REVIEW

J. Indian Chem. Soc.,
Vol. 97, No. 9b, September 2020, pp. 1426-1441

A review on recent advances in the synthesis of indole and its analogs via C-H activation as a key step

Atiur Ahmed

Memari College, Memari, Purba Bardhaman-713 146, West Bengal, India

E-mail: atiur.chem@gmail.com

Manuscript received online 09 July 2020, accepted 28 August 2020

Indole is widely found as the building block in various pharmaceuticals, natural products, agrochemicals, dyes and fragrances. Thus chemists were attracted in developing new methods to prepare this moiety. Over the years, various strategies including C-H activation have been employed to afford these heterocycles. Therefore the continuous updates of the new approaches developed are essential. In this review, significant attention has been gained by C-H activation strategies that give a complete overview on transition metal-catalyzed and -free synthesis of indole scaffold as well as indole based natural product and pharmaceutics with mechanistic insight appeared in the literature since 2015 to date.

Keywords: Indole, its natural product and pharmaceutics, transition metal-catalyzed and -free C-H activation.

Introduction

Indoles are a prominent class of nitrogen containing heterocyclic compounds. The indole core is found to be present extensively in variety of biologically active natural products along with synthetic drugs. Again indole motif is also present in tryptophan, an essential amino acid. Thus the scaffold is present as core structure in various peptide-based naturally occurring alkaloids too[1]. Indole based compounds are found to play critical roles in human life, like bazedoxifene has found to work efficiently like the hormone estrogen reducing the probability of cancer of the uretus[2]. Tryprostatin A and B are cytotoxic drugs that are used in the treatment of cancer[3]. Ramosetron is discovered as the powerful agent for IBS-D treatment[4] as well as fluvastatin has been developed as the potential HMG-CoA reductase inhibitor (Fig. 1)[5]. Then, the chemists were attracted severely in the development of the new strategies for the preparation of indole scaffolds. The first production of indole was achieved by Fischer and Jourdan by employing aryl hydrazones[6]. Then, various synthetic strategies have been discovered for the formation of the ubiquitous indole moity[1].

Recently, C-H activation has been immensely developed in various syntheses, and was famous as a Holy Grail in Chemical Research in 1995[7]. The transition metal complexes

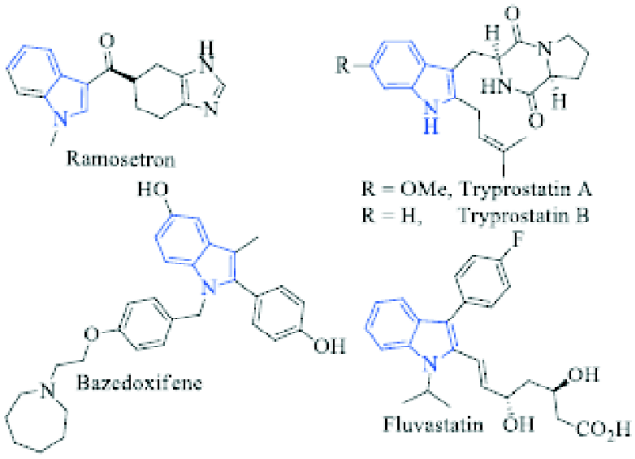


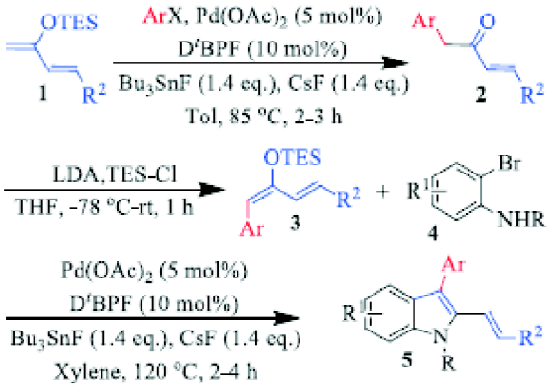
Fig. 1. Few promising bioactive molecules containing indole scaffold.

as well as few transition metal-free compounds are used as efficient catalysts for activating inert C-H bonds. The long-lasting and benign features have made the method promising. Again to get the same C-C bond by employing the activation, there is no requirement of the functionalization of substrate. Thus, the method is an efficient and atom economic route. In this review, notable attention has been acquired by the strategies that give a comprehensive overview on indole scaffold as well as indole based natural product and pharmaceutics synthesis via C-H activation as a key step

appeared in the literature since 2015 to date. Different aspects of the transformation via C-H activation and mechanistic details are depicted extensively in this report.

Indole and its analogs synthesis

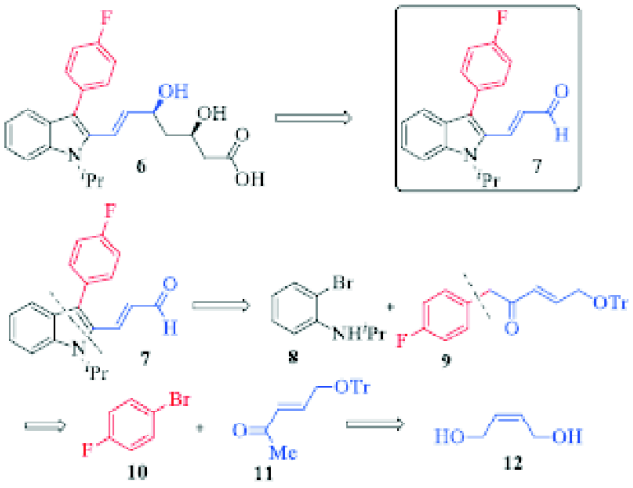
A variety of transition metals including palladium, rhodium, ruthenium, iridium, iron, copper, silver and gold have been employed severely to construct indole scaffolds via C(sp^3)-H, C(sp^2)-H and/or C(sp)-H activation. In 2015, Kale and co-workers reported an interesting method for the formation of 2-alkenyl-3-aryl indoles via shortest intermolecular annulation approach[8a]. In the synthesis of **5**, the α-arylation was employed as prominent tool. The reactions between **3** and *o*-bromoanilines **4** delivered **5** efficiently at 120°C (Scheme 1). Moreover, they employed this method successfully to produce fluvastatin **6**. Herein, the α-arylation of **9** with **8** enabled the production of the indole **7** easily (Scheme 2). Again the α-arylation of **11** with **10** was widely used to produce the precursor **9**.



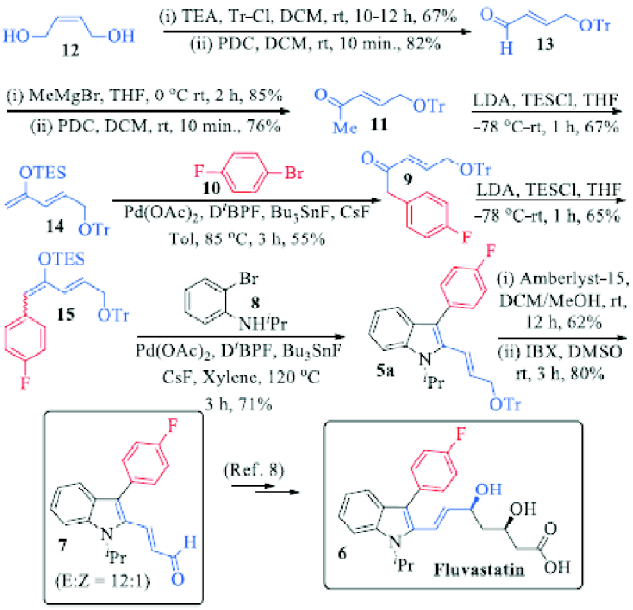
Scheme 1. The synthesis of 2-alkenyl indoles by α-arylation.

Then, the preparation of fluvastatin **6** was started with the construction of **11** from readily available 1,4-diol **12** (Scheme 3). Next, the transformation of **11** into **14**, and followed by arylation with **10** gave **9** in 55% yield. The enolization, and subsequent palladium-catalyzed reaction produced **5a** in 71% yield. Finally, fluvastatin **6** can easily be obtained from **7** by employing the strategy provided by Hayashi and group members[8].

Rhodium(III) was introduced as an efficient catalyst by Mishra and co-workers in the direct functionalization of aniline



Scheme 2. Disconnection approach of fluvastatin.

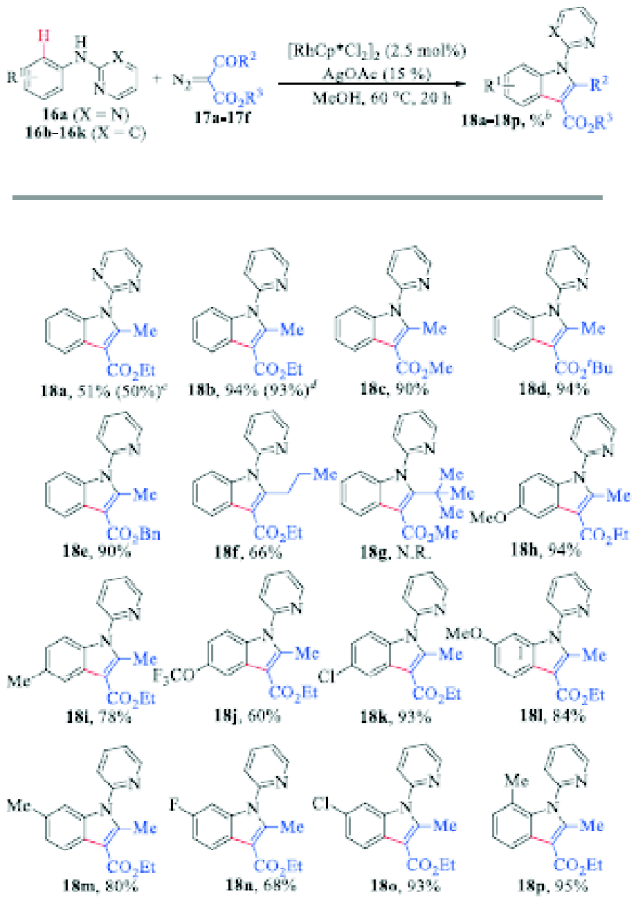


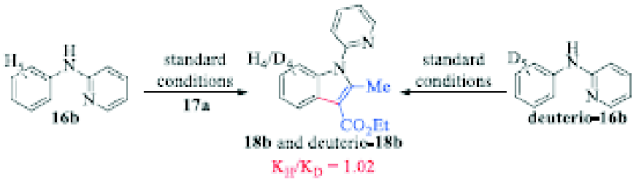
Scheme 3. Preparation of fluvastatin.

