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Recent Advances in the Construction of Indole Scaffolds

Fateh V Singh*, Saesh R Mangaonkar

Chemistry Division, School of Advanced Science, VIT University, Chennai Campus,
Chennai-600127, Tamilnadu, India

ABSTRACT

Indole scaffolds are important chemical entity found in biologically important synthetic and naturally active compounds. Various synthetic approaches are available for the construction of functionalized indoles including several classical and non-classical approaches. In classical approaches, numerous metal catalysts such as palladium, copper, rhodium, ruthenium and iron have been used successfully in recent few years. In this review, various aspects of classical and non-classical approaches used to construct functionalized indoles are discussed.

Keywords: Indoles, Cyclization reactions, Fischer Indole synthesis, Classical and non-classical reactions

INTRODUCTION

The indole ring system represents a key structural component that is widely distributed in nature [1]. Functionalized indoles are known as ubiquitous heterocycle in nature as it displays vast number of application in pharmaceuticals, chemical and agricultural industries [2,3]. Various indole-cored architectures are existing in nature and considered as important scaffolds in synthetic and medicinal chemistry [4]. Several synthetic compounds having indole functionality are known for various biological activities.

Indomethacin 1 and sumatriptan 2 are known as potent non-steroidal anti-inflammatory agents [5,6]. Serotonin 3 is mainly found in animals and plays an important role in controlling the central nervous system [7]. Several naturally occurring compounds containing indole scaffold have clinical importance. Mersicarpine 4 is a tetracyclic dihydroindole derivative that was isolated from the bark of Malayan *Kopsia fruticosa* and *Karborea* [8-12]. Cryptotackiene 5 is an antiplasmodial agent that was isolated from the West African shrub *Cryptolepis Sanguinolenta* [13-15]. Scytonine 6 is a pigment that was isolated from the organic extract of plant species *Scytonema* 10 [16]. Thienodolin 7 was found in the culture broth of *Streptomyces Albogriseolus* and it exhibits both growth-promoting and growth-inhibiting activities in rice seedling [17]. Bombyx batryticatus (BB-3) 8 is an analgesic drug obtained from dried larvae of the silkworm *Bombyx Mori* [18]. Caulersin 9 is a bisindole-based naturally occurring compound which is isolated from algae *Caulerpa serrulata*. It exhibits antitumor activity [19].

In past few decades, various synthetic methods have been used for the construction of functionalized indoles. Functionalized indoles have been synthesized by both classical and non-classical approaches. In this review, we have covered various classical and non-classical approaches appeared in past five years for the construction of functionalized indoles

Classical approach for the synthesis of functionalized indole

Pd-catalyzed synthesis of functionalized indoles

In 2012, Yoshikai and co-workers reported the synthesis of 2,3-disubstituted indoles **11** via Pd(II)-catalyzed oxidative cyclization of *N*-aryl imines **10** (Scheme 1) [20]. All the reactions were carried out in DMSO at 60 °C using Pd(OAc)₂ as catalyst, Cu(OAc)₂ as additive in the presence of atmospheric O₂. The reaction products were isolated in useful yields and functional groups were tolerated successfully in this reaction. In addition, fused indoles were also synthesized in useful yields using similar approach.

Chowdhury and co-workers developed the synthesis of functionalized indole derivatives **14** in moderate yields via Pd(II)-catalyzed cyclic condensation of *N*-protected-anilines **12** with aryl iodides **13** [21]. All the reactions were carried out in DMF at 85 °C under

argon atmosphere using PdCl₂PPh₃ catalytic system in the presence of K₂CO₃ base and phase transfer catalyst Bu₄NBr (TBAB) (Scheme 2). Using this approach wide range of functionalized indoles were prepared as this catalytic system display excellent functional group tolerance. In addition, the similar catalytic approach was successfully applied for the construction of 2-substituted quinolines.

Furthermore, Liang and co-workers developed an efficient Pd(II)-catalyzed approach for the construction of functionalized fused indoles **17** [22]. This approach allows the preparation of structurally diverse fused indole systems from simple substrate. In this methodology, anilines **15** were treated with 1,2-phenyl acetylene **16** in dimethylacetamide (DMAc) using palladium acetate as catalyst, Cu(OAc)₂.CuCl₂ as an oxidant and NaOAc as base (Scheme 3). Additionally, additives such as pivalic acid (PivOH) and tetrabutylammonium bromide (TBAB) were also used to improve the overall yield of the reaction. Finally, fused indoles **17** were isolated in good to excellent yields and various electron-donating and -withdrawing functional groups were tolerated in this reaction.

After this report, Takemoto and co-workers reported a new method for the synthesis of functionalized indole [23]. This methodology involves Pd(II)-catalyzed cascade reaction of *o*-methylphenyl isocyanides **18** with aryl halides **19** which gave 2-arylidindoles **20** as reaction product (Scheme 4) in moderate yields. In this reaction, methyl phenyl isocyanide is coupled with aryl iodide in presence of palladium acetate and bulkier ligand such as Ad₂PⁿBu. Additionally, the same catalytic approach was successfully applied for the construction of fused indole systems.

