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Synthesis of Indole Moieties by Ruthenium Catalysts

Dr. Md Ashif Ali, Assistant Professor, Ramakrishna Mission Residential College (Autonomous)

Narendrapur, Kolkata, India, ashif.chem@gmail.com

Abstract This review article has been focused on the ruthenium-catalyzed synthesis of indole moieties. Indoles are very important heterocyclic compounds found in nature. Indole skeletons are present in natural products, drugs, perfumes, and many other materials of considerable importance. Hence 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 moieties. Recently, old methods have been replaced by transition metal-catalyzed coupling methods for indole synthesis. Transition metals such as palladium, copper, rhodium, ruthenium, iridium cobalt have been successfully used for indole synthesis via cross-coupling reactions. In this review, we will discuss the synthesis of indole skeletons using ruthenium-catalyzed reactions.

Keywords: **Organic chemistry, synthesis, ruthenium, catalysis, heterocycles, indoles.**

INTRODUCTION

Indoles are very common heterocyclic compounds found in nature. It is termed as a privileged heterocyclic compound due to its various utility and typical biological, pharmaceutical and therapeutic activity (Figure 1).[1-3] Indole moieties are used in different fields like drug industries, perfumes industries, materials science, and agrochemicals. Indole derivatives can also act as glucokinase activator, neurotransmitter, neuroprotective, antimigrain and anti-inflammatory drugs.[4-6] It's diverse biological activities are attributed to its high binding affinity with various receptors. Because of its utility in various fields, chemists are interested to synthesize indole moieties since decades.[7-9] The well known classical methods for the synthesis of indole skeletons are Fischer, Madelung, and Bischler indole synthesis (Figure 2).[9-11] These methods require stoichiometric reagents and harsh reaction conditions which are not environmentally benign. Furthermore, these stoichiometric methods produced lots of by-products and offers less yields of the targeted products. To overcome these disadvantages, stoichiometric methods have been replaced by transition-metal catalyzed catalytic methods which demand less harsh reaction conditions.[12] For examples, palladium, ruthenium, iridium, copper and nickel catalyzed methods are well established.[13-17] As a part of our research interest of transition-metal catalyzed synthesis of indole derivatives,[17] in this short review we will discuss the ruthenium catalyzed synthesis of indole skeletons.

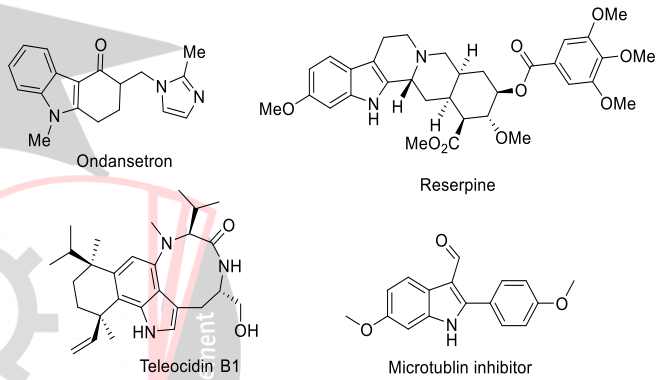


Figure 1. Bioactive indoles moieties.

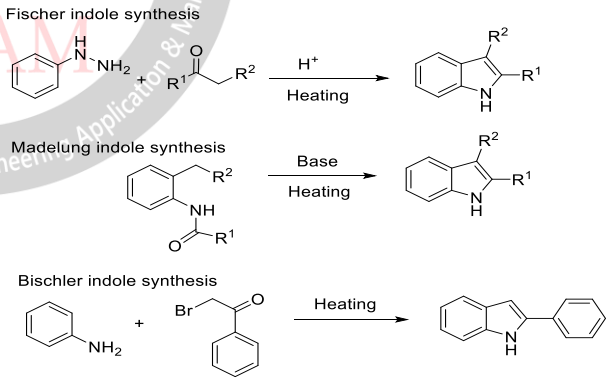
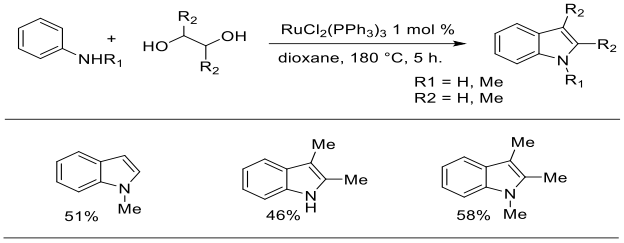


Figure 2. Classical methods for indole synthesis.

