Communication

# Palladium-Catalyzed Aerobic Oxidative Cyclization of N-Aryl Imines: Indole Synthesis from Anilines and Ketones

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# Palladium-Catalyzed Aerobic Oxidative Cyclization of *N*-Aryl Imines: Indole Synthesis from Anilines and Ketones

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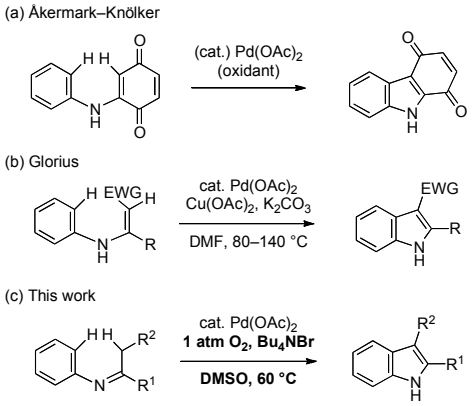
Supporting Information Placeholder

**ABSTRACT:** We report here an operationally simple, palladium-catalyzed cyclization reaction of *N*-aryl imines, affording indoles via the oxidative linkage of two C–H bonds under mild conditions using molecular oxygen as the sole oxidant. The process allows quick and atom-economical assembly of indole rings from inexpensive and readily available anilines and ketones and tolerates a broad range of functional groups.

The indole ring system represents a key structural element that occurs ubiquitously in biologically active natural and unnatural compounds as well as in optoelectronic functional materials.[1] Consequently, practical and atom-economical synthesis of indoles from simple starting materials is critical to the pharmaceutical and fine chemical industries.[2] Given the low cost and wide variety of commercially available anilines, their use as starting materials for indole synthesis is highly attractive, while well-established methods often require modified aniline derivatives such as aryl hydrazines (Fischer indole synthesis) and *o*-haloanilines (e.g., Larock indole synthesis).[3,4] In this context, a significant breakthrough was recently made by Glorius and coworkers, who developed a palladium(II)-catalyzed, copper(II)-mediated oxidative cyclization reaction of *N*-aryl enamines derived from anilines and β-dicarbonyl compounds to afford the corresponding indoles (Scheme 1b).[5,6,7] The origin of this novel palladium(II) catalysis can be traced back to the long-standing seminal studies of Åkermark and Knölker on palladium(II)-mediated or -catalyzed oxidative synthesis of carbazoloquinones and carbazoles (Scheme 1a).[8] Building on these pioneering works, we have now developed a palladium(II)-catalyzed oxidative cyclization reaction of *N*-aryl *imines* to indoles that likely involves palladation of *N*-aryl *enamines* formed via imine–enamine tautomerization (Scheme 1c). The reaction features operational simplicity, mild aerobic conditions, and tolerance of a broad range of functional groups, thus allowing expedient and atom-economical assembly of indole rings from readily available anilines and ketones.

**Scheme 1.** Indole Synthesis via Palladium-Catalyzed/Mediated Oxidative Cyclization




An illustrative example is the gram-scale reaction of imine **1a** derived from *p*-anisidine and acetophenone (eq 1). A mixture of **1a** (2.25 g, 10 mmol), $Pd(OAc)_2$ (0.22 g, 1 mmol), and $Bu_4NBr$ (6.45 g, 20 mmol) in DMSO (50 mL) was stirred under oxygen atmosphere (1 atm) at 60 °C for 24 h to afford 1.87 g of indole **2a** (84% yield). The discovery of this deceptively simple yet unprecedented transformation was serendipitously guided by our interests in ortho C–H bond functionalization of aromatic imines[9,10] and oxidative palladium catalysis.[11,12] Thus, while our initial intention was to oxidatively functionalize the ortho C–H bond of the phenyl ring of **1a** via imine-directed cyclopalladation,[13,14] we did not observe any products arising from ortho C–H functionalization under any conditions examined in this study.