C-H bonds. They observed that the presence of pyridinyl group **16a-16k** made the *ortho*-alkylation easier resulting the production of **18a-18p** in excellent yields (Table 1)[9].

The mechanism of the reaction was established by the kinetic isotope effect (KIE) experiments of **16b** and deuterio-**16b** (Scheme 4). The results of the experiment helped to conclude that the C-H bond cleavage was not involved in the rate-determining step. Then, based on the precedent litera-

Table 1. Rhodium(III)-catalyzed *ortho*-alkylation

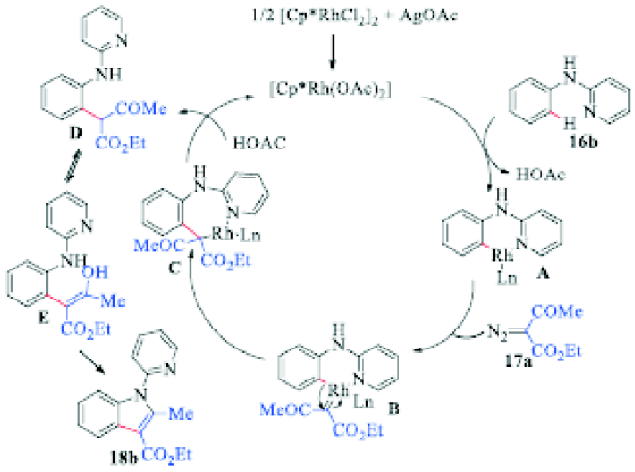




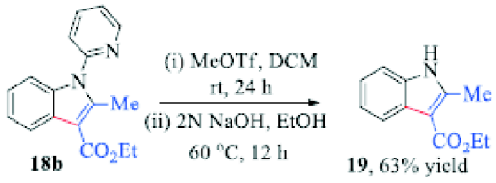
Scheme 4. KIE experiments.

tures on C-H functionalization, the authors have depicted a plausible mechanism for the construction of indole (Scheme 5).

The course of the reaction starts with the coordination to a rhodium(III) catalyst. Then, C-H cleavage occurs to give a six-membered intermediate **A**. Next, **B** is produced by coordination and subsequent liberation of N_2. The *ortho*-alkylatation to afford **D** is completed by the protonation of **C** obtained upon migratory insertion. The keto-enol tautomerization helps to give the enol **E**, which on dehydration delivers **18b**. In addition, when **18b** was reacted with MeOTf and base, free (NH)-indole 1**9** was obtained in moderate yield (Scheme 6).



Scheme 5. Proposed reaction pathway.



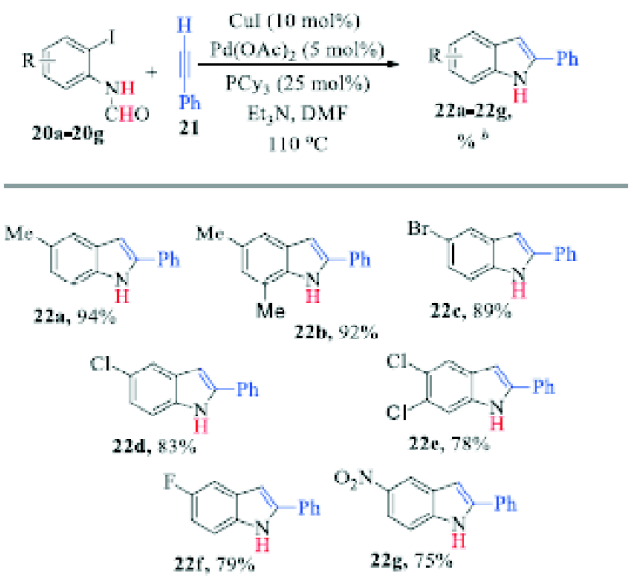
Scheme 6. Preparation of free (NH)-indole.

Recently, we have also discovered a promising method for the synthesis of the free (NH)-indoles. In this approach, *N*-formyl-2-iodoanilines **20a-20g** were treated with phenylacetylene **21** under Sonogashira reaction conditions, resulting the formation of the free (NH)-indoles **22a-22g** directly in one-pot (Table 2)[10].

The advantages of this protocol like overall high yields, cheap starting materials, mild reaction conditions, easy protection and deprotection of amino group, offer a practical means of 1*H*-indole synthesis.

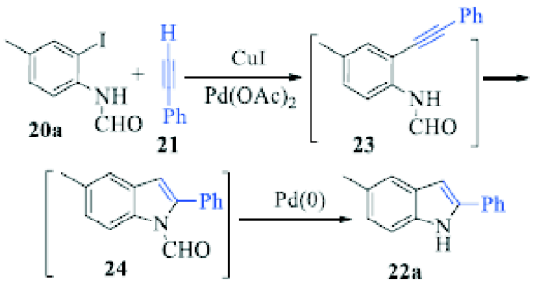
Next, a proposed mechanistic course for the formation of **22a** was also depicted in that report (Scheme 7). The first step of the cascade reaction is believed to be the usual Sonogashira cross-coupling reaction to give **23**. Then, the

Table 2. Synthesis of 1*H*-indoles[a]



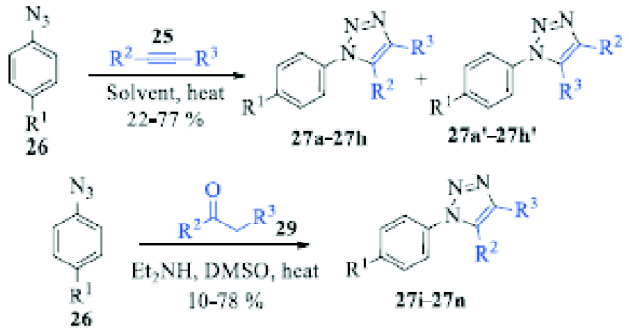
[a]All the reactions were carried out with **20a**-**20g** (1 mmol), **21** (1.01 mmol). [b]Isolated yields.

intramolecular C-N bond formation occurs to give the intermediate **24** and subsequent palladium(0)-catalyzed decarbonylation[11] delivers the free (NH)-indole **22a**.

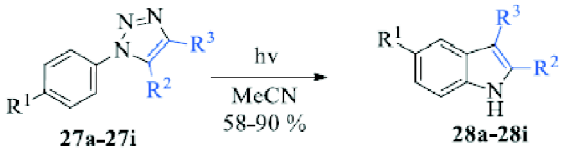


Scheme 7. Proposed mechanistic pathway.

In 2017, a completely new strategy was provided by Alimi and co-workers where indole scaffold was produced by employing the photolysis of *N*-aryltriazoles. The triazoles **27** can easily be prepared by [3+2] cycloaddition between **25** and **26** (Scheme 8). Hence, the copper-catalyzed reaction between alkyne and azide leads to the formation of indole moiety **28** efficiently in a step by the photolysis of **27** (Scheme 9)[12]. The production of the same indole even on using regioisomeric triazoles have made the method prominent.



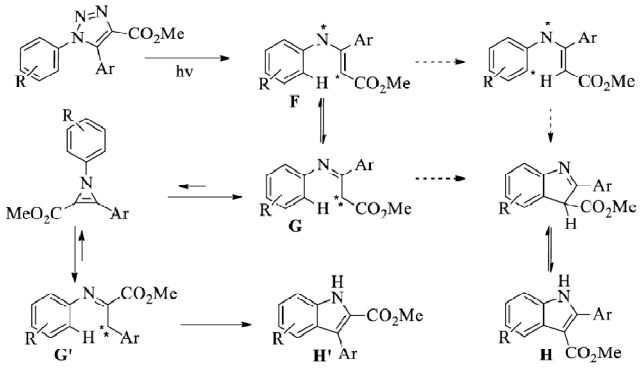
Scheme 8. Preparation of triazoles.



Scheme 9. Photolysis of the triazoles.

Then, the mechanistic course of the reaction was depicted hypothetically. Initially, they thought that the generated biradical **F** would undergo the closer C-H bond insertion (Scheme 10). However, the transformation of regioisomeric triazoles to same indole contradicts this hypothesis. On the other hand, Mitchell and Rees[13] depicted that **G** is obtained on photolysis of **27**, which on C-H insertion gives **H**. Alternatively, after isomerisation of **G** to **G′**, the C-H insertion occurs to give **H′**. The results of getting **H′** all the times helps them to conclude that **G′** is always formed as the intermediate due to its higher stability or reactivity.

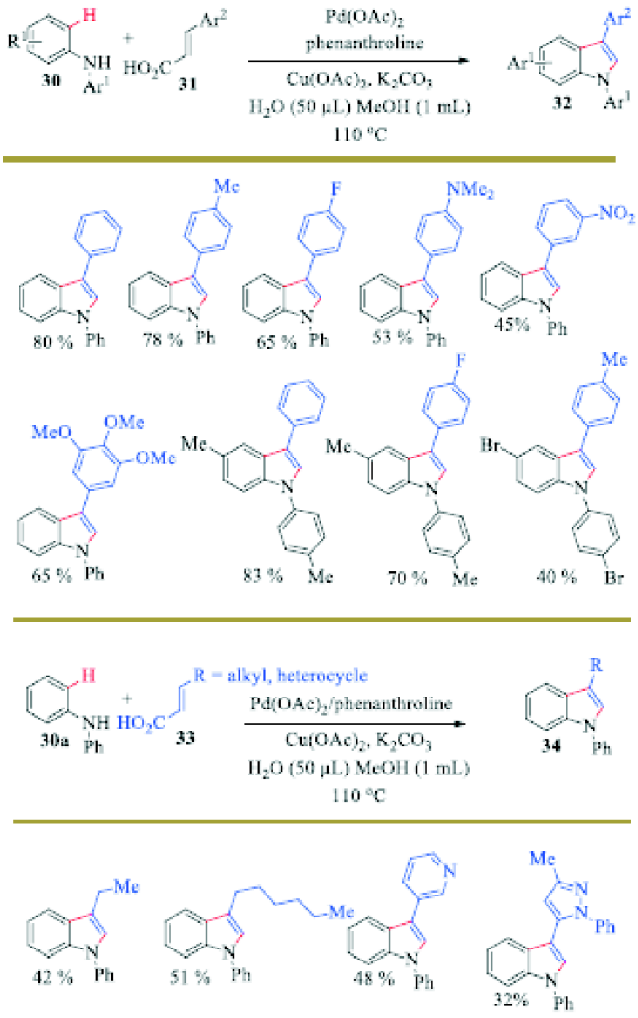
Kancherla and his group have made a successful attempt