DISCUSSION

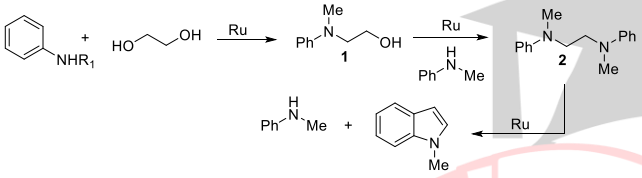
We start with the work of Watanabe and co-workers.[18,22] They have reported ruthenium catalyzed synthesis of indole with *N*-methyl aniline and ethylene glycol (Scheme 1). It was the first report of homogeneously catalyzed *N*-heterocyclization to construct indole ring. *N*-Methyl aniline reacted with ethylene glycol in the presence of catalytic amount of ruthenium catalyst in dioxane at 180 °C. The reaction worked well 2.5:1 molar ratio of *N*-methylaniline and ethylene glycol respectively and provided 51% of the desired *N*-methylindole. Increase or

decrease in amount of *N*-methylaniline provided less amount of the desired *N*-methyl indole. 2,3-Butanediol also can be used in place of ethylene glycol and it reacted well with both aniline and *N*-methylaniline to give the corresponding indole moieties.



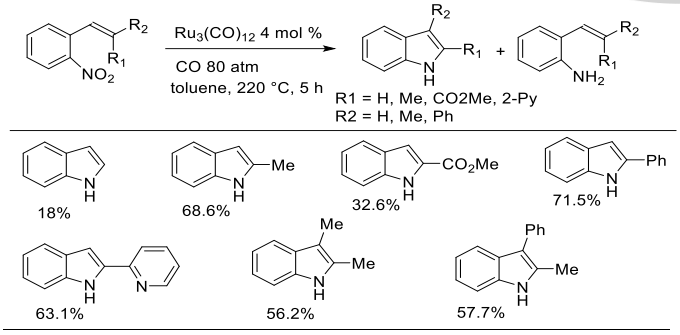
Scheme 1.

They have also established the mechanistic pathway of the transformation.[22] *N*-Methylaniline reacts with ethylene glycol in the presence of ruthenium catalyst to give 2-(N-methyl-N-phenylamino)ethanol (**1**). The compound **1** then reacts with *N*-methylaniline to give intermediate **2**. The intermediate **2**, then converts to the product in the presence of the catalyst (Scheme 2).



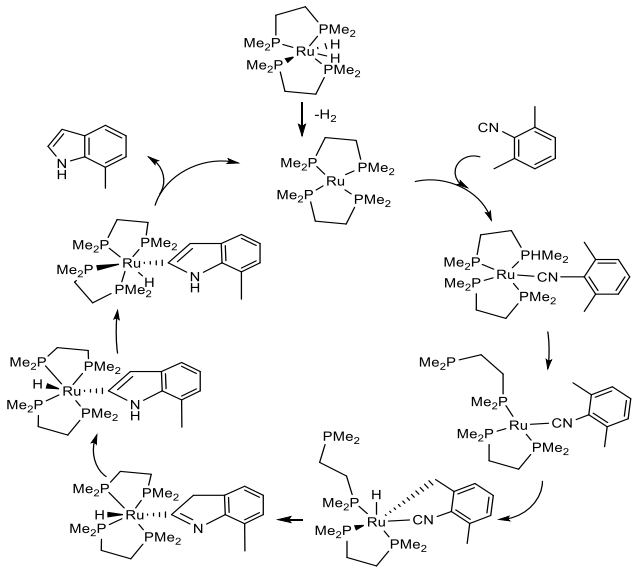
Scheme 2. Mechanistic pathway.

Deoxygenation of ortho-nitrostyrene with carbon monoxide and ruthenium carbonyl complex have been used by Cenini and co-workers to construct indole skeleton (Scheme 3).[19] The standard reaction condition required the use of 4 mol % of the $Ru_3(CO)_{12}$ catalyst in toluene at 220 °C for 5 h. The reaction proceeds via nitrene intermediate followed by niterene insertion and hydrogen migration. They have also observed that the phenyl group migrates preferentially over methyl group when no hydrogen is present. Along with the indole, reduced amines were formed as byproducts.



