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INDOLINE-BASED HETEROCYCLIC SCAFFOLD: SYNTHETIC METHODS, CHEMICAL REACTIONS AND BIOLOGICAL PROSPECT

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Abstract

Indolines are significant compounds because of their diversity of applications in synthetic organic chemistry, pharmaceutical, industrial chemistry as well as they are present in several biologically active compounds in both natural and synthetic origins. Recently,there are high expectations that they exhibit interesting applications in selective potentiate the activity of β-lactam antibiotics in MRSA as well as other pharmacological arena, such as anticancer, anti-inflammatory, antioxidant, anticoagulant agents, etc. Furthermore, they are considered as considerable compounds due to their widespread use as building blocks and as chiral support in asymmetric synthesis. As a result, a new trends for the indoline-based nucleus in medicinal chemistry studies require to be reviewed especially many reports have been suggested that the indoline-based compounds have a very high therapeutic value (in MRSA) and needs to be explored for further studies. So, this review deals with the main innovations regarding indoline-based heterocycle scaffold stressing on their synthesis, reactions and their pharmacological activities.

Keywords: Synthesis, Metal-catalyzed, Metal free-catalyzed, Reactions, Bioactivities.

Contents

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1. Introduction

Indoline or 2,3-Dihydro-1H-indole or 2,3-Dihydroindole or 1-Azaindan is nitrogen containing heterocyclic aromatic compound with the chemical formula C_8H_9N. It is bicyclic heterocycles consisting of a benzene ring fused with a five-membered nitrogen-containing ring. [1] Indoline is one of the most promising motif which play an important role not only in the field of organic and medicinal chemistry [2] but also in bioactive alkaloids and natural products [3, 4] (Figure1). For example, strychnine and communesin [5, 6] families exhibit a range of cytotoxic and insecticidal properties and piperidine-fused indoline derivatives have also considerable attention in biosynthesis of certain alkaloids.[7] Moreover, indoline with various functionalities exhibit broad spectrum of biological activities such as, anticancer, [8, 9] anti-inflammatory, [10, 11] anticoagulant, [12] etc. Additionally, they are considered as substantial compounds due to their widespread use as building blocks and as chiral support in asymmetric synthesis.[13] Likewise, many reports have been suggested that the indoline-based compounds have need further studies and investigations.[8, 9] Subsequently, this review deals with the essential studies concerning to indoline-based heterocyclic scaffolds with focusing on their synthesis, reactions and their pharmacological activities.

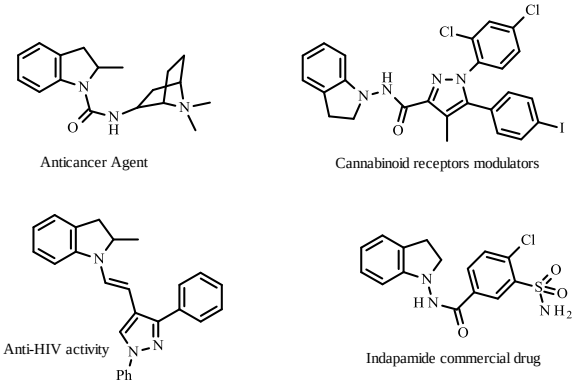


Figure1. Examples of natural products and synthetic drugs containing the indoline scaffolds.

2. Synthesis of Indolines

Disquiet of their existence in a significant pharmaceuticals, bioactive compounds and their synthetic utility, a growing of synthetic methods have been explored. The common synthetic methods are transition metal-catalyzed processes [14, 15, 16] which have the biggest role in the synthesis of these heterocycles and the metal free-catalyzed processes. Herein, this review will focus on recently methodology using transition metal-catalyzed (Pd, Ni, Cu, Au, Fe and Rh) as well as transition metal free-catalyzed methods.

2. 1. Transition metal-catalyzed processes

In general the catalytic cycle for the reaction of compound (**A**) with compound (**B**) using metal-catalyzed methods is summarized in Figure 2.

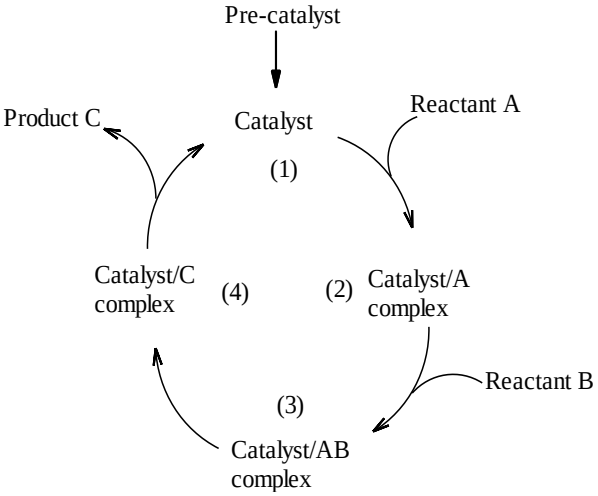


Figure 2. Catalytic cycle for the synthesis of (C) from the comound (A) and compound (B).

2. 1. 1. Palladium-catalyzed methods

The transition metal-catalyzed C–H activation/C–heteroatom bond forming reactions have received main heed due to their ability to produce such ingredient in a rapid manner. [17] Pd-catalyzed reactions occur between a nucleophile (R^2M) and an electrophile (R^1X) as represented in Eq. (1). The proposed and common mechanism of palladium catalyzed reaction is illustrated in Figure 3.

2. 1. 1. 1. Palladation-catalyzed C–N /C–C bond formation

Since the introduction of palladium as a promising catalyst for many organic transformations, its use has gradually increased in research and industry.[18] As example, the formation of a 2–benzylindoline product (**3**) was achieved *via* intramolecular cyclization of from 2–allylanilines. [19, 20, 21] (Scheme 1)

$$R^1X + R^2M \longrightarrow R^1\text{-}R^2 + MX \qquad \text{Eq. 1}$$

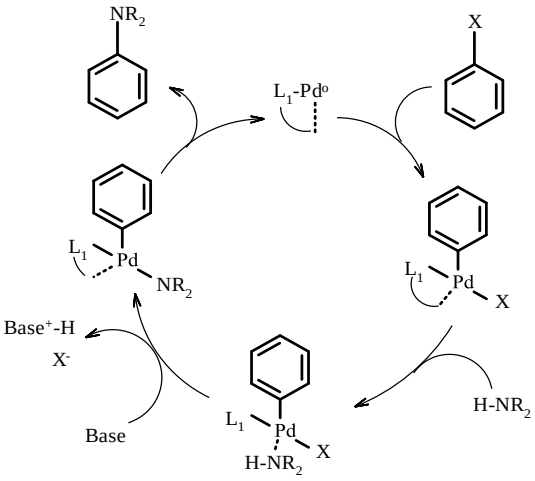
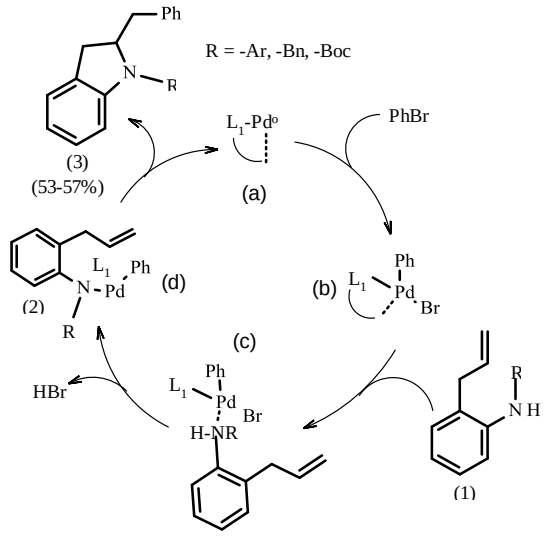
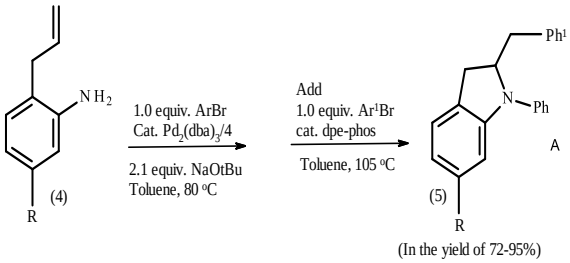


Figure 3. *The common catalytic cycle of palladium catalyzed*

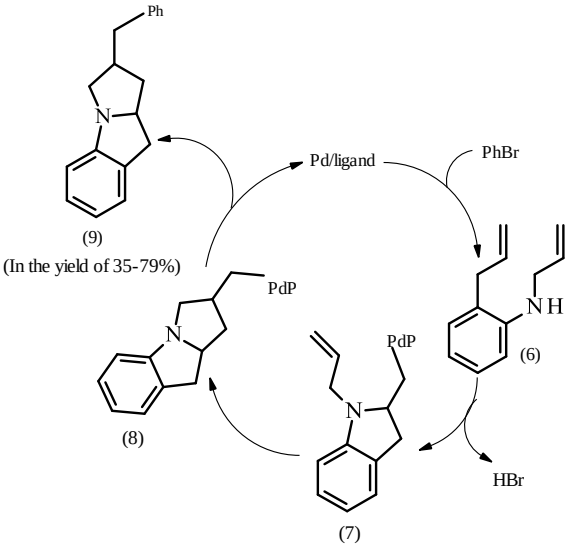


Scheme 1. Synthesis indoline through aminopalladation/carbopalladation.

A similar route for the preparation of N–aryl–2–benzylindolines from 2–allylanilines was involved through two different sequential palladium-catalyzed reactions that lead to formation of two C–N bonds and one C–C bond in a one-pot method. [22] (Scheme 2) Noteworthy, the use of electron rich phosphine ligands was essential in performing these transformations. It gives solubilization and stabilization to organo-palladium complexes and for controlling the reactivity and selectivity of the palladium promoted reactions. Recently, the cascade reaction transforms a simple substrates into complex products through formation of three bonds, two stereocenters, and two rings in one–step protocol e.g. benzo-fused pyrrolizidines (**9**) from aryl halides and N–allyl–2–allylaniline (**6**) in the range of 35-79% yield. [20] (Scheme 3)

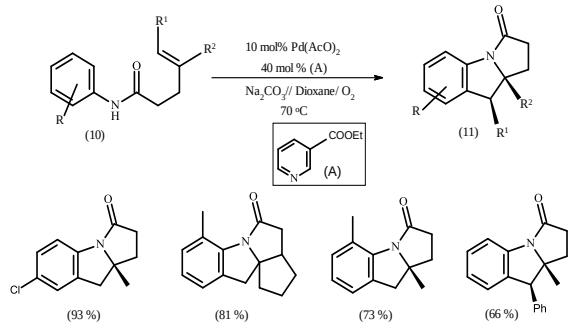


Scheme 2. Synthesis of *N–aryl–2–benzylindolines* from 2–allylanilines.



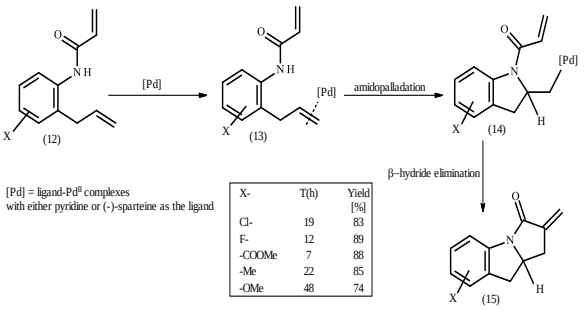
Scheme 3. Cascade synthesis of benzo-fused pyrrolizidines.

A similar cyclizations were successful for the formation of polycyclic heterocycles (**6**) from benzamide derivatives (**5**) using palladium-catalyzed oxidative cascade cyclization reaction up to yield of 96 % (Scheme 4). [23]



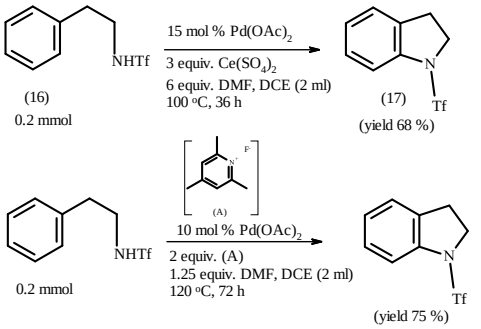
Scheme 4. Cascade synthesis of indolines from benzamide derivatives.

The above oxidative cascade approach has also been applied to form indolines in high yields using Pd $(OAc)_2$/pyridine as the catalyst and oxygen as a green oxidant. The applicability of this method, the mechanism, the electronic effects of cyclization reveals that electron-deficient anilides cyclized faster than their electron-rich one.[24] Scheme 5 illustrates the mechanism of palladium-catalyzed oxidative cascade cyclizations. The electron-deficient PdII complex coordinates to the *o*-allyl group of anilide (**12**) to generate intermediate (**13**) which undergoes amidopalladation to gives-alkylpalladium intermediate (**14**). Following intramolecular olefin insertion to obtain the product (**15**) by β-hydride elimination. [24]



Scheme 5. Indoline synthesis by Palladium-catalyzed oxidative cascade cyclizations.

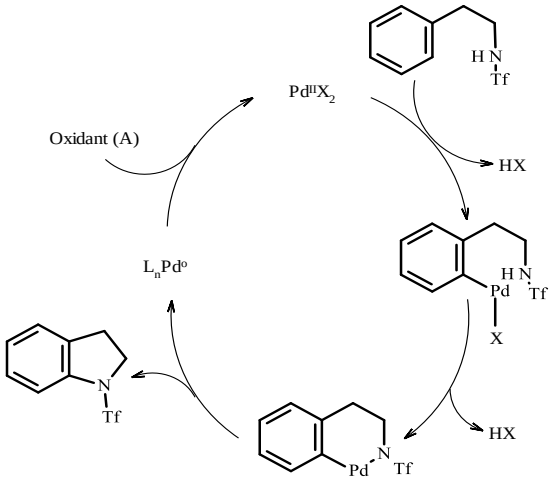
A several functionalized indolines with acetyl, cyano, and nitro functional groups were proceeded using the one-electron oxidant $Ce(SO_4)_2$ or the two-electron oxidant N–fluoro–pyridinium **(A)** [25] *via* the Shilov-type mechanistic hypothesis. [26, 27, 28] As illustrated in Scheme 6, improved yields, and functional group tolerance, and excellent regioselectivities, were observed when *N*-fluoropyridinium (**A)** was used as the oxidant. The mechanism of this reaction is illustrated in Scheme 7.



