Progress of Transition Metal Complex-Catalyzed Indole Hydrogen Borrowing Method

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Abstract: Accompanied by the in-depth study of hydrogen borrowing method, transition metal-catalyzed alkylation of indole C3 with N-H, which avoids the use of alkylating reagents by borrowing hydrogen activation from the substrate, is one of the hotspots of green chemistry research in recent years. The review mainly covers the literature published since 2015, which catalyzes the alkylation of indole C3 with N-H from metal complexes, removes one molecule of water, and completes the hydrogen borrowing. The Borrowed Hydrogen (BH) method is an excellent and widely recognized process without the need for a cumbersome separation process and only water is formed as a by-product.The BH approach is expected to replace the reaction using conventional alkylation reagents and give indoles (the special structure of the drug molecule) to have good reaction pathways in bonding at the C3 to N1 position and in building complex drug molecules.

Keywords: Indole-C3; Indole-N-H; Hydrogen Method; Drug Molecule

Introduction

The rise of green chemistry has attracted great attention to molecular bonding strategies in organic chemistry that avoid the use of mutagenic or toxic reagents [1-3], and hydrogen borrowing is one of the key focuses of green chemistry research in recent years, which eliminates the need for hazardous alkylating reagents in the alkylation of indoles at the C3 and N-H sites. Instead, the indole structure was chosen as a substrate for the hydrogen borrowing method due to the fact that the indole part is a special structure in medicinal chemistry. It is present in many natural alkaloids that show a wide range of biological activities as well as in pharmaceutical preparations [4-6]. Whereas traditionally indole alkylation is carried out with alkyl halides, this is not an ideal method because of its poor regioselectivity. Regioselective alkylation with indoles can be achieved in reactions with aldehydes, unsaturated ketones, and other reagents. However, most of these reactions require large amounts of acid and expensive reagents, give low yields even after prolonged reactions, and sometimes yield indole dimers. Therefore atom-economical methods for the synthesis of indole-containing compounds under mild conditions and the associated functionalization have been the focus of research by synthetic organic chemists, and so the use of atom-economical hydrogen-borrowing methods for indole C3-site reactions is a hot topic today. The hydrogen borrowing method starts with metal-catalyzed dehydrogenation and relies on three steps (Fig. 1): dehydrogenation, intermediate reaction and hydrogenation [7-8]. Through this dehydrogenation, usually less reactive donor molecules are temporarily converted into more reactive substrates (e.g., alkanes into olefins, alcohols into aldehydes, or ketones and amines into imines) [9]. The intermediates are converted to give unsaturated compounds, and the hydrogen in the donor molecules is stored by the catalytic metal fragments, which are released during the hydrogenation step to reduce to produce the final product.

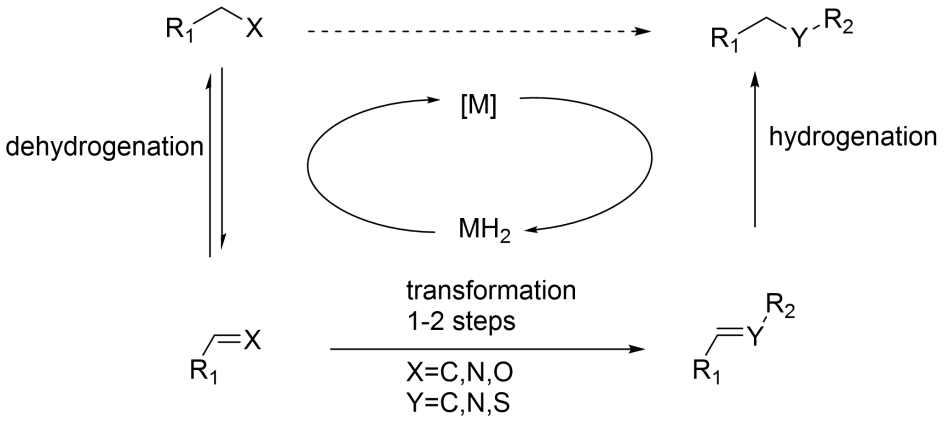

Fig. 1 Reaction Mechanism of Hydrogen Method

In most of the transition metal-catalyzed indole hydrogen borrowing reactions, alcohols are utilized as the substrate for the reaction to achieve C3 and N-H alkylation reactions with indoles to build complex molecules. Since alcohols are attractive electrophilic reagents for the interconversion of functional groups and water is the only stoichiometric by-product [10-11], this method is widely recognized. In addition to this, the catalytic systems borrowed for hydrogen catalysis involve metal complexes or stable metal particles [12-13]. For example, such metal complexes of ruthenium (Ru), iridium (Ir), and rhodium (Rh), and palladium (Pd) are typical homogeneous complexes and the resulting metal complexes are stable and highly reactive [14]. It provides an effective path for future research workers when constructing complex molecules using indole structures.

