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Recent Advances in the Synthesis of Pyrido[1,2-*a*]indoles

Yunxin Yao,^a Mouad Alami,^a Abdallah Hamze,^{a*} Olivier Provot^{a*}

Abstract: The pyrido[1,2-*a*]indole unit found in many organic compounds such as natural products, pharmaceuticals, and materials, has intensively stimulated the research of new synthetic pathways giving access to this heterocyclic nucleus in very recent years. In this review, the synthesis of pyrido[1,2-*a*]indoles will be divided into two parts, which concern accesses to this skeleton using or not metal catalysis.

1. INTRODUCTION

The pyrido[1,2-*a*]indole unit is a tricyclic aromatic nucleus combining an indole and a pyridine linked by the N5 and C9a atoms (Figure 1a). The pyrido[1,2-*a*]indole system and its analogues are found in a large variety of natural compounds (Figure 1b), including, for example, canthin-6-ones,¹ dibenzopyrrocoline² and homofascaplysin B and C.³ This chemical pattern is also present in many synthetic or natural organic compounds having, for example, anticancer (Figure 1c),^{4,5} antiinflammatory,^{6,7} and antisuppressive properties (Figure 1d).⁸ Moreover, pyrido[1,2-*a*]indoles also have a range of applications in other material applications as fluorescent molecular probes and sensors,^{9,10} and also as organic

semiconductors¹¹ (Figure 1e). In the present review, we report a compilation of the most significant and recent methods used these two last decades to synthesize variously substituted-pyrido[1,2-*a*]indoles including indolo(*iso*)quinolines when a benzene ring is linked to C6 and C7 or to C8 and C9. The synthesis of dihydropyrido[1,2-*a*]indoles, as logical precursors of pyrido[1,2-*a*]indoles by oxidation, will be treated too. The manuscript will be divided into two parts of equivalent size dealing, in section 2, with non-metallic methods and, in section 2, with organometallic accesses to pyrido[1,2-*a*]indoles.

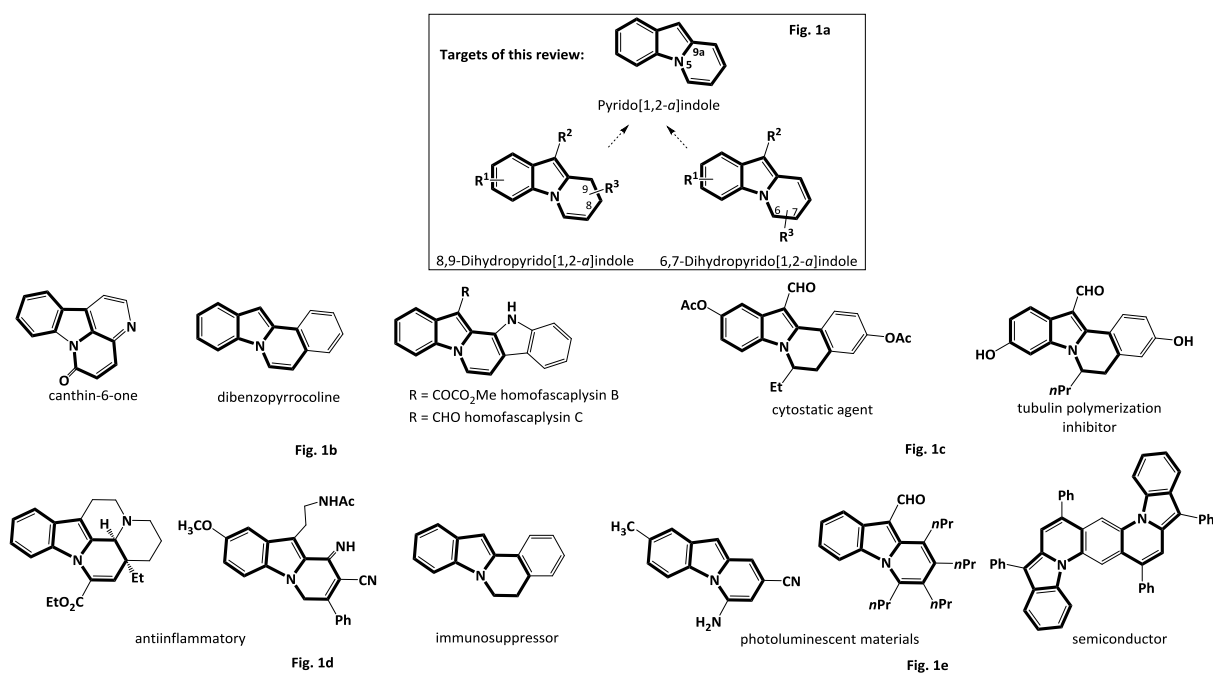


Figure 1. Pyrido[1,2-*a*]indoles and representative compounds

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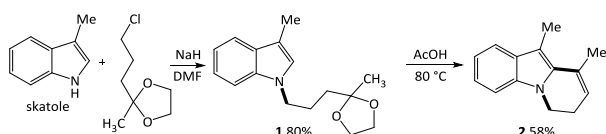
† Dedicated to Pr. R.C. Larock for his advances in heterocyclic chemistry.

Section 1 will deal successively with (i) reactions allowing the creation of pyridine and indole rings of the pyrido[1,2-*a*]indole system *via* electrophilic cyclizations, (ii) annulation reactions in the presence of alkynes or (iii) pre-formed benzyne, and (iv) cyclizations of triarylmethanols or triarylmethanes in medium acid. In section 3, metal-catalyzed cyclization reactions will be reported according to the type of metal used.

2. REACTIONS PROMOTED BY NON-METALLIC REAGENTS

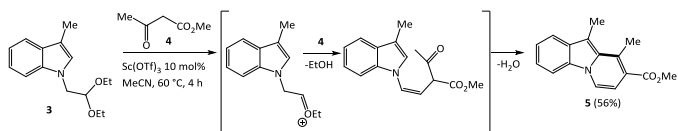
2.1 Creation of the pyridine C- or indole B-rings of pyrido[1,2-*a*]indoles by electrophilic cyclization.

As part of work dedicated to indole chemistry, Eberle reported the synthesis of 6,7-dihydropyrido[1,2-*a*]indole **2** with the formation of the C-ring from skatole in two steps¹² (Scheme 1).



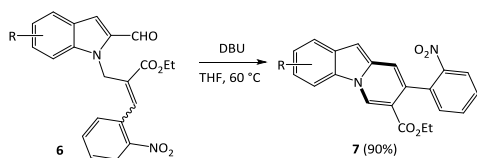
Scheme 1. Alkylation/deprotection/cyclization of skatole.

After *N*-alkylation of skatole by 5-chloro-2-pentanone ethylene ketal, the ketone's deprotection was studied in detail under mildly acidic conditions. In acetic acid, ethylene ketal **1** was transformed into 6,7-dihydro-9,10-dimethylpyrido[1,2-*a*]indole **2** after ketone deprotection and cyclization between the carbonyl function and C2 position of the indole. It should be noted that this rapid access to dihydropyridoindoles, which can be oxidized¹³ to pyrido[1,2-*a*]indoles, is however, limited to only skatole and C3-electron-rich indoles since the replacement of the methyl on C3 by H, CO₂Me or CH₂CO₂Me did not allow the cyclization.



Scheme 2. [4+2] Annulation of diethylacetal **3** in the presence of β -ketoester **4** and Sc(OTf)₃.

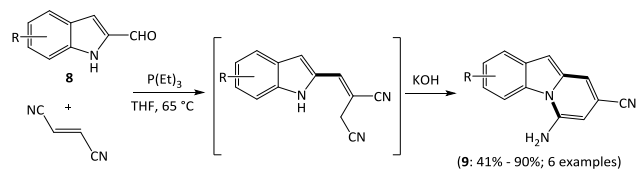
Comparable access was reported recently by Gu¹⁴ by [4+2] annulations (Scheme 2). In the presence of a catalytic amount of Sc(OTf)₃, diethylacetal **3** was activated into a 1,4-donor-acceptor oxonium intermediate, trapped by β -ketoester **4** in [4+2] annulation. Then pyrido[1,2-*a*]indole **5** was formed through an intramolecular condensation reaction. The study of this transformation giving access to various indolizines and, by extension, to pyridoindoles revealed that Sc(OTf)₃ catalyst was a superior Lewis-acid than FeCl₃, AlCl₃, Bi(OTf)₃, Fe(OTf)₃ and others to achieve this rapid transformation. The authors also proposed to achieve this reaction in a "one-pot" manner as 1,4-donor-acceptor reagents can also be prepared *via* an IBX oxidation of ethanolic precursors before reacting with β -ketoesters in the presence of the catalyst. As part of the anti-inflammatory and anti-nociceptive properties of melatonin analogs, Elmegeed et al prepared, using a similar approach, two substituted-pyridoindoles from melatonin⁶ which displayed anti-inflammatory and anti-nociceptive properties (2 examples 75% and 82%).



Scheme 3. Synthesis of **7**.

Kim proposed an annulation approach to build 7,8-disubstituted pyrido[1,2-*a*]indole **6** (Scheme 3) by cyclizing *N*-substituted-indole-2-carboxyaldehyde **6** in the presence of DBU to create the pyridine C-ring of pyrido[1,2-*a*]indole **7**.¹⁵

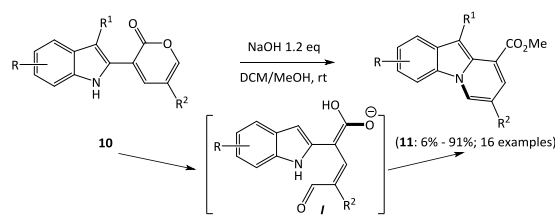
A new class of photo-luminescent materials that exhibit reversible pH-dependent optical properties with a blue shift in emission protonation,¹⁶ was synthesized by Bragg and Townsend's group starting from variously substituted 1*H*-indole-2-carbaldehydes (Scheme 4).



Scheme 4. Synthesis of photo-luminescent 5-amino-7-cyanopyridoindoles **9**.

The access to 6,9-disubstituted pyrido[1,2-*a*]indoles **9** proceeded *via* conjugate addition of triethylphosphine to fumaronitrile followed by a proton [1,2]-shift and a Wittig olefination in good to high yields. NMR analysis and acid titration indicate that C-protonation and loss of aromaticity of compounds **9** are at the origin of the observed photophysical changes.

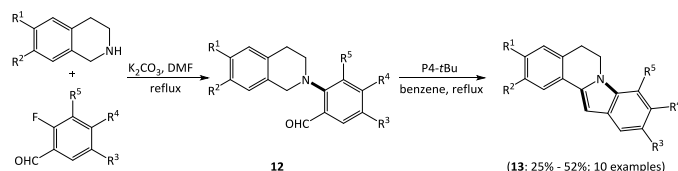
The C-ring of pyrido[1,2-*a*]indoles **11** was very recently built by a remodeling strategy of the 2*H*-pyran-2-one moiety of indoles **10** (Scheme 5).¹⁷



Scheme 5. Synthesis of 9-carboxymethylpyridoindoles **11** from indole-pyrones **10**.

NaOH or alcohols as nucleophiles attack the pyran-2-one ring to produce *in situ* a dienolate of type *I*, which is then transformed into pyridoindole **11** after the creation of the C-N bond. Thus, a variety of pyridoindole derivatives **11** having on C9 an ester function was rapidly synthesized in mild conditions with different functional groups on the A-, B- and C-rings.

