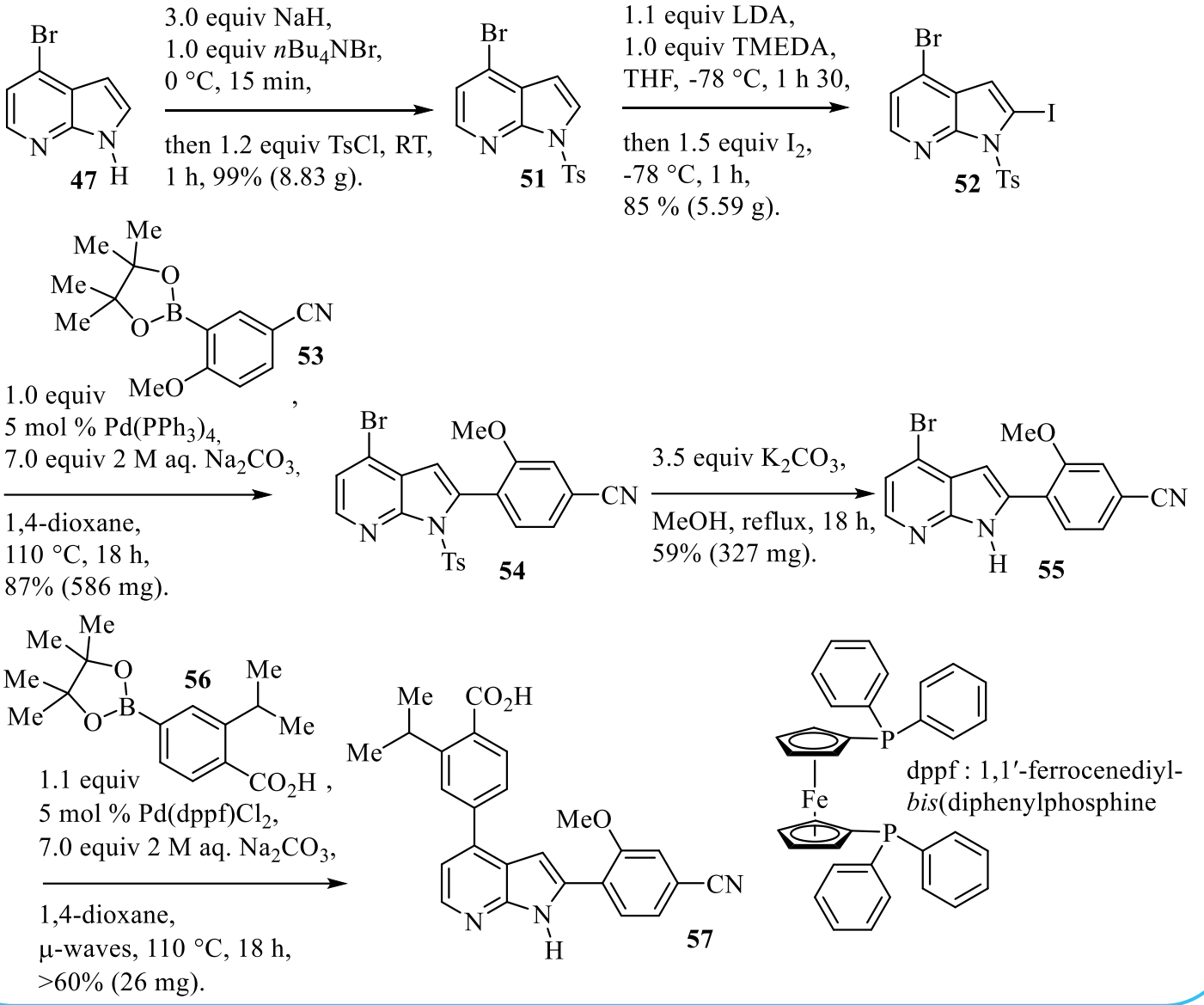
[18] M. Gehringer, M. Forster, S. A. Laufer, *ACS Comb. Sci*. **2015**, *17*, 5-10.



SCHEME 11

During the development of potent Pf CLK3 inhibitors as a new class of antimalarial agent, the key 7-azaindole intermediate **57** was prepared as described in Scheme 12.[19] Protection of 4-bromo-7-azaindole **47** under basic conditions with TsCl (*para*-toluenesulfonyl chloride) provided the corresponding *N*-tosyl-7-azaindole **51** which was regioselectively metaled at C-2 position by treatment with LDA (lithium diisopropylamide). The resulting organometallic species was then trapped with iodine giving the desired 2-iodoazaindole **52** in 85% for the two steps on gram scale. Then, this latter compound **52** was subsequently subjected to Suzuki coupling reaction with (5-formyl-2-methoxyphenyl)boronic acid **53** to afford the 2-aryl substituted azaindole **54** in 87% yield. Finally, tosyl group cleavage on compound **54** was carried out using K_2CO_3 in refluxing methanol providing the intermediate **55**, followed by a second Suzuki coupling reaction at the C-4 position with the pinacol boronate ester **56** to give the key 7-azaindole intermediate **57** in around 40% overall yield.