1.1 Iron complexes catalyze indole hydrogen borrowing alkylation reaction

In 2016, Singh's group [15] reported an efficient and simple one-pot, three-component reaction for the synthesis of indole C3-position products. The optimization of the reaction conditions of different alcohols aliphatic and aromatic alcohols by iron complexes revealed that aromatic alcohols proceeded well in the reaction under all conditions except aliphatic and unsaturated alcohols and the corresponding products were obtained. The reaction progressed well for both electron-donating and electron-absorbing groups, was simple and safe to operate in large-scale synthesis, and is an efficient method for the synthesis of compounds at the C3-position of indoles.In 2017, in the context of an iron complex catalyzed enabling hydrogen borrowing method Gregorio et al [16] reported a hydrogen borrowing method to synthesize the coupling of sterbenzyl and sec-benzyl alcohols to indoles (Fig. 1.1) for the first time, by an earth-rich iron complex catalyzed the generation of 3-benzylindole and water. This conversion accommodates a wide range of substrates, has higher yields (99%) relative to the method of Singh's group, is simpler to operate, is more sustainable, and is highly functional group tolerant.

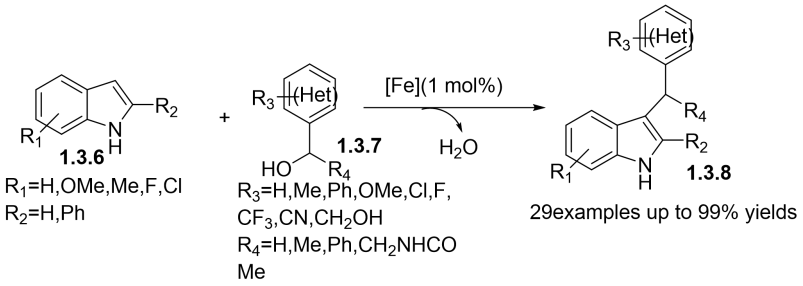

Fig. 1.1 Coupling Reaction of Primary Benzyl Alcohol and Secondary Benzyl Alcohol with Indole Catalyzed by Iron Complex

The methodology for the C3-position and N-alkylation of indoles catalyzed by iron complexes has been successively improved in the following years, among which in 2018, Seck et al[17]cyclopentadienone carbonyl iron complexes alkylated

indoles with various benzyl alcohols and fatty alcohols (butanol, ethanol, methanol, and 2-methylpentanol) by a self-hydrogen-transfer strategy in the presence of bifunctional iron complexes and bases under mild reaction conditions. This alkylation process provided high yields of indole C3-position compounds. Iron complexes have shown broad applicability under mild conditions, expanding the range of substrates for iron-catalyzed C-C bond formation, and in 2019, Dambatta et al[18]reported a versatile and efficient iron-catalyzed indole carbon-alkylation reaction. This hydrogen borrowing method employs (cyclopentadienone) carbonyl iron complexes (2 mol %) and has a wide range of reactions, allowing the use of phenyl and simple primary and secondary aliphatic alcohols as alkylating agents, with a wide range of indoles undergoing selective C3 alkylation.

1.2 Pt complex-catalyzed hydrogen borrowed alkylation of indoles

In 2015, Hakim Siddiki's team [19] developed the first catalytic method for the synthesis of indoles C3-position with N-alkylated products using hydrogen borrowing method with Pt/HBEA catalyst (Figure 1.2). Compared to previous homogeneous catalytic systems, this method has the following advantages: easy catalyst/product separation, reusable catalyst, mild and simple conditions, and no need for excess alcohols. It is an important discovery in the hydrogen borrowing method of synthesis.