In 2013, Jia and co-workers reported a direct method for the synthesis of polycyclic indoles **22** via intramolecular Larock indole synthesis [24]. In this report, 2-iodoaniline derivatives **21** were cyclized into tricyclic indoles **22** in good to excellent yields using Pd(OAc)₂/PPh₃ catalytic system in DMF (Scheme 5). Furthermore, the reactions products **22** were found as useful substrates for synthesis of bioactive compound fargesine **23**.

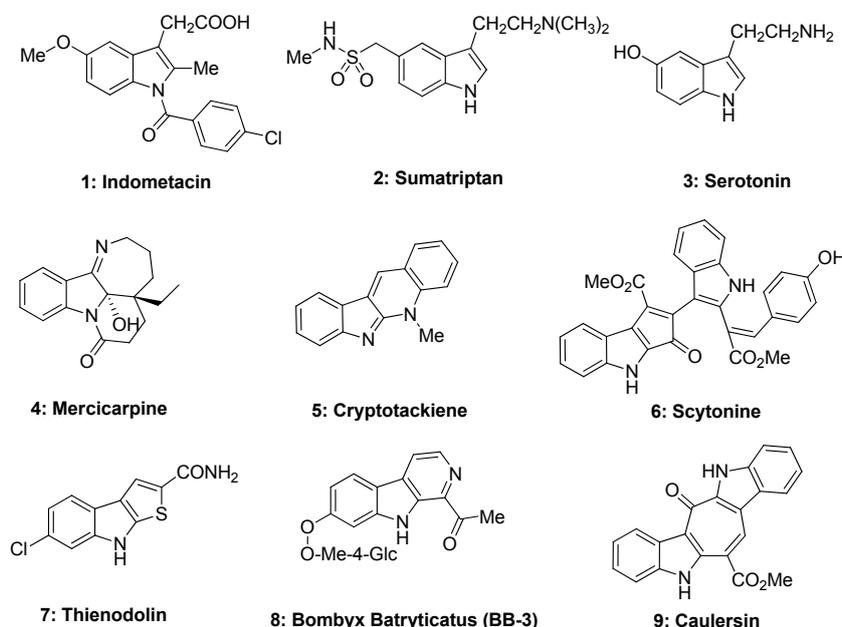
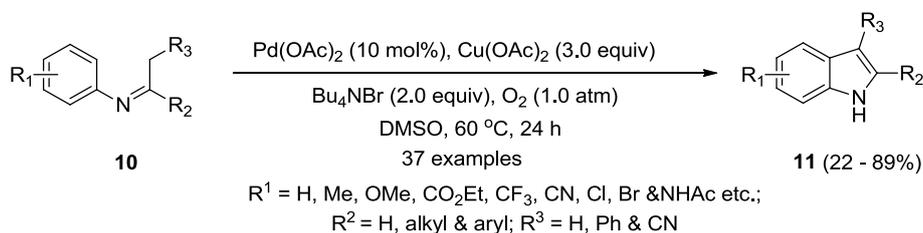
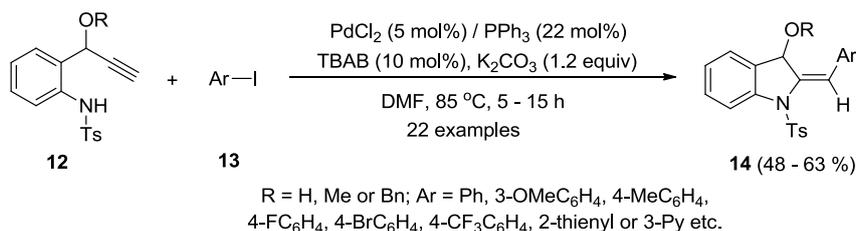


Figure 1: The structures of indole-based biologically active compounds 1-3 and naturally occurring compounds 4-9



Scheme 1: Pd(II)-catalyzed synthesis of functionalized indoles **11** from *N*-aryl imines **10**



Scheme 2: Pd(II)-catalyzed cyclic condensation of anilines **12** with aryl iodides **13** to indoles **14**

In 2014, Ghorai and co-workers developed an efficient strategy for the synthesis of 2,3-disubstituted indole derivatives **25** by Pd(II)-catalyzed aerobic oxidative cyclisomerization of *o*-allylanilines **24** using Pd(OAc)₂/PPh₃ catalytic system in DMF under oxygen atmosphere (Scheme 6) [19,25]. All the reactions were working smoothly and reaction products were isolated in good to excellent yields. Various electron-donating and –withdrawing functionalities were tolerated under this reaction condition.

