

# Copper Catalyzed Synthesis of Indole Derivatives via Cross-Coupling Reaction

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**Abstract:** This mini-review article has been focused on the copper-catalyzed synthesis of indole skeletons. Indoles are very important heterocyclic compounds found in nature. Indole moieties are present in natural products, drugs, perfumes and many other materials of great importance. Therefore, since decades many strategies have been developed for the synthesis of indole skeletons. For examples, Fischer indole synthesis is the classical method for the synthesis of indole rings. Recently transition metal-catalyzed coupling methods have been introduced successfully for indole synthesis. One of the main strategy for the synthesis of indole rings using transition metal is cross-coupling reactions. Transition metals such as palladium, copper, rhodium, ruthenium, iridium cobalt have been used for indole synthesis via cross-coupling reactions. In this review we will discuss the synthesis indole skeletons using copper-catalyzed cross-coupling reactions.

**Keywords:** Organic Chemistry, Copper-Catalysts, Synthesis, Cross-coupling, Indoles, Heterocycles.

## I. INTRODUCTION

Indoles are most common heterocyclic compounds that are used in various fields like drug industries, perfumes industries, materials science, and agrochemicals.[1]-[3] It is also termed as one of the privileged structure in heterocyclic chemistry.[4] The biological activity of indole derivatives may be attributed to its high binding affinity with many receptors. Therefore indole heterocycles are compounds of deep interest for the organic chemists. Over a period of hundred years, a large number methods have been developed for the synthesis and functionalizations of indole skeletons.[5] Fischer indole synthesis is one of the oldest classical protocol for the construction of indole skeletons (Scheme 1).[6] Most of the classical methods suffer from the requirement of harsh reaction conditions. To overcome these drawbacks researcher have developed transition-metal-catalyzed reactions which works under comparatively milder conditions.[7] Although transition-metal catalyzed reactions are milder but most of the transition metals are very expensive and are not readily available. In this copper catalysts are easily accessible and very cheap compared to palladium, iridium and rhodium metal catalysts.[8] Hence in this mini-review, we will consider the copper catalyzed synthesis of indole skeletons.

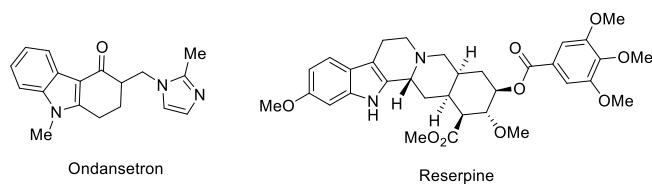
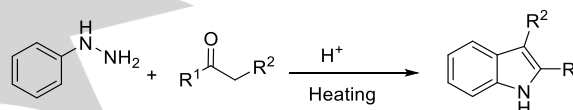


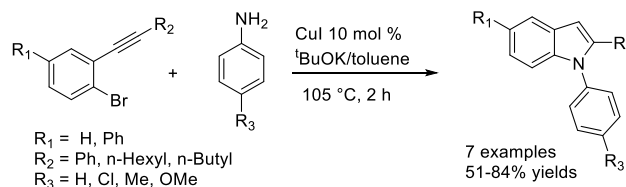
Figure1. Bioactive indole compounds



Scheme 1. Fischer indole synthesis

## II. DISCUSSION

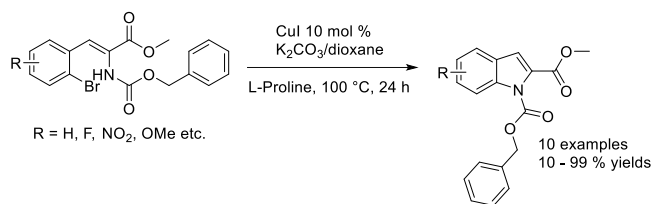
In 2005 Ackerman[9] has reported the synthesis of indole framework by using copper catalyst. A variety of *ortho*-haloalkenylarenes undergo cross-coupling with substituted aryl amine followed by cyclization to give various substituted indole skeletons. The reaction condition is very simple and work under mild condition. The reaction works well with different alkenyl-substituted halo arenes like *n*-Hexyl, *n*-Butyl alkenyl substituents successfully reacts with different aryl amine like *para*-chloro, *para*-methoxy and *para*-methyl substituted amines (Scheme 2). This reaction condition provides very good yields of the corresponding products.



Scheme 2. Copper-catalyzed syntheses of the indole framework starting from *o*-alkynylhaloarenes.