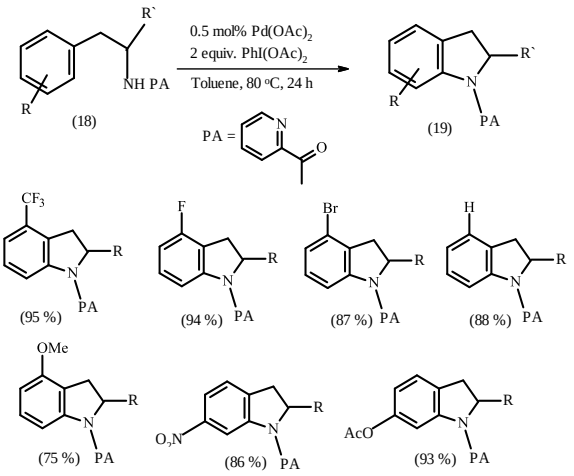
Scheme 6. Comparison between the use of $Ce(SO_4)_2$ and N–fluoro–pyridinium **(A)** in synthesis of indoline.

Additionally, an efficient method, high yield, low catalyst loadings, mild operating conditions as well as the use of inexpensive reagents was described for the formation of indolines from protected β-arylethylamine (Scheme 8) [29, 30] or by tandem iodination/ amination reaction.[31] The addition of base was fundamental to obtain this conversion. Without base, the catalyst did not turn over and $[Pd(PPh_3)_2I_2]$ was not formed. Interestingly, the addition of super-stoichiometric amounts of iodine (sodium iodide or tetrabutylammonium iodide) relative to palladium the reaction was closed completely. [31]

In the same manner, the palladium-catalyzed tandem iodination/amination reaction of compound (**20**) was proceeded to give a mixture of products (**21**) and (**22**) (Scheme 9). The formation of (**22**) could be minimized by using more CuI to accelerate the reaction of the mono-iodinated precursor. [25]

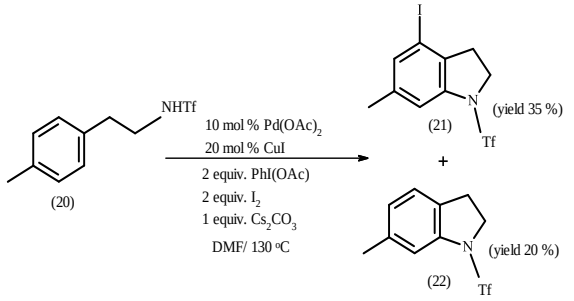


Scheme 7. The mechanism of synthesis of indoline from β-arylethylamines.



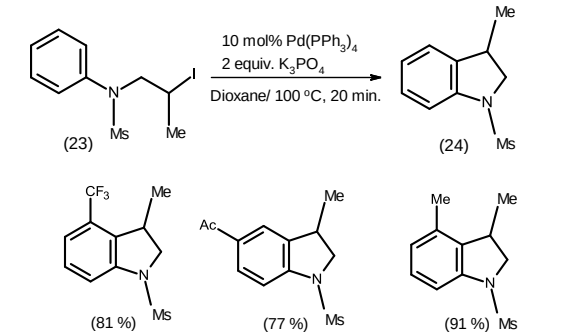
Scheme 8. Synthesis of indolines from protected β−arylethylamine.

The intramolecular Pd-catalyzed C–H alkylation of arenes and heteroarenes was carried out with different inactivated primary and secondary alkyl halides, including those with β–hydrogens. [31] (Scheme 10) The mild catalytic reaction conditions and highly functional group tolerant make this method to be used for the synthesis of wide range of interesting heterocyclic systems.

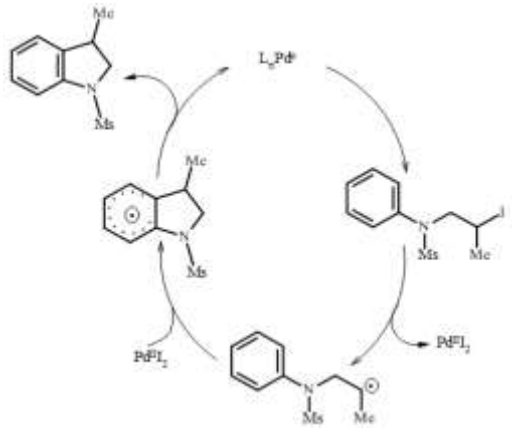


Scheme 9. Synthesis of indolines by tandem iodination/ amination reaction.

Herein the assumed mechanism was illustrated in Scheme 11. [32]

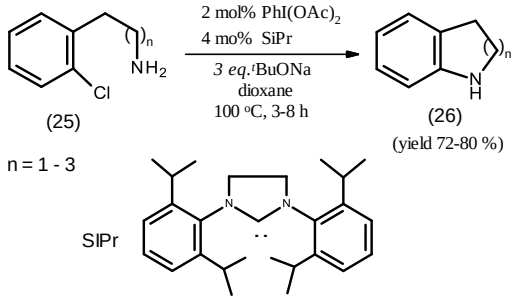


Scheme 10. Synthesis of indolines via C–H alkylation of arenes.



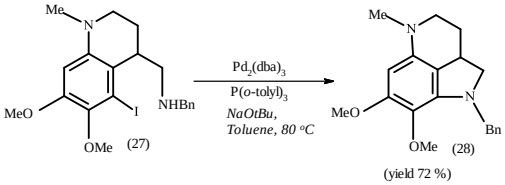
Scheme 11. The mechanism of C–H alkylation of arenes.

On the other hand, the use of N,N′–bis(2,6–diisopropylphenyl)dihydroimidazol–2–ylidene (SiPr) as a ligand and *t*-BuONa as the base for sequential palladium-catalyzed intra- followed by intermolecular aryl amination was utilized for the synthesis of indoline derivatives. The applicability of this method on the creation of N–arylated five–, six– and seven-membered nitrogen heterocycles has been studied in yields of 72–84 %. [33] (Scheme 12)



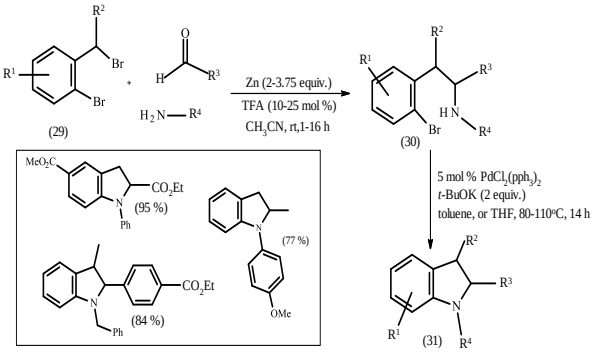
Scheme 12. Synthesis of indolines by aryl amination.

Additionally, the tricyclic indoline derivative (**10**) was synthesized through the Pd mediated intramolecular aryl amination and aryl amidation under basic condition (Scheme 13). [34]



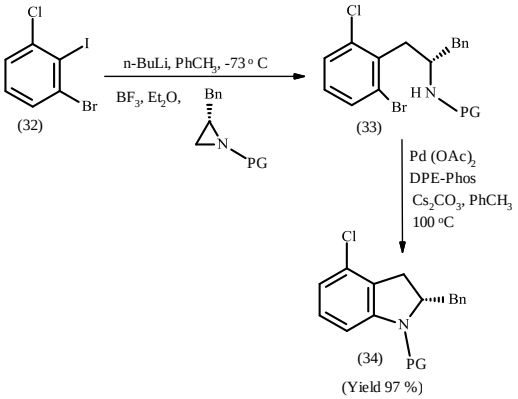
Scheme 13. Synthesis of indolines using palladium–catalyzed aryl amination.

Recently, the 1,2–disubstituted and 1,2,3–trisubstituted indolines have been prepared by an intramolecular cyclization of the compound (**11**) using Pd as catalyst. [35] (Scheme 14)



Scheme 14. Synthesis of indolines by intramolecular cyclization using Pd as catalyst.

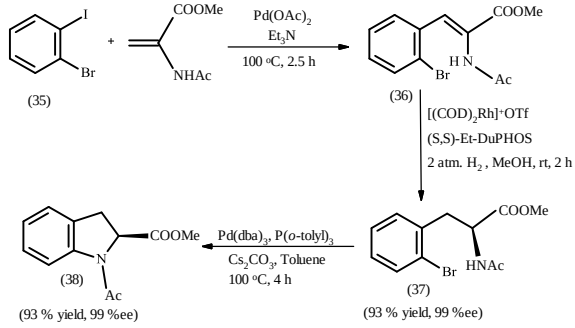
Notably, this intramolecular cyclization is appropriate to the synthesis of *N*–substituted enantiomerically pure indolines.[36] As example, the synthesis of optically active 2–or 2,3–substituted indolines from phenethylamines (**33**) (Scheme 15). [37]



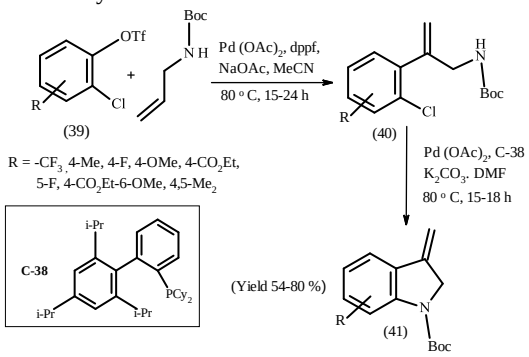
Scheme 15. Synthesis of chiral 2–substituted indolines from phenethylamines.

Moreover, the stereocontrolled transformation was proceeded for the asymmetric synthesis of (s)–N–acetylindoline–2–carboxylate methyl ester (**38**) through an asymmetric hydrogenation of the dehydro-aminoester (**36**) followed by the palladium-catalyzed intramolecular coupling of the resulting enantiomerically enriched amine (**37**). [36] (Scheme16)

Methylene-substituted indolines (**41**) from 2–aryl–N–Bocallylamines (**40**) was achieved through an efficient two-step region-controlled reaction method as shown in Scheme 17. [38]



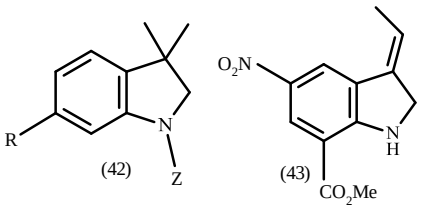
Scheme 16. Synthesis of chiral 2–substituted indolines.



Scheme 17. Synthesis of methylene-substituted indolines.

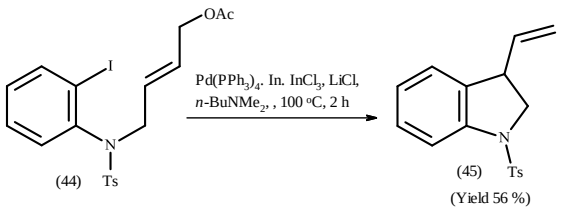
2. 1. 1. 2. Via intramolecular Heck cyclization

Further, the indoline derivatives **42** and **43** were afforded by intramolecular Heck cyclization of the corresponding N–allyl–*o*–halo–anilines. This methodology developed an efficient intramolecular cyclization under mild conditions. [39]



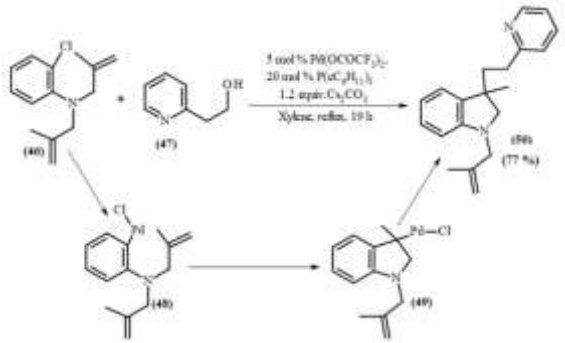
Moreover, the 3–vinyl indoline (**45**) was proceeded *via* the treatment of allyl acetates derivative (**44**) with indium and indium trichloride in the presence of Pd^0 catalyst and n–$BuNMe_2$ in DMF (Scheme 18). [40]

Interestingly, the modified oxidative coupling approach has also been applied to introduction of pyridine moiety into indoline frame by chelation-assisted cleavage of a C_{sp3}–C_{sp3} bond method.



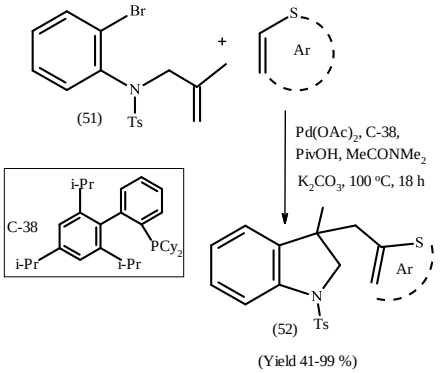
Scheme 18. Synthesis of 3–vinyl indolines.

The reaction of (**46**) with (**47**) gave the pyridylethyl-substituted dihydro-indole (**50**) in good yield. The initial oxidative adduct (**48**) converted into a dihydro-indolylmethylpalladium intermediate (**49**) *via* intramolecular carbo-palladation cyclization.[41] (Scheme 19)



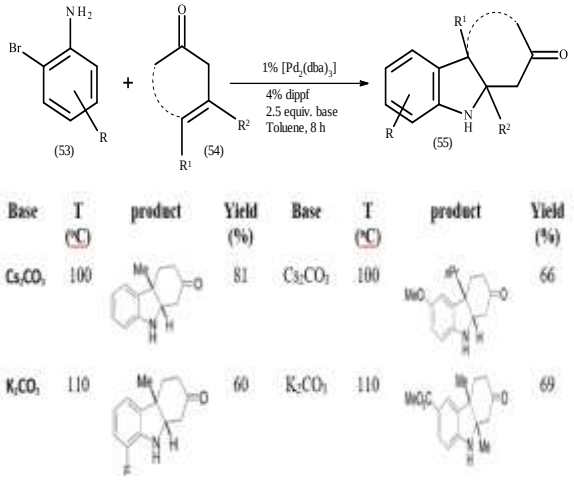
Scheme 19. Synthesis of pyridylethyl-substituted dihydroindole.

In the same manner, the sulfur-containing heterocycles indoline (**52**) was obtained by direct arylation reaction of the *o*–bromo–N–allyl aniline with a variety of sulfur-containing heterocycles in yields up to 99%. [42] (Scheme 20)



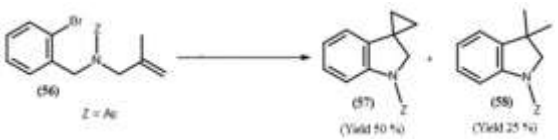
Scheme 20. Synthesis of indolines by cross–coupling reaction.

A convenient two-step, one-pot synthesis of keto-indolines from simple starting materials (α,β-or β,γ-unsaturated cyclopentenones). This methodology is broad, with high level of functional-group tolerance. Electron-rich and electron-neutral of bromo-anilines can be transformed into indolines using Cs_2CO_3 at 100 °C. However, electron-poor bromo-anilines transformation necessitate the use of K_2CO_3 at 110 °C. Notably, the indolines obtained may be acyclic, mono- or disubstituted at the 2- and 3- positions. [43] (Scheme 21)



Scheme 21. One-pot ketoindolines.