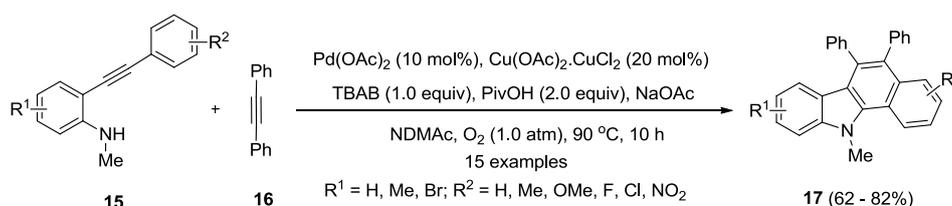
Recently Yu and co-workers reported the synthesis of functionalized indole by Pd-catalyzed oxidative annulation of functionalized pyrroles **26** with ketones **27** using Pd(OAc)₂ as catalyst, Cu(OAc)₂.H₂O as oxidant in the presence of sodium acetate (Scheme 7) [26]. Tetrabutylammonium bromide (TBAB) and pivalic acid (PivOH) were used as additive to increase the reaction yields. All the reactions were carried out in the mixture of DMSO and DMF (1:9) and reaction products **28** were isolated in moderate yields.

Cu-catalyzed synthesis of functionalized indoles

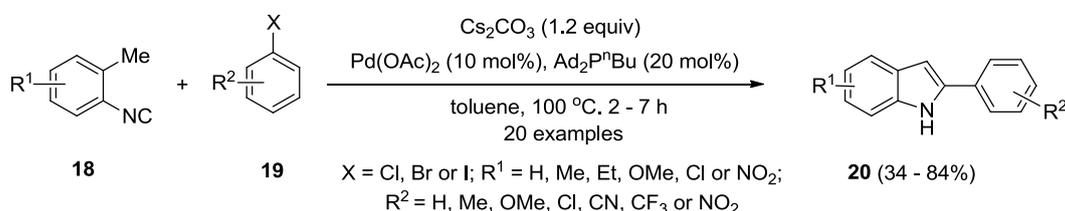
Like palladium, Cu is another transition metal which is more commonly used as catalyst during the construction of indoles. In 2005, Cusack and co-workers developed Cu-catalyzed approach for the synthesis of functionalized indoles **31** by intramolecular cyclization of ene-carbamates **29** using CuI as catalyst, L-proline **30** as ligand in the presence of K₂CO₃ in 1,4-dioxane (Scheme 8) [27]. The reactions were found quite slow and reaction products **31** were isolated in poor yields.

In 2011, Wang and co-workers reported another Cu-catalyzed approach for the construction of indole systems. In this report, alkynes **33** were directly coupled with *N*-tosylhydrazones **32** using catalytic amount of CuBr (Scheme 9) [28]. All the reactions were carried out in acetonitrile at 100 °C and reaction products **34** were isolated in 38-74% yields. Various electron-donating and electron-withdrawing functionalities were successfully tolerated under mentioned reaction condition.

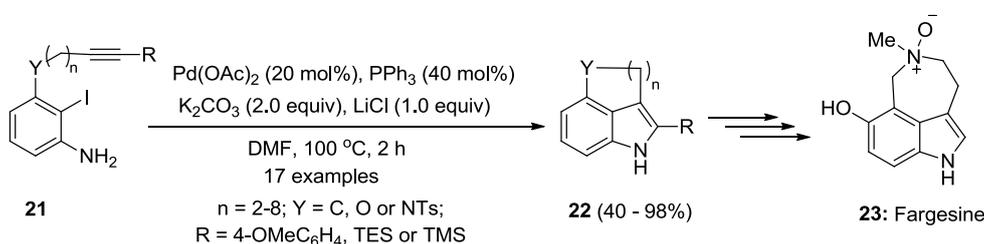
In 2015, Hwang and co-authors developed the synthesis of functionalized indoles **37** through photo-induced copper-catalyzed three-component coupling of anilines **35**, aryl acetylenes **33**, and substituted benzoquinones **36** using catalytic amount of CuCl (Scheme 10) [29]. All the reactions were carried out in methanol at room temperature under visible light. Various electron-donating and withdrawing functionalities on all the precursors were successfully tolerated and reaction products **37** were isolated in good to excellent yields.



