METHODOLOGIES FOR THE SYNTHESIS OF β-CARBOLINES

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Abstract. *β-Carbolines are an important class of heterocyclic compounds that are widely distributed in nature, being found in several families of naturally occurring alkaloids. Due to their diverse biological activities, the synthesis of β-carbolines is of high importance. Besides traditional methodologies, like the Pictet-Spengler and the Bischler-Napieralski reaction, many alternative strategies have been developed for the synthesis of the β-carboline motif. This review summarizes methodologies and strategies for the synthesis of β-carbolines published between 2000 and 2021.*

Contents

1. Introduction

Pyrido[3,4-*b*]indoles, commonly known as β-carbolines, are tricyclic alkaloids that are widely distributed in nature present in a multitude of animal and plant species. The three rings in β-carbolines are referred to as the A-, B- and C-ring, as labelled in Figure 1. Among the four carboline isomers, β-carbolines are the most commonly found motif in nature. β-Carboline containing natural products and their synthetic derivatives possess a remarkable spectrum of important biological and pharmacological properties,[1] namely cytotoxicity and antitumoral activity,[2-6] antiviral properties[7] and anti-inflammatory activity.[8] Several β-carboline-based compounds also possess high binding affinity to monoamine oxidase[9] as well as serotonin[10] and benzodiazepine receptors[11] in the central nervous system. Owing to their diverse biological activity, naturally occurring β-carbolines have remained a popular synthetic target for many years, and the synthesis of unexplored β-carbolines with novel substitution patterns has become increasingly popular in obtaining further understanding of the structure activity relationship for this class of compounds.

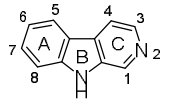


Figure 1. Tricyclic framework of β-carbolines.

Herein, we will provide an update on Love's 1996 review,[12] covering a general outline of synthetic routes toward β-carbolines reported between 2000 and 2021. Hereby, we will focus on the preparation of fully aromatic β-carbolines. Tetrahydro-β-carbolines (THBCs) and dihydro-β-carbolines (DHBCs), which are biologically interesting compounds in their own right, will be only covered as intermediates in the synthesis of fully aromatic β-carbolines. Furthermore, the synthesis and biological activity of TBHCs has recently been reviewed.[13] In the time since Love's comprehensive review, Domínguez and Pérez-Castells have discussed the use of β-carbolines as synthetic intermediates as well as further transformations of β-carbolines.[14-15] Milen and Ábrányi-Balogh discussed newly developed synthetic approaches in their 2016 microreview,[16] while Zhang *et al.* compared representative synthetic strategies for all four classes of carbolines.[17] Devi *et al.* reviewed the synthesis and application of 1- and 3-formyl-β-carbolines as valuable building blocks for the synthesis of biologically active compounds.[18] Recently, Szabó *et al.* summarized the synthesis of naturally occurring β-carboline alkaloids[19] and Singh *et al.* reviewed β-carboline-derived natural products, which were accessed through a Pictet-Spengler reaction.[20]

Since Love reviewed the synthesis and functionalization of β-carbolines,[12] which focused mainly on the Pictet-Spengler and Bischler-Napieralski reaction, significant progress has been achieved in the synthesis of this biologically important molecular scaffold through a variety of newly developed methodologies. In particular, progress in the field of transition metal catalysis has enabled a significant number of new methodologies to synthesize differentially substituted β-carbolines. Furthermore, while in Love's review the majority of procedures were target-driven to achieve the synthesis of one or more β-carboline-derived natural products, most procedures described here are rather driven by the development of new synthetic methodologies. Consequently, new substitution patterns on the carboline core can now be achieved that enable opportunities to find new biologically active entities.

Two main synthetic strategies for the synthesis of β-carbolines exist, either through the formation of the pyridine, the C-ring, or the generation of the central pyrrole, the B-ring. The former method is by far the most commonly applied strategy, possibly due to the availability of substituted indole derivatives. Initially, we will detail routes to access β-carbolines from THBCs and DHBCs through oxidative aromatization, and from then focus on the direct synthesis of fully aromatic β-carbolines. Recent developments for the Pictet-Spengler and Bischler-Napieralski reaction will be discussed, followed by an overview of methodologies that generate the pyridine ring from indole precursors, including cylclocondensation reactions, iminoannulations, metal-catalyzed transformations, and other reactions. This discussion will be followed by a summary of procedures that generate the central pyrrole ring, mainly focussing on palladium-catalyzed transformations. Finally, cascade reactions will be discussed that generate both, the B- as well as the C-ring in a single reaction sequence.

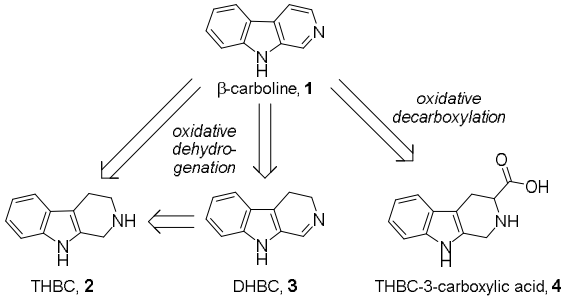
2. Oxidation of tetrahydro- and dihydro-β-carbolines

The Pictet-Spengler and Bischler-Napieralski reaction (see section 3.1 and 3.2) are transformations in which the C-ring is generated. These traditional reactions are the most widely employed methods for preparing β-carbolines.[12] Both reactions rely on tryptophan or tryptamine-based substrates providing either THBCs or DHBCs. In most cases, an additional aromatization step is required to provide fully aromatic tricyclic β-carbolines.

The oxidation of THBCs **2** and DHBCs **3** to β-carbolines **1** has been widely explored (Scheme 1). While an extensive discussion of these methods is beyond the scope of this review, a general overview of the various ways to aromatize **2** and **3** to fully aromatic β-carbolines should be provided. Traditional methods for the oxidative dehydrogenation to transform THBCs **2** into β-carbolines **1** include palladium on carbon,[21-26] sulfur in refluxing xylene or DMSO,[2,11,27] activated manganese oxide,[3,28] selenium dioxide,[29] potassium permanganate,[21,27,30-34] or lead(IV) acetate.[27] These reagents require quite harsh reaction conditions, often high temperatures, large excess of oxidant, long reaction times and only tolerate certain functional groups, namely ester, aryl and alkyl functionalities.

Oxidative decarboxylation can be applied to transform THBC-3-carboxylic acids **4** into the respective β-carbolines **1** (Scheme 1). Reagents reported for this transformation include ammonium persulfate in the presence of catalytic silver nitrate,[35] trichloroisocyanuric acid (TCCA),[36-37] catalytic iodine in the presence aqueous hydrogen peroxide,[38] iodobenzene diacetate ($PhI(OAc)_2$),[39] *N*-chlorosuccinimide (NCS),[34,40] selenium dioxide,[32] copper salts,[41] and heating in dimethyl sulfoxide (DMSO).[42] Alternatively, these

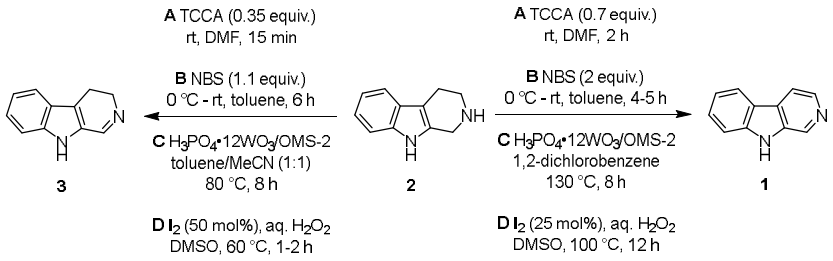
conditions can be used in the presence of a C3 ester functionality to aromatize the pyridine moiety. In general, THBC esters with an electron donating substituent in C1 position are more easily dehydrogenated.[36,39]



Scheme 1. Oxidation of THBCs **2** and **4** and DHBC **3** to β-carboline **1**.

Although oxidative dehydrogenation reactions are often used to transform THBCs **2** directly to β-carbolines **1**, specific reaction conditions have been developed that give selectively DHBCs **3** (Scheme 2). Manasa *et al.* reported the use of trichloroisocyanuric acid (TCCA) as a mild oxidant at room temperature.[36] When using 0.7 equiv. of TCCA for 2 h, the reaction proceeded straight to β-carboline **1** (Scheme 2A), whereas when using only 0.35 equiv. of TCCA for 15 min, the reaction selectively provided DHBC **3** (Scheme 2A). Hati and Sen reported the use of *N*-bromosuccinimide (NBS) in the selective dehydrogenation of THBC **2** to DHBC **3** or β-carboline **1**, similarly by altering the equivalents of the oxidant.[43] When 2 equiv. of NBS were used, the reaction proceeded from **2** to the fully aromatic β-carboline **1** (Scheme 2B), whereas when only 1.1 equiv. of NBS were used, the reaction provided selectively DHBC **3** (Scheme 2B).

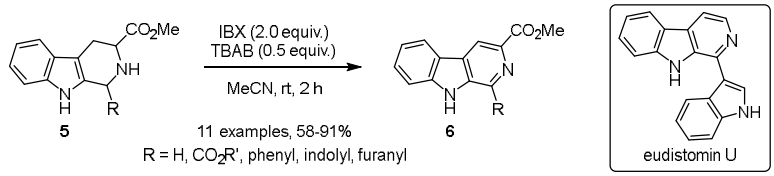
Bi *et al.* described a chemoselective catalyst for the dehydrogenation of THBCs **2** employing oxygen (from air) as the effective oxidant (Scheme 2C).[44] They described the preparation of $H_3PO_4 \cdot 12WO_3$/OMS-2, a nanocomposite catalyst featuring a manganese oxide octahedral molecular sieve, doped with 2 mol% sodium phosphotungstate. This catalyst enabled selective aerobic oxidation of THBC **2** to either DHBC **3** or β-carboline **1**. When the oxidation was conducted in a 1:1 mixture of toluene and acetonitrile at 80 °C, the reaction provided selectively DHBC **3**. Conversely, when using 1,2-dichlorobenzene at 130 °C, the reaction afforded the fully dehydrogenated β-carboline **1**. Gaikwad *et al.* developed a temperature controlled chemoselective dehydrogenation of THBCs **2** using iodine and hydrogen peroxide in DMSO (Scheme 2D).[45] Depending on the time and the reaction temperature, either DHBC **3** at 60 °C or β-carboline **1** at 100 °C could selectively be obtained. This methodology was applied to the total synthesis of a number of natural products, including kumujian C and eudistomin U.



Scheme 2. Chemoselective oxidation of THBC **2** to either DHBC **3** or β-carboline **1**.

Panarese and Waters reported a method for the oxidative dehydrogenation of THBCs **5** to β-carbolines **6** under mild conditions using 2-iodoxybenzoic acid (IBX) and tetrabutylammonium bromide (TBAB) (Scheme 3).[46] As mentioned above, having an electron-donating group at the C1 position enabled higher

yields and a faster reaction rates. The authors also reported that the ester functionality at C3 was important for the oxidation to proceed rapidly under the reported conditions. This procedure was applied in a four-step total synthesis of eudistomin U. Later, the same authors extended this methodology to develop a route to β-carbolines carrying a C1 carbonyl group. Tandem oxidation provided aromatic β-carbolines from THBCs as well as a carbonyl group from an alkyl chain in C1 position.[47] The utility of this methodology was demonstrated in total syntheses of the marine natural products eudistomins Y_1-Y_7.