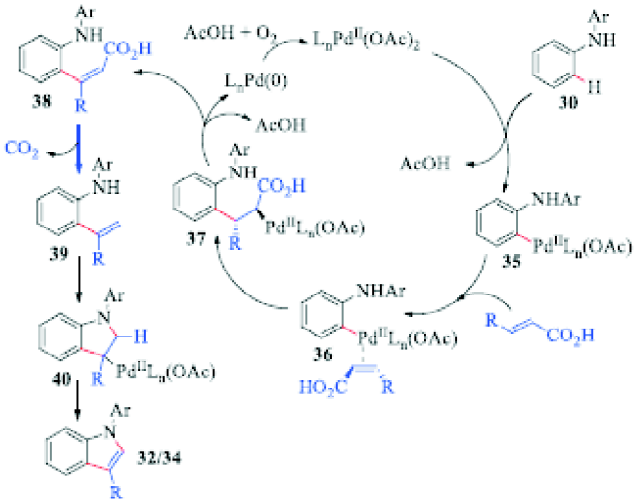
Scheme 10. Mechanistic rationale.

to afford 3-substituted indoles **32** by the reaction of **30** with **31** (Scheme 11)[14]. The combination of 10 mol% $Pd(OAc)_2$ with 20 mol% 1,10-phenanthroline enabled the reaction to give **32** in highest yield. The results of the substrate scope showed that the reaction was more efficient with electron releasing group when **31** was employed as the coupling partner. However, a reverse trend was found with **33**. Then, they suggested that the course of the reaction is completed by *ortho*-palladation as well as metal interactions with olefin (Scheme 12). Next, a sequence of steps like β-hydride elimination, CO_2 extrusion and cyclization are obeyed to deliver the desire indole.

In 2018, Kumar and co-workers depicted an approach to afford 3-substituted indoles **42** starting from β- aminoketones

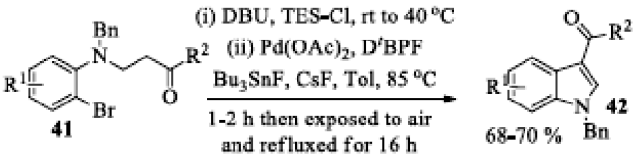


Scheme 11. Production of 3-substituted indole.



Scheme 12. Proposed mechanistic pathway.

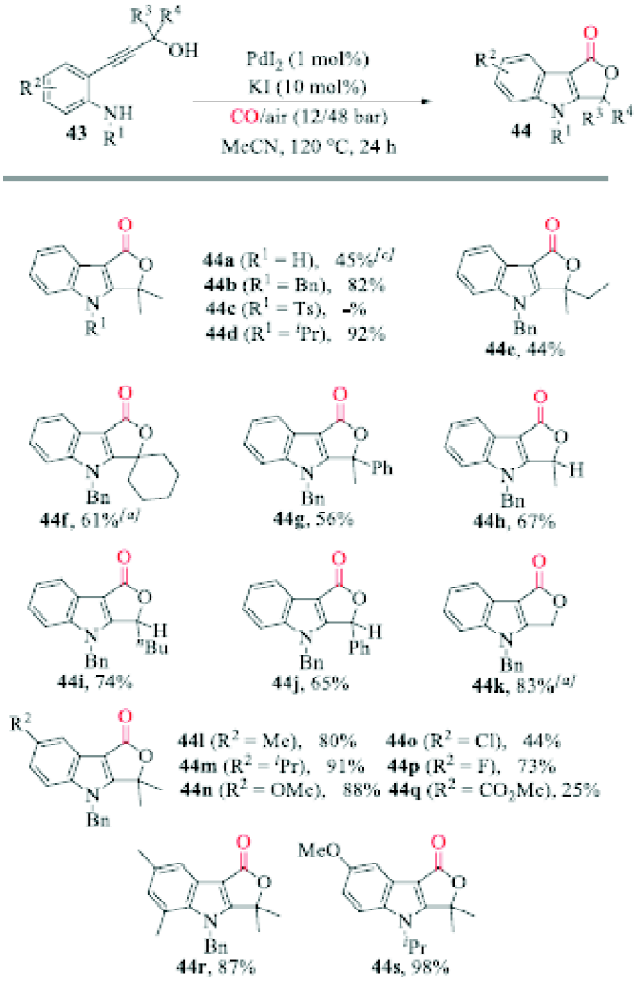
41 (Scheme 13)[15]. At first, **41** was transformed to silylenol ethers which on α-arylation using Pd-catalyst gave 3-substituted indolines exclusively. However, 3-substituted indole was obtained solely when the reaction time was extended allowing the oxidation of indolines.



Scheme 13. Intramolecular α-arylation approach.

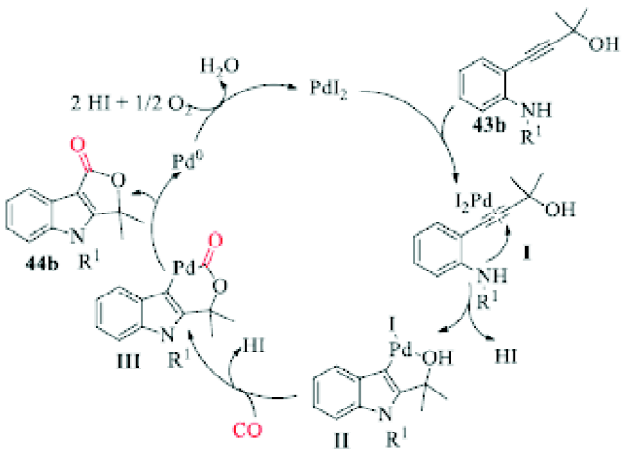
Acerbi and his group discovered a promising method to construct polycyclic furo [3,4-*b*]indol-1-ones **44** introducing palladium-catalyst. The product **44** was obtained obeying several steps like cyclization of **43**, CO insertion and annulation in a sequence way (Scheme 14)[16]. Hence, the transformation helps to generate three new bonds (C-N, C-C and C-O). The use of molecular O_2 as oxidant have made the strategy simpler. Moreover, a proposed mechanistic pathway was described (Scheme 15) where the reaction proceeds with the generation of **I**. The complex is then attacked by the nitrogen atom to give the **II**. CO insertion and subsequent reductive elimination delivers the lactone **44b**.

Bellezza and group members explored a new approach to afford various 1*H*-indoles **46** employing $Pd(OAc)_2$/P(*p*-



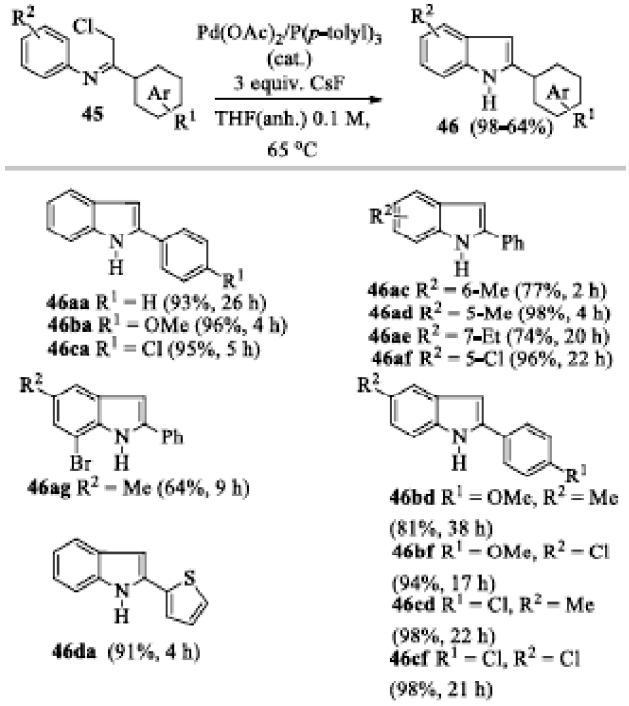
[*a*] reaction conditions and 36 h.

Scheme 14. Synthesis of furo[3,4-*b*]indol-1-ones.



Scheme 15. Proposed reaction patways.

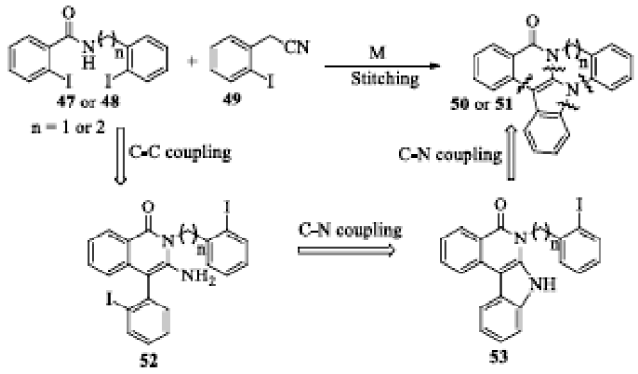
tolyl)$_3$ as the catalyst for the ring closure of *N*-aryl imines **45** (Scheme 16)[17]. The palladium(II) complexes produced at the beginning help the heterocyclization via C-H activation. Several substituted anilines were produced from various ketones in a step.



Scheme 16. C-C ring closure in 1*H* indole synthesis.

The strategy of Kavala and his group for accessing 1,2,3-polycyclic fused indole derivatives **50** or **51** was the construction of indole core from 2-iodobenzamide derivatives **47** or **48** and 2-iodobenzylcyanide **49** (Scheme 17)[18]. The method provides linear couplings to form *one Carbon-Carbon* and *two Carbon-Nitrogen* bonds along with an angular coupling to give *one C-N* bond. When a thorough screening was performed by varying base, solvent, catalyst, temperature and time, it was observed that the combination of CuCl with L-proline completed the reaction most effectively. On exploration the scope of the method, it was noticed that the benzamides having bromo, and methoxy groups delivered the products **50** or **51** excellently.

Keramamide A and L (Fig. 2) are two prominent naturally occurring peptides having crucial role in the production of promising drugs[19]. The isolations of Keramamide A (**54**)[20]



Scheme 17. Strategy for accessing indole fused polyheterocycles.

and keramamide L (**55**)[21a] were achieved by Kobayashi and co-workers from a marine sponge. However, the first ever synthesis of these two natural products were carried out by Junk and other.