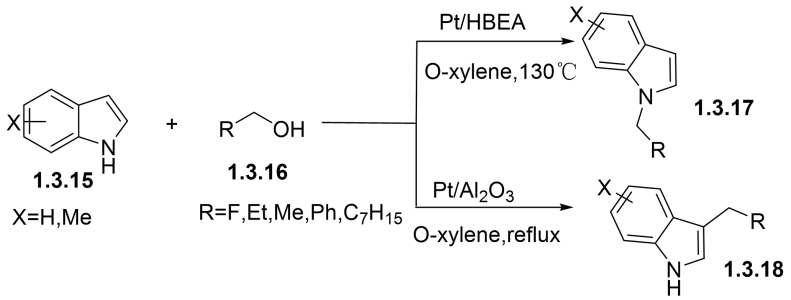

Fig.1.2 Pt/HBEA catalyzed synthesis of indole C3 position with N-alkylation product

HBEA

In 2018, Hakim Siddiki et al [20] reported a versatile, selective, and recyclable multiphase catalytic method (Fig. 1.3) for methylation of carbon-hydrogen bonds in alcohols, ketones, and indoles over Pt/C catalysts in the absence of oxygen and in the presence of sodium hydroxide. The reaction employs the hydrogen borrowing principle, starting with the dehydrogenation of ethanol to produce aldehydes, followed by condensation reactions with nucleophilic reagents (aldehydes, ketones, or indoles), and then hydrogenation of the condensation products by the Pt-H substance to produce the desired products. In the methylation reaction, the turnover rate of Pt/C catalyst was significantly higher than that of other homogeneous catalytic systems.

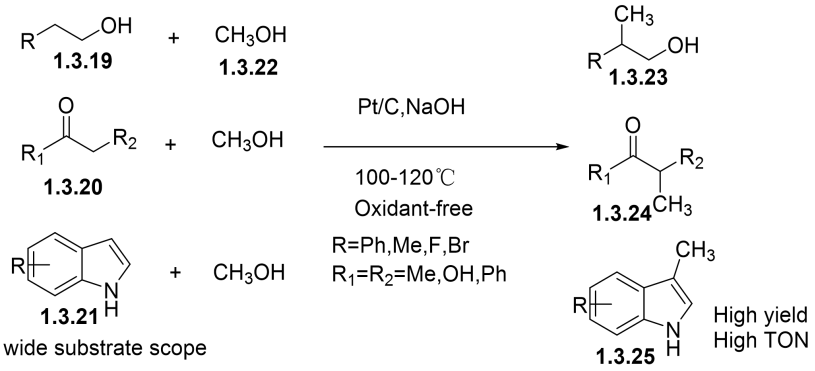

Fig. 1.3 Hydrogenation of Indoles, Alcohols and Ketones Catalyzed by Pt / C

1.3 Ir complex catalyzed indole hydrogen-borrowed alkylation reaction

In 2012, Wong's team [21] found that Ir(III) complexes catalyzed the intramolecular cyclization of indole derivatives at the C3 position (Figure 1.4), and that Ir(III) complex catalysts were the key factor in the efficient formation of C-N, C-C bonds, and that the formation of indoles proceeded via two reaction pathways of 2-(hydroxy-1-alkynyl)aniline substrates: hydroamidation and hydroalkoxylation Lewis acid-mediated isomerization. The method accomplishes intramolecular ring closure of indoles using hydrogen borrowing and possessed good yields (57-91%). It is an important reference in the hydrogen borrowing method of the ring closure reaction and the use of iridium complexes as catalysts can successfully realize the hydrogen borrowing method of the ring closure reaction.

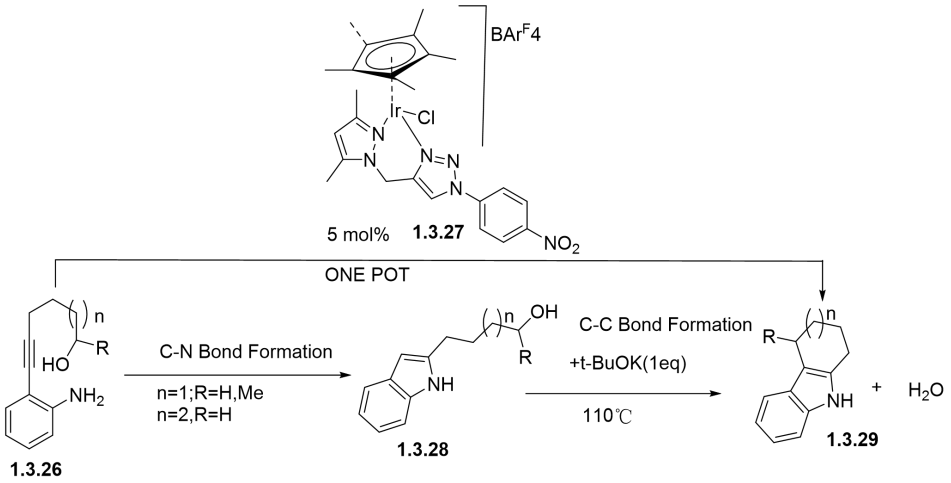

Fig. 1.4 Ir (III) Catalyzed Intramolecular Cyclization of Indole Derivatives at C3 Position