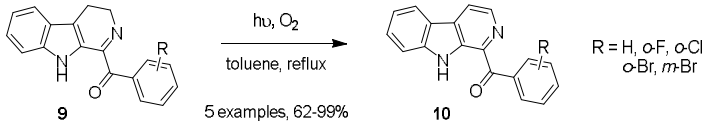
Scheme 3. IBX-mediated oxidation of THBCs **5** to β-carbolines **6**.

Another procedure for the dehydrogenation of THBCs **7** to β-carbolines **8** applying mild reaction conditions was reported by Bai *et al.* (Scheme 4).[48] Using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant, THBCs **7** were converted to β-carbolines **8** in just 30 min at room temperature in high yields. A variety of C1 aryl substituted β-carboline derivatives **8** were synthesized and found to have strong cytotoxic activity against five different tumor cell lines. Equivalently, Liew *et al.* applied DDQ oxidation of THBCs in the synthesis of C1 indolyl substituted β-carbolines that showed cytotoxic as well as antimalaria activity.[49] Furthermore, Mondal and Chowdhury applied a DDQ-mediated oxidation in their synthesis of β-carbolines (see section 3.5.).[50]

Scheme 4. Oxidation of THBCs **7** to β-carbolines **8** with DDQ.

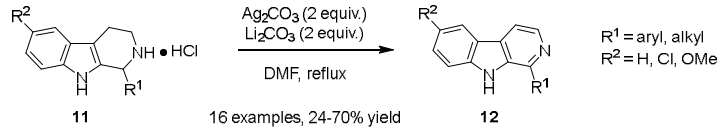
Brahmbhatt *et al.* reported the aromatization of DHBCs carrying a C3 ester functionality under basic conditions in DMF.[51] Similarly, Shi and co-workers reported the dehydrogenative oxidation of DHBCs and THBCs under basic conditions in DMSO in the presence of air as clean and cheap oxidant.[52] The authors found that the aromatization of THBCs to β-carbolines was best carried out using NaOH at 125 °C when C3 was a hydrogen atom. However, with an ester functionality in C3 position, superior results were obtained with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at ambient temperature. The same group applied this oxidation procedure in the total synthesis of eudistomins Y_1–Y_7.[53] Subsequently, they found that $CuBr_2$ in the presence of an amine base under air effectively catalyzed the oxidation of DHBCs to β-carbolines.[54] This oxidation procedure was applied in the total synthesis of 6-hydroxymetatacarboline D.

García *et al.* reported a photo-oxidation reaction using molecular oxygen as the oxidant (Scheme 5).[55] After heating DHBCs **9** in toluene under reflux, applying a 500 W halogen lamp whilst bubbling O_2 through the solution, β-carboline derivatives **10** were formed in high yields. Comparably, Huang *et al.* developed a dehydrogenation of THBCs by *in situ* generated superoxide ions providing a general, green route to β-carbolines.[56]



Scheme 5. Photo-oxidation of DHBCs **9** to β-carbolines **10** with molecular oxygen.

Durham *et al.* applied silver carbonate as the oxidant for the synthesis of β-carbolines **12** (Scheme 6).[57] This methodology could be applied to THBC salts **11** containing reduction sensitive functional groups providing **12** in 24-70% yield. This procedure allowed for the oxidation of THBCs **11** containing both alkyl or aryl substituents, with either electron-donating or electron-withdrawing properties.



Scheme 6. Synthesis of β-carbolines **12** *via* silver-mediated oxidation of THBCs **11**.

3. Methodologies that generate the pyridine ring

As previously mentioned, the majority of methodologies for the synthesis of β-carbolines apply indole-derived precursors and generate the pyridine ring (C-ring) to form the tricyclic carboline core. In this section, traditional methods, like the Pictet-Spengler and Bischler-Napieralski reaction, will be discussed as well as modern synthetic approaches using transition metal-catalyzed procedures.

3.1. Pictet-Spengler reaction

The Pictet-Spengler (PS) reaction is defined as the condensation reaction between a tryptophan or tryptamine derivative and an aldehyde or ketone. It occurs endogenously to produce β-carbolines in nature. The PS reaction has a long-lasting presence in organic synthesis and is in combination with dehydrogenative aromatization the most widely used route to access β-carbolines. Several review articles summarize the use of the PS reaction in organic synthesis.[58-60] The power of this method has been proven by the synthesis of a variety of natural products containing the β-carboline scaffold, among other eudistomin Y_1, pityriacitrin, merinacarboline A and B, fascaplysin[61] as well as shishijimicin A (Figure 2).[62]

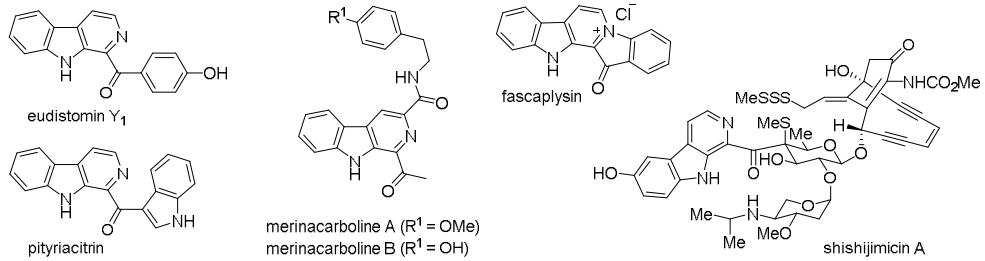
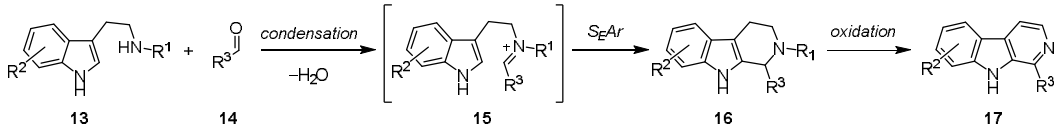


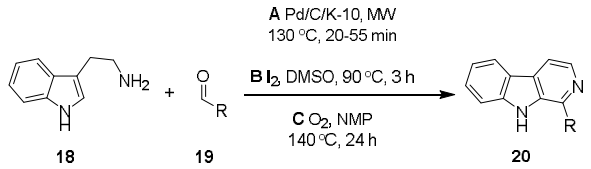
Figure 2. Examples of natural products containing the β-carboline scaffold.

The PS reaction proceeds through the condensation between an electron-rich tryptamine derivative **13** and an aldehyde **14** to form an iminium ion **15** (Scheme 7). The iminium ion is attacked by the indole to form THBC **16** after rearomatization of the indole ring, which can then be further oxidized to form the fully aromatic β-carboline **17**. The cyclization of the iminium ion in the PS reaction is most commonly catalyzed by strong Brønsted acids. Here, trifluoroacetic acid (TFA)[25, 48] and *p*-toluenesulfonic acid (PTSA)[63] are widely used. Other acids, such as acetic acid,[2] sulfuric acid and hydrochloric acid can also be used to catalyze the reaction,[58-60] along with less commonly used catalysts such as Lewis acids,[64] iodine[61] or a combination of $AuCl_3$ and AgOTf.[65]



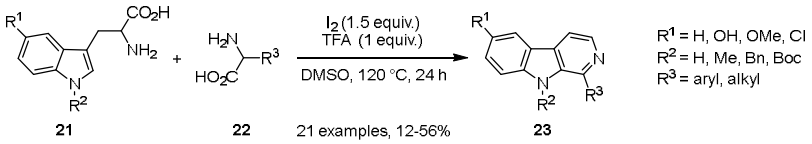
Scheme 7. General mechanism of the PS reaction to THBCs **16** and oxidation to β-carbolines **17**.

Although the PS reaction typically requires an additional oxidation step to achieve fully aromatic β-carbolines, one-pot/cascade methods have been developed in which the PS cyclization is used to form the β-carboline directly. In 2009, Kulkarni *et al.* reported a one-pot procedure using a heterogeneous Pd/C/K-10 catalyst and microwave irradiation to afford β-carbolines **20** in short reaction times and good yields (Scheme 8A).[66]. Subsequently, other one-pot methodologies have been reported. Battini *et al.* used stoichiometric iodine in DMSO at 90 °C generating β-carbolines **20** (Scheme 8B),[61] while Zhu *et al.* similarly explored iodine in DMSO with additional H_2O_2 as an oxidant.[67] Ramu *et al*. reacted tryptamine derivatives **18** with an aldehyde **19** in NMP under an atmosphere of oxygen to afford a variety of β-carbolines **20** in high yields (Scheme 8C).[68] The same authors applied this methodology to the synthesis of the alkaloids perlolyrin, flazin, eudistomin U and harmane.[69]



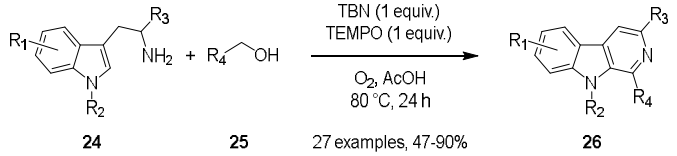
Scheme 8. PS reaction conditions that lead directly to fully aromatized β-carbolines **20**.

Similar to procedure B,[61] Wang *et al.* reported a biometric procedure for a one-pot synthesis of β-carbolines from tryptophan derivatives **21** and a second amino acid **22** using I_2 and TFA in DMSO at elevated temperatures (Scheme 9).[70] While only providing poor to moderate yields of β-carbolines **23**, this reaction proceeds *via* an impressive decarboxylation, deamination, PS reaction and oxidation sequence applying readily available starting materials.



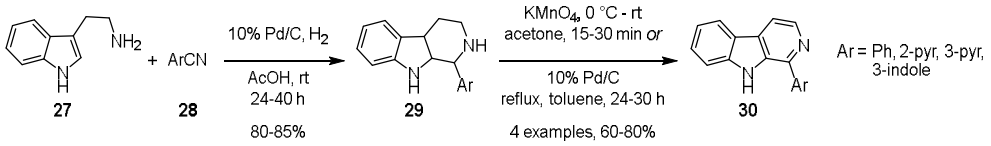
Scheme 9. Direct biomimetic synthesis of β-carbolines **23** from two amino acids.

Whilst PS reactions typically occur between a tryptamine derivative and an aldehyde, aldehyde-free procedures have been developed. Xu *et al.* report the selective synthesis of THBCs, DHBCs and β-carbolines from various tryptamine derivatives **24** and alcohols **25** employing oxygen as the oxidant and various amounts of *tert*-butyl nitrite (TBN) and 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO).[71] For the synthesis of β-carbolines **26** stoichiometric amounts of TBN and TEMPO were required (Scheme 10). Similarly, Yang *et al.* reported the synthesis of THBCs from alcohols and tryptamine derivatives applying a nickel-catalyzed borrowing hydrogen annulation in the presence of hexafluoroisopropanol (HFIP).[72]



Scheme 10. Synthesis of β-carbolines **26** *via* alcohol-based aerobic oxidative PS reaction.