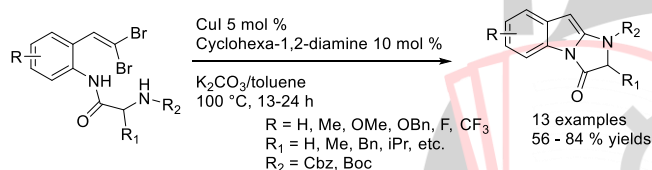
Cusack and co-workers have reported the synthesis of substituted indole backbone by copper catalyst in the presence of L-proline ligand.[10] This protocol works well and provides the corresponding indole moieties in moderate to good yield. The reaction condition involve the use of

$K_2CO_3$  base and 1,4-dioxane solvent and the working temperature is 100 °C (Scheme 3). A variety of substrate fit well in this reaction conditions, like substrates having F, OMe,  $NO_2$  substituents works better and the OMe substituted starting material provides best yield.



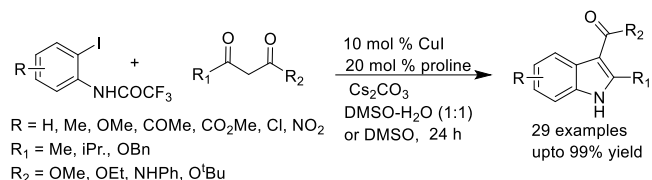
**Scheme 3.** Intramolecular cyclization of ene-carbamates using copper catalyst.

Substituted imidazo-indole compounds were synthesized by Lautens and coworkers via tandem carbon nitrogen bonds formation.[11] The standardize reaction conditions required the use of 5 mol % of copper iodide, 10 mol % of trans-1,2-cyclohexanediamine, potassium carbonate base and toluene as solvent at 100 °C temperature. Variety substrates undergo cross-coupling reaction to give the corresponding imidazoindolones products with good yields. This reaction is an unique example coupling reaction where two cross-coupling takes place simultaneously (Scheme 4).



**Scheme 4.** Copper-catalyzed tandem intra-molecular amidation using gem-dibromovinyl compounds.

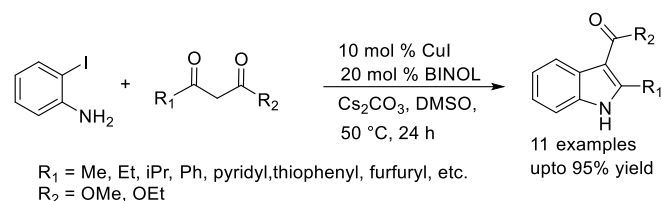
Dawei Ma and coworkers have reported the synthesis of poly-substituted indole skeletons by using copper iodide/L-proline catalytic system via carbon-carbon cross coupling of 2-halotrifluoroacetanilides with  $\beta$ -keto esters and amides followed by in situ acidic hydrolysis and cyclization strategy.[12] The standard protocol is very efficient and large number of substrates undergo cross-coupling reaction to give indole derivatives. For examples, different  $\beta$ -keto esters and amides could be cross-coupled with different 2-halotrifluoroacetanilides having electron donating and electron withdrawing substituents (Scheme 5).



**Scheme 5.** Copper/L-proline-catalyzed cross-coupling of 2-halotrifluoroacetanilides with  $\beta$ -keto esters.

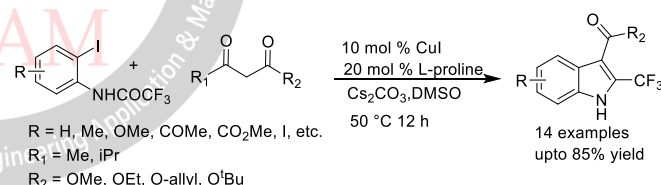
Shinji Tanimori and co-workers[13] reported one-step synthesis of 2,3-disubstituted indoles via cross-coupling of 2-iodoaniline and  $\beta$ -keto esters in the presence of CuI/BINOL catalytic system. The reported protocol involve

the use of 10 mol % of CuI, 20 mol % of cesium carbonate as base in DMSO at 50 °C temperature. Variety of  $\beta$ -keto esters, for examples, methyl, ethyl, isopropyl, furfuryl, thiophenyl, and pyridyl substituents are compatible under this protocol and gives the desired product in good yields (Scheme 6).