We will conclude this sub-section dedicated to electrophilic cyclization reactions leading to pyrido[1,2-*a*]indoles with the creation of the pyridoindole B-ring with the synthesis of 5,6-dihydropyrido[1,2-*a*]indoles **13** having strong immunosuppressive activities⁸ (Scheme 6).



Scheme 6. Synthesis of immunosuppressive compounds **13**.

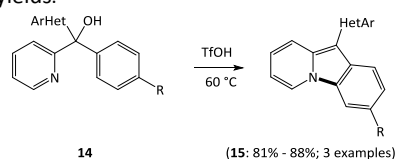
Unlike the previous examples depicted in schemes 1-5, the synthesis of 5,6-dihydropyrido[1,2-*a*]indoles **13** was carried out by building, during the last step, the B-ring of the indole nucleus and not the pyridine C-ring. *Ortho*-fluorobenzaldehydes reacted in hot DMF with tetrahydroisoquinolines by S_NAr to give **12** (37% to 66%).

It was shown that P4-tBu, a sterical phosphazine base generated a series of derivatives **13**, which exhibited immunosuppressive activity against IL-10 and IL12 (interleukins) and IFN- γ (interferon- γ).

In this part, the methods used to prepare pyrido[1,2-*a*]indoles and reduced analogs appear simple and easy to implement. However, access to the tricyclic nucleus occurs in two distinct steps (*N*-alkylation followed by electrophilic cyclization). The generalization of these rapid accesses to pyridoindoles through poly-functionalized molecules seems possible but has not been reported by the authors.

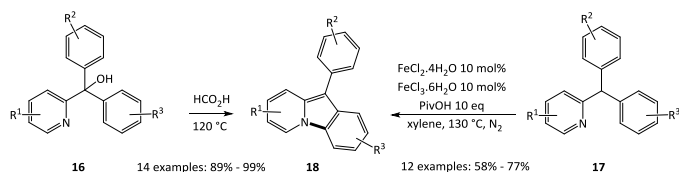
2.2 Cyclization of triarylmethanols and triarylmethanes allowing the synthesis of the B-ring of pyrido[1,2-*a*]indoles.

In 2011, Klumpp studied the reactivity of triarylmethanols in the presence of CF₃SO₃H at 60 °C (Scheme 7).¹⁸ It was shown that triarylmethanol derivatives of type **14** underwent cyclization reactions under acidic conditions to give 10-arylpyrido[1,2-*a*]indoles **15** with high yields.



Scheme 7. Cyclization of triarylcannabinols **14** in triflic acid.

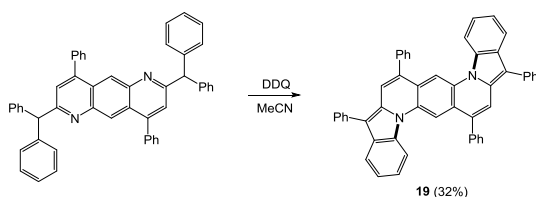
The same team extended the cyclization process used with tricationic superelectrophiles to tetra-, penta- and hexacationic electrophiles with success.¹⁹ However, on the contrary to tricationic (and more protonated) electrophilic cations, single pyridine containing triarylcannabinols did not give any cyclization products in triflic acid. This limitation was solved few years later by Sekar,²⁰ who showed that diaryl-heteroarylcarbinols **16**, at the origin of dicationic intermediates, cyclized well into pyrido[1,2-*a*]indoles **18** in formic acid (Scheme 8).



Scheme 8. Cyclization of triarylcannabinols **18**.

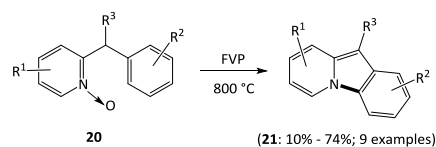
It was shown that the pyridine nitrogen of triaryl cannabinols acted as the nitrogen source to give pyrido[1,2-*a*]indoles **18** in high yields through aza-Nazarov type cyclization. It was also reported by the same team²¹ that 2-benzhydrylpyridines **17** gave the same products **18** with slightly lower yields in the presence of an iron bimetallic system under a nitrogen atmosphere (Scheme 8).

In view of synthesizing a new class of heteroatomic semiconductors of type **19**,²² Ahmed et al. reported that a pyridine-diphenyl containing triarylmethane derivative was successfully transformed into **19** (32%) via an oxidizing intramolecular cyclization using DDQ in MeCN (Scheme 9).



Scheme 9. Synthesis of semiconductor **19** by DDQ promoted intramolecular cyclization.

Earlier, Igeta reported the synthesis of a series of methylpyrido[1,2-*a*]indoles **21** by flash vacuum pyrolysis (FVP) of 2-benzylpyridine *N*-oxides **20** at 800 °C under 0.1 mm Hg (Scheme 10).²³

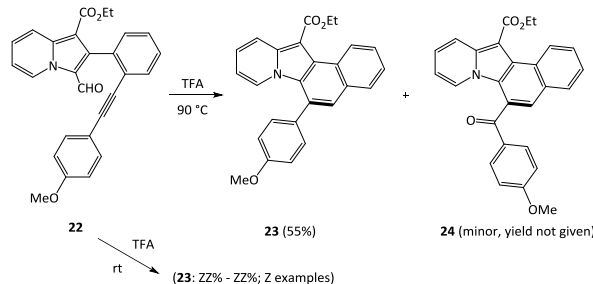


Scheme 10. Flash vacuum pyrolysis of 2-benzylpyridine *N*-oxides **20**

If this method is interesting from a chemical point of view, it does not seem reasonable to use it to prepare significant quantities of fragile pyridoindole substrates. It is noted that all pyrido[1,2-*a*]indole derivatives **21**, which were obtained, according to a radical pathway, in moderate yields, were appreciably unstable and were isolated by recrystallization or column chromatography on alumina. The synthesis of pyridoindole derivatives using triarylmethane carbinols (including one or two pyridine rings) or triarylmethanes allowed rapid access to complex molecules incorporating in structure the pyridoindole nucleus. However, if the synthesis of starting triarylcannabinols appears easy (from the reaction of di(het)arylketones with Grignard reagents), the acidic conditions used in this process (triflic acid or formic acid) are probably not be suitable for sensitive substrates. Concerning the intramolecular cyclization of triarylmethanes to produce pyrido[1,2-*a*]indoles, this reaction would deserve to be improved by finding satisfactory oxidizing conditions on a series of functionalized substrates.

2.3 Cyclization reactions in the presence of alkynes.

The construction of the A-ring of pyrido[1,2-*a*]indoles is poorly documented. Kim, during a study on the reactivity of 2-substituted indolizine-3-carbaldehyde **22** in hot TFA, observed the major formation of benzo[*e*]pyrido[1,2-*a*]indole **23** besides a small quantity of expected alkyne-carbonyl metathesis substrate **24** (Scheme 11).²⁴

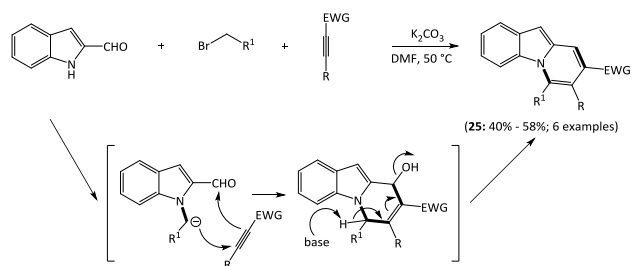


Scheme 11. Deformylative intramolecular hydroarylation of **23**: formation of the pyrido[1,2-*a*]indole A-ring.

By decreasing the temperature from 90 °C to rt, the ratio of **23/24** increased considerably. In this study, Kim also showed that Lewis acids such as In(OTf)₃, Bi(OTf)₃, and more interestingly AgOTf (2 eq) could replace TFA. The generality of the method using AgOTf in DCE was demonstrated through various substrates that were transformed into the expected pyridoindole derivatives. To explain this surprising transformation in TFA, it was suggested that an initial attack of the C3 site of indolizine **22** to the neighboring alkyne triple bond led to an indolizinium salt according to a 6-*endo-dig* process. A deformylation reaction by TfO⁻ restored the aromaticity of the pyridoindole system to produce **23**.

To create the C-ring of pyrido[1,2-*a*] indoles **25**, Zou et al. developed a "one-pot" multicomponent approach using as starting material,

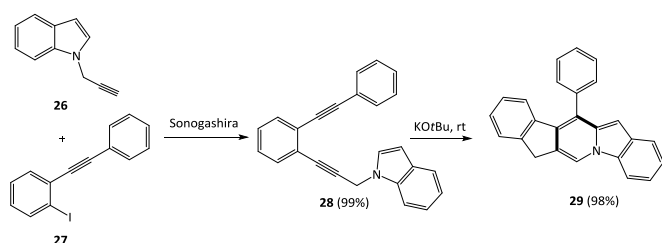
1*H*-indole-2-carboxaldehyde in the presence of alkynes and α -bromoketones (Scheme 12).²⁵



Scheme 12. “One pot” synthesis of pyrido[1,2-*a*]indoles **25**.

In a sequential manner, 1*H*-indole-2-carboxaldehyde was first *N*-alkylated with α -bromoketones in the presence of K_2CO_3 , and the resulting anion added next to electron-poor alkynes. The newly formed anion intermediates reacted on the C2 aldehyde function to give after aromatization the expected pyridoindoles **25**.

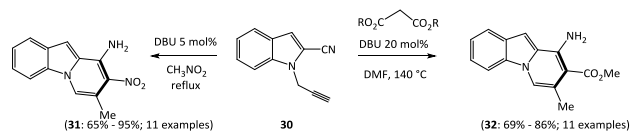
Wang proposed another access to [1,2-*a*]pyridoindole **29** from the cyclization of indole **28** (Scheme 13).²⁶



Scheme 13. Cascade cyclization reaction of indole **28** in basic media.

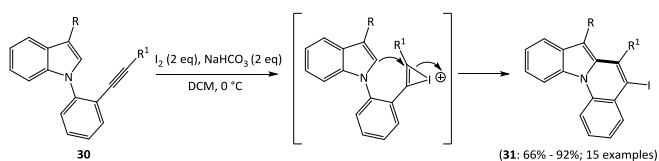
A Sonogashira coupling reaction between indole **26** and aryl iodide **27** led to diene compound **28** (99%). Treatment of **28** with KOtBu at rt for 48 h produced the indeno-fused pyrido[1,2-*a*]indole **29** in an excellent yield of 98%. Authors proposed that indole **28** underwent a KOtBu-promoted 1,3-prototropic rearrangement to the corresponding allene intermediate, which cyclized into **29** after a cascade reaction process.

To prepare 6,7,8-trisubstituted pyridoindoles, Voskressensky reported very recently an elegant method using 1-(prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile **30** as starting material (Scheme 14).²⁷



Scheme 14. Aza-Henri and aza-Knoevenagel cyclization reactions.

Optimization of aza-Henry cyclization reaction conditions revealed that 7-methyl-8-nitropyrido[1,2-*a*]indol-9-amine **31** were obtained in excellent yields when indole **30** was heated under reflux for one h in the presence of 5 mol% of DBU. Replacing CH_3NO_2 by malonate anions using DBU (20 mol%) in hot DMF led to an Aza-Knoevenagel/cyclization domino process, **32** were obtained in satisfactory yields.



