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

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*Supporting Information

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 component that occurs ubiquitously in biologically active natural and unnatural compounds as well as in optoelectronic functional materials. Consequently, practical and atom-economical synthesis of indoles from simple starting materials is critical to the pharmaceutical and fine chemical industries. 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). In this context, a significant breakthrough was recently made by Glorius and co-workers, 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). 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). 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.

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 Bu₄NBr (6.45 g, 20 mmol) in DMSO (50 mL) was stirred under an oxygen atmosphere (1 atm) at 60 °C for 24 h to afford 1.87 g of indole 2a (84% yield).

Table 1 summarizes key results obtained during the optimization of the reaction on a small scale (0.2 mmol). The Pd-catalyzed reaction of 1a using O₂ only at 40 °C afforded 2a in 27% yield (entry 1). A clear improvement of the yield was observed when Bu₄NBr (1 equiv) was added (entry 2), while other ammonium salts did not show apparent positive effects (entries 3–5). By using 2 equiv of Bu₄NBr, 2a was obtained in 76% and 89% yields at 25 and 60 °C, respectively (entries 6 and 7). A change of the oxygen atmosphere to open air in the latter case afforded 2a in 67% yield. The use of Cu(OAc)₂ instead of O₂/Bu₄NBr also allowed efficient and...
scalable cyclization, affording 2a in 93% and 87% yields on 0.2 and 50 mmol scales, respectively (entries 8 and 9). Curiously, Glorius’s catalytic system (Scheme 1b) did not promote the reaction at all, although its difference from the present Pd/Cu system is merely the use of K₂CO₃ additive and DMF solvent. Thus, DMSO appears to play a critical role in the oxidative cyclization. Other oxidants examined were either poorly effective (BzOOBF₄, BQ entries 10 and 11) or entirely ineffective (CuCl₂, AgOAc, PhI(OAc)₂ etc.). Note that the dicyanoindole (2a) yield (%)

Table 1. Influence of Reaction Conditions on Oxidative Cyclization of 1a

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant/additive</th>
<th>temp (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O₂ (1 atm)</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>O₂ (1 atm)/Bu₄NB₄ (1 equiv)</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>O₂ (1 atm)/Bu₄NCI (1 equiv)</td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>O₂ (1 atm)/Bu₄NI (1 equiv)</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>O₂ (1 atm)/Bu₄NOAc (1 equiv)</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>O₂ (1 atm)/Bu₄NB₄ (2 equiv)</td>
<td>25</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>O₂ (1 atm)/Bu₄NI (2 equiv)</td>
<td>60</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)₂ (3 equiv)</td>
<td>40</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)₂ (2 equiv)</td>
<td>40</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>Bu₄OBF₄ (3 equiv)</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>11</td>
<td>benzoquinone (2 equiv)</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>none</td>
<td>40</td>
<td>52</td>
</tr>
</tbody>
</table>

“Reaction was performed on a 0.2 mmol scale for 12—16 h. GC yield determined using n-tridecane as an internal standard. Isolated yield. Reaction was performed on a 50 mmol scale using 5 mol % of Pd(OAc)₂. *1 equiv of Pd(OAc)₂ was used.

Two-fold cyclization of phenylenediamine-derived diimines 1al and 1am readily provided the fused indoles 2al and 2am, respectively, albeit in modest yields (Scheme 2a,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. Two-fold

yield, which was accompanied by a ketone byproduct (33%) arising from benzylic oxidation. 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-diallylindoles 2ag and 2ah were obtained in good yields. These examples demonstrate the utility of the present cyclization for regiocontrolled synthesis of 2,3-diallylindoles, which is difficult with the Larock- and Fagnou-type annulation reactions using diarylalkynes. 2-Cyclopentyl- and 2-tert-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 benzyloxycyanitrole, resulting in the formation of 2-phenyl-3-cyanindole 2ak in 85% yield.
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 2c). Such multifold cyclizations may serve as attractive routes to extended π-conjugated systems for potential applications in organic electronics.19

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 little product formation was observed with the Pd/O2 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 3a). 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-d5 exhibited a modest KIE of 1.7 (Scheme 3b). Comparison of parallel independent reactions of 1aq and 1aq-d5 also indicated a modest KIE of 1.6 ± 0.4 in their early stage (0−20 min, Scheme 3c). 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

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 involving a Pd(II)/Pd(0) redox process (Scheme 4a). 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 3H-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 4b), which may indirectly support the formation of the putative C(sp3)−Pd species B in the proposed catalytic cycle.22,23

Scheme 2. Two-fold Oxidative Cyclizations

Scheme 3. H/D Kinetic Isotope Effect Experiments

Scheme 4. Possible Catalytic Cycle (a) and Dehydrogenative Aromatization of Tetralone-Derived Imine (b)
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 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

■ 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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Notes
The authors declare no competing financial interest.

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■ REFERENCES


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

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


(25) A provisional patent application of this work has been filed, application no. 61577528.