Indole synthesis through transition metal-catalyzed C–H activation

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Indole synthesis is among one of the most important tasks in N-heterocyclic chemistry. Versatile synthetic methods have been developed for the establishment of an indole backbone, but concise and straightforward routes to access indole derivatives have been strongly desired. This digest paper summarizes the major advances in catalytic synthesis of indoles through transition-metal-catalyzed C–H activation during the last five years. Brief discussions are given for possible applications of these synthetic protocols.

Introduction

Indole functionality exists in many natural products and pharmaceuticals. A lot of efforts have been devoted to develop synthetic methods to access diverse indoles since Fisher indoles were prepared in 1883. Although indole derivatives can be obtained by functionalizing simple indoles, specific methodologies have to be established to synthesize various indoles. Transition-metal-catalyzed cross-couplings involving C–H activation have recently been paid considerable attention for the construction of C–C and C–N bonds. For the synthesis of indole derivatives, C–H activation has been considered as an alternative strategy to supplement the relevant traditional synthetic protocols. Åkermark and Knölker reported the first examples of palladium-catalyzed oxidative intramolecular C–H/C–H cross-coupling of ArXAr (X = O, N) to synthesize carbazoles and dibenzofurans, respectively, which initiated the investigation on transition-metal-catalyzed C–H activation during the last five years in transition-metal-catalyzed indole synthesis.
synthesis through C–H activation, usually under oxidative conditions, are summarized with brief discussion of their possible applications. This digest is presented by the classifications of reaction types.

**Intramolecular C–H/C–H cross-couplings**

The intramolecular CDC reactions have been applied as a powerful tool to access functionalized indoles. Glorius et al. reported palladium(II)-catalyzed, copper(II)-mediated cyclization of enamine methyl (Z)-3-phenyl(aminobut-2-enoate and its analogues to form indoles (Scheme 1).8 A proposed mechanism suggests that the reaction begins with an electrophilic palladation of the nucleophilic enamine at α-C atom, followed by deprotonation, resulting in a palladium complex intermediate suitable for intramolecular C–H activation. Subsequent reductive elimination generates the indole product and a Pd(0) species which can be reoxidized to the Pd(II) complex by the terminal oxidant Cu(OAc)2.8a With similar substrates by means of 10 mol % FeCl3/1.5 equiv Cu(OAc)2/CuCl2/K2CO3/DMF as the catalytic system, Liang et al. prepared the same types of indole products.9 In the presence of PdCl2/Cu(OAc)2/TFA/CH3CN, 1,3-disubstituted indoles were synthesized through the cyclization of N-alkyl aryl tertiary enamines.10 For these transformations, solvents were found to play an important role.11

Multisubstituted indoles were also prepared from N-aryl enamines through C–H activation under copper catalysis. With 5 mol % CuI as the catalyst and 35 mol % 1,10-phenanthroline as the ligand in the presence of a base such as Li2CO3 (2 equiv), intramolecular oxidative C–H/C–H cross-coupling of N-aryl enamines occurred in N,N-dimethylformamide (DMF) to afford the corresponding indole products in up to 83% yields (Scheme 2).12 In this case, air acted as the effective terminal oxidant, featuring a monometallic catalyst system.

Due to the possible tautomerization of imines to enamines, N-aryl imines were rendered to undergo intramolecular CDC reactions to form indoles, providing a new route to indoles from anilines and ketones (Scheme 3).13 A KIE of 5.2 was obtained for the aromatic C–H of the N–Ar moiety, which is of a similar magnitude to those commonly observed in palladium-catalyzed aromatic C–H functionalization involving a concerted metatation–deprotonation mechanism. Two-fold oxidative cyclizations also occurred to give the fused indoles or bis(indolyl)benzene (Scheme 4).
The one-pot oxidative condensation of aniline and ketone was also realized by means of the Pd(OAc)$_2$/Cu(OAc)$_2$ catalyst system. Thus, $p$-anisidine reacted with acetone and ethyl pyruvate to afford the corresponding indoles derivatives (Scheme 5), while only trace amount of the target products was observed with the Pd(OAc)$_2$/O$_2$ system. A copper(II)-mediated indole synthesis has recently been documented by means of $\alpha$-oxo ketene N,S-acetals as the substrates and CuCl$_2$ as the mediator (Scheme 6)\textsuperscript{14}. The presence of a thioalkyl was crucial for the intramolecular dehydrogenative C–H/C–H coupling to form an indole core. Such a thioalkyl can be rendered diverse transformations that this method provides a concise route to access highly functionalized indole derivatives.