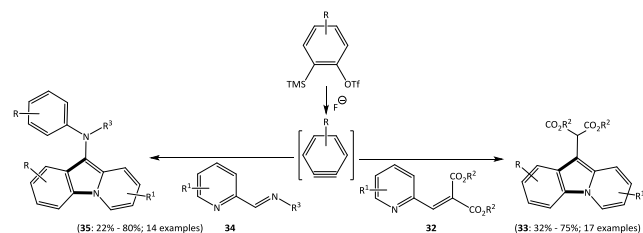
Scheme 15. Electrophilic iodo-cyclization reactions of alkynes **30**.

To close this section devoted to reactions involving cyclization reactions in the presence of alkynes, we now present the work of Verma, which used I_2 as an activating agent of alkynes triple bonds (Scheme 15).²⁸ In this work, the authors studied the halo-cyclization reaction of indole-alkynes **30** in the presence of various halogenation reagents such as I_2 , ICl, NBS. Similarly to the halocyclization reactions developed by Larock, the use of I_2 (2 eq), $NaHCO_3$ (2 eq) in DCM at 0° C gave the best results to convert **30** into **31**.²⁹ Initially, I_2 activates the alkyne triple bond to give an iodonium complex, which undergoes a nucleophilic attack by the C2 of indole. A 6-*endo-dig* cyclization occurs regioselectively to provide the expected heterocycles having an iodine atom useful for subsequent diversifications. It was showed that starting indoles **30** may be substituted or not on the C3-position and that substituents linked to the alkyne triple bond can be of aromatic or heteroaromatic nature.

In this section involving alkynes, which are interesting electrophiles in cyclization reactions, benzyne have also been studied in the cyclization process as attractive electrophiles and will be presented in the following section.

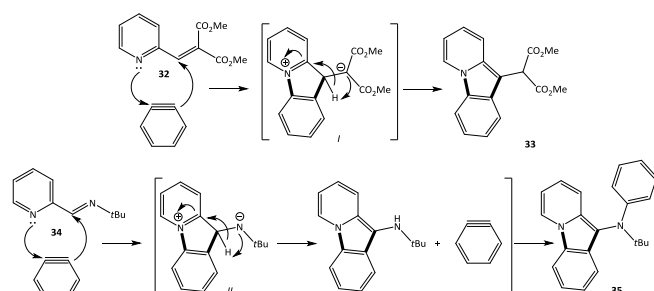
2.4 Cyclization reactions with benzyne.

The construction of the B-ring of various pyrido[1,2-*a*]indoles was reported in 2012 by Larock from addition reactions of 2-substituted pyridines with arynes used as electrophilic-nucleophilic reagents (Scheme 16).³⁰



Scheme 16. Synthesis of pyridoindoles **33** and **35** from arynes and 2-(pyridin-2-yl(methylene)malonates **32** and *N*-pyridin-2-yl-methanimines **34**.

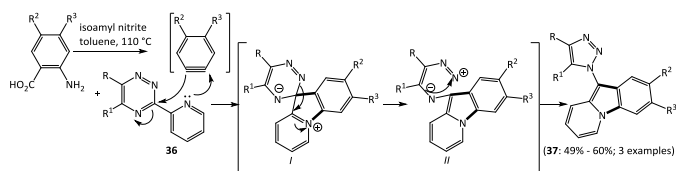
Arynes substrates, which were prepared *in situ* using silylated Kobayashi's precursors³¹ and fluorides, reacted well with strong electrophiles as dialkyl 2-(pyridin-2-ylmethylene)malonates **32** to give the expected 10-substituted pyridoindoles **33**. Similarly, using an excess of arynes, expected pyridoindoles **35** bearing on C10 disubstituted amines were obtained by reacting arynes with *N*-pyridin-2-yl-methanimines **34** with remarkable diversity and good to high yields. Concerning the mechanism, the pyridyl nitrogen attacks the electrophilic aryne to give a vinylic anion which then reacts on the Michael acceptor to give intermediate *I*. After prototropy and aromatization, *I* lead to pyridoindoles **33** (Scheme 17).



Scheme 17. Proposed mechanism for formation of substituted pyridoindoles **33** and **35**.

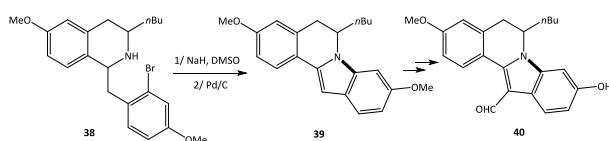
Arynes-mediated rearrangement of 2-substituted pyridines was later studied in detail by a Russian team that used various 2-pyridyl-

1,2,4-triazines as benzyne partners (Scheme 18).³² Arynes, which were prepared *in situ* in hot toluene with isoamyl nitrite³³ and anthranilic acids, reacted with a wide range of 3-(2-pyridyl)-1,2,4-triazines of type **36** to give in moderate to good yields, 10-substituted pyrido[1,2,4-*a*]indoles **37**. It is of note that some polyfluorinated pyridoindoles **37** exhibited a strong fluorescence with emission of green light. The proposed mechanism of this [2+3] cycloaddition starts as above for malonates **32** and imines **34** (see Scheme 16). Then cleavage of N3-C4 bond of extremely unstable intermediate *I* occurs to give *II* which rearranges by creating a *N-N* bond and furnishes pyridoindole **37** having on C10 a substituted 1,2,3-triazole.



Scheme 18. Synthesis and selection of pyridoindoles **37** prepared from aroynes and 2-pyridyl-1,2,4-triazines.

In a medicinal chemistry project, von Angerer et al. prepared the 6,7-dihydro[1,2-*a*]pyridoindole derivative **40** as a potent tubulin polymerization inhibitor by creating the pyridoindole B-ring through a benzyne intermediate (Scheme 19).⁵ In the presence of NaH, used as a strong base, tetrahydroisoquinoline **38** was transformed into dihydropyridoindole **39** by a benzyne cyclization process. Then, a formylation reaction followed by a selective *O*-demethylation reaction led to tubulin polymerization inhibitor **40** ($IC_{50} = 8.9 \mu M$).



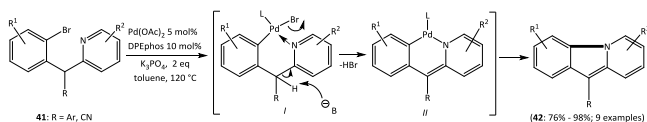
Scheme 19. Synthesis of tubulin inhibitor **40**.

After having regrouped in this section, the recent reactions which do not use metals, we will now examine in the following section 3, accesses to pyridoindoles *via* organometallic processes which will be classified according to the metal used even if the chronology of these discoveries will not be respected.

3. ORGANOMETALLIC METHODOLOGIES

3.1 Palladium-catalyzed transformations

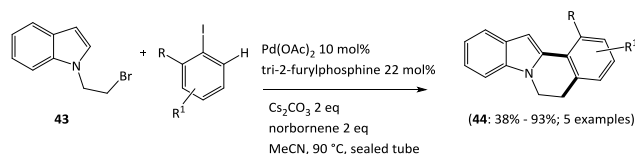
Gevorgyan reported the synthesis of the B-ring of pyrido[1,2-*a*]indoles **42** from the Pd-catalyzed cyclization of *ortho*-picolylbromoarenes **41** (Scheme 20).³⁴



Scheme 20. Pd-catalyzed cyclization of **41**.

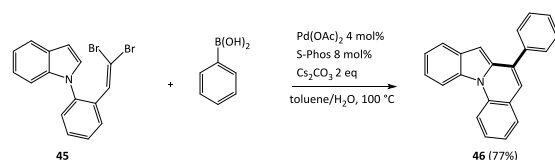
It was found that if the nitrogen atom of **41** can act as a ligand of Pd(PPh₃)₄ in the cyclization reaction, the best association producing pyridoindoles combined Pd(OAc)₂ with DPEphos. In the presence of K₃PO₄ as a base in hot toluene, a series of substituted pyridoindoles **42** with phenyl or a cyano-substituent on C10 were synthesized with excellent yields. The reaction underwent efficient cyclization providing a small library of pyridoindoles, but only aryl- and CN-groups have been studied. Most of the palladium-catalyzed reactions giving access to the pyridoindole unit consists of creating the C ring of this nucleus from a *N*-functionalized indole.

Thus, Lautens reported the synthesis of 6,7-dihydroindoles **44** possibly oxidizable into pyrido[1,2-*a*]indoles from the Pd-catalyzed reaction of 1-(2-bromoethyl)-1*H*-indole **43** with aryl iodides in the presence of norbornene (Scheme 21).³⁵



Scheme 21. Synthesis of 6,7-dihydropyrido[1,2-*a*]indoles **44** *via* Pd-catalyzed tandem alkylation/direct arylation reaction.

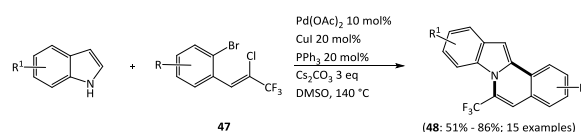
It was demonstrated that both electron-donating and electron-withdrawing groups are well tolerated on indoles and aryl iodides. Moreover, the process was successfully transposed to 1-(2-bromopropyl)-1*H*-indoles to give a variety of seven-membered C-ring annulated indoles. However, this process is probably limited to aryl iodides having on *ortho*-position a H atom (due to the reaction mechanism³⁵) on *ortho'*-position a substituent (R on Scheme 21) different of H to avoid possible mixtures of isomers. A few years after, Lautens et al. studied, in an article devoted to the synthesis of pyrrolo[1,2-*a*]quinolines, another tandem reaction involving dibromovinyl indole **45** (Scheme 22).³⁶



Scheme 22. Suzuki/arylation tandem reaction of dibromovinyl indole **45**.

It was demonstrated that, in the presence of Pd(OAc)₂, S-Phos as a ligand, Cs₂CO₃ as a base in a mixture toluene/H₂O, the tandem reaction began (*i*) by the Suzuki coupling reaction on the most accessible bromine atom followed by (*ii*) a C2 arylation reaction. Water has been shown to pre-activate the catalyst and thereby increase the Suzuki reaction rate and, therefore, decrease the by-products' formation in the tandem process.

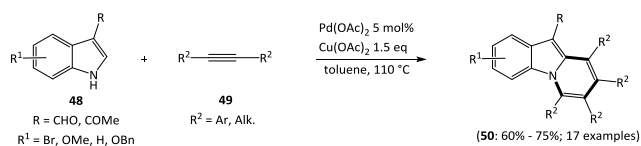
Few years after this work, Zhang reported the synthesis of various indolo[2,1-*a*]isoquinolines **48** having a pyrido[1,2-*a*]indole core from a Pd(OAc)₂/CuI catalyzed tandem reaction of indoles with *ortho*-bromo-chlorovinylbenzenes **47** (Scheme 23).³⁷



Scheme 23. Tandem reaction of indoles with *ortho*-bromo-chlorovinylindoles **47**.