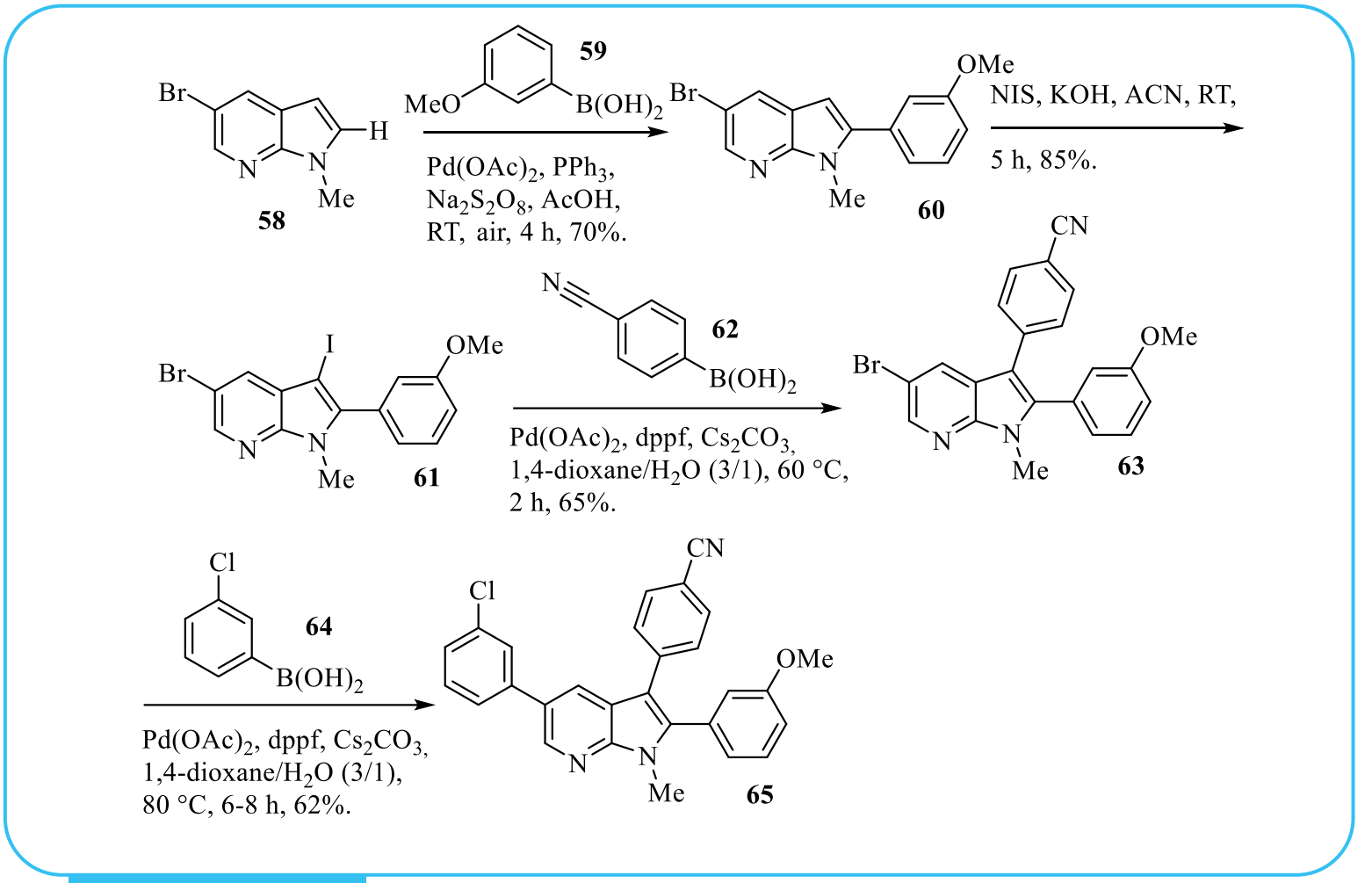
[19] A. Mahindra, O. Janha, K. Mapesa, A. Sanchez-Azqueta, M. M. Alam, A. Amambua-Ngwa, D. C. Nwakanma, A. B. Tobin, A. G. Jamieson, *J. Med. Chem*. **2020**, *63*, 9300-9315.