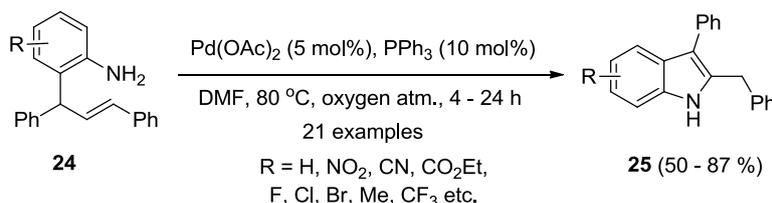
Scheme 3: Synthesis of fused indoles **17** through Pd(II)-catalyzed intermolecular cyclization of anilines **15** and 1,2-diphenylacetylene **16**



Scheme 4: Pd(II)-catalyzed synthesis of 2-arylidole **20** from *o*-methylphenyl isocyanides **18** with aryl halides **19**



Scheme 5: Pd(II)-catalyzed synthesis of tricyclic indoles **22** from 2-iodoanilines **21**



Scheme 6: Pd(II)-catalyzed aerobic oxidative cyclisomerization of *o*-allylanilines **24** to 2,3-disubstituted indole **25**

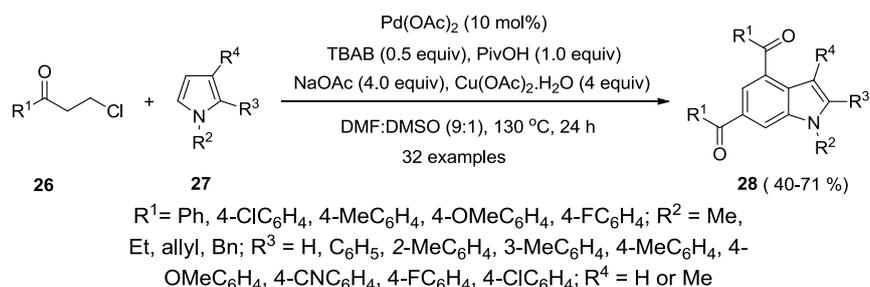
Recently, Lu and co-workers developed an efficient strategy for the synthesis of functionalized indole derivatives using copper catalyzed sequential reaction [30]. In this report, allenylidenes 38 were coupled with functionalized anilines 39 using CuI as catalyst, bisoxazoline (box) 40 as ligand in the presence of $^i\text{Pr}_2\text{Net}$ (DIPEA) in methanol. Initially, pivotal 3-aminoindoline intermediate 41 was observed that undergo aza-Cope rearrangement on treatment with Lewis acid (TFA or $\text{BF}_3 \cdot \text{Et}_2\text{O}$) and 3-aminoindolines 42 were isolated in good to excellent yields. In addition, 1,3-proton shift was observed when intermediate 41 was treated with base (CS_2CO_3) and different indole derivatives 43 were isolated in moderate to excellent yields (Schemes 11 and 12). Furthermore, same catalytic approach was successfully applied for the synthesis of natural product 10*H*-indolo[3,2-*b*]quinolone.

Rh-catalyzed synthesis of functionalized indoles

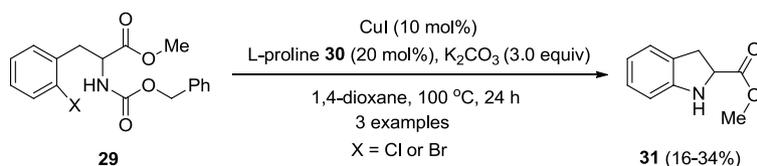
Rhodium metal is also used successfully in the synthesis of indole scaffolds. In 2006, synthesis of functionalized indole 45 was reported by Rh-catalyzed reductive cyclization of (*E*)-2-nitro-pyrrolidinostyrene 44 using Rh/C as catalyst, $\text{Fe}(\text{OAc})_2$ as an additive in THF (Scheme 12) [31]. Functionalized indoles 45 were isolated as reaction products in good to excellent yields. It was noted that reaction product 45 was isolated in slightly poor yield when OBn group was attached at *ortho*-position to nitro group in 44 ($\text{R}^3 = \text{OBn}$).

In 2008, Fagnou and co-workers developed a different strategy for the synthesis of functionalized indoles in presence of rhodium catalyst 48 [32]. In this methodology, functionalized acetanilides 46 were treated with internal alkyne 47 using catalytic amount of $[\text{Rh}(\text{Cp}^*)\text{Cl}]_2$ 48 in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (oxidant) in *tert*-amyl alcohol (1,1-dimethylpropanol) (Scheme 13). Additionally, silver salt was used as additive to improve the reaction yields. All the reactions were completed in short reaction time and 2,3-disubstituted indoles 49 were isolated in good to excellent yields. Various acetanilides bearing electron-donating and -withdrawing functionalities were used as precursors but reaction products 49 were obtained in higher yields with electron-donating functionalities. Interestingly, both aliphatic and aromatic alkynes were successfully employed as substrates in this reaction.