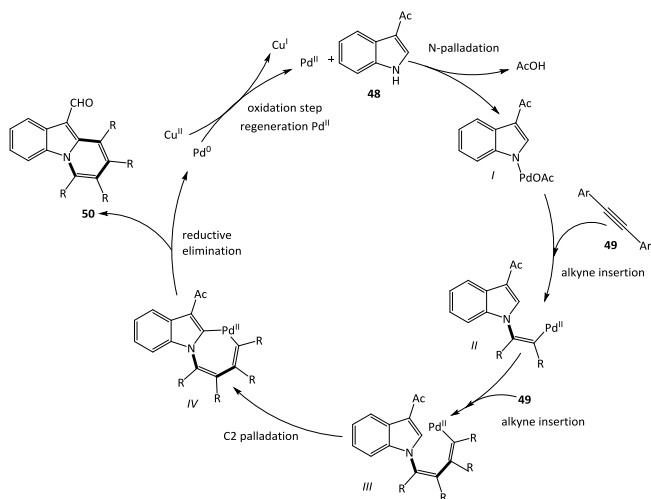
It has been shown that this tandem reaction is optimal by associating to Pd(OAc)₂, CuI as co-catalyst, and PPh₃ as a ligand in the presence of Cs₂CO₃ in hot DMSO. The reaction worked well with electron-rich and electron-poor indoles and bromobenzene derivatives to give the expected products **48** with good yields. Authors proved that this tandem reaction starts with the Cu-catalyzed *N*-alkenylation of the indolic nitrogen atom³⁸ followed by a Pd-catalyzed cyclization reaction on the C2 position of the indole ring. Pyrroles as nucleophilic and electrophilic nuclei are also well-tolerated in the tandem reaction to replace indoles to give the expected compounds with moderate to good yields.

In view of synthesizing highly fluorescent heterocycles, Patra and Kundu reported a “one-pot” synthesis of highly substituted pyrido[1,2-*a*]indoles **50** obtained from the reaction of 3-acylindoles **48** with diphenylacetylenes **49** (Scheme 24).¹⁰



Scheme 24. Synthesis of pyridoindoles **50** through CH/NH activation.

A series of ¹H NMR measurements showed that the Pd-catalyst first activates the NH bond of the 3-formyl indole **48** and the C2-H bond remained unaffected to give an indole-1-yl-palladium intermediate *I*. Then two alkyne molecules **49** inserts between the vinylpalladium *II* intermediates. A seven-membered palladacycle of type *IV* is then formed by intramolecular C2 alkenylation to furnish after reductive elimination, pyridoindoles **50** together with Pd(0) oxidized into Pd(II) by Cu(OAc)₂ and therefore able to continue the catalytic palladacycle (Scheme 25).

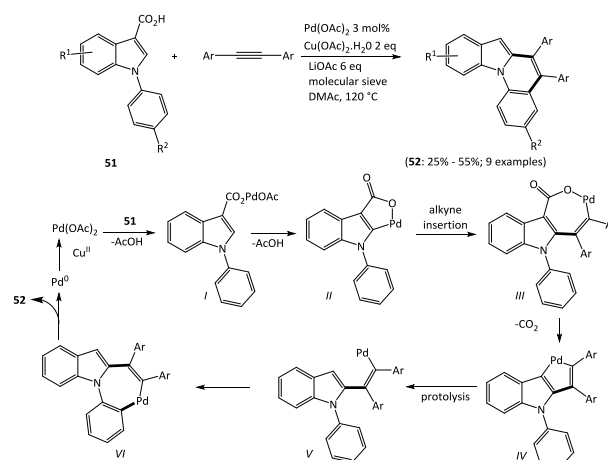


Scheme 25. Mechanism for the Pd/Cu formation of pyridoindoles **50**.

Some of these pyridoindoles **50** which exhibited a high fluorescence quantum yield, were chosen for cellular imaging. It was shown that, at a concentration superior to 100 μM, HeLa (human cancer) cells incubated with the most active pyridoindole **50** (R = CHO, R¹ = H, R² = *n*Pr) for 2 h, died. At inferior concentrations, under a fluorescence microscope, this cytotoxic pyridoindole was localized in the nucleus of the cancer cells. Moreover, the authors also demonstrated that, when this pyridoindole (PI) was coupled on C10-position with a tetraphenylethylene (TE) moiety, PITE exhibited strong reversible pH-dependent fluorescence in both solution and the solid-state and displayed interesting properties for a study of extensive microscopic fluorescence.³⁹

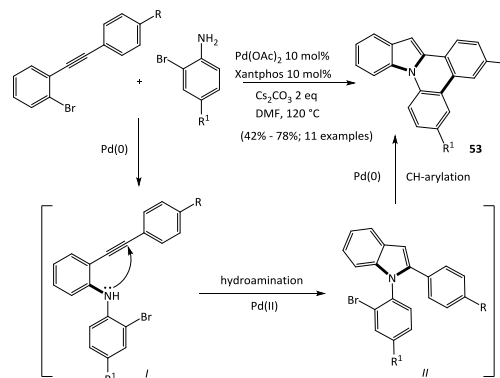
In 2009, a series of 5,6-diarylindolo[1,2-*a*]quinolines **52** were synthesized by Miura by coupling 1-arylindole-3-carboxylic acids **51** with diarylacetylenes (Scheme 26).⁴⁰ The reaction of **51** with the palladium catalyst starts by the coordination of the carboxyl oxygen to Pd(OAc)₂ with liberation of AcOH to give a palladium(II) carboxylate *I*, which directed palladation at the C2-position forming a 5-membered palladacycle intermediate *II*. A subsequent alkyne insertion followed by a decarboxylation occurs to give intermediate *IV*. A protolysis reaction would give a vinylpalladium intermediate *V*

and then 5,6-diarylindolo[1,2-*a*]quinoline **52** after a subsequent cyclopalladation on the phenyl group followed by reductive elimination of the Pd-catalyst. It is of note that most 5,6-diarylindolo[1,2-*a*]quinolines **52** showed solid-state fluorescence in a range of 470-560 nm.



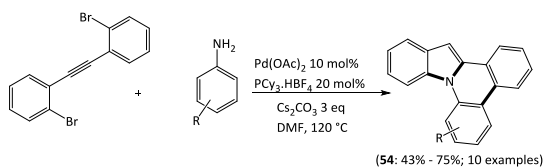
Scheme 26. Synthesis of 5,6-diarylindolo[1,2-*a*]quinolines **52** under Pd/Cu catalysis and mechanism of action.

The construction of B- then C-rings of indolophenanthridines **53** was carried out from *ortho*-bromodiarylalkynes and *ortho*-bromoanilines by a Pd-catalyzed process involving successively (i) a Buchwald-Hartwig coupling reaction, (ii) a hydroamination reaction, and a (iii) C-H arylation (Scheme 27).⁴¹



Scheme 27. Synthesis of pyridoindoles **53** from *ortho*-bromoanilines and *ortho*-bromodiarylalkynes.

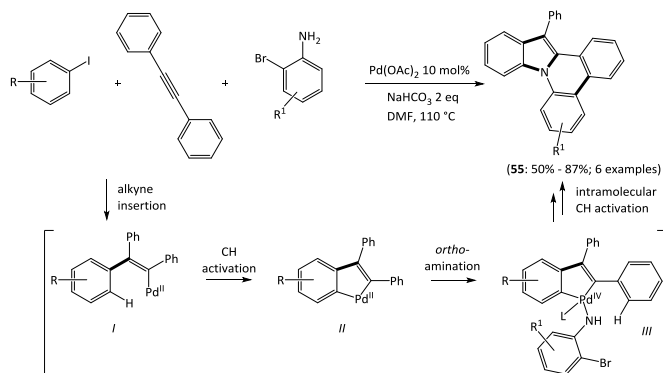
In this domino process, Pd(OAc)₂ revealed the more efficient Pd-catalyst when associated with 10 mol% of Xantphos or DPEphos in the presence of Cs₂CO₃ as the base in hot DMF. To confirm the reaction's mechanism proposed in Scheme 27, the authors isolated intermediate *II*, and ¹H NMR confirmed its structure. The authors also reported that this 3-step domino process takes place with very acceptable yields but remains limited to *ortho*-brominated diarylalkynes, their chlorinated homologues not allowing this type of transformation. Keeping this idea in mind, it was also reported that anilines reacted well with *ortho-ortho'*-diarylalkynes to give indolophenanthridines **54** in a complementary domino process (Scheme 28).



Scheme 28. Synthesis of indolophenanthridines **54** from 1,2-bis-(2-bromophenyl)ethyne and anilines.

By replacing Xantphos with $\text{Cy}_3\text{P}\cdot\text{HBF}_4$ and increasing the amount of Cs_2CO_3 , indolo[1,2-*f*]phenanthridines **54** were obtained in moderate to good yields. Comparison of the two strategies in view of synthesizing same compounds indicates that slightly better yields were obtained when *ortho*-bromoanilines were reacted under Pd-catalysis with *ortho*-bromodiarylalynes.

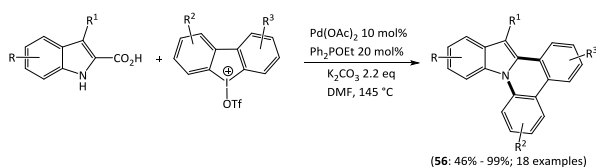
Recently, Habibi reported the synthesis of phenanthridines **55** from the Pd-catalyzed reaction of aryl iodides with internal alkynes and *ortho*-bromoanilines (Scheme 29).⁴² If there are some similarities with the previous work (creation of the B- then C-ring of indolophenanthridines **55** with similar intermediates, no additional Pd-ligand is necessary to build the indolophenanthridine system *via* the creation of four C-C and C-N bonds.



Scheme 29. Synthesis of **55** from a domino process between aryl iodides and internal alkynes and *ortho*-bromoanilines.

Interestingly, unsymmetrical 1-methyl-2-phenyl-acetylene reacted regioselectively for steric hindrance considerations in this domino process, not limiting this tandem reaction to the use of diphenylacetylene. This multi-component reaction begins with a carbopalladation reaction with diphenylacetylene and an aryl-palladium species to give styryl palladium(II) intermediate of type *I*. After C-H activation, this latter evolves into a 5-membered palladacycle *II*, which is trapped by anilines to give a Pd(IV) intermediate *III*. After reductive elimination and regeneration of Pd(0), intramolecular activation of C-H occurs to give **55**.

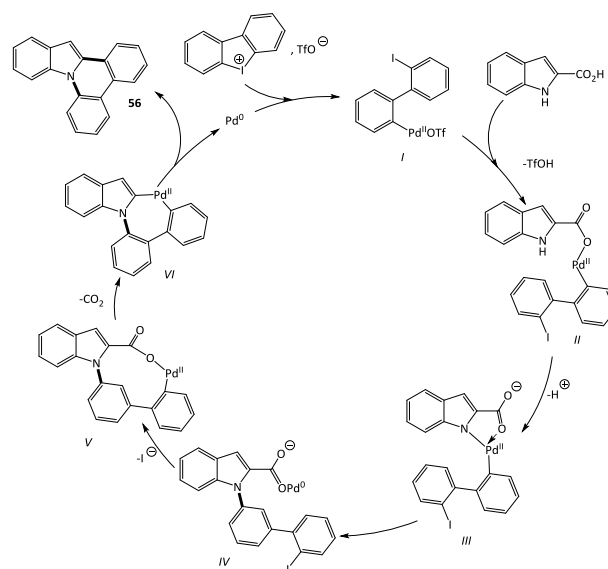
The last example of this section devoted to pyrido[1,2-*a*]indoles synthesis using Pd as catalyst, concerns the use of cyclic diaryliodonium salts in the presence of indole-2-carboxylic acids (Scheme 30).⁴³



Scheme 30. Synthesis of pyrido[1,2-*f*]phenanthridines **56** by N1-C2 annulation.

This cascade decarboxylative annulation, which used diaryliodonium salts, afforded indolo-phenanthridines **56** with excellent yields and

great functional group tolerance and diversity. Compared with the two last processes giving access to pyrido[1,2-*f*]phenanthridines, Zhang's protocol creating two novels C-N and C-C bonds (Scheme 31), gave the best yield for identical compounds. As above, $\text{Pd}(\text{OAc})_2$ and hot DMF were used in these three processes as catalyst and solvent of choice, respectively. The mechanism of this reaction, where the iodonium salt acts as a clamp between the N1 and C2 atoms of the indole nucleus, starts by a Pd(0)/Pd(II) catalytic cycle. First, in the presence of $\text{Pd}(\text{OAc})_2$, the diphenyliodonium salt opens to give intermediate *I*, which is added to the indole-2-carboxylic acid to generate *II*.