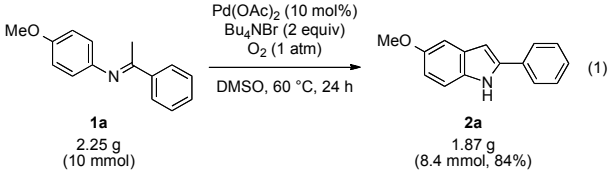
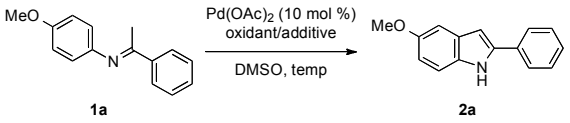



Table 1 summarizes key results obtained during the optimization of the reaction on a small scale (0.2 mmol).[15] The Pd-catalyzed reaction of **1a** using $O_2$ only at 40 °C afforded **2a** in 27% yield (entry 1). A clear improvement of the yield was observed when $Bu_4NBr$ (1 equiv) was added (entry 2), while other ammonium salts did not show apparent positive effects (entries 3–5). By using 2 equiv of $Bu_4NBr$, **2a** was obtained in 76% and 89% yields at 25 °C and 60 °C, respectively (entries 6 and 7). A change of the oxygen atmosphere to an open air in the latter case afforded **2a** in 67% yield. The use of $Cu(OAc)_2$ instead of $O_2$/$Bu_4NBr$ also allowed efficient and scalable cyclization, affording **2a** in 93% and 87% yields on 0.2 mmol

and 50 mmol scales, respectively (entries 8 and 9). Curiously, Glorius' catalytic system (Scheme 1b) did not promote the reaction at all, while its difference from the present Pd/Cu system is merely the use of $K_2CO_3$ additive and DMF solvent. Thus, DMSO appears to play a critical role in the oxidative cyclization. Other oxidants examined were either poorly effective (BzOO*t*Bu, BQ; entries 10 and 11) or entirely ineffective ($CuCl_2$, AgOAc, $PhI(OAc)_2$ etc.). Note that the reaction took place in 52% yield with a stoichiometric amount of $Pd(OAc)_2$ in the absence of an oxidant (entry 12).

**Table 1.** Influence of Reaction Conditions on Oxidative Cyclization of **1a**[a]



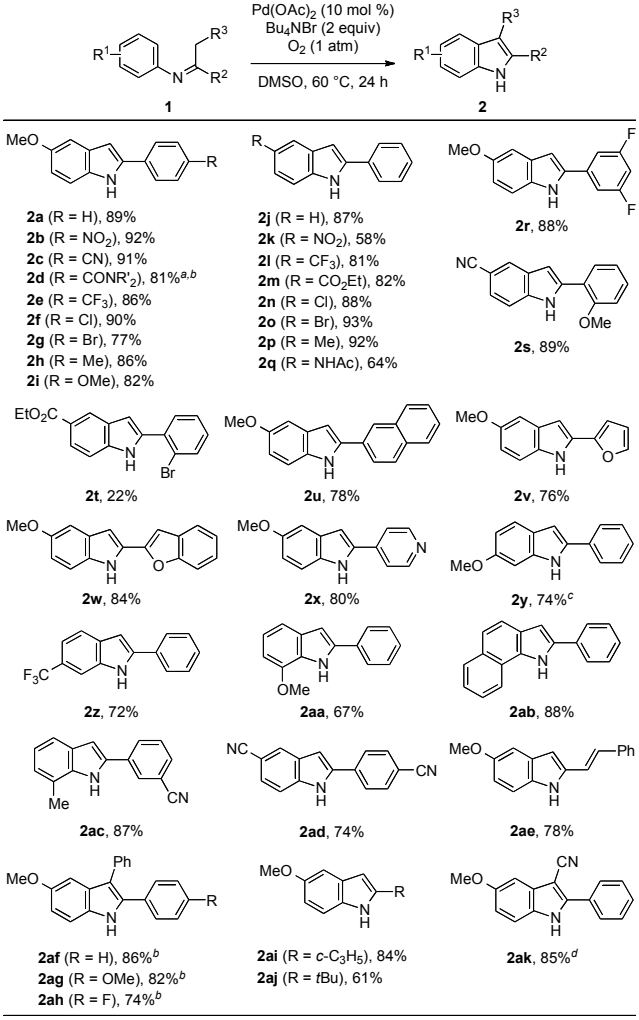

**1a** **2a**

| Entry | Oxidant/additive | Temp (°C) | Yield (%)[b] |
|---|---|---|---|
| 1 | $O_2$ (1 atm) | 40 °C | 27 |
| 2 | $O_2$ (1 atm)/$Bu_4NBr$ (1 equiv) | 40 °C | 48 |
| 3 | $O_2$ (1 atm) /$Bu_4NCl$ (1 equiv) | 40 °C | 24 |
| 4 | $O_2$ (1 atm) /$Bu_4NI$ (1 equiv) | 40 °C | 31 |
| 5 | $O_2$ (1 atm) /$Bu_4NOAc$ (1 equiv) | 40 °C | 22 |
| 6 | $O_2$ (1 atm)/$Bu_4NBr$ (2 equiv) | 25 °C | 76[c] |
| 7 | $O_2$ (1 atm)/$Bu_4NBr$ (2 equiv) | 60 °C | 89[c] |
| 8 | $Cu(OAc)_2$ (3 equiv) | 40 °C | 93[c] |
| 9[d] | $Cu(OAc)_2$ (2 equiv) | 40 °C | 87[c] |
| 10 | BzOO*t*Bu (3 equiv) | 40 °C | 23 |
| 11 | Benzoquinone (2 equiv) | 40 °C | 8 |
| 12[e] | None | 40 °C | 52 |