SCHEME 12

Das *and Coll*. published an elegant strategy to prepare chemoselective multi-arylated 7-azaindole derivatives bearing three different aryl groups at C-2, C-3, and C-5 positions, as outlined in Scheme 13.[20] Direct and regioselective Pd-catalyzed C-2 arylation of 7-azaindole **58** by C-H activation using arylboronic acid **59** as coupling partner provided the desired coupled adduct **60** in 70% yield. Then, NIS (*N*-Iodosuccinimide)-mediated iodination of the previous *N*-methyl-2-aryl-5-bromo-7-azaindole **60** afforded the corresponding 3-iodo derivative **61** in good yield. Finally, two sequential Suzuki-Miyaura coupling reactions at the C-3 iodide and C-5 bromide sites were performed with the arylboronic acids **62** and **64** respectively *via* the intermediate **63** to give the 7-azaindole derivatives **65** bearing different aryl units at C-2, C-3, and C-5 positions in 40% yield for the two steps.

[20] P. Das et al., *Org. Lett.* **2013**, *15*, 5718-5721.



SCHEME 13

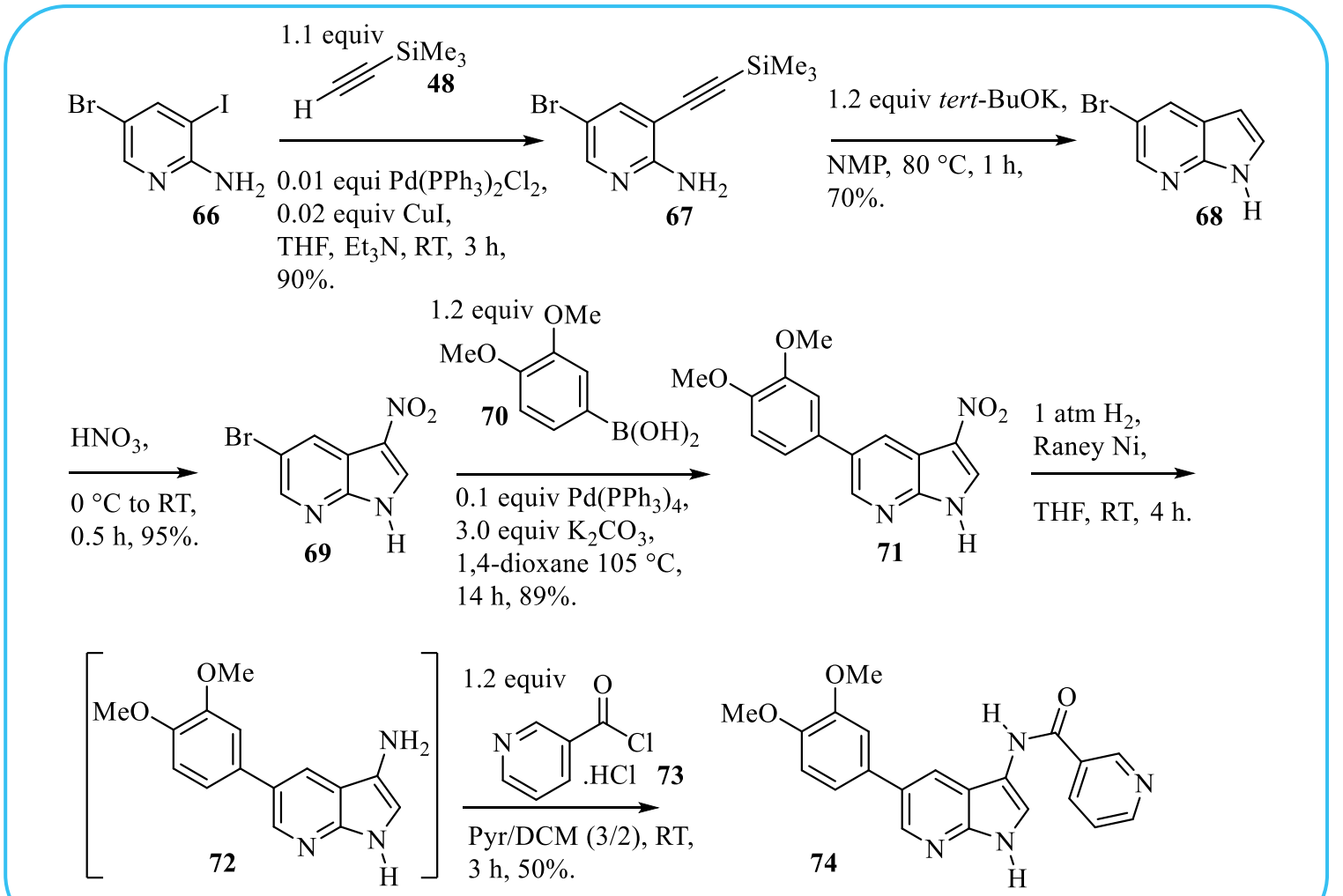
Metal-catalyzed cross-coupling reactions to form substituted azaindoles