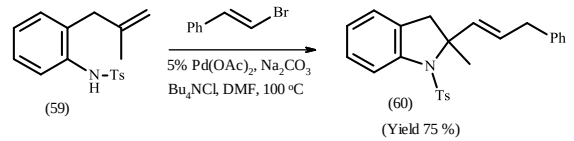
The spiro-indoline derivative (**57**) with a minor amount of a compound (**58**) were obtained from the reaction of compound (**56**) *via* Pd-catalyzed cross–coupling cyclization in the absence of any trapping agent. [44] (Scheme 22)



Reaction condition: $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), n-Bu_4NBr (1.3 equiv), K_2CO_3 (5 equiv), AcOH (3 equiv), DMF, 120 °C, overnight.

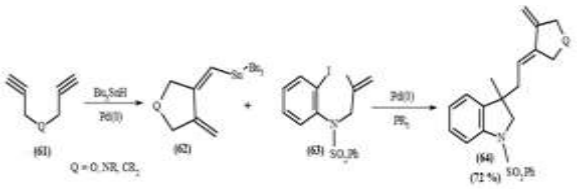
Scheme 22. Synthesis of spiro-indoline derivatives.

The 2–vinylindolines was acquired utilization of the Pd-mediated cyclization cross-coupling of *o*–allylic and *o*–vinylic anilides with vinyl halides.[45] (Scheme 23)



Scheme 23. Synthesis of 2–vinyl indolines from *o*–allylic anilides.

Recently, a new catalytic methodology in situ to generation of the compound **(62)** in excellent yield from terminal 1,6–diynes **(61)** followed by cyclization-anion capture cascade method with *o*–iodoanilides to furnish indolines **(63)** using palladium as catalyst. Transition metals are utilized to catalyze the decomposition of Bu_3SnH to Bu_6Sn_2 and H_2 and this side reaction can be prevented by slow addition of Bu_3SnH *via* a syringe pump. [46] (Scheme 24)

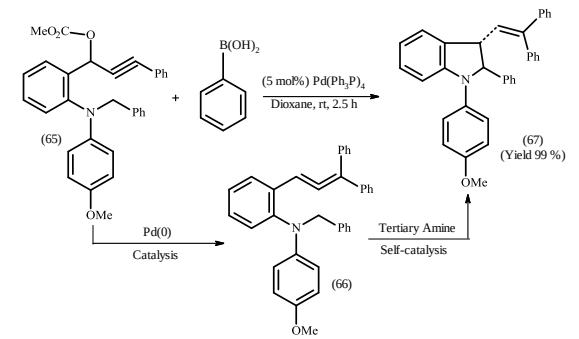


Scheme 24. Synthesis of indolines from terminal 1,6-diynes.

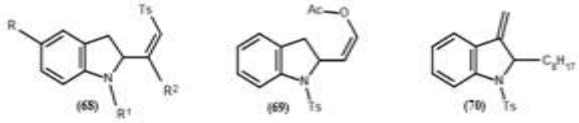
The allenylation of propargyl carbonate with organo-boron and subsequent tertiary amine self-catalyzed Csp_3–H functionalization in a one-pot process was proceeded leading 3–alkenyl indolines. All reaction conditions, reaction mechanism, effect of solvent, and electronic influence of the substituent were investigated. [47] (Scheme 25)

Vinylogous of indolines [68, 69 and 70] were achieved via hetero-annulation of o–iodo–anilines with dienyl sulfones,[48] or 1–acetoxy–1,3–dienes, [49] allenes or 1–sulfonyl–1,3–dienes [50] using palladium as catalyst. The reaction is compatible with both electron-donating and electron-withdrawing substituents in the para position of the aniline, and with an alkyl substituent at C–2 of the dienylsulfones. [48]

Palladium-catalyzed diene 1,2–carbo–amination reaction was involved through a urea–directed *o*–CH–olefination/cyclization sequence under mild conditions in relatively nonacidic media.[51] Herein, the palladium tosylate is considered a key promoter (Scheme 26). [52]



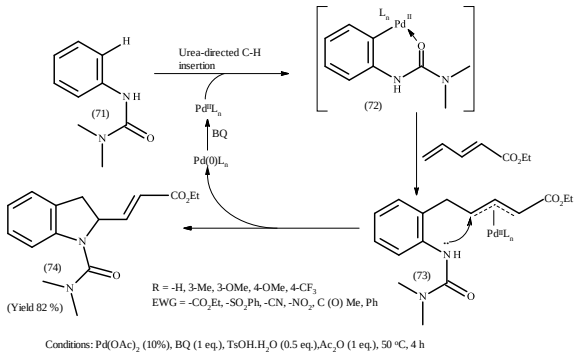
Scheme 25. Synthesis of 3–alkenyl indolines.



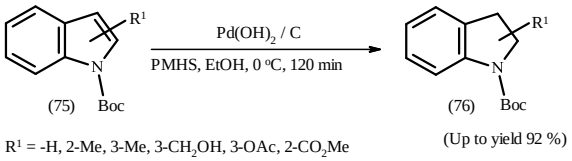
2. 1. 1. 3. Palladium-catalyzed diene 1,2–carbo–amination reaction

1. 1. 1. 4. Via palladium catalyzed reduction

On the other hand, Palladium catalysts have been used to selective reduction of the indole ring. As example the reduction of N−(tert−butoxy−carbonyl)indoles give N−(tert−butoxycarbonyl)−indolines in good yields by using polymethyl-hydrosiloxane (PMHS) as reducing agent at room temperature. [53] (Scheme 27)



Scheme 26. Synthesis of indolines by *o*–CH–olefination /cyclization.



Scheme 27. Transformation of indoles into indoline.

2. 1. 2. Nickel- promoted of synthesis of indolines

The proposed and common mechanism of Ni-catalyzed reaction is illustrated in Figure 4.

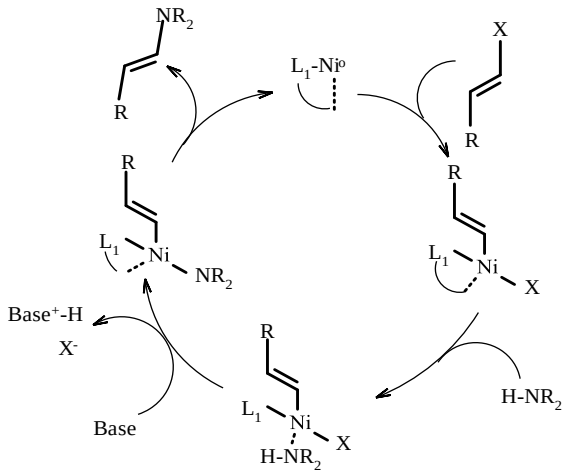
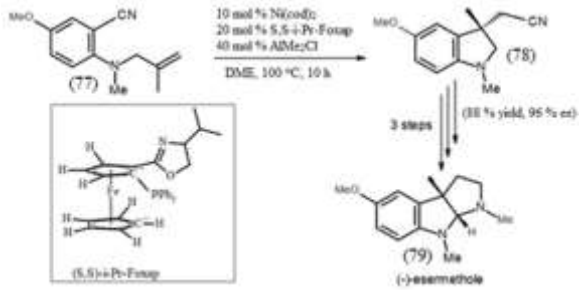


Figure 4. The common Ni-catalytic cycle.

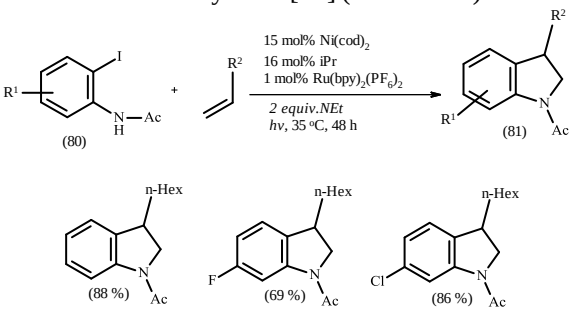
For example, the enantioselective cyclization of 2−amino−benzonitriles bearing an olefinic moiety (**75)** was successfully applied to the total synthesis of (−)−esermethole, which serves as a synthetic precursor of potent acetylcholinesterase inhibitors such as (−)−physostigmine and (−)−phenserine by using commercially available (*S*,*S*) −*i*-Pr-Foxap.[54] (Scheme 28) It is worth noting that, the electron density on the benzene ring slightly affected the

enantioselectivity of the reaction, aryl-halogen bonds were tolerated, and that the C−CN bonds were activated by the nickel/$AlMe_2Cl$ cooperative catalyst. However, the observed drop in the reaction rate and yield could be attributed to some competitive side reactions occurring through activation of the aryl-halogen bonds. Also, the size of the N−substituents affected both chemical yield and enantioselectivity. Larger substituents might retard oxidative addition of the Ar−CN bond as well as coordination of the double bond to nickel. [55]



Scheme 28. Nickel- promoted of synthesis of indolines.

On the other hand, using one step reaction, a very high regioselectivity for 3–substituted indolines had been obtained from intermolecular cyclization 2–iodoaniline derivatives and terminal alkenes using nickel as catalyst. The formation Csp_3–N bond was achieved by dual catalytic systems of nickel within the same reaction system. [56] (Scheme 29)

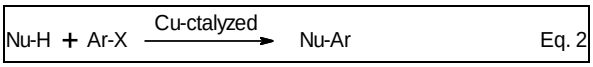


Scheme 29. Synthesis of indolines using Nickel/photoredox catalysis.

2. 1. 3. Copper-catalyzed of synthesis of indolines

On the different, copper-catalyzed C–N bond formation reactions are considerably less utilized, in spite of copper utilization has increased due to advantage of its cheaper price and low toxicity. [57] Cu-catalyzed reactions occur between a nucleophile (Nu-H) and an electrophile (ArX) as represented in Eq. 2. The proposed and common mechanism of Cu-catalyzed cross-coupling reaction is illustrated in Figure 5.

In addition, these reactions are promoting by the amino acids (N–methylglycine, L–proline and N,N–dimethylglycine) (Scheme 30) *via* their reactivity as the coupling agents and coordination ability. Notably, these promoters are inexpensive and readily available



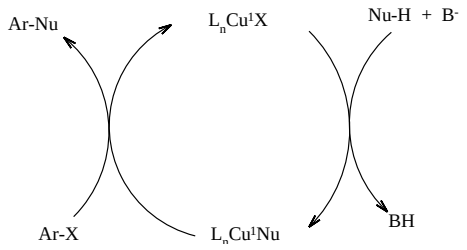
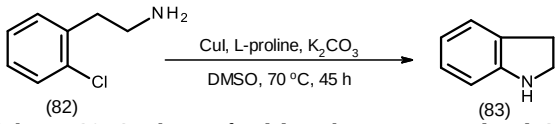


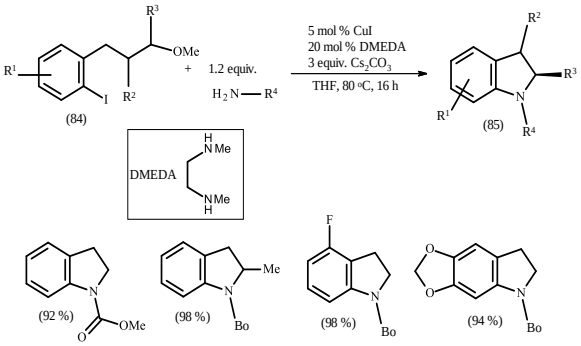
Figure 5. The common Cu-catalytic cycle.

as well as they can be easily removed from the crude products by simply washing with water. On given these advantages, the present reactions should find considerable applications in organic synthesis. [58]



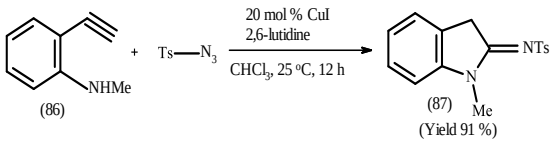
Scheme 30. Synthesis of indolines by copper–catalyzed C–N bond formation.

Interestingly, Minatti and Buchwald reported an access to synthesis of chiral 2–ethylindolines by enantioselective one-pot procedure based on a domino Cu–catalyzed amidation/nucleophilic substitution reaction (Scheme 31). [16] In this reaction no erosion of optical purity was observed.



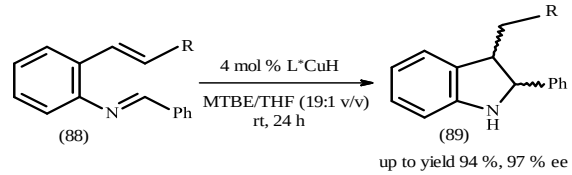
Scheme 31. Synthesis of chiral 2–ethylindolines by domino Cu-catalyzed reaction.

Further, 2–sulfonylimino-indolines can be efficiently synthesized by the Cu-catalyzed cyclization reaction. This route is characterized by mild reaction conditions, facile introduction of functional groups at the 2–position of the indoline ring, and the wide substrate scope. [59, 60] (Scheme 32)



Scheme 32. Indoline synthesis from amino alkynes.

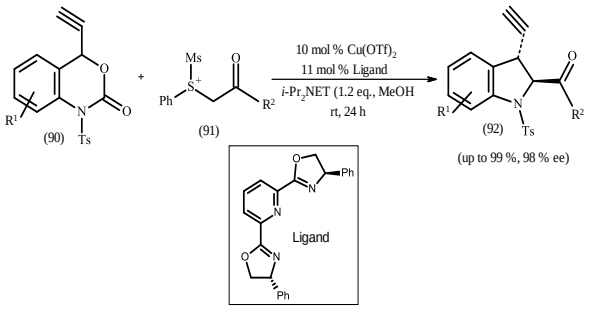
Additionally, a versatile of *cis*–2, 3–disubstituted indolines in high yield and enantioeselectivity were synthesized using CuH-catalyzed C–H insertion reaction (Scheme 33). [61] This technique is highly valuable for the synthesis of a variety of *cis*–2, 3–disubstituted indolines in high yield with enantioeselectivity manner.



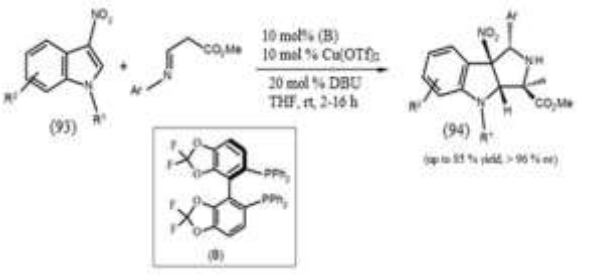
Scheme 33. Synthesis of cis-dihydro-indoles.