It is noted that iridium(I)-induced, visible light-driven intramolecular C–H functionalization of tertiary amines, metal-free iodine-catalyzed,\textsuperscript{16} and PhI(OAc)$_2$-mediated\textsuperscript{17} cyclizations of $N$-aryl enamines were achieved for indole synthesis, and Larock-type $m$-iodoaryl substituted anilines could also be employed to prepare vinyl indoles in the presence of an alkyne under palladium catalysis.\textsuperscript{18}

### Annulation of anilides (anilines) with alkynes

#### Annulation of aryldiamides (anilines) with alkynes

Fagnou and co-workers first reported indole synthesis via rhodium-catalyzed oxidative coupling of acetanilides and internal alkynes (Scheme 7).\textsuperscript{19a} With [Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ as the precatalyst under atmospheric oxygen the same reactions could be conducted at 60°C to achieve up to 90% yield for the target indole products.\textsuperscript{19b} Using enynes as the functionalized alkyne substrates, 2-alkenylindoles were constructed in a similar fashion (Scheme 8).\textsuperscript{19c} In the presence of 5 mol % Pd/C catalyst, the 2-alkenylindoles were efficiently reduced to the corresponding 2-alkylindoles by 1 atm H$_2$, and the dimethylurea protecting group could be removed by saturated aqueous potassium hydroxide in ethanol. Under Rh(III) catalysis, the urea-protected aniline reacted with an alkynyl MIDA (N-methyliminodiacetic acid) boronate to form an indole MIDA boronate, which was transformed to the corresponding indole in a reasonable yield (Scheme 9).\textsuperscript{20}

The Rh(III)-catalyzed reaction of $N$-tolyl trans-crotyl-amide with an alkyne also gave the indole product.\textsuperscript{21} It is noteworthy that...
the cyclization of an aniline with alkenes such as allyl carbonates can also be used to synthesize indole derivatives (Scheme 10).

Annulation of anilines with alkenes

\[ \text{N-Unprotected anilines reacted with functionalized alkenes to form 2,3-disubstituted indoles in up to 99\% yields by means of 10 mol \% Pd(OAc)\textsubscript{2} as the catalyst and dioxygen as the oxidant (Scheme 1).} \]

A mixture of DMA and PivOH (4:1) as the solvent can be readily removed under basic conditions, demonstrating a useful method to access bioactive indoles (Scheme 1). Visible light-driven gold catalysis was also used for the same purpose. Annulation of arylhydrazines and related compounds with alkenes (Scheme 1).

Annulation of aryldiazines and related compounds with alkenes

Through a mechanism different from that for Fischer indole synthesis, Glorius et al. developed a Ru(II)-catalyzed hydrazine-directed C–H activation protocol for the synthesis of indoles. Acetic acid promoted the reaction as an additive. The three-component reaction of aryldiazine, C=O compound, and alkyne was also utilized to synthesize N-unprotected indoles under Ru(II) catalysis by in situ condensation of aryldiazine with the C=O source to form an hydrazone intermediate (Scheme 1).

Rh(III)-catalyzed denitrogenative annulation of N-sulfonyl-1,2,3-(hetero)A

\[ \text{N-aryl-} \text{N}-\text{nitriles were efficiently transformed into (hetero)A through N–N bond cleavage indole derivatives were efficiently prepared.} \]

The broad scope of substrates was well tolerated to construct unprotected indoles with excellent regioselectivity. An efficient Cu/Rh-catalyzed method was developed to synthesize substituted 3-indolylinelines and indole-3-carboxaldehydes from N-propargylinelines through Rh(II)-catalyzed denitrogenative annulation of N-sulfonyl-1,2,3-
Further hydrolysis or reduction of the imine intermediates afforded the corresponding aldehyde products.

**Cyclization of o-alkynylanilines**

Palladium-catalyzed coupling of ortho-alkynylanilines with terminal alkynes or alkenes gave 3-alkynyl- or 3-alkenylindoles. The reaction media and atmosphere played an important role in the reaction efficiency. 2,3-Disubstituted 3-alkynylindoles were thus obtained in moderate to excellent yields (Scheme 21). With a diene as the coupling partner, rhodium- and platinum-catalyzed [4+3] cycloaddition of o-alkynylanilines underwent with concomitant indole annulation to afford cyclohept[b]indoles (Scheme 23).

Furans participated in the reactions to afford tetracyclic indole derivatives in moderate to good yields. 3-Aroylindoles were constructed by copper-catalyzed oxidative cyclization of o-(1-alkynyl)N,N-dimethylamines via a sp³ C–H activation α to the nitrogen atom (Scheme 24). In the overall reaction, tert-butyl hydroperoxide (TBHP) acted as the oxidant. The combination of 10 mol % PdBr₂/10 mol % Cul/LiCl (2 equiv)/TBHP also enabled the same reactions in toluene at 100 °C. Variation of the reaction parameters made the reactions of o-alkynylanilines with internal alkynes yield carbazole derivatives (Scheme 25).