Metal-catalyzed cross-coupling such as the well-known Sonogashira, Heck, and Suzuki reactions have been used to construct the azaindole scaffolds, some representative recent examples are depicted in the following schemes.[21]

The preparation of azaindoles from the Sonogashira coupling reaction following by ring closure of the Sonogashira adducts using bases, metal salts, metal catalysts, acids and other reagents is an extremely versatile strategy, as presented in this paragraph. For example, in the chemistry of 7-azaindode derivatives, the commercially available 5-bromo-3-nitro-7-azaindole **69** (more than 70 suppliers, 25g/300€) is a popular starting material as exemplified in the Scheme 14, through the preparation of a series of thirty 3,5-disubstitutedpyrrolo[2,3-b]pyridines as inhibitors of adaptor-associated Kinase 1 (AAK1) with broad-spectrum activity.[22] From the commercially available 5-bromo-3-iodo-2-aminopyridine **66**, a regioselective Sonogashira coupling reaction with the trimethylsilylacetylene **48** gave the corresponding 2-alkynyl derivative **67** with an excellent yield of 90%. From this latter 2-alkynylaniline type derivative **67**, intramolecular addition of the NH_2 function to the triple bond promoted by *tert*-BuOK in NMP (*N*-methylpyrrolidinone) at 80 °C gave the 5-bromo-7-azaindole **68** which was stirred in fuming nitric acid to furnish the 3-nitro-5-bromo-7-azaindole **69** in 66% yield for the two steps.

[21] For an excellent review on this field, see: A. S. Santos, A. C. Mortinho, M. M. B. Marques, *Molecules* **2018**, *23*, 2673.
[22] S. De Jonghe *et al*., *J. Med. Chem.* **2019**, *62*, 5810-5831.

Suzuki coupling reaction of compound **69** with 3,4-dimethoxyphenylboronic acid **70** afforded the expected adduct **71** in 89% yield. Ni-catalyzed hydrogenation of the nitro moiety in **71** yielded the corresponding amino derivative **72** which was directly coupled without further purification with nicotinoyl chloride hydrochloride **73** in a mixture of pyridine and DCM to give the desired 3,5-disubstitutedpyrrolo[2,3-b]pyridine **74** in 50% overall yield.

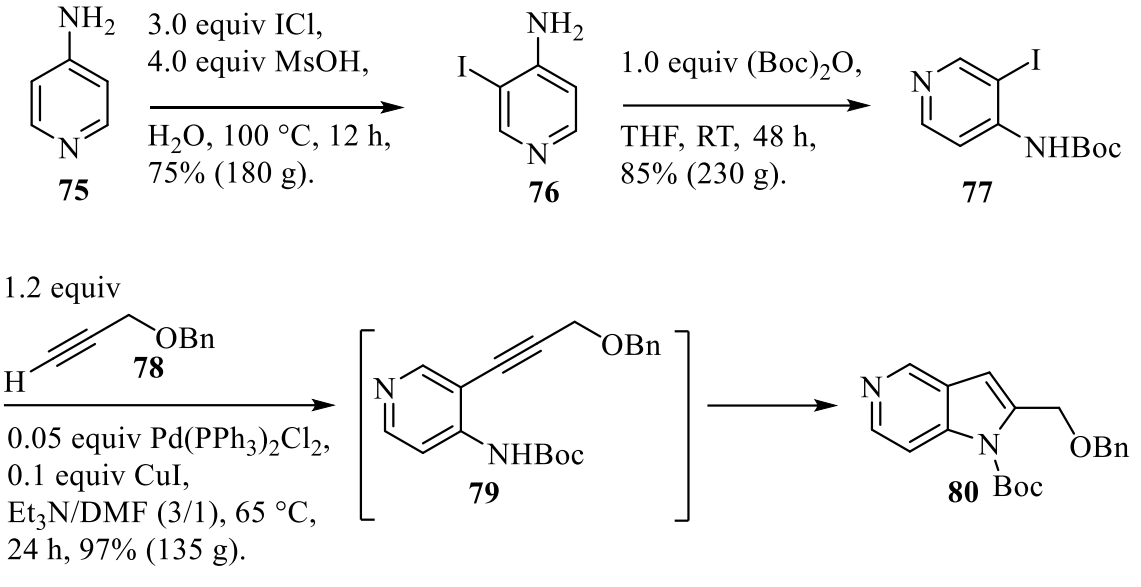


SCHEME 14

An efficient and straightforward multi-hundred gram synthesis of 7-azaindode derivatives involving a tandem processes based on Sonogashira cross-coupling reaction followed by a cyclization reaction to build the pyrrolo[3,2-c]pyridine skeleton as presented in Scheme 15.[23] To obtain exclusively monoiodinated pyridine derivative **76** in good yield, under optimized conditions the 4-aminopyridine **75** was treated with 3 equivalents of ICl (iodine monochloride) and 4 equivalents of MsOH (methanesulfonic acid) at 100 °C for 12 h in water. Then, the corresponding Boc (*tert*-butyloxycarbonyl) derivative **77** was prepared under classical conditions and submitted to Sonogashira conditions with the benzyl propargyl ether **78** to afford directly *via* subsequent cyclization the 2-substituted-5-azaindole **80** in an excellent yield of 97% on 135 g scale. Concerning this latter transformation,

[23] A. Gupta *et al., Org. Process Res. Dev.* **2018**, *22*, 1276-1281.