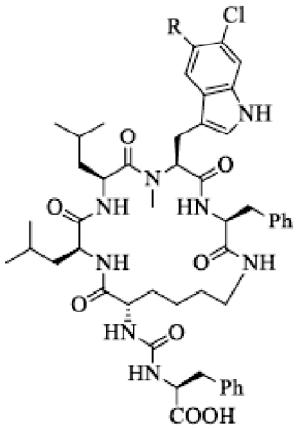
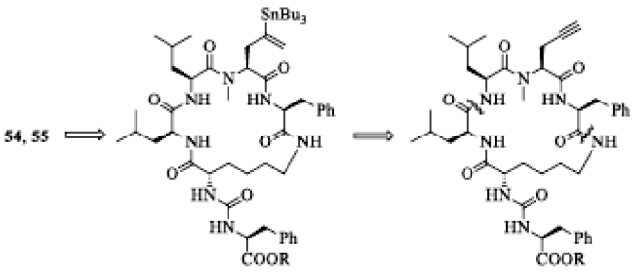


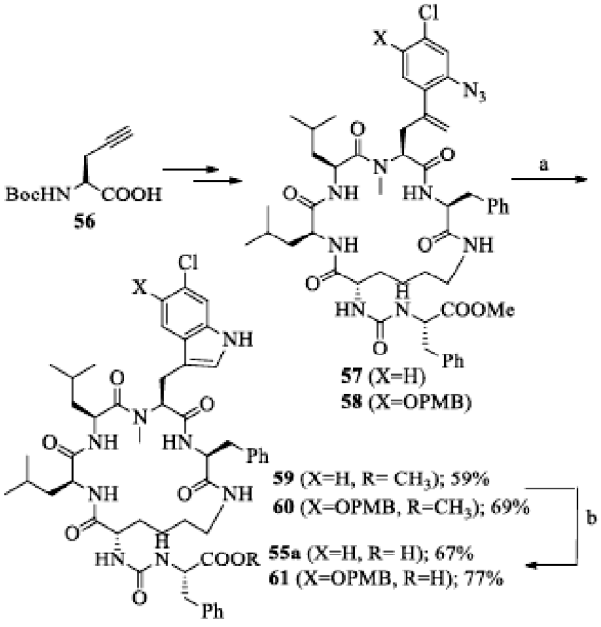
Fig. 2. Structures of keramamides A and L.

Junk and group aimed the construction of keramamides A and L from the same precursor suggesting the disconnection strategy described in Scheme 18. At first, they targeted the preparation of tripeptides **57** and **58**[21b] from the glycine **56** employing few operationally simple steps as shown in Scheme 19. The tripeptides on photochemical C-H insertion, and subsequent Me_3SnOH promoted saponification led to the production of **55a** and **61** satisfactorily.

In 2018, Ning and co-workers reported a practical method to synthesize indoles employing Pd-^{t}BuONO and molecular



Scheme 18. Disconnection approach to keramamides A and L.

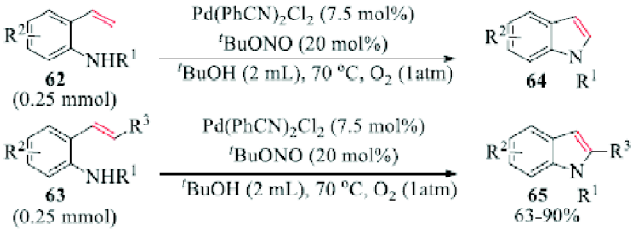


(a) *h*ν, acetonitrile, rt, 7 h/5 h; (b) Me_3SnOH, dichloroethane, 80°C, 23.5 h/41 h.

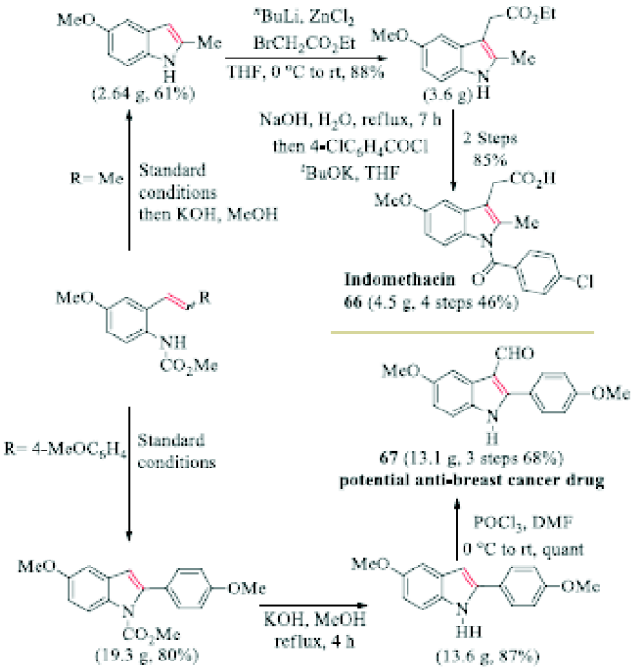
Scheme 19. Synthesis of keramamide A and L.

O_2 as co-catalyst and oxidant respectively (Scheme 20)[22]. In this approach, the reactions with a variety of 2-vinylanilines (**62** and **63**) proceeded smoothly to give the indoles **64** and **65** in moderate to excellent yields. The method was also successfully applied in the synthesis of 4.5 grams of indomethacin **66** (Scheme 21, top) and compound **67** (Scheme 21, bottom). The pharmaceuticals **66** and **67** are promissing *anti*-inflammatory and *anti*-breast cancer agents respectively.

Xie and his group developed a pioneer method to produce dihydrothiazoles **68** selectively *Z*-isomers and aryl ketones **69** in satisfactory yields by the bicyclization of isothiocyanates **70** and propargylamine derivatives **71**

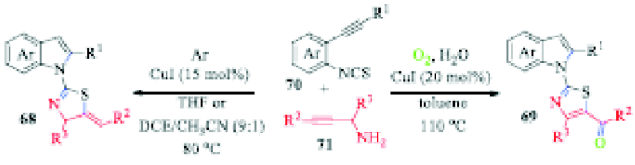


Scheme 20. Pd-^{t}BuONO co-catalyzed reaction of terminal and internal 2-vinylanilines.



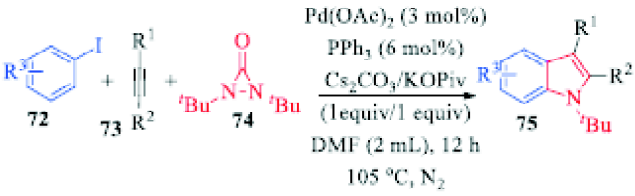
Scheme 21. Gram-scale synthesis of pharmaceuticals.

(Scheme 22)[23]. The reaction involved an intramolecular 5-*exodig* hydrothiolation and an intramolecular hydroamination.



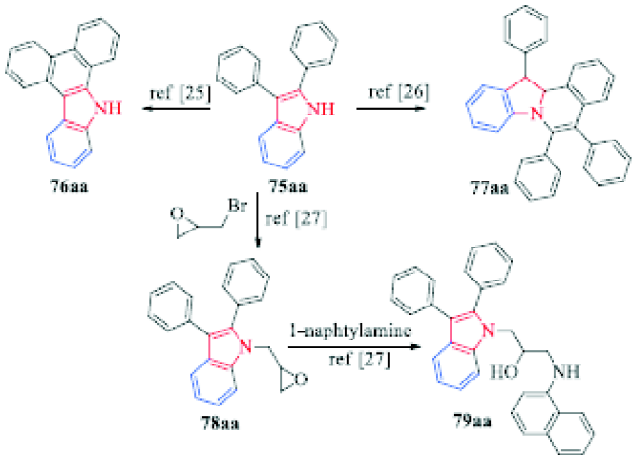
Scheme 22. Synthesis of *N*-heterocyclic indoles.

Zhou and co-workers discovered a Pd-catalyzed novel approach to construct indoles **75** by a three component reaction of **72**, **73** and diaziridinone **74** (Scheme 23)[24]. The



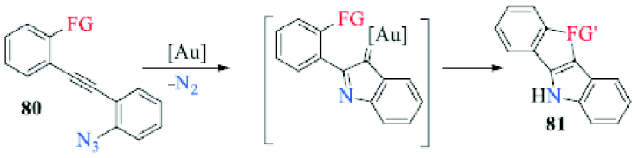
Scheme 23. Zhou indole production.

strategy showed an excellent regioselectivity on introducing unsymmetrical alkynes in the cyclization. It was believed that the transformation proceeded via the generation of C,C-palladacycles which on subsequent reaction with **74** delivers indoles. Moreover, the previous reports (Ref. 25, 26 and 27) can be utilized to get various biologically active compounds such as **76aa**, **77aa** and **79aa** from the product **75aa** obtained by the method (Scheme 24). **76aa** and **77aa** are potent semiconductors whereas **79aa** is used in the treatment of Alzheimer's disease.



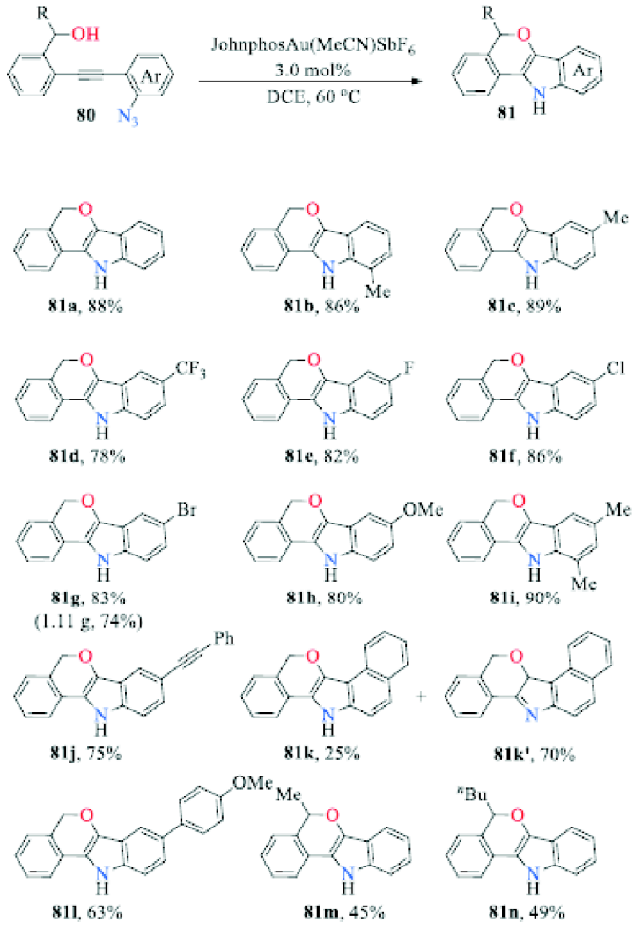
Scheme 24. Transformation of the indole products.