Palladium(II)-catalyzed oxidative intramolecular diamination of internal diarylalkynes afforded indolo[3,2-c]iso-quinolinones (Scheme 26). This protocol combined the cyclization of o-(1-alkynyl)benzamides and the Cacchi indole synthesis under oxidative conditions. In a similar fashion, rhodium(III)-catalyzed intramolecular annulation of rhodium- and platinum-catalyzed [4+3] cycloaddition of o-alkynylanilines underwent with concomitant indole annulation to afford cyclohept[b]indoles (Scheme 23).
alkyne-tethered acetonilides proceeded to give fused tricyclic indoles (Scheme 27). It is noted that under reductive conditions, nitroaromatics and nitrosamines can be used as the precursors to acetonilides for annulation with alkynes to form indoles.

C–H amination of aryl and alkenyl azides

Aryl and alkenyl azides were used as the starting substrates to construct indoles with release of nitrogen gas. FeBr2-catalyzed intramolecular C–H amination/[1,2]-shift tandem reactions of aryl azides afforded 2,3-disubstituted indoles (Scheme 28). The preference for the 1,2-shift component of the tandem reaction was established to be Me < 1’ < 2’ < Ph. Similar reactions occurred from β-nitro styryl azides under rhodium(III) catalysis, undergoing nitro-group migration to give 3-nitroindoles (Scheme 29). Using other β-electron-withdrawing group-substituted styryl azides as the substrates led to the same type of indole products. Rhodium carboxylate complexes catalyzed cascade reactions of β,β-disubstituted styryl azides to produce 2,3-disubstituted indoles. Thus, polycyclic complex functionalized N-heterocycles were constructed (Scheme 30). A one-pot CuI-catalyzed S,NAr reaction of α-bromochalcones with sodium azide and subsequent intramolecular cyclization through nitrene C–H insertion produced 2-carbonyl substituted indoles. Azidoaarylates also underwent the similar intramolecular C–H amination by means of Fe(OTf)2 as the catalyst (Scheme 31).

Cyclization of aryl isocyanides

Copper(I)-catalyzed borylative cyclization of 2-alkenyl-aryl isocyanides using diboronate B2pin2 was realized to prepare 2-borylindoles which can be applied as versatile intermediates in organic synthesis (Scheme 32). The reactions proceeded at ambient temperature under neutral conditions and showed high tolerance to functional groups, such as Br, CO2R, COR, CONMe2, and CN. A palladium-catalyzed tandem process consisting of β,β-disubstituted styryl azides to produce 2,3-disubstituted indoles. Thus, polycyclic complex functionalized N-heterocycles were constructed (Scheme 33). A bulky phosphine ligand is necessary for the reaction to smoothly occur.

Intramolecular C–H/C-halo cross-coupling

Transition-metal-catalyzed tandem C–H alkynylation and amination provides a convenient route to polycyclic aromatic compounds. Intramolecular C–H/C-halo cross-coupling has recently become a common method to access an indole core. Niobium-catalyzed C(sp3)-H insertion to an in situ generated fluorine-substituted carbene intermediate gave N-fused indoles (Scheme 34). Multi-component reactions were also employed to synthesize indole derivatives by dual palladium-catalyzed coupling reactions (Scheme 35).

Versatile synthesis of indoles involving C–H activation

2-Chloro-N-(2-vinyl)anilines underwent oxidative cyclization to produce indole products in good to excellent yields (Scheme 36).

while the C–H/C-Cl cross-coupling occurred under basic conditions. Acetonilides reacted with allyl acetates to afford N-Ac indoles under Rh(III) catalysis. Heterogenous ceria-supported ruthenium catalysts effected the synthesis of indole (>99%) via dehydrogenative N-heterocyclization (Scheme 37). An iron(II)-catalyzed C–H amination via ring opening of 2H-azirines efficiently formed 2,3-disubstituted indoles (Scheme 38). Rh(II)-catalyzed cyclization of 2-acety1-1-arylhydrazines with diazo compounds via C–H activation was developed to prepare 1-aminoindoles (Scheme 39).

Conclusions and perspectives

The present results summarize and highlight the recent major advances in the synthesis of indoles through processes involving transition-metal-catalyzed C–H bond activation. Development of concise and straightforward synthetic approaches to construct
indoles has been the challenging task for organic chemists. Transition-metal-catalyzed dehydrogenation C–H/C–H and C–H/N/H coup-lings are among the most concise and straightforward routes to indole motifs although preparation of the starting substrates is not so easy in some cases. In a view of application, one-pot protocols are desired to produce highly functionalized or function-alizable indole derivatives, and the relevant metal-free synthetic methodologies should also be paid considerable attention in this area.

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References and notes