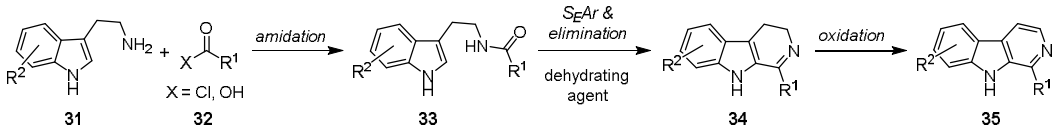
Kusurkar and Pakhare reported a reductive PS cyclization in which tryptamine **27** was reacted with a series of aryl nitriles **28** in place of aldehydes (Scheme 11).[21] They found that nitriles could be successfully used in the presence of 10% Pd/C in acetic acid under H_2 atmosphere to afford THBCs **29**, which were oxidized to form the corresponding β-carbolines **30** using either $KMnO_4$ or Pd/C. This methodology was applied to the synthesis of the naturally occurring β-carbolines eudistomin U and canthine.



Scheme 11. Synthesis of THBCs **29** *via* reductive PS reaction and aromatization to β-carbolines **30**.

3.2. Bischler-Napieralski reaction

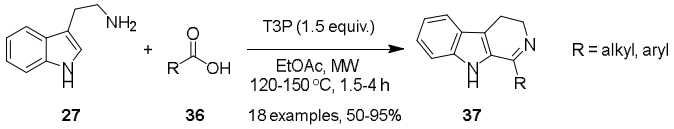
The Bischler-Napieralski (BN) reaction has also a long-standing presence in organic synthesis.[73] Similar to the Pictet-Spengler reaction, the BN reaction is an intramolecular cyclization of an acylated tryptophan or tryptamine derivative. Starting from tryptamines **31** and carbonyl derivatives **32**, tryptamine-based amides **33** are generated that cyclize and eliminate water to form DHBCs **34** (Scheme 12). As discussed in section 2, DHBCs **34** can be further oxidized to form fully aromatic β-carbolines **35**. Compared to the PS reaction, DHBCs generated in the BN reaction are generally more easily oxidized to the fully aromatic compounds **35**.



Scheme 12. General mechanism of the BN reaction to DHBCs **34** and oxidation to β-carbolines **35**.

The BN cyclization requires commonly quite harsh reaction conditions using $POCl_3$ as dehydrating agent and high-boiling solvents, such as xylene or toluene at refluxing temperature.[53,74] Alternative approaches include the use of polyphosphoric acid (PPA),[30] triflic anhydride,[75] $(PhO)_3P{\cdot}Cl_2$[76] and propanephosphonic acid cyclic anhydride (T3P).[77]

Ábrányi-Balogh *et al.* reported the use of T3P as the dehydrating agent (Scheme 13).[77] This method achieved BN cyclization in a one-pot manner from tryptamine **27** and various carboxylic acids **36** to form DHBCs **37**. Only 1.5 equiv. of T3P were required to remove 2 equiv. of water. Spaggiari *et al.* reported a procedure employing milder reaction conditions utilizing $(PhO)_3P{\cdot}Cl_2$.[76] Tryptamides were treated at –30 °C in dichloromethane in the presence of triethylamine to produce the corresponding DHBCs.



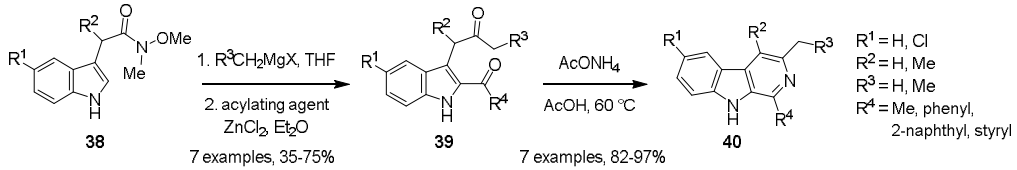
Scheme 13. T3P-promoted BN reaction to DHBCs **37**.

Movassaghi and Hill reported the use of trifluoromethanesulfonic anhydride in the presence of 2-chloropyridine as an electrophilic amide activator to promote BN cyclizations.[75] DHBCs with C1 aryl substituents were sensitive to oxidation under these reaction conditions providing a simple direct route to β-carbolines.

3.3. Condensation reactions

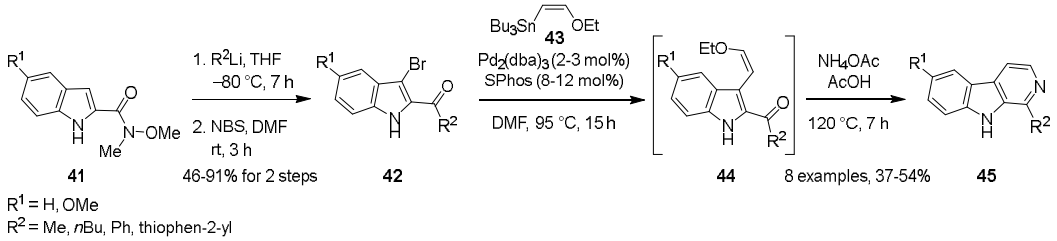
Cyclocondensation reactions of dicarbonyl substituted indole derivatives with amines have been widely used for the synthesis of β-carbolines. In 2004, Duval and Cuny reported the condensation of diketoindoles to β-carbolines (Scheme 14).[78] They used C3 Weinreb amide substituted indoles **38**, converting them to the corresponding ketones using Grignard reagents. To introduce the second keto functionality, the 3-substituted indoles were subjected to Friedel-Crafts acylation to give diketones **39**. The condensation with ammonium acetate in acetic acid afforded a variety of functionalized β-carbolines **40** in good yields. Variations to this method have been explored, altering starting materials and reagents, and

shortening the reaction sequence. In 2020, Untergehrer and Bracher reported an improved protocol using alternative staring materials, shortening the reaction sequence to either a two-step or a one-pot cascade reaction.[79]



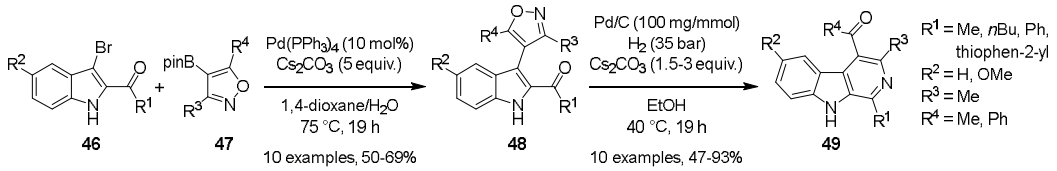
Scheme 14. Condensation of diketoindole derivatives **39** to β-carbolines **40**.

Kamlah *et al.* reported a complementary cyclocondensation procedure for the generation of β-carbolines (Scheme 15).[80] C2-substituted Weinreb amides **41** were functionalized with organolithium reagents. To introduce the second carbonyl functionality, the indole was brominated in C3 position to generate **42**. Conducted in a one-pot procedure, palladium-catalyzed Stille cross-coupling with tributyl[(*Z*)-2-ethoxyvinyl]stannane **43** to introduce a masked carbonyl group gave intermediate **44**. This was followed by cyclocondensation with ammonium acetate to provide access to C1-functionalized β-carbolines **45**.



Scheme 15. Formation of β-carbolines **45** using ethoxyvinyl stannane **43** as C3/C4 building block.

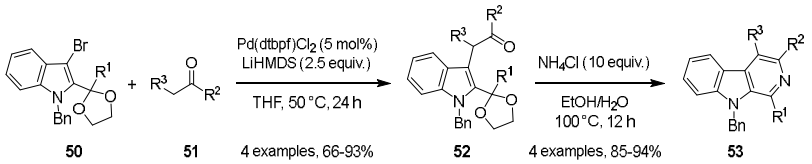
The same authors also applied an alternative cyclocondensation strategy to form 1,3,4-trisubstituted β-carbolines **49** (Scheme 16).[81] 2-Acyl-3-bromoindoles **46** and isoxazole-4-pinacol boronates **47** were coupled by Suzuki-Miyaura cross-coupling to afford 2-acyl-3-isoxazolydinylindoles **48**. Ring-closure to a number of β-carbolines **49** was achieved by palladium-catalyzed hydrogenation in the presence of superstoichiometric amounts of Cs_2CO_3. Advatanges of this procedure included the use of readily available building blocks, a small number of synthetic operations, and access to β-carbolines with predictable substitution patterns.



Scheme 16. Reductive ring transformation of 2-acyl-3-isoxazolylindoles **48** to β-carbolines **49**.

Donohoe and co-workers synthesized β-carbolines **53** from 3-bromoindoles **50** and carbonyl derivatives **51** through an enolate arylation/hydrolysis/condensation reaction sequence (Scheme 17).[82] Unlike the other cyclocondensation methods discussed here, protection of the indole nitrogen was required. While the acetal-protected carbonyl at C2 was preinstalled, the second carbonyl functionality at C3 was added *via* palladium-catalyzed enolate arylation. Simultaneous deprotection and cyclization of **52** was achieved using ammonium chloride in an ethanol/water mixture. This procedure could either be conducted

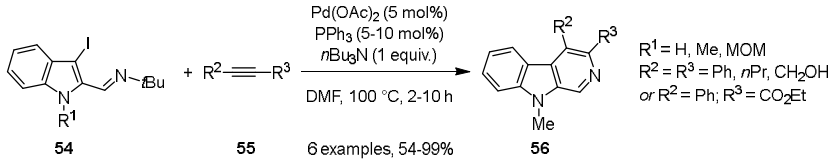
as a multi-step or as a one-pot process and allowed for a variety of functional groups to be installed in C1, C3 and C4 positions of **53**.



Scheme 17. Catalytic enolate arylation of 3-bromoindoles **50** and condensation to β-carbolines **53**.

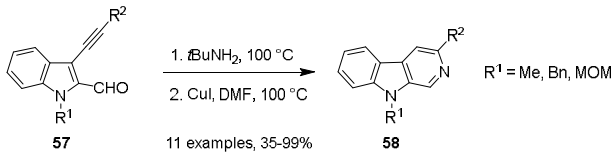
3.4. Iminoannulation reactions

Zhang and Larock reported a palladium-catalyzed iminoannulation of internal and terminal alkynes for the synthesis of β- and γ-carbolines.[83-84] Imines **54** and internal alkynes **55** were used in the presence of catalytic amounts of palladium acetate and an organic base to give β-carbolines **56**, with tributylamine providing the best results (Scheme 18).[83] By using PPh_3 in the reaction, both an increase in yield and acceleration in reaction rate were observed compared to phosphine-free conditions. However, when unsymmetrically substituted alkynes were applied in this procedure, only poor regioselectivities were observed.[84]



Scheme 18. Synthesis of β-carbolines **56** by palladium-catalyzed iminoannulation of internal alkynes **55**.

Based on this strategy, the same authors also reported a two-step synthesis of β-carbolines utilizing terminal alkynes.[85-86] Firstly, Sonogashira coupling provided functionalized indoles **57**. Imine intermediates were generated using *tert*-butylamine followed by copper-catalyzed cyclization to give β-carbolines **58** (Scheme 19). Similarly to this methodology, Rossi and co-workers reported a procedure for the synthesis of 1,3- and 3-substituted β-carbolines by combining a palladium-catalyzed Sonogashira coupling followed by 6-*endo-dig* cycloamination in the presence of ammonia.[87]

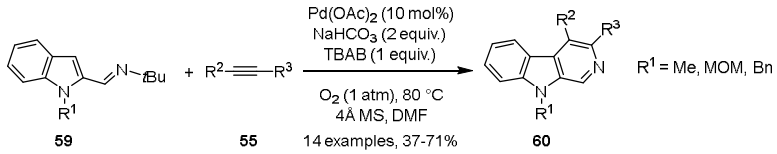


Scheme 19. Synthesis of β-carbolines **58** by a copper-catalyzed iminoannulation.