In 2015, Spadoni et al. [22] reported the direct synthesis of various functionalized acetylpropanamides via a modern "hydrogen borrowing" strategy (Fig. 1.5). The iridium-catalyzed alkylation of C3 indoles utilizes N-acetylethanolamine as a simple aminovinyl alkylating agent and hydrogen source, avoiding the use of external reducing agents. The experimental procedure for this metal-catalyzed direct alkylation reaction of indoles is simple, with only water as a by-product. This highly atom-economical and environmentally friendly process requires only inexpensive reagents, is tolerant to a range of functional compounds, and can be applied in natural product synthesis and medicinal chemistry.

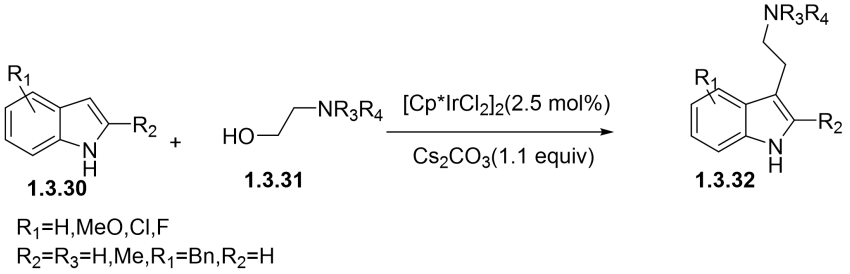

Fig. 1.5 Iridium Catalyzed Alkylation of C3 Indole

In 2015, Cai et al [23] reported the iridium complex-catalyzed methylation of indoles and pyrroles using methanol as a methylating agent (Fig. 1.6). This conversion was carried out by the hydrogen borrowing method, which constitutes a direct route to 3-methylindole and methylpyrrole. [Cp*IrCl2]2 was the catalyst with the best activity and selectivity. Yields increased sequentially with increasing catalyst content and methylation was accomplished in 90% yield even in air.

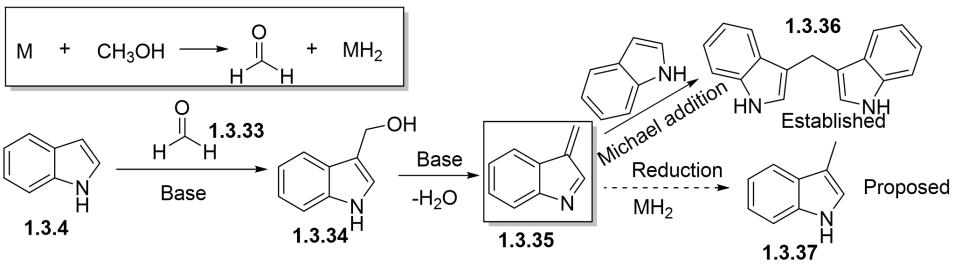

Fig. 1.6 Iridium Catalyzed C3 Alkylation of Indole and Pyrrole

In 2016, Bartolucci et al [24] reported the synthesis of tryptamine derivatives of indole at C3 position by hydrogen borrowing method using indole and 1,n-amino alcohols as starting materials (Fig. 1.7). This catalytic approach with amino alcohols as suitable electrophilic reagents allows the synthesis of branched and unbranched tryptophan, as well as tryptophan-based natural products. We have extended the selective indole alkylation reaction using [Cp*IrCl2]2-catalyzed hydrogen borrowing. The reaction has a broad substrate applicability. This catalyzed reaction occurs at the C3 position of the indole, and the amine portion of the structure reacts rapidly with the indole to obtain tryptophan derivatives.

