



HAL
open science

Novel access to α -carbolines with biological applications

Olivier Provot

► **To cite this version:**

Olivier Provot. Novel access to α -carbolines with biological applications. *European Journal of Medicinal Chemistry*, 2024, 276, pp.116700. 10.1016/j.ejmech.2024.116700 . hal-04697354

HAL Id: hal-04697354

<https://hal.science/hal-04697354v1>

Submitted on 13 Sep 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Novel access to α -carbolines with biological applications

Olivier Provot^{a*}

^a *Université Paris-Saclay, CNRS, BioCIS, 94400, Orsay, France.*

**Corresponding author. Email: olivier.provot@universite-paris-saclay.fr*

Summary

In recent years, the 9H-pyrido[2,3-b]indole nuclei, also named α -carboline which is found in many organic compounds such as natural products, pharmaceuticals, and materials, have intensively stimulated the research of new synthetic pathways. After a brief report published in 2015 describing novel accesses and biological applications of α -carbolines, this update reports between 2015 and 2023 on the emergence of original syntheses to this heterocyclic nucleus. Examples representing these processes are described and the biological activities of α -carbolines are mentioned when they have been prepared for therapeutic purposes.

Keywords: Carboline, Synthesis, Catalysis, Heterocycle, Biological activity, Cancer.

Contents

1. Introduction	2
2. Synthesis of α -carbolines by creating the pyrrole ring	4
3. Synthesis of α -carbolines by creating the pyridine ring	7
4. Synthesis of α -carbolines by creating two rings from anilines and benzene derivatives	15
5. Biological activities of α -carbolines prepared by functionalization of a preformed α -carboline ring	19
6. Conclusion	21
References	22

1. Introduction

The 9*H*-pyrido[2,3-*b*]indole ring, commonly referred to as α -carboline, is a tricyclic system resulting from the fusion between the C2 and C3 atoms of an indole with the C'2 and C'3 atoms of a pyridine (Figure 1).

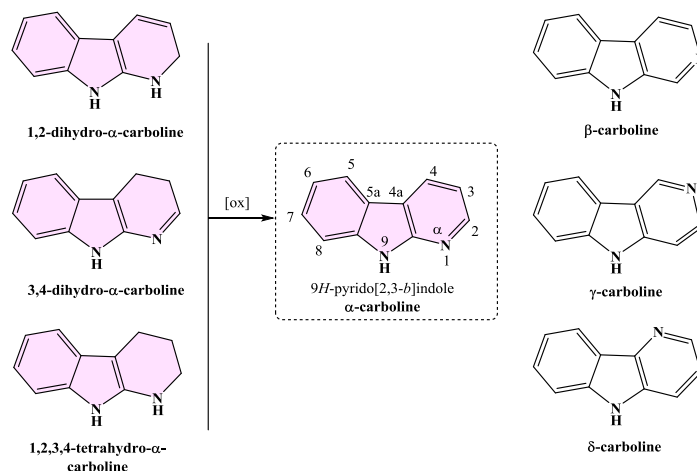


Figure 1. The four types of carbolines and α -carboline precursors.

α -Carbolines have been studied less than their β - and γ -isomers, probably because this skeleton is less naturally abundant and more difficult to synthesize. Although, to our knowledge, there are as yet no drugs with this type of pharmacophore, α -carbolines have received particular attention in recent years, as this is at the heart of a wide variety of natural and synthetic compounds with biological activities[1] and also have electronic properties.[2,3,4,5,6,7,8,9,10,11].

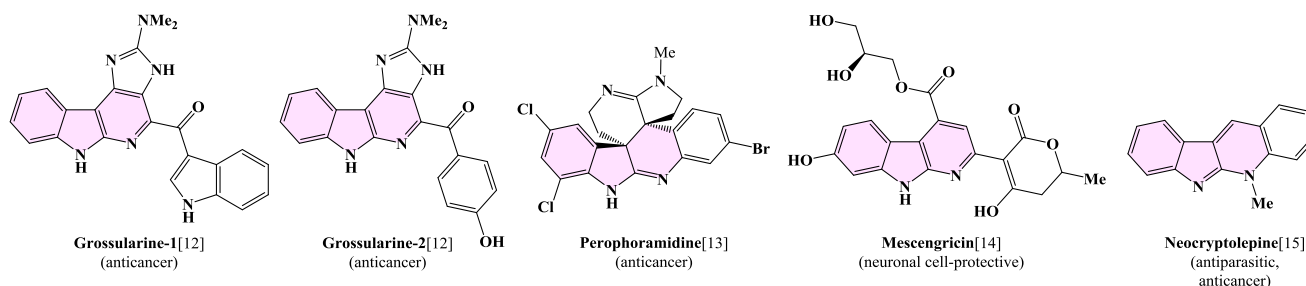


Figure 2. Selection of α -carbolines of natural origin.

Grossularine-1 and Grossularine-2 (Figure 2), isolated from the tunicate *Dendrodoa grossularia*, displayed cytotoxic activity on L1210 leukaemia cells [12]. Perophoramidine, isolated from the Philippine ascidian *Perophora namei*, is also a potent anti-cancer agent of natural origin, which exhibited cytotoxicity toward HCT116 colon carcinoma cells and induced apoptosis *via* PARP cleavage.[13] Seto, isolated in 2000 from *Streptomyces griseoflavus* Mescengricin[14], is a protecting chick primary mesencephalic neurons from L-glutamate toxicity with an EC₅₀ value of 6.0 nM. Neocryptolepine, a tetracyclic α -carboline compound isolated from the roots of an African plant *Cryptolesis sanguinolenta*, is a potent antiplasmodial[15] and a DNA-intercalating agent.[16] These biological results show this type of nucleus's high potential. This has led the scientific community to prepare and evaluate a whole series of α -carbolines. These synthetic compounds include, for example, anti-cancer α -carbolines **1**,[17] **2** [18], and **3**[19], anti-plasmodial tetracyclic derivative **4**[20] and, antidepressant α -carboline **5**[21] (Figure 3).

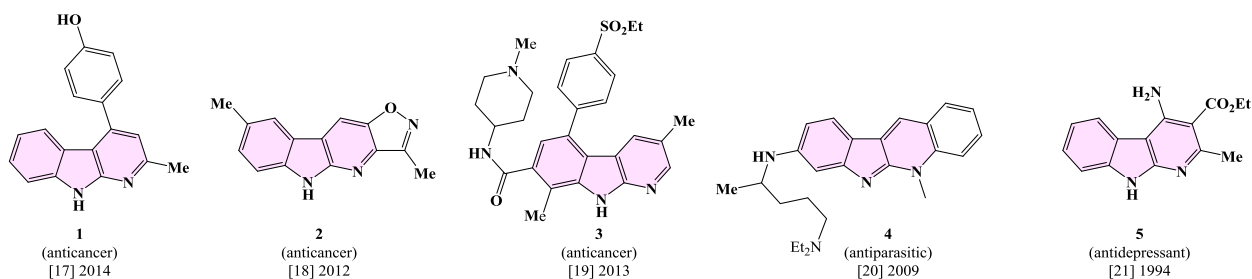


Figure 3. Selection of synthetic α -carbolines described before 2015.

In 2015, Brimble reported the only brief review concerning α -carboline syntheses, summarized in Figure 4.[22] The most common and ancient access to the α -carboline skeleton is based on modifying the Graebe-Ullmann carbazole synthesis.[23] Previous reports deal with Diels Alder-type cycloaddition reactions, pyridine ring creation from substituted indoles, benzene ring creation from azaindoles or enones and 2-nitro-phenylacetonitriles[17]. It should also be noted that many syntheses of the α -carboline nucleus have required cross-coupling reactions, S_NAr , or photocyclization reactions.[22]

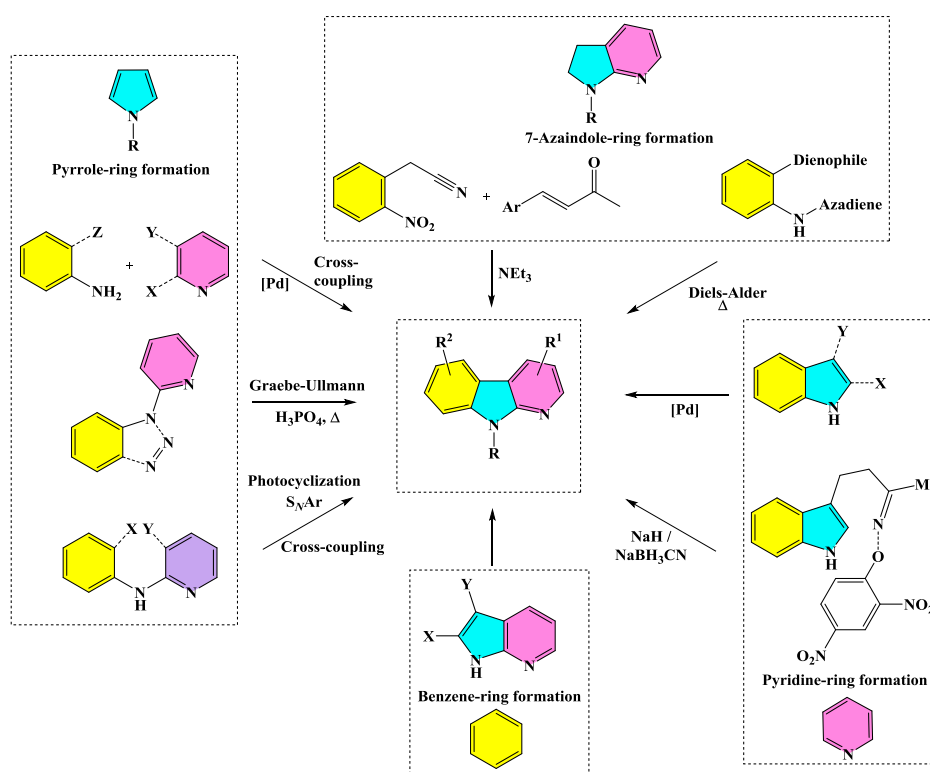


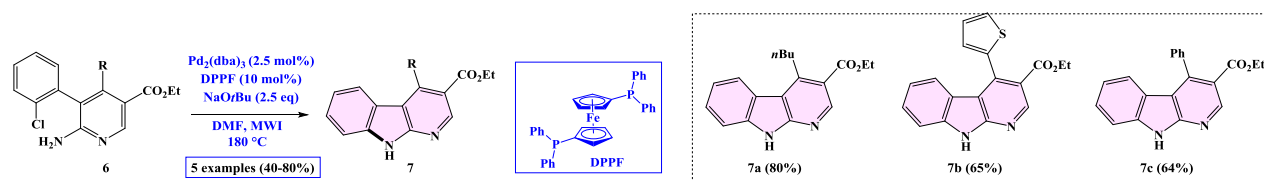
Figure 4. Synthetic strategies to the α -carboline nucleus reported by Wadsworth before 2015.

In this review, we present new accesses to this core that have emerged over the 2015-2023 period and some improvements to older processes. The first section provides an inventory of the recently reported methodologies to prepare α -carbolines by creating the central pyrrole ring through cyclization reactions or coupling functionalized anilines with pyridines. Next, in the following sections, we report syntheses of α -carbolines from functionalized indoles and anilines or benzene nuclei, respectively. We present representative examples of functionalized α -carbolines that illustrate the potential of these methods. We also evoke the biological properties of original α -carbolines when prepared for a therapeutic objective.

2. Synthesis of α -carbolines by creating the pyrrole ring

2.1 Creation of C–N bond(s)

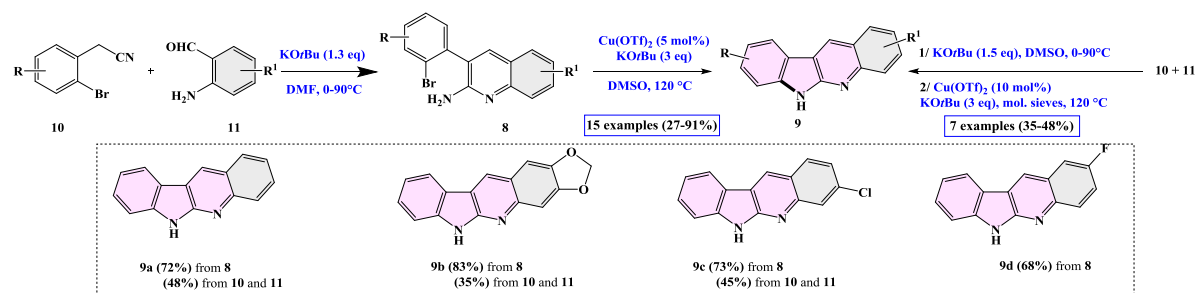
Shimizu, in 2019, reported a synthetic method for α -carbolines **7** using the Pd-catalyzed intramolecular amination of 3-(2-chlorophenyl)-2-aminopyridines **6** under microwave irradiation (Scheme 1).[24]



Scheme 1. Synthesis of α -carbolines **7** by Pd-catalyzed intramolecular amination of aminopyridines **6**.

Optimization of the cyclization conditions revealed that the best combination required $\text{Pd}_2(\text{dba})_3$ as the catalyst source, 1,1'-ferrocenebis(diphenylphosphine) (DPPF) as the ligand, and NaOtBu (3 eq) as the base in hot DMF under microwave irradiation. Aromatic rings of different natures were tolerated with varying yields (R = Ph (80%), 4-MeOPh (42%), 4-FPh (40 %), and 2-thienyl (65%) as well as an alkyl group (R = *n*Bu (64%)). This synthetic method is attractive because the ester group of carbolines **7** can be easily transformed.

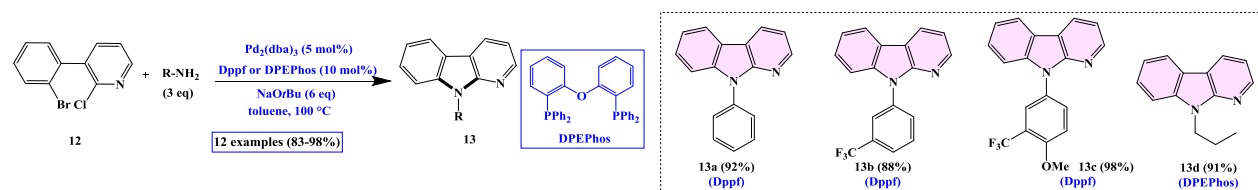
Peruncheralathan proposed in 2023 to use $\text{Cu}(\text{OTf})_2$ as a catalyst to achieve a *N*-arylation reaction with various 2-amino-3-arylquinolines **8** (Scheme 2).[25]



Scheme 2. Synthesis of indoloquinolines **9** from *N*-arylation of **8** or one-pot, two-step process from **10** and **11**.

At the beginning of this study, the authors prepared a series of 2-amino-3-arylquinolines **8** by reacting benzylic anions of **10** with 2-aminobenzaldehydes **11**. The investigations of the *N*-arylation conditions of 2-amino-3-arylquinolines **8** with various bases and copper catalysts revealed that the best combination required the use of $\text{Cu}(\text{OTf})_2$ (5 mol%) with KOtBu (3 eq) in hot DMSO (120 °C). This process tolerated various functional groups with good yields (15 examples). The *N*-methylation of **9a** furnished the natural product neocryptolepine[15], showing the synthetic utility of this process. The authors also presented a one-pot, two-step efficient protocol for synthesizing indoloquinolines **9** from benzonitriles **10** and 2-aminobenzaldehydes **11** by heating the same reagents in DMSO in the presence of molecular sieves 4Å (7 examples).

Dang and Langer published an efficient protocol to construct the pyrrole ring of α -carbolines using primary amines with the dihalogenated biaryl compound **12** by forming two C–N bonds in the presence of $\text{Pd}_2(\text{dba})_3$ (Scheme 3).[26]

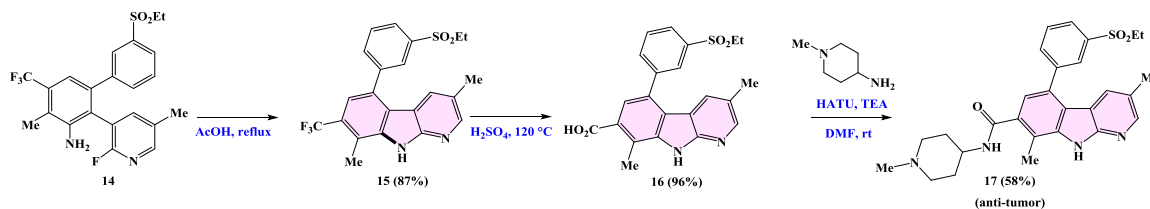


Scheme 3. Synthesis of α -carbolines **13**.

The authors studied the cyclization of 3-(2-bromophenyl)-2-chloropyridine **12** with various anilines by varying palladium sources, ligands, solvents, and temperatures. The screening of these parameters revealed that the best

combination required the use of Pd₂(dba)₃ as the Pd-catalyst, Dppf or DPEPhos (for alkylamines and benzylamines, respectively) as the ligands, and toluene as the solvent at 100 °C. The cyclization proceeded efficiently with excellent yields and tolerated electron-rich and electron-poor anilines, alkylamines, and benzylamines. *Para*-phenylenediamine was also a suitable substrate for this protocol and led to a *bis*- α -carboline with a 46% yield.