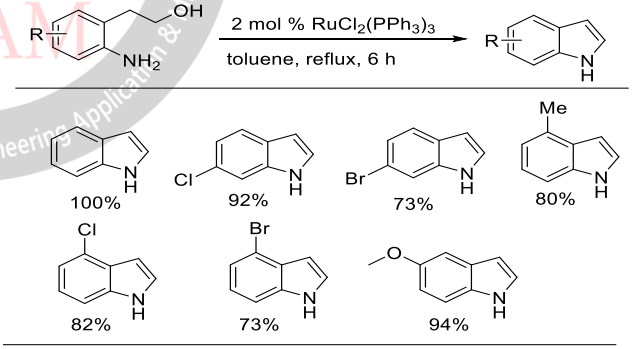
Scheme 3.

Jones and co-worker have used benzylic sp^3 C-H activation strategy to make indole skeleton under milder condition. They have used ruthenium 1,2-bis(dimethylphosphanyl)ethane based catalyst and 2,6-dimethylisocyanide as starting material. A detail reaction pathway have been outlined by the authors (Scheme 4). [20]



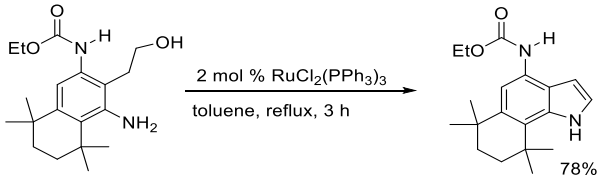
Scheme 4.

Tris(triphenylphosphine)ruthenium dichloride catalyzed synthesis of indole derivatives was developed by Watanabe and co-workers (Scheme 5).[21,23] 2-Aminophenethyl alcohol efficiently cyclized to give indole skeleton almost quantitatively in the presence of 2 mol % of ruthenium catalyst in toluene under reflux for five hours. The presence of triphenylphosphine ligand is very crucial for catalytic activity of the catalyst. The catalyst is ineffective in absence of any phosphine ligand and is moderately active (provides 45% of the desired product) in the presence of tributylphosphine ligand. Other 2-aminophenethyl alcohol derivatives having substituents such as methyl, chloro, bromo were also compatible and provided the desired products with very good yields.



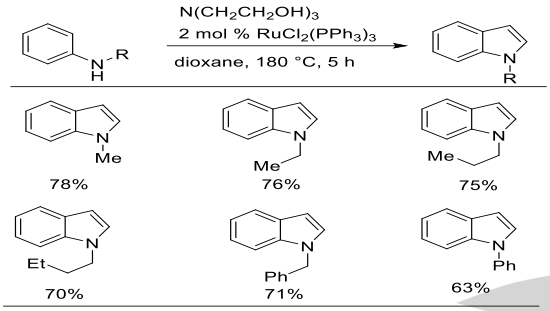
Scheme 5.

The above protocol was used by Webb and co-workers for the synthesis of tetramethyl substituted teleocidin analogue which are biologically active compounds (Scheme 6).[24] The reaction condition was compatible and provided good yield of the targeted tetramethyl substituted teleocidin intermediate.



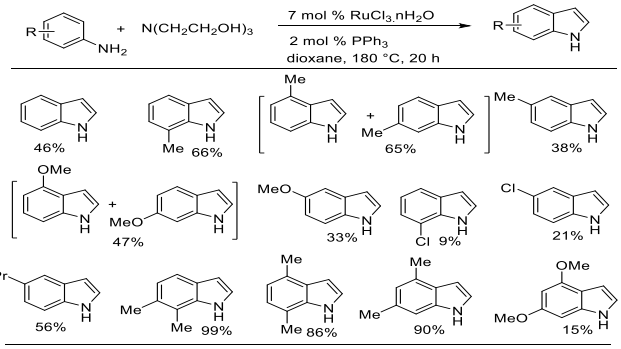
Scheme 6.