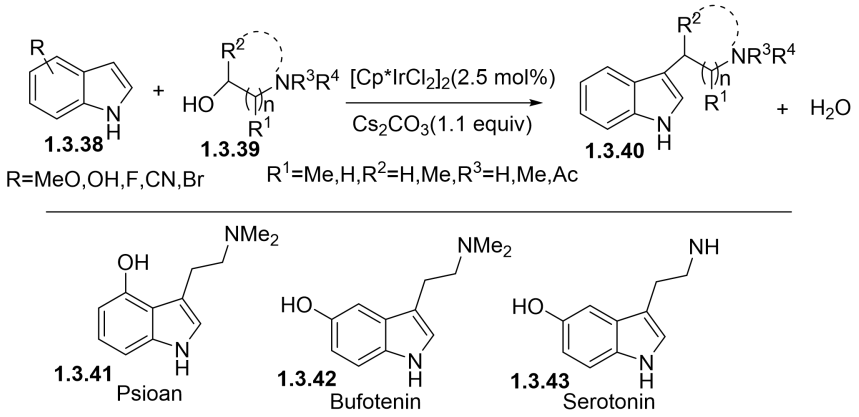

Fig. 1.7 Synthesis of Tryptamine Derivatives at C3 Position of Indole by Hydrogen Method

In 2017, Jiang et al [25] reported the study of iridium complex catalysts for selective dehydrogenation of N-alkylation and C3 alkylation of indoles (Fig. 1.8). The use of iridium complex catalysts plays a variety of roles in catalyzing the dehydrogenation reactions of amines and alcohols and subsequent coupling transformations. The catalyst catalyzed the hydrogen borrowing reaction of indoles and benzyl alcohols to give up to 93% yield of the product at the C3 position of the indole.

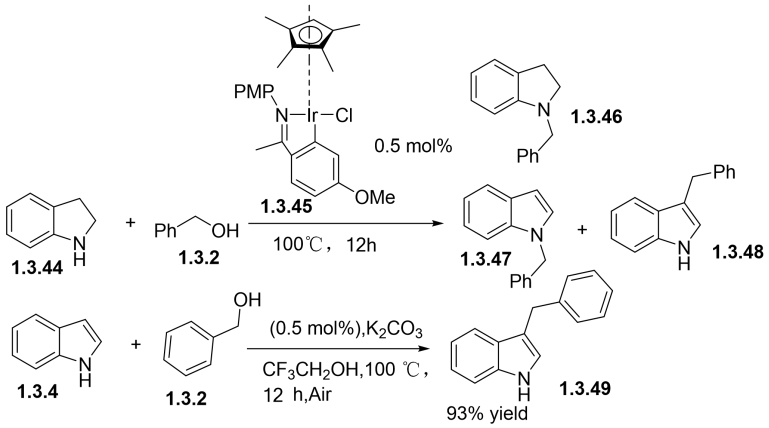

Fig. 1.8 N-alkylation and C3 Alkylation of Indole Catalyzed by Iridium Complex

In 2019, Chen et al [26] presented an iridium complex-catalyzed receptor-free dehydrogenation cross-coupling reaction of benzoylamines with indole derivatives (Fig. 1.9), which was able to synthesize a variety of quinoline-indole-linked bis-heterocyclopentadienyl products and obtain a variety of quinoline-indole-linked N-bis-heterocyclopentadienyl products in moderate to good yields. The reaction is carried out via a hydrogen borrowing strategy with readily available catalyst systems, good substrate and functional compatibility, mild conditions, high atomic efficiency, and no need for oxidizing and halogenated coupling agents. This provides an environmentally friendly way to directly obtain N-bisheterocyclopentadienyl systems, showing the potential for oxidant-free cross-coupling reactions and obtaining molecules with bioactivity and functional materials in high yields.

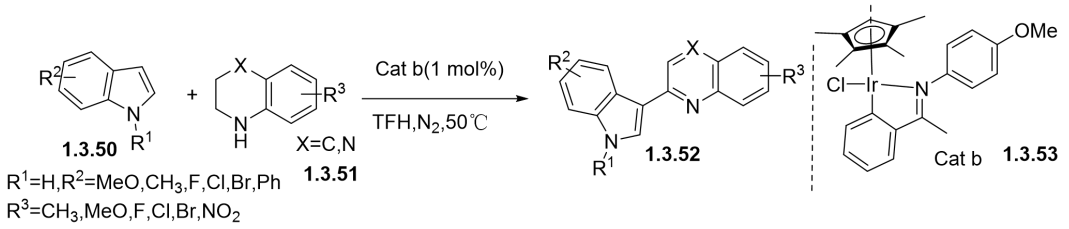

Fig. 1.9 Iridium Catalyzed Dehydrogenation of Benzoylamine with Indole Derivatives

1.4 Catalyzed Dehydroalkylation of Indole with Other Transition Metal Complexes

In 2015, Li et al [27] reported a simple and efficient ruthenium complex-catalyzed direct C3 alkylation reaction of indoles (Figure 1.10). This new hydrocarbon activation method demonstrated a wide range of substrates such as different substituted indoles, pyrroles, and other azoles were able to give the final indole C3-position product in high yields. Further synthesis of the alkylated products leads to more attractive tricyclic indoles. Direct C3 alkylation of C-H activated indoles with unsaturated ketones via ruthenium catalyzed C-H activation without the assistance of chelating groups. It was also possible to obtain indole C3-substituted compounds in high efficiency and yield.