[a] Reaction was performed on a 0.2 mmol scale for 12–16 h. [b] GC yield determined using *n*-tridecane as an internal standard. [c] Isolated yield. [d] The reaction was performed on a 50 mmol scale using 5 mol % of $Pd(OAc)_2$. [e] 1 equiv of $Pd(OAc)_2$ was used.

We next explored the scope of the oxidative cyclization with the $Pd/Bu_4NBr/O_2$ system (Scheme 2).[16] A series of 2-(hetero)arylindoles could be obtained in good to excellent yields from the corresponding imines derived from substituted anilines and acetophenones (**2a** to **2ad**). A variety of electron-donating, electron-withdrawing, and potentially sensitive functional groups could be tolerated on both the aniline- and acetophenone-derived moieties, including nitro (**2b** and **2k**), cyano (**2c**, **2s**, **2ac**, and **2ad**), amide (**2d** and **2q**), trifluoromethyl (**2e**, **2l**, and **2z**), chloro (**2f** and **2n**), bromo (**2g**, **2o**, and **2t**), ester (**2m** and **2t**), and fluoro (**2r**) groups. Note that the dicyanoindole **2ad** is a precursor of an acid-sensing ion channel-3 inhibitor that was previously synthesized by Suzuki coupling of an expensive protected indole boronic acid.[17] Heteroaryl groups such as 2-furyl, 2-benzofuryl, and 4-pyridyl groups could be tolerated (**2v**–**2x**). Imines derived from *m*-methoxy and -trifluoromethyl anilines underwent cyclization preferentially at the less-hindered position to afford the indoles **2y** and **2z**, respectively, while the former case was accompanied by a small amount (7%) of the minor regioisomer. Substituents at the ortho positions of the acetophenone- and the aniline-derived moieties (**2s**, **2t**, and **2aa**–**2ac**) were tolerated, while the yield was only modest for the indole derived from *o*-bromoacetophenone (**2t**).

**Scheme 2.** Indole Synthesis from *N*-Aryl Imines

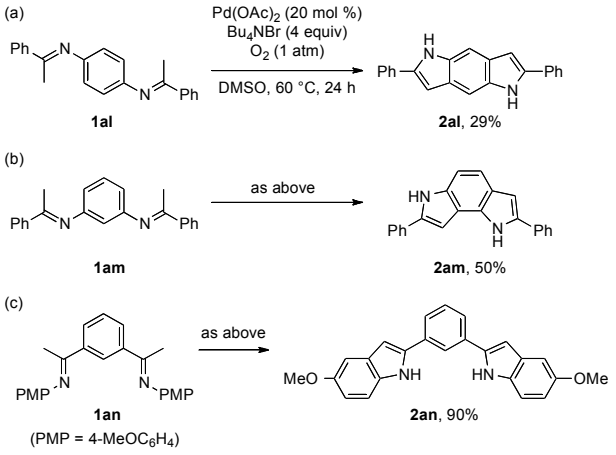



[a] $NR'_2$ is a morpholino group. [b] $Cu(OAc)_2$ was used as the oxidant (conditions in Table 1, entry 8). [c] A regioisomeric product was obtained in 7% yield. [d] The starting material was in the form of enamine.

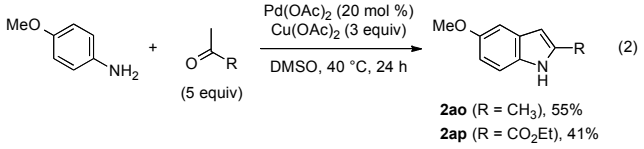
An α,β-unsaturated imine underwent cyclization smoothly to give 2-alkenylindole **2ae** in 78% yield. An imine derived from 2-phenylacetophenone afforded 2,3-diphenylindole **2af** in 40% yield, which was accompanied by a ketone byproduct (33%) arising from benzylic oxidation.[18] However, by using $Cu(OAc)_2$ as the oxidant, the yield of **2af** was improved to 86% with a complete suppression of benzylic oxidation. Similarly, 2,3-diarylindoles **2ag** and **2ah** were obtained in good yields. These examples demonstrate the utility of the present cyclization for regiocontrolled synthesis of 2,3-diarylindoles, which is difficult with the Larock- and Fagnou-type annulation reactions using diarylalkynes.[2,7] 2-Cyclopropyl- and 2-*t*-butylindoles **2ai** and **2aj** were also obtained in good yields from the corresponding imines, while attempts to synthesize 2-*n*-alkylindoles have not been successful. In addition to these examples, the present method was also applicable to an enamine derived from benzoylacetonitrile,[5] resulting in the formation of 2-phenyl-3-cyanoindole **2ak** in 85% yield.