Remarkably, copper-catalyzed asymmetric decarboxylative [4 + 1]-cycloaddition of propargylic carbamates and sulfur ylides provides a chiral indolines bearing synthetically flexible alkyne groups in good yields with high enantio- and diastereoselective style. [62] (Scheme 34)

Similar approaches were also successful for the building of the complexed pyrrolo-indolines by stereoselective reactions between electron poor indoles and azomethine ylides derived in situ from imino esters using the combination of $Cu(OTf)_2$ and (R)–difluorphos as catalyst. [63] (Scheme 35)



Scheme 34. Synthesis of chiral indolines.

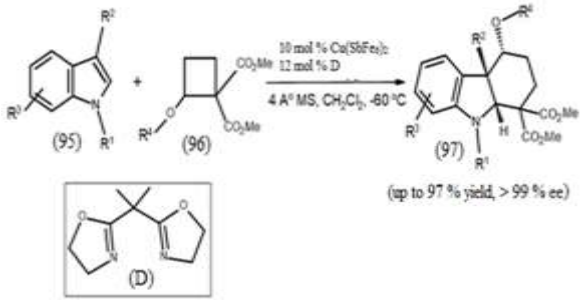


Scheme 35. Stereoselective reactions between indoles and azomethineylides.

Furthermore, the diastereospecific [4+2] cyclization reactions between substituted indoles (**95**) and donor-acceptor cyclobutanes (**96**) under catalysis of the combination of $Cu(SbF_6)_2$ and the achiral BOX ligand (**D**) were examined to afford cyclohexane-fused indolines (**97**). [64] (Scheme 36)

2. 1. 4. Gold-mediated cyclization

On the other hand, gold is used as catalyst in synthesis of indolines. The Figure (6) shows the general Au-catalytic cycle.



Scheme 36. Synthesis of cyclohexane-fused indolines.

As example, a highly functionalized cyclobutane-fused indolines (**99**) in yields of up to 98% were produced *via* intramolecular tandem 3,3−rearrangement/[2+2] cyclization of propargyl 3-indoleacetates (**98**) using gold as catalyst. [65] (Scheme 37)

Cyclobutane-fused indolines (**102**) were achieved by Au-catalyzed intermolecular enantioselective [2+2] cyclization reactions of allenyl amide (**101**) with indoles (**100**). [66] (Scheme 38)

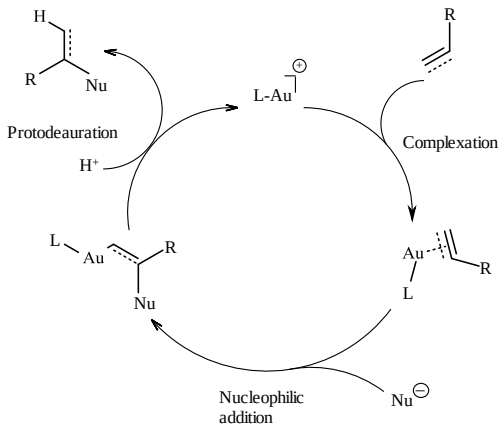
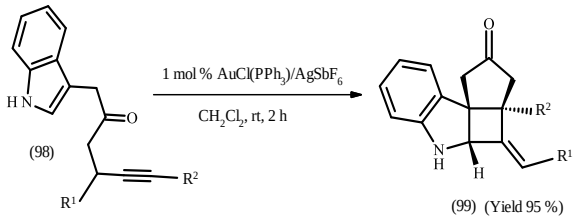
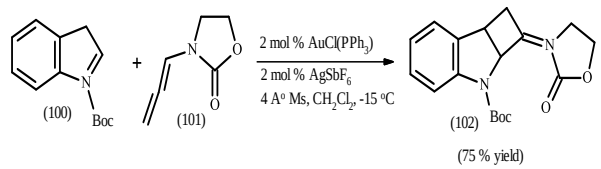


Figure 6. The common Au-catalytic cycle.

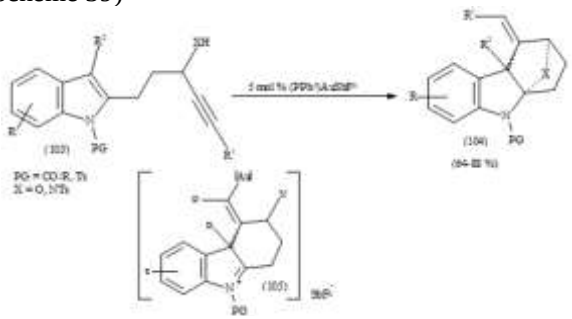


Scheme 37. Synthesis of cyclobutane-fused indolines.



Scheme 38. Synthesis of cyclobutane−fused indolines by [2+2]cyclization reactions.

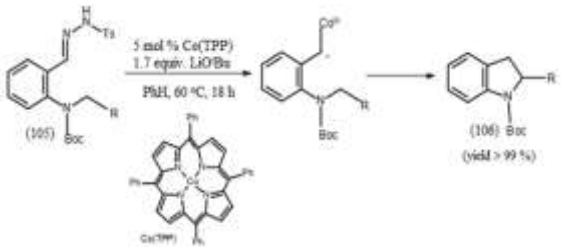
Interestingly, the fused-tetracyclic indoline were achieved from the compound (**104**) using Au-catalyzed hydroarylation of alkynes cyclization reactions of indolyl-propargylic alcohols/amines **(103)** under mild conditions. The initial regioselective site-selective indole attack (C3 position) to the C–C triple bond, with the trapping of the iminium ion (**105)** by *O*- or *N*-based nucleophiles. [67] (Scheme 39)

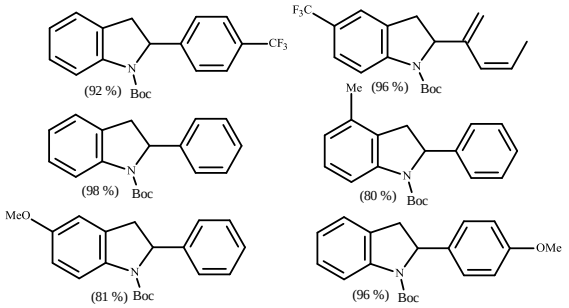


Scheme 39. Synthetic plan for a polycyclic indoline alkaloid.

2-1-5- Cobalt-promoted of synthesis of indolines

The synthesis of indolines from *o*–aminobenzylidine–N–tosylhydrazones was performed through a cobalt(III)-carbene radical intermediate. The advantages of this reaction are utilized inexpensive, commercially available reagents and air- and moisture-stable catalyst. Herein, the steric and electronic effects of substituents on the aniline ring and computational investigations were evaluated. [68] (Scheme 40) Finally, the preparation of indoline (**111**) was extensively studied *via* the Co-catalyzed intramolecular cross-coupling reaction of allylamine

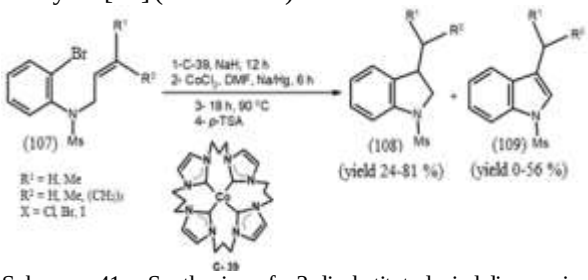




Scheme 40.Co-promoted of synthesis of indolines.

Also, the tetrahedral Co(II)-crown carbene complex (**C–39**) was utilized for the synthesis of 3–disubstituted indoline derivatives *via* reductive method with NaH. [69] (Scheme 41)

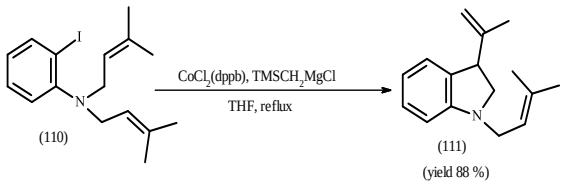
N–allyl–*o*–haloanilines using [$CoCl_2$(dpph)] (DPPH = [1,6-bis(diphenylphosphino)hexane]) as catalyst . [70] (Scheme 42)



Scheme 41. Synthesis of 3-disubstituted indolines via reductive activation.

2. 1. 6. Rhodium-mediated of synthesis of indolines

In recent periods the utilization of rhodium as catalyst have seen successful development of



Scheme 42. Synthesis of indolines via the Co–catalyzed reactions.

synthetic methods for the preparation of indoline derivatives. The proposed Rh-catalytic cycle for the reactions is shown in the following Figure 7.

A stereoselective synthesis of 2,3–dihydro–1H–indoles was produced *via* enantioselective C–H insertions of intermediates (**114**) using a RhII as catalyst.[71] (Scheme 43) This intramolecular cyclization occurs selectively to the more hindered *ortho*–site of the substrate under the action of RhII as catalyst. [72]

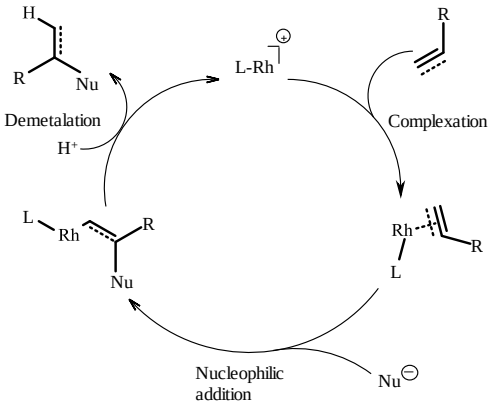
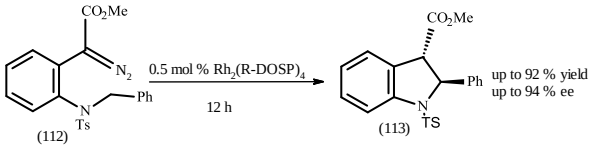


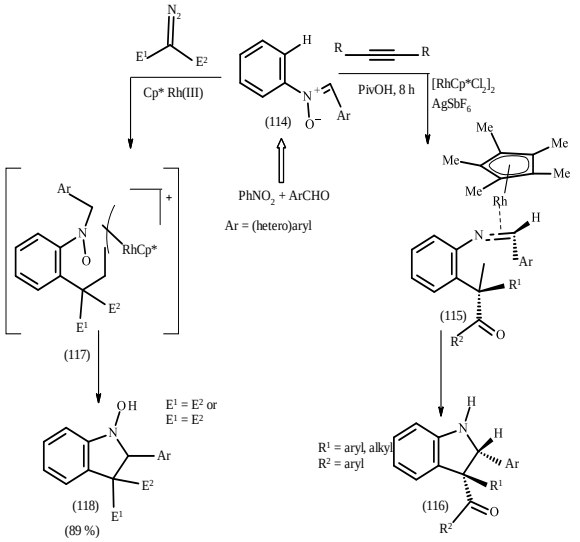
Figure 7. Common Rh-catalytic cycle.

Likewise, indoline derivatives (**119**) or (**121**) were achieved in good yields *via* stereo-selective intermolecular coupling of arylnitrones with internal alkynes [73] or diazo compounds [74] respectively using Rh(III)-catalyzed process. This method was carried out under external oxidant-free conditions with high diastereoselective approach. The dual role of CpRh(III) catalyst mediating both the C–H bond activation and O–atom transfer was observed. (Scheme 44)



Scheme 43. Stereo-selective synthesis of 2,3–dihydro–1H–indoles.

On the other hand, 4,5,6,7–tetrasubstituted indolines in excellent yields were achieved by [2+2+2]–cycloaddition reaction between the compound (**122**) and alkynes using rhodium as catalyst (Scheme 45). [75]



Scheme 44. Synthesis of indolines using Rh(III) as catalyst.

Recently, 2,2,3,3–tetrasubstituted indoline **(124)** was achieved though intramolecular carbenylative amination of *o*–vinylaniline (**123**) with *N*–sulfonyl–1,2,3–triazole **(122)** using $Rh_2(OAc)_4$ as catalyst in toluene at room temperature. [76] (Scheme 46)

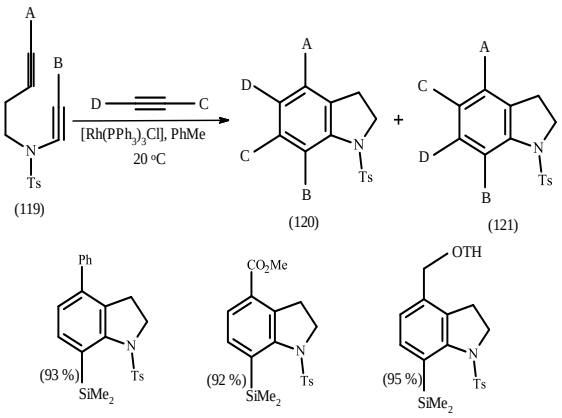
Additionally, $Rh_2(OAc)_4$-catalyzed diazo decomposition reaction of diazo esters with 2-aminophenyl ketones was reported for the synthesis of 3–hydroxy–2,2,3–trisubstituted indolines in good yields with excellent diastereoselectivities *via* an intramolecular aldol-type trapping of ammonium ylides with ketone units. [77] (Scheme 47)

Further, tetracyclic indolines (**131**) were afforded using Rh-catalyzed intramolecular [3+2] cyclization reactions of indolyltriazoles (**130**). [78] (Scheme 48)

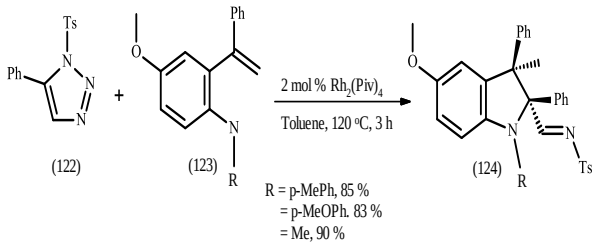
Also, cyclopentene-fused indolines (**134**) in good yields (up to 87%) with high region- and enantiocontrol (up to 98% *ee*) were synthesized *via[3+2] cyclization reactions of indoles (**132**) with electrophilic enol carbenes generated in situ from enol diazo-acetamides. [79] (Scheme 49)*

2.1.7. Iorn - mediated of synthesis of indolines

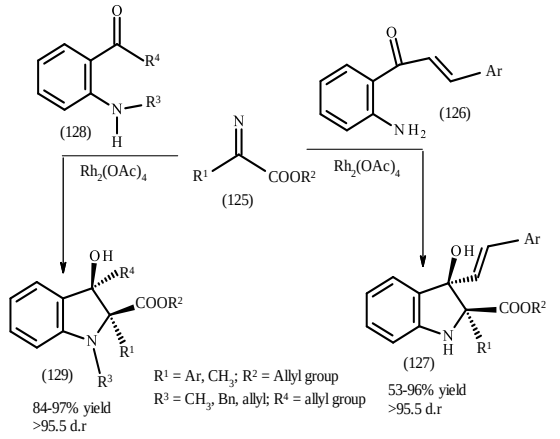
Furthermore, ion-catalyzed synthesis of indolines through the general reaction is represented in Eq. 3 and in Figure 8.