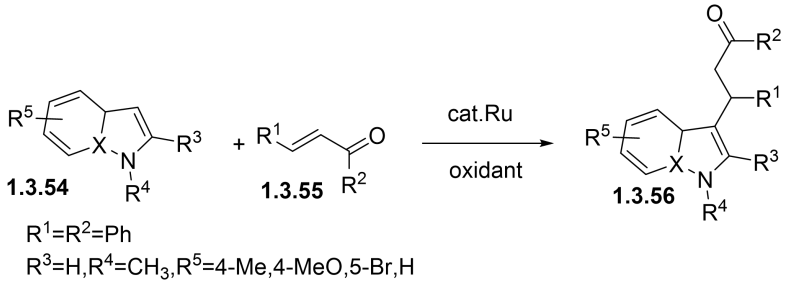

Fig. 1.10 Ruthenium Catalyzed Direct C3 Alkylation of Indole

In 2015, Sipocz et al [28] reported the direct alkylation reaction of indole C3 nucleophilic nature using hydrogen borrowing method (Fig. 1.11). The reaction was characterized by good yields. The complex transition metal catalyst was successfully replaced with an inexpensive multiphase nickel complex catalyst. The reaction was optimized for the ethylation of indole and further alkylation with primary alcohols to broaden the reaction scope.The transient protection of N atoms improved the selectivity and avoided the substitution of N atoms. The transient protection of the N atom improves the selectivity and avoids the substitution of N atom, which provides an effective idea for future researchers to apply other catalytic systems in hydrogen borrowing method.

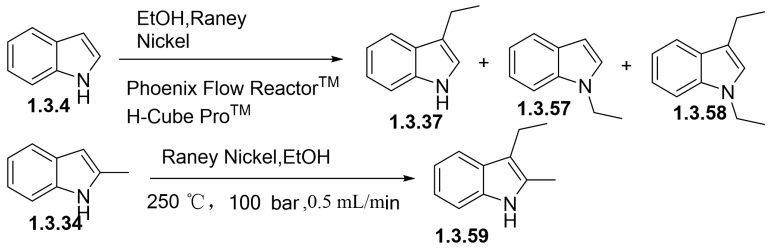

Fig.1.11 Nickel Catalyzed Direct C3 Alkylation of Indole

In 2019, Zou et al [29] reported a Foucault reaction in which indole derivatives were dehydroalkylated catalyzed by transition metal rhodium complexes (Fig. 1.12). The method involves metal-free 1,2-phosphorylation of indole C3-position methanol via phosphine oxides or phosphonates. This alternative has a broad substrate range, with acyclic methanone amides, methanone esters, 1,2-diphenyl ketones and compounds derived from diaryl ketones also participating in the reaction in moderate to excellent yields under mild conditions. Mechanistic studies showed that the reaction proceeds via the 1,2 addition pathway, in which the electron-withdrawing group near the hydroxyl group of the C3-indolylmethane alcohol plays a decisive role, and the final product is efficiently obtained via the hydrogen borrowing principle.

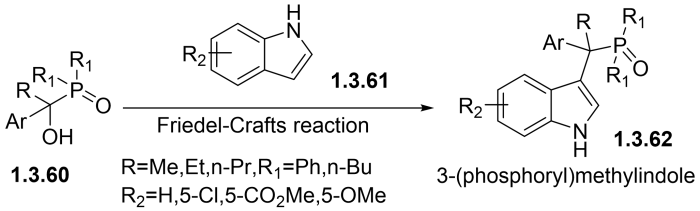

Fig.1.12 Rhodium Catalyzed Dehydroalkylation of Indole Derivatives

In 2017, Bisht et al [30] reported a Ru-NHC-catalyzed aminolysis reaction with good air stability (Fig. 1.13). The final product was synthesized from 2-indole and tert-butanol under ruthenium complex-catalyzed conditions using hydrogen borrowing method in a one-pot reaction. The reaction takes place in air and the product can be converted to hydrocarbon alkylation or hydrocarbon hydroxyalkylation, forming the C3 alkylation product 3-hydroxyindolin-2-one by alkylation and hydroxylation. This ruthenium complex catalyst is readily available, air stable, atomically economical. And key intermediates of indole natural products and alkaloids were synthesized in good yields.