Twofold cyclization of phenylenediamine-derived diimines **1al** and **1am** readily provided the fused indoles **2al** and **2am**, respectively, albeit in modest yields (Scheme 3a, b). These products particularly underline the power of the present cyclization reaction, as any of conventional methods would not allow their synthesis with such great ease. The regioselectivity observed for the latter case poses an intriguing mechanistic question that cannot be answered at present. Twofold cyclization was also achieved for a diimine **1an** derived from 1,3-diacetylbenzene, affording a 1,3-bis(indolyl)benzene **2an** in 90% yield (Scheme 3c). Such multifold cyclizations may serve as attractive routes to extended π-conjugated systems for potential applications in organic electronics.[19]

**Scheme 3.** Twofold Oxidative Cyclizations

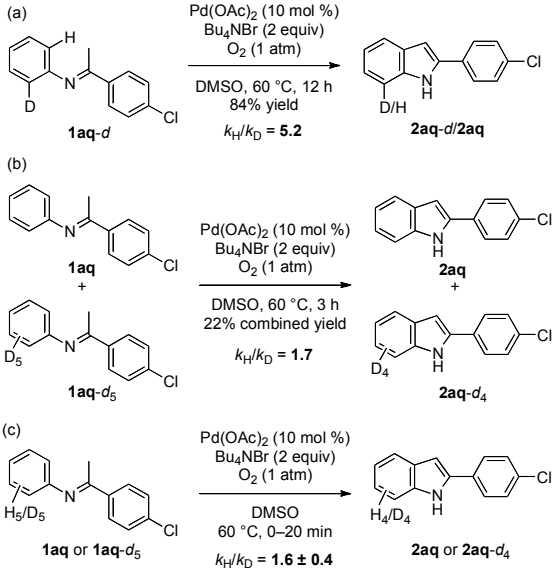



We further demonstrated the feasibility of one-pot oxidative condensation of aniline and ketone. Thus, with the aid of the Pd/Cu catalytic system, *p*-anisidine reacted with acetone and ethyl pyruvate to afford the indoles **2ao** and **2ap** in 55% and 41% yields, respectively (eq 2), while no product formation was observed with the $Pd/O_2$ system. Attempts on one-pot reaction of *p*-anisidine and acetophenone were not successful under the standard reaction conditions, presumably because of slow formation of the imine.




We next performed a series of kinetic isotope effect (KIE) experiments. First, we probed the nature of the aromatic C–H bond activation step by an intramolecular competition experiment using monodeuterated imine **1aq**-*d*, which exhibited a large KIE of 5.2 (Scheme 4a). The KIE value is of a similar magnitude to those commonly observed in Pd-catalyzed aromatic C–H bond functionalization reactions involving a concerted metalation–deprotonation mechanism.[5,20] On the other hand, an intermolecular competition of imine **1aq** and its pentadeuterated analogue **1aq**-$d_5$ exhibited a modest KIE of 1.7 (Scheme 4b). Comparison of parallel independent reactions of **1aq** and **1aq**-$d_5$ also indicated a modest KIE of 1.6 ± 0.4 in their early stage (0–20 min, Scheme 4c). These observations suggest that the aromatic C–H activation is one of turnover-controlling steps of the reaction but is not an exclusive turnover-limiting step.[21]

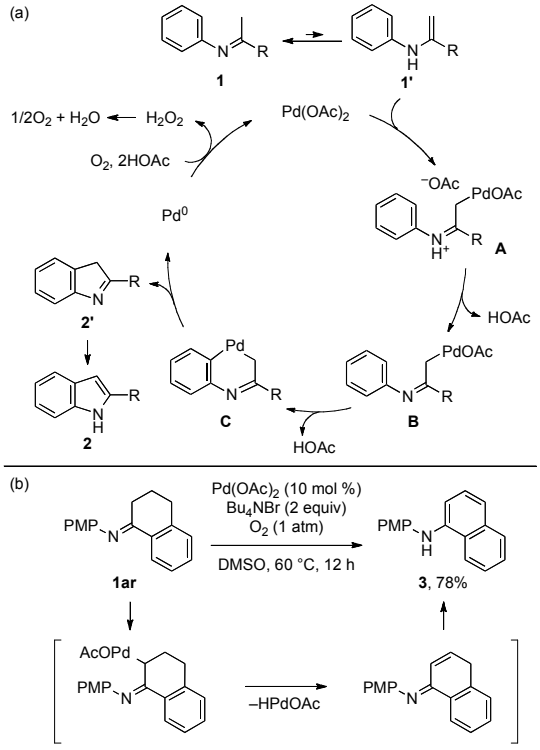
**Scheme 4.** H/D Kinetic Isotope Effect Experiments




From the above results and the fact that a stoichiometric amount of $Pd(OAc)_2$ promotes the reaction in the absence of oxidant (Table 1, entry 12), we suggest a possible catalytic cycle that involves a Pd(II)/Pd(0) redox process (Scheme 5a). Enamine **1'** generated via tautomerization of imine **1** would be electrophilically attacked by $Pd(OAc)_2$ (**A**), followed by elimination of HOAc to give an α-palladated imine **B**.[22] The intermediate **B** would then undergo intramolecular aromatic C–H palladation to give a six-membered palladacycle **C**. Subsequent reductive elimination affords 3*H*-indole **2'** and Pd(0). The former tautomerizes quickly to indole **2** while the latter is oxidized back to Pd(II) with the aid of molecular oxygen and HOAc.[12] Note that, under the standard conditions, tetralone-derived imine **1ar** underwent dehydrogenative aromatization to afford aminonaphthalene **3** presumably via β-hydride elimination of an α-palladated imine (Scheme 5b), which may indirectly support the formation of the putative $C(sp^3)$–Pd species **B** in the proposed catalytic cycle.[22,23] Further studies are underway to address more details of the reaction mechanism including the role of the ammonium salt.[24]

In summary, we have developed a simple, mild, and scalable palladium-catalyzed aerobic oxidative cyclization reaction of *N*-aryl imines, enabling two-step assembly of substituted indoles, 2-arylindoles in particular, from readily available anilines and ketones without any non-essential prefunctionalization steps. Thus, the present method would not only serve as a practical, versatile, and atom-economical alternative to existing synthetic methods but also allow facile construction of indole skeletons that have not been easily accessible. Further studies should lead to more robust, benign, and broadly applicable catalytic systems that could find applications in complex settings relevant to medicinal chemistry and materials science, and hence could have a significant impact on the laboratory- and industry-scale synthesis of indoles.[25]

**Scheme 5.** Possible Catalytic Cycle (a) and Dehydrogenative Aromatization of Tetralone-Derived Imine (b)




## ASSOCIATED CONTENT

**Supporting Information**. Detailed experimental procedures, characterization data and complete ref 17. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ACKNOWLEDGMENT

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(3) Approximate prices of aniline derivatives (per mole, Sigma-Aldrich): Aniline, $2; phenylhydrazine, $13; *o*-chloroaniline, $50; *o*-bromoaniline, $500; *o*-iodoaniline, $1,000.

(4) Numbers of commercially available aniline derivatives (according to Reaxys analysis): Anilines (with at least one ortho-hydrogen atom), ~24,000; arylhydrazines (with at least one ortho-hydrogen atom), ~800; *o*-chloroanilines, ~900; *o*-bromoanilines, ~500; *o*-iodoanilines, ~200.

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(15) See the Supporting Information for more detail of the screening experiments.

(16) Results obtained with the Pd/Cu system (Table 1, entry 8) are shown in the Supporting Information for comparison.

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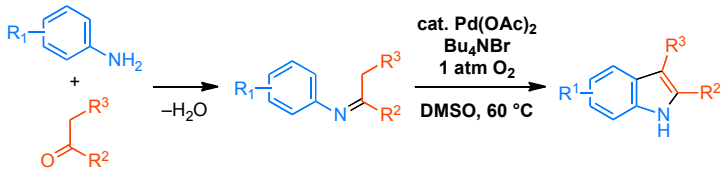
(25) A provisional application of this work has been filed, application no. 61577528.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+
R3
O
R2
–H2O
R1
N
R3
R2
cat. Pd(OAc)2
Bu4NBr
1 atm O2
DMSO, 60 °C
R1
N
H
R3
R2