Gold-catalysts have been severely employed to construct various C-C and C-heteroatom bonds transforming alkynes recently. By using this strategy, Cai and his group discovered a gold-catalyzed intramolecular bicyclization of diaryl alkynes **80**. In this reaction, *N*-heterocycles **81** were obtained in a sequence of two steps namely O-H/N-H insertion into the carbenoid intermediate, and subsequent aromatic electrophilic substitution (Scheme 25)[28]. The superiority of the gold-catalyst was proved observing that the reaction failed to deliver **81** in the presence of other metal-catalysts. The



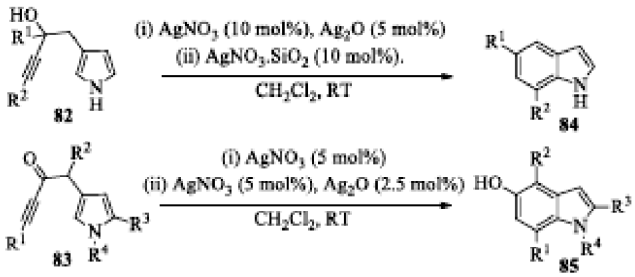
Scheme 25. Gold-catalyzed bicyclization of diaryl alkynes.

result of the substrate scope tested under optimal conditions was described widely in Scheme 26. Moreover, a plausible mechanism was also depicted showing that gold(I) activated alkyne system is generated first which on 5-*endodig* nucleophilic cyclization gives **81**. In this reaction, 1,3-*H* shift preferably happens to get more stable 1*H*-indole.



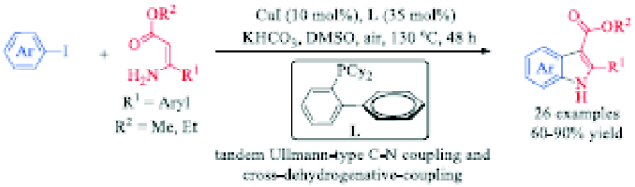
Scheme 26. Substrate scope.

Clarke and his group reported a facile silver(I)-catalysed "back-to-front" approach to produce indoles **84**, and importantly 5-hydroxy-indoles **85** from the ynol **82** and ynone **83** respectively (Scheme 27)[29]. The DFT helped to understand that the pyrrole C-3 position, the most nucleoplilic centre of the moiety undergoes nucleophilic attack onto the activated alkyne, rather than C-2 position.



Scheme 27. Silver(I)-catalysed ynol and ynone cyclisation to indoles.

In 2018, dehydrogenative coupling has played a significant role towards the construction of multisubstituted indoles. For example, Li and group members discovered a strategy for the preparation of indoles employing copper-catalyst in the Ullmann-type coupling to construct C-N bond, followed by intramolecular cross-dehydrogenation (Scheme 28)[30].

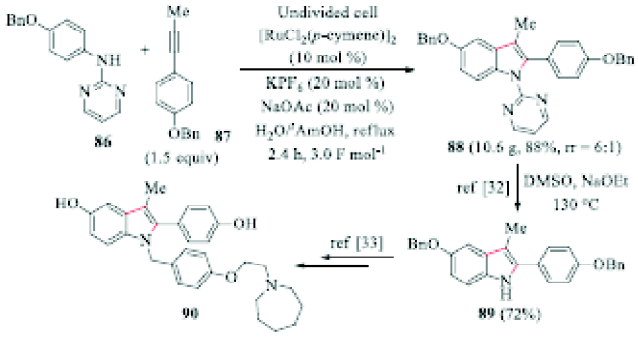


Scheme 28. Copper-catalyst in C-N bond construction/intramolecular dehydrogenation.

Ruthenium-catalyst was also introduced by Xu and his group to dehydrogenate electrochemically in the annulation of anilines and alkynes to prepare indoles[31]. The use of electric current was significant which enabled the H_2 evolution easier in water. Moreover, this strategy was utilized to afford indoles **88** in gram scale on annulation of **86** and **87** (Scheme 29). The free indole **89** could then be obtained from **88** by removing 2-pyrimidyl moiety obeying literature[32].

The indole **89** is used as the precursor in the synthesis of anti-osteoporotic agent bazedoxifene **90** (Scheme 29)[33].

Zafirlukast (**91**) is found to play a crucial role in the treatment of asthma. Hence, Paladugu and others developed a

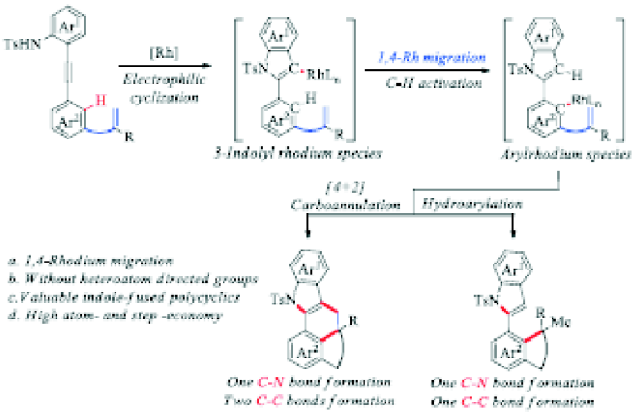


Scheme 29. Synthetic application of ruthenium-catalyzed electrochemical dehydrogenative annulation.

general approach to produce indoles **92** in the presence of sodium persulfate via oxidative cyclization (Scheme 30)[34]. The strategy is synthetically important because neither transition-metal nor peroxide was required in the C-H activation. Again the turnaround time for obtaining the target compound **91** from **93** was only 28 h without protection.

Scheme 30. Sodium persulfate promoted sp^3 C-H bond activation.

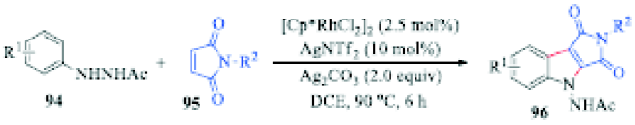
In 2019, rhodium catalysts have been extensively introduced towards the construction of plethora indole scaffolds by the activation of C-H bond. For example, the synthesis of the diversified indole-fused polycyclics was developed by Guo and his group where Rh(III) was introduced as potent catalyst in C-H activation (Scheme 31)[35]. The reaction proceeds via the initial production of rhodium complex by the cyclization of an electrophile intramolecularly. Then, the 1,4-rhodium migration was achieved to carry out the activation as well as



Scheme 31. Rhodium-catalyst in C-H activation/alkene insertion.

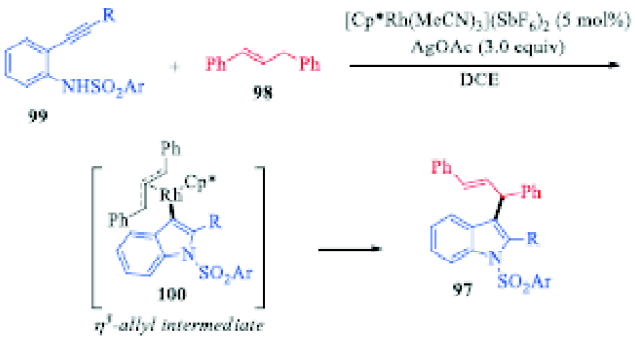
[4+2] carboannulation or hydroarylation of olefins.

A Rh(III)-catalyst was also utilized by Li and his group in an oxidative annulation where 2-acetyl-1-phenylhydrazines were treated with maleimides using Ag_2CO_3 oxidant. The [3+2] annulations delivered several pyrrolo[3,4-*b*]indole-1,3-diones **96** smoothly (Scheme 32)[36]. It is synthetically useful as the reaction was tolerant to various functional groups including halogens, -COOR, -CN, and $–NO_2$.



Scheme 32. Rh(III)-catalysed [3+2] annulation approach.

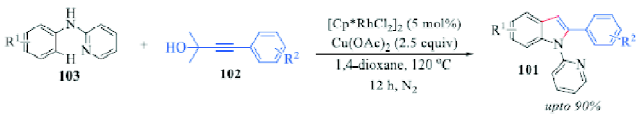
Sun and others explored rhodium(III)-catalyzed a mild synthetic strategy to afford 3-allylindoles **97** via the activation of olefinic C-H bond (Scheme 33)[37]. The reaction progressed by a sequence of nucleophilic cyclization and oxi-



Scheme 33. Rhodium(III)-catalyzed olefinic C-H activation strategy.

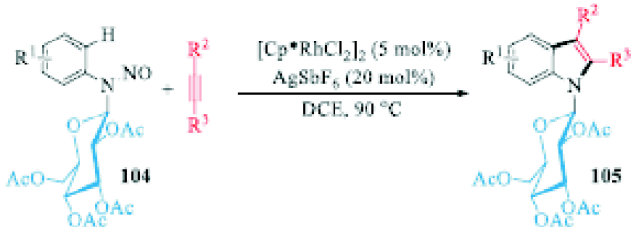
dative coupling via the generation of an η^3-allyl species **100**.

The discovery of Yan and group members to produce 2-arylindoles **101** was based on rhodium-catalyzed/copper-mediated cascade annulation via C-H/C-C activation. The reaction showed high selectivity for the breaking of C-C bond on employing the alcohols **102**. Moreover, the method was also equally applicable to get 2-arylindoles efficiently via *ortho* C(sp^2)-H bond activation (Scheme 34)[38].