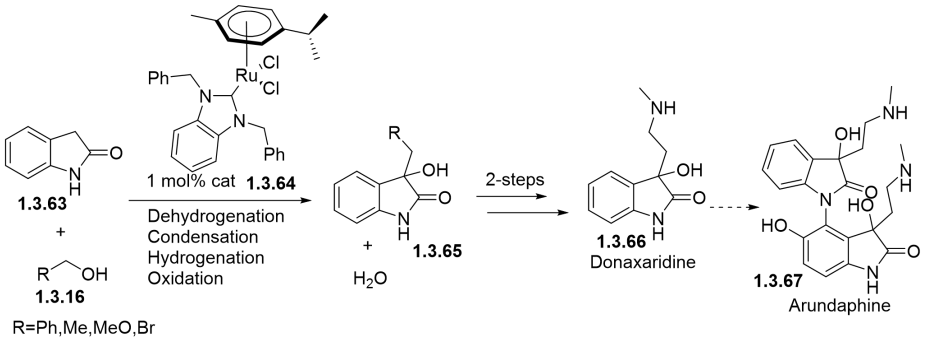

Fig.1.13 Ruthenium Catalyzed C3 Alkylation of Indole

2. Indole N-Alkylation Reaction

Similar to indole C3 alkylation, the product of indole core N-alkylation is one of the most prevalent structures found in bioactive natural products and drug molecules. Substituted indoles have been preferred structures in the creation of new potential drugs because of their high affinity for many biological targets. Therefore, great efforts have been made in the preparation and direct functionalization of indoles. However, direct nitrogen alkylation of indoles remains challenging

because indole nitrogen atoms are inert to electrophilic reagents, despite the structurally novel and attractive biological activities of nitrogen alkylated indoles. Indole N-alkylation has been less studied in hydrogen borrowing method, in which transition metal-catalyzed indole N-alkylation reaction is still on the rise in recent years, so there is still a promising application in the study of indole N-alkylation reaction.

2.1 Pd complex-catalyzed indole alkylation by hydrogen borrowing

In 2017, Li et al [31] described a palladium-catalyzed formal aromatic transfer coupling reaction (Figure 1.14) between phenolic compounds and pyrrolidines or indoles to produce the corresponding N-cyclohexylpyrroles or indoles. During this conversion, the aromaticity of the phenolic compound is formally transferred to the pyrrolidine or indoline structural unit. This method can be used for the rapid construction of a variety of N-cyclohexylpyrroles and indoles, atomically economical and under mild conditions. Final products were obtained in moderate to excellent yields.

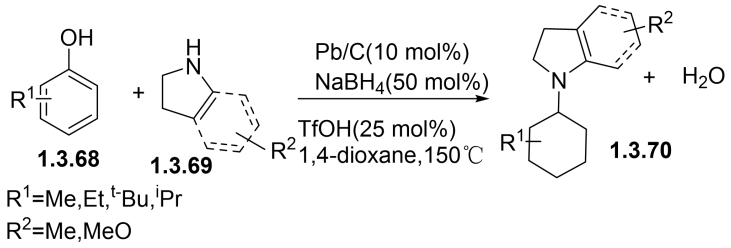

Fig.1.14 Palladium Catalyzed Aromatic Transfer Coupling Reaction of Indoles

In 2019, Wang et al [32] reported that N-alkylation of indoles is one of the important routes to construct various biologically active indole molecules. The use of ketones as reagents for indole N-alkylation is a great challenge. The reaction is resistant to various functional groups and other heterocyclic compounds and is a new strategy for de-aromatization and re-aromatization. N-alkylated indoles were generated from N- H indoles and ketones under palladium catalysis (Figure 1.15). The method successfully improved the nitrophilicity of the indole by de-aromatization and avoided the competitive alkylation reaction at the C3 position of the indole. A high degree of chemoselectivity was also shown in the reaction system: various functional groups, including acids, esters, alcohols, phenols, ethers, and heterocyclic compounds were able to generate N-sec-alkyl derivatives in moderate to excellent yields.