Triethanolamine was found to be efficient alkyl group transferring reagent in ruthenium catalyzed synthesis of indole skeleton (Scheme 7).[25] N-Alkylatedaniline reacted with triethanolamine in the presence of tris(triphenylphosphine)ruthenium chloride in dioxane at 180 °C for 5 h. The molar ratio of *N*-alkylatedaniline and triethanol amine is crucial for the reaction and best result was obtained with 10:1 molar ratio of *N*-alkylatedaniline and triethanolamine respectively. Other mono and diethanolamine provided less yield compared to triethanolamine. Simple aniline did not worked under these reaction conditions.

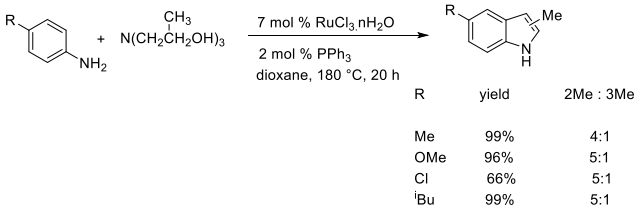


Scheme 7.

Indole moieties was synthesized using anilines and triethanolamine in the presence of catalytic amount(7 mol %) ruthenium chloride, triphenylphosphine (2 mol %) and tin (II) chloride (1 equiv) in dioxane at 180 °C for 20 h (Scheme 8).[26-27] A variety of substituted anilines underwent reaction to give the corresponding indole in good yields. For examples, *ortho*, *meta*, *para*-toluedine, *ortho* and *para*-anisidine, *ortho* and *para*-chloroaniline and disubstituted anilines. The chloro and methoxy substituted anilines provided less yield of the desired indoles compared to other methyl substituted anilines. Similarly, *para* substituted anilines reacted with tri(propen-2-ol)amine to give 2-methyl and 3-methyl substituted indoles in almost 5:1 molar ratio respectively favoring the 2-methylindole (Scheme 9).

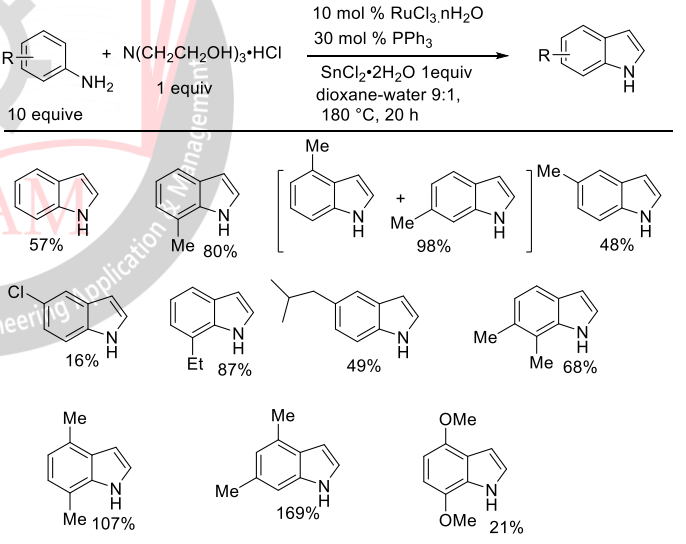


Scheme 8.



Scheme 9

Ruthenium catalyzed heteroannulation using the same catalytic (as Scheme 8) was reported using triethanolamine hydrochloride and anilines by the same group.[28-29] A little modification have been made in solvent system, and the best solvent system is the use of water and dioxane in 1:9 ratio. $SnCl_2{\cdot}2H_2O$ is essential to get good yield of the product. Without $SnCl_2{\cdot}2H_2O$ only 32% desired indole formed. Different ruthenium salts were found to be effective, for examples $RuCl_3{\cdot}nH_2O$/1.5dppm, $RuCl_3{\cdot}nH_2O$/3PPh_3, $RuCl_2(PPh_3)_3$, $Ru_3(CO)_{12}$, and $RuH_2(PPh_3)_4$ provide good yields but Cp*$RuCl_2$(CO) and Cp*$RuCl_2(PPh_3)$ catalysts were found to be ineffective. Under the standard reaction condition large number of anilines were converted to corresponding indole derivatives. The yield of the products were affected by the electronic nature and position of the substituents. For examples electron withdrawing substituent such as chlorine provided less yield whereas electron rich substituents give good yields. *Ortho*- and *meta*- substituted anilines give better yield compared to *para*-substituted one (Scheme 10). Diethanolaminehydrochloride salts were also effective as triethanolaminehydrochloride salts. Triisopropanolammonium chloride also worked well and provided exclusively 2-methylindole derivatives. A plausible reaction pathway was proposed based on the supportive reactions (Figure 3).[29]



Scheme 10.