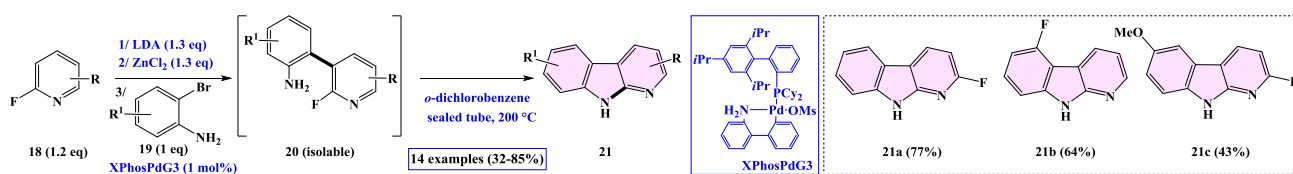
Minemo and Mizufune synthesized a potent Aurora B kinase inhibitor **17** having antineoplastic activities in three steps, starting with an intramolecular S_NAr intramolecular cyclization of 2-fluoropyridine **14** in hot AcOH (Scheme 4).[27]



Scheme 4. Synthesis of α -carboline **15** according to a S_NAr strategy.

The S_NAr reaction worked very well, but the preparation of 2-fluoropyridine **14** had several drawbacks for large-scale preparation. The authors have, therefore, proposed another access to compound **17**[27] using a Pd-catalyzed intramolecular amination, as seen above.

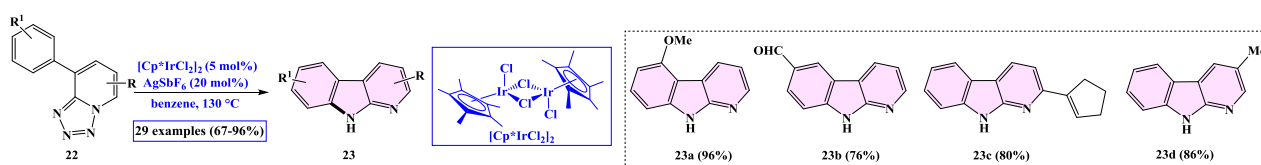
In 2022, Roesner and Sathiyalingam also used the S_NAr reaction for preparing α -carbolines and proposed a one-pot, two-step sequence to build the central pyrrole of α -carbolines **21** from 2-fluoropyridines **18** and 2-bromoanilines **19** (Scheme 5).[28]



Scheme 5. One-pot synthesis of α -carbolines **21** from 2-fluoropyridines **18** and 2-bromoanilines **19**.

At the beginning of this process, the lithiation of 2-fluoropyridines **18** with LDA occurred in *ortho*-position to the fluorine atom. A transmetalation reaction with ZnCl₂ furnished arylzinc species next coupled with 2-bromopyridines to give 2-aminobiaryl compounds **20**. These biarylated compounds **20** can be isolated or directly cyclized by S_NAr in hot *ortho*-dichlorobenzene to provide α -carbolines **21** in a one-pot sequence. The main advantages of this process are its tolerance towards a variety of functional groups and the neutral conditions used for cyclization. However, this process is probably unsuitable for fragile substrates, given the high temperatures of cyclizing 2-aminobiaryl derivatives **20**.

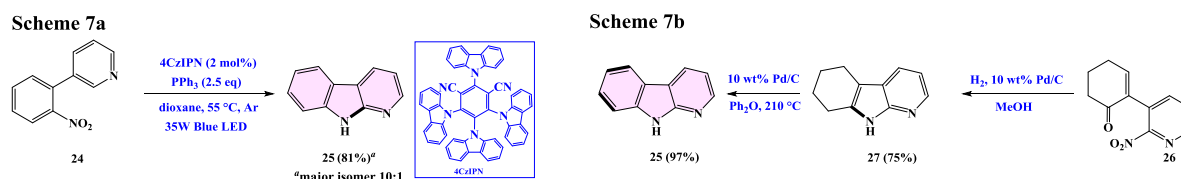
Chattopadhyay proposed a protocol to construct α -carbolines by using an intramolecular denitrogenative transannulation/C(sp²)-H amination of biaryl-1,2,3,4-tetrazoles **22** to provide α -carbolines **23** using a combination of [Cp*IrCl₂]₂ with AgSbF₆ (Scheme 6).[29]



Scheme 6. Ir-catalyzed cyclization of 1,2,3,4-tetrazoles **22** leading to α -carbolines **23**.

At the beginning of this study, the authors tested a variety of metal catalysts (Cu, Zn, Co, Fe, Mn, Ru, and Rh), but tetrazole derivatives **22** remain unchanged. This is probably because these catalysts might strongly coordinate with both of the nitrogen atoms of the tetrazole. When [Cp*IrCl₂]₂ was tested as the catalyst (5 mol%) in combination with AgSbF₆ (20 mol%) in benzene, the reaction furnished the expected α -carbolines **23** with good to excellent yields. While the use of benzene in this new concept is questionable, it is remarkable that all types of functionalities (halogens, esters, aldehydes, alkenes, OMe, etc.) are tolerated well on each aromatic ring. Mechanistic studies have shown that this

reaction occurs *via* an unprecedented electrocyclization process.[29] In 2022, Chattopadhyay proposed to replace the Cp*Ir(III)-AgSbF₆ combination with the couple Zn-dust (60 mol%) and an iron metalloporphyrin (Fe(TTP)Cl) which is a less expensive, non-toxic and a biocompatible catalyst.[30] Under these experimental conditions, the reaction was efficient (28 examples, 65-97%) and transposable to substrates bearing organic azides instead of a tetrazole ring. Since 2015, very few syntheses of the α -carboline motif using the Cadogan reaction have been reported in the literature. In 2022, Deters showed that using P(OEt)₃ under microwave irradiation is suitable for synthesizing various δ -carbolines by reducing and cyclizing 2-aryl-3-nitropyridines according to a Cadogan process.[31] In this study, the authors also reported that these operating conditions proved inoperative in cyclizing 3-aryl-2-nitropyridines to α -carbolines (4 examples, 0-8%). However, Huang showed in 2021 that it was possible to prepare various α -carbolines by a Cadogan reaction using PPh₃ with an organic photocatalyst and a light source (Scheme 7a).[32]

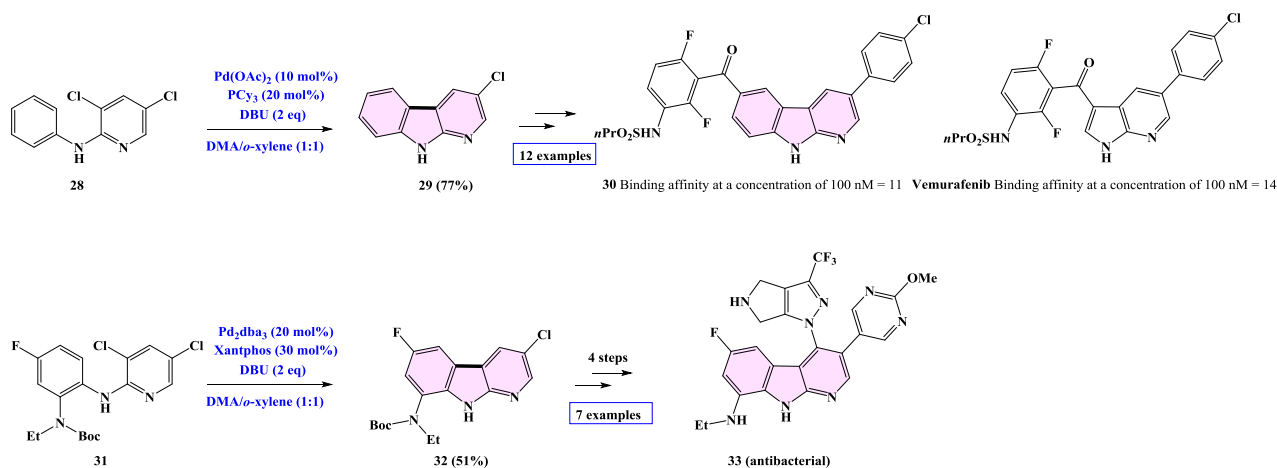


Scheme 7. Cadogan reactions leading to α -carboline **25**.

The reaction worked well with good regioselectivity at a reasonable temperature of 55 °C but was not extended to functionalized substrates. The Cadogan reaction also worked well when the nitro-substituent was on the 2-position of the pyridine ring (Scheme 7b). In an approach to α -, β -, γ -, and δ -carbolines *via* the oxidation of their tetrahydro counterparts, Banwell prepared α -carboline **25**[33] in a two-step sequence from the reductive cyclization of 2-pyridylcyclohex-ene-1-one **26** (75%) followed by a total oxidation reaction (97%) in hot diphenyl ether. Given the use of 10 wt. % of Pd/C in these two steps, the authors failed to achieve the synthesis of carboline **25** from compound **26** in a one-pot process.

2.2 Creation of the C–C bond (selected examples)

In 2013, Wüstefeld identified the mitogen-activated protein kinase kinase 4 (MKK4) as a significant hepatocyte regeneration regulator.[34] Only a few MKK4 inhibitors increase hepatocyte regeneration capacity, as most bind to other targets involved in the regeneration process (e.g., MKK7, JNK1 itself, the JNK1-downstream regulated activating transcription factor 2 (ATF2), and ETS transcription factor 1 (ELK1)). In 2022, Laufer replaced the 7-azaindole nucleus of Vemurafenib, a MKK4 inhibitor, with a α -carboline and evaluated a series of analogues towards MKK4 and other MKK-kinases (Scheme 8).[35]



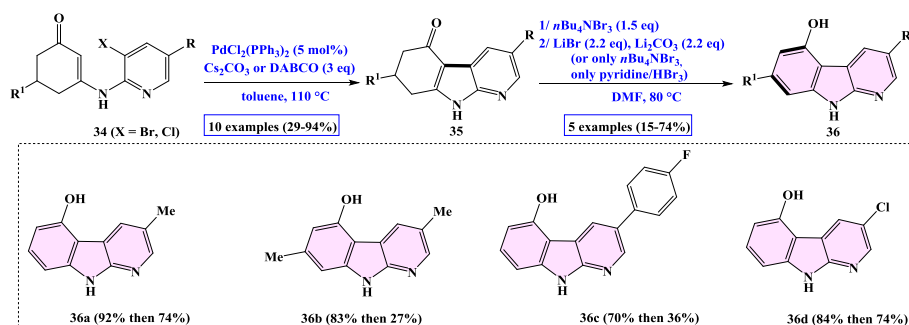
Scheme 8. Synthesis of bioactive α -carbolines **30** and **33**.

The α -carboline nucleus was constructed from diarylamine **28** according to an intramolecular Buchwald-Hartwig coupling using Pd(OAc)₂ as the catalyst and tricyclohexylphosphine as the Pd-ligand in a mixture of DMA and *o*-xylene (1/1) at 150 °C. Then, the functionalization of C3–Cl and C6–H bonds of carboline **29** furnished a series of twelve Vemurafenib analogues. Their evaluation indicated that α -carbolines showed increased selectivity towards a range of non-targeted kinases without affecting MKK4 affinity.

In 2022, Tan used the same solvents to build α -carboline **32** from diarylamine **31** (51%) but replaced Pd(OAc)₂ with Pd₂dba₃ and tricyclohexylphosphine with Xantphos.[36] Four steps after the construction of α -carboline **32**, Tan identified α -carboline **33** as a lead compound with gram-negative activity targeting DNA gyrase and topoisomerase IV.

The Buchwald-Hartwig coupling of diarylamines having a chlorine atom on the C3 atom of the pyridine was reported by Zifcsak in *Org. Synth.* using Pd(OAc)₂ as the catalyst and PPh₃ as the Pd-ligand in DMF at 100 °C (7 examples, 35–89%), demonstrating the ease of use of this process.[37]

In 2017, Sera and Mizufune published a two-step efficient strategy for furnishing α -carbolin-5-ols **36** from a Pd-catalyzed cyclization of enamines **34** followed by an aromatization reaction (Scheme 9).[38]



Scheme 9. Two-step synthesis of α -carbolin-5-ols **36**.

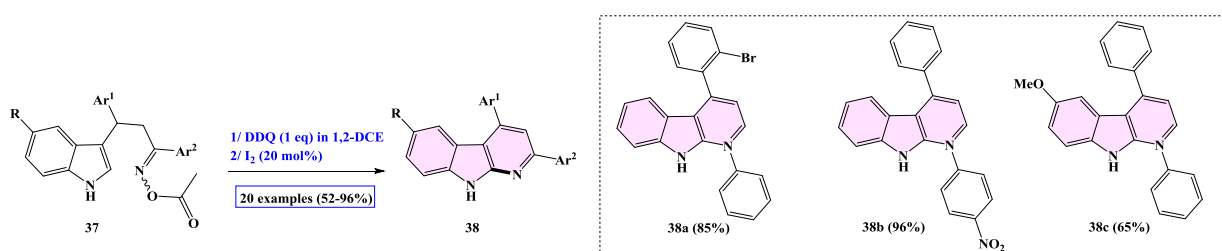
The authors achieved the cyclization of enamines **34** using an intramolecular Pd-catalyzed α -arylation reaction with various bases (Cs₂CO₃, DABCO, and K₃PO₄) depending on the substrates in toluene. The reaction tolerated various functional groups on C3 (Me, Cl, CF₃, Br) and on C7 (Me, Ph, 2-furyl) of compounds **34** and produced pyrido[2,3-*b*]indol-5-ones **35** with average yields. The aromatization of ketones **35** was achieved by a sequence α -bromination of the keto-group using *n*Bu₄NBr₃ (1.5 eq) followed by elimination using various conditions in a substrate-dependent process.

3. Synthesis of α -carbolines by creating the pyridine ring

In the post-2015 period, most new accesses to the α -carboline motif have been obtained from functionalized indoles by creating the pyridine ring.

3.1 Synthesis of α -carbolines from C2–H indoles

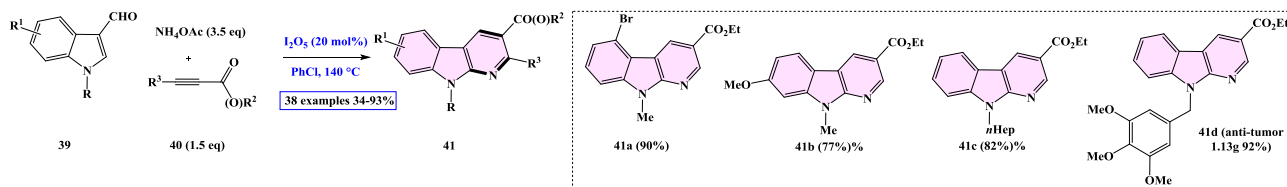
Yao synthesized α -carboline derivatives **38** from the cyclization of indoyloxime esters **37** in a metal-free protocol (Scheme 10).[39]



Scheme 10. Synthesis of α -carbolines **38** according to an oxidation-cyclization process.

The process started with a first oxidation reaction that led to a 3-indoyl alkenyl oxime ester, which then underwent 6π -electrocyclization to give α -carbolines **38**. Various groups of different natures were well-tolerated in this process, which was achieved at 60 °C. These operating conditions are highly advantageous compared with the works of Walton[40] or Moody[41], who carried out this transformation by flash pyrolysis at 650 °C or by cyclization at 250 °C under microwave irradiation, respectively. Interestingly, Yao also showed that mixing indoyloxime esters **37** with I₂ (40 mol%) in DME at 100 °C furnished a mixture of δ - and α -carbolines where δ -carbolines predominated.

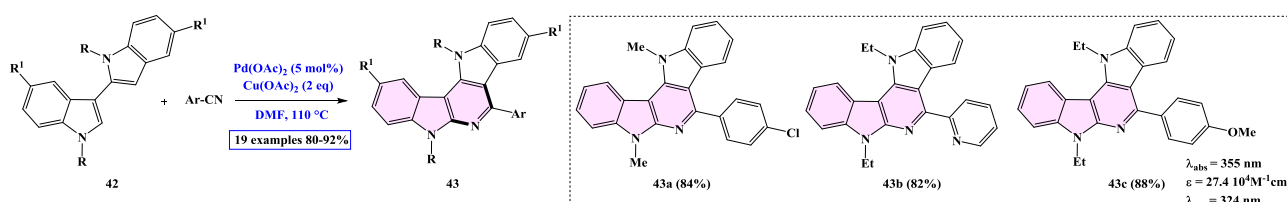
Recently, Chen and Deng proposed a chemoselective three-component synthesis of α -carbolines **41** from indole-3-carboxaldehydes **39**, ammonium acetate, and alkyl propiolates **40** (Scheme 11).[42]



Scheme 11. Three-component synthesis of α -carbolines **41**.

The process tolerated functional groups of different natures on the benzene ring ($R^1 = \text{Br, OMe, NO}_2, \text{CN, ...}$), alkyl, aryl, and benzyl groups on the nitrogen atom of the indole, and electron-poor alkynes **40**. The authors demonstrated the synthetic interest of this process by the large-scale obtention of compound **41d** (1.13 g, 92%), which displayed a sub-micromolar level of cytotoxicity against HL-60, COLO205 and Hep 3B cancer cells. This reaction does not proceed *via* an amino-aldehyde condensation to provide γ -carbolines; it only gives α -carboline derivatives **41** chemoselectively. In this three-component process, the reaction begins with a Michael-addition of NH₃ on the electron-poor alkyne **40**, providing an enaminoester intermediate which reacts on the aldehyde function. After dehydration and activation of the indole double bond by I⁺, an intramolecular cyclization occurs to form **41**, and HI is then oxidized by O₂ or I₂O₅ to continue the catalytic cycle.