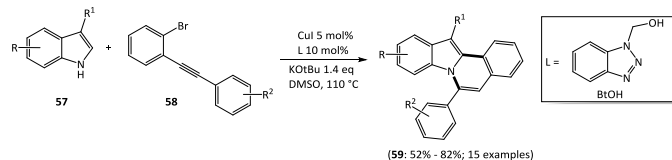


Scheme 31. Proposed mechanism for the synthesis of **56** using iodonium salts.

The N-H activation next step leads to a cyclopalladate(II) species of type *III*, which gives after reductive elimination *IV* and finally pyridoindole **56** after a cascade of oxidative addition, decarboxylation, and reductive elimination.

3.2 Copper-catalyzed transformations.

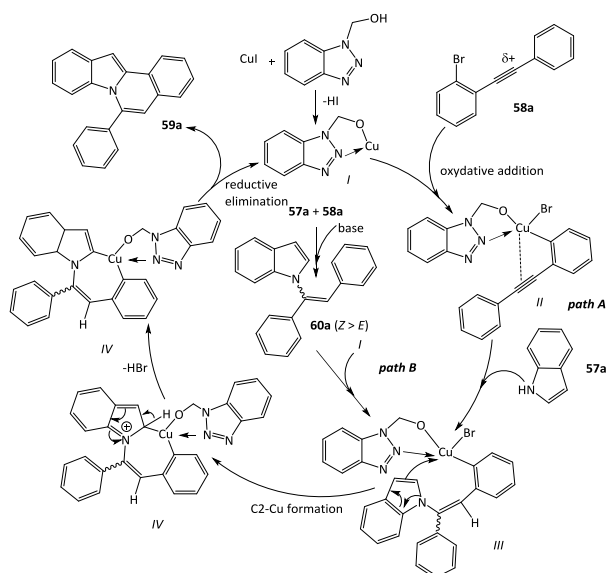
In continuation to *N*-arylation reactions using copper as a catalyst, benzotriazole as a ligand⁴⁴ and alkynes as substrates, Verma and Larock in 2009, developed an elegant process to prepare a variety of pyrido[1,2-*a*]indoles **59** according to a "one-pot" reaction between indoles **57** having no substituent on N1 and C2 and *ortho*-bromodiarylalynes **58** (Scheme 32).⁴⁵



Scheme 32. CuI/BtOH -catalyzed synthesis of pyridoindoles **59**.

The mechanism of this transformation creating the ring C of pyridoindoles was the subject of intensive and convincing works orchestrated by Verma *et al.*^{45a} First, according to the structure of compounds **59** determined by ^1H NMR and X-ray crystallographic analyzes, authors demonstrated that this process does not take place by an *N*-arylation mechanism followed by an electrophilic cyclization. Following these results, two possible mechanisms were proposed (Scheme 33). In *path A*, CuI and BtOH generated a Cu-complex *I* under basic conditions. After oxidative addition, *I* gave *II*

in which the alkyne triple bond was pre-activated by the copper atom. Then, regioselective nucleophilic addition of indole **57a** occurs on the most electrophilic alkyne atom⁴⁶ of *ortho*-substituted compound **58a** to provide *III*. A C2-Cu bond is then created, followed by HBr elimination giving *V* and then **59a** ($R = R^1 = R^2 = H$) together with the regeneration of the Cu-complex *I* after reductive elimination. However, the formation of *III* can also be explained (*path B*) in the absence of CuI and BtOH by a first hydroamination reaction between **57a** and **58a** to give enamine **60a** followed by oxidative addition of Cu-complex *I*. In *path A*, CuI and BtOH generated a Cu-complex *I* under basic Verma, after having isolated a series of enamines of type **60** for which the *Z/E*



Scheme 33. Plausible mechanisms for the CuI/BtOH formation of pyridoindole **59a**.

selectivity was studied showed that such enamines were formed in the only presence of the base and the absence of CuI and BtOH. This result strongly suggests that *path B* is undoubtedly the more plausible access leading to pyridoindole **59a**.

The formation of the B-ring of indolo[2,1-*a*]isoquinolines **63** by Cu-catalyzed oxidative desiazo[4+1] annulation was reported recently by Jiang (Scheme 34).⁴⁷ In the presence of *t*BuOOH as the radical source and $\text{Cu}(\text{MeCN})_4\text{PF}_6$ as the catalyst, *N*-aryl-1,2,3,4-tetrahydroisoquinolines (*N*-ArTHIQs) **61** reacted with α -diazoketones **62** to give indolo[2,1-*a*]isoquinolines **63** in an [4+1] annulation reaction. As it can be seen in Scheme 34, electronic groups of different nature were well tolerated on aromatic rings at different positions. It is of note that this oxidative [4+1] annulation reaction remained effective at a millimole scale. It was shown that the addition in the media of TEMPO or BHT as radical scavengers decreased or suppressed the efficiency of the method suggesting a possible radical mechanism (Scheme 34). In the presence of Cu(II) and *t*BuOOH, a single electron is transferred (SET) from Cu(II) and **61** to give *I*, which lose a proton to provide a stabilized benzylic radical

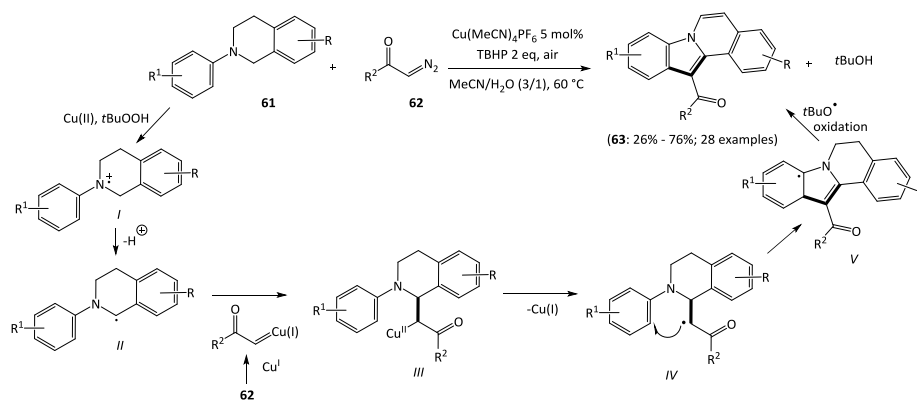
II. This latter reacts with a copper-carbene species, generated from the reaction of diazoketone **62** and Cu(I), to yield key organocopper intermediate *III*. A C-C bond is then created according to a 5-*endo-trig* cyclization to form the B-ring of the pyridoindole skeleton *IV* and regenerating the CuI catalyst. A subsequent H-abstraction in the presence of *t*BuO furnishes **63** after an ultimate oxidative dehydrogenation reaction.

In 2020, Zhao reported a copper-catalyzed cascade cyclization reaction between enaminones **64** and *in situ* generated symmetrical electron-poor diynes **67** to create successively the C- and B- rings of pyrido[1,2-*a*]indoles **64** (Scheme 35).⁴⁸ Examination of the reaction conditions revealed that CuI was superior to CuCl, CuBr, CuOAc, or $\text{Co}(\text{OAc})_2$. Also 2,2'-bipyridine was more efficient than its substituted congeners to achieve this cascade cyclization reaction. Under optimized conditions, various pyridoindoles **66** were obtained after creating four novel bonds with good yields and interesting functional group diversity. It was demonstrated that this process fails in the absence of oxygen and that air as an oxidant is more efficient than pure oxygen. The mechanism starts with a homocoupling reaction of terminal alkynes under CuI catalysis and air leading to diynes of type **67**. The authors demonstrated that the *in-situ* synthesis of compounds **64** is more advantageous than unstable pre-formed diynes to achieve these reactions. Then, the nitrogen atom of enaminone **64** or enaminoester derivatives attacks the C-C triple bond of diynes previously activated by CuI to give intermediates *I* then *II* after a second cyclization reaction realized according to a 6-*endo-dig* fashion rather than a 5-*exo-dig* mode. After protonation, *II* leads to *III*, which undergoes an oxidative insertion to form a six-membered Cu(III)-cycle *IV*. Aromatization of *IV* with the help of iodides and elimination of HI furnishes *V* then **66** after reductive elimination and regeneration of the CuI catalyst.

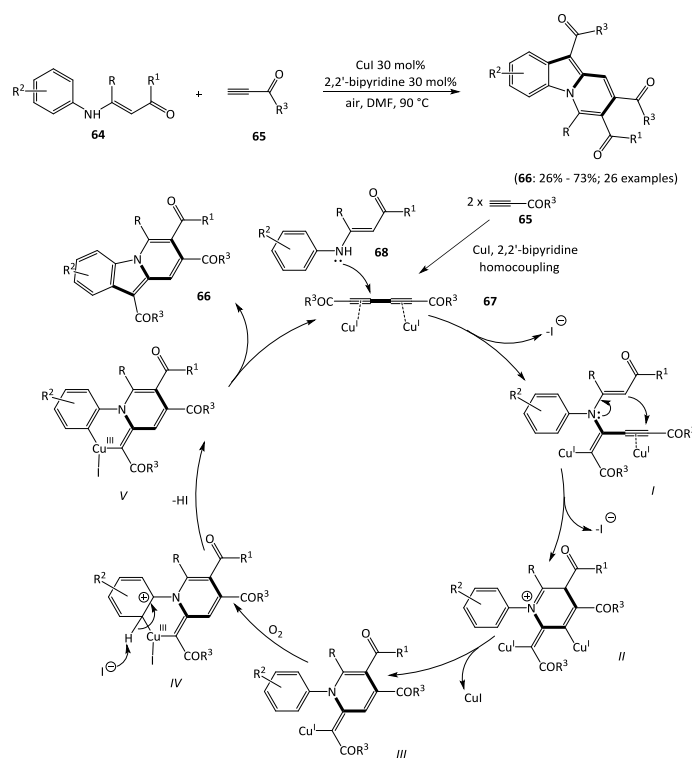
3.3 Rhodium-catalyzed transformations

Rhodium is, along with palladium, the most metal used in recent years to build the pyrido[1,2-*a*]indole unit. Most of the methodologies employed require as starting materials, an indole nucleus having no substituent on N1 and/or on C2 as the nucleophile reagent and an alkyne substrate activated by the rhodium catalyst as an electrophile.

In 2015, You et al. developed a regioselective Rh(III)-catalyzed C-H activation/cyclization process to prepare indolo[1,2-*a*]quinolines **69** using internal alkynes and indole-3-carbaldehydes **68** in which the aldehyde function served as a traceless directing group (Scheme 36).⁴⁹ The best conditions found to achieve this transformation used $[\text{Cp}^*\text{RhCl}_2]_2$ as catalyst associated with $\text{Cu}(\text{OAc})_2$ as oxidant and CsOPiv as an additive in hot dioxane. Under these conditions, electron-rich and electron-poor indoylaldehydes **68** were found to be useful to realize this transformation. Similarly, variously substituted aryl- and heteroaryl-nuclei were well tolerated on the nitrogen N1 atom of **68**.