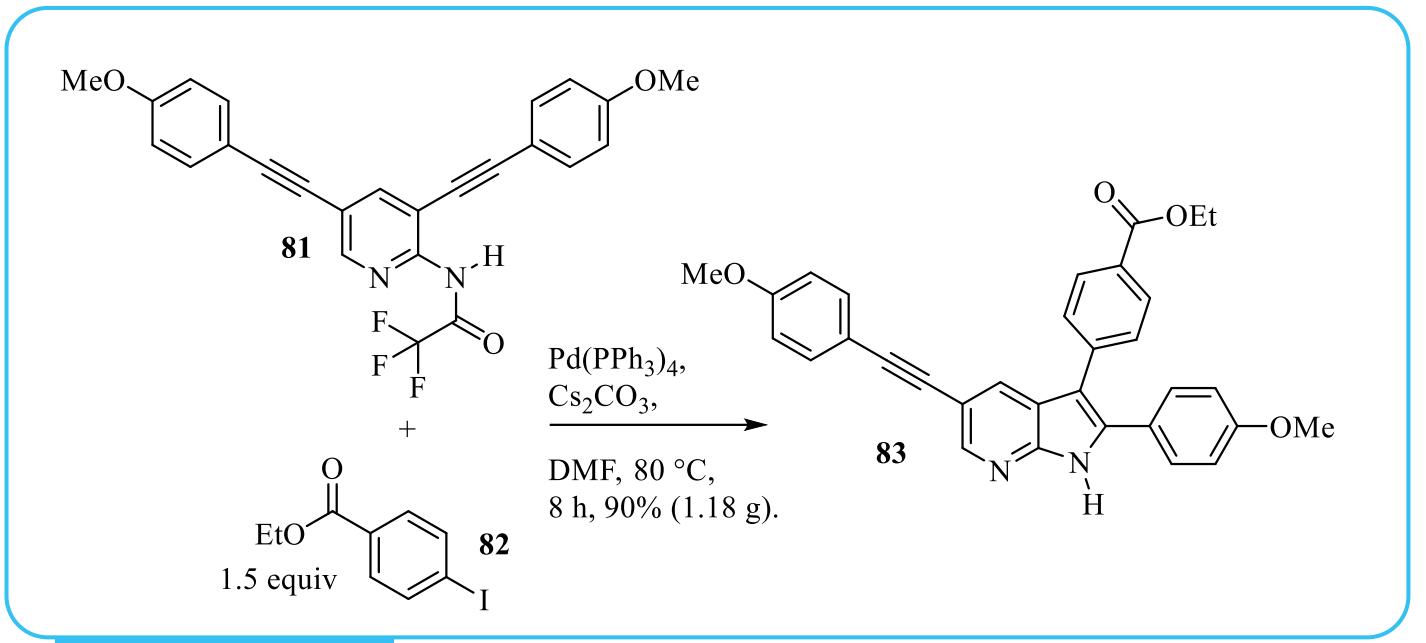
it should be pointed out that it is necessary to heat the reaction mixture at 65 °C for 24 h. Indeed, after 12 h LCMS analysis showed the disappearance of starting material **77** along with 25% formation of intermediate **79** and 75% formation of the desired cyclized intermediate **80**. This one-pot Sonogashira reaction and subsequent cyclization was scaled up to >2 kg in a single batch with reproducible yields.



SCHEME 15

As an extension, Cacchi *and Coll*. reported an elegant strategy for the synthesis of 2,3-disubstituted indoles from 2-alkynylanilines using palladium, as a catalyst, and potassium or cesium carbonate, as a base, in the presence of vinyl triflates or aryl halides.[24] It should be pointed out that in this aminopalladation-reductive elimination process the basicity of the nitrogen of the starting acetamidopyridines is a key parameter, so in this context the trifluoroacetamido derivatives have been largely used. A representative example of the Cacchi reaction is displayed in Scheme 16, through the preparation of the 2,5-disubstituted 7-azaindole derivative **83** from the trifluoroacetamido derivative **81** and the iodoaryl **82**.[25] It should be noted that the 2,5-disubstituted 7-azaindole **83** displays promising biological activity against the gastrointestinal protozoal parasite *Giardia duodenalis*.