Relatedly, Swamy synthesized various indole fused α -carbolines **43** *via* a Pd-catalyzed double C–H activation of 2,3'-bisindoles **42** followed by a nitrile insertion forming a C–C and a C–N bond (Scheme 12) simultaneously.[43].



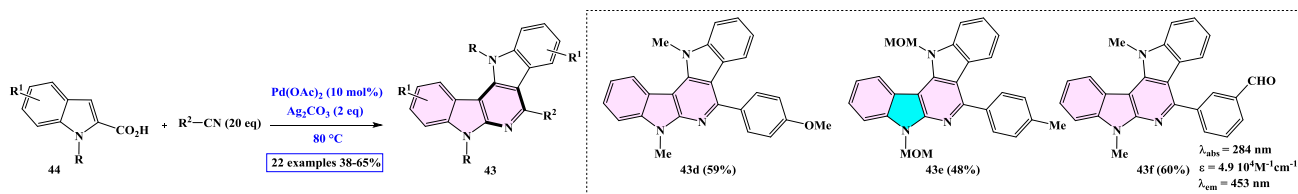
Scheme 12. Synthesis of indole fused α -carbolines **43**.

The screening of Pd-catalysts, oxidants, and solvents revealed that the best combination required the use of Pd(OAc)₂ (5 mol%) associated with Cu(OAc)₂ as an oxidizing agent in hot DMF. Benzonitrile derivatives having various substituents on the phenyl ring (H, Cl, Br, Me, OMe) and heteroaromatic nitriles (2-pyridyl, 2-furyl) worked well.

3.2 Synthesis of α -carbolines from C3–H indoles

3.2.1 Synthesis of α -carbolines from indole-2-carboxylic acids

Swamy showed that it was possible to synthesize similar indole fused α -carbolines **43** using a nitrile insertion reaction from indole-2-carboxylic acids **44** (Scheme 13).[44]



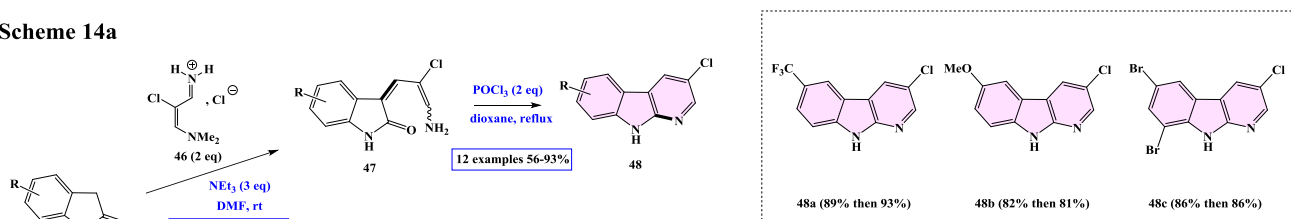
Scheme 13. Pd-catalyzed decarboxylative nitrile insertion of indole-2-carboxylic acids **44**.

After observing that *N*-methyl-indole-2-carboxylic acid ($R^1 = H$) reacted with acetonitrile (used as a solvent) in the presence of palladium acetate and silver carbonate, Swamy optimized this unexpected result to synthesize numerous functionalized indole fused α -carbolines **43**. Electronic groups of different natures were tolerated on the indole ring ($R^1 = Me, OMe, OBn, F, Cl$), and alkyl-, phenyl- and heteroaryl-nitriles were adequate partners for this process.

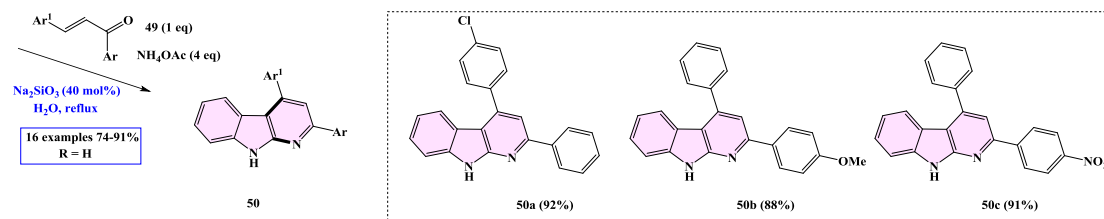
3.2.2 Synthesis of α -carbolines from indolin-2-ones

In 2018, Xu et al proposed an elegant synthesis of 3-chloro- α -carbolines **48** by mixing at room temperature indolin-2-one derivatives **45** with the 3-chlorovinamidinium salt **46** (Scheme 14a).[45]

Scheme 14a



Scheme 14b



Scheme 14. Synthesis of α -carbolines **48** and **50** using indolin-2-one derivatives.

The authors identified the best reaction conditions to transform indolin-2-ones **45** into 3-(3-amino-2-chloropropylidene)-2-indolinones **47**, using NEt_3 as the base, and two equivalents of the Michael acceptor salt **46** in DMF. Then, in a second step, the cyclization was examined with various acids ($HCl, H_2SO_4, ZnCl_2, BF_3-Et_2O$ and $FeCl_3$) but without success. However, activating the lactam function of compounds **47** with $POCl_3$ at $100\text{ }^\circ C$ in dioxane furnished the desired 3-chlorocarbolines **48** on a 1g-scale with excellent yields and functional group compatibility. At around the same time, Fazlinia and Sheikh developed a similar approach: a one-pot, three-component synthesis of α -carbolines **50** in an aqueous medium using indolin-2-one **45** ($R = H$), chalcones **49** and NH_4OAc (Scheme 14b).[46] The authors showed that metal silicates ($Na_2SiO_3, Li_2SiO_3, MgSiO_3,$ and $ZnSiO_3$) were efficient catalysts for synthesizing 2,4-diaryl- α -carbolines **50**. They also observed that solvents of low boiling points ($Et_2O,$ hexane, and DCM) and aprotic solvents (MeCN and EtOAc) were inoperative to achieve this transformation in contrast to protic solvents ($EtOH$ and H_2O) and solvent-free conditions. As mentioned above, the reaction begins with the condensation of indolin-2-one enolate and chalconimines by creating the C4–C4a bond of **50**. After cyclization and creation of the C–N bond, loss of H_2O , and oxidation, various 2,4-diaryl- α -carbolines **50** were formed with excellent yields, regardless of the silicate source used.

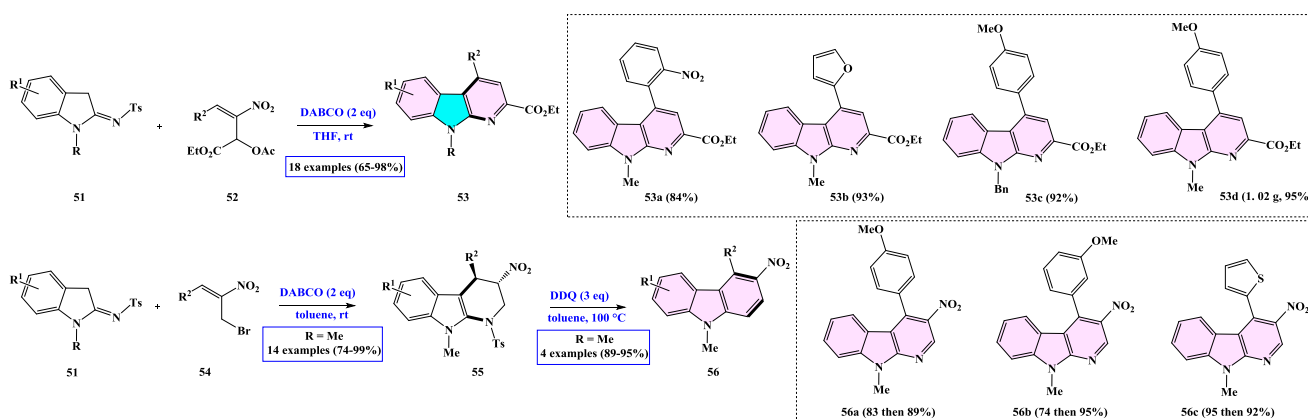
3.2.3 Synthesis of α -carbolines from tosyliminoindolines

In the last decade, many authors have used the *N*-tosyliminoindoline unit as the precursor of choice to prepare indole-related tricyclic heterocycles that can be subsequently converted into α -carbolines. Thus, various α -carbolinones have been prepared using *N*-tosyliminoindolines as *C,N*-bis-nucleophiles in alkaline media with *bis*-electrophiles such as unsaturated succinimides,[47] α -halogenated aldehydes,[48] bromoenals,[49] and acrylates.[50] Dihydro- α -carbolines

having anti-cancer properties were also obtained by a cascade three-component reaction of *N*-tosyliminoindolines with aromatic aldehydes and malonitrile.[51] Annulation between *N*-tosyliminoindolines and nitroallylic acetates[52] or Morita-Baylis-Hillman (MBH) bromides[53] led to tetrahydro- α -carbolines which suppressed the proliferation of colorectal cancer cells by inducing apoptosis and autophagy.[52]

In 2021, Namboothiri synthesized a series of α -carboline derivatives **53** having an ethyl ester function on C2 and aromatic nuclei on C4 by reacting *N*-tosyliminoindolines **51** with Morita-Baylis-Hillman acetates **52** (Scheme 15).[54] In the presence of DABCO (2 eq), which was superior to NEt₃, DBU, KOH, Cs₂CO₃, and other bases, the C3 anion of **51** reacted with MBH acetate **52** according to a S_N2' reaction, creating the C4–C4a bond of carbolines **53** by elimination of an acetate anion. Then, a 6-*endo-trig* cyclization occurred according to an azaMichael-addition, giving a tetrahydro- α -carboline intermediate aromatized by eliminating HNO₂ and *Tol*-SO₂H. Methyl-, Bn-, and H-substituents were tolerated on the indole nitrogen atom. Various aromatic rings of different natures and heteroaromatic nuclei (R² = 2-thiophene or 2-furan) worked well in this mild reaction. This process, successively creating C–C and C–N bonds, was (i) realized at rt, (ii) applicable at a gram-scale, and (iii) particularly efficient with excellent yields.

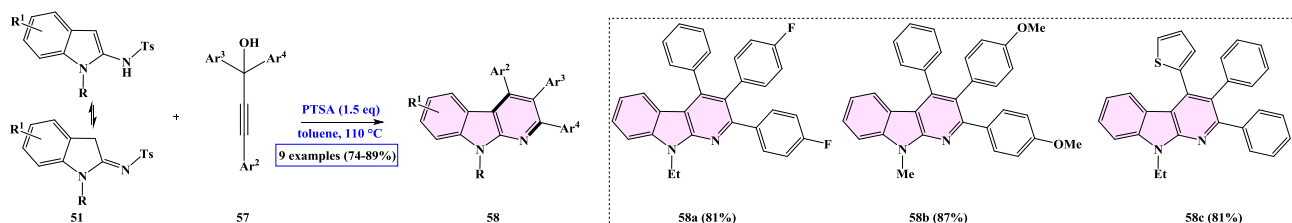
One year after this work, Namboothiri reacted *N*-tosyliminoindolines **51** with MBH bromides of nitroalkenes **54** (Scheme 15).[53]



Scheme 15. Synthesis of α -carbolines **53** and **56** using *N*-tosyliminoindolines **51** with MBH acetates **52** or MBH bromides **54**.

The reaction of *N*-tosyliminoindolines **51** with MBH bromides **54** led stereoselectively to a series of tetrahydro- α -carbolines **55** with a broad substrate scope and excellent yields. The reaction achieved with MBH bromides **54**, stopped at the tetrahydro- α -carbolines **55** stage and a further addition of DDQ was necessary to obtain α -carbolines **56**. There is no mention that this oxidation reaction in toluene can occur in a one-pot process.

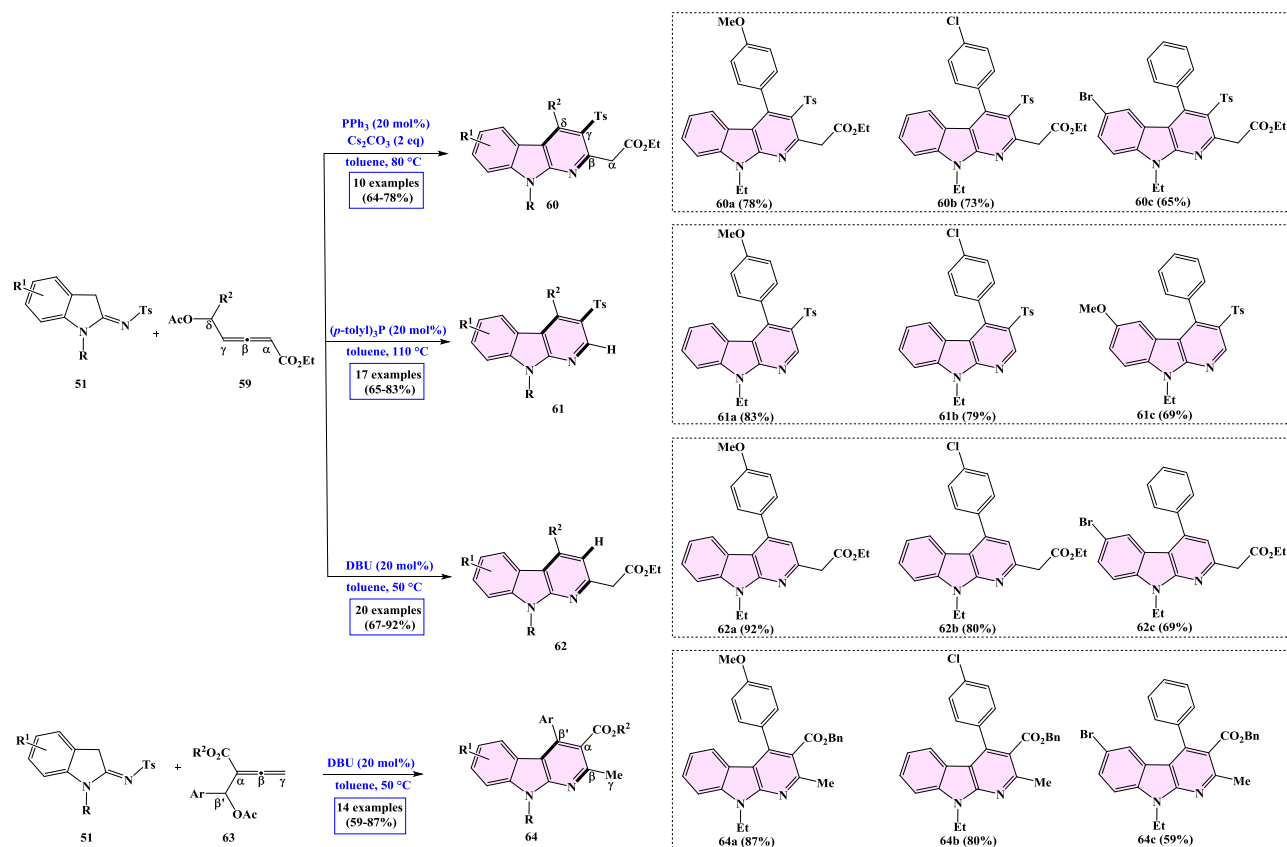
Swamy studied the reaction of *N*-tosyliminoindolines **51** with various *bis*-electrophiles allenic precursors derived from propargylic alcohols **57** (Scheme 16).[55]



Scheme 16. Synthesis of 2,3,4-triaryl-substituted- α -carbolines **58**.

The reaction was efficient with *N*-alkylindolines **51** having Me- or Et-groups; it tolerated aromatic rings and heteroaromatic rings of different natures on propargyl alcohols **57** to give (2,3,4)-triaryl-substituted- α -carbolines **58** with high yields.

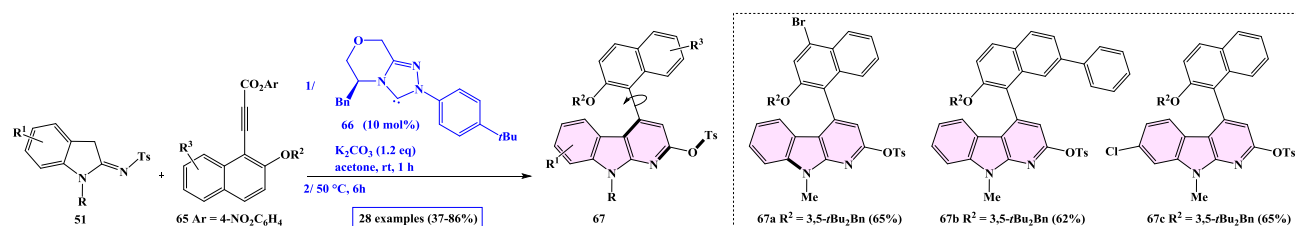
The same team then studied [3+3] annulations of acetoxy-allenoates **59** with iminoindolines **51** under various experimental conditions (Scheme 17).[56,57]



Scheme 17. Synthesis of α -carbolines **60-62** and **64** from annulations of acetoxy-allenoates **59** and **63** with iminoindolines **51**.