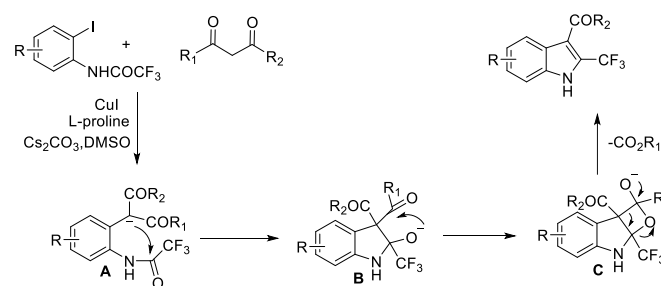


**Scheme 6.** Copper-catalyzed synthesis of 2,3-disubstituted indoles via carbon-carbon cross-coupling reaction.

In 2008 Dawei Ma and coworkers have reported the synthesis of poly-substituted indole framework from 2-halotrifluoroacetanilides and  $\beta$ -keto esters.[14] The reaction works well to give the desired products in good yields. Here both 2-halotrifluoroacetanilides and  $\beta$ -keto esters have broad variety. For examples, 2-iodotrifluoroacetanilides having substituents such as Me, COMe, OMe,  $CO_2Me$ , and halogens can be cross-coupled with  $\beta$ -keto esters to give variety of 2-(trifluoromethyl)indoles derivatives (Scheme 7). They also have proposed a plausible mechanism which has been outlined in figure 2. At first 2-halotrifluoroacetanilides undergo cross-coupling with  $\beta$ -keto esters. Then the carbanion can attack the carbonyl group of the trifluoroacetamide moiety to give intermediate **B**. After that alkoxy ion can attack carbonyl carbon to give intermediate **C**, which after rearrangement and acyl elimination may give the indole moieties.



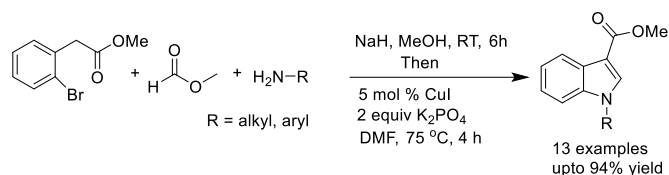
**Scheme 7.** Copper iodide/L-proline-catalyzed coupling of 2-halotrifluoroacetanilides with  $\beta$ -keto esters.



**Figure 2.** Mechanism of action.

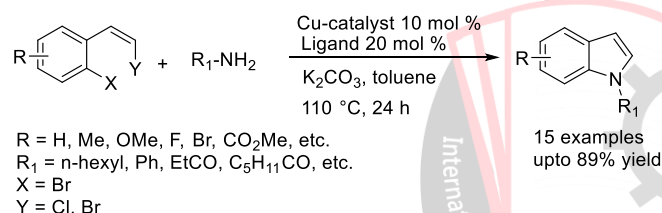
An efficient synthesis of *N*-substituted 1*H*-indole-3-carboxylic acid derivatives was reported by Karchava and co-workers using copper(I)-catalyzed carbon-nitrogen cross-coupling reaction (Scheme 8).[15] The reaction conditions required the use of CuI along with  $K_3PO_4$  base in *N,N*-dimethylformamide solvent at 75 °C

temperature. In this standard reaction condition methyl 2-(2-bromophenyl)acetate, methyl formate and different primary amine reacts in one pot to give the indole moieties in good yield.



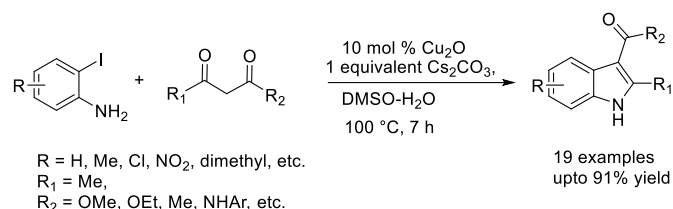
**Scheme 8.** Copper-catalyzed synthesis of indole skeletons via C-N cross-coupling reaction.

Willis and coworker[16] have demonstrated the synthesis of indole backbone by tandem carbon-nitrogen bonds formation reactions. In the standard reaction condition 2-(2-haloalkenyl)-aryl halide which was prepared by Wittig reaction, reacts with amine to give N-substituted indole derivatives. Copper catalysts, mainly copper iodide and copper acetate along with potassium carbonate base in toluene at 110 °C are the best combination for the cross-coupling reaction. Different primary amine source like, alkyl amine, aryl amine, and amides are capable to cross-couple with 2-(2-haloalkenyl)-aryl having substituents such as Me, OMe, F, Br, etc under those reaction conditions (Scheme 9).