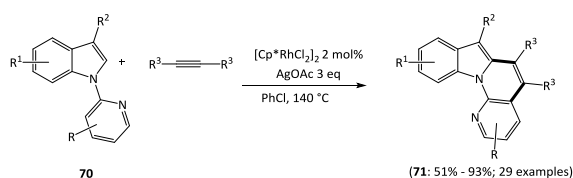
Scheme 34. Synthesis of **63** and proposed mechanism.



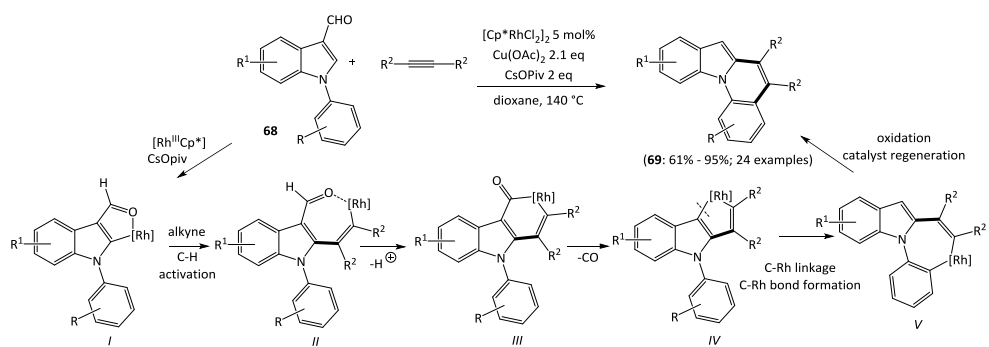
Scheme 35. Synthesis of poly-substituted pyrido[1,2-*a*]indoles **66** and proposed mechanism.

The use of functionalized internal symmetrical alkylalkynes was also permitted to give indolo[1,2-*a*]quinolines **69** in good yields, but the reaction gave a mixture of regioisomers with a low selectivity when 1-phenyl-2-ethylacetylene as unsymmetrical alkyne was used. In the presence of the Rh-catalyst and CsOPiv,⁴⁹ a five-membered rhodacycle *I* is certainly formed, which then inserts diarylalkyne to give a seven-membered rhodacycle of type *II*. Subsequent cleavage of the aldehyde C-H bond occurs on *II* to furnish a six-membered rhodacycle *III*, which undergoes a decarbonylation reaction. After protonolysis and rearrangement, the resulting 5-membered rhodacycle *IV* is transformed onto a seven-membered rhodacycle *V*, which is the precursor of **69** after reductive elimination and re-oxidation of the rhodium-catalyst. The same year, Miura et al. proposed a similar approach to prepare indolo[1,2-*a*][1,8]naphthyridines **71** from the Rh-catalyzed dehydrogenative reaction of *N*-pyridylindoles **70** with diarylalkynes (Scheme 37).⁵⁰ In this exquisite process, the nitrogen atom of the pyridyl moiety was

first used to activate the C2-H bond *via* a coordination to the rhodium catalyst to afford, after alkyne insertion, a 7-membered rhodacycle.⁵¹ After protonolysis, a rollover cyclometallation step takes place to allow the C-cycle creation, after reductive elimination and regeneration of the catalyst by oxidation.

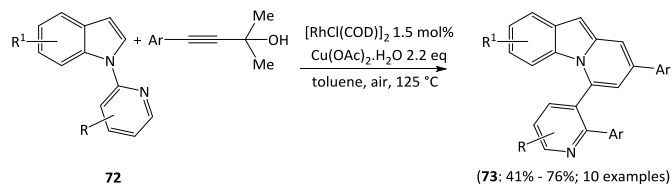


Scheme 37. Synthesis of **71** between *N*-pyridylindoles **70** from a dehydrogenative coupling reaction.



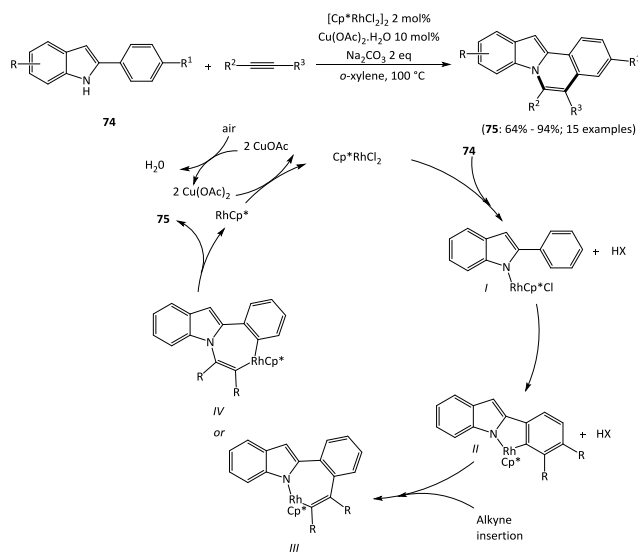
Scheme 36. Synthesis of indolo[1,2-*a*]quinolines **69** through C-H activation/cyclization of indoyl aldehydes **68** under Rh-catalysis.

In 2015, Wen et al. reported the synthesis of pyrido[1,2-*a*]indoles **73** also using *N*-pyridylindoles **72** with γ -substituted propargyl alcohols under Rh-catalysis (Scheme 38).⁵² This unusual cascade transformations involve the cleavage of six bonds (two C-H, three C-C, one C-N) and the formation of seven bonds (two C-H, four C-C, one C-N).



Scheme 38. Synthesis of 6,8-diarylsubstituted pyrido[1,2-*a*]indoles **73** from 1-(pyridin-2-yl)1*H*-indoles **72** and γ -propargyl alcohols.

Substituents of different nature are well tolerated on the indole nucleus and the pyridine ring even if the C5-position is preferential for steric considerations. Several experiments were carried out to explain this intriguing process, but it is clear that the first step consists of the alkynylation of the C2-position of the indole ring, the following transformations giving access to the pyridoindole skeleton having a 3-substituted pyridine **72** remain unclear. It is also possible to build the pyridoindole unit from indoles having a free NH and a (substituted)phenyl on the C2-position. To this end, Miura et al. proposed a versatile synthesis of indoloisoquinolines **75** having in structure the pyridoindole skeleton, from coupling 2-phenylindoles **74**, with internal alkynes (Scheme 39).⁵³

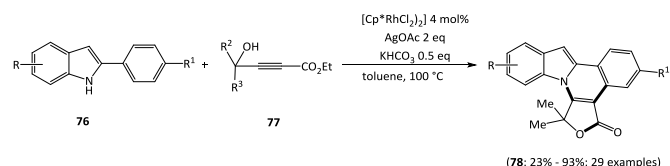


Scheme 39. Synthesis of **75** and proposed mechanism.

To achieve this transformation on a model substrate, the best conditions associated $[\text{Cp}^*\text{RhCl}_2]$ as the catalyst with AgOAc or $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as oxidizing agents in the presence of Na_2CO_3 as the base in hot *o*-xylene. It was demonstrated that the reaction worked well under a mixture (N_2/air : 5/1) and that the copper co-oxidant increased the yield of the coupling reaction considerably. Examination of the reaction's scope showed that various functional groups of different natures were well tolerated on the indole and the aromatic rings linked to the C-C alkyne triple bond. From a mechanistic point of view, the first step of this transformation is the coordination of the nitrogen atom of indole with the Rh(III) catalyst

to give intermediate *I*. After elimination of HX, the 5-membered rhodacycle *II* inserts an alkyne substrate to give intermediate *III* (C-N insertion) or *IV* (C-C insertion) as precursors of compound **75** and a Rh(I) species after the reductive elimination step.

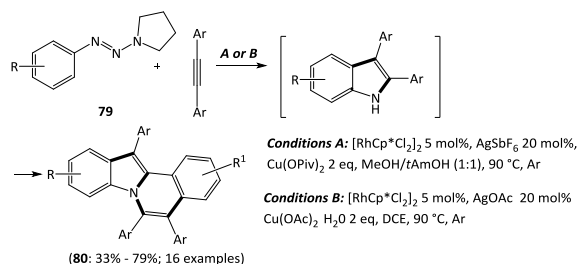
In a very recent paper based on the above work, Cul et al reported the synthesis of furo[3,4-*c*]indolo[2,1-*a*]isoquinolines **78** through a Rh(III)-catalyzed cascade reactions of 2-phenylindoles **76** with 4-hydroxy-2-alkynoates **77** (Scheme 40).⁵⁴



Scheme 40. Synthesis of furo[3,4-*c*]indolo[2,1-*a*]isoquinolines **78**.

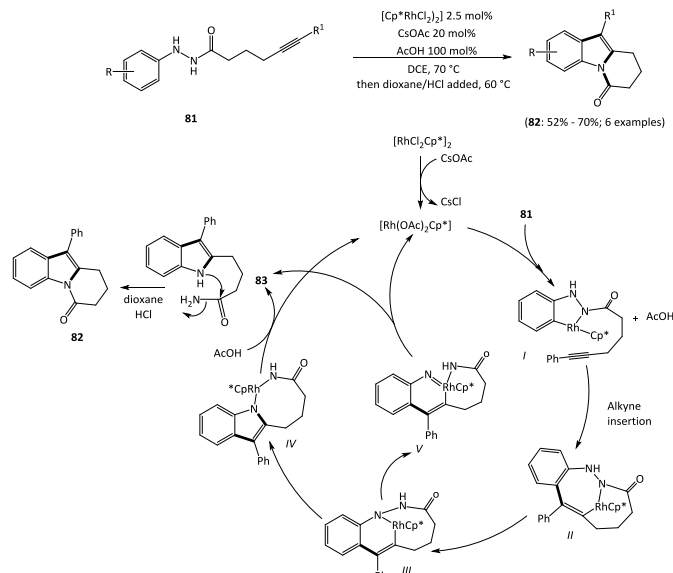
The optimized conditions were close to those of Miura⁵³ and the only changes were the replacement of Na_2CO_3 by KHCO_3 and *o*-xylene by toluene. The reaction was general with variations on 2-phenylindoles **76** and on propargylalcohols **77** to give the corresponding lactones **78** with excellent regioselectivity. The authors studied the fluorescence emission between 450 and 550 nM of such compounds, and the maximum wavelengths and shapes correlated well with the substituents' nature.

Indolo[1,2-*a*]isoquinolines **80** have been synthesized *via* a Rh-catalyzed annulations cascade realized between triazenes of type **79** and diarylalkynes (Scheme 41).⁵⁵



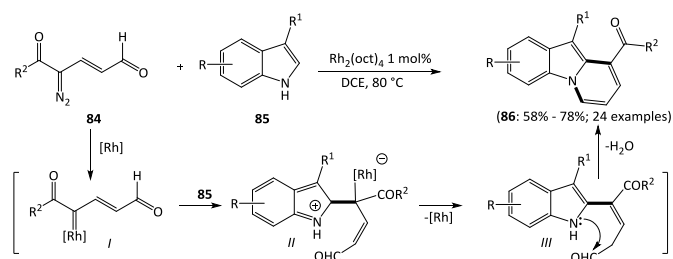
Scheme 41. Synthesis of indoloisoquinolines **80** using internal cleavable triazene directing groups **79** with alkynes under Rh-catalysis.