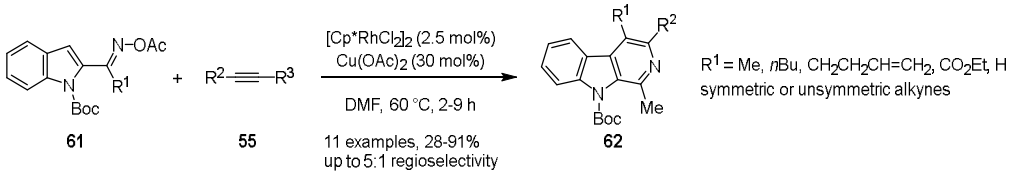
Related to this, Ding *et al.* developed a ligand-free palladium-catalyzed procedure that was applicable to synthesize both β- and γ-carbolines (Scheme 20).[88] This method utilized molecular oxygen as an oxidant in the direct C–H bond activation. In contrast to Larock and Zhang, Ding *et al.* reported $NaHCO_3$ as the most effective base for their iminoannulation of **59** and **55** to β-carbolines **60**. This method tolerated alkyl, aryl and ester functional groups. Notably, when an unsymmetrically substituted alkyne with an ester and aryl group was employed, only one regioisomer was formed. Other unsymmetrically substituted alkynes **55** produced mixtures of regioisomers. The same authors extended this methodology to the synthesis of β- and γ-carbolinones from indolecarboxamides with internal alkynes.[89]

Too *et al.* used a bimetallic copper/rhodium catalyst to generate β-carbolines **62** from *O*-acetyl oximes **61** and internal alkynes **55** (Scheme 21).[90] $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$ were applied in DMF at 60 °C to

afford β-carbolines **62** in moderate to good yields. For unsymmetrically substituted internal alkynes, regioisomeric mixtures of C3/4-substituted β-carbolines were obtained in ratios ranging from 1:1 up to 5:1.



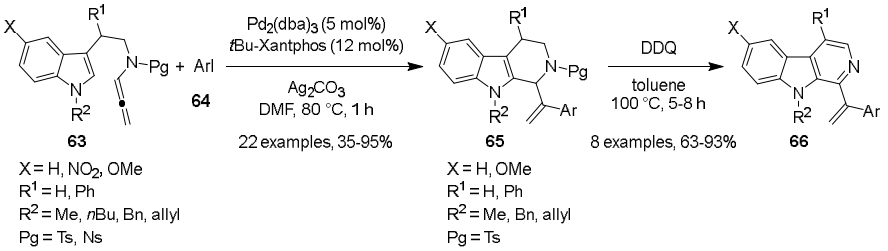
Scheme 20. Palladium-catalyzed synthesis of β-carbolines **60** by iminoannualtion of internal alkynes **55**.



Scheme 21. Synthesis of β-carbolines **62** from aryl ketone *O*-acetyl oximes **61** and internal alkynes **55** by Cu–Rh bimetallic relay catalysis.

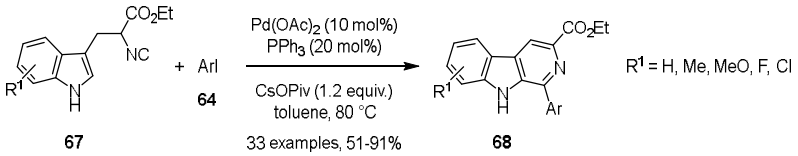
3.5. Palladium-catalyzed reactions

Mondal and Chowdhury reported a palladium-catalyzed procedure that accessed β-carbolines through THBCs (Scheme 22).[50] This method provided a quick route to C1 vinyl-substituted THBCs **65** starting from *N*-allenyl-tryptamines **63** and aryl iodides **64**. The resulting THBCs **65** were easily oxidized to the corresponding β-carbolines **66** using DDQ. This synthetic strategy was applied to the total synthesis of eudistomin Y_1 and Y_2.



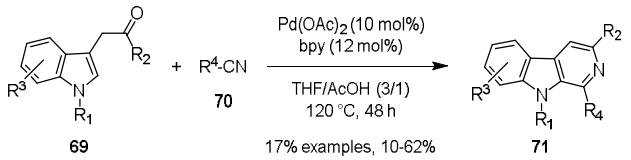
Scheme 22. Pd-catalyzed synthesis of 1-vinyltetraheydro-β-carbolines **65** and oxidation to **66** by DDQ.

Tang *et al.* applied tryptophan-derived isocyanides **67** and aryl iodides **64** to synthesize β-carbolines **68** through a palladium-catalyzed imidoylative cyclization (Scheme 23).[91] This reaction proceeded through isocyanide insertion, intramolecular C–H imidoylation and aerobic dehydrogenative aromatization enabled by stirring the reaction mixture under air before workup. The electronic nature of a substituent in the *para* position of the aryl iodide was found to affect the yield of the β-carboline product, with electron-donating substituents providing superior results.



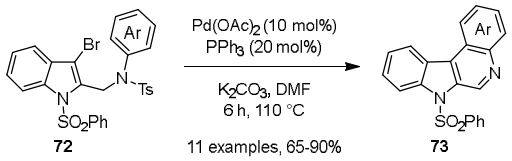
Scheme 23. Synthesis of β-carbolines **68** *via* palladium-catalyzed imidolative cyclization.

Wang *et al.* demonstrated a redox-free palladium-catalyzed C–H addition of indoles to nitriles followed by cyclization for the synthesis of functionalized β- and γ-carbolines.[92] β-Carbolines **71** were prepared from 3-substituted indoles **69** (Scheme 24), while γ-carbolines could be obtained from 2-substituted indole esters. Both aliphatic and aromatic nitriles **70** could be applied giving access to a diverse set of carbolines from readily available starting materials.



Scheme 24. Synthesis of β-carbolines **71** *via* palladium-catalyzed C–H addition of indoles **69** to nitriles **70** and subsequent cyclization.

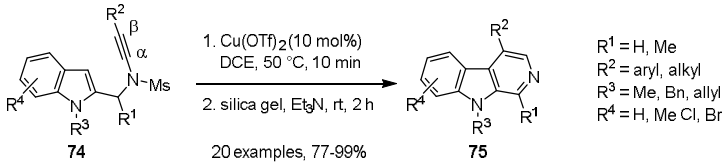
Raju *et al.* reported a one-pot synthesis of 3,4-benzo-β-carbolines involving palladium-catalyzed intramolecular Heck coupling of **72** generating the desired products **73** in good yields (Scheme 25).[93] Under the optimized reaction conditions, the ring closure was followed by elimination of the tosyl protecting group and aromatization giving access to tetracyclic benzo-β-carbolines **73**.



Scheme 25. Synthesis of 3,4-benzo-β-carbolines **73** by intramolecular palladium-catalyzed Heck reaction.

3.6. Other transition metal-catalyzed reactions

Li *et al.* reported a methodology for the synthesis of β-carbolines **75** from arene-ynamides **74** through a copper-catalyzed 6-*endo-dig* cyclization (Scheme 26).[94] The initial nucleophilic attack was expected to happen at the α position of the ynamide triggering a 5-*exo-dig* cyclization. However, under copper catalysis, the regioselectivity was reversed and the ynamide was selectively attacked at the β position. Practically, the copper catalyst was added to ynamide **74** in 1,2-dichloroethane (DCE) and stirred at 50 °C for 10 min to trigger the fast cyclization. This was followed by the addition of triethylamine and silica gel to enable demesylation and aromatization to provide β-carbolines **75** in high yields. This procedure was applied to the synthesis of several biologically active compounds.

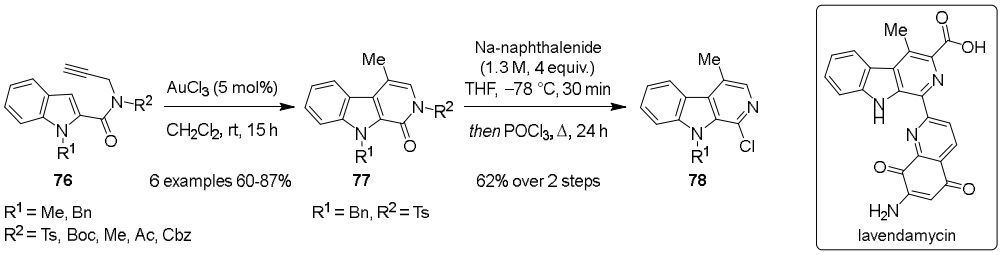


Scheme 26. Copper-catalyzed arene-ynamide cyclization to access β-carbolines **75**.

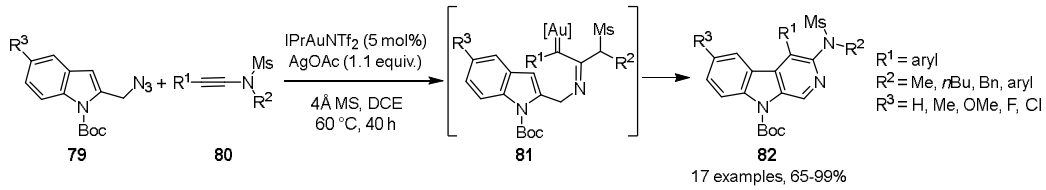
Verniest *et al.* used a gold(III)-catalyzed 6-*exo-dig* cyclization of *N*-propargylamides **76** to afford β-carbolinones **77**, which were subsequently converted to the corresponding β-carbolines **78** on deprotection of the nitrogen followed by treatment with $POCl_3$ (Scheme 27).[95] This method was applied for the synthesis of lavendamycin analogues using a variety of palladium-catalyzed cross-coupling procedures for further functionalization of **78**.[96]

Shu *et al.* applied a gold-catalyzed formal [4+2]-cycloaddition between indolyl azides **79** and ynamides **80** to form 3-amino-β-carbolines **82** *via* α-imino gold carbenes **81** (Scheme 28).[97] Although

$IPrAuNTf_2$ alone as a catalyst was sufficient to provide the desired products, higher yields were achieved by adding stoichiometric amounts of AgOAc as an oxidant. The reaction was applied in the synthesis of variously substituted 3-amino-β-carbolines **82** in good to excellent yields. Based on this procedure, the same authors attempted to develop a procedure to access 2-amino-γ-carbolines through a gold-catalyzed intramolecular amination of ynamides with 3-indoyl azides.[98] However, an unexpected 1,2-alkyl migration occurred under the applied reaction conditions giving exclusively 3-amino-β-carbolines **82**.



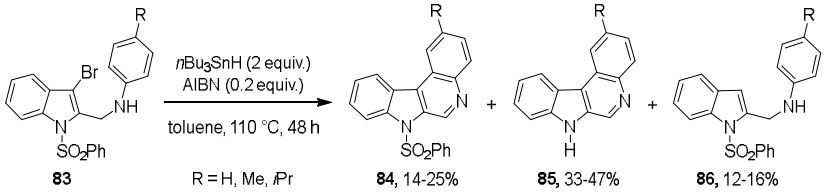
Scheme 27. Synthesis of β-carbolines **78** *via* Au(III)-catalyzed cycloisomerization of *N*-propargylamides **76**.



Scheme 28. Synthesis of β-carbolines **82** by gold-catalyzed cycloaddition of azides **79** and ynamides **80**.