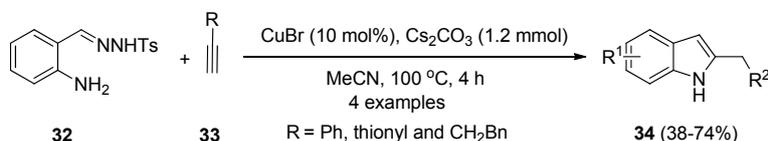
Furthermore, same research group reported a new rhodium(III)-complex $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ 50 and used as catalyst for the



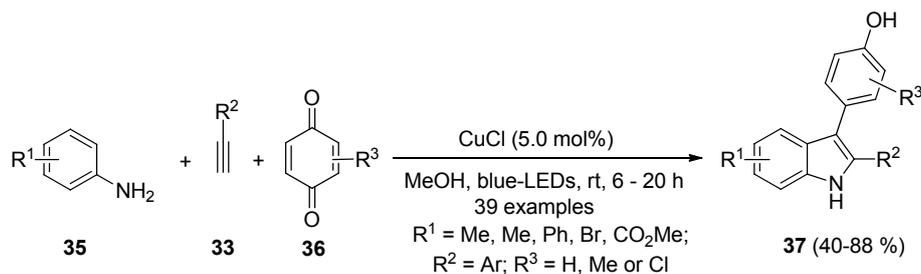
Scheme 7: Pd(II)-catalyzed oxidative annulation of pyrroles 26 with ketones 27 to indoles 28



Scheme 8: Cu(I)-catalyzed synthesis of 2-substituted indoles 31 from ene-carbamates 29



Scheme 9: Cu(I)-catalyzed synthesis of functionalized indoles 34 from alkynes 33 with *N*-tosylhydrazones 32



Scheme 10: Photo-induced Cu(I)-catalyzed synthesis of functionalized indoles 37 from anilines 35, aryl acetylenes 33 and substituted benzoquinones 36

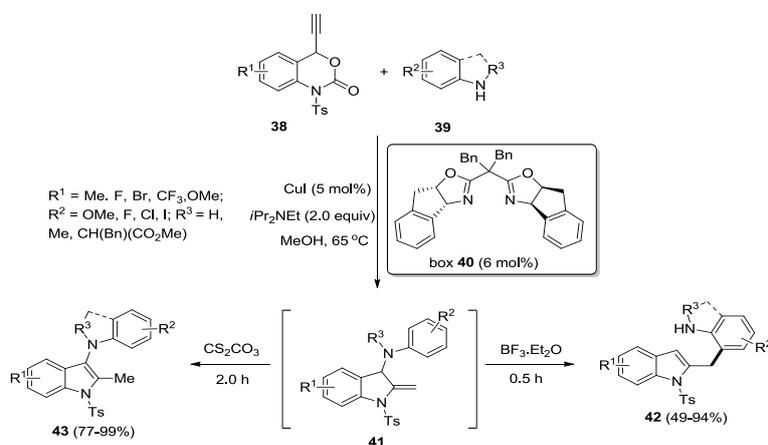
synthesis of similar indoles 49 [33]. According to this report, similar 2,3-disubstituted indoles 49 were synthesized from acetanilides 46 and internal alkynes 47 using a catalytic amount of Rh(III)-complex 50 in *tert*-amyl alcohol (1,1-dimethylpropanol) without using any additive (Scheme 14). Additionally, Cu(OAc)₂·H₂O was used in a catalytic amount (20 mol%) while atmospheric oxygen was used mainly as an oxidant. Various functionalities were successfully tolerated both precursors acetanilides 46 and alkynes 47 and reaction products 49 were isolated in good to excellent yields. It was also noted that a TMS group on external alkyne 47 (R³=TMS) could not work well and the corresponding indole product 49 (R³=TMS) was isolated in 20% yield.

Fe-catalyzed synthesis of functionalized indoles

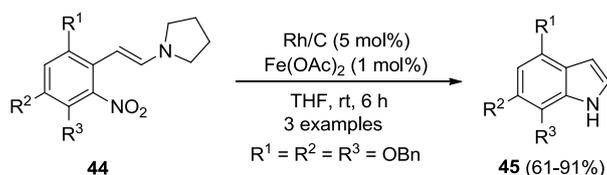
In a literature, a solitary report on Fe-catalyzed synthesis of functionalized indoles is available. In the report, the synthesis of functionalized indoles was achieved by intramolecular cyclization of *N*-substituted anilines 51 using FeCl₃ as catalyst, Cu(OAc)₂·CuCl₂ as oxidant in the presence of K₂CO₃ (Scheme 15) [34]. All the reactions were carried out in DMF at 120 °C and reaction products 52 were isolated in 32-72% yields. Cyclization reactions were working with arenes bearing an electron-donating group at both the *para*- and *ortho*-position in substrates 51 but reaction products 52 were obtained in better yields in the substituent at *para*-position than *ortho*-position. Interestingly, opposite reaction pattern was observed in case of arenes bearing electron-withdrawing functionalities at both *para*-position than *ortho*-position 51.

