Rhodium-Catalyzed Site-Selective Coupling of Indoles with Diazo Esters: C4-Alkylation versus C2-Annulation

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Supporting Information

ABSTRACT: A Rh(III)-catalyzed site-selective C−H activation of C(3)-functionalized indoles in a coupling with diazo esters has been realized with carbonyl as a weakly coordinating group. The coupling selectivity is dictated by the temperature and additives, affording either C4-alkylated indoles or C2-annulated lactones in moderate to excellent efficiency.

Introduction:
Indoles are among the most important heterocyclic structural motifs that have been widely found in a plethora of natural products, functional materials, and pharmaceuticals.1 Therefore, as a step-economic strategy, metal-catalyzed C−H activation has received increasing attention in indole functionalization.2 Various C3-selective functionalizations of indoles have been reported via an electrophilic substitution mechanism.3 Regioselective C2−H functionalization can also be realized using a directing group (DG) or under specific conditions.4 In contrast, it is a bigger challenge to realize direct functionalization at the C4−C7 positions because of their inherently poor reactivity, which amounts to limited literature reports.5−7 You and co-workers recently reported the Rh(III)-catalyzed regioselective C4−H activation of indolyl aldehydes or ketones with alkynes as a coupling partner (Scheme 1a).6c The Jia, Prabhu, Shi, and You groups also independently reported the functionalization of indoles at the C4 position with a Pd(II), Ru(II), Ir(III), or Rh(III) catalyst, leading to arylation, amination, olefination, and trifluoroethylation (Scheme 1a).6 Inspired by these outcomes and by Yu’s seminal C−H activation using diazo compounds, we reasoned that the unprecedented general C4-alkylation of indole might be realized when a suitable transition-metal catalyst and DG are employed.

Scheme 1. Selective Functionalization of Indoles

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significantly augmented to 96% (entry 7). However, further lowering the temperature resulted in diminished yield (entry 8). The effects of the additive and solvent were further investigated, which revealed that other silver salts or solvents all gave inferior results (entries 8–12). Thus, the conditions in entry 7 were adopted for the C4-alkylation (conditions A), while the C2-annulation was performed under conditions B as defined in entry 6.

With the establishment of the optimal reaction conditions, we next explored the scope of indole substrate for C4 alkylation under the conditions A. As shown in Scheme 2, a range of substituted indