Indole Synthesis

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Efficient and Versatile Synthesis of Indoles from Enamines and Imines by Cross-Dehydrogenative Coupling**

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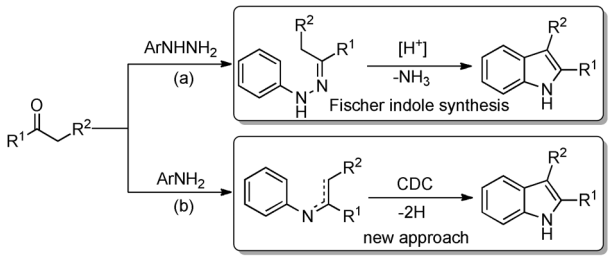
C–H activation · dioxygen · enamines · imines · indoles

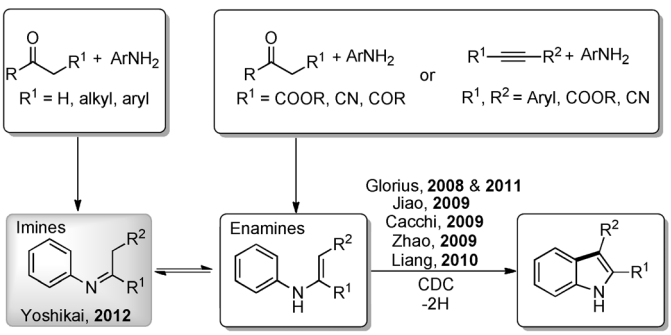
The indole unit is one of the most abundant and relevant heterocycles in natural products and pharmaceuticals. The synthesis of indoles has been a topic of research for over 100 years, and a variety of well-established classical methods are now available. The venerable Fischer indole synthesis, discovered in 1883, remains one of the most powerful and versatile routes to the indole heterocycle, although this method suffers from several drawbacks.[1] A variety of synthetic modifications have been introduced to increase the practicality and lessen the environmental impact of the Fischer cyclization such as using mild acids, reusable catalysts, and ionic liquids.[2] However, it is important to note that hydrazines are carcinogenic and that certain hydrazines are difficult to prepare, are unstable, or display only moderate functional-group tolerance under acidic conditions (Scheme 1 a).



Scheme 1. a) The Fischer indole synthesis and b) the new CDC approach to indole synthesis.

Safe, straightforward protocols for indole synthesis that deliver excellent yields are always in demand by organic chemists. Utilizing the same disconnection as the Fischer indole synthesis, but instead of hydrazines the more readily available imines and enamines (prepared by condensation of anilines and ketones) by means of cross-dehydrogenative coupling (CDC)[3] would be very attractive (Scheme 1 b). The origin of this novel transformation can be traced back to indolequinone or carbazole synthesis through the electrophilic aromatic palladation of electron-rich aniline substrates under acidic conditions, developed by the groups of Åkermark and Knölker.[4] However, the limited scope of these reactions, the frequent requirement of stoichiometric quantities of the palladium complex, and the low yields often observed limit the usefulness of these methods.

In analogy to keto–enol tautomerism, imines are in equilibrium with the corresponding enamines. The interconversion of enamines and imines is called imine–enamine tautomerism, where the equilibrium position is usually mainly located on the imine side. However, the enamine form can be stabilized by conjugation with an electron-withdrawing group. In 2008, Glorius et al. developed a palladium(II)-catalyzed oxidative cyclization of such stabilized *N*-aryl enamines. The mechanism starts with the attack of the enamine onto the Pd^{2+} catalyst (electrophilic substitution) and proceeds with an intramolecular C–H activation of the aniline ring, affording the corresponding indoles.[5] Unfortunately, this method required the use of stabilized enamine substrates (R^2 = EWG such as ester; Scheme 2) and stoichiometric amounts of $Cu(OAc)_2$ as the oxidant. Subsequent to this work, much effort was devoted to improving this transformation. Jiao et al. reported a one-pot indole synthesis from simple anilines and electron-deficient alkynes using O_2 as the oxidant.[6]



Scheme 2. The development of the CDC approach to indoles.

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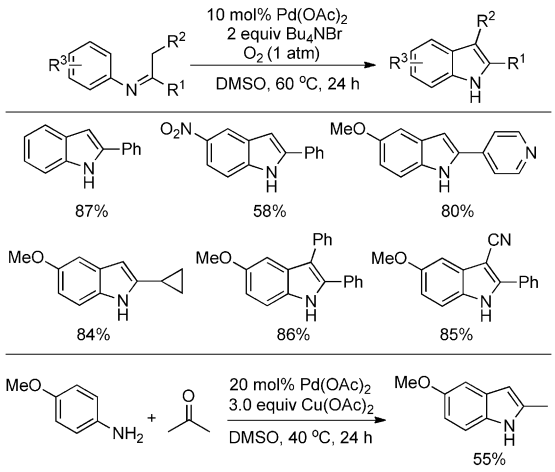
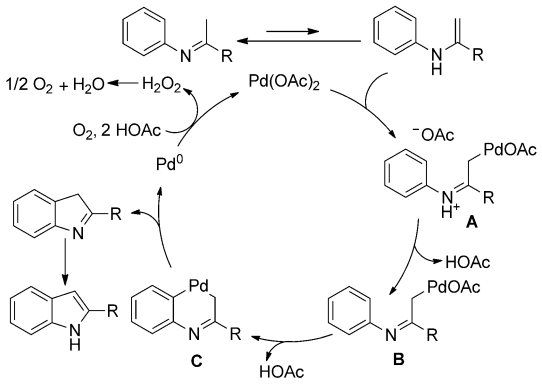
Cacchi et al. described a copper-catalyzed approach to the construction of a multisubstituted indole skeleton from *N*-aryl enaminones.[7] Zhao et al. disclosed a PIDA-mediated indole synthesis (PIDA = $PhI(OAc)_2$) from *N*-aryl enamines.[8] Liang et al. explored an iron-catalyzed system for indole synthesis from *N*-aryl enaminones.[9] However, the use of rather special starting materials determines the limitations of the products, and this substrate problem remains unsolved in these methods (Scheme 2).

Most recently, the Yoshikai group has made a significant breakthrough for indole synthesis through twofold C–H bond cleavage from common *N*-aryl imines prepared from simple anilines and ketones.[10] This transformation proceeds with catalytic $Pd(OAc)_2$ in combination with 2 equivalents of NBu_4Br in DMSO under an atmosphere of O_2. In contrast to the previous reports, this process works with imine substrates and thus possesses a broader scope. A variety of electron-donating, electron-withdrawing, halogenated, and potentially sensitive functional groups could be tolerated on both the aniline- and acetophenone-derived moieties. Furthermore, this indole synthesis could readily be scaled up to gram quantity without difficulty. With the aid of a copper oxidant, the indole product could be obtained directly from anilines and ketones by means of a condensation–CDC cascade (Scheme 3).



Scheme 3. Palladium-catalyzed aerobic oxidative cyclization of *N*-aryl imines through CDC.

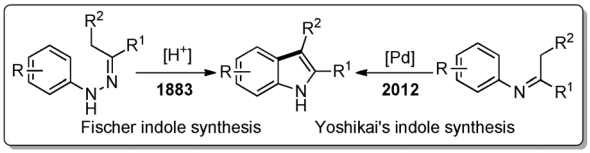
Mechanistic studies have revealed a Pd^{II}/Pd^0 redox process: the transformation begins with an electrophilic palladation of the nucleophilic enamine, which is generated in situ by tautomerization of the imine, followed by deprotonation. The resulting palladium complex **B** is suitable for electrophilic aromatic palladation by a concerted metalation–deprotonation (CMD) mechanism. Subsequent reductive elimination generates the 3*H*-indole product which can tautomerize quickly to give the indole product and a Pd^0 complex, which can be reoxidized to the Pd^{II} complex by O_2 and HOAc (Scheme 4).



Scheme 4. Proposed catalytic cycle of the palladium(II)-catalyzed indole formation through CDC.

In summary, the Yoshikai group has disclosed a mild, and efficient method for the synthesis of polyfunctionalized indoles through the palladium-catalyzed aerobic oxidative cyclization reaction of *N*-aryl imines. This approach, utilizing the same retrosynthetic disconnection as the Fischer indole synthesis, exhibits many advantanges over the classical process (Table 1). Further studies should focus on achieving higher turnover numbers and rendering the process more attractive for industry. Finally, one can reasonably anticipate that future studies will provide new applications in the preparation of complex molecules, particularly in the area of medicinal chemistry and materials science.

Table 1: Comparison of Fischer indole synthesis and Yoshikai's indole synthesis.



	Fischer indole synthesis	Yoshikai's indole synthesis
starting materials	hydrazines + ketones/ aldehydes	anilines + ketones
yield	high	high
system	acidic	neutral
catalyst	inexpensive	expensive, heavy metal
scaleable	yes	yes
compatible	good	good
atom economy	$-NH_3$	$-H_2O$
applications	total synthesis, industry	none yet

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