Ru-catalyzed synthesis of functionalized indoles

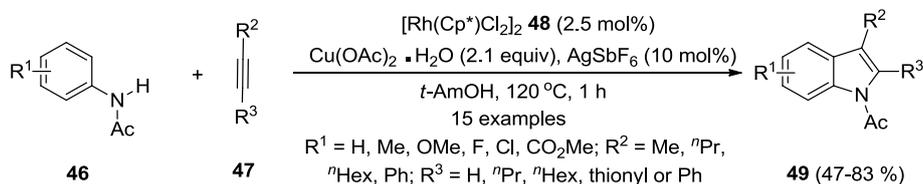
Like other transition metals (Pd, Cu, Rh and Fe), ruthenium has been also used as a catalyst to synthesize functionalized indoles. In 2012, Lygin and Ackermann developed a Ru-catalyzed approach for the synthesis of functionalized indoles 54 by oxidative



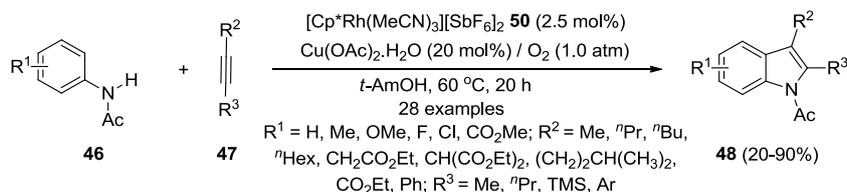
Scheme 11: Cu(I)-catalyzed synthesis of functionalized indoles 42 and 43 from allenylidenes 38 and anilines 39 using ligand 40



Scheme 12: Rh-catalyzed reductive cyclization of (*E*)-2-nitro-pyrrolidinostyrene 44 to indoles 45



Scheme 13: Rh-catalyzed synthesis of indoles 49 by intermolecular cyclization of acetanilides 46 and internal alkynes 47



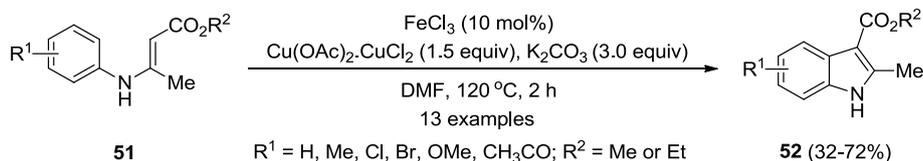
Scheme 14: Rh(III)-catalyzed synthesis of functionalized indoles 49 from acetanilides 46 with alkynes 47 using Rh(III) complex 50 as catalyst

annulation of *N*-2-pyrimidyl anilines **52** with internal alkyne **47** using $\text{RuCl}_2(p\text{-cymene})_2$ **54** as catalyst and KPF_6 as co-catalyst (scheme 16) [35]. Water was used as green solvent that makes this approach simpler and environmentally friendly. The reaction products **55** were isolated in moderate to excellent yields and various functional groups were tolerated successfully on both substrates under mentioned reaction conditions.

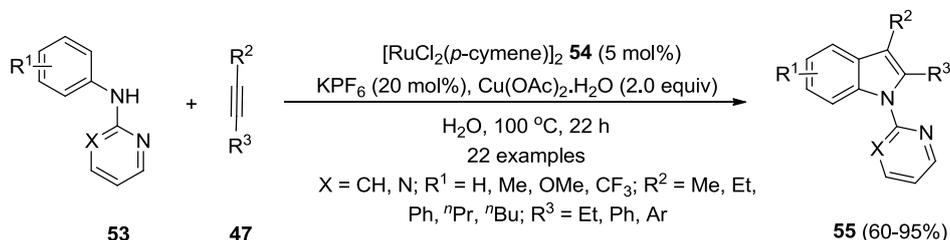
Non-classical approaches for the synthesis of functionalized indoles

There are few non-classical approaches available in the literature for the synthesis of indoles. In 1991, Tobinaga and co-workers achieved the synthesis of functionalized indole derivatives by Diels-Alder cycloaddition of 3-thioacetylpyrrol with substituted alkyl dienophile [36]. In 1998, Barluenga and co-workers reported the synthesis of polycyclic indoles via intramolecular cycloaddition reaction. This was the first intramolecular carbometalation approach of lithiated double bonds [31,37]. In 2004, O'Shea and co-workers developed a non-classical approach for the synthesis of functionalized indoles **55** by intramolecular carbolithiation of *ortho*-aminostyrenes **54** with organolithium reagents [38]. After this report, Wang and co-workers developed a direct method for the synthesis of functionalized indoles **58** by domino reaction of *N*-aryl amides **56** with ethyl diazoacetate (EDA) **57** (Scheme 17) [39]. All the reactions were carried out in dichloromethane in presence of 2-chloropyridine (2-CIPy) as nucleophile and 2,6-dichloropyridine (2,6-Cl₂Py) as additive. The reaction products **58** were isolated in good to excellent yields.