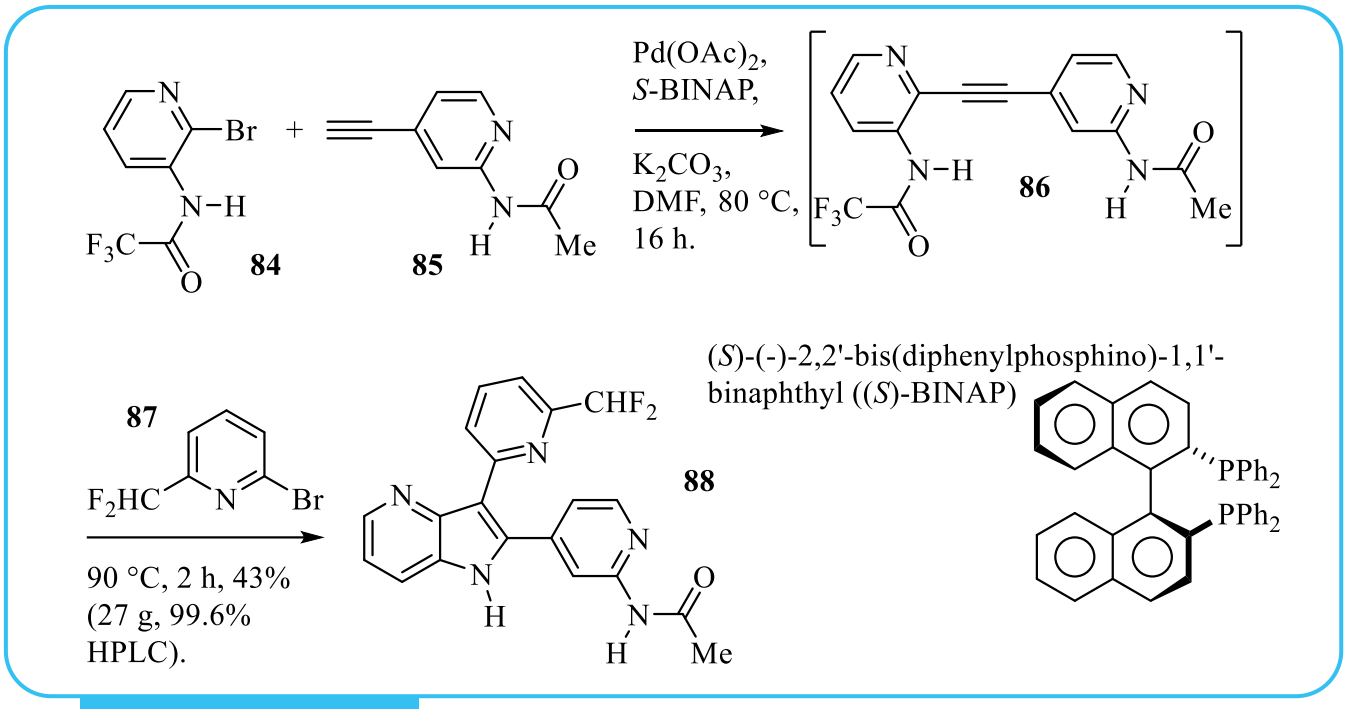
[24] S. Cacchi, G. Fabrizi, L. M. Parisi, *J. Comb. Chem.*, **2005**, *7*, 510-512.
[25] T. C. Leboho, S. Giri, I. Popova, I. Cock, J. P. Michael, C. B. de Koning, *Bioorg. Med. Chem.* **2015**, *23*, 4943-4951.



SCHEME 16

Very recently, Li *and Coll*. from Bristol-Meyers Squibb took advantage of this methodology to optimize a twenty-gram scale preparation of the potent TGFβ receptor kinase inhibitor **88**, for the preclinical studies to treat cancers, as outlined in Scheme 17.[26] Unlike the original Cacchi method, they developed from *N*-(4-ethynylpyridin-2-yl)acetamide **85** a one-pot procedure *via* a domino copper-free Sonogashira-Cacchi reactions by sequential addition of *N*-(2-bromo-pyridin-3-yl)-2,2,2-trifluoroacetamide **84** and 2-bromo-6-(difluoromethyl)pyridine **87** to provide, *via* the formation of the intermediate **86**, the targeted disubstituted azaindole **88** in 43% yield. During the optimization of the Pd-catalyzed Sonogashira and Cacchi reactions, the screening of sixteen ligands showed that BINAP (for development (*S*)-BINAP was used due to a limited supply of large quantities of high-quality racemic BINAP) was the most efficient providing a very clean reaction profile.