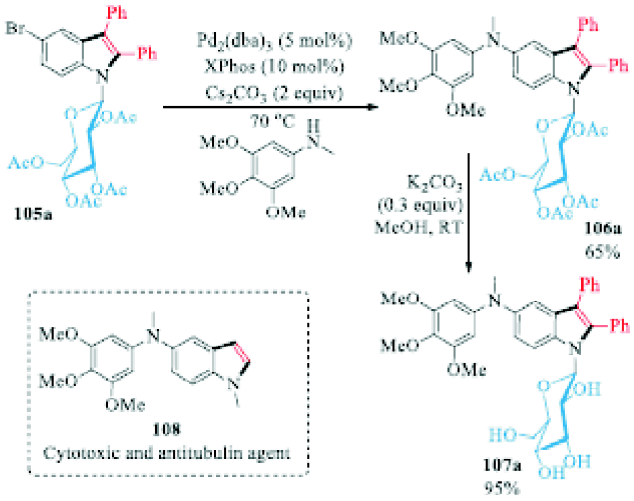
Scheme 34. Yan indole synthesis.

Recently, Zhao and his group discovered a general approach for the stereo-selective construction of *N*-glycosyl indoles **105** via C-H activation of β-*N*-aryl glycosides **104** introducing $[Cp^*RhCl_2]_2$ as an efficient catalyst (Scheme 35)[39]. When substrate scope was explored, it was noticed that the symmetrically substituted diaryl alkynes with electron-donating groups delivered the desired indoles more efficiently compare to the presence of electron-withdrawing groups. Furthermore, the product **105a** obtained by this strategy was transformed to the compound **106a** which is analogue to **108** having potent cytotoxic activity via a simple Buch-wald-Hartwig cross-coupling (Scheme 36).



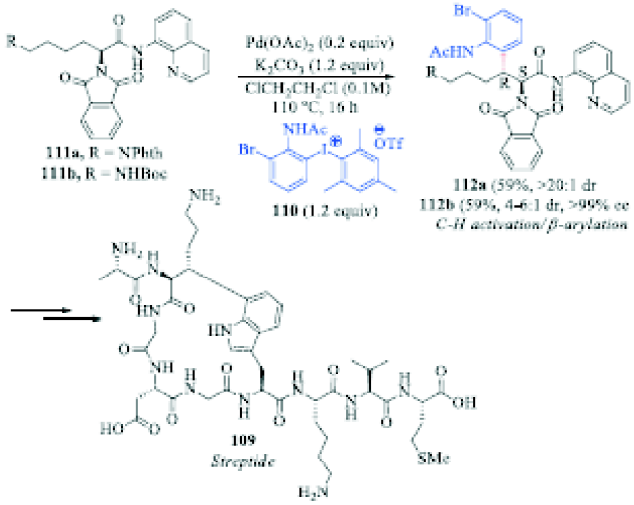
Scheme 35. Rh(III)-catalyzed construction of several *N*-glycosyl indoles.

C-H activation was utilized as prominent tool by Isley and co-workers in 2019 to produce Streptide **109**, a peptide-derived macrocycle obtained from *Streptococcus thermophilus*. In this report, the lysine core was afforded through macrocyclization via palladium(0)-promoted C-H activation in the presence of hypervalent iodine(III) complexes **110**



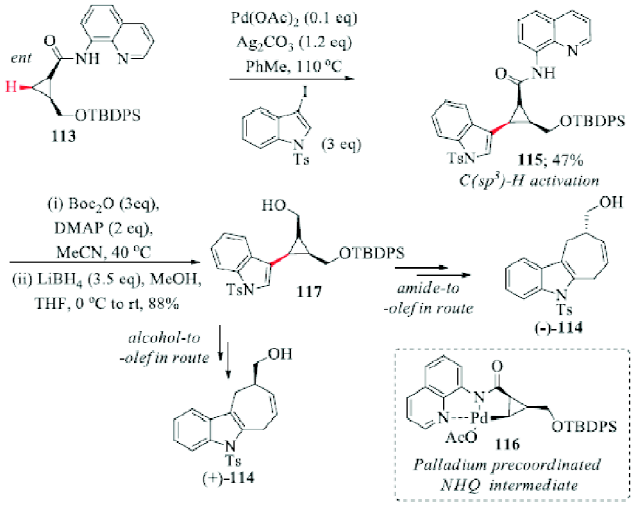
Scheme 36. Preparation of bioactive compounds **106a** and **107a**.

(Scheme 37)[40]. The synthesis also helped to establish the proper configuration of Streptide.



Scheme 37. Synthesis of Streptide.

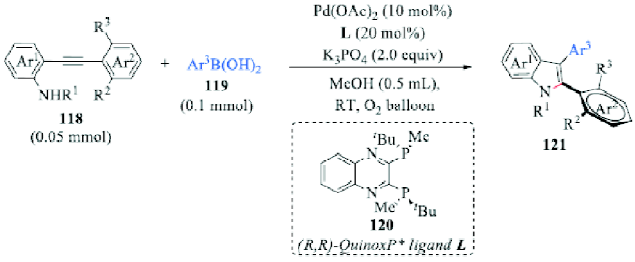
Hafner and his group invented a general strategy to deliver cyclohepta[*b*]indoles **114** employing palladium-catalyst in C(sp^3)-H activation of cyclopropane **113** (Scheme 38)[41]. It was observed that all the three substituents attached at 1, 2 and 3 positions of the cyclopropane moiety in the product **115** were fully *cis* in relationship. The result was achieved due to the precoordination of the catalyst to the substrate via NHQ in intermediate **116**[42]. Then, the pure compound **117**



Scheme 38. Palladium-catalyst in C(sp^3)-H activation of cyclopropane.

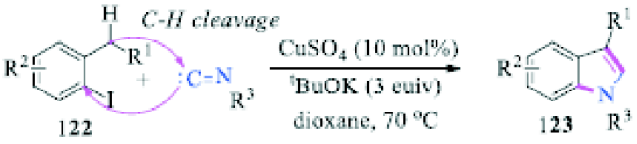
produced from **115** was employed to afford both the enantiomers of cyclohepta[*b*]indole **114** in pure forms via "amide-to-olefin" and "alcohol-to-olefin" routes.

He and co-workers introduced palladium-catalyst in Cacchi reaction to obtain chiral indoles enantionselectively. The reaction between 2-alkynylanilides **118** and boronic acids **119** in the presence of $Pd(OAc)_2$-catalyst, chiral ligand **L** (**120**) and O_2, delivered enantioenriched indoles **121** efficiently (Scheme 39)[43].



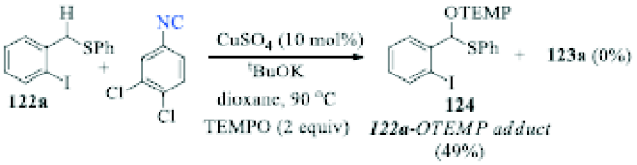
Scheme 39. $Pd(OAc)_2$-catalyzed enantioselective axially chiral 2,3-disubstituted indoles.

$CuSO_4$ salt obtained directly from the nature was utilized for the cyclization of toluenes **122** with isonitriles via tandem insertion of C(sp^3)-H bond to get the indoles **123** by Shan and co-workers (Scheme 40)[44]. The ability of the salt to show the catalytic activity solely reduced the cost of the reaction tremendously. The arylthio- or alkylthio-substituted toluenes

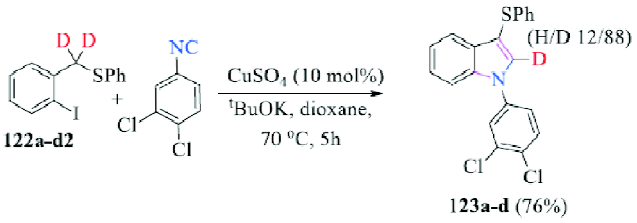


Scheme 40. $CuSO_4$-catalyzed benzylic C(sp^3)-H activation.

were found to be more effective in the reaction due to the participation of the groups in the stabilization of the radicals generated in the course of the reaction. To get the mechanistic insight, radical trapping (Scheme 41) and isotope labeling (Scheme 42) experiments were carried out. The results of these experiments helped to conclude that the addition was completed through the production of benzylic radical.

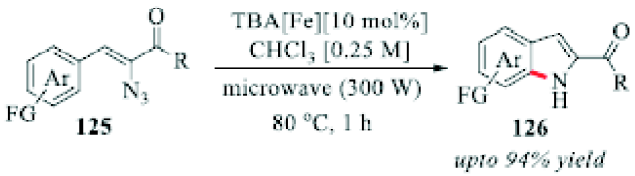


Scheme 41. Radical trapping experiment.



Scheme 42. Isotope labeling experiment.

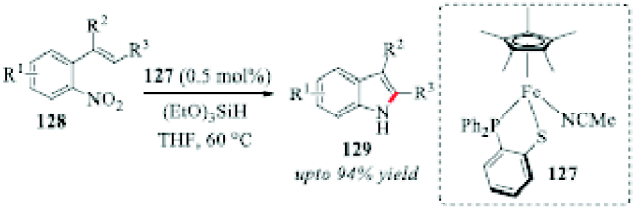
A variety of iron complexes have been extensively introduced as catalysts in the preparation of indole moiety via C-H activation approach. Thermal or photochemical-induced aminations of various azides have been frequently reported[45]. However, the methods to activate the C-H- or C-C-bond of aryl or alkyl azides employing transitionmetal catalysts have yet to be developed. Baykal and Plietker used a nucleophilic complex (TBA[Fe]) as catalyst in the direct preparation of the indoles **126** via C(sp^2)-H-bond activation of the azides **125** in 2019 (Scheme 43)[46]. In order to understand the mechanistic pathway, control experiments were performed. Then, azirine obtained by following the literature procedures[47]



Scheme 43. (TBA[Fe])-catalyzed C(sp^2)-H amination of azides.

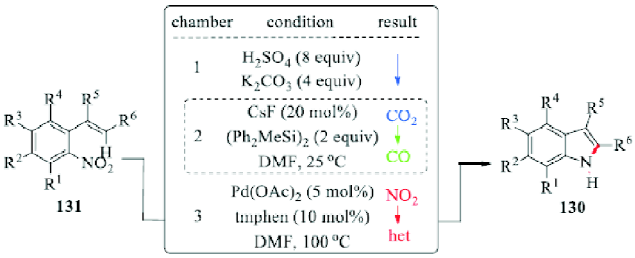
was subjected to the above condition. But TBA[Fe] failed to deliver **126** suggesting that the amination must not be ended via the *in situ* production of azirines.

Recently, nitroarenes **128** have been transformed to the indoles **129** by an iron(II) compound **127**. For example, Song and co-workers employed Fe(II) with $(EtO)_3SiH$ to deliver various indole derivatives **129** through intramolecular reductive coupling in one-pot (Scheme 44)[48].