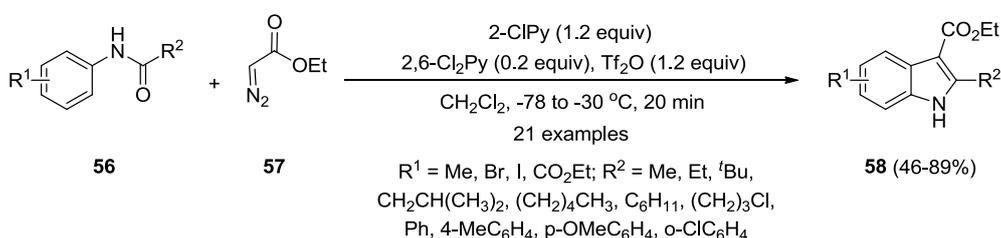
Furthermore, Knochel and Stoll reported an efficient strategy for the synthesis of 2,4,5,6,7-pentasubstituted indoles **60** by direct potassium hydride mediated cyclization of polyfunctionalized anilines **59** (Scheme 18) [40]. Fully functionalized indoles **60** were isolated in good to excellent yields. Various functional groups such as esters, nitriles and halogenides were successfully tolerated in mentioned conditions and it is one of the unique approaches that provide an easy access for the synthesis highly functionalized indoles in high yields.



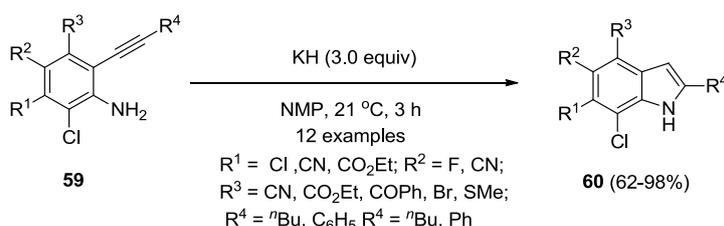
Scheme 15: Fe-catalyzed synthesis of functionalized indoles **52** from *N*-substituted anilines **51** using FeCl_3 as catalyst



Scheme 16: Ru(II)-catalyzed oxidative annulation of *N*-2-pyrimidyl anilines **52** with internal alkyne **47** to indoles **55** using catalytic amount of $\text{RuCl}_2(p\text{-cymene})_2$ **54**



Scheme 17: Synthesis of indoles **58** via domino reaction of *N*-aryl amides **56** with ethyl diazoacetate (EDA) **57**



Scheme 18: Synthesis of highly functionalized indoles **60** through potassium hydride mediated cyclization of anilines **59**

In 2009, Zhao and co-workers reported the construction 2,3-disubstituted indoles **63** by iodine(III) mediated oxidative cyclization of *N*-aryl imines **61** using PIDA **62** as an electrophile in 1,2-dichloroethane (DCE) (Scheme 19) [41]. In most of the reactions, functionalized indoles **63** were isolated in excellent yields except imines bearing OMe or F groups on aryl ring. This approach is quite efficient due to easy availability and environmental friendly nature of PIDA **62** as an electrophile [42].

Furthermore, Greaney and co-workers employed a traditional route for the construction of functionalized indoles **66** via Fischer-Indole cyclization. In this approach, functionalized indoles **66** were synthesized by the reaction of arylne precursor **64** with tosylhydrazone **65** in presence of CsF followed by the addition of $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 20) [43]. All the reactions were carried out in acetonitrile and reaction products **66** were isolated in moderate to high yields.

In 2011, Moody and Inman developed the synthesis of functionalized indole derivatives in moderate to excellent yields [44]. Initially the starting substrates *N*-protected aryl hydrazines **68** were prepared from corresponding aryl iodides **67** by halogen-magnesium exchange reaction and then condensed with ketones **69** under acidic reaction conditions. The cyclization reactions were carried out in different reaction conditions A, B and C and reaction products were isolated in useful yields in all the three conditions (Scheme 21). The wide range of functionalized indoles **70** were synthesized in this reaction as reaction system display excellent functional group tolerance.

Furthermore, the same group extended their work for the synthesis of functionalized azaindoles **72**. In this report, the synthesis of 4- and 6-azaindoles **73** and **74** was achieved by acid-mediated condensation of *N*-protected pyridyl hydrazines **71** and **72** with ketone **69** in 4% H_2SO_4 at reflux temperature (Scheme 22) [45]. It was observed that 6-azaindoles **74** were isolated in better yields than 4-azaindoles **73** under similar reaction and conditions. In addition, the same approach was applied for the synthesis of functionalized 6*H*-thieno[2,3-*b*]pyrroles.