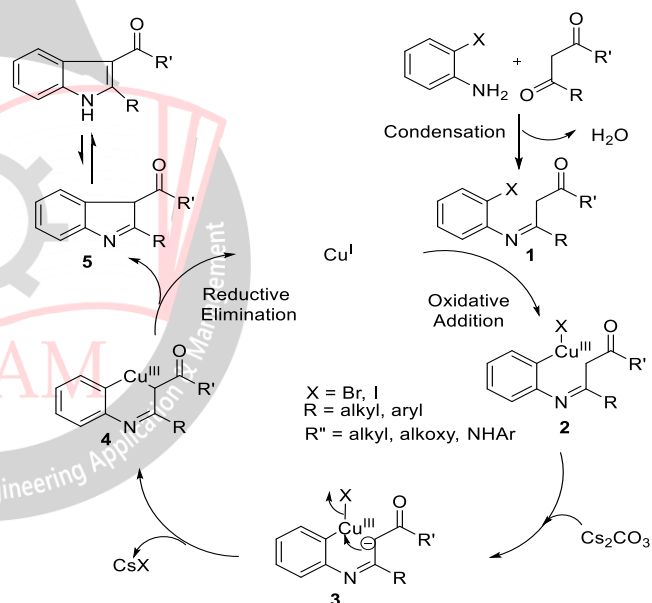
**Scheme 9.** Synthesis of indole framework via tandem carbon-nitrogen bonds formation.

We have also synthesis the poly-substituted indole derivatives by copper oxide catalyzed carbon-carbon bonds formation followed by cyclization strategy (Scheme 10).[17] The standardized reaction conditions required the use of 10 mol % of cuprous oxide (Cu<sub>2</sub>O), one equivalent cesium carbonate and dimethylsulphoxide water solvent mixture at 100 °C temperature. This reaction condition is highly efficient to catalyze the reaction of 2-iodoanilines with β-keto esters and amides to produce poly-substituted indole skeletons. 2-Iodoanilines having substituents such as Cl, Me, NO<sub>2</sub>, dimethyl can react with various β-keto esters and amides to give good yield of the corresponding products. We have also proposed a possible reaction mechanism that is shown in figure 3. At the beginning, 2-iodoaniline may undergo condensation with β-keto esters to give intermediate **1**, which can react copper oxide to give intermediate **2**. The intermediate **2** can react with base to give intermediate **3** and then intermediate **3** can form intermediate **4** by substitution reaction. The intermediate **4** thus formed may undergo reductive elimination to give product **5** which then can undergo tautomerism to give desired indole.

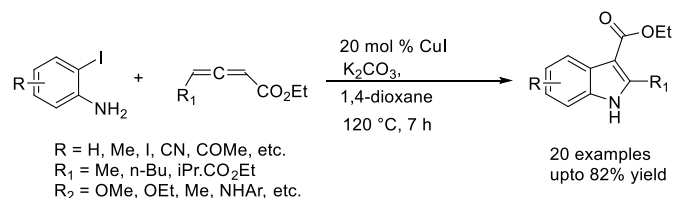


**Scheme 10.** Copper oxide catalyzed synthesis of poly-substituted indoles.

Huang and coworker[18] have reported the synthesis of ethyl 2-methyl-1*H*-indole-3-carboxylate derivatives by reacting of 2-iodoanilines with ethyl buta-2,3-dienoate (Scheme 11). Their developed methods involves the use of copper iodide with potassium carbonate base 1,4-dioxane solvent at 120 °C temperature. 2-Iodoanilines with different substituents reacts with ethyl buta-2,3-dienoate derivatives to give poly-substituted indoles in good yield. They have outlined a reaction mechanism which is given in figure 4. Initially, in the presence of base, 2-iodoaniline can react with buta-2,3-dienoate to give intermediate **I**, which may react with copper iodide to give intermediate **II** that can undergo oxidative addition to give intermediate **IV**. Intermediate **IV** can give the product after reductive elimination.