3.7. Miscellaneous reactions

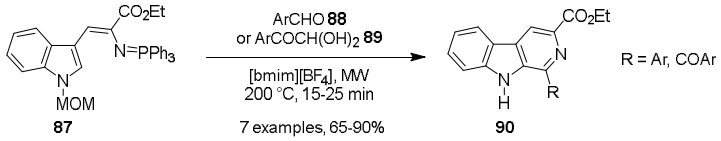
Related to the palladium-catalyzed procedure by Raju *et al.* (Scheme 25),[93] Kannadasan and Srinivasan reported a radical-mediated cyclization to tetracyclic 3,4-benzo-β-carbolines **84** and **85** applying a set of similar substrates **83** (Scheme 29).[99] However, the reaction was quite unselective leading to a mixture of products **84**, **85** and **86** under the applied conditions.



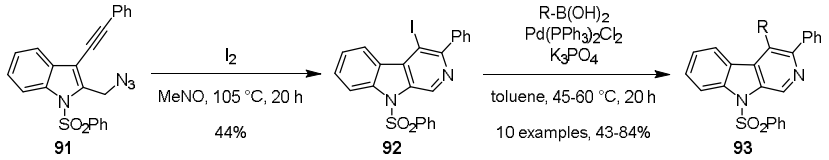
Scheme 29. Synthesis of 3,4-benzo-β-carbolines **84** and **85** *via* radical-mediated cyclization.

Similar to the PS reaction, Fresneda and Blázquez reported a tandem aza-Wittig/electrocyclic ring-closure reaction of iminophosphorane **87** and aryl carbonyl derivatives **88** and **89** that gave fully aromatic β-carbolines **90** carrying either an aryl or aroyl substituent in C1 and an ester functionality in C3 position (Scheme 30).[100] Conducted in an ionic liquid as the solvent and using mircrowave irradiation for heating, **90** was obtained in good yields in short reaction times. Noteworthy, under the applied reaction conditions, concominant deprotection of the *N*-methoxymethyl (MOM) group was observed.

Liu *et al.* applied an intramolecular iodine-mediated electrophilic cyclization of indole azide **91** to obtain **92**, which was further functionalized to generate a small library of 3-phenyl-4-substituted β-carbolines **93** *via* Suzuki cross-coupling (Scheme 31).[101] The products **93** were tested *in vitro* against three tumor cell lines demonstrating high cytotoxicity.

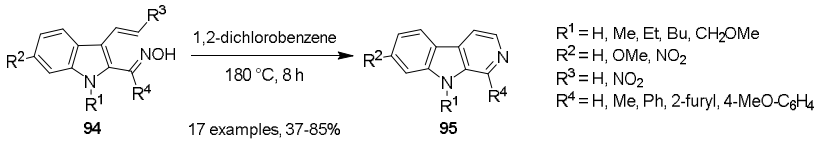


Scheme 30. Synthesis of β-carbolines **90** applying an aza-Wittig procedure.



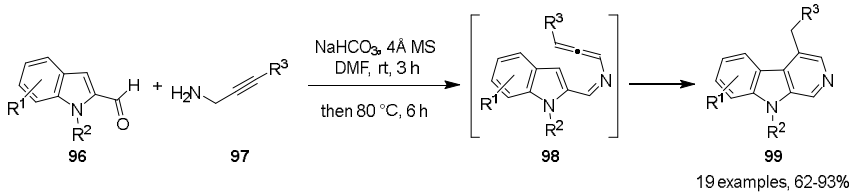
Scheme 31. Synthesis of β-carboline **92** *via* iodine-mediated electrophilic cyclization.

Thermal electrocyclization of oxime functionalized indoles **94** has been used to generate β-carbolines **95**, including various naturally occurring alkaloids.[102-103] Upon heating in refluxing 1,2-dichlorobenzene, the azahexatriene system underwent an electrocyclization to form the tricyclic β-carboline core (Scheme 32). Hibino and co-workers applied the same strategy in the total synthesis of oxopropalines D and G[104] as well as three pyridindolol alkaloids.[105] Related to this, Black and co-workers reported a method that generated β-carbolines by electrocyclization of an azahexatriene system.[106] For example, treatment of the 2,4-dinitrophenyl ether of 3-arylindole-2-ketoximes with triethylamine in refluxing THF initiated the electrocyclization to aryl-fused β-carbolines.



Scheme 32. Synthesis of β-carbolines **95** *via* thermal electrocyclization of azahexatrienes **94**.

Uredi *et al.* reported a condensation/azacyclization reaction sequence for the synthesis of C4-substituted β-carbolines **99** (Scheme 33).[107] Initially, an aldehyde **96** and a propargylic amine **97** formed an imine, which underwent a base-mediated isomerization to an allene intermediate **98** followed by 6π-azacyclization to generate β-carbolines **99**. The reaction conditions were mild, metal-free and compatible with a variety of functional groups. Furthermore, this strategy could be applied to the synthesis of β- as well as γ-carbolines. The authors applied this methodology in a formal synthesis of oxopropalines D and G.



Scheme 33. Synthesis of β-carbolines **99** from indole-2-carbaldehydes **96** and propargylic amines **97** *via* 6π-azacyclization.

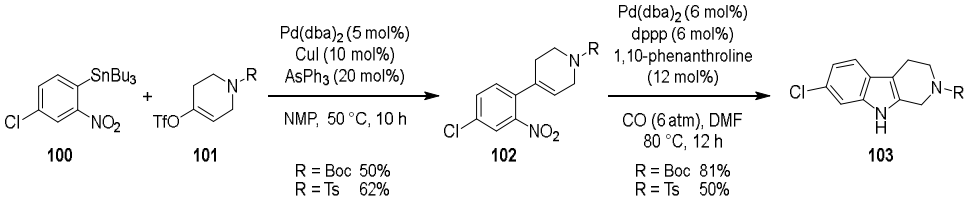
4. Methodologies that generate the central pyrrole ring

Despite most β-carboline syntheses forming the pyridine ring (C-ring) in the final step, this section will discuss methodologies that alternatively involve the generation of the central pyrrole ring (B-ring). In general, routes that form the pyrrole ring in the final step are more flexible in providing different carboline

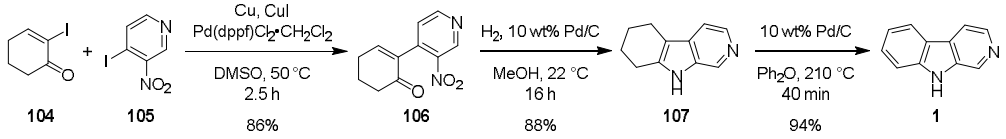
regioisomers (α, β, γ, δ), while most methodologies discussed in section 3 and 5 are specific to only β-carbolines.

4.1. Palladium-catalyzed procedures

Palladium-catalyzed reductive cyclizations has were examined by both Dantale *et al.*[108] (Scheme 34) and Yan *et al.* (Scheme 35).[109] Dantale *et al.* afforded THBCs **103** in good yields using a Stille-type coupling between **100** and **101** followed by reductive palladium-catalyzed *N*-heteroannulation of nitroaryl **102**. However, oxidation of these substrates to the fully aromatic β-carbolines proved to be difficult due to the lack of substituents on the C-ring. Yan *et al.* alternatively used a fully aromatized pyridine ring precursor **106**, which was prepared by palladium-catalyzed Ullmann coupling of **104** and **105** After reductive cyclization to give tricyclic **107**, the benzene ring was aromatized using palladium on carbon. This method afforded **1** in excellent yields over the whole reaction sequence. Furthermore, the authors were able to access all four carboline regioisomers with this methodology. Compared to all other procedures discussed in this review, this method forms an exception as it does not start from a fully aromatic benzene ring (A-ring) but uses cyclohexenone **104** as a precursor.

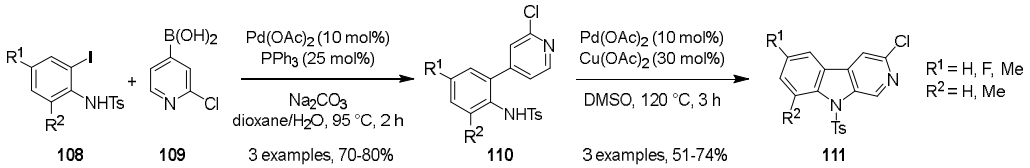


Scheme 34. Pd-catalyzed synthesis of THBCs **103** *via* Stille coupling and reductive *N*-heteroannulation.



Scheme 35. Cross-coupling/reductive cyclization protocol for the synthesis of β-carboline **1**.

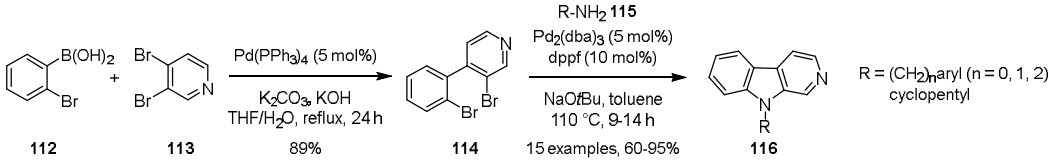
Dhara *et al.* synthesized C3-chlorosubstituted β-carbolines **111** using $Pd(OAc)_2$ as the catalyst and $Cu(OAc)_2$ as an oxidant, required for the oxidation of Pd(0) back to Pd(II) (Scheme 36).[110] Biaryl precursors **110** were prepared by palladium-catalyzed Suzuki cross-coupling of **108** and **109**. They found that the C–Cl bond remained untouched throughout the reaction sequence. Subsequently, the authors were able to functionalize the halogen substituent using various cross-coupling procedures. This method could be applied for the preparation of α, β and γ-carbolines.



Scheme 36. Synthesis of β-carbolines **111** *via* palladium-catalyzed C–H/N–H activation.

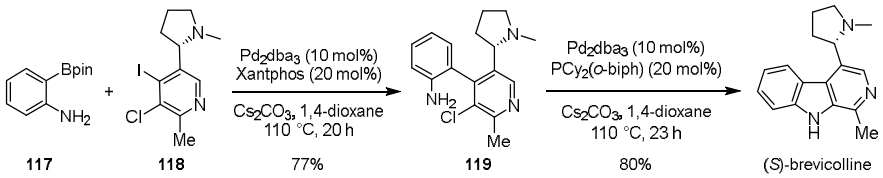
Hung *et al*. reported the synthesis of β- and γ-carboline derivatives from 3,4-dibromopyridine **113** as a common starting material.[111] Employing a series of palladium-catalyzed coupling reactions, β-carbolines **116** were obtained by site-selective Suzuki-Miyaura coupling of **113** with 2-bromophenylboronic acid **112** and subsequent cyclization of biaryl **114** by double Buchwald-Hartwig amination with a variety of primary amines **115** (Scheme 37). After studying the effects of various monodentate and bidentate ligands in

combination with different palladium sources, they found that bidentate ligands significantly improved the yield of the carboline products. A combination of $Pd_2(dba)_3$ and dppf (1,1′-bis(diphenylphosphino)ferrocene) provided **115** in up to 95% yield. This methodology was modified by the same authors using a copper(I) iodide/L-proline catalyst system instead of palladium.[112]



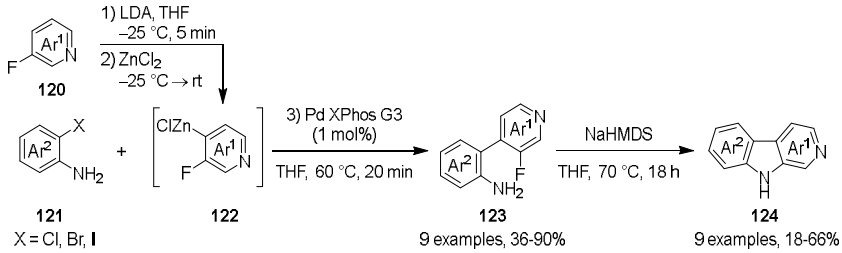
Scheme 37. Synthesis of β-carbolines **116** by site-selective palladium-catalyzed C–C coupling and subsequent cyclization by double C–N coupling with amines **115**.