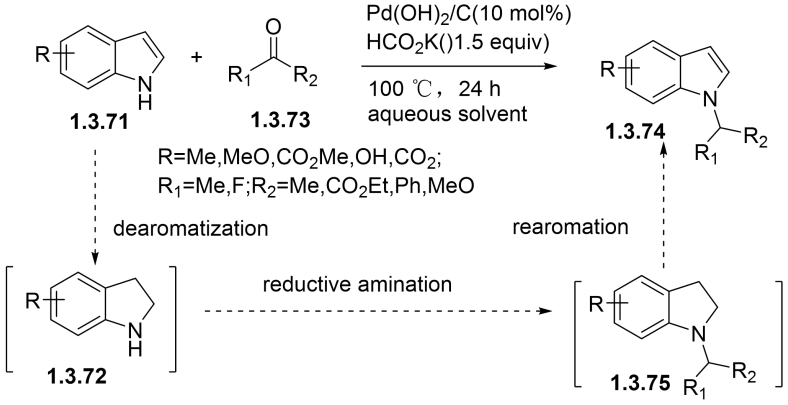

Fig.1.15 Direct N-alkylation of Dope Catalyzed by Palladium

In 2020, Chen et al [33] reported a new catalytic system for naphthol transfer hydrogenation of indole with 2-naphthol using hydrogen transfer mediated activation (Fig. 1.16), and indole can be used as an ideal hydrogen donor for the alkylation reaction under palladium catalysis.Pd/C catalysts and bases were used to react a variety of naphthols with indoles to generate N-aryl substituted heterocyclic compounds, where the indolines acted as a novel hydrogen donors. The highest yield (76%) was obtained with NaOCH3 and Pd/C and xylene as solvents.

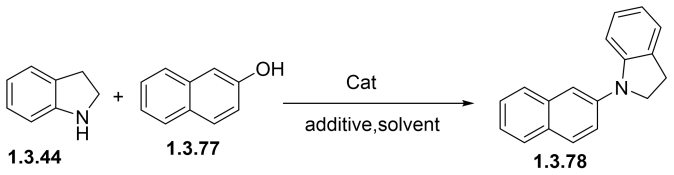

Fig.1.16 Pd / C Catalyzed Direct N-alkylation of Indole

2.2 Cu complex-catalyzed hydrogen borrowing alkylation of indole

In 2017, Ling et al [34] described a new method for the direct N-alkylation of indoles, i.e., the reductive cross-coupling of hydrazones with indole reagents catalyzed by KOH and a certain amount of CuI and tris(p-toluene)phosphine, to obtain a variety of N-alkylated indoles in moderate to good yields (Fig. 1.17). It was also demonstrated that the existing method possesses good substrate universality in the synthesis of biologically active N-alkylated indole derivatives. The starting materials for this method are readily available as hydrazones are easily prepared from the corresponding aldehydes or ketones. In addition, the N-alkylated indole aspect has potential applications that are biologically important in organic synthesis.

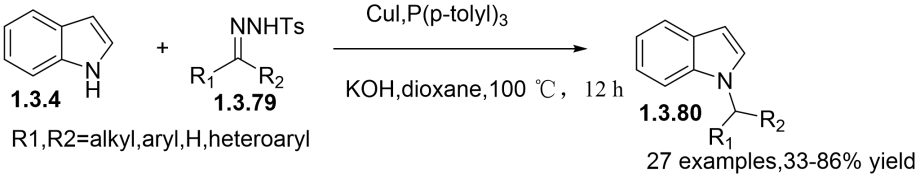

Fig. 1.17 CuI Catalyzed Direct N-alkylation of Indole

3. Summary and Outlook

In the above literature, we have summarized the BH strategies for the synthesis of C3, N-H alkylated indole compounds in recent years. The emergence of a series of new catalytic systems has transformed indole into a versatile reagent for a variety of syntheses. In addition, complexes based on iron or other catalysts [35-38] (e.g., iridium, ruthenium, platinum, and palladium) are used for such reactions. A few examples of reactions using specific ionic liquids or solid-loaded catalysts are available, but further research is needed, including a wider range of substrates and milder reaction conditions.

The metal hydrides that may be formed during hydrogen activation in the reaction are too stable to readily release activated hydrogen and are therefore inactive for BH methodology. Considering that the intermediate reaction step of the hydrogen borrowing method is a common organic reaction involving dehydrogenated substrates (e.g., aldehydes), the involvement of a metal at this point is not absolutely necessary, although this assumption may not always hold true since the electrophilic metal component of the catalyst can increase the electrophilic nature of the C-O bond and thus improve its reactivity. Therefore studying the metal-free catalyzed alkylation reaction of indoles may become a focus of future research.

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