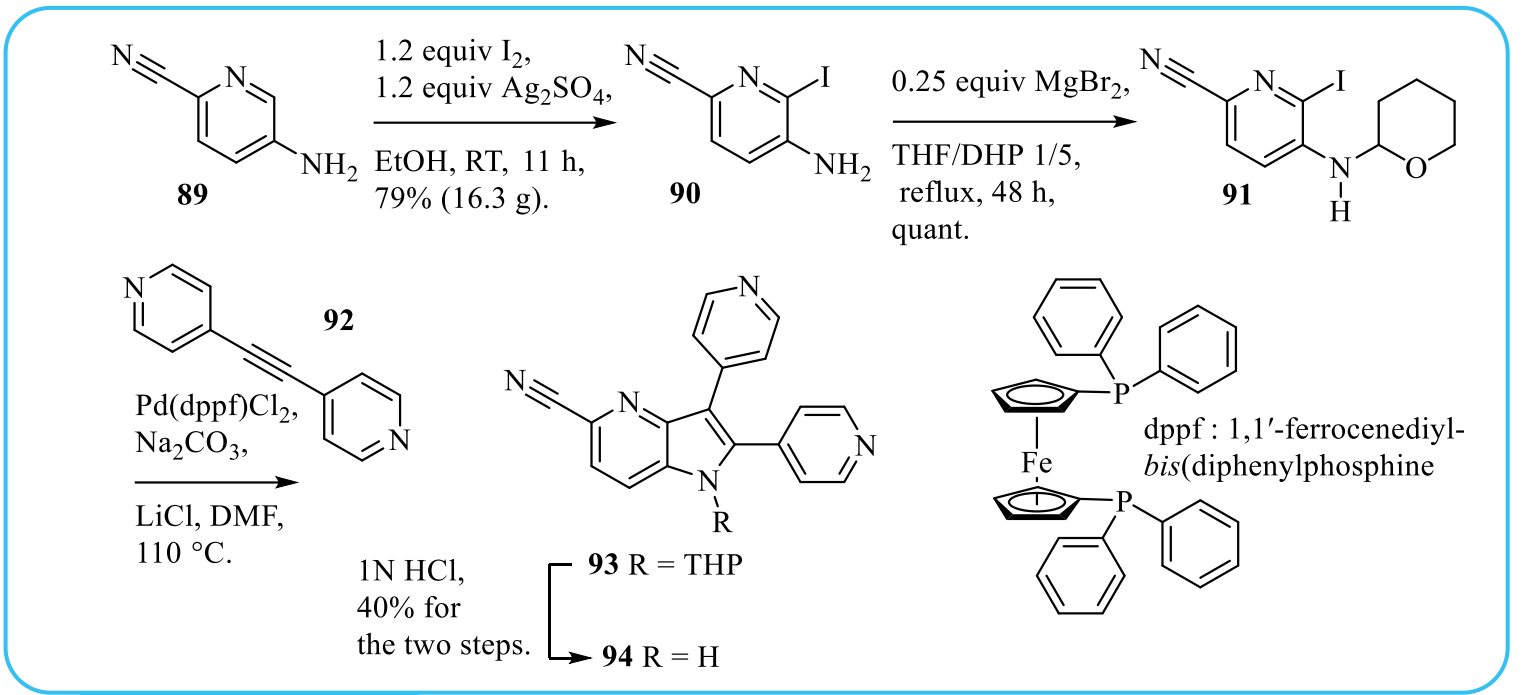
[26] J. Li et al., *Org. Process Res. Dev.* **2020**, *24*, 454-458.