Wagner and Comins reported a six-step total synthesis of the natural product (*S*)-brevicolline.[113] Starting from enantiopure (*S*)-nicotine, the key steps in their synthesis were a palladium-catalyzed Suzuki cross-coupling between **117** and **118** followed by an intramolecular Buchwald amination of biaryl **119** providing the β-carboline natural product in 17% overall yield (Scheme 38). While the two final palladium-catalyzed transformations only differ by the ligand, streamlining them into a one-pot procedure could not be achieved.



Scheme 38. Key steps in the synthesis of the alkaloid (*S*)-brevicolline.

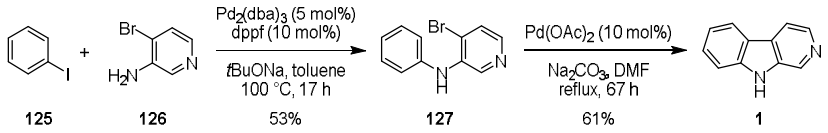
Recently, we reported a procedure for the synthesis of α- and β-carbolines.[114] Starting from fluoropyridines **120** and 2-haloanilines **121**, 2-fluorobiaryls **123** were obtained in a three-step, one-pot sequence by directed *ortho*-lithiation, zincation and Negishi cross-coupling.[115] Biaryls **123** were the precursor for an intramolecular nucleophilic aromatic substitution, enabling access to a diverse set of functionalized β-carbolines **124** (Scheme 39). Furthermore, it was demonstrated that arylzinc intermediates **122** could also be generated under continuous flow conditions. This two-step reaction sequence was applied to the synthesis of the naturally occurring β-carbolines norharmane and harmine. More recently, this methodology was expanded to access benzofuropyridines and dibenzofurans from fluoropyridines or fluoroarenes and 2-bromophenyl acetates.[116]



Scheme 39. Synthesis of β-carbolines **124** by a metalation/Negishi cross-coupling/S_NAr reaction sequence.

While previous procedures in this section initially generate the C–C bond followed by C–N coupling, the following procedures invert this reaction order. Ikawi *et al.* reported a synthetic strategy combining two

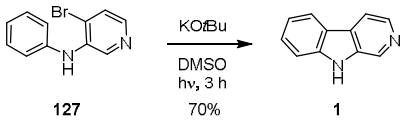
palladium-catalyzed reactions to access all four carbolines regioisomers.[117] Firstly, *ortho*-bromosubstituted anilinopyridine **127** was prepared by a palladium-catalyzed Buchwald-Hartwig amination of iodobenzene **125** with aminopyridine **126**, which was then subjected to a palladium-catalyzed intramolecular Heck-type arylation reaction to provide β-carboline **1** in moderate yield (Scheme 40). This strategy was adapted by Hostyn *et al.*[118] as well as Bogányi and Kámán[119] in their approaches towards the synthesis of benzo-β-carboline isoneocryptolepine derivatives. Similarly, Cook and co-workers afforded β-carbolines through palladium-catalyzed Heck coupling.[120-121]



Scheme 40. Synthesis of β-carboline **1** *via* a palladium-catalyzed amination/arylation reaction sequence.

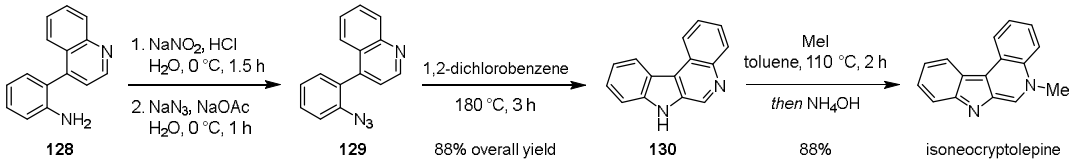
4.2. Miscellaneous procedures that generate the pyrrole ring

As an alternative to the previously discussed palladium-catalyzed transformations, Laha *et al.* reported a photostimulated metal-free $S_{RN}1$ cyclization of anilinohalopyridine **127** to give β-carboline **1** (Scheme 41).[122] Furthermore, the authors demonstrated that this method was suitable for the synthesis of all four carboline regioisomers.



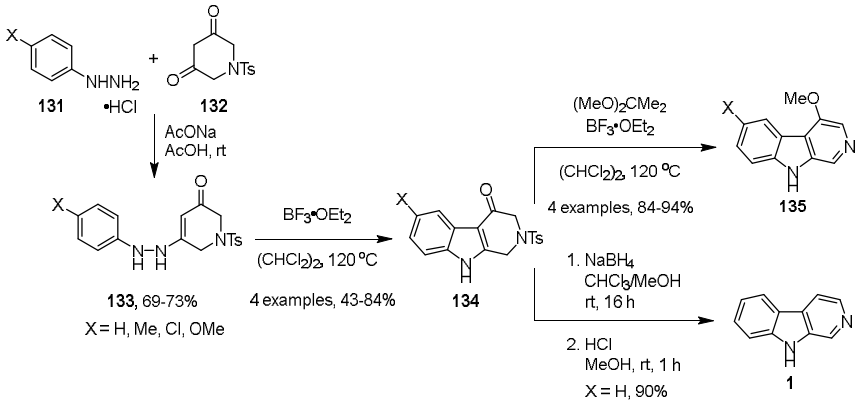
Scheme 41. Synthesis of β-carboline **1** by photostimulated cyclization of anilinohalopyridine **127**.

Hostyn *et al.* synthesized β-carboline **130** from biaryl azide **129** *via* thermal intramolecular nitrene insertion (Scheme 42).[118] Diazotization of biaryl aniline **128** followed by introduction of the azido group *via* nucleophilic aromatic substitution provided aryl azide **129**, which gave benzo-β-carboline **130** upon thermal decomposition in boiling 1,2-dichlorobenzene. Tetracyclic β-carboline **130** could be further functionalized to give isoneocryptolepine. Related to this procedure, Pumphrey *et al.* synthesized α-, β- and δ-carbolinium ions from aryl azides using rhodium-catalyzed C–H activation.[123] While transformation to neutral β-carbolines was not attempted, the authors demonstrated reduction of the β-carbolinium ions to the corresponding THBCs.



Scheme 42. Synthesis of benzo-β-carboline **130** *via* an intramolecular nitrene insertion.

Suzuki *et al.* applied Fischer indolization to generate C4-substituted β-carbolines from substrates **131** and **132** (Scheme 43).[124] They found that classical Fischer conditions, HCl in MeOH or PTSA in benzene, applied to hydrazine **133** did not provide synthetically useful yields of **134**. Instead, conducting the reaction with an excess of boron trifluoride etherate (≥20 equiv.) gave superior results. The cyclization step generated tetrahydro-2-tosyl-9*H*-β-carbolin-4-ones **134**, which could be further functionalized to produce β-carboline derivatives **135** and **1**.



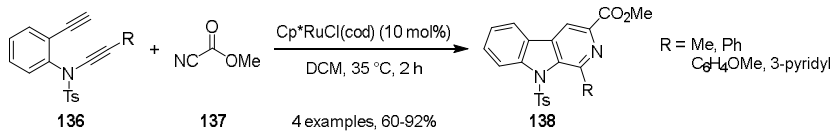
Scheme 43. Synthesis of β-carbolines **135** and **1** by Fischer indolization.

5. Cascade reactions that generate the pyrrole as well as the pyridine ring

In this section, cascade reactions will be reviewed that generate the pyrrole as well as the pyridine ring (ring B and C) in a single reaction sequence. The substrates for these transformations usually involve elaborated alkyne-substituted aryl derivatives.

5.1. Transition metal-catalyzed cycloadditions

Nissen *et al.* reported a [2+2+2]-cycloaddition procedure for the formation of β-carbolines **138** and regioisomeric γ-carbolines.[125] Functionalized yne-ynamides **136** underwent a transition metal-catalyzed cycloaddition with methylcyanoformate **137** (Scheme 44). Using either a ruthenium or a rhodium-based catalyst system, the reaction delivered either β- or γ-carbolines with high selectivity. Furthermore, the steric influence of the ynamine substituents had direct influence on the product distribution. Mixtures of regioisomeric β- and γ-carbolines were obtained when symmetrically substituted yna-ynamines **136** were subjected to the [2+2+2]-cycloaddition. The synthetic utility of this method was highlighted by the total synthesis of the marine alkaloid eudistomin U[125] and the antitumor antibiotic lavendamycin.[126] Dassonneville *et al.* continued exploring this methodology and utilized it in the total synthesis of the β-carboline natural product perlolyrine and regioisomeric isoperlolyrine.[127]



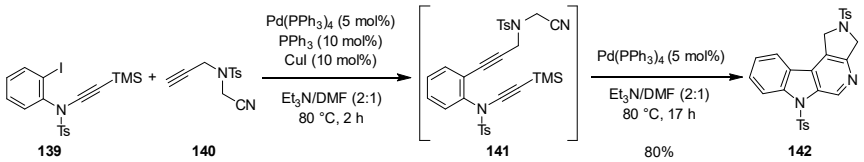
Scheme 44. Synthesis of β-carbolines **138** by ruthenium-catalyzed [2+2+2]-cycloaddition of yne-ynamides **136** with methylcyanoformate **137**.

Mulcahy and Varelas reported a palladium-catalyzed Sonogashira/desilylation/[2+2+2]-cyclization starting from **139** and **140** *via* intermediate yne-ynamide **141** to form 3,4-annulated β-carboline **142** generating three rings in a one-pot procedure (Scheme 45).[128] Reaction yields were optimized by addition of additional 5 mol% $Pd(PPh_3)_4$ after 2 h followed by overnight heating. The same authors extended this methodology to six other fused carboline derivatives varying the constitution and ring size of the fourth ring.[129] In this case, a rhodium/SEGPHOS-based catalyst system was found to provide better yields.

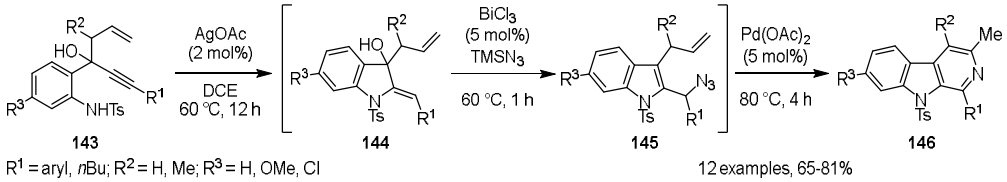
5.2. Other cascade sequences

In recent years, cascade/domino reactions have become increasingly popular. Dhiman *et al.* described a one-pot trimetallic relay catalysis for the synthesis of 1,3,4-trisubstituted β-carbolines **146** starting from aryl derivatives **143** *via* intermediates **144** and **145** using silver acetate, bismuth chloride and palladium

acetate as catalysts (Scheme 46).[130] Alternatively, the authors demonstrated the synthesis of 1,3-disubstituted 4-hydroxy-β-carbolines through a one-pot bimetallic relay catalysis procedure. This strategy could be extended to the synthesis of benzofuro[2,3-*c*]pyridines, benzothieno[2,3-*c*]pyridines and isoquinolines.