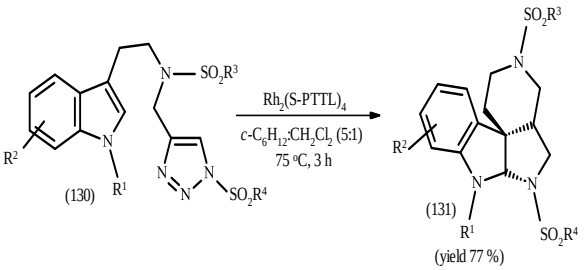
Scheme 45. Synthesis of 4,5,6,7–tetrasubstituted indolines.



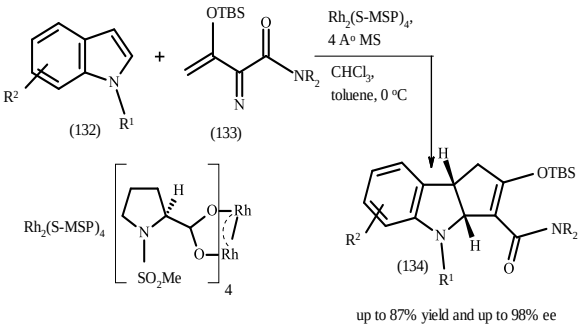
Scheme 46. Synthesis of 2,2,3,3–tetra– substituted indoline.



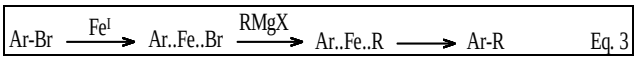
Scheme 47.Synthesis of 3–hydroxy–2,2,3–trisubstituted indolines.



Scheme 48. Synthesis of tetracyclic indolines by intramolecular [3+2] cyclization.



Scheme 49. Synthesis of cyclopentene-fused indolines *via* [3+2] cyclization reactions.



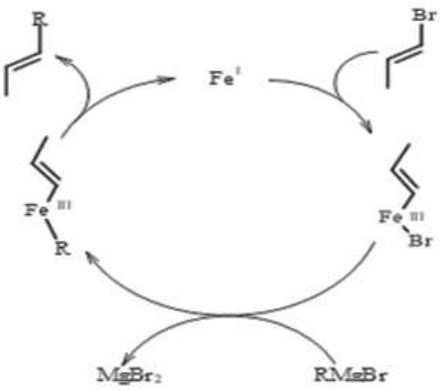
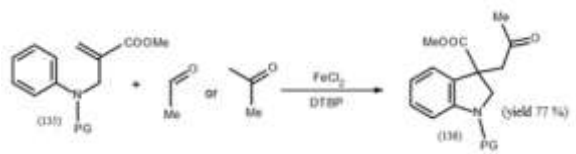


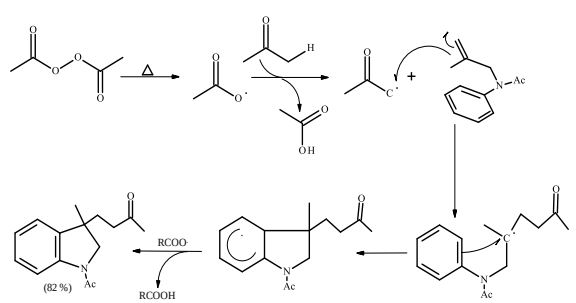
Figure 8. The common Fe-catalytic cycle.

Iorn-mediated of synthesis of indolines bearing ketone side chains was achieved through the difunctionalization/annulation of activated olefins using aldehydes [80] or ketones [81] as the carbonyl sources using $FeCl_3$ and lauroyl peroxide(LPO) as catalyst. (Scheme 50) This reaction tolerates a series of functional groups to provide 3–(3–oxobutyl)indolines in good yields. The proposed mechanism [81] is illustrated in Scheme 51 *via* radical-cyclization reaction.

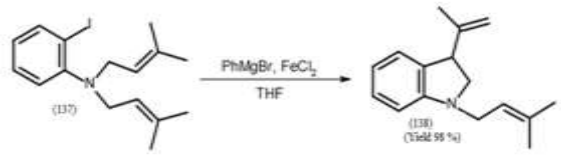
Also, the prenyl–3–isopropenyl–2,3–dihydroindole (**138**) in 98% yield *via* radical-cyclization reaction was synthesized as shown in Scheme 52. [82] Furthermore, the corresponding indoline (**61**) was achieved using Fe complex $Bu_4N[Fe(CO)_3(NO)]$ catalyzes the intramolecular amination of Csp_3–H bonds in alkylarylazides. The catalyst $Fe(CO)_5$ is inexpensive, accessible in one-step reaction, on multigram scale and makes this process particularly attractive from a synthetic point of view.[83]



Scheme 50. Iorn-mediated of synthesis of indolines.

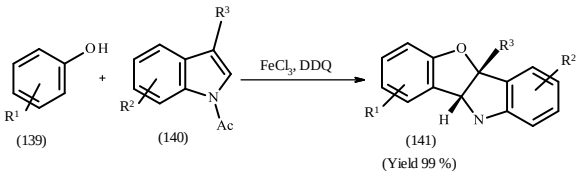


Scheme 51. The proposed mechanism of synthesis of indolines via radical-cyclization reaction. [81]



Scheme 52. Synthesis of indoline derivatives via radical–cyclization.

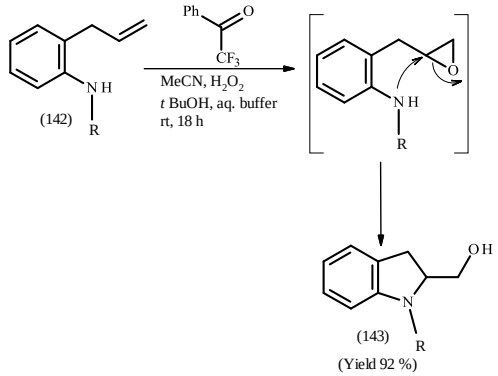
Other approaches were based on the oxidative [3 + 2]−annulation between phenols and 3−substituted N−acetylindoles for the synthesis of benzofuro[3,2]indolines using excess amount of $FeCl_3$ and 2,3−dicyano−5,6−dichlorobenzoquinone (DDQ).[84] (Scheme 53) Recently, other route using electricity instead of $FeCl_3$ is considered as straightforward and atom economic way in a simple undivided cell with 99% yield.[85]



Scheme 53. Synthesis of benzofuro[3,2−b]indolines.

2. 2. Metal-free approaches

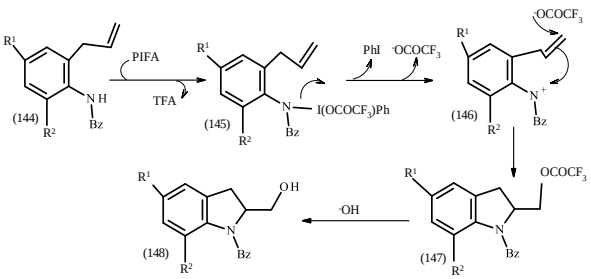
Although the popularity of metals promoted methods, metal toxicity and high levels of inorganic waste make their application harmful for the environment as well as these methods suffer from functional group intolerance, the necessity of expensive noble transition metal catalysts, harsh reaction conditions, and/or require the use of protecting groups that need certain conditions for their removal. Thus, the development of a new metal free methods for the synthesis of such heterocycles remains a challenge in synthetic organic chemistry.[86] However no metal contamination can be expected by metal free methods, the stoichiometric amount of acid waste still remains. The one-pot synthesis of indolines was developed by employing H_2O_2 and 2,2,2–trifluoro–acetophenone-mediated metal-free intramolecular aminohydroxylation and dioxygenation reactions of unfunctionalized olefins [87] (Scheme 54) or from Brønsted Acid–assisted intramolecular amino–hydroxylation of N–alkenyl–sulfonamides *via* the formation of epoxide intermediates.[88] These catalysts are consider cheap, general and environmentally-friendly one. Also, a variety of substitution patterns, both aromatic and aliphatic moieties, are well tolerated leading to the diverse nitrogen heterocycles in up to 92% yields.



Scheme 54. Synthesis of indolines using trifluoro-acetophenone as catalyst.

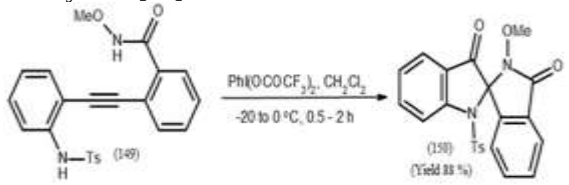
On the other hand, the organohypervalent iodines have played a dynamic role as green recyclable reagents to produce a diversity of bioactive heterocycles. Due to freely available, accessible and shorter reaction times, organohypervalent iodine reagents have extended special attention as multipurpose and benign oxidants in several organic transformations.[89]

Thus, a metal-free method for the synthesis of indoline derivatives was achieved by employing the environmentally friendly iodine reagent phenyliodine–(III) bis–(trifluoroacetate) (PIFA) as mediated amido-hydroxylation reaction. The essential key step here depends on the ability of iodine reagent to generate N–acylnitrenium intermediates (**146**).[89, 90] (Scheme 55)



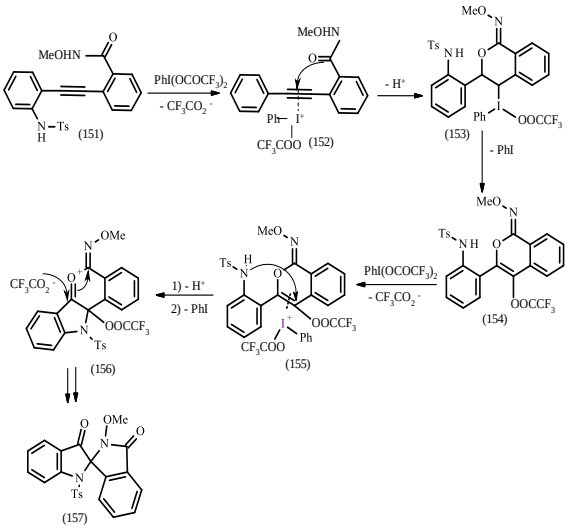
Scheme 55. Metal-free approach to the synthesis of indoline derivatives.

As indicating in Scheme 56, spiro-indolines were achieved by cascade annulation reactions of diarylacetylene using hypervalent iodine reagents [phenyliodine-bis(trifluoroacetate) (PIFA)] in up to 88 % yields.[91]



Scheme 56. Synthesis of spiro-indolines by cascade annulation reactions.

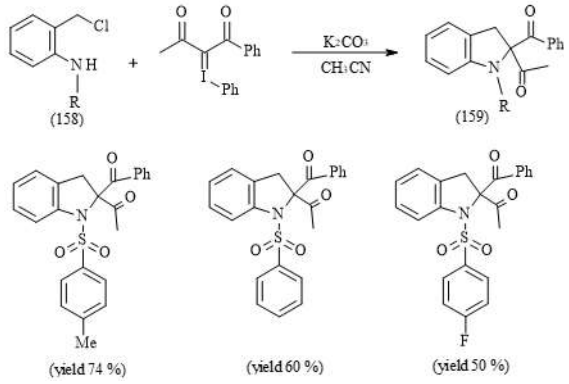
Recently, *o*−alkynyl oxime derivatives and diaryliodonium salts were reacted under mild metal-free conditions producing a variety of 2,3−quaternary fused indolines in good yields with high diastereoselectivity from. The reaction initially goes through a selective *N*−arylation to provide *o*−alkynyl nitrones which undergoes regioselective intramolecular (3 + 2) cycloaddition followed by a [3,3]−sigmatropic rearrangement to afford the target compounds in a one-pot approach. (Scheme 57) The applicability of this method is cheap materials, multiple bond formation, gram scalable preparation and diversity of fused indoline scaffolds.[92]



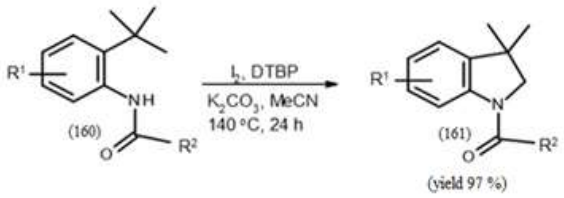
Scheme 57. Synthesis of 2,3−quaternary fused indolines.

A transition-metal-free method for the synthesis of indolines from the cyclization reaction of *N*−(*ortho*−chloromethyl)aryl amides and iodonium ylides in the presence of K_2CO_3 has been developed. (Scheme 58) This method is proceeded smoothly at room temperature in good yields.[93]

On the other hand, the indolines have been produced by iodine-mediated oxidative intramolecular amination of anilines. The reaction could be performed on a gram scale for the synthesis of functionalized indolines.[94] (Scheme 59)

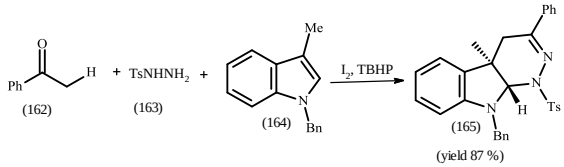


Scheme 58. Synthesis of indolines from N−(ortho-chloromethyl)aryl amides.



Scheme 59. Iodine-mediated oxidative intramolecular amination.

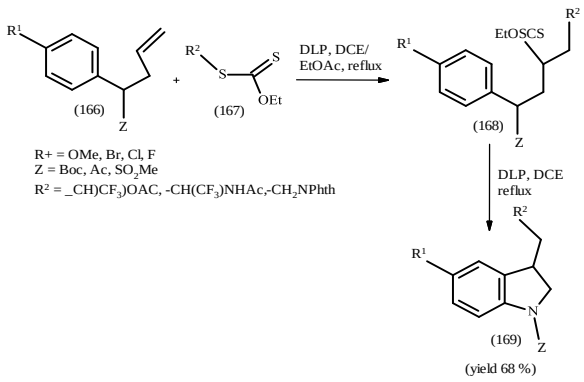
Likewise, the indoline can be prepared via intermolecular dearomative oxidative coupling of indoles with ketones and sulfonylhydrazines catalyzed by I_2.[95] (Scheme 60)



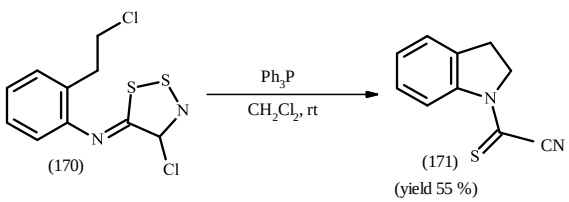
Scheme 60. Synthesis of indoline via intermolecular dearomative oxidative coupling reaction.