After having reported the synthesis of free NH indoles using an equimolar quantity of triazenes as internally cleavable directing groups with alkynes,⁵⁶ Zhang demonstrated that combining the indole synthesis and a second NH/CH annulation was possible to give indoloisoquinolines **80** by increasing the quantity of alkyne. The solvent effect was found to be crucial, as well as the effects of the substituents on **79**. For example, triazenylbenzenes **79** bearing electron-poor substituents reacted smoothly with alkynes under conditions A to give the expected indoloisoquinolines with good yields. On the contrary, substrates **79** having halogen, alkyls, and EDGs required the use of AgOAc as an additive, $\text{Cu}(\text{OAc})_2$ as oxidant, and DCE as solvent (conditions B) in place of AgSbF_6 , $\text{Cu}(\text{Opiv})_2$ and $\text{MeOH}/t\text{AmOH}$, respectively. Substrates **79** having one *ortho*-position substituted afforded poor yields in **80** because the first indole step was inefficient. Mechanistic considerations and DFT calculations are reported and discussed in detail.^{55,56}



Scheme 42. Synthesis of pyrido[1,2-*a*]indol-6-ones **82** their possible mechanism of formation.

At the same time, Li reported the synthesis of pyridoindol-6-ones **82** having on C6 a C=O group from a Rh(III)-catalyzed redox neutral CH-activation/cyclization of alkyne-tethered arylhydrazines of type **81**. In this process, the hydrazine function of **81** was used as a welcome cleavable *ortho*-directing group (Scheme 42).⁵⁷ The key step was the formation of indoles of type **83**, which were isolated in good yields with substituents of different natures on the indole nucleus. To explain the formation of indole **83**, the mechanism begins by forming a 5-membered rhodacycle *I*, which gives a seven-membered rhodacycle *II* after coordination of the internal triple bond with Rh(III) followed by alkyne insertion. Then a possible rearrangement leads to a more stable 6-membered rhodacycle *III*, which can evolve according to two possible pathways. After reductive elimination creating the indole system and oxidative addition, *III* is transformed in intermediate *IV* and then in indole **83** after a subsequent reductive elimination of the rhodium catalyst. Intermediate *III* may also undergo an acylamino migration to furnish a Rh(V) nitrene of type *V* and then **83** after reductive elimination. A final cyclization of the nitrogen atom of indole **83** on the amide function, with the help of HCl, furnishes pyrido[1,2-*a*]indol-6-one **82** in a “one pot” fashion. This process where two C-N bonds and one C-C bond were formed was used to prepare, in a formal manner, (\pm)-goniomitine a natural indole of the aspidosperma family. The last example of this section devoted to the formation of pyridoindoles by using rhodium catalysts involved an indole **85** unsubstituted in N1 and C2 and a diazoenal **84** (Scheme 43).⁵⁸

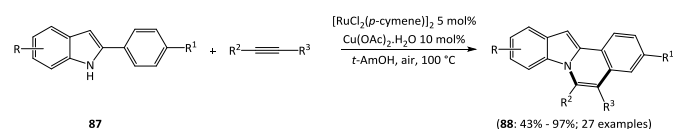


Scheme 43. Synthesis of pyrido[1,2-*a*]indoles **86** via a pyridoannulation of indoles **85** with diazoenals **84** under rhodium catalysis.

In this [4+2] annulation reaction, indoles **85** play the role of a nucleophilic clamp, and rhodium enalcarbenoids *I* (generated from enaldiazo compounds **84** and Rh-catalyst), serve as *bis*-electrophiles. A first C2-nucleophilic attack occurs on a rhodium carbene *I* to give an unstable intermediate *II*. After the removing of the Rh-catalyst, an intramolecular cyclization of *III* furnishes pyrido[1,2-*a*]indoles **86** after elimination of H₂O and aromatization. It is important to note that the C3-position of indoles **85** must be occupied in this process to avoid the formation of 4-substituted carbazoles.⁵⁹ This process allows quick and efficient preparation of trisubstituted pyridoindoles **86** with substituents of different nature on the pyridoindole core.

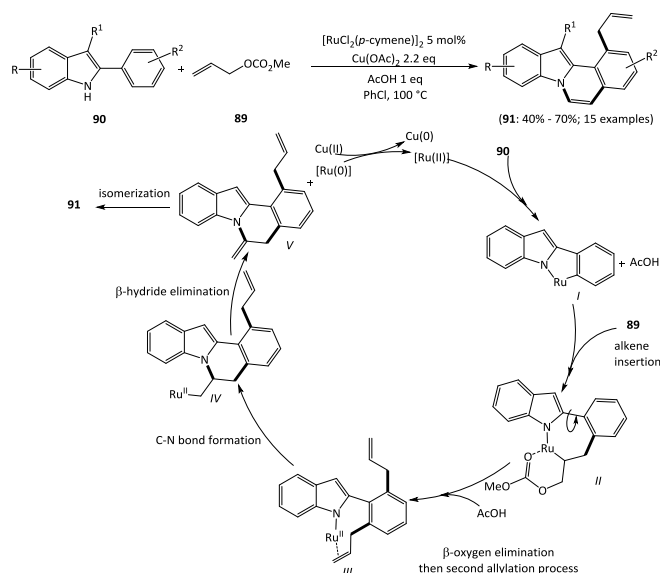
3.4 Ruthenium-catalyzed transformations

In 2012, Ackermann, in view of preparing indolo[2,1-*a*]isoquinolines **88**, reported the first ruthenium-catalyzed annulation of diarylalkynes by 2-phenylsubstituted indoles **87** (Scheme 44).⁶⁰ By using the same starting compounds as Miura two years earlier,⁵³ namely indoles having on C2 a phenyl group and internal alkynes, it was showed that [Cp*RhCl₂] can be replaced by [RuCl₂(*p*-cymene)]₂ to catalyze the oxidative annulation of alkynes. The C-H/N-H bond functionalization also occurred using Cu(OAc)₂·H₂O as co-catalyst at a temperature of 100 °C. However, contrary to the protocol with a Rh(III)-catalyst, the presence of a base was not necessary. The comparison of these two processes in terms of yields is not evident with substrates dependent performances. It should be noted that the ruthenium process is superior to that of rhodium when dialkylalkynes were used as electrophiles. These observations show that these two processes, which tolerate numerous functional groups, are complementary. It is reasonable to assume that the two reaction mechanisms are also similar.⁶¹



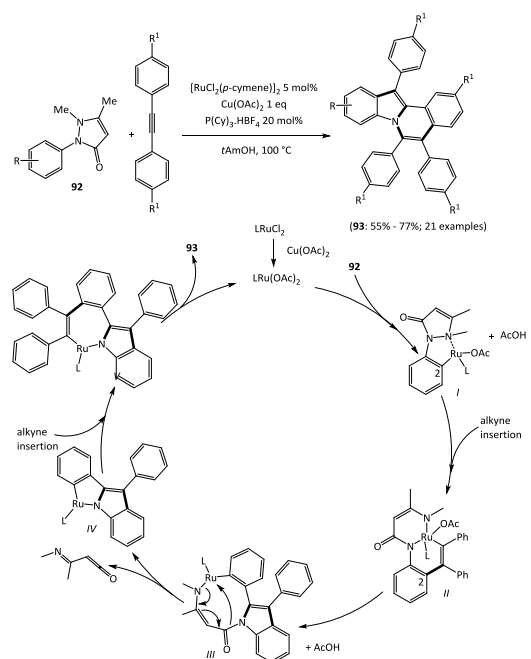
Scheme 44. Synthesis of indolo[2,1-*a*]isoquinolines **88** via ruthenium catalysis.

In 2017, Dong et al. successfully reused the catalytic system combining [RuCl₂(*p*-cymene)]₂ and Cu(OAc)₂ to prepare allylated indoloisoquinolines **91** from 2-phenylindoles **90** and allyl carbonates **89** (Scheme 45).⁶² Substituents on the indole ring are well tolerated giving the expected allylated indoloisoquinolines **91** with satisfactory yields for the creation of two C-C and one C-N bonds.



Scheme 45. Synthesis and mechanism of formation of allylated indolo[2,1-*a*]isoquinolines **91**.

Based on a previous report of Glorius,⁶³ a mechanism was proposed in which two allyl carbonates **89** were successively inserted. Initially, the Ru(II) coordination to the nitrogen atom of indole facilitated the C-H activation of the phenyl ring. Then intermediate *I* inserts the first equivalent of allyl carbonate **89** to give *II*. After a β -oxygen elimination followed by a second allylation process, intermediate *III* evolves by forming the C6-N1 bond. A subsequent β -hydride elimination furnishes the C6-N1 bond. A subsequent β -hydride elimination furnishes the C6-N1 bond and aromatization.

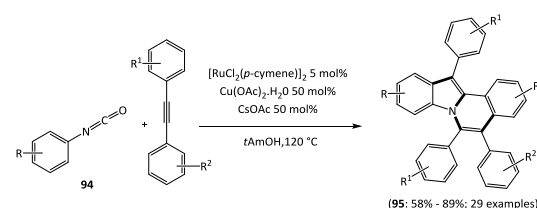


Scheme 46. Synthesis and mechanism of formation of poly-substituted indolo[2,1-*a*]isoquinolines **93**.

Gogoi reported in 2019 a ruthenium(II)-catalyzed oxidative double C-H activation and annulation reaction to prepare, from antipyrine **92** and internal alkynes, a series of poly-substituted indolo[2,1-*a*]isoquinolines **93** with high yields (Scheme 46).⁶⁴ In this process,

where two C-C and two C-N bonds were formed, the Ru-catalyst activates C2-H bond of substituted antipyrines **92** to give intermediate *I*. Then metal-alkyne coordination followed by migratory alkyne insertion provides a Ru(IV) intermediate *II* after cleavage of the weak N-N bond. After reductive elimination and CH activation of the phenyl ring, a nine membered Ru-ring *III* is possibly created. After migration of the N-CO bond to Ru(II) and elimination of a ketene (unfortunately not detected and not identified by mass spectroscopy), an intermediate of type *IV* is certainly obtained. Insertion of a second equivalent of an alkyne into the C-Ru bond of *IV* leads to *V* and then to **93** after reductive elimination. It is of note that, when unsymmetrical alkynes were used in this process, a mixture of isomers was obtained.

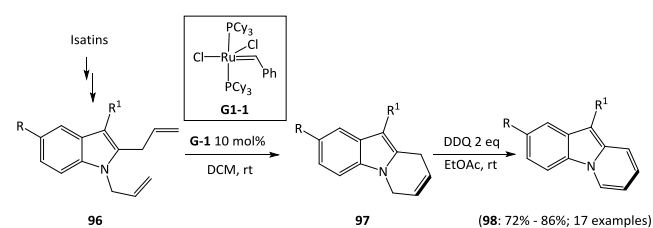
Following this work, Tadigoppula reported the “one-pot” synthesis of indolo[2,1-*a*]isoquinolines **95** by Ru(II)-catalyzed through double oxidative annulation reaction of phenyl isocyanates **94** with internal di(het)arylalkynes in *t*AmOH (Scheme 47).⁶⁵



Scheme 47. Ruthenium(II) catalyzed synthesis of indolo[2,1-*a*]isoquinolines **95** through oxidative annulation of phenyl isocyanates **94** with internal arylalkynes.

In a plausible mechanism, it was proposed that phenyl isocyanates **94** were *in-situ* transformed into urea derivatives,⁶⁶ which then inserted alkynes under ruthenium catalysis. There are some similarities with the previous publication of Gogoi⁶³ in terms of functionalities with the previous publication of Gogoi⁶³ in terms of functional groups tolerance and yields. Likewise, when using unsymmetrical diarylalkynes, the reactions resulted in an unresolvable mixture of regioisomers. Finally, the authors showed that this reaction could be carried out with some efficiency with diheteroarylalkynes.