The authors showed that δ -acetoxy-allenoates **59** used as δ -, β -bis-electrophiles reacted with *N*-tosyliminoindolines **51** under PPh_3 catalysis to afford various α -carbolines **60** according to a [3+3] annulation process. At 80 °C, the combination $\text{PPh}_3\text{-Cs}_2\text{CO}_3$ causes a cascade reaction involving addition-elimination, aza-Claisen rearrangement, tosyl migration on C3, and aromatization to give α -carbolines **60**.^[56] To prepare similarly α -carbolines **61** but having no substituent on C2, (*p*-tolyl) $_3\text{P}$ replaced PPh_3 , and the reaction was achieved at a higher temperature of 110 °C.^[57] The authors also showed the versatility of this metal-free process, which furnished α -carbolines **62** that had no substituent on C3 and a $-\text{CH}_2\text{CO}_2\text{Et}$ substituent on C2. The robustness of these cyclization reactions was demonstrated by 1g-scale reactions offering a choice of functionalized α -carbolines with good to excellent yields. By displacing the ester function of acetoxy-allenoates **59**, Swamy's team synthesized another class of α -carbolines **64** by mixing various iminoindolines **51** with acetoxy-allenoates **63** at 50 °C in toluene in the presence of DBU. Based on control experiments, consistent proposed reaction mechanisms explain the formation of various substituted α -carbolines, which depend solely on operating conditions.^[56,57]

Wei and Du proposed an atroposelective synthesis of axially chiral 4-aryl- α -carbolines **67** by reacting iminoindolines **51** with arylpropiolates **65** using *N*-heterocyclic carbenes (NHCs) (Scheme 18).^[58]

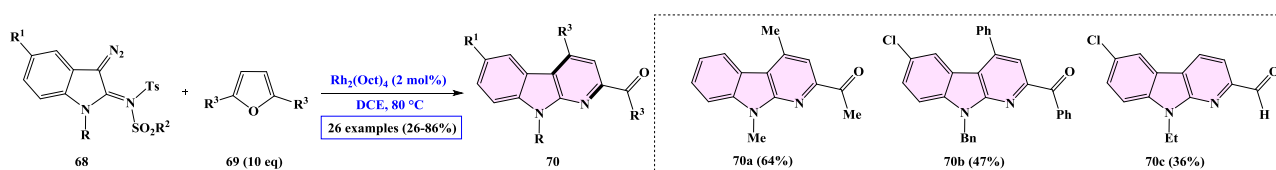


Scheme 18. Synthesis of axially chiral 4-aryl- α -carbolines **67**.

As mentioned above, iminoindolines **51** used as C–N 1,3 *bis*-nucleophiles reacted with naphthyl propiolates **65** in the presence of NHC-catalysts in a formal [3+3] annulation reaction. After examining experimental conditions where NHC catalyst **66**, acetone as the solvent and K_2CO_3 as the base gave the best results, the authors prepared various α -carbolines **67** with an excellent axial chirality. The reaction tolerated various functional groups ($R = Et, allyl, Bn, Ph, Me$; $R^1 = Cl, Br, OMe, Me$; $R^3 = Ar, thienyl, Br, Me, CN, \dots$). The authors applied this process to a scale-up synthesis (1 mmol-scale) and achieved late-stage modifications to demonstrate the utility of this method. DFT calculations, achieved for understanding the origin of the stereoselectivity, were consistent with the experimental observations in a mechanism where an allenolate intermediary is proposed.

3.3 Synthesis of α -carbolines from other indoles and indole derivatives

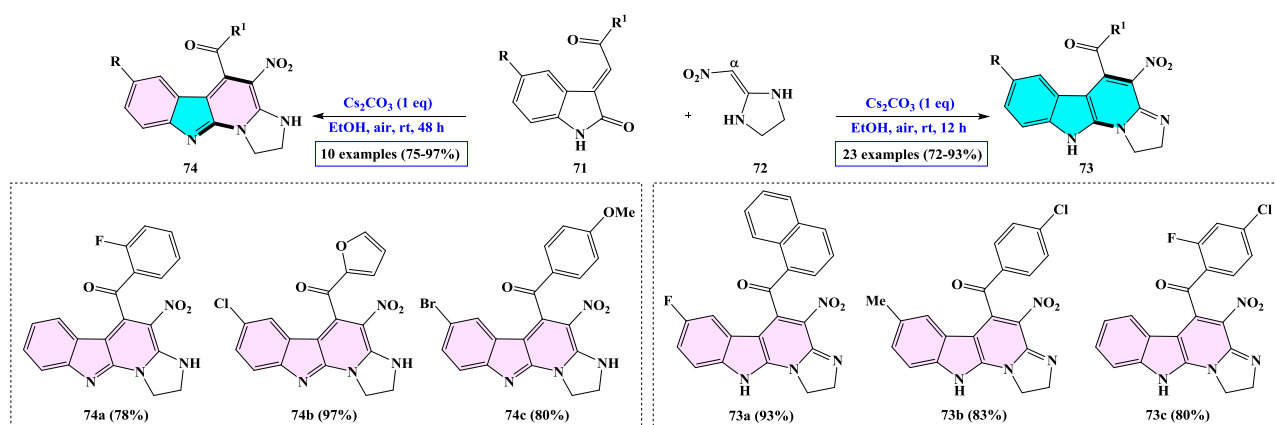
Wang and Lu proposed another access to α -carbolines **70** having a carbonyl function on C2 by mixing 3-diazo-indolin-2-imines **68** with furan derivatives **69** under rhodium catalysis (Scheme 19).[59]



Scheme 19. Rh-catalyzed reactions of 3-diazo-indolin-imines **68** with furan derivatives **69**.

The authors showed that various substituents were compatible with this reaction, affording α -carbolines **70** in variable yields ($R^2 = Tol, 64\%$; $R^2 = Ph, 65\%$; $R^2 = p-FC_6H_4, 61\%$; $R^2 = p-ClC_6H_4, 57\%$; $R^2 = 2-naphthyl, 61\%$; $R^2 = Me, 26\%$). Electron-donating groups ($R^1 = Me, OMe$) and electron-withdrawing substituents ($R^1 = Cl, Br, F$) were tolerated in this reaction, furnishing the expected α -carbolines **70** in average yields. Interestingly, the reaction worked well with unsubstituted furan ($R^3 = H$), providing a series of α -carbolines **70** having on C2 an aldehyde function (5 examples; 33 to 48%). The reaction also worked with mono-substituted furan derivatives but gave mainly a mixture of α -carbolines with variable ratios and generally with modest yields. The authors proposed a reasonable cascade reaction mechanism where an α -imino rhodium carbene intermediate is formed and acts as an electrophilic-nucleophilic entity towards furan derivatives **70** in a [3+3] cyclization process.

Lin and Yan recently published a metal-free synthesis of poly-substituted α -carbolines **73** and **74** via the reaction of indolin-2-ones **71** having on C3 an enone function with 2-(nitromethylene)imidazolidine **72** (Scheme 20).[60]

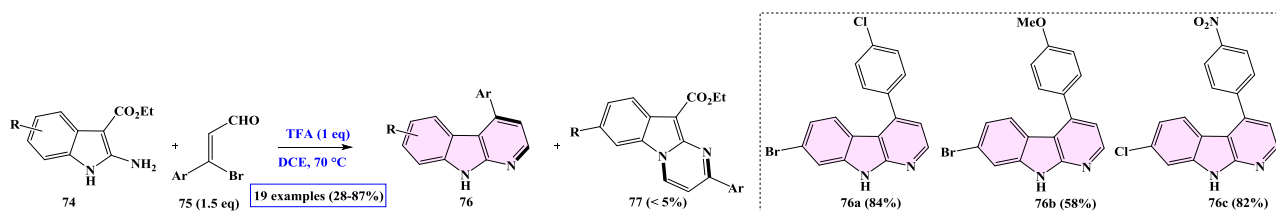


Scheme 20. Green synthesis of α -carbolines **73** and **74** from the reaction between indolin-2-ones **71** with 2-(nitromethylene)imidazolidine **72**.

Examination of experimental conditions revealed that this reaction, achieved in EtOH, was optimized when realized with a base where Cs_2CO_3 gave the best results. The authors observed that using a prolonged reaction time of 48 h, α -carbolines **73** were converted to their more stable isomers **74**. In the presence of Cs_2CO_3 , the creation of the C–C bond

starts with a Michael-addition on the α -carbon of enamine **72** to the unsaturated double bond of **71**. Then, the cyclization step, creating the C–N bond, involves a 1,2-addition of the intermediate's secondary enamine, followed by H₂O elimination and air oxidation. As seen in Scheme 20, the reaction tolerated electronic groups of different natures on both starting materials. This protocol is of great interest for synthesizing these original heterocycles simply by mixing the reagents in EtOH in the presence of a small quantity of Cs₂CO₃ for 12 or 48 hours.

Yao proposed to create the pyridine ring of 4-aryl- α -carboline **76** by mixing 2,3-disubstituted indoles **74** with 3-bromopropenals **75** (Scheme 21).[61]

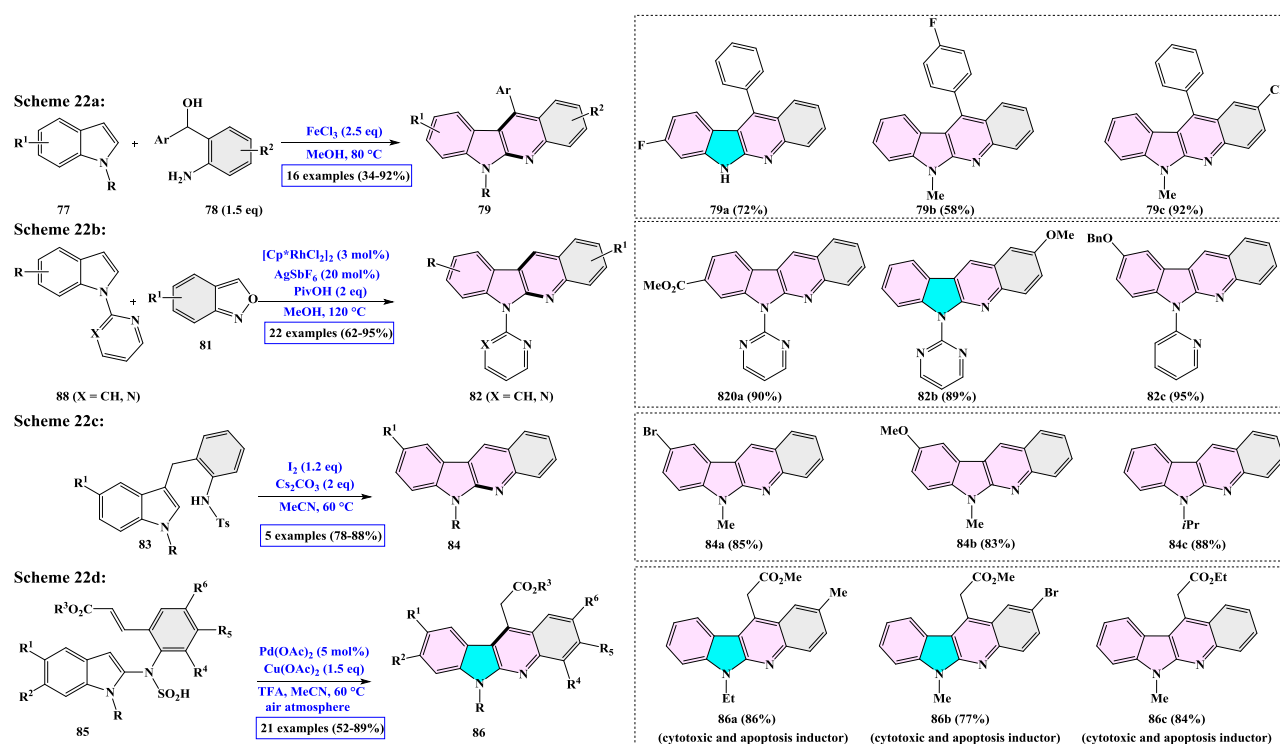


Scheme 21. Synthesis of 4-aryl-substituted α -carboline **76** from the reaction of indoles **74** with 3-bromopropenals **75**.

The screening of various solvents revealed that 1,2-dichloroethane (DCE) gave better results when compared with 1,2-dimethoxyethane (DME), 1,2-dibromoethane (1DCE), 1,4-dioxane, and toluene. The reaction conducted in DCE was examined with different additives (camphor sulfonic acid, AcOH, FeCl₃, BF₃·Et₂O, HCl, I₂, and TFA). Optimizing conditions required to heat at 70 °C in 1,2-DCE, 2-amino-1*H*-indoles **74** with 3-bromopropenals **75** (1.5 eq) and TFA (1 eq). The reaction is general, as various substituents of different natures were well tolerated on indoles **74** (R = Cl, Br, OMe, CF₃) and electron-poor and electron-rich aromatic rings on 3-bromopropenals **75**. After imine formation, the reaction evolved according to a 6 π -electrocyclization, creating the pyridine ring after eliminating one equivalent of EtOCOBBr.

3.4 Synthesis of tetracyclic α -carboline

The last part of this section concerning the creation of the pyridine ring of α -carboline is dedicated to preparing tetracyclic compounds in which a phenyl ring is linked to the pyridine ring of α -carboline (Scheme 22).



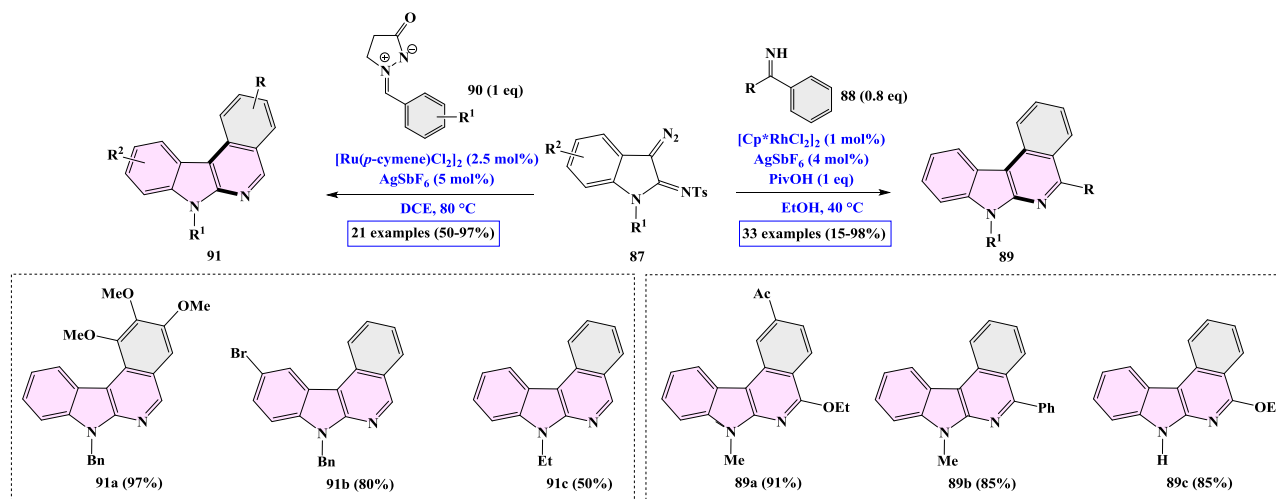
Scheme 22. Synthesis of 6*H*-indolo[2,3-*b*]quinolines from indoles.

Wang published in 2016 a green access to 6*H*-indolo[2,3-*b*]quinolines **79** as neocryptolepine analogues[62] by coupling *ortho*-substituted aniline derivatives **78** with indoles **77** having no substituent on C2 and C3 (Scheme 22a).[63] An examination of various metal salts showed that 2.5 eq of FeCl₃ gave 6*H*-indolo[2,3-*b*]quinolines **79** with the best yields. This strong Lewis-acid generated a benzylic carbocation which added indole **77** in a Friedel-Craft reaction. Then, ferric chloride enabled total oxidation, producing the desired product **79** with moderate to good yields.

The same year, Li constructed the pyridine ring of 6*H*-indolo[2,3-*b*]quinolines **82** by forming C–N and C–C bonds using *N*-substituted indoles **80** and substituted-anthranilic derivatives **81** (Scheme 22b).[64] *N*-Pyrimidinylindoles and *N*-pyridinylindoles **80** bearing electron-donating or electron-withdrawing substituents at different positions coupled with anthranilic derivatives **81**, giving 6*H*-indolo[2,3-*b*]quinolines **82** with good to excellent yields. Similarly, electronic groups of various natures (OMe, F, Cl, Br) at different ring positions of anthranilic derivatives **81** were well tolerated in this process. The authors removed the pyrimidinyl ring on the nitrogen atom of indole **80** (R = H) to prepare neocryptolepine in a formal synthesis.