At first hydroxyamine hydrochloride reacts with the catalyst to form **A**, which converts to **B** and then **B** converts to **C** by reacting with aniline. Likewise, **C** converts to *N*,*N*-diphenylethane-1,2-diamine in the presence of the catalyst. Then *N*,*N*-diphenylethane-1,2-diamine reacts with the ruthenium catalyst to give intermediate the intermediate **D**. Next, the intermediate **D** converts to ruthenium inserted intermediate **F** via intermediate **E**. Intermediate **E** undergo C-C bond formation to give intermediate **G** which gives the desired indole after removal of aniline.

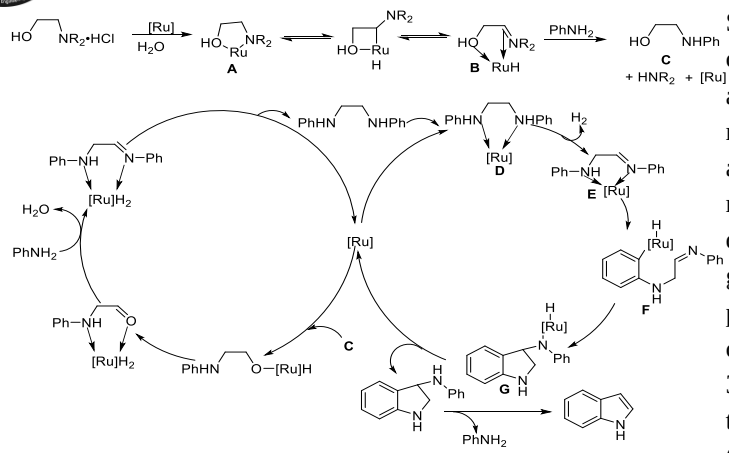
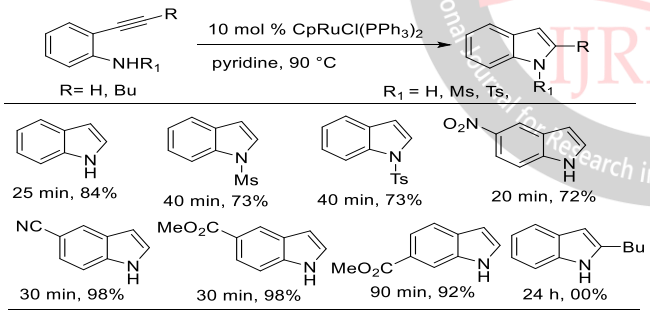


Figure 3.

Ruthenium catalyzed cycloisomerization strategy has been used to construct indole moieties from benzenealkynylamines (Scheme 11).[30-31] $CpRuClPPh_3$ Catalyst was found to be effective in pyridine to cycloisomerize 2-ethynylaniline to indole at 90 °C. Other solvent such as toluene, DMF, DCE, THF and water isopropanol mixture were also effective. Ruthenium catalyst such as $CpRuCl(PPh_3)_2/AgBF_4$, $CpRuCl(NCCH_3)_2PF_6$, CpRu(dppm)Cl and $Cp^*RuCl(PPh_3)_3$ were also active to catalyze the transformation. Different substituted 2-ethynylaniline having substituents such as NO_2, CN, and CO_2Me were suitable for ruthenium catalyzed cycloisomerization. Substitution of ethylene part stopped the product formation. A plausible mechanism of the transformation were proposed (Figure 4).



Scheme 11.