**Figure 3.** The plausible reaction pathway



**Scheme 11.** Copper catalyzed one-pot synthesis of multi-substituted indoles.

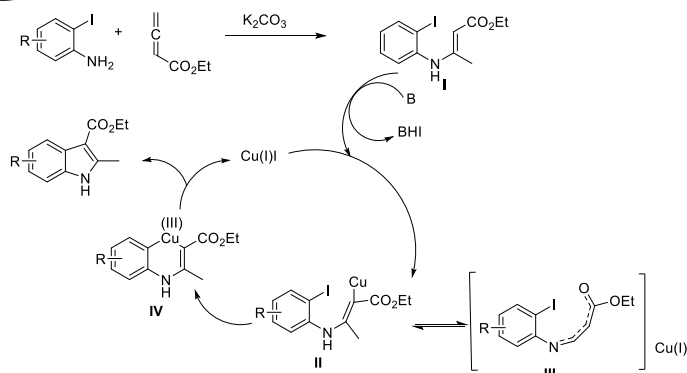
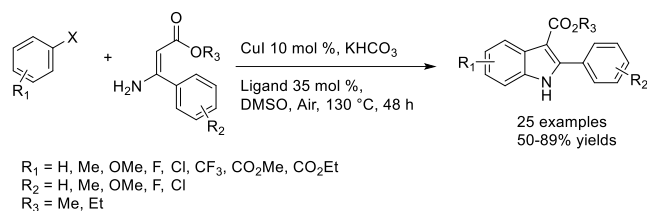


Figure 4. Possible mechanistic pathway

In 2018, Chen and coworkers have reported the synthesis of indole subunits via copper catalyzed tandem Ullmann type carbon-nitrogen cross-coupling followed by dehydrogenative carbon-carbon bond formation (Scheme 12). This protocol provides good yields of poly-substituted indoles form readily

available aryl iodides and enamines. Variety of *ortho*, *meta*, *para*, disubstituted and fused aryl iodides can reacts with enamines under this reaction condition. Furthermore, aryl bromides and aryl chlorides are also effective and provide good yields of the corresponding products. Aryl iodides having electron-donating and -withdrawing groups, such as  $-Me$ ,  $-OMe$ ,  $-F$ ,  $-Cl$ ,  $-CF_3$ ,  $-CO_2Et$ , and  $CO_2Me$ , also react smoothly. In addition, the *meta*-substituted aryl iodides produces two regio-isomers of the desired products indication that both the *ortho*-hydrogens are almost equally probable to undergo cross-dehydrogenative coupling reaction. On the other hand, different enamines can under reaction with aryl iodides. Enamines having substituents such as  $Me$ ,  $OMe$ ,  $F$ ,  $Cl$  on the aryl fragments are well tolerated under this method and provides good yields of the corresponding products. The authors have also proposed a mechanistic pathway for the reaction (Figure 5). At first, enamine reacts with copper iodide to give intermediate **1**, which then reacts with aryl iodide to produce intermediate **2**. The intermediate **2** then undergoes base mediated deprotonation to produce intermediate **3**, which after reductive elimination gives intermediate **4** and can regenerate the copper catalyst. The intermediate **4** thus formed can again reacts with copper catalyst to generate intermediate **5**. The intermediate **5** may undergoes deprotonation to give intermediate **6** and **7** and the later one can undergoes base promoted deprotonation to give intermediate **8** or **9**. The intermediate **8** or **9** may undergo reductive elimination to give the indole subunit and copper species **10**, which can reproduce the active catalyst after dehydrogenation.



Scheme 12. Copper catalyzed tandem carbon-nitrogen cross-coupling and dehydrogenative carbon-carbon cross coupling reactions for indole derivatives.

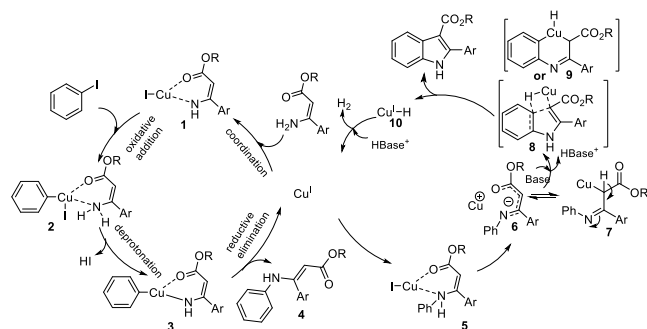


Figure 5. Plausible reaction mechanism for the tandem coupling reaction.

### III. CONCLUSIONS

In conclusion, this mini-review article has outlined a details of copper catalyzed synthesis of indole skeletons. As copper catalysts are readily available and cheaper compare to the other transition metal catalysts such as palladium and hence these methods are very important regarding synthetic view point. It is also very clear that there are plenty of opportunity to develop this field as only few different kinds of substrates are effective like 2-haloanilines and its derivatives and  $\beta$ -keto esters and amides are compatible in this cross-coupling strategy. Also copper catalyzed C-H activation methods will be very interesting as it eliminates the requirement of prefunctionalized starting materials like 2-haloanilines and hence will have broad substrate scope. Nevertheless, this mini-review will guide the researchers to contribute in this particular research area.

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