Also in 2016, Sekar prepared indoles fused tetracycles, including 6*H*-indolo[2,3-*b*]quinolines **84** via iodine-mediated domino C2 aminating cyclization of *N*-tosylaniline derivatives **83**, followed by a *N*-detosylation reaction and subsequent aromatization (Scheme 22c).[65] This metal-free protocol was evaluated in a variety of solvents (MeCN, CCl₄, toluene, THF, DMSO, and EtOH), and best results were obtained in hot MeCN (60 °C). The substrate scope examined with C5-substituted indole derivatives **83** revealed that electron-rich and electron-poor substituents did not interfere in this process (**84a**, R¹ = Br 85%; **84b**, R¹ = OMe 83%).

In 2015, Pal synthesized as apoptosis inducers, various 6*H*-indolo[2,3-*b*]quinolines **86** having on C11 an ethyl acetate function using a Pd-catalyzed intramolecular oxidative alkenylation of the indole ring of (*E*)-alkyl-3-(2-(1*H*-indol-2-ylamino)phenyl)acrylates **85** followed by a *N*-desulfonylation reaction (Scheme 22d).[66] This cyclization reaction achieved with Pd(OAc)₂, found as the best Pd-catalyst in MeCN, was dramatically increased using TFA as an additive. This reaction did not require an inert atmosphere and did not proceed without Pd(OAc)₂ and Cu(OAc)₂, indicating the pivotal role played by the Pd-catalyst and the oxidant. Functional groups (Et, Me, Hex, OMe, F, Br, Cl) installed on different positions of the tetracycle showed the generality of the present method. Compounds **86a-c** inhibited the growth of various cancer cell lines (A549, lung; Cal27, tongue; MCF-7, breast; TZM-BL, cervical) with a comparable efficacy as Gemcitabine. These cytotoxic compounds were next tested as apoptosis inducers in zebrafish embryos and showed remarkable effects with low EC₅₀ values of 2.20, 4.18, and 1.59 μM, respectively. Interestingly, when evaluated in zebrafish embryos, these promising 6*H*-indolo[2,3-*b*]quinolines **86a-c** displayed no significant teratogenicity (therapeutic index (TI) for **86c** = 6.26).

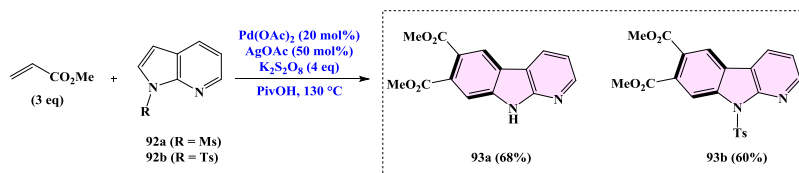


Scheme 23. Synthesis of 7*H*-indolo[2,3-*c*]isoquinolines **89** and **91** from 3-diazoindolin-2-imines **87**.

Recently, two accesses to the 7*H*-indolo[2,3-*c*]isoquinoline scaffold have been obtained from the reaction of 3-diazoindolin-2-imines **87** with imine derivatives **88**[67] or azomethine ylides **90**[68] (Scheme 23).

In 2016, the group of Li et al constructed the indolo[2,3-*c*]isoquinoline core of compounds **89** via a [3+3] cyclization reaction of diazo compounds **87** with aryl imines (R = Ph, 4-FC₆H₄, 4-BrC₆H₄) or arylimidates **88** (R = OEt, *On*Pr, *Or*Pr) under Rh(III)-catalysis. Best conditions required mixing compounds **88** with a slight excess of **87** (1.2 eq) in the presence of [Cp**Rh*Cl₂]₂ (1 mol%), AgSbF₆ (4 mol%), and PivOH (1 eq) in EtOH at 40 °C. The reaction creating the C–C and C–N bonds of the pyridine ring was effective on a 1-gram scale and was compatible with several functional groups (R² = H, Me, Et, F, Br, Cl, CO₂Et, Ac, OBn, Bn; R¹ = H, Me, Et, Bn). In 2023, Shankaraiah prepared a series of indolo[2,3-*c*]isoquinolines **91** from diazo compounds **87** with *N,N'*-cyclic azomethine ylides **90** in the presence of various catalysts (CuI/CuCl/CuBr; (*n*Bu₄N)₂Cu₂I₄, Pd(PPh₃)₄, [RhCp*Cl₂]₂, where [Ru(*p*-cymene)Cl₂]₂ predominated (Scheme 23).[68] The [3+3] annulation process was efficient at a 2.6 mmol scale and provided indolo[2,3-*c*]isoquinolines **91** having substituents of different natures at variable positions of the tetracycle with excellent yields.

We conclude this section concerning the synthesis of α -carbolines obtained from modifications of indole derivatives by evoking, to our knowledge, the single example of access to this nucleus from 7-azaindoles **92a,b** (Scheme 24).[69]



Scheme 24. Synthesis of α -carbolines **93a,b** from 7-azaindoles **92a,b**.

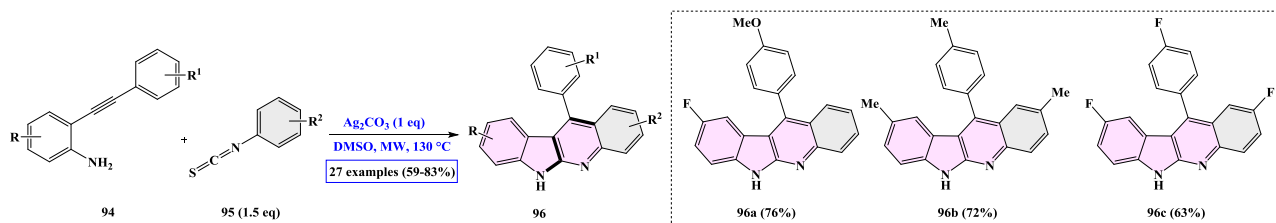
In 2015, Laha et al proposed a tandem approach to 2,3-disubstituted carbazoles (not showed) from indoles and methyl acrylate according to two successive oxidative Heck reactions followed by thermal electrocyclization and oxidation (9 examples, 65-88%). To build the benzene ring of carbazoles, optimization of reaction conditions showed that PivOH was superior to DMSO as a solvent, and an association of K₂S₂O₈ with AgOAc resulted in an excellent conversion of starting materials. The reaction tolerated acrylates, styrene, and styrene derivatives as Heck partners and substituents of different natures (Cl, OMe, F) on the nucleophilic aromatic ring. However, the reaction did not work with 1*H*-indoles and with *N*-alkylindoles. As an extension of this work, Laha demonstrated that the process is also applicable with a similar efficiency to 7-azaindoles **92a,b**. Notably, 7-azaindole **92a** having an *N*-Ms group gave (NH)-free α -carboline **93a** (68%), compensating for unsubstituted heterocycles' lack of reactivity.

4. Synthesis of α -carbolines by creating two rings from anilines and benzene derivatives

4.1 Synthesis of α -carbolines from anilines and nitrobenzene substrates

We begin this section by discussing access to α -carbolines and benzene-fused α -carbolines from *ortho*-substituted primary anilines and their nitro-precursors. We then present recent syntheses of α -carbolines from secondary anilines and trisubstituted anilines.

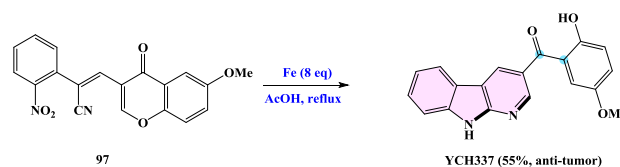
Patel published a microwave-assisted cascade strategy for the construction of 4-aryl-indolo[2,3-*c*]isoquinolines **96** from aryl *ortho*-(phenylethynyl)anilines **94** and phenyl isothiocyanates **95** in the presence of Ag₂CO₃ under microwave irradiation (Scheme 25).[70]



Scheme 25. Synthesis of 4-aryl-indolo[2,3-*c*]isoquinolines **96** from the reaction of *ortho*-(phenylethynyl)anilines **94** and phenyl isothiocyanates **95**.

This synthetic route, which successively creates three new bonds and two adjacent heterocycles, works perfectly with all kinds of electron-withdrawing or electron-donating substituents on each aromatic ring, whatever their position. The authors demonstrated the superiority of Ag_2CO_3 as the metal salt used as a desulfurizing agent. This methodology is significant in that it is transposable to a 1-gram scale and uses readily available alkynes **94** obtained *via* Sonogashira couplings and commercially available phenyl isocyanates **95**.

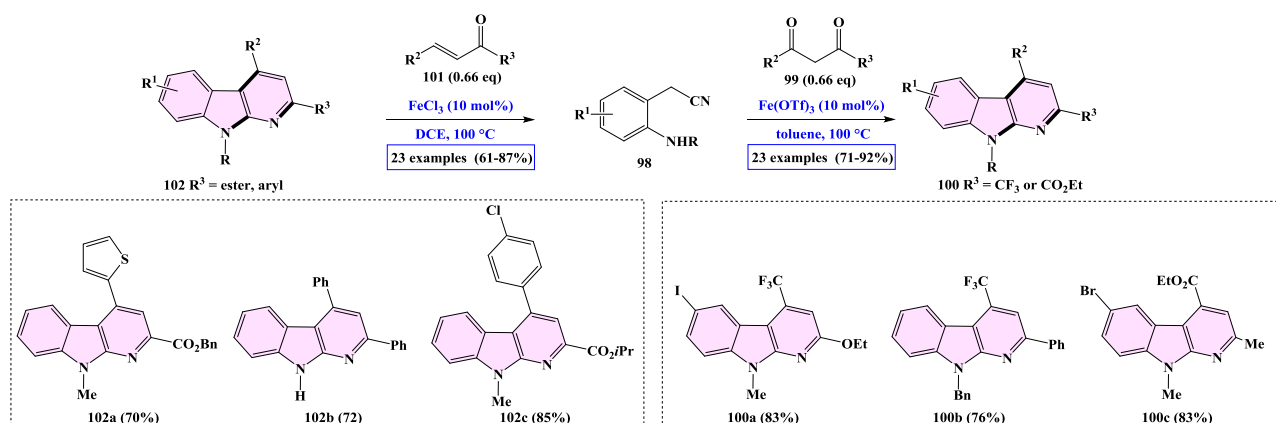
Yi and Zhang proposed rapid and easy access to **YCH337**, a synthetic 3-substituted α -carboline with a dual anti-cancer activity targeting microtubules and topoisomerase II (TopII) (Scheme 26).[71]



Scheme 26. Synthesis of **YCH337** from 2-nitrophenylacetonitrile derivative **97**.

2-Nitrophenylacetonitrile derivative **97** was first synthesized *via* an aldolization reaction realized under alkaline conditions (NaOAc) with 2-(2-nitrophenyl)acetonitrile and 6-methoxy-4-oxo-4*H*-chromene-3-carbaldehyde.[72] Then, the nitro group of **97** was reduced with iron in AcOH , furnishing an aniline intermediate which cyclized on the nitrile function used as an electrophilic-nucleophilic group to give **YCH337**, after a second cyclization creating the pyridine ring. Biological tests revealed that **YCH337** inhibited microtubule polymerization by binding to the colchicine site, leading to spindle assembly disruption of HeLa cells. **YCH337** blocked the cellular cycle of these cancer cells in the G2/M phase and induced apoptosis at a low concentration. The authors also showed that **YCH337** suppressed TopII and caused DNA double-strand breaks. Finally, *in vivo* results revealed that **YCH337** inhibited the proliferation and growth of human colon cancer HT29 xenografts in nude mice.

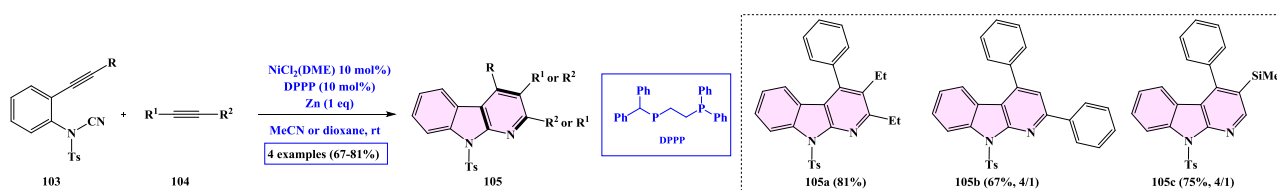
Wan and Liu developed an efficient approach to α -carbolines **100** and **102** from the reaction of secondary anilines **98** with trifluoromethyl ketones ($\text{R}^3 = \text{CF}_3$) or acetopyruvates ($\text{R}^3 = \text{CO}_2\text{Et}$) **99** and with unsaturated α -ketoesters **101**(Scheme 27).[73]



Scheme 27. Synthesis of α -carbolines **100** and **102** *via* iron-catalyzed tandem cyclization reactions.

Optimization of reaction conditions by varying metal salts ($\text{Zn}(\text{OTf})_2$, $\text{Cu}(\text{OTf})_2$, $\text{Fe}_2(\text{SO}_4)_3$, FeCl_2 , FeCl_3 , $\text{Fe}(\text{OTf})_3$,...) and solvents (PhCl, DCE, DMSO, MeCN, MeNO_2 , dioxane, and toluene) revealed that best results were obtained by mixing aniline derivatives **98** in slight excess (1.5 eq) with ketones **99** or **101** (1 eq) in the presence of $\text{Fe}(\text{OTf})_3$ (10 mol%) in hot toluene or DCE (100 °C) for 8 h. In the presence of $\text{Fe}(\text{OTf})_3$, aniline **98** through intramolecular cyclization gave an indolimine intermediate, which was not isolated and reacted as a nucleophilic reagent with *bis*-electrophilic ketones **99** and **101** with total regioselectivity. Using catalytic environmental-benign iron salts and a straightforward protocol, α -carbolines derivatives **100** and **102** bearing on C4 position, CF_3 -, esters-, and aryl-groups were obtained in good to excellent yields with a large variety of functional groups on different positions of the tricyclic nucleus (Cl, Br, I, Me, OMe, CF_3 ,...).

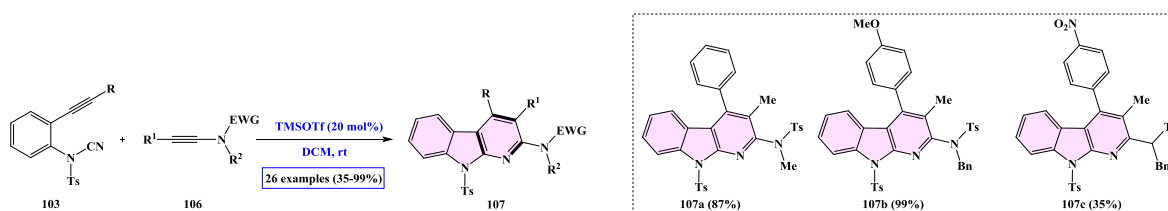
Under Ni-catalysis, Liu synthesized α -carbolines **105** from the reaction of *N*-tosyl-ynamide nitriles **103** with alkynes **104** (Scheme 28).[74]



Scheme 28. Synthesis of α -carbolines **105** from the reaction of *N*-tosyl-ynamide nitriles **103** with alkynes under Ni-catalysis.

This method, which created the indole and the pyridine-ring of α -carbolines **105** successively through a [2+2+2] cycloaddition of *N*-tosyl-ynamide nitriles **103** with alkynes under Ni(0) catalysis, worked well with internal alkynes and terminal alkynes. The authors observed high regioselectivity when *N*-tosyl-ynamide nitriles **103** were mixed with terminal alkynes. The regioselectivity was governed by electronic effects rather than steric factors (**105b** and **105c**). Interestingly, Liu showed that this catalytic method gave rapid access to a range of δ -carbolines (not showed) by replacing the *ortho*-alkyne function of compounds **103** with an *ortho*-cyano group (26 examples, 50-94%).

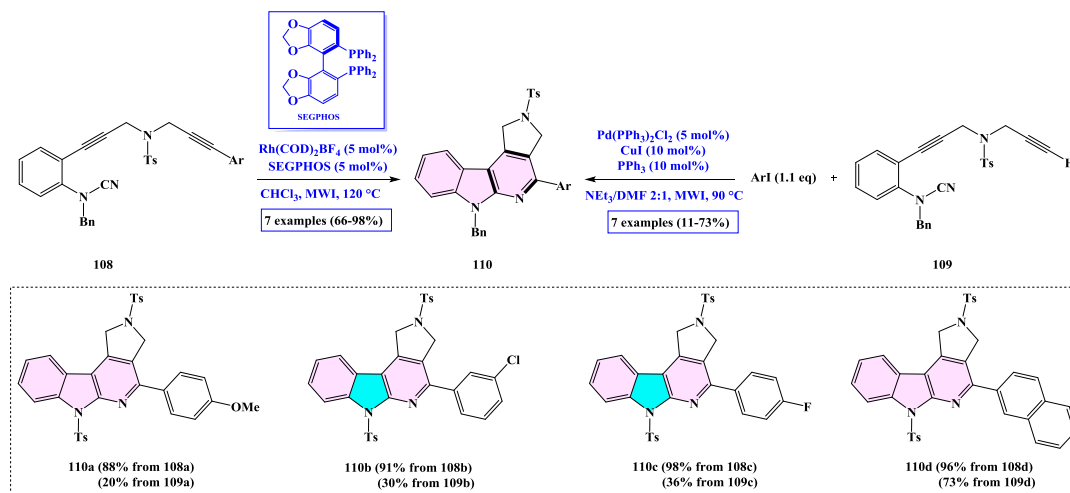
In 2019, Wang and Chang prepared a series of α -carbolines **107** via a metal-free [2+2+2] cycloaddition of *N*-tosyl-ynamide nitriles **103** with ynamides **106** (Scheme 29).[75] Optimization of the [2+2+2] cycloaddition revealed that, among a variety of catalysts ($\text{BF}_3\text{-Et}_2\text{O}$, AlCl_3 , ZnI_2 , Tf_2O , TfOMe , TMSOTf , TfOH , TFA , and CSA), TMSOTf (20 mol%) gave the best results on a model substrate (99%, $\text{R} = \text{Ph}$; $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Bn}$; $\text{EWG} = \text{Ts}$) when the reaction was achieved in DCM at rt.