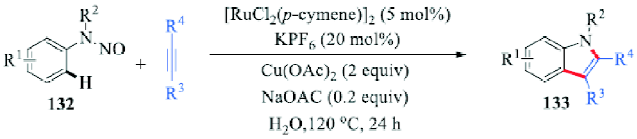
Scheme 44. Iron(II)-catalyzed intramolecular reductive coupling.

Guan and others also established a general strategy for the construction of indoles **130** by a palladium-catalyzed reductive cyclization of nitroarenes **131** (Scheme 45)[49]. It was a three-chamber process where a mixture of disilane and fluoride was used to deoxygenate CO_2 to CO superstoichiometrically. Finally, the preparation of indoles with functional diversity was completed via reductive amination.



Scheme 45. Palladium-catalyzed reductive cyclization of nitroarenes.

Chen and his group used *N*nitrosoanilines **132** for the formation of indoles **133** employing Ru(II)-catalyst in C-H bond [3+2] cycloaddition with several alkynes in water (Scheme 46)[50]. When substrate scope was explored, it was found that various functional groups including Me, OMe, halogens, COOMe, CN remained intact at the end of the reaction. Interestingly, the *meta* substituted *N*-nitrosoanilines showed excellent regioselectivity in this Ru(II)-catalyzed transformation. The possible mechanistic pathway was investigated by

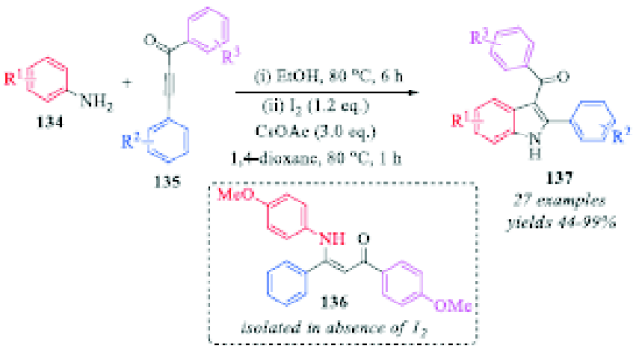


Scheme 46. Ru(II)-catalyst in C-H bond [3+2] cycloaddition.

carrying out some control experiments. The reversbility of the C-H activation step was proved by H/D exchange test. The other results indicated that the breaking of C-H bond probably takes place in the slowest step.

Su and co-workers discovered a synthetic method for the direct formation of indole from aniline in a step.

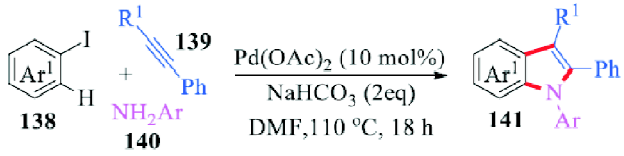
Herein, the reaction ended via I_2-moderated aza-Michael addition/C-H functionalization. The intermediates **136** were obtained on aza-Michael addition between **134** and ynones **135**, which were then subsequently functionalized to produce different indoles **137** without employing transition metal (Scheme 47)[51]. When the substrate scope was explored for the generality of this protocol, it was found that *para*-substitution afforded the desired product in around 90% yield. Contractedly, the *meta*- and specially *ortho*-substitution led



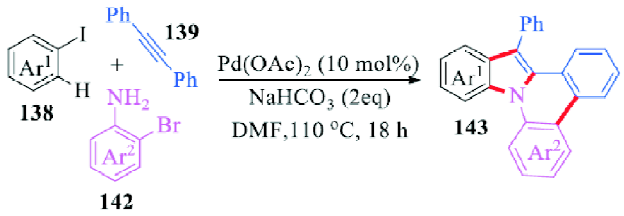
Scheme 47. I_2-mediated C-H functionalization.

to the indole formation in 44% yield. The role of I_2 was proved by getting **137** in 95% yield utilizing the isolated enaminone **136** in the C-H functionalization. The radical mechanistic pathway was proposed by allowing the reaction in the presence of radical scavenger, TEMPO, which showed the formation of few **137**.

Jafarpour and his group discovered amination method via *ortho*- or *ipso*-substitution selectively on reaction between aniline and aryl halide. The reaction proceeded through a sequence of steps including insertion of alkyne, C-H activation and amination (Scheme 48)[52]. On exploring the scope of the reaction introducing *ortho*-bromoanilines **142**, the [1,2-*f*]phenanthridines **143** was produced with the construction of four C-C and C-N bonds (Scheme 49). The result of the control experiments suggested that the reaction goes through palladacycle intermediate.

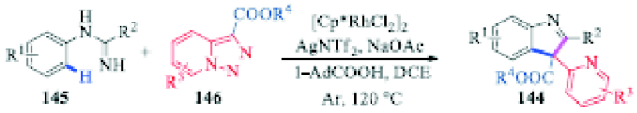


Scheme 48. Palladium-catalyst in selective amination.



Scheme 49. Preparation of indolo[1,2-*f*]phenanthridines.

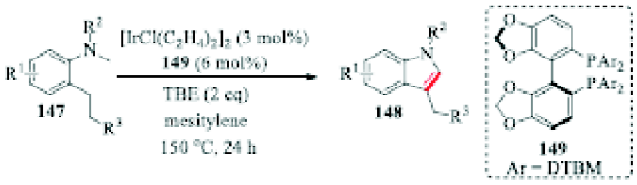
In recent times, Xu and co-workers discovered a synthetic route to *3H*-indoles **144** via Rh-catalyzed C-H activation of *N*-phenylbenzimidamides **145** as well as couplings with pyridotriazoles **146** (Scheme 50)[53]. It was observed that the *para*-positioned electron-withdrawing group influenced the reaction more effectively compare to that of electron-donating group suggesting the easy decomposition of the latter in the reaction medium. Interestingly, substituent at *meta*-position activated C-H bond at less hindered site regioselectively. Consequently, the result of the deuterium labeling test proved the reversibility of the C-H activation, whereas the



Scheme 50. Rhodium-catalyzed selective C-H activation.

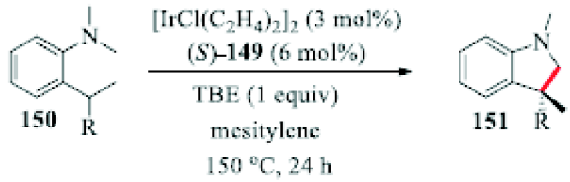
kinetic isotopic tests referred that the C-H bond breaking was not occurred in the turnover-limiting step. Moreover, the chemoselectivity was also noticed where the products were obtained with the pyridyl substituted quaternary carbon center.

In 2020, Ohmura and co-workers explored a novel strategy in the direct transformation of 2-ethyl-*N*-methylanilines **147** to 3-methylindoles **148** in high yields introducing an iridium catalyst. In this reaction, DTBM-SEG-PHOS **149** and TBE were utilized as ligand and hydrogen scavenger respectively (Scheme 51)[54]. The dehydrogenation of the -Et group delivered vinyl moiety, which on subsequent C-H/C-H coupling with the *N*-methyl group produced **148**.



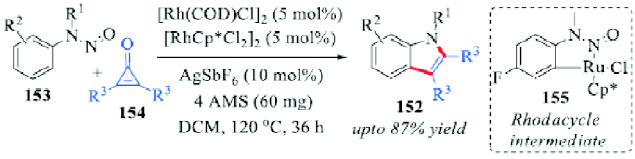
Scheme 51. Ir-catalyzed C-H/C-H coupling via dehydrogenation.

The Ir/**149**-catalyst system showed its potential during the transformation with the *ortho*-branched alkyl substituents. The sterically more demanding substrates **150** obeyed the sequence more easily to give indoline **151** efficiently. Moreover, a high enantioselectivity was noticed for R = Ar group (Scheme 52).



Scheme 52. Asymmetric conversion of **150** affording enantioenriched indolines **151**.

In 2020, Shi and co-workers reported condition-controlled divergent syntesis of indoles **152**, where Ag salt played a potent role in the C-H activation of cyclopropenones **154** with **153** (Scheme 53)[55]. Herein, Rh(I)-catalyst along with Rh(III)-cocatalyst system was utilized to get the sequence of decarbonylation/C-H activation/[3+2] annulations more effectively. The result of the H/D exchange test clarified about the reversibility of the *ortho*-C-H metalation, whereas that of KIE experiment suggested that the breaking of the C-H bond of **153** was not likely occurred in the slowest step of the course. Moreover, the hypothetical five-membered rhoda-cycle intermediate **155** was substantiated by crystallographical analyses.



Scheme 53. Rh(I)-and Rh(III)-cocatalyzed synthesis of indoles.

Conclusion

Herein, I have disclosed strategies that give a comprehensive overview on indole scaffold as well as indole based natural product and pharmaceutics synthesis via C-H activation as a potent tool appeared in literature since 2015 to date[56]. Different aspects of the transformation via transition metal-catalyzed as well as free-C-H activation with mechanistic understandings are discussed thoroughly in this report. It is expected that the review will be useful towards the heterocyclic chemists working in the field of indole bearing bioactive natural products and pharmaceutics.