Interestingly, many biologically active natural products contain indoline scaffolds [(−)–communesin F, communesin A and B] were synthesized by intramolecular oxidative coupling using iodine as an oxidant.[96] The indoline derivatives were generated through xanthate addition to the double bond of *N*–aryl allylamines followed by intramolecular radical ring closure onto the phenyl ring.[97] (Scheme 61)

Alternatively, N–arylimino–1,2,3–dithiazoles (**170**) derived from 2–chloroethylaniline, 2–hydroxyethylaniline and its mesylate undergo ring opening of the dithiazole moiety followed by intramolecular cyclisation into indoline derivatives.[98](Scheme 62)

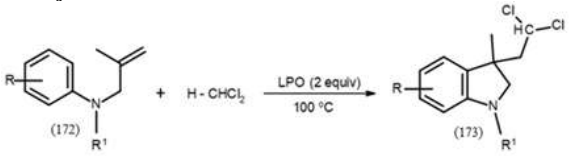


Scheme 61. Synthesis of indolines derivatives using xanthate.



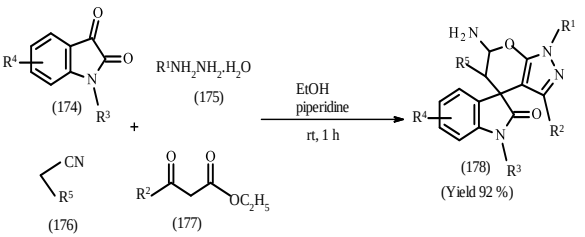
Scheme 62. Synthesis of indolines from N–arylimino–1,2,3–dithiazoles.

Recently, the synthesis of polychloro-substituted indolines was achieved in the yield of 72% - 74% *via* metal-free radical cascade difunctionalization of unactivated alkenes using dichloromethane, chloroform or tetrachloromethane as the polychloromethyl sources under metal-free and additive-free conditions. (Scheme 63) The substituents (electron-withdrawing or electron-donating groups) at phenyl ring reacted with DCM leading to the corresponding products in good yields. Also, substrates with different N–protecting groups, such as propionyl, formamido and BOC are worked efficiently producing the corresponding dichloro-methylated indolines.[99]



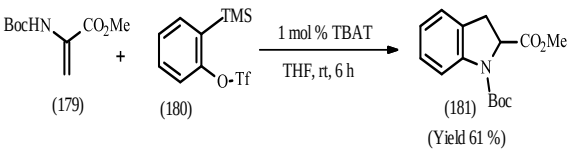
Scheme 63.Synthesis of polychloro-substituted indolines.

The one-pot synthesis of spiro[indoline-3,4′-pyrano[2,3- c]pyrazole] derivatives from the reaction of four-component of hydrazine, β-keto ester, isatin, and malononitrile or ethyl cyanoacetate in the presence of piperidine under ultrasound irradiation was studied. (Scheme 64) These processes take place in water involving of two rings with five new bonds (two C–C, two C–N and one C═N) in a single synthetic operation and with reducing the waste generated due to the absence of extraction and purification steps.[100]



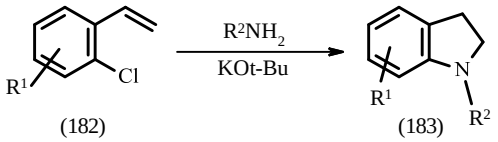
Scheme 64. Synthesis of spiro[indoline–3,4′–pyrazolo[3,4–*b*]pyridine derivatives.

Additionally, the substituted indolines were obtained from the reaction of *N*–carbamoyl-functionalized enamine derivatives with benzyne using tetrabuty-ammonium difluoro-triphenylsilicate (TBAT) as fluoride source and THF as solvent. [101](Scheme 65) A fluoride-induced intermolecular coupling between allyl-derivative (**179**) and benzene derivative (**180**) derivatives.



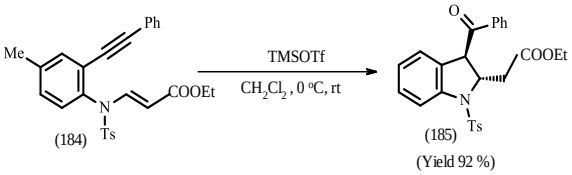
Scheme 65. Synthesis of substituted indolines from N-carbamoyl-functionalized enamine.

Further, the N–substituted 2,3–dihydro-indoles in good yields have been achieved through the metal-free intramolecular base–promoted amination of aromatic C−Cl bonds. Due to the formation of aryne intermediates, either meta-substituted anilines or N–substituted anilines are produced with good selectivities manner.[102] (Scheme 66)



Scheme 66. Synthesis of substituted N–indolines through aryne intermediates.

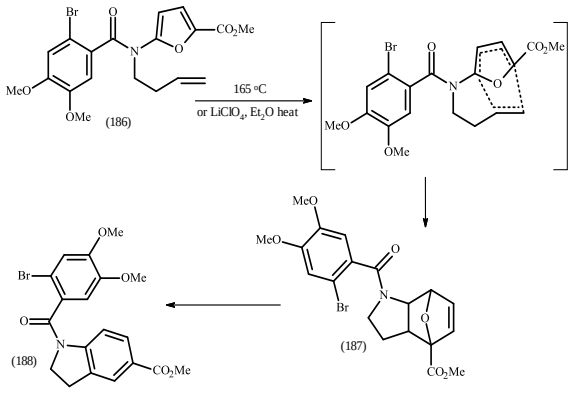
In the same manner, by using trimethylsilyl–trifluoro–methanesulfonate (TMSOTf) as catalyst, the stereoselective formation of *trans*–2,3–disubstituted indolines (**185**) in good yield were obtained through intramolecular alkyne iminium ion cyclization of vinylogous carbamates (**184**) which was obtained from the reaction of aniline derivative and ethyl propionate.[103] (Scheme 67)



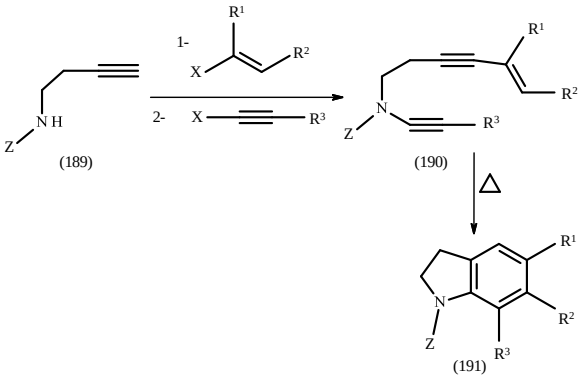
Scheme 67. Stereoselective formation of trans–2,3–disubstitutedindolines.

Likewise, indoline (**66**) was synthesized by inter-and intramolecular Diels-Alder reactions of 2–substituted aminofurans. This transformation was utilized in the preparation of alkaloid oxoassoanine.[104] (Scheme 68)

Moreover, a highly substituted indolines and indoles were achieved *via* intramolecular [4+ 2] cycloaddition of ynamides with conjugated enynes.[105] (Scheme 69)

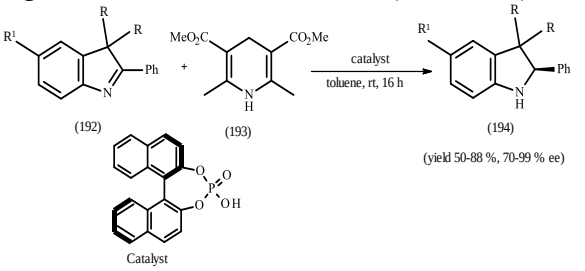


Scheme 68. Syntheses of indolines by Diels-Alder reactions.



Scheme 69. Syntheses of indolines via intramolecular [4+ 2] cycloaddition.

On the other hand, a highly enantioselective metal-free reduction of compound (**192**) using dihydropyridine as the hydrogen source has been developed. This method is efficient one for the synthesis of various optically active indolines with high enantioselectivite mode.[106] (Scheme 70)

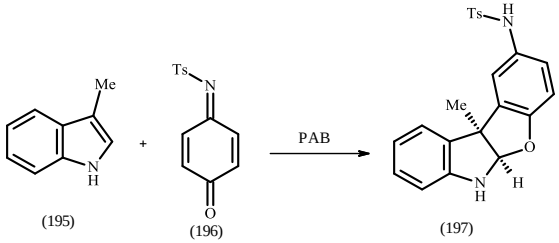


Scheme 70. Synthesis of indoline using dihydropyridine.

Further, the benzofuroindoline (**197**) in nearly quantitative yield with the highest *ee* value was obtained through [3+2]–coupling of 3–methyl indole (**195**) with 4–methyl–N– (4−oxocyclohexa–2,5–dienylidene)benzenesulfonamide (**196**) in toluene at 25 °C using a chiral phosphoric acid (PAB).[107] (Scheme 71)

1. Reaction of indolines

The functionalization of the indoline ring system through reactions with electrophiles are often limited and occurred at (3−), 5−, and 7−positions beside the
regioselective functionalization of the 4−position is considered difficult.[108] Herein, the electrophilic

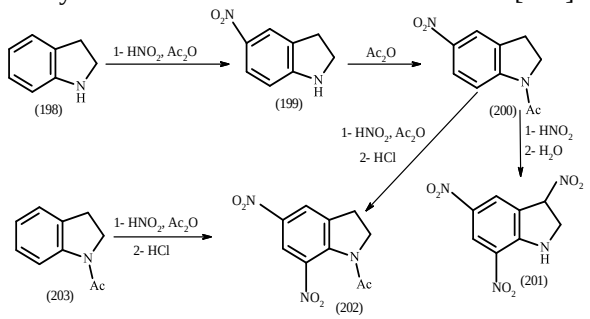


Scheme 71. Transformation of indoles into indoline using [3+2]–coupling reaction.

substitution reactions of indolines have been collected with the aim of introducing substituents into the benzene or pyrrole ring of the indoline molecule.

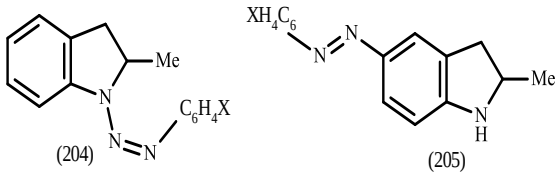
3.1. Electrophilic substitution reactions at benzene ring

Electrophilic substitution (EAS) at benzene ring of indolines takes place at 5-position of indoline. Herein, some of these reactions will be discussed as the following: When indolines are nitrated with the nitrating mixture, the nitro-group enters into position 5 in high yields. While the nitration of 1−acylindolines gave a series of l−acyl−5,7−dinitroindolines.[109] (Scheme 72) In other instances, 5−and 6−aminoindolines have been obtained by the reduction of the corresponding readily available nitroindolines.[110]

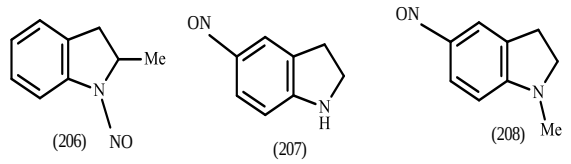


Scheme 72. Nitration of indolines.

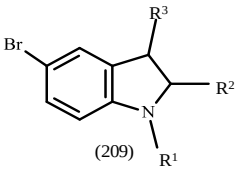
Azo-coupling of 2−methyl indoline with phenyldiazonium salts in the presence of sodium acetate forms diazoamino-compounds (**204**). While in a strongly acid medium the diazo-compounds (**205**) in Figure 7 are obtained.[111]

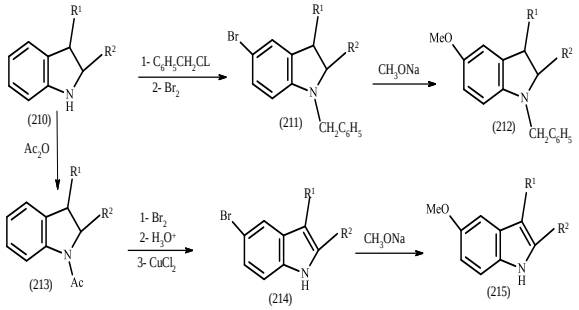


Furthermore, the nitrosation of 2−Methyl-indoline gives 2−Methyl−1−nitrosoindoline (**206**) which undergoes the Fischer-Hepp rearrangement yielding 5−nitroso− derivatives (**207**) in Figure 8.[110] Also, l−Methyl−5−nitrosoindoline (**208**) has been obtained from the reaction of butylnitrite with 1−methylindoline.[112]



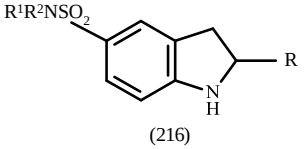
Also, 5−Bromo−derivatives (**209**) are formed by bromination of indolines in acetic acid.[113] While 5−Iodoindoline has been obtained by the action of IC1 on 1−acetyl-indoline.[111] Interestingly, 5−bromo−indolnes are considered as the precursors for the preparation of methoxy−derivative.[114] (Scheme 73)



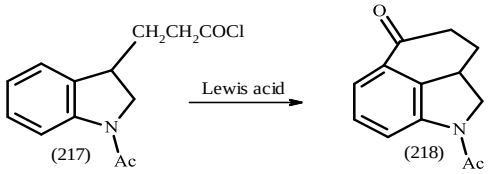


Scheme 73. Bromination of indolines.

On the other hand, 1−Acetyl−indoline−5−sulphonyl chlorides are obtained by chlorosulphonation of 1−acetylindoline, from which a number of indoline−5−sulphonamides are achieved (**216**).[111]

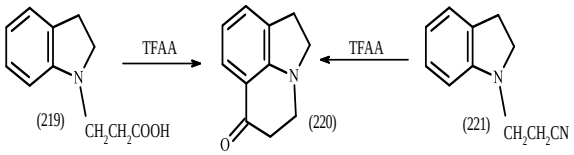


The Friedel−Crafts acylation of 1−acetylindolines yields the 5−derivative−indolines. Also the intramolecular C−acylation of derivatives of indolinealkanoic acid derivative (**217**) has been achieved. As example, the synthesis of tricyclic derivative (**218**).[111] (Scheme 74)



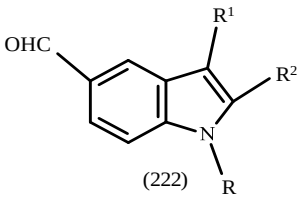
Scheme 74. The intramolecular acylation of indoline alkanoic acids.

Also, the intramolecular cyclization of indoline−1−propionic acid by heating with trifluoroacetic anhydride (TFAA) led to the corresponding tricyclic ketone. The same oxo-derivative (**220**) was obtained from cyano derivative of indoline (**221**). [115] (Scheme 75)



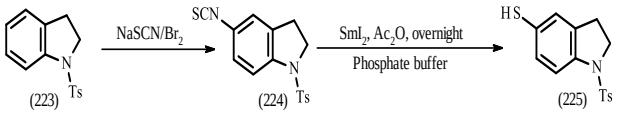
Scheme 75. The intramolecular cyclization of indoline derivatives.