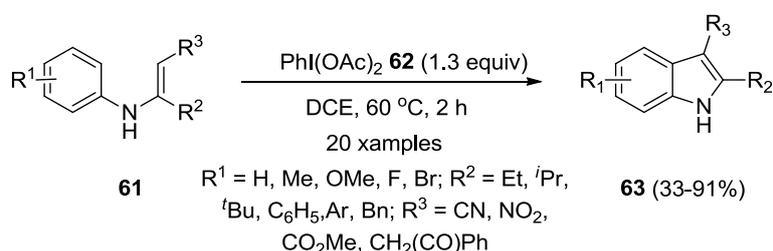
In 2012, König and co-workers reported a new approach for the synthesis of functionalized indoles using a reaction medium consisting of low melting L-(+)-tartaric acid and dimethyl urea (DMU) mixture in 3:7 ratio [46]. In this report, phenyl hydrazines **75** were treated with ketone **69** in the mixture of L-(+)-tartaric acid and dimethyl urea (DMU) mixture in 3:7 ratio at 70 °C. The reaction products **76** were obtained in excellent yield (Scheme 23). Furthermore, the reaction product **70** was found as useful substrate for synthesis of bioactive compounds pyridoindolobenzodiazepine and Dimebon [47-49].

CONCLUSION

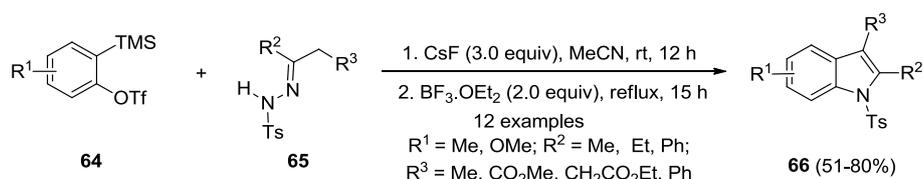
This review article summarizes possible synthetic routes for the construction of functionalized indoles. During the preparation of this manuscript, our main goal was to discuss various aspects of both classical and non-classical approaches for the synthesis of indoles. Various indole systems are important synthetic intermediates for the construction of biologically active synthetic and naturally occurring scaffolds. This review would be quite informative for the organic chemists specially working in chemistry of nitrogen containing heterocyclic scaffolds.

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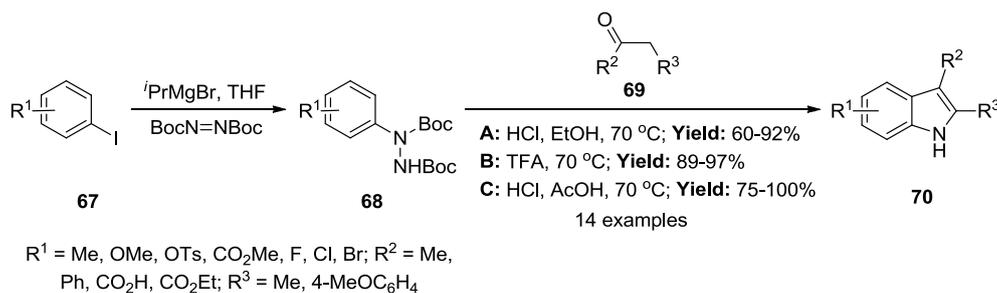
Fateh V Singh and is thankful to Science and Engineering Research Board (SERB), New Delhi for providing financial support (Start-UP Research Grant: SB/FT/CS-068/2014). Fateh V Singh and Saesh R. Manganonkar are thankful to VIT University, Chennai Campus, Chennai.



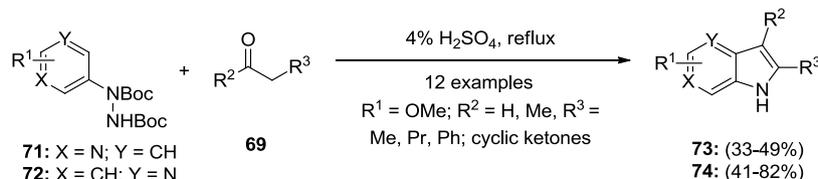
Scheme 19: Iodine(III)-mediated oxidative cyclization of *N*-aryl imines **61** to functionalized indole **63** using PIDA **62** as an electrophile



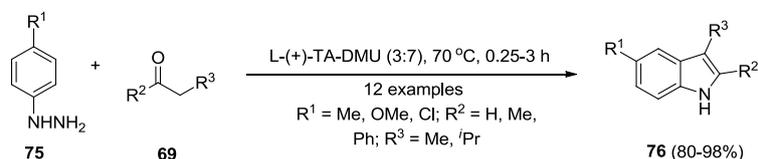
Scheme 20: Lewis acid-mediated synthesis of indoles **66** by the reaction of arynes **64** with *N*-tosylhydrazone **65**



Scheme 21: Synthesis of functionalized indoles 70 via acid-mediated intermolecular cyclization of anilines 68 with ketone 69



Scheme 22: Synthesis of azaindoles 73 and 74 by acid-catalyzed cyclization of pyridyl hydrazine 71 and 72 respectively with ketones 69



Scheme 23: Synthesis of functionalized indoles 76 by the reaction of substituted phenyl hydrazines 75 with ketone 69 in L-(+)-TA-DMU (3:7) melt

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