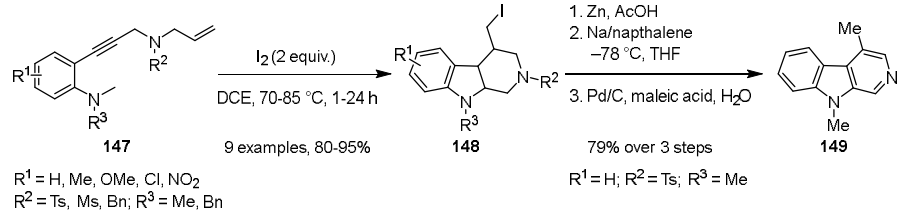


Scheme 45. Synthesis of annulated β-carboline **142** *via* a one-pot palladium-catalyzed Sonogashira coupling/intramolecular [2+2+2]-cycloaddition reaction sequence.



Scheme 46. Synthesis of β-carbolines **146** *via* one-pot trimetallic relay catalysis.

Song *et al.* applied an iodine-promoted electrophilic cascade cyclization of **147** for the synthesis of 4-iodomethyl substituted THBCs **148** (Scheme 47).[26] This methodology involved two successive cyclizations in a one-pot fashion. The differences in reactivity between alkynes and alkenes allowed the reaction to proceed with high selectivity for the desired β-carboline. Two equivalents of iodine were required to achieve full conversion. Transformation of **148** to the corresponding β-carboline **149** was demonstrated and required three synthetic operations. The authors applied this methodology to the formal synthesis of oxopropaline G.



Scheme 47. Preparation of THBCs **148** by cascade electrophilic iodocyclization and further elaboration to β-carboline **149**.

6. Conclusions

Throughout the last 20 years, a wide variety of synthetic routes to β-carbolines has been presented in the literature. These methods have been used to access an extensive array of β-carboline containing natural products and synthetic derivatives. Whilst Pictet-Spengler and Bischler-Napieralski reactions do not form β-carbolines directly and require oxidation to form the aromatic pyridine ring, they still dominate the current literature. Recent developments of these routes have seen the application of one-pot procedures to directly yield β-carbolines. In relation to the oxidation of DHBCs and THBCs to β-carbolines, milder reaction conditions have been established in favour of traditional oxidation methods that often require harsh reaction conditions and high temperatures. This follows an overall trend across different reaction pathways towards more ecological methods utilizing milder conditions, lower temperatures, reusable reagents, and non-toxic solvents. Cyclocondensation reactions and transition metal-catalyzed procedures have proven to be popular cyclization methods involving closure of the pyridine ring from indole-derived substrates. In addition, a

number of methods, which involve formation of the central pyrrole ring as the final cyclization step, have been reported. These procedures are in general more flexible to generate a larger range of carboline regioisomers. Cascade reactions represent an elegant way to synthesise carboline derivatives, but often require highly elaborated substrates. As β-carbolines are present as the core unit of many biologically active naturally occurring alkaloids and synthetic derivatives, continuous progress in the development of new synthetic strategies of this core motif is anticipated.

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References

1. Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479-500.
2. Formagio, A. S.; Tonin, L. T.; Foglio, M. A.; Madjarof, C.; de Carvalho, J. E.; da Costa, W. F.; Cardoso, F. P.; Sarragiotto, M. H. *Bioorg. Med. Chem.* **2008**, *16*, 9660-9667.
3. Ma, C.; Cao, R.; Shi, B.; Zhou, X.; Ma, Q.; Sun, J.; Guo, L.; Yi, W.; Chen, Z.; Song, H. *Eur. J. Med. Chem.* **2010**, *45*, 5513-5519.
4. Soni, J. P.; Yeole, Y.; Shankaraiah, N. *RSC Med. Chem.* **2021**, *12*, 730-750.
5. Kumar, S.; Singh, A.; Kumar, K.; Kumar, V. *Eur. J. Med. Chem.* **2017**, *142*, 48-73.
6. Ishida, J.; Wang, H.-K.; Bastow, K. F.; Hu, C.-Q.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3319-3324.
7. Ishida, J.; Wang, H.-K.; Oyama, M.; Cosentino, M. L.; Hu, C.-Q.; Lee, K.-H. *J. Nat. Prod.* **2001**, *64*, 958-960.
8. Yang, M. L.; Kuo, P. C.; Hwang, T. L.; Chiou, W. F.; Qian, K.; Lai, C. Y.; Lee, K. H.; Wu, T. S. *Bioorg. Med. Chem.* **2011**, *19*, 1674-1682.
9. Glover, V.; Liebowitz, J.; Armando, I.; Sandler, M. *J. Neural Transm.* **1982**, *54*, 209-218.
10. Grella, B.; Teitler, M.; Smith, C.; Herrick-Davis, K.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4421-4425.
11. Cox, E. D.; Diaz-Arauzo, H.; Huang, Q.; Reddy, M. S.; Ma, C.; Harris, B.; McKernan, R.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1998**, *41*, 2537-2552.
12. Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 1-64.
13. Maity, P.; Adhikari, D.; Jana, A. K. *Tetrahedron* **2019**, *75*, 965-1028.
14. Domínguez, G.; Pérez-Castells, J. *Eur. J. Org. Chem.* **2011**, *2011*, 7243-7253.
15. Rosillo, M.; González-Gómez, A.; Domínguez, G.; Pérez-Castells, J. in Targets in Heterocyclic Systems; Attanasi, O. A.; Spinelli, D.; Eds.; Italian Chemical Society, Rome **2008**, *12*, 212-257.
16. Milen, M.; Ábrányi-Balogh, P. *Chem. Heterocycl. Compd.* **2017**, *52*, 996-998.
17. Zhang, H.; Zhang, R.-H.; Wang, L.-X.; Li, Y.-J.; Liao, S.-G.; Zhou, M. *Asian J. Org. Chem.* **2021**, *10*, 429-452.
18. Devi, N.; Kumar, S.; Pandey, S. K.; Singh, V. *Asian J. Org. Chem.* **2018**, *7*, 6-36.
19. Szabó, T.; Volk, B.; Milen, M. *Molecules* **2021**, *26*, 663.
20. Singh, R.; Kumar, S.; Patil, M. T.; Sun, C.-M.; Salunke, D. B. *Adv. Synt. Catal.* **2020**, *362*, 4027-4077.
21. Pakhare, D. S.; Kusurkar, R. S. *Tetrahedron Lett.* **2015**, *56*, 6012-6015.
22. Bharate, S. B.; Manda, S.; Joshi, P.; Singh, B.; Vishwakarma, R. A. *Med. Chem. Commun.* **2012**, *3*, 1098-1103.
23. Schott, Y.; Decker, M.; Rommelspacher, H.; Lehmann, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5840-5843.
24. Wu, N.; Song, F.; Yan, L.; Li, J.; You, J. *Chem. Eur. J.* **2014**, *20*, 3408-3414.
25. Eagon, S.; Anderson, M. O. *Eur. J. Org. Chem.* **2014**, *2014*, 1653-1665.
26. Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2013**, *15*, 3274-3277.
27. Zhao, M.; Bi, L.; Wang, W.; Wang, C.; Baudy-Floc'h, M.; Ju, J.; Peng, S. *Bioorg. Med. Chem.* **2006**, *14*, 6998-7010.

28. Yin, W.; Majumder, S.; Clayton, T.; Petrou, S.; VanLinn, M. L.; Namjoshi, O. A.; Ma, C.; Cromer, B. A.; Roth, B. L.; Platt, D. M.; Cook, J. M. *Bioorg. Med. Chem.* **2010**, *18*, 7548-7564.
29. Chen, H.; Gao, P.; Zhang, M.; Liao, W.; Zhang, J. *New J. Chem.* **2014**, *38*, 4155-4166.
30. Ivanov, I.; Nikolova, S.; Statkova-Abeghe, S. *Heterocycles* **2005**, *65*, 2483-2492.
31. Singh, V.; Hutait, S.; Batra, S. *Eur. J. Org. Chem.* **2009**, *2009*, 6211-6216.
32. Xin, B.; Tang, W.; Wang, Y.; Lin, G.; Liu, H.; Jiao, Y.; Zhu, Y.; Yuan, H.; Chen, Y.; Lu, T. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4783-4786.
33. Ramesh, S.; Nagarajan, R. *J. Org. Chem.* **2013**, *78*, 545-558.
34. Singh, D.; Kumar, V.; Devi, N.; Malakar, C. C.; Shankar, R.; Singh, V. *Adv. Synth. Catal.* **2017**, *359*, 1213-1226.
35. Huang, W.; Li, J.; Ou, L. *Synth. Commun.* **2007**, *37*, 2137-2143.
36. Manasa, K. L.; Tangella, Y.; Ramu, G.; Nagendra Babu, B. *ChemistrySelect* **2017**, *2*, 9162-9167.
37. Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384-393.
38. Meesala, R.; Arshad, A. S. M.; Mordi, M. N.; Mansor, S. M. *Tetrahedron* **2016**, *72*, 8537-8541.
39. Kamal, A.; Tangella, Y.; Manasa, K. L.; Sathish, M.; Srinivasulu, V.; Chetna, J.; Alarifi, A. *Org. Biomol. Chem.* **2015**, *13*, 8652-8662.
40. Kamal, A.; Sathish, M.; Prasanthi, A. V. G.; Chetna, J.; Tangella, Y.; Srinivasulu, V.; Shankaraiah, N.; Alarifi, A. *RSC Adv.* **2015**, *5*, 90121-90126.
41. Meesala, R.; Mordi, M. N.; Mansor, S. M. *Synlett* **2014**, *25*, 120-122.
42. Abramyants, M. G.; Lomov, D. A.; Zavyazkina, T. I. *Russ. J. Org. Chem.* **2017**, *52*, 1610-1615.
43. Hati, S.; Sen, S. *Tetrahedron Lett.* **2016**, *57*, 1040-1043.
44. Bi, X.; Tao, L.; Yao, N.; Gou, M.; Chen, G.; Meng, X.; Zhao, P. *Dalton Trans.* **2021**, *50*, 3682-3692.
45. Gaikwad, S.; Kamble, D.; Lokhande, P. *Tetrahedron Lett.* **2018**, *59*, 2387-2392.
46. Panarese, J. D.; Waters, S. P. *Org. Lett.* **2010**, *12*, 4086-4089.
47. Panarese, J. D.; Waters, S. P. *Org. Biomol. Chem.* **2013**, *11*, 3428-3431.
48. Bai, B.; Li, X.-Y.; Liu, L.; Li, Y.; Zhu, H.-J. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 96-98.
49. Liew, L. P. P.; Fleming, J. M.; Longeon, A.; Mouray, E.; Florent, I.; Bourguet-Kondracki, M.-L.; Copp, B. R. *Tetrahedron* **2014**, *70*, 4910-4920.
50. Mondal, A.; Chowdhury, C. *J. Org. Chem.* **2021**, *86*, 3810-3825.
51. Brahmbhatt, K. G.; Ahmed, N.; Singh, I. P.; Bhutani, K. K. *Tetrahedron Lett.* **2009**, *50*, 5501-5504.
52. Dong, J.; Shi, X.-X.; Yan, J.-J.; Xing, J.; Zhang, Q.; Xiao, S. *Eur. J. Org. Chem.* **2010**, *2010*, 6987-6992.
53. Trieu, T. H.; Dong, J.; Zhang, Q.; Zheng, B.; Meng, T.-Z.; Lu, X.; Shi, X.-X. *Eur. J. Org. Chem.* **2013**, *2013*, 3271-3277.
54. Meng, T.-Z.; Zheng, J.; Trieu, T. H.; Zheng, B.; Wu, J.-J.; Zhang, Y.; Shi, X.-X. *ACS Omega* **2018**, *3*, 544-553.
55. García, M. D.; Wilson, A. J.; Emmerson, D. P.; Jenkins, P. R. *Chem. Commun.* **2006**, 2586-2588.
56. Huang, Y.-Q.; Song, H.-J.; Liu, Y.-X.; Wang, Q.-M. *Chem. Eur. J.* **2018**, *24*, 2065-2069.
57. Durham, S. D.; Sierra, B.; Gomez, M. J.; Tran, J. K.; Anderson, M. O.; Whittington-Davis, N. A.; Eagon, S. *Tetrahedron Lett.* **2017**, *58*, 2747-2750.
58. Calcaterra, A.; Mangiardi, L.; Delle Monache, G.; Quaglio, D.; Balducci, S.; Berardozzi, S.; Iazzetti, A.; Franzini, R.; Botta, B.; Ghirga, F. *Molecules* **2020**, *25*, 414.
59. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797-1842.
60. Stockigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 8538-8564.
61. Battini, N.; Padala, A. K.; Mupparapu, N.; Vishwakarma, R. A.; Ahmed, Q. N. *RSC Adv.* **2014**, *4*, 26258-26263.
62. Nicolaou, K. C.; Lu, Z.; Li, R.; Woods, J. R.; Sohn, T.-i. *J. Am. Chem. Soc.* **2015**, *137*, 8716-8719.
63. Yang, M.-L.; Kuo, P.-C.; Damu, A. G.; Chang, R.-J.; Chiou, W.-F.; Wu, T.-S. *Tetrahedron* **2006**, *62*, 10900-10906.
64. Srinivasan, N.; Ganesan, A. *Chem. Commun.* **2003**, 916-917.
65. Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521-2523.
66. Kulkarni, A.; Abid, M.; Török, B.; Huang, X. *Tetrahedron Lett.* **2009**, *50*, 1791-1794.
67. Zhu, Y. P.; Liu, M. C.; Cai, Q.; Jia, F. C.; Wu, A. X. *Chem. Eur. J.* **2013**, *19*, 10132-10137.