SCHEME 17

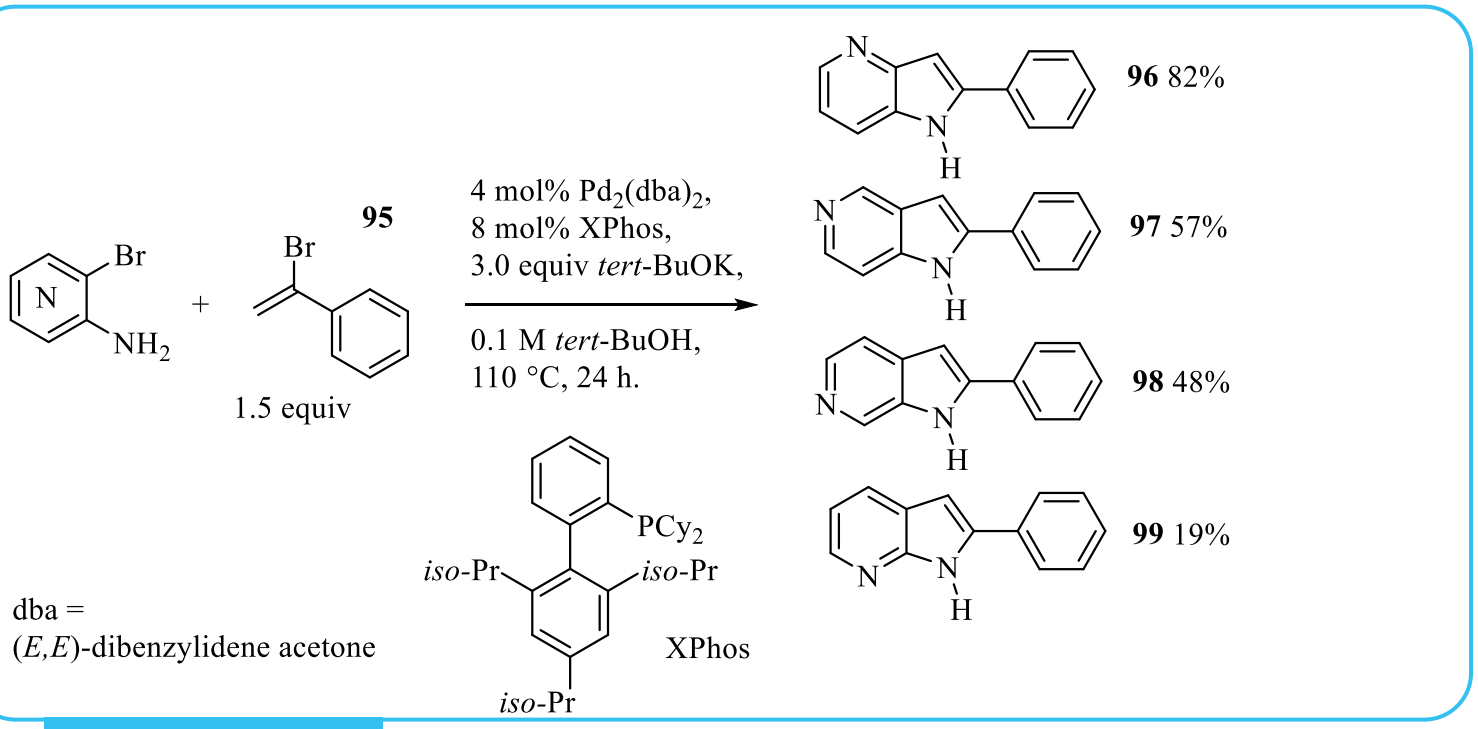
In 1991, Larock published a palladium-catalyzed heteroannulation between internal alkynes and *ortho*-iodoanilines giving 2,3-disubsituted indoles in a single step.[27] This Larock indole synthesis, involving *ortho*-iodopyridines has been largely used to prepare azaindoles as reported in Scheme 18.[28] Iodation of the 5-aminopicolinonitrile **89** with iodine and silver sulfate provided the 5-amino-6-iodopicolinonitrile **90** in 79% yield (16.30 g). Treatment of the latter intermediate **90** in a mixture of THF and of DHP (3,4-dihydro-2H-pyran) under Lewis-acid catalysis provided quantitatively the THP-protected amino derivative **91**. The Larock reaction was performed on the protected iodo-aminopyridine **91** with the symmetrical 1,2-*bis*(4-pyridyl) acetylene **92**, using Pd(dppf)Cl_2 (dppf : 1,1′-ferrocenediyl-*bis*(diphenylphosphine)) as catalyst in the presence of Na_2CO_3 and LiCl, to give the 4-azaindole intermediate **93** which was treated with TFA to remove the THP-protecting group leading to the 2,3-dipyridinyl-4-azaindole **94** in 40% yield for the two steps.

[27] R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689-6690.
[28] H. Koolman, T. Heinrich, H. Böttcher, W. Rautenberg, M. Reggelin, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1879-1882.



SCHEME 18

An original palladium-catalyzed cascade C-N cross-coupling/Heck reaction of alkenyl bromides with *ortho*-amino-bromopyridine derivatives using a $Pd_2(dba)_3$ (*tris*(dibenzylideneacetone)dipalladium) as palladium source with XPhos as the ligand in the presence of an excess of *tert*-BuOK afforded a straightforward access to substituted 4-, 5-, 6-, and 7-azaindoles **96**-**99** as presented in Scheme 19 with α-bromostyrene **95**.[29]



SCHEME 19

[29] M. J. D. Pires, D. L. Poeira, S. I. Purificação, M. M. B. Marques, *Org. Lett.* **2016**, *18*, 3250-3253.

Conclusion

From aminopyridines, Sonogashira, Larock-type, Heck, Suzuki and Cacchi reactions and more recently C-H activation have been successfully used for the preparation of azaindoles. New one-pot protocols involving metal-catalyzed cascade reactions have recently emerged to prepare functionalized azaindoles and will certainly have a great impact in Medicinal Chemistry.

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