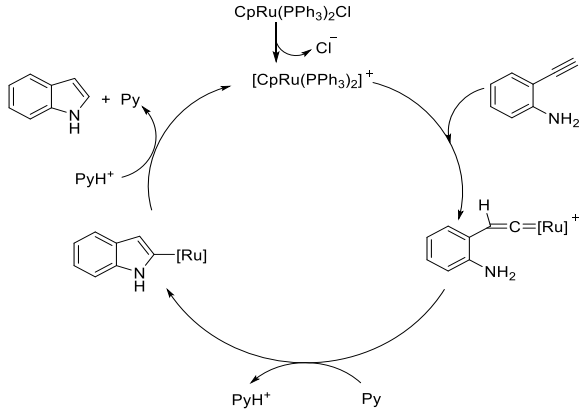
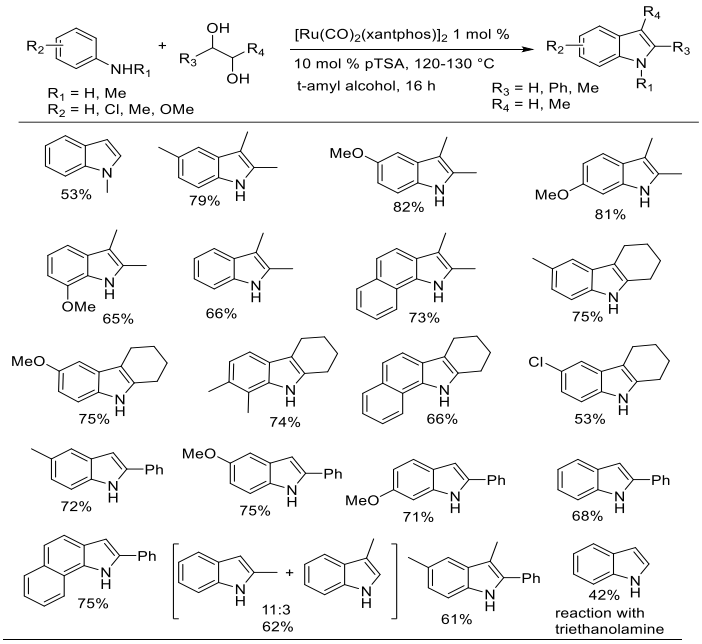


Figure 4.

Synthesis of indole skeletons were reported by cooperative catalysis of $[Ru(CO)_2(xantphos)]_2$ and p-TSA using anilines and vicinal diols.[32] The advantages of this particular method over previously reported methods are the use of less amount of catalyst and less reaction temperature. Electron rich substrates give better yields compared to electron deficient substrates and strongly electron withdrawing groups such as NO_2 and CF_3 failed to give the desired products. *Ortho*- substituted anilines give less yields compared to *meta*- and *para*-substituted anilines and 3-methoxy aniline provided only one regioisomer (reaction took place at the sterically less hindered position) eliminating the other regioisomer. Unsubstituted ethyleneglycol did not give any product with aniline but reacted with N-methylaniline. Similarly unsymmetrical vicinal diol were also tested and the results have been summarized in scheme 12. 1-Phenylethane-1,2-diol and 1-phenylpropane-1,2-diol were compatible under these reaction conditions and provided 2-phenylindole derivatives with good yields. Likewise, propane-1,2-diol afforded regioisomeric mixture of 2- and 3-methyl indole derivatives with good regioselectivity (11:3). Triethanol amine can also act as starting material instead of 1,2-diol but use of one equivalent of p-TSA is needed.



Scheme 12

CONCLUSION

In conclusion, in this mini review, we have outlined the synthesis of indole moieties using various ruthenium catalysts. Ruthenium catalysts are found to be effective for the catalytic conversion of different starting materials to indole skeletons. Like other transition metals, ruthenium catalyst are efficient and very less amount of catalysts are effective to get very high yield of indole derivatives. Although these methods provides variety of indole derivatives but only few specific types of ruthenium catalysts

have been reported. Most of the reported methods have similar types of substrates. For examples, only vicinal diols, alkynes and triethanol amines are effective source of C2-C3 fragments of indoles. Therefore, there are enormous scope for the development of this field of research. As for examples, only few ruthenium catalysts have been reported so far and hence there are scope to introduce other ruthenium catalysts as the literature of ruthenium complexes are very rich. Other types of starting materials for C2-C3 fragments other than vicinal diols, alkynes and triethanol amines should be tested. From the strategic point of view, the number of strategy to construct indole system are also less. Implication of ruthenium nanoparticles also will be a good improvement if possible because nano-catalysts are heterogeneous and could be recycled. Hence this review repot will be helpful for the researcher who are working in this research field.

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