68. Ramu, S.; Srinath, S.; Kumar, A. A.; Baskar, B.; Ilango, K.; Balasubramanian, K. K. *Mol. Catal.* **2019**, *468*, 86-93.
69. Srinath, S.; Ramu, A.; Baskar, B.; Balasubramanian, K. K. *J. Heterocycl. Chem.* **2020**, *57*, 2121-2127.
70. Wang, Z.-X.; Xiang, J.-C.; Cheng, Y.; Ma, J.-T.; Wu, Y.-D.; Wu, A.-X. *J. Org. Chem.* **2018**, *83*, 12247-12254.
71. Liu, H.; Han, F.; Li, H.; Liu, J.; Xu, Q. *Org. Biomol. Chem.* **2020**, *18*, 7079-7085.
72. Yang, P.; Zhang, C.; Gao, W.-C.; Ma, Y.; Wang, X.; Zhang, L.; Yue, J.; Tang, B. *Chem. Commun.* **2019**, *55*, 7844-7847.
73. Heravi, M. M.; Nazari, N. *Curr. Org. Chem.* **2015**, *19*, 2358-2408.
74. Pal, B.; Jaisankar, P.; Sesha Giri, V.; Mondal, S.; Mukherjee, M. *Tetrahedron Lett.* **2004**, *45*, 6489-6492.
75. Movassaghi, M.; Hill, M. D. *Org. Lett.* **2008**, *10*, 3485-3488.
76. Spaggiari, A.; Davoli, P.; Blaszczak, L. C.; Prati, F. *Synlett* **2005**, *2005*, 661-663.
77. Ábrányi-Balogh, P.; Földesi, T.; Grün, A.; Volk, B.; Keglevich, G.; Milen, M. *Tetrahedron Lett.* **2016**, *57*, 1953-1957.
78. Duval, E.; Cuny, G. D. *Tetrahedron Lett.* **2004**, *45*, 5411-5413.
79. Untergehrer, M.; Bracher, F. *Tetrahedron Lett.* **2020**, *61*, 151597.
80. Kamlah, A.; Lirk, F.; Bracher, F. *Tetrahedron* **2016**, *72*, 837-845.
81. Kamlah, A.; Bracher, F. *Eur. J. Org. Chem.* **2020**, *2020*, 2708-2719.
82. Alves Esteves, C. H.; Smith, P. D.; Donohoe, T. J. *J. Org. Chem.* **2017**, *82*, 4435-4443.
83. Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083-3086.
84. Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318-9330.
85. Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048-7056.
86. Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359-1362.
87. Abbiati, G.; Beccalli, E. M.; Marchesini, A.; Rossi, E. *Synthesis* **2001**, *2001*, 2477-2483.
88. Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540-1543.
89. Shi, Z.; Cui, Y.; Jiao, N. *Org. Lett.* **2010**, *12*, 2908-2911.
90. Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159-6168.
91. Tang, S.; Wang, J.; Xiong, Z.; Xie, Z.; Li, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2017**, *19*, 5577-5580.
92. Wang, T. T.; Zhang, D.; Liao, W. W. *Chem. Commun.* **2018**, *54*, 2048-2051.
93. Raju, P.; Saravanan, V.; Pavunkumar, V.; Mohanakrishnan, A. K. *J. Org. Chem.* **2021**, *86*, 1925-1937.
94. Li, L.; Chen, X.-M.; Wang, Z.-S.; Zhou, B.; Liu, X.; Lu, X.; Ye, L.-W. *ACS Catal.* **2017**, *7*, 4004-4010.
95. Verniest, G.; England, D.; De Kimpe, N.; Padwa, A. *Tetrahedron* **2010**, *66*, 1496-1502.
96. England, D. B.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631-3634.
97. Shu, C.; Wang, Y.-H.; Zhou, B.; Li, X.-L.; Ping, Y.-F.; Lu, X.; Ye, L.-W. *J. Am. Chem. Soc.* **2015**, *137*, 9567-9570.
98. Zhou, B.; Zhang, Y.-Q.; Liu, X.; Ye, L.-W. *Sci. Bull.* **2017**, *62*, 1201-1206.
99. Kannadasan, S.; Srinivasan, P. C. *Synth. Commun.* **2004**, *34*, 1325-1335.
100. Fresneda, P. M.; Blázquez, J. A. *Tetrahedron Lett.* **2012**, *53*, 2618-2621.
101. Liu, L.; Xu, Y. Y.; Yang, Z. Q.; Xiang, J. N.; Xu, G. Y. *Chin. Chem. Lett.* **2012**, *23*, 1230-1232.
102. Kusurkar, R. S.; Goswami, S. K. *Tetrahedron* **2004**, *60*, 5315-5318.
103. Kusurkar, R. S.; Goswami, S. K.; Vyas, S. M. *Tetrahedron Lett.* **2003**, *44*, 4761-4763.
104. Choshi, T.; Kuwada, T.; Fukui, M.; Matsuya, Y.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **2000**, *48*, 108-113.
105. Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S. *J. Org. Chem.* **2001**, *66*, 8793-8798.
106. Wahyuningsih, T. D.; Kumar, N.; Black, D. S. *Tetrahedron* **2007**, *63*, 6713-6719.
107. Uredi, D.; Motati, D. R.; Watkins, E. B. *Org. Lett.* **2018**, *20*, 6336-6339.
108. Dantale, S. W.; Söderberg, B. C. G., *Tetrahedron* **2003** *59*, 5507-5514.
109. Yan, Q.; Gin, E.; Banwell, M. G.; Willis, A. C.; Carr, P. D. *J. Org. Chem.* **2017**, *82*, 4328-4335.
110. Dhara, S.; Singha, R.; Ahmed, A.; Mandal, H.; Ghosh, M.; Nuree, Y.; Ray, J. K. *RSC Adv.* **2014**, *4*, 45163-45167.

111. Hung, T. Q.; Hieu, D. T.; Van Tinh, D.; Do, H. N.; Nguyen Tien, T. A.; Van Do, D.; Son, L. T.; Tran, N. H.; Van Tuyen, N.; Tan, V. M.; Ehlers, P.; Dang, T. T.; Langer, P. *Tetrahedron* **2019**, *75*, 130569.
112. Van Phuc, B.; Do, H. N.; Quan, N. M.; Tuan, N. N.; An, N. Q.; Van Tuyen, N.; Anh, H. L. T.; Hung, T. Q.; Dang, T. T.; Langer, P. *Synlett* **2021**, *32*, 1004-1008.
113. Wagner, F. F.; Comins, D. L. *Org. Lett.* **2006**, *8*, 3549-3552.
114. Sathiyalingam, S.; Roesner, S. *Adv. Synth. Catal.* **2022**, *364*, 1769-1774.
115. Roesner, S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 10463-10467.
116. Clarkson, G. J.; Roesner, S. *J. Org. Chem.* **2023**, *88*, 684-689.
117. Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1505-1510.
118. Hostyn, S.; Maes, B. U. W.; Pieters, L.; Lemière, G. L. F.; Mátyus, P.; Hajós, G.; Dommisse, R. A. *Tetrahedron* **2005**, *61*, 1571-1577.
119. Bogányi, B.; Kámán, J. *Tetrahedron* **2013**, *69*, 9512-9519.
120. Namjoshi, O. A.; Gryboski, A.; Fonseca, G. O.; Van Linn, M. L.; Wang, Z.-j.; Deschamps, J. R.; Cook, J. M. *J. Org. Chem.* **2011**, *76*, 4721-4727.
121. Phani Babu Tiruveedhula, V. V. N.; Methuku, K. R.; Deschamps, J. R.; Cook, J. M. *Org. Biomol. Chem.* **2015**, *13*, 10705-10715.
122. Laha, J. K.; Barolo, S. M.; Rossi, R. A.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 6421-6425.
123. Pumphrey, A. L.; Dong, H.; Driver, T. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 5920-5923.
124. Suzuki, H.; Tsukakoshi, Y.; Tachikawa, T.; Miura, Y.; Adachi, M.; Murakami, Y. *Tetrahedron Lett.* **2005**, *46*, 3831-3834.
125. Nissen, F.; Richard, V.; Alayrac, C.; Witulski, B. *Chem. Commun.* **2011**, *47*, 6656-6658.
126. Nissen, F.; Detert, H. *Eur. J. Org. Chem.* **2011**, 2845-2853.
127. Dassonneville, B.; Witulski, B.; Detert, H. *Eur. J. Org. Chem.* **2011**, 2836-2844.
128. Mulcahy, S. P.; Varelas, J. G. *Tetrahedron Lett.* **2013**, *54*, 6599-6601.
129. Varelas, J. G.; Khanal, S.; O'Donnell, M. A.; Mulcahy, S. P. *Org. Lett.* **2015**, *17*, 5512-5514.
130. Dhiman, S.; Mishra, U. K.; Ramasastry, S. S. *Angew. Chem. Int. Ed.* **2016**, *55*, 7737-7741.