Scheme 29. TMSOTf catalyzed synthesis of 2-amino- α -carbolines **107** from *N*-tosyl-ynamide nitriles **103** with ynamides **106**.

This environmentally friendly methodology gives rapid access to variously substituted 2-amino- α -carbolines **107** with high to excellent yields, generally superior to 80%, except for compound **107c** bearing on C4, a *para*-nitrophenyl substituent. Substituents such as Ts, Cs, Ns, and Bn were tolerated in this protocol, which is also compatible with various substituents on the C4 position of α -carbolines **107** ($\text{R} = \text{Ar}$, 2-thiophene, Bn, *n*-hex, *c*-Pr, TMS, and H). As previously published by Liu[74], replacing the *ortho*-alkyne with a nitrile in *N*-tosyl-ynamide nitriles **103** with a nitrile in this [2+2+2] cyclization process gave amino- δ -carbolines rapid access.

At the same period, Mulcahy proposed complementary access to various 2-aryl- α -carboline derivatives **110** via a [2+2+2] cyclotrimerization of cyanamides **108** under Rh-catalysis (Scheme 30).[76]

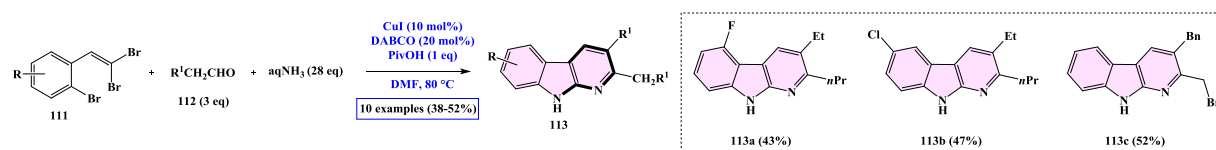


Scheme 30. Synthesis of 2-aryl- α -carbolines **110** from cyanamides **108** and **109**.

The [2+2+2] cyclotrimerization of cyanamides **108** having a disubstituted alkyne function worked well under Rh-catalysis to furnish 2-aryl- α -carbolines **110** bearing electron-rich or electron-poor phenyl rings at C2 position with excellent yields. This approach offers the advantage of rapid synthesis (20 minutes) using microwave irradiation (MWI) to construct the α -carboline scaffold of compounds **110**. The authors also showed that α -carbolines **110** were obtained in modest yields directly from cyanamides **109** having a terminal alkyne function according to a Sonogashira reaction followed by a cyclotrimerization reaction in a one-pot process. The main disadvantage of this process is the relatively long synthesis of cyanamides **108** and **109**, for which 6 or 5 steps, respectively, are needed from 2-iodoanilines, which complicates the introduction of substituents on the phenyl ring of α -carbolines **110**.

4.2 Synthesis of α -carbolines from benzene derivatives

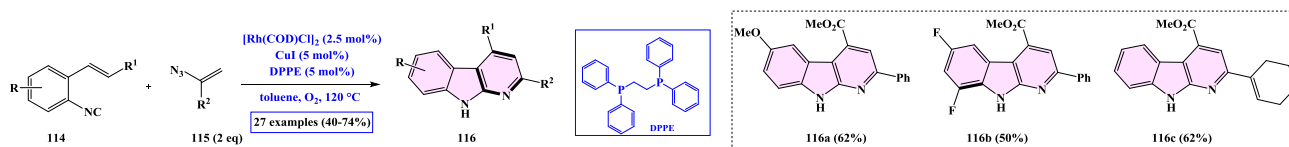
Zhang and Fan proposed attractive access to C2-C3 disubstituted- α -carbolines **113** via a one-pot cascade reaction of *ortho*-bromo-2-(2,2-dibromovinyl)benzene derivatives **111** with enolizable aldehydes **112** and aqueous ammonia under CuI-catalysis (Scheme 31).[77]



Scheme 31. Synthesis of α -carbolines **113** from the condensation of tribromo-derivatives **111** with aldehydes and aqueous ammonia.

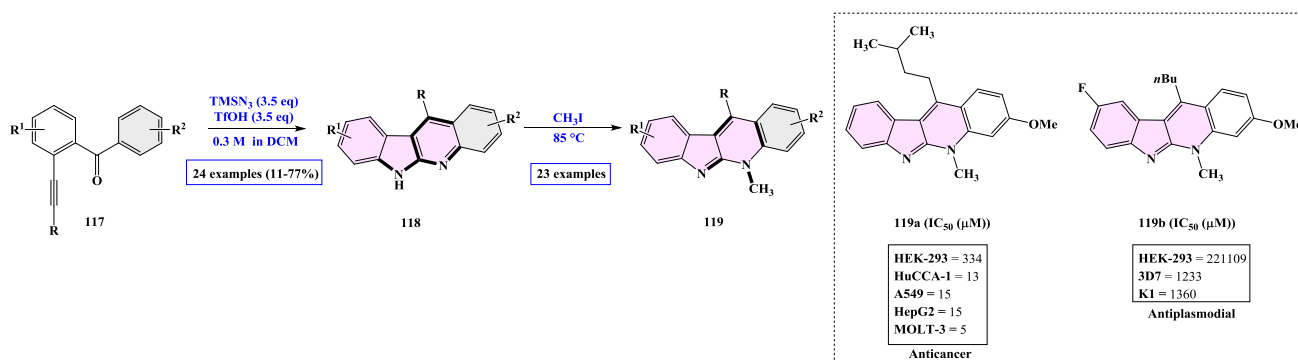
The reaction evolved in different ways when achieved with aromatic aldehydes and with enolizable aldehydes subject to aldolization, giving respectively pyrimido[4,5-*b*]indoles (not showed) or α -carbolines **113**. The results of this study revealed that acetaldehyde, propionaldehyde, butyraldehyde, 3-methylbutanal, and 3-phenylpropanal reacted with NH_4OH and compounds **111** under CuI catalysis to give α -carbolines **113** having on C2 and C3 substituents which differ by only one methylene group. Notably, with acetaldehyde ($\text{R}^1 = \text{H}$), a mono-substituted 2-methyl- α -carboline was obtained (38%), while the other aldehydes, having a longer carbon chain, gave 2,3-disubstituted-carbolines. Because the mechanism of this process starts with an auto-condensation reaction of aldehydes **112**, the authors also showed that α,β -unsaturated aldehydes such as cinnamaldehyde, reacted under these conditions with *ortho*-bromo-2-(2,2-dibromovinyl)benzene **111** ($\text{R} = \text{H}$) and NH_4OH to give 2-phenyl- α -carboline (50%) after creating multiple C–N and C–C bonds.

In 2020, Zhao mixed *ortho*-alkenyl arylisocyanides **114** with vinyl azides **115** under Rh/Cu co-catalysis to synthesize 2,4-disubstituted- α -carbolines **116** (Scheme 32).[78]



Scheme 32. Synthesis of 2,4-disubstituted- α -carbolines **116** by mixing *ortho*-alkenyl aryl isocyanides **114** with vinyl azides **115** under Rh/Cu co-catalysis.

In this reaction, vinyl carbodiimides intermediates[79] generated from the Rh-coupling of *ortho*-alkenyl aryl isocyanides **114** with vinyl azides **115** underwent intramolecular [4+2] cycloaddition to give 2,4-disubstituted- α -carbolines **116** in good yields. This process is of great interest, as it forms the 7-azaindole ring of carbolines **116** in a single electron movement by creating two C–C bonds and one C–N bond. This coupling cyclization tolerated isocyanides **114** bearing various substituents ($R = \text{Me, OMe, Cl, Br, Ph}$) and ($R^1 = \text{CO}_2\text{Me, C}_6\text{F}_5, 2\text{-Py}$). Similarly, the reaction showed broad tolerance to various vinyl azides **115** ($R^2 = \text{Ph, 4-MeC}_6\text{H}_4, 3\text{-MeC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 3\text{-FC}_6\text{H}_4, \text{Bn, } c\text{-Hexenyl, ...}$). The authors proposed a convincing mechanism based on control experiments (absence of the Rh-catalyst, standard conditions without O_2 , reaction achieved with a vinyl carbodiimide, the addition of CuI after 3.5 h of reaction).[78,79]



Scheme 33. Synthesis of indoloquinolines **118a,b** and **118a,b**.

In 2020, Tummatorn published a domino N_2 -extrusion/cyclization of *ortho*-substituted diarylketones **117** in the presence of TMSN_3 [80] for synthesizing original indoloquinolines **119** having anti-cancer and antiplasmodial activities after an *N*-methylation reaction of compounds **118** (Scheme 33).[81] This synthetic transformation tolerated various functional groups ($R^1 = \text{alkyl, Ar}$; $R^2 = \text{alkyl, OMe}$; $R^3 = \text{Me, Cl, F, OMe}$) and provided the expected indoloquinolines **118** with average yields. After a *N*-methylation reaction (yields not given), twenty-three neocryptoline analogues **119** were evaluated against four cancer cell lines (HuCCA-1; human cholangiocarcinoma, A549; human lung adenocarcinoma, HepG2; human liver carcinoma, MOLT-3; human acute lymphoblastic leukaemia) and compared the results with normal human embryonic kidney HEK-293 cell line. Interestingly, indoloquinoline **119a** was the most promising compound of the series, with micromolar level of cytotoxicity and an excellent selectivity index (from ~ 20 to ~ 70). Indoloquinolines **119** were next evaluated for their antiplasmodial activities using two standard laboratory *P. falciparum* isolates, chloroquine-sensitive (CQ-S) clone 3D7 and chloroquine-resistant (CQ-R) clone K1. The results were disappointing: only indoloquinoline **119b** displayed a modest millimolar level of antimalarial activity.

5.0 Biological activities of α -carbolines prepared by functionalization of a preformed α -carboline ring

The eight year period from 2015-2023 has witnessed a rising interest in synthesizing novel α -carboline derivatives as potential ligands simply by functionalizing a preformed α -carboline ring. Figure 5 grouped a selection of biologically active α -carbolines synthesized this way after 2015.

For example, anti-cancer α -carbolines **120**[82] and **TJY-16**[83] were cytotoxic, induced apoptosis and blocked the cellular cycle of cancer cells in the G2/M phase, whereas carbolines **121**[84], **122**[85], and **123**[86] acted as kinase inhibitors.

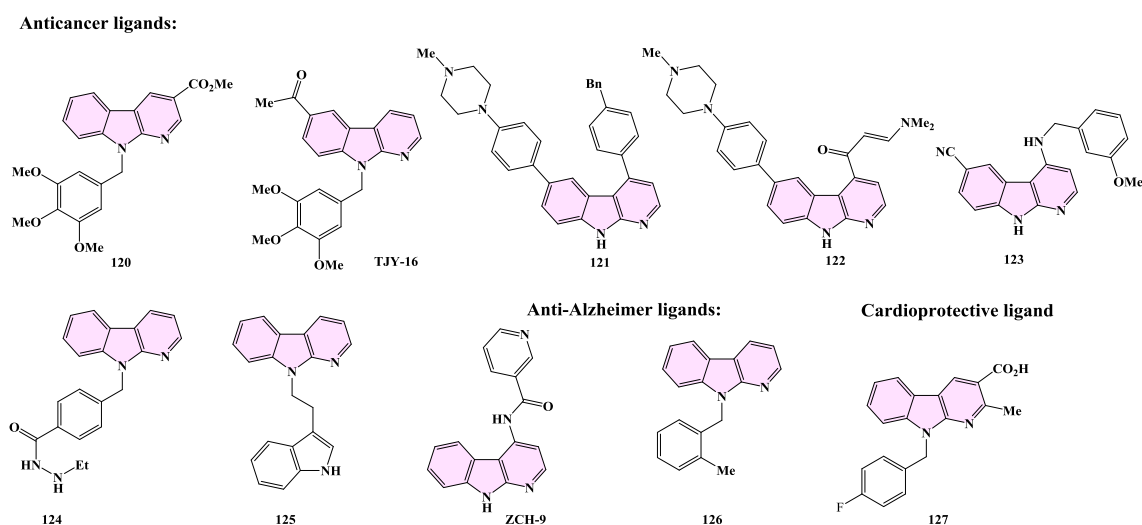


Figure 5. Selection of α -carbolines described after 2015 prepared by functionalization of the α -carboline skeleton.

Carboline derivative **124**, prepared from *N*-functionalization of the α -carboline skeleton, has an IC_{50} value of $0.037 \mu M$ toward HDAC6, and significantly higher IC_{50} values against other HDAC isoforms, indicating its high inhibitory activity and an excellent selectivity toward HDAC6.[87] In 2022, carboline **125** was identified as a potent DNA methyl transferase inhibitor (DNT1), but was less effective than its carbazole analogue.[88] In addition to these ligands with antitumor activity, α -carbolines **ZCH-9**[89] and **126**[90] were designed and synthesized as potential ligands in Alzheimer's disease therapy by inhibiting activity against NO production ($IC_{50} = 1.45 \mu M$) and by decreasing the hyperphosphorylation of tau protein in okalix acid treated SH-SY5Y cells, respectively. Wang and Li showed that α -carboline **127**[91] was a promising cardioprotective agent against H_2O_2 -induced oxidative injury.

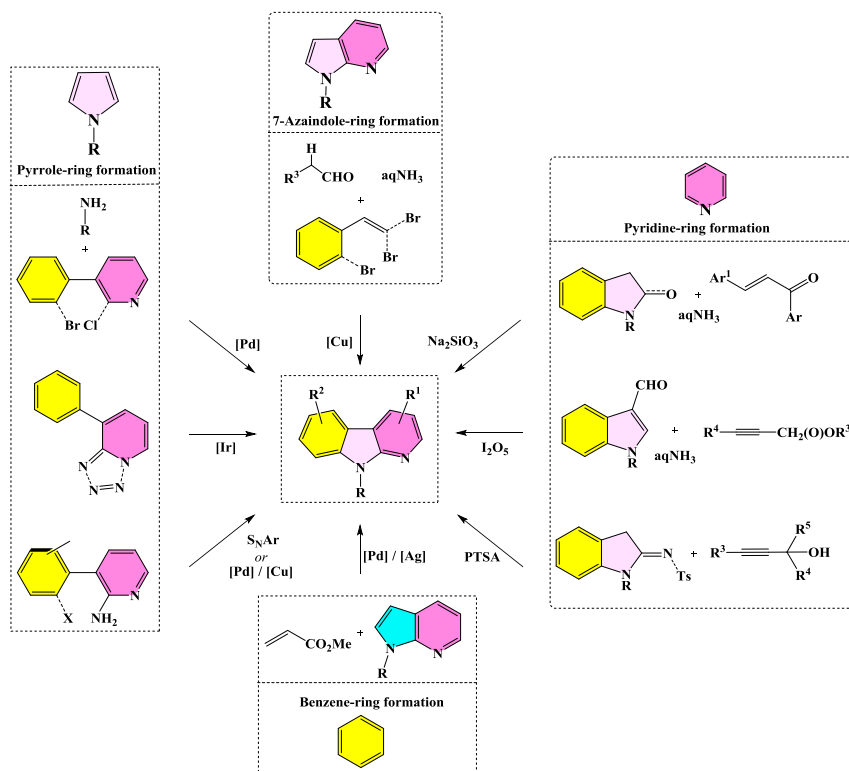


Figure 6. Summary of recent accesses described in this review to the α -carboline nucleus.