One of the most obvious pathways to prepare the pyrido[1,2-*a*]indole moiety is to create its C-ring by ring-closing metathesis (RCM) of 1,2-diallylindole derivatives followed by a dehydrogenation reaction (Scheme 48).¹³

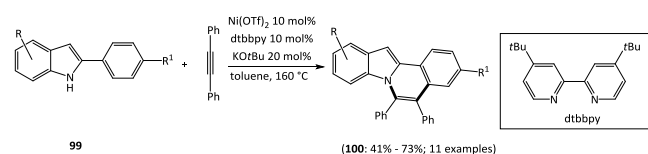


Scheme 48. Synthesis of dihydropyridoindoles **97** and pyridoindoles **98** from the RCM of 1,2-diallyl indoyl derivatives **96**.

In four steps, isatin derivatives were rapidly transformed into 1,2-diallyl indoyl derivatives **96** in good yields. A subsequent RCM using Grubbs' G1-1 catalyst provided the dihydro-pyridoindoles **97** then transformed into **98** by DDQ oxidation.⁶⁷ It is important to note that halogen atoms, useful for other transformations, are welcome in this process.

3.5 Other metals-catalyzed transformations.

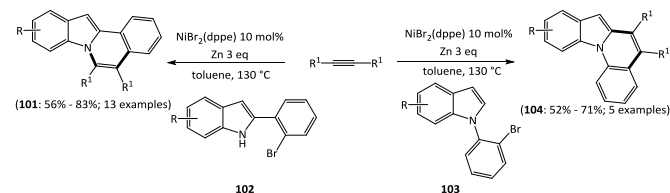
In a study devoted to the construction of various heterocycles having complicated structures, Chatani proposed in 2019, the first Ni(II)-catalyzed CH/NH annulation reaction of 2-phenylindoles **99** with diphenylacetylene (Scheme 49).⁶⁸



Scheme 49. Synthesis of indolo[2,1-*a*]isoquinolines **100**.

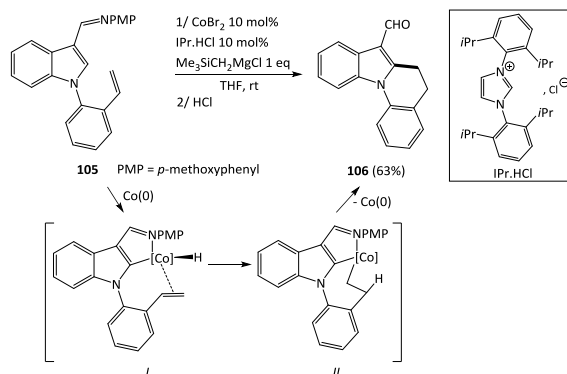
Chatani described two catalytic systems to transform 2-phenylindoles **99** into indolo[2,1-*a*]isoquinolines **100** in the presence of diarylalkynes. The first one, combining catalytic amounts of Ni(OTf)₂ with KOtBu as the base,⁶⁹ and 4,4-*di*-*tert*-butyl-2,2-dipyridyl (dtbbpy) as the ligand, was found to have a certain efficiency to obtain indoloisoquinolines **100** with average yields. The second catalytic system which use Ni(cod)₂ and dtbbpy has shown comparable efficacy and avoids the use of a strong base and toluene as solvent. The scope of this reaction revealed that other nitrogen-containing heterocycles such as 2-arylimidazoles, 2-arylpyrazoles and 2-phenylpyroles reacted well with alkynes under Ni-catalysis to provide the expected heterocycles in good yields. To gain insights into the reaction mechanism, the authors achieved a series of control experiments (use of radical traps, the base's role, deuterium-labeling experiments...). On the base of these results and according to DFT calculations, a reaction mechanism close to the one of Miura (see Scheme 39) with Rh(III) catalyst was proposed.⁶⁸

In 2020, Parthasarathy et al. demonstrated that NiBr₂(dppe) associated with Zn constituted an efficient catalytic system to prepare indolo[2,1-*a*]isoquinolines **101** or indolo[1,2-*a*]quinolines **104** by coupling diarylalkynes with 2-(2-bromophenyl)-1*H*-indoles **102** or with 1-(2-bromophenyl)-indoles **103**, respectively (Scheme 50).⁷⁰ A plausible classical mechanism was proposed for the synthesis of indolo[2,1-*a*]isoquinolines **101** and indolo[1,2-*a*]quinolines **104**. First, Zn(0) reduces the Ni(II)-catalyst to a Ni(0) species, which then inserts into the C-Br and C-H bonds to give a five-membered nickelacycle. Coordinative insertion of alkyne generates a seven-membered nickelacycle and then indoloisoquinoline **101** or indoloquinoline **104** after reductive elimination.⁷⁰



Scheme 50. Ni(II)/Zn association promoted the synthesis of indoloquinolines and indoloisoquinolines.

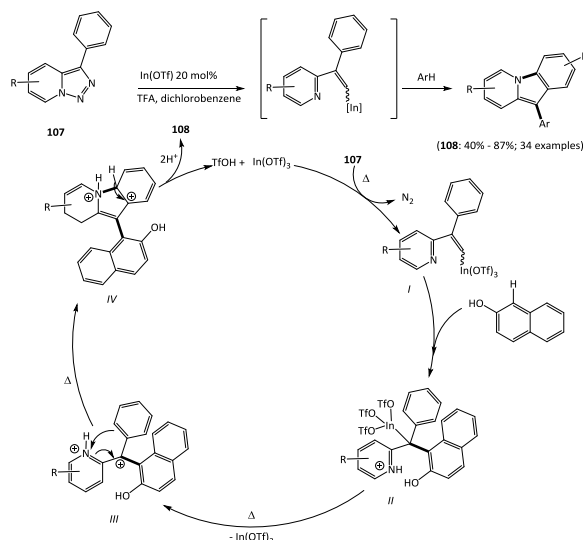
Yoshikai et al. examined the case of a cobalt-catalyst during the cyclization of indoles having various olefin tethers.⁷¹ In this study, they listed only one example concerning the preparation of indolo[1,2-*a*]quinoline **106** (Scheme 51).



Scheme 51. Cobalt-catalyzed synthesis of 5,6-dihydroindolo[1,2-*a*]quinoline-7-carbaldehyde **106**.

The cobalt-catalyzed intramolecular olefin hydroarylation starts by chelation-assisted oxidative addition of the C2-H bond to Co(0) to give intermediate *I*. Subsequent insertion of the styryl double bond into the 5-membered cobaltacycle *I* provide a 7-membered cobaltacycle intermediate *II*, which is the precursor of **106** after reductive elimination and regeneration of the Co(0)-catalyst.

The last example of this review concerns the creation of the B-ring of indolo[1,2-*a*]indoles **108** by using In(OTf)₃ with pyridotriazoles **107** (Scheme 52).⁷² After an extensive study to enhance the electrophilicity of carbenes obtained from the opening of pyridotriazoles, it was shown that In(OTf)₃ associated with TFA in dichlorobenzene reacted well with pyridotriazoles **107** in the presence of arenes. Thus, according to a dehydrogenative transannulation of pyridotriazoles with arenes, the authors constituted a small library of pyridoindoles with an interesting functional group diversity. Based on control experiments and DFT calculations, a plausible mechanism has been proposed which starts with the dinitrogenation of **107** with In(OTf)₃.



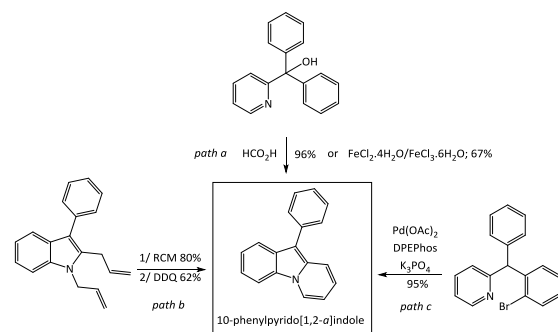
Scheme 52. Formation of pyrido[1,2-*a*]indoles **108** and plausible reaction pathway.

Indium carbenoid intermediate *I* may insert an arene molecule as 2-naphtol to give *II* which upon elimination of In(OTf)₃ under acidic condition furnishes a *bis*-cationic pyridinium tertiary carbocation of

type *III*. Then the pyridoindole B-ring-closure occurs to give intermediate *IV*, via a C-H amination reaction, followed by an oxidation process, thus delivering compound **108**.

4 CONCLUSION

In conclusion, in this review, we have seen about fifty different methods giving access to the pyrido[1,2-*a*]indole core identified over the past 20 years. Due to the presence of the pyridoindole unit in natural products, pharmaceuticals and photoluminescent materials, there has been a real craze to synthesize this nucleus through modern methods in recent years.



Scheme 53. Synthesis of 10-phenylpyrido[1,2-*a*]indole.

However, it is not possible to compare the efficiency of these discoveries, which are more complementary than competitive. To illustrate this purpose, we have grouped in Scheme 53 three different accesses to 10-phenylpyrido[1,2-*a*]indole reported in this review. In *path a*, the cyclization of triarylmethanol derivative was very efficient but needed HCOOH as strong acid, and, in milder conditions (FeCl₂/FeCl₃), the yield is significantly lowered. In *path b*, the access to diallylindole from isatin is easy and fast, but the DDQ-oxidation is sometimes capricious. In *path c*, the Pd-catalyzed intramolecular coupling reaction revealed to be particularly efficient, but the access to starting material required several steps. We believe that these different methods are complementary and should be used depending on the desired substrates. Greener methodologies, using neither metal catalysts nor acids or high temperatures, will be welcome shortly.

Conflicts of interest

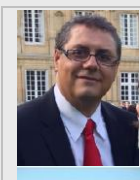
The authors declare no conflicts of interest.

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Dr. Mouad Alami, is a Research Director at the CNRS (Faculty of Pharmacy, BioCIS, France). He did his PhD at UPMC in Paris (1987) and after two years of post-doctoral position in collaboration with the Elf-Atochem company, he joined in 1989 the CNRS at the ENS-Paris (Dr. G. Linstremelle). In 1993, he spent one year at the University of Santa-Barbara (Pr. B. H. Lipshutz). In 1999, he became CNRS Research Director at the Faculty of Pharmacy (University Paris-Saclay). His fields of specialization include: (i) development of novel selective synthetic methodologies involving organometallic chemistry and (ii) synthesis of structurally challenging and biologically relevant products with antitumoral activity.



Abdallah Hamze received his Ph.D. in organic chemistry in 2003 from University of Montpellier, France, under the supervision of Prof. J. Martinez and Dr. J. F. Hernandez. After a post-doctoral position (Pr. H. Vial), Hamze moved in 2004 to the Department of Medicinal and Organometallic Chemistry at the University of Paris-Sud in the group of Dr. M. Alami and Prof. J.-D. Brion where he now holds the rank of Full Professor. His research interests include all aspects of synthetic methodology, including organometallic chemistry (Pt, Pd, Ni, Sn, Si, etc.), and the preparation of molecules and molecular scaffolds of biological and therapeutic interest.



Dr. Olivier Provot was born in 1963 in the beautiful city of Caen (Normandy, France) and received his PhD in total synthesis in the Lab of Pr. G. Lhommet in 1991 (UPMC, Paris VI). After a post-doctoral position in industry for two years and then in the Lab of Medicinal Chemistry of Pr. R. Milcent (University Paris VII), he moved in the Lab of Pr. H. Moskowitz as assistant Professor in 1993 (University of Paris-Sud) and worked on the synthesis of natural peroxides having antimalarial activities. In 2003, he joined the group of Pr. J.-D. Brion and Dr. M. Alami (University Paris-Saclay) to develop novel organometallic methodologies to prepare novel anti-cancer drugs related to Combretastatin A-4.

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