In addition, l−Alkyl−5−formylindolines (**222**) have been obtained by the formylation of N−alkylindolines with methylformanilide and phosphorus oxychloride (Vilsmeier reaction).[111] 5−Formylindolines are considered as key substances in the synthesis of various 5−analogues of tryptamine and tryptophan.



3. 2. Thiocyanation of indolines

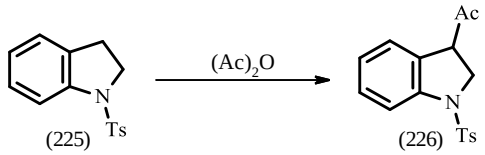
5−Mercapto-derivatives of indolines, the thio−analogues of hydroxyl-indole derivatives which exhibit high pharmacological activity, have been investigated. 5−Thiocyanato−derivatives have been obtained by the thiocyanation of indoline derivatives.[116] (Scheme 76)



Scheme 76. Preparation of indoline thiols.

3. 3. Electrophilic substitution reactions at pyrrole ring

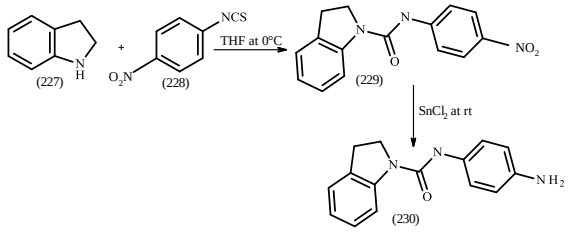
The indolines react with acid anhydrides, arene sulphonyl chlorides or diketen, etc., yielding the corresponding 3−substituted−N−substituted indoline.[111] (Scheme 77)



Scheme 77. Acylation of indolines.

3-4-Reaction of indoline with 4−nitrophenyl isothiocyanate

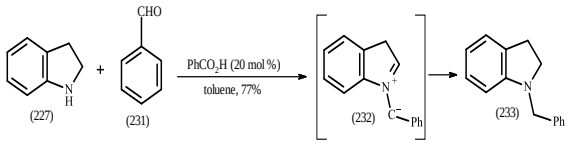
Also, indoline reacts with 4−nitrophenyl isothiocyanate (**228**) in THF at 0°C to produce the compound (**229**) which on treating with $SnCl_2$ at RT gave N−substituted indoline (**230**).[117] (Scheme 78)



Scheme 78. Reaction of indoline with 4−nitrophenyl isothiocyanate.

3. 5. Reaction of indolines with benzaldehyde

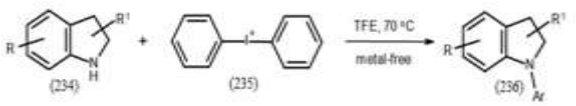
Indoline have been condensed with benzaldehyde in the presence of benzoic acid as catalyst; *N*–benzylindole is formed through intermediate azomethine ylide.[118](Scheme 79)



Scheme 79. Reaction of indoline with benzaldehyde.

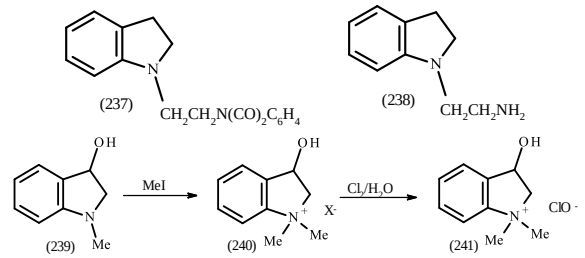
3. 6. N−Alkyl-indolines and quaternary indolinium salts

The N−aryl indolines could be obtained in up to 85% yield using diaryliodonium salts as electrophilic arylating reagents without the use of any additional additives.[119] (Scheme 80) Herein, authors observed that using the different base additives did not improve the product yield. By utilization of different substituents, electron-donating no N−aryl indoline could be isolated but with electron-withdrawing groups the decrease of the yield was observed. Further yield was increased by using 2,2,2−trifluoroethanol (TFE) as solvent.



Scheme 80. Formation of N-aryl indolines.

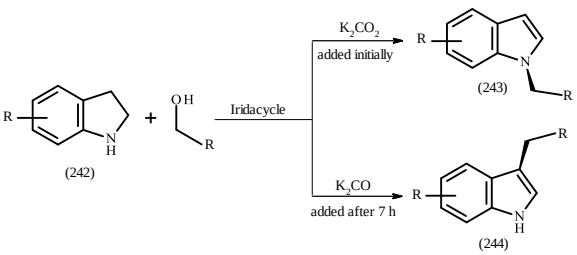
N−Alkylation of indolines has been investigated. Particularly, the preparation of derivatives (**237**) which used for the synthesis of 1−isotryptamines (**238**).[120] Also the quaternary 3−hydroxyindolinium salt has served as the starting material for the preparation of the quaternary indolinium salt.[111] (Scheme 81)



Scheme 81. Preparation of quaternary 3−hydroxyindolinium salt.

3. 7. The dehydrogenative coupling of indolines with alcohols

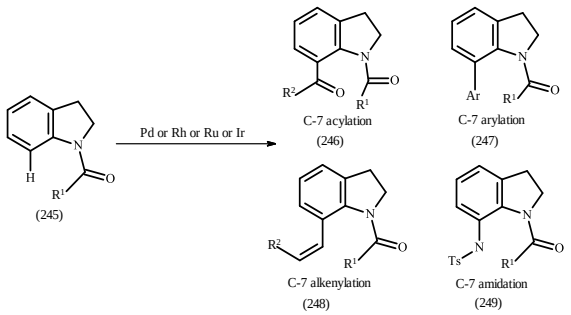
Indolines have been coupled with alcohols to afford both N- and C^3-alkylated indoles selectively using iridacycle as catalyst, by simply changing the addition time of a base additive. This catalyst dehydrogenates both amines and alcohols and catalyzes the coupling reactions. The proposed mechanism revealed that abstracting hydrogen-dehydrogenation process and a dehydrogenation-abstracting hydrogen process are achieved in N–alkylation and C^3-alkylation reactions, respectively. The direct coupling of two sp^3 carbon centers affords C^3-alkylation reaction. [121] (Scheme 82)



Scheme 82. Dehydrogenative coupling of indolines with alcohols.

3. 8. C–7– Functionalizations of indolines

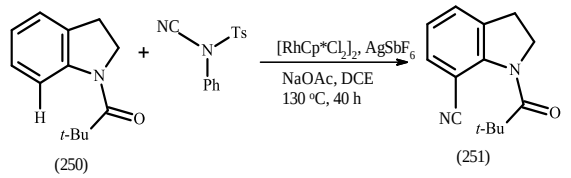
Recently, the directing group-assisted C–7–functionalizations of indolines has been make heavy research aiming to overtake the inherent selectivity of indoles. In this case, acylation [122], arylation [123], alkenylation [124], alkylation [125], and amidation [126] reactions were developed as illustrated in Scheme 83.



Scheme 83. C–7– Functionalizations of indolines.

3. 8. 1. C–7– Selective C–H cyanation of indolines

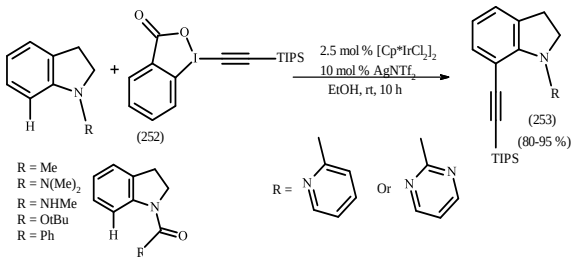
The rhodium-catalyzed selective cyanation of C–H bonds of indolines and indoles with *N*–cyano–*N*–phenyl–*para*–methylbenzenesulfonamide is described. This method offers a facile access to C–7–cyanated indolines and C–2–cyanated indoles with high site selectivity and excellent functional group tolerance.[127] (Scheme 84)



Scheme 84. C–7– Selective C–H cyanation of indolines.

3. 8. 2. C–7–Alkynylated indolines

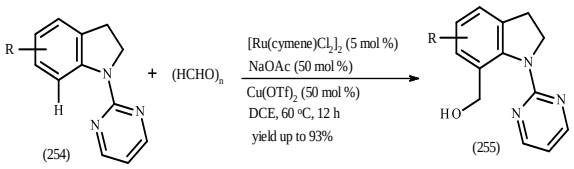
An iridium-catalyzed direct C–7 selective C–H alkynylation of indolines at room temperature has been developed *via* C–H bond activation. The utility of this methodology is the resulting product can be readily transformed into C–7–alkynylated indoles which undergoes to further transformation into other C–7 derivatization of indoles [128] (Scheme 85)



Scheme 85. C–7–Alkynylated indolines.

3. 8. 3. C–7–Hydroxymethylation of indolines

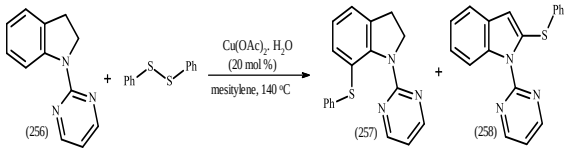
A variety of C–7– hydroxymethylated indolines has been achieved by one-pot regioselective addition of C–7–H bonds of indolines to formaldehyde using Ru(II)-catalyzed C–H activation under mild reaction conditions. [129] (Scheme 86)



Scheme 86. C–7– Hydroxymethylation of indolines.

3. 8. 4. C–7– Directed C–H functionalization

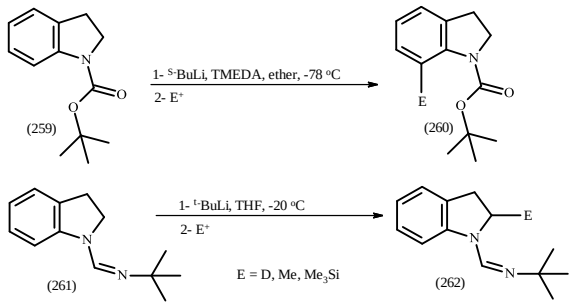
Ackermann developed a copper-catalyzed C–H chalcogenation of indoles and indolines that is positionally selective depending on the substrate. Indole was selectively functionalized at C–2 while indolines were instead reactive at C–7 (66% yield). The arene of sulfide is tolerant of halides and ethers, selenides are also suitable coupling partners. [130] (Scheme 87)



Scheme 87. C–7– Directed C–H functionalization of indolines.

3. 9. Metallation and alkylation properties of indolines

Indoline shows interesting metallation and alkylation properties which are dependent on the nature of the nitrogen substituent. When the *N*–substituent is *t*–butoxycarbonyl, metallation and alkylation occur exclusively at the *ortho* (C–7) position, whereas reaction occurs exclusively at the alkyl C–2 position in the case of the *N*–formamidine. [131] (Scheme 88)

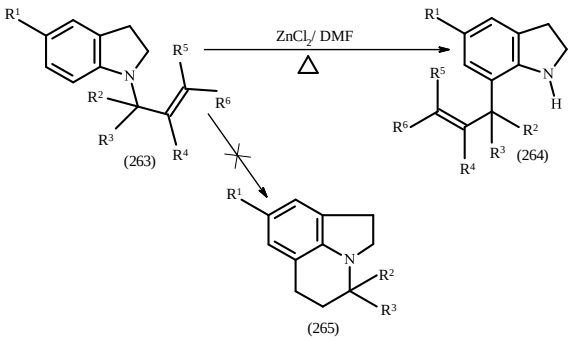


Scheme 88. Metallation and alkylation of indolines.

3. 10. Amino-Claisen rearrangement of N–allylindolines

N–allylindolines in 77% yield have been achieved *via* amino-Claisen rearrangement using $ZnCl_2$–*N*,*N*–dimethylformamide catalytic system. This rearrangement tolerated electron rich as well as electron deficient substituents on the arene ring of indolines without the formation of any cyclized

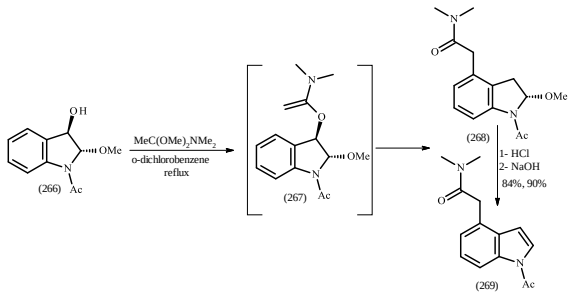
product providing an excellent regioselectivity manner. [132] (Scheme 89)



Scheme 89. C–7 directed C–H functionalization of indolines.

3. 11. Reaction of 3–hydroxy–2–methoxyindoline with N,N–dimethylacetamide

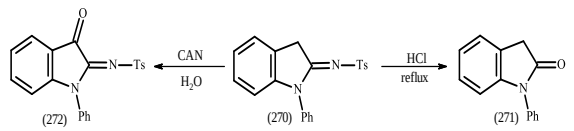
Reaction of 3–hydroxy–2–methoxyindoline with *N,N*–dimethylacetamide dimethylacetal undergoes a Claisen rearrangement to yield a mixture of the 4–substituted indoline and indole as shown in Scheme 90. [131]



Scheme 90. Reaction of 3–hydroxy–2–methoxyindoline with *N,N*–dimethyl-acetamide.

3. 12. Oxidation of indoline into isatin and oxindoles

As an isatin analogue and oxindoles are important building blocks in organic synthesis and medicinal chemistry. The transformation of indoline compounds such as 1−phenyl−2−(*p*−toluenesulfonyl)iminoindoline into an isatin analogue was successfully established upon treatment with cerium(IV) ammonium nitrate (CAN). [60] (Scheme 91)



Scheme 91. Oxidation of indolidine into isatin and oxindoles.

4. Biological Activities

The indoline and their derivatives are a significant class of heterocyclic compounds, because many of this skeleton have highly interesting bioactive compounds. Herein some of these biological activities will be discussed.

4. 1. Resistance-modifying agents (RMAs) in combination with antibiotics

It has become reasonable that the resistance to traditional antibiotic classes showing health crisis. [133] The multidrug-resistant methicillin-resistant *Staphylococcus aureus*(MRSA) has been amplified, [134] and new strains of *Gram-negative* bacteria that are resistant to all antibiotics have been recognized. [135] However, there are not sufficient analogs in the stream antibiotic manufacture to conflict these problems. [136]

Subsequently, a tri- and tetra-cyclic indolines, **Of1**, **Kf18** and (**272**) in Figure 9 were discovered to be selectively potentiate the activity of β-lactam antibiotics in (MRSA), but not in methicillin-sensitive *S. aureus*. These studies suggest that **Of1** may need further modification to fight against resistant bacteria in the clinic. [137]

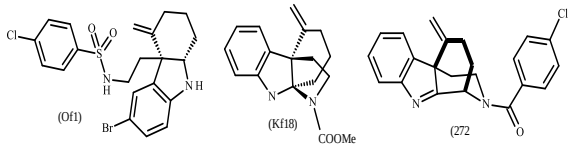


Figure 9. Some resistance-modifying agents (RMAs) with antibiotics.