5. Conclusion

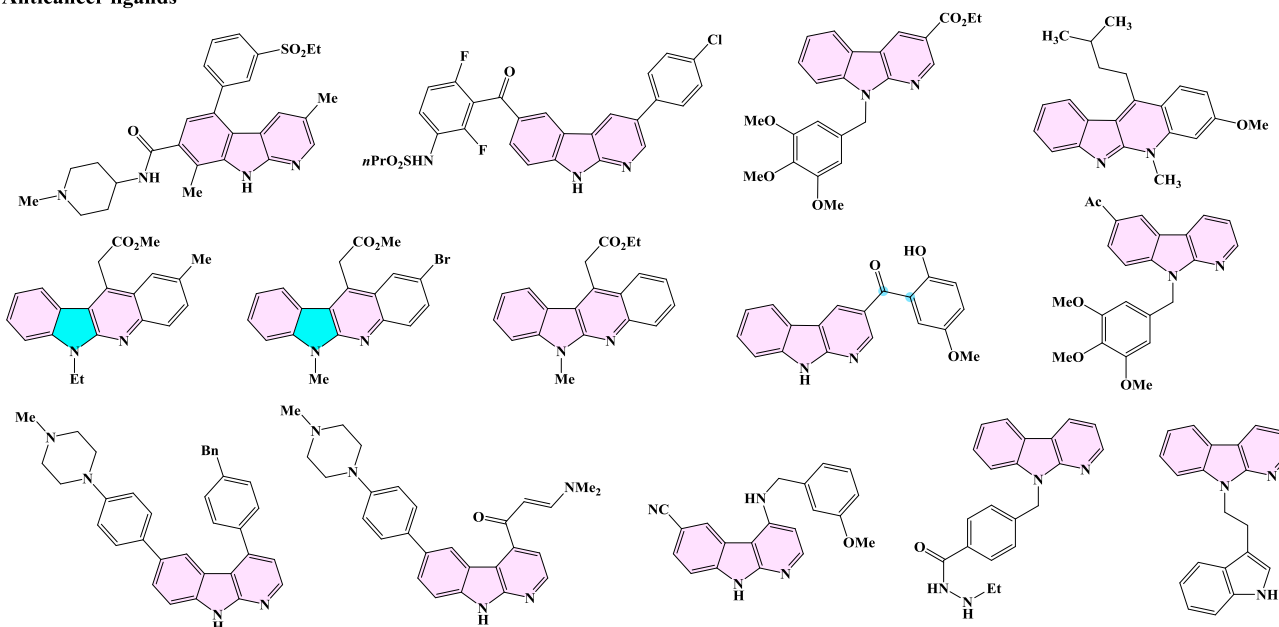
In the only other report about the synthesis of α -carbolines in 2015,[22] Wadsworth concluded, "many syntheses of α -carbolines described are limited by low yields, expensive reagents, starting material that are difficult to prepare or obtain...".

Eight years later, this update shows considerable progress in accessing the α -carboline skeleton with good yields according to modern methodologies compatible with environmental requirements.

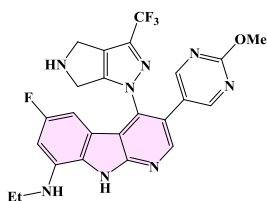
Figure 6 summarizes the recent methods and improvements described for preparing variously substituted α -carbolines by forming the pyrrole central ring, the benzene ring, the pyridine ring and the 7-azaindole ring of this tricyclic system from accessible starting materials. This simplicity of synthesis and the wide tolerance towards functional groups should encourage medicinal chemists to develop biological projects using this type of core as a pharmacophore.

Indeed, although many biological properties have been attributed to this nucleus (Figure 7) and its indoloquinoline analogues (anti-cancer, antiplasmodial, antibacterial, anti-Alzheimer, antidepressant, MKK4 inhibitor, etc.), few structure-activity relationship studies have been conducted.

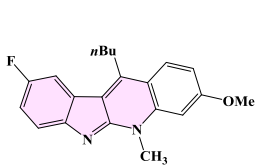
Anticancer ligands



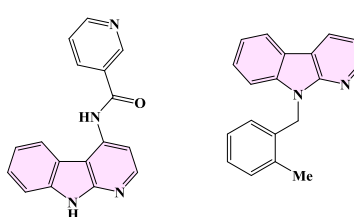
Antibacterial ligand



Antiplasmodial ligand



Neuroprotective ligands



Cardioprotective ligand

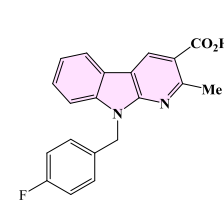


Figure 7. Some bioactive α -carbolines described in this review.

As part of our structure-activity studies, we will shortly insert this type of core into various *iso*Combretastatin A4[92,93] analogues to examine its effect on human cancer cell lines.

This review will hopefully encourage the chemical community to propose access to this heterocycle *via* totally "green" and economical processes and to introduce this tricyclic nucleus in various medicinal projects.

Declaration of competing interest

The author declares having no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We gratefully acknowledge the support of this project by the University of Paris-Saclay and CNRS.

References

-
- [1] For a review, see: D. Li, R. Yang, J. Wu, B. Zhong, Y. Li, Comprehensive review of α -carboline alkaloids: Natural products, updated synthesis, and biological activities, *Front. Chem.* 10 (2022) doi: 10.3389/fchem.2022.988327.
 - [2] Y.K. Wang, Y.L. Deng, X.Y. Liu, X.D. Yuan, Z.Q. Jiang, L.S. Liao, A facile way to synthesize high-triplet-energy hosts for blue phosphorescent organic light-emitting diodes with high glass transition temperature and low driving voltage, *Dyes Pigments* (2015) 6-12.
 - [3] S.Y. Byeon, J.M. Choi, J.Y. Lee, Pyridindole based intramolecular charge transfer type host material for blue phosphorescent organic light-emitting diodes, *Dyes Pigments* (2016) 285-290.
 - [4] Z. Tang, J. Zhu, S. Pan, Z. Wang, Y. Zheng, G. Chen, W. Zhu, B. Wei, Synthesis of carboline-based host materials for forming copper(I) complexes as emitters: A promising strategy for achieving high-efficiency and low-cost phosphorescent organic light-emitting diodes, *Dyes Pigments* (2018) 387-392.
 - [5] D.K. You, M. Kim, S. Yi, Y.J. Seo, W. Lee, K.M. Lee, Intriguing photophysical and mechanochromic characteristics of carboline-based benzothiadiazole donor-acceptor triad compounds, *Dyes Pigments* (2022) 110515.
 - [6] J.W. Jun, K.M. Lee, O.Y. Kim, J.Y. Lee, S.H. Hwang, Synthesis of a dibenzothiophene/carboline/carbazole hybrid bipolar host material for green phosphorescent OLEDs, *213 Synth. Met.* (2016) 7-11.
 - [7] J. Han, B. Thirupathiah, G. Kwon, C. Kim, S. Seo, Synthesis and characterization of carbazole- and α -carboline-based thiophene derivatives as organic semiconductors for organic thin-film transistors, *Dyes Pigments* (2015) 78-84.
 - [8] C. Tang, R. Bi, X. Cao, C. Fan, Y. Tao, S. Wang, H. Zhang, W. Huang, Cost-effective synthesis of α -carboline/pyridine hybrid bipolar host materials with improved electron-transport ability for efficient blue phosphorescent OLEDs, *5 RSC Adv.* (2015) 65481-65486.
 - [9] E. Varathan, D. Vijay, V. Subramanian, Quantum chemical design of carbazole- and pyridindole-based ambipolar host materials for blue phosphorescent OLEDs, *6 RSC Adv.* (2016) 74769-74784.
 - [10] J.S. Kang, T.R. Hong, H.J. Kim, J.H. Son, R. Lampande, B.Y. Kang, C. Lee, J.K. Bin, B.S. Lee, J.H. Yang, J. Kim, S. Park, M.J. Cho, J.H. Kwon, D.H. Choi, High-performance bipolar host materials for blue TADF devices with excellent external quantum efficiencies, *4 J. Mater. Chem. C* (2016) 4512-4520.
 - [11] Q. Wu, M. Wang, X. Cao, D. Zhang, N. Sun, S. Wan, Y. Tao, Carbazole/ α -carboline hybrid bipolar compounds as electron acceptors in exciplex or non-exciplex mixed cohosts and exciplex-TADF emitters for high-efficiency OLEDs, *6 J. Mater. Chem. C* (2018) 8784-8792.
 - [12] N. Helbecque, C. Moquin, J.L. Bernier, E. Morel, M. Guyot, J.P. Henichart, Grossularine-1 and grossularine-2, α -carbolines from *dendrodoa grossularia*, as possible intercalative agents, *9 Cancer Biochem. Biophys.* (1987) 271-279.
 - [13] S.M. Verbitski, C.L. Mayne, R.A. Davis, G.P. Conception, C.M. Irland, Isolation, Structure Determination, and Biological Activity of a Novel Alkaloid, Perophoramidine, from the Philippine Ascidian *Perophora namei*, *67 J. Org. Chem.* (2002) 7124-7126.
 - [14] K. Shin-Ya, J.S. Kim, K. Furihata, Y. Hayakawa, H. Seto, A novel neuronal cell protecting substance Mescengricin produced by *Streptomyces griseoflavus*, *2 J. Asian Nat. Prod. Res.* (2000) 121-132.
 - [15] K. Cimanga, T. De Bruyne, L. Pieters, A.J. Vlietinck, C.A. Turger, In Vitro and in Vivo Antiplasmodial Activity of Cryptolepine and Related Alkaloids from *Cryptolepis sanguinolenta*, *60 J. Nat. Prod.* (1997) 688-691.
 - [16] L. Guittat, P. Alberti, F. Rosu, S. Van Miert, E. Thetiot, L. Pieters, V. Gabelica, E. De Pauw, A. Ottaviani, J. Riou, J.L. Mergny, Interaction of cryptolepine and neocryptolepine with unusual DNA structures, *85 Biochimie*, (2003) 535-547.
 - [17] X. Zhang, Q. He, H. Xiang, S. Song, Z. Miao, C. Yang, Rapid access to α -carbolines via a one-pot tandem reaction of α,β -unsaturated ketones with 2-nitrophenylacetonitrile and the anti-proliferative activities of the products, *12 Org. Biomol. Chem.* (2014) 355-361.
 - [18] E. Rajanarendar, H.G. Reddy, S. Ramakrishna, M.N. Reddy, B. Shireesha, G. Durgaiah, Y.N. Reddy, Synthesis and in vitro and in vivo anticancer activity of novel 3-methyl-5*H*-isoxazolo[5',4':5,6]pyrido[2,3-*b*]indoles, *22 Bioorg. Med. Chem. Lett.* (2012) 6677-6680.
 - [19] P. Farrell, L. Shi, J. Matuszkiewicz, D. Balakrishna, T. Hoshino, L. Zhang, S. Elliott, R. Fabrey, B. Lee, P. Halkowycz, B. Sang, S. Ishino, T. Nomura, M. Teratani, Y. Ohta, C. Grimshaw, B. Paraselli, T. Satou, R. de Jong, Biological Characterization of TAK-901, an Investigational, Novel, Multitargeted Aurora B Kinase Inhibitor, *12 Mol. Cancer Ther.* (2013) 460-470.
 - [20] I. El Sayed, P. Van der Veken, K. Steert, L. Dhooghe, S. Hostyn, G. Van Baelen, G. Lemièrre, B.U.W. Maes, P. Cos, L. Maes, J. Joossens, A. Haemers, L. Pieters, K. Augustyns, Synthesis and Antiplasmodial Activity of Aminoalkylamino-Substituted Neocryptolepine Derivatives, *52 J. Med. Chem.* (2009) 2979-2988.

- [21] M. Thompson, I.T. Forbes, 9*H*-Pyrido[2,3-*b*]indole carboxylic acid ester compounds having useful pharmaceutical activity, **1990** US1989-307068.
- [22] A.D. Wadsworth, B.J. Naysmith, M.A. Brimble, A review on the synthesis of α -carbolines, *97 Eur. J. Med. Chem.* (2015) 816-829 and references therein.
- [23] W. Lawson, W.H. Perkin, R. Robinson, LXXVI.—Harmine and harmaline. Part VII. A synthesis of *apoharmine* and of certain carboline and copyrine derivatives, *125 J. Chem. Soc. Trans.* (1924) 626-657.
- [24] I. Hachiya, S. Shimada, M. Fukutomi, R. Miura, M. Shimizu, Synthesis of α -Carbolines Using Palladium-Catalyzed Intramolecular Amination of 3-(2-Chlorophenyl)-2-Aminopyridines, *4 ChemistrySelect* (2019) 469-472.
- [25] A. Bhattacharya, N.R. Babu, D. Bandyopadhyay, S. Peruncheralathan, Cu(OTf)₂ Enhanced Intramolecular Nucleophilic *N*-Arylation of 2-Amino-3-arylquinolines, *88 J. Org. Chem.* (2023) 8843-8853.
- [26] T.Q. Hung, T.T. Dang, J. Janke, A. Villinger, P. Langer, Efficient synthesis of α - and δ -carbolines by sequential Pd-catalyzed site-selective C–C and two-fold C–N coupling reactions, *13 Org. Biomol. Chem.* (2015) 1375-1386.
- [27] M. Minemo, M. Sera, T. Ueda, H. Mizufune, A. Zanka, C. O'Bryan, J. Brown, N. Scorch, Integrated Cross-Coupling Strategy for an α -Carboline-Based Aurora B Kinase Inhibitor, *80 J. Org. Chem.* (2015) 1564-1568.
- [28] S. Sathiyalingam, S. Roesner, Synthesis of α - and β -Carbolines by a Metalation/Negishi Cross-Coupling/S_NAr Reaction Sequence, *364 Adv. Synth. Catal.* (2022) 1769-1774.
- [29] S.K. Das, S. Roy, H. Khatua, B. Chattopadhyay, Ir-Catalyzed Intramolecular Transannulation/C(sp²)–H Amination of 1,2,3,4-tetrazoles by Electrocyclization, *140 J. Am. Chem. Soc.* (2018) 8429-8433.
- [30] S.K. Das, S. Das, S. Ghosh, S. Roy, M. Pareek, B. Roy, R.B. Sunoj, B. Chattopadhyay, An Iron(II)-based metalloradical system for intramolecular amination of C(sp²)–H and C(sp³)–H bonds: synthetic applications and mechanistic studies, *13 Chem. Sci.* (2022) 11817-11828.
- [31] D. Limbach, M. Geffe, H. Detert, Synthesis of Carbolines via Microwave-Assisted Cadogan Reactions of Aryl-Nitropyridines, *3 ChemistrySelect* (2022) 249-252.
- [32] Z. Qu, P. Wang, X. Chen, G.J. Deng, H. Huang, Visible-light-driven Cadogan reaction, *32 Chin. Chem. Lett.* (2021) 2582-2586.
- [33] Q. Yan, E. Gin, M.G. Banwell, A.C. Willis, P.D. Carr, A Unified Approach to the Isomeric α -, β -, γ -, and δ -Carbolines via their 6,7,8,9-Tetrahydro Counterparts, *82 J. Org. Chem.* (2017) 4328-4335.
- [34] T. Wüestefeld, M. Pesic, R. Rudalska, D. Dauch, T. Longerich, T.W. Kang, T. Yevsa, F. Heinzmann, L. Hoenicke, A. Hohmeyer, A. Potapova, I. Rittmeier, M. Jarek, R. Geffers, M. Scharfe, F. Klawonn, P. Schirmacher, N.P. Malek, M. Ott, A. Nordheim, A. Vogel, M.P. Manns, L.A. Zender, Direct in vivo RNAi screen identifies MKK4 as a key regulator of liver regeneration, *153 Cell* (2013) 389-401.
- [35] M. Juchum, B. Pfaffenrot, P. Klövekorn, R. Selig, W. Albrecht, L. Zender, S.A. Laufer, Scaffold modified Vemurafenib analogues as highly selective mitogen activated protein kinase kinase 4 (MKK4) inhibitors, *240 Eur. J. Med. Chem.* (2022) 114584.
- [36] Y. Hu, H. Shi, M. Zhou, Q. Ren, W. Zhu, W. Zhang, Z. Zhang, C. Zhou, Y. Liu, X. Ding, H.C. Shen, S.F. Yan, F. Dey, W. Wu, G. Zhai, Z. Zhou, Z. Xu, Y. Ji, H. Lv, T. Jiang, W. Wang, Y. Xu, M. Vercruyse, X. Yao, Y. Mao, X. Yu, K. Bradley, X. Tan, Discovery of Pyrido[2,3-*b*]indole Derivatives with Gram-Negative Activity Targeting Both DNA Gyrase and Topoisomerase IV, *63 J. Med. Chem.* (2020) 9623-9649.
- [37] L. He, S.P. Allwein, B.J. Dugan, K.W. Knouse, G.R. Ott, C.A. Zificsak, Synthesis of α -carboline, *93 Org. Synth.* (2016) 272-285.
- [38] M. Sera, H. Mizufune, T. Ueda, M. Mineno, A. Zanka, Integrated Pd-catalyzed cross-coupling strategies for furnishing α -carbolines, *73 Tetrahedron* (2017) 5946-5958.
- [39] T.H. Yang, C.W. Kuo, V. Kavala, A. Konala, C.Y. Huang, C.F. Yao, Regioselective switching approach for the synthesis of α and δ carboline derivatives, *83 Chem. Commun.* (2017) 1676-1679.
- [40] F. Portela-Cubillo, B.A. Surgenor, R.A. Aitken, J.C. Walton, Thermal Rearrangement of Indoyle Esters to Pyridoindoles, *73 J. Org. Chem.* (2008) 8124-8127.
- [41] S.J. Markey, W. Lewis, C.J. Moody, A New Route to α -Carbolines Based on 6 π -Electrocyclization of Indole-3-alkenyl Oximes, *15 Org. Lett.* (2013) 6306-6308.
- [42] W. Feng, C. Zhang, X. Zhou, K. You, G.J. Deng, S. Chen, Chemoselective three-component synthesis of α -carbolines under metal-free conditions, *10 Org. Chem. Front.* (2023) 5457-5462.
- [43] A. Kalyani, R.N.P. Tulichala, S. Chauhan, K.C.K. Swamy, Palladium catalyzed nitrile insertion and cyanation of biindoles: Synthesis of indole fused α -carboline scaffolds *via* double C–H activation, *89 Tetrahedron Lett.* (2022) 153600.
- [44] R.N.P. Tulichala, K.C.K. Swamy, Palladium-catalysed decarboxylative nitrile insertion *via* C–H activation or self-coupling of indole-2-carboxylic acids: a new route to indolocarbolines and triindoles, *51 Chem. Commun.* (2015) 12008-12011.
- [45] S. Tian, Y. Mao, Y. Jiang, G. Xu, The Application of Vinamidinium Salt to the Synthesis of 3-Chloro- α -carbolines, *29 Synlett* (2018) 949-953.