References

1. (a) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev*., 2003, **103**, 893; (b) G. R. Humphrey and J. T. Kuethe, *Chem. Rev*., 2006, **106**, 2875; (c) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev*., 2010, **110**, 4489; (d) D. F. Taber and P. K. Tirunahari, *Tetrahedron*, 2011, **67**, 7195; (e) M. Platon, R. Amardeil, L. Djakovitch and J.-C. Hierso, *Chem. Soc. Rev*., 2012, **41**, 3929; (f) M. Inman and C. J. Moody, *Chem. Sci*., 2013, **4**, 29.
2. B. S. Komm and A. A. Chines, *Ther. Adv. Musculoskelet Dis*., 2012, **4**, 21.
3. T. Yamakawa, E. Ideue, J. Shimokawa and T. Fukuyama, *Angew. Chem., Int. Ed.,* 2010, **49**, 9262.
4. S. Fukudo, M. Ida, H. Akiho, Y. Nakashima and K. Matsueda, *Clin. Gastroentero. Hepatol*., 2014, **12**, 953.
5. M. S. N. Reddy, B. K. Reddy, C. K. Reddy, M. K. Kumar, S. T. Rajan and M. S. Reddy, *Orient. J. Chem.,* 2008, **24**, 167.
6. E. Fischer and F. Jourdan, *Ber. Dtsch. Chem. Ges*., 1883, **16**, 2241.
7. B. A. Arndtsen, R. G. Bergman, T. A. Mobley and T. H. Peterson, *Acc. Chem. Res.,* 1995, **28**, 154.
8. (a) A. P. Kale, G. S. Kumar and M. Kapur, *Org. Biomol. Chem*., DOI: 10.1039/c5ob01632k; (b) O. Tempkin, S. Abel, C.-P. Chen, R. Underwood, K. Prasad, K.-M. Cheng, O. Repic and T. J. Blacklock, *Tetrahedron*, 1997, **53**, 10659; (c) J. T. Zacharia, T. Tanaka and M. Hayashi, *J. Org. Chem.*, 2010, **75**, 7514; (d) A. Kim and I. S. Kim, *Bull. Korean Chem. Soc*., 2011, **32**, 3748.
9. I. S. Kim, N. K. Mishra, M. Choi, H. Jo, Y. Oh, S. Sharma, S. H. Han, T. Jeong, S. Han and S. Lee, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC07767B.
10. A. Ahmed, M. Ghosh, S. Dhara and J. K. Ray, *Synlett,* 2014, **25**, 2455.
11. J. W. Wilt and W. W. Pawlikowski, *J. Org. Chem.,* 1975, **40**, 3641.
12. I. Alimi, R. Remy and C. G Bochet, *Eur. J. Org. Chem.,* 10.1002/ejoc.201700300.
13. (a) C. Rivalle, C. Ducrocq, J. M. Lhoste and E. Bisagni, *J. Org. Chem.,* 1980, **45**, 2176; (b) R. B. Miller and J. G. Stowell, *J. Org. Chem.,* 1983, **48**, 888.
14. R. Kancherla, T. Naveen and D. *Maiti, Chem. -Eur. J*., 2015, **21**, 8723.
15. G. S. Kumar, D. Singh, M. Kumar and M. Kapur, *J. Org. Chem*., 2018, **83**, 3946.
16. A. Acerbi, C. Carfagna, M. Costa, R. Mancuso, B. Gabriele and N. D. Ca, *Chem. Eur. J*., 2018, **24**, 4835.
17. D. Bellezza, B. Noverges, F. Fasano, J. T. Sarmiento, M. Medio-Simón and G. Asensio, *Eur. J. Org. Chem.,* DOI: 10.1002/ejoc.201801607.
18. V. Kavala, Z. Yang, A. Konala, T.-H. Yang, C-.W. Kuo, J.-Y. Ruan and C.-F. Yao, *Eur. J. Org. Chem.,* DOI: 10.1002/ejoc.201701618.
19. (a) E. A. Felnagle, E. E. Jackson, Y. A. Chan, A. M. Podevels, A. D. Berti, M. D. McMahon, M. G. Thomas and A. M. Podevels, *Mol. Pharm*., 2008, **5**, 191; (b) T. Dang and R. D. Sgssmuth, *Acc. Chem. Res*., 2017, **50**, 1566; (c) R. D. Sgssmuth and A. Mainz, *Angew. Chem. Int. Ed*., 2017, **56**, 3770; *Angew. Chem*., 2017, **129**, 3824.
20. J. Kobayashi, M. Sato, M. Ishibashi, H. Shigemori, T. Nakamura and Y. Ohizumi, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2609.
21. (a) H. Uemoto, Y. Yahiro, H. Shigemori, M. Tsuda, T. Takao, Y. Shimonishi and J. Kobayashi, *Tetrahedron*, 1998, **54**, 6719; (b) L. Junk and U. Kazmaier, *Angew. Chem., Int. Ed*., 2018, **57**, 11432 .
22. X.-S. Ning, X. Liang, K.-F. Hu, C.-Z. Yao, J.-P. Qu and Y.-B.

Kang, *Adv. Synth. Catal.,* DOI: 10.1002/adsc.201701512.

23. J. Xie, Z. Guo, Y. Huang, Y. Qu, H. Song, H. Song, Y. Liu and Q. Wang, *Adv. Synth. Catal.,* DOI: 10.1002/adsc.201801193.
24. B. Zhou, Z. Wu, D. Ma, X. Ji and Y. Zhang, *Org. Lett*., 2018, **20**, 6440.
25. C. A. Mudry and A. R. Frasca, *Tetrahedron*, 1974, **30**, 2983.
26. L. Zheng and R. Hua, *Chem.-Eur. J.,* 2014, **20**, 2352.
27. C. Wang, H. Sun, Y. Fang and Y. Huang, *Angew. Chem., Int. Ed*., 2013, **52**, 5795.
28. J. Cai, B. Wu, G. Rong, C. Zhang, L. Qiu and X. Xu, *Org. Lett*., DOI: 10.1021/acs.orglett. 8b00939.
29. A. K. Clarke, J. M. Lynam, R. J. K. Taylor and W. P. Unsworth, *ACS Catal*., DOI: 10.1021/acscatal.8b00745.
30. Y. Li, J. Peng, X. Chen, B. Mo, X. Li, P. Sun and C. Chen, *J. Org. Chem*., 2018, **83**, 5288.
31. F. Xu, Y.-J. Li, C. Huang and H.-C. Xu, *ACS Catal.*, DOI: 10.1021/acscatal.8b00373.
32. L. Ackermann and A. V. Lygin, *Org. Lett.,* 2012, **14**, 764.
33. C. P. Miller, M. D. Collini, B. D. Tran, H. A. Harris, Y. P. Kharode, J. T. Marzolf, R. A. Moran, R. A. Henderson, R. H. W. Bender, R. J. Unwalla, L. M. Greenberger, J. P. Yardley, M. A. Abou- Gharbia, C. R. Lyttle and B. S. Komm, *J. Med. Chem.,* 2001, **44**, 1654.
34. S. Paladugu, P. S. Mainkar and S. Chandrasekhar, *ACS Omega*, 2018, **3**, 4289.
35. S. Guo, R. Pan, Z. Guan, P. Li, L. Cai, S. Chen, A. Lin and H. Yao, *Org. Lett*., DOI: 10.1021/acs.orglett.9b02198.
36. H. Li, S. Zhang, X. Feng, X. Yu, Y. Yamamoto and M. Bao, *Org. Lett*., 2019, **21**, 8563.
37. J. Sun, K. Wang, P. Wang, G. Zheng and X. Li, *Org. Lett*., 2019, **21**, 4662.
38. X. Yan, R. Ye, H. Sun, J. Zhong, H. Xiang and X. Zhou, *Org. Lett*., DOI: 10.1021/acs.orglett. 9b02767.
39. G. Zhao, M. Zhu, O. Provot, M. Alami and S. Messaoudi, *Org. Lett*., DOI: 10.1021/acs.orglett. 9b03893.
40. N. A. Isley, Y. Endo, Z.-C. Wu, B. C. Covington, L. B. Bushin, M. R. Seyedsayamdost and D. L. Boger, *J. Am. Chem. Soc*., DOI: 10.1021/jacs.9b09067.
41. M. Hafner, Y. M. Sokolenko, P. Gamerdinger, E. Stempel and T. Gaich, *Org. Lett*., DOI: 10.1021/acs.orglett.9b02687.
42. V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc*., 2005, **127**, 13154.
43. Y.-P. He, H. Wu, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.,* DOI: 10.1002/anie.201914049; *Angew. Chem.,* DOI: 10.1002/ange.201914049.
44. X.-H. Shan, M.-M. Wang, L. Tie, J.-P. Qu and Y.-B. Kang, *Org. Lett*., DOI: 10.1021/acs.orglett. 9b03751.
45. J. Aube and G. L. Milligan, *J. Am. Chem. Soc.,* 1991, **113**, 8965.
46. A. Baykal and B. Plietker, *Eur. J. Org. Chem.,* 10.1002/ejoc.201901864.
47. D. Knittel, *Synthesis*, 1985, **2**, 186.
48. H. Song, Z. Yang, C.-H. Tung and W. Wang, *ACS Catal*., DOI: 10.1021/acscatal.9b03604.
49. X. Guan, H. Zhu, Y. Zhao and T. G. Driver, *Eur. J. Org. Chem.,* DOI: 10.1002/ejoc.201901629.
50. X. Chen, X. Cui, L. Bai, Y. Wang, Y. Xie, S. Wang, R. Zhai, K. Zhao, D. Kong and Y. Li, *Asian J. Org. Chem.,* DOI: 10.1002/ajoc.201900553.
51. J. Su, K. Zhang, M. Zhuang, F. Ma, W.-Q. Zhang, H. Sun, G. Zhang, Y. Jian and Z. Gao, *Asian J. Org. Chem.,* DOI: 10.1002/ajoc.201900152.
52. F. Jafarpour, M. Ghasemi, F. Mohaghegh, S. Asgari and A. Habibi, *Org. Lett*., DOI: 10.1021/acs.orglett.9b04202.
53. H.-B. Xu, Y.-Y. Zhu and L. Dong, *J. Org. Chem.*, DOI: 10.1021/acs.joc.9b02468.
54. T. Ohmura, K. Yagi, S. Kusaka and M. Suginome, *ACS Catal*., DOI: 10.1021/acscatal.9b05579.
55. Y. Shi, H. Xing, T. Huang, X. Liu, J. Chen, X. Guo, G.-B. Li and Y. Wu, *Chem. Commun.*, 2020, DOI: 10.1039/C9CC08926H.
56. For other selected indole synthesis via C-H activation, see; (a) L. Zhang, J. Chen, J. Chen, L. Jin, X. Zheng, X. Jiang and C. Yu, *Tetrahedron Lett*., 2019, **60**, 1053; (b) H. Lv, J. Shi, B. Wu, Y. Guo, J. Huanga and W. Yi, *Org. Biomol. Chem*., 2017, **15**, 8054; (c) Y. Shang, K. Jonnada, S. L. Yedage, H. Tu, X. Zhang, X. Lou, S. Huang and W. Su*, Chem. Commun*., 2019, DOI: 10.1039/C9CC04529E; (d) H. J. Kim, D. C. Fabry, S. Madera and M. Rueping, *Org. Chem. Front*., 2019, DOI: 10.1039/c9qo00206e (e) X.-F. Cui, Z.-H. Ban, W.-F. Tian, F.-P. Hu, X.-Q. Zhou, H.-J. Ma, Z.-Z. Zhana and G.-S. Huang, *Org. Biomol. Chem*., 2019, **17**, 240.