The various derivatization of **Of1** on the indoline ring were synthesized and evaluated as resistance-modifying agents (RMAs) for various β-lactams. The authors observed that, the **Of1** with halogen moiety is considered the best, but a methyl group is tolerated with slight loss of activity.[138] A series of *aza*-tricyclic indolines (Figure 10) were synthesized for optimization of their pharmacokinetics (absorption, metabolism distribution),. [139, [127]] These compounds especially tetracyclic indoline derivatives may be need further SAR studies. [141]

Additionally, *spiro*-indoline-based hetrocycles were achieved and evaluated as potentially active antimicrobial agents. [142] (Figure 11)

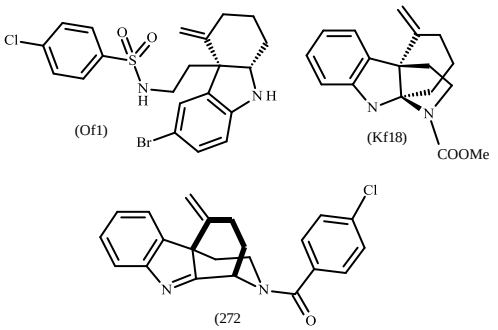


Figure 10. Compound from the Aza-Of1 series.

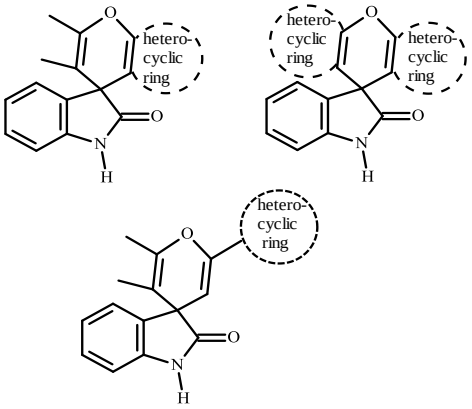
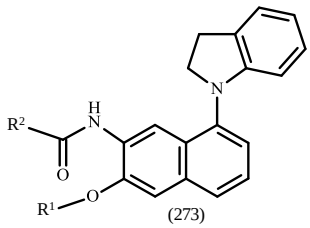


Figure 11. *Spiro*-indoline-based hetrocycles as antimicrobial agents.

4. 2. Anti-cancer

Recent drug discovery studies have focused on the design and synthesis of small molecules that have an indoline-based nucleus as tubulin inhibitors [143] or as inhibitors of aminopeptidase *N*-(*APN*).[144] A large number of synthetic indoline-containing drugs and clinical candidates have been examined over the past few years.[10, 8]

The quinazolines bearing 2,3−dihydro−indole (**273**) were synthesized and evaluated for the IC50 values against three cancer cell lines (*A549, MCF−7* and *PC−3*). Most of these compounds showed excellent antiproliferative activity against cancer cell lines.[145]



(273)

Furthermore, 2–substituted indoline derivatives show significant antitumor activity.[146] For example, *AC−93253* and *ICNP* are significantly enhanced acetylation of tubulin and exhibited submicromolar selective cytotoxicity towards tumor cell lines (*DU145, MiaPaCa2, A549* and *NCI-H460*).[147] Also, indoline−2−carboxylic acid N−(substituted)phenylamide derivatives (**274**) in Figure 12 were synthesized and investigated for cytotoxicity against various cancer cell lines as well as the structure activity relationship study. [148]

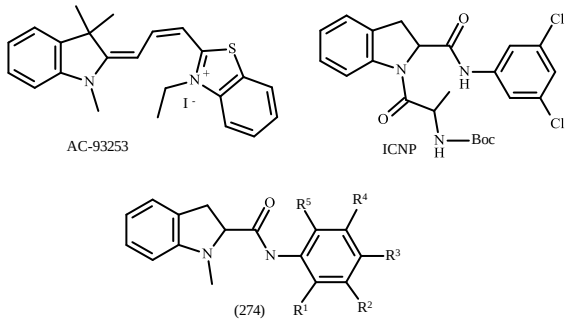
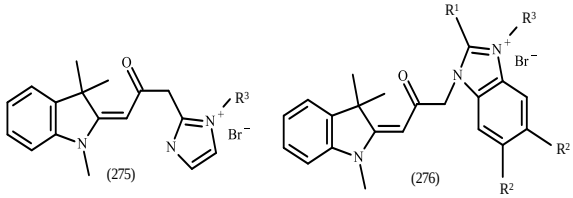


Figure 12. Some indoline derivatives with significant antitumor activity.

In the same manner, 2–substituted indoline imidazolium salt derivatives has been prepared and evaluated *in vitro* against a panel of human tumor cell lines. Such as compounds (**88** and **89**) in Figure 7 were found to be exhibited cytotoxic activity selectively against *MCF–7, SW480, SMMC-7721* and *HL–60* cell lines. Thus indoline-based imidazolium salts can be considered promising leads for further structural modifications guided as cytotoxic agents.[8]



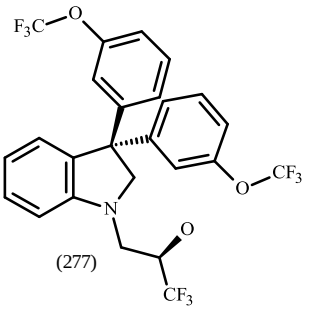
4. 3. Cholesterol Ester Transfer Protein) inhibitors

On the other hand, the indoline derivatives with an ionizable moiety were synthesized to find a bioavailable *acyl-CoA:cholesterol acyltransferase* (*ACAT*) inhibitor with antiperoxidative activity as candidate for anti-hyperlipidemic and anti-atherosclerotic drugs.[149]

Indoline-based with a methane sulfonamide group at the 5–position were synthesized and their lipophilicity and biological activities were evaluated. Hepatic *ACAT* inhibitory and anti-foam cell formation activity was increased depending on lipophilicity of derivatives with various alkyl chains at the 1-position. It was observed that, the indoline-based *ACAT* inhibitors activities were increased by introducing the methane-sulfonamide group. [150]

Additionally, the 1–alkyl–7–amido–indoline-based anti-oxidative acyl-CoA: *cholesterol acyltransferase (ACAT*) inhibitors have been reported and are expected to lower plasma cholesterol levels due to the inhibition of intestinal and hepatic *ACAT*, and to inhibit cholesterol accumulation in macrophages due to the inhibition of low density lipoprotein (*LDL*) oxidation.[151] Such as the

compounds (**277**) may be a useful template to design additional classes of *CETP* inhibitors.[152]



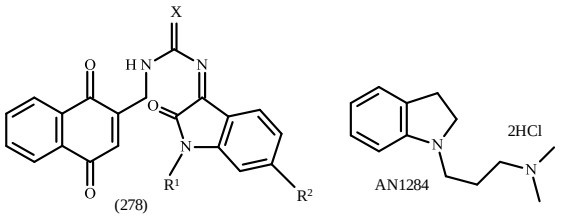
(277)

4. 4. Anti-inflammatory

Because the inflammation is steering the majority of the diseases so the need of discovering novel anti-inflammatory drugs must be reputable, leading the indoline-based anti-inflammatory agents are continually explored.[10, 153]

Substituted indoline-based dihydroxy-carbamides (**278**) were synthesized and evaluated as the *cyclooxygenase-2 (COX-2)* inhibitors to confirm their anti–inflammatory effect.[10]

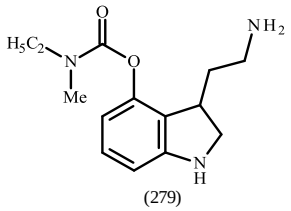
Interestingly, the indoline derivatives prevented the symptoms of colitis and were 500−50 times more potent and more effective than 5–*ASA*.[154] Also, the compound (**AN1284**) is highly potent anti-inflammatory agents and more effective in justifying of *GalN/LPS*-induced acute liver failure in mice. [153]



(278) AN1284

4. 5. Anti-oxidant

The carbamate derivatives of indoline–3–propionic acid esters and indoline–3– (3–aminopropyl) have the advantage over the corresponding indoles of being sufficiently basic to form water-soluble acid addition salts. Surprisingly, the indolines were found to display about a 100–fold higher antioxidant activity than the indoles. Beside, to inhibit *acetylcholinesterase (AChE)* and*butyryl cholinesterase*, they also showed cytoprotective activity against cytotoxicity induced by *ROS*.[155]



(279)

The indoline carbamates (**279**) were found to reduce the release of *TNF–α* and *IL–6* from *LPS* stimulated macrophages at concentrations of 1 nM or less.[153] Further, the 1-substituted indolines with carrying amino, ester, amide, or alcohol groups, and some have additional substituents, Cl, MeO, Me, F, HO, or BnO, on the benzo-ring (Figure 13) were synthesized and explored for their antioxidant anti-inflammatory effect. [156]

3. 6. Antihypertensive agent

Indapamide is the first-line antihypertensive agent with low frequency of side effects and a simple once-daily dosage regimen. [157] It was reported that the indoline functional group was aromatized to indole through a dehydrogenation pathway by *cytochromes P450*.[158]

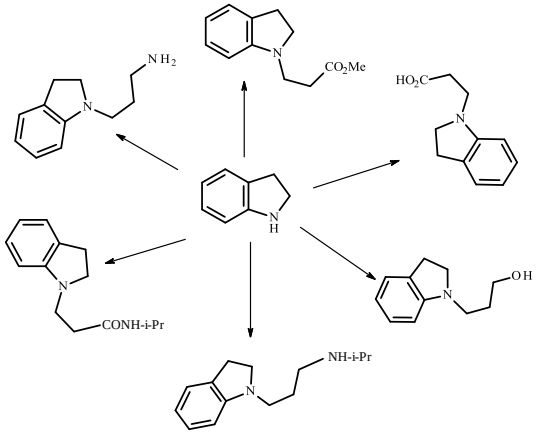
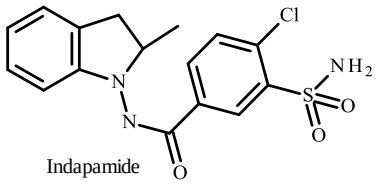


Figure 13. 1– Substituted indolines as antioxidant anti-inflammatory agents.



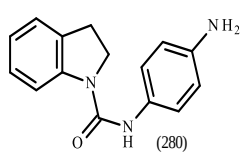
Indapamide

4. 7. Antidiabetic

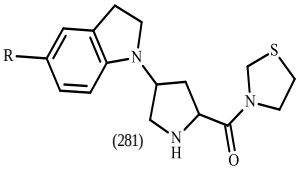
Dipeptidyl peptidase IV (DPP-IV) inhibitors are looked to as a potential antidiabetic agent class.[159] For example the compound (**280**) showed high *DPP-IV*-inhibitory activity comparable to that of *NVP-DPP728* and also displayed improved inhibitory

selectivity for *DPP-IV* over *DPP8* and *DPP9*. Suggesting that indoline compounds (**280**) have a rigid conformation with double restriction of the aromatic moiety by proline and indoline structures to promote interaction with the binding site in the *S2* pocket of *DPP-IV*.[11]

Furthermore, the antidiabetic activity of synthesized *N*–(4–aminophenyl)indoline–1–carbothiamides) (**281**) was examined using standard *α-amylase* inhibition assay method.[117]



(280)



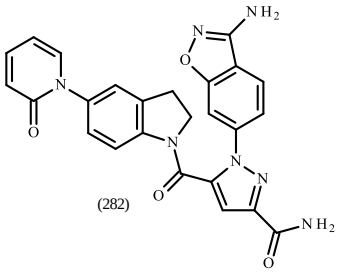
(281)

4. 8. Anticoagulant activity

The indolines are potent inhibitor of coagulation factor *Xa* (activated factor *X*) with anticoagulant activity. The enantiomerically pure (**282)** with carboxy-methylsulfonyl group on the nitrogen atom exhibited potent anticoagulant activities both *in vitro* and *ex vivo*. Besides, (**282)** showed no fatal contrary reaction after oral administration in mice. [160]

4. 9. Anti-depressant

The 2,3–dihydroindole an indole derivatives which are potent serotonin reuptake inhibitors. These derivatives also possess antagonistic activity at *5-HT$_{1A}$* receptors and are considered to be useful for the treatment of depression [161, 162, 163]



(282)

5. Conclusion

Indoline derivatives are very important heterocyclic compounds which widely found in bioactive natural products and pharmaceutically important compounds. Consequently, many synthetic protocols have been developed to prepare this heterocyclic compound.

In spite of metal-catalyzed methods are popular, metal toxicity and high levels of inorganic waste make their application harmful for environments. The development of a new metal free strategy for the synthesis of this heterocyclic scaffold remains a challenge in synthetic organic chemistry. In addition, these derivatives are considered as substantial compounds due to their widespread use as building blocks and as chiral support in asymmetric synthesis of very complex compounds.

Subsequently, the collected data in this area can be used to provide new strategy for the synthesis of unfamiliar indoline derivatives that could be utilized to develop potentially bioactive agents in future studies, so more efforts and investigations well be needed in this line.

6. References

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حلقات غير متجانسة قائمة علي الاندولين: طرق تشييدها ، تفاعلاتها الكيميائية واحتمالاتها البيولوجي

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مجمل هذا المرجع ان الاندولينات هي مركبات هامة بسبب تنوعها في تطبيقات الكيمياء العضوية الصناعية والصيدلانية ، فضلا عن انها موجودة في العديد من المركبات النشطة بيولوجيا في كل من الطبيعية والاصطناعية الاصل. وفي السنوات الأخيرة هناك توقعات عالية في ظهور تطبيقات مثيره للاهتمام في التحفيز الانتقائي لنشاط المضادات الحيوية-β-لاكتام فضلا عن نشاطات حيوية أخرى ، مثل مضادات للسرطان ، مضادات للالتهابات ، ومضادات الأكسدة ، عوامل مضادة للتخثر ، الخ. وعلاوة علي ذلك ، فأنها تعتبر من المركبات الهامة بسبب استخدامها علي نطاق واسع كلبنات للتشييد والدعم في التوليف الغير متناظر للمركبات المختلفة. ونتيجة لذلك ، فان الاحداث الحالية للنواة القائمة علي الاندولين في مجال دراسات الكيمياء الطبية تتطلب جمعها والتعرف عليها بشكل خاص وقد اقترح العديد من الأطروحات والابحاث ان المركبات القائمة علي الاندولين لها قيمه علاجيه عالية جدا ولهذا يجب استجلاؤها لا جراء المزيد من الدراسات عليها. لذا ، فان هذا العرض يتناول الابتكارات والابحاث الرئيسية المتعلقة بالحلقات الغير متجانسة المستندة إلى الاندولين خاصة علي تشييدها وتفاعلاتها وأنشطتها الدوائية.