- [46] S. Sheikh, A. Fazlinia, Preparation of Pyrido[2,3-*b*]indole Derivatives Using Silicates of Group 1 and 2 Metals, 55 *J. Heterocyclic Chem.* (2018) 2291-2296.
- [47] L. Chen, X. Zhang, K.J. Shi, H.J. Leng, Q.Z. Li, Y. Liu, J.H. Li, Q.W. Wang, J.L. Li, Bifunctional Brønsted Base Catalyzed [3+3] Annulations of Indolin-2-Imines and α,β -Unsaturated Imides: An Enantioselective Approach to α -Carbolinones, 85 *J. Org. Chem.* (2020) 9454-9463.
- [48] K.C. Yang, Q.Z. Li, Y. Liu, Q.Q. He, Y. Liu, H.J. Leng, A.Q. Jia, S. Ramachandran, J.L. Li, Highly Stereoselective Assembly of α -Carbolinone Skeletons via *N*-Heterocyclic Carbene-Catalyzed [4+2] Annulations, 20 *Org. Lett.* (2018) 7518-7521.
- [49] L. Yi, Y. Zhang, Z.F. Zhang, D. Sun, S. Ye, Synthesis of Dihydropyridinone-Fused Indoles and α -Carbolines via *N*-Heterocyclic Carbene-Catalyzed [3 + 3] Annulation of Indolin-2-imines and Bromoenals, 19 *Org. Lett.* (2017) 2286-2289.
- [50] H. Liu, A.M.Z. Slawin, A.D. Smith, Isothiourea-Catalyzed Enantioselective Synthesis of Tetrahydro- α -carbolinones, 22 *Org. Lett.* (2020) 1301-1305.
- [51] H.J. Leng, Y.T. Wang, X.H. He, H.L. Xia, P.S. Xu, P. Xiang, Q.Q. He, G. Zhan, W. Huang, Design and Efficient Synthesis of Ra1A Inhibitors Containing the Dihydro- α -carboline Scaffold, 16 *ChemMedChem* (2021) 851-859.
- [52] G. Li, X.H. He, H.P. Li, Q. Zhao, D.A. Li, H.P. Zhu, Y.H. Zhang, G. Zhan, W. Huang, Design, Synthesis, and Biological Evaluation of Tetrahydro- α -carbolines as Akt1 Inhibitors That Inhibit Colorectal Cancer Cell Proliferation, 17 *ChemMedChem* (2022) e202200104.
- [53] S.T. Sivanandan, D. Chauhan, I.N.N. Namboothiri, One-Pot Regio- and Diastereoselective Synthesis of Tetrahydro- α -carbolines via Cascade Reactions of Iminoindolines with Morita-Baylis-Hillman Bromides of Nitroalkenes, *Eur. J. Org. Chem.* 2022, e202101426.
- [54] S.T. Sivanandan, I.N.N. Namboothiri, Metal-Free and Regioselective Synthesis of Functionalized α -Carbolines via [3+3] Annulation of Morita-Baylis-Hillman Acetates of Nitroalkenes with Iminoindolines, 86 *J. Org. Chem.* (2021) 8465-8471.
- [55] K. Selvaraj, K.C.K. Swamy, Transition-Metal-Free, Brønsted Acid-Mediated Cascade Sequence in the Reaction of Propargyl Alcohols with Sulfonamido-indoles/-indolines: Highly Substituted δ - and α -Carbolines, 83 *J. Org. Chem.* (2018) 15043-15056.
- [56] S. Debnath, A.S. Kumar, S. Chauhan, K.C.K. Swamy, Divergent Reactivity of δ - and β' -Acetoxy Allenates with 2-sulfonamidoindoles via Phosphine Catalysis: entry to Dihydro- α -carboline, α -carboline, and Spiro-cyclopentene Motifs, 86 *J. Org. Chem.* (2021) 11583-11598.
- [57] S. Debnath, A.S. Kumar, S. Chauhan, K.C.K. Swamy, Lewis-Base Dependent (3 + 3) Annulations of Acetoxy Allenates with Iminoindolines: α -Carbolines Scaffolds with Varied Substituents, 364 *Adv. Synth. Catal.* (2022) 4316-4332.
- [58] R. Ma, X. Wang, Q. Zhang, L. Chen, J. Gao, J. Feng, D. Wei, D. Du, Atroposelective Synthesis of Axially Chiral 4-Aryl α -Carbolines via *N*-Heterocyclic Carbene Catalysis, 23 *Org. Lett.* (2021) 4267-4272.
- [59] C. Wang, H. Zhang, B. Lang, A. Ren, P. Lu, Y. Wang, Rh-Catalyzed Reactions of 3-Diazoindolin-2-imines: Synthesis of Pyridoindoles and Tetrahydrofuropyrroloindoles, 17 *Org. Lett.* (2015) 4412-4415.
- [60] C.H. Zhang, R. Huang, Z.W. Zhang, J. Lin, S.J. Yan, An Environmentally Benign Cascade Reaction of 1,1-Enediamines (EDAMs) for Site-Selective Synthesis of Highly Functionalized 2,10-Dihydro-1*H*-imidazo[1',2':1,6]pyrido[2,3-*b*]indoles and Porphyrins, 86 *J. Org. Chem.* (2021) 5744-5756.
- [61] T.H. Yang, V. Kavala, C.W. Kuo, C.F. Yao, Synthesis of Pyrido[2,3-*b*]indoles via Brønsted-Acid-Promoted Decarboxylative Annulation of 3-Bromopropenals and Ethyl 2-Amino-1*H*-3-carboxylates, 9 *Asian J. Org. Chem.* (2020) 1053-1058.
- [62] N. Altwaijry, S. El-Ghlban, I.E.T. El Sayed, M. El-Bahnsawye, A.I. Bayomi, R.M. Samaka, E. Shaban, E.I. Elmongy, T.A. El-Masry, H.M.A. Ahmed, N.G.M. Attallah, In Vitro and In Vivo Antitumor Activity of Indolo[2,3-*b*]Quinolines, Natural Products from Neocryptolepine Alkaloid, 26 *Molecules* (2021) 754.
- [63] Z. Yan, C. Wan, J. Wan, Z. Wang, An efficient iron-promoted synthesis of 6*H*-indolo[2,3-*b*]quinolines and neocryptolepine derivatives, 14 *Org. Biomol. Chem.* (2016) 4405-4408.
- [64] S. Yu, Y. Li, X. Zhou, H. Wang, L. Kong, X. Li, Access to Structurally Diverse Quinoline-Fused Heterocycles via Rhodium(III)-Catalyzed C-C/C-N Coupling of Bifunctional Substrates, 18 *Org. Lett.* (2016) 2812-2815.
- [65] S. Badigenchala, V. Rajeshkumar, G. Sekar, Iodine mediated intramolecular C2-amidative cyclization of indoles: a facile access to indole fused tetracycles, 14 *Org. Biomol. Chem.* (2016) 2297-2305.
- [66] R. Sunke, V. Kumar, M.A. Ashfaq, S. Yellanki, R. Mediseti, P. Kulkarni, E.V.V.S. Ramarao, N.Z. Ehtesham, M. Pal, A Pd(II)-catalyzed C-H activation approach to densely functionalized *N*-heteroaromatics related to neocryptolepine and their evaluation as potential inducer of apoptosis, 5 *RSC Adv.* (2015) 44722-44727.
- [67] H. Wang, L. Li, S. Yu, Y. Li, X. Li, Rh(III)-Catalyzed C-C/C-N Coupling of Imidates with α -Diazo Imidamide: Synthesis of Isoquinoline-Fused Indoles, 18 *Org. Lett.* (2016) 2914-2917.
- [68] D.G. Valapil, P. Mishra, K. Jungare, N. Shankaraiah, Ru(II)-catalyzed synthesis of indolo[2,3-*c*]isoquinolines via [3+3] annulation of *N,N'*-cyclic azomethyne ylides and 3-diazoindolin-2-imines, 47 *New J. Chem.* (2023) 17586-17591.
- [69] J.K. Laha, N. Dayal, A Tandem Approach to Functionalized Carbazoles from Indoles via Two Successive Regioselective Oxidative Heck Reactions Followed by Thermal Electrocyclization, 17 *Org. Lett.* (2015) 4742-4745.

- [70] H. Wang, L. Li, S. Yu, Y. Li, X. Li, Rh(III)-Catalyzed C–C/C–N Coupling of Imidates with α -Diazo Imidamide: Synthesis of Isoquinoline-Fused Indoles, 18 *Org. Lett.* (2016) 2914-2917.
- [71] J.M. Yi, X.F. Zhang, X.J. Huan, S.S. Song, W. Wang, Q.T. Tian, Y.M. Sun, Y. Chen, J. Ding, Y.Q. Wang, C.H. Yang, Z.H. Miao, Dual targeting of microtubule and topoisomerase II by α -carboline derivative YCH337 for tumor proliferation and growth inhibition, 6 *Oncotarget* (2015) 8960-8973.
- [72] X. Zhang, Q. He, H. Xiang, S. Song, Z. Miao, C. Yang, Rapid access to α -carbolines via a one-pot tandem reaction of α,β -unsaturated ketones with 2-nitrophenylacetonitrile and the anti-proliferative activities of the products, 12 *Org. Biomol. Chem.* (2014) 355-361.
- [73] Y. Xu, X. Chen, Y. Gao, Z. Yan, C. Wan, J.B. Liu, Z. Wang, Synthesis of Trifluoromethyl- and Ester Group-Substituted α -Carbolines via Iron-Catalyzed Tandem Cyclization Reaction, 85 *J. Org. Chem.* (2020) 4354-4364.
- [74] G. Wang, X. You, Y. Gan, Y. Liu, Synthesis of δ - and α -Carbolines via Nickel-Catalyzed [2+2+2] Cycloaddition of Functionalized Alkyne Nitriles with Alkynes, 19 *Org. Lett.* (2017) 110-113.
- [75] J. Zhang, M. Guo, Y. Chen, S. Zhang, X.N. Wang, J. Chang, Synthesis of Amino-Substituted α - and δ -Carbolines via Metal-Free [2+2+2] Cycloaddition of Functionalized Alkyne-Nitriles with Ynamides, 21 *Org. Lett.* (2019) 1331-1336.
- [76] K.M. Medas, R.W. Lesch, F.B. Ediom, S.P. Wreen, V. Ndahayo, S.P. Mulcahy, Metal-Catalyzed Cyclotrimerization Reaction of Cyanamides: Synthesis of 2-Aryl- α -carbolines, 22 *Org. Lett.* (2020) 3135-3139.
- [77] B. Li, S. Guo, J. Zhang, X. Zhang, X. Fen, Selective Access to 3-Cyano-1*H*-indoles, 9*H*-Pyrimido[4,5-*b*]indoles through Copper-Catalyzed One-Pot Multicomponent Cascade Reactions, 80 *J. Org. Chem.* (2015) 5444-5456.
- [78] M. Yang, X.H. Meng, Z. Wang, Y. Gong, Y.L. Zhao, Rhodium/copper cocatalyzed coupling-cyclization of *o*-alkenyl arylisocyanides with vinyl azides: one-pot synthesis of α -carbolines, 7 *Org. Chem. Front.* (2020) 3493-3498.
- [79] Z. Li, T. Huo, L. Li, S. Feng, Q. Wang, Z. Zhang, S. Pang, Z. Zhang, P. Wang, Z. Zhang, Rh-Catalyzed reaction of vinyl azides with isocyanides and alkynes/benzynes, 20 *Org. Lett.* (2018) 7762-7766.
- [80] B. Akkachairin, J. Tummatom, N. Khamsuwan, C. Thongsornkleeb, S. Ruchirawat, Domino N₂-Extrusion–Cyclization of Alkynylketone Derivatives for the Synthesis of Indoloquinolines and Carbocycle-Fused Quinolines, 83 *J. Org. Chem.* (2018) 11254-11268.
- [81] B. Akkachairin, W. Rodphon, O. Reamtong, M. Mungthin, J. Tummatom, C. Thongsornkleeb, S. Ruchirawat, Synthesis of neocryptolepines and carbocycle-fused quinolones and evaluation of their anticancer and antiparasitic activities, 98 *Bioorg. Chem.* (2020) 103732.
- [82] Y.C. Lin, Y.F. Chen, L.S. Tseng, N.H. Lee, S.L. Morris-Natschke, S.C. Kuo, N.S. Yang, K.H. Lee, L.J. Huang, Synthesis and structure-activity relationship of novel 3,9-substituted α -carboline derivatives with high activity against colorectal cancer cells, 110 *Eur. J. Med. Chem.* (2016) 98-114.
- [83] H.C. Huang, W.T. Liu, K.S. Hua, H.C. Hung, J.Y. Tsai, S.C. Kuo, L.J. Huang, P.W. Gean, α -Carboline derivative TJY-16 inhibits tumor growth by inducing G2/M cell cycle arrest in glioma cells, 32 *J. Biomed. Sci.* (2016) 271-276.
- [84] L. Mologni, A. Orsato, A. Zamboni, S. Tardy, W.H. Bisson, C. Schneider, M. Cecon, M. Viltadi, J. D'Attoma, S. Pannilunghi, V. Vece, D. Gueyraud, J. Bertho, L. Scapozza, P. Goekjian, C. Gambacorti-Passerini, Identification of non-ATP-competitive inhibitors of the anaplastic lymphoma kinase, 238 *Eur. J. Med. Chem.* (2022) 114488.
- [85] L. Mologni, S. Tardy, A. Zamboni, A. Orsato, W.H. Bisson, M. Cecon, M. Viltani, J. D'Attoma, S. Pannilunghi, V. Vece, J. Bertho, P. Goekjian, L. Scapozza, C. Gambacorti-Passerini, Discovery of Novel α -Carboline Inhibitors of the Anaplastic Lymphoma Kinase, 7 *ACS Omega* (2022) 17083-17097.
- [86] C. Hempel, F. Totzke, C. Schächtele, A. Najjar, W. Sippl, C. Ritter, A. Hilgeroth, Discovery of novel dual inhibitors of receptor tyrosine kinases EGFR and IGF-1R, 32 *J. Enzyme Inhib. Med. Chem.* (2017) 271-276.
- [87] K. Yue, S. Sun, G. Jia, M. Qin, X. Hou, C.J. Chou, C. Huang, X. Li, First-in-Class Hydrazide-Based akt1HDAC6 Selective Inhibitor with Potent Oral Anti-Inflammatory Activity by Attenuating NLRP3 Inflammasome Activation, 65 *J. Med. Chem.* (2022) 12140-12162.
- [88] E. Li, K. Wang, B. Zhang, S. Guo, S. Xiao, Q. Pan, X. Wang, W. Chen, Y. Wu, H. Xu, X. Kong, C. Luo, S. Chen, B. Liu, Design, synthesis, and biological evaluation of novel carbazole derivatives as potent DNMT1 inhibitors with reasonable PK properties, 37 *J. Enzyme Inhib. Med. Chem.* (2022) 1537-1555.
- [89] W. Dan, Y. Cao, Y. Sun, J. Zhang, J. Liu, J. Gao, R. Han, J. Dai, Novel *N*¹ or *N*² modified α -carboline analogues as potential ligands in Alzheimer's disease therapy: Synthesis and neurobiological activity evaluation, 133 *Bioorg. Chem.* (2023) 106378.
- [90] H. Chen, C. Yu, W. Liu, C. Zhu, X. Jiang, C. Xu, W. Liu, Y. Huang, Z. Xu, Q. Zhao, Discovery of novel α -carboline derivatives as glycogen synthase kinase-3 β inhibitors for the treatment of Alzheimer's disease, *Arch. Pharm.* 2022, doi: 10.1002/ardp.202200156.
- [91] R.R. Zhang, D. Yang, X.M. Liao, H. Zhang, G.Q. Chen, W.L. Zhang, Y.C. Wang, C. Wang, S.G. Liao, M. Zhou, Y.L. Wang, Y.J. Li, Design, synthesis, and in vitro protective effect evaluation of α -carboline derivatives against H₂O₂-induced cardiomyocyte injury, 238 *Eur. J. Med. Chem.* (2022) 114469.
- [92] S. Pecnard, A. Hamze, J. Bignon, B. Prost, A. Deroussent, L. Gallego-Yerga, R. Peláez, J.-Y. Paik, M. Diederich, M. Alami, O. Provot, Anticancer Properties of Indole Derivatives as IsoCombretastatin A-4 analogues, 223 *Eur. J. Med. Chem.* (2021) 113656.

[93] Khelifi, I.; Naret, T.; Hamze, A.; Bignon, J.; Levaique, H.; Garcia, C.; Dubois, J.; Provot, O.; M. Alami. *N,N*-bis-Heteroaryl Methylamines: Potent Anti-Mitotic and Highly Cytotoxic Agents. 168 Eur. J. Med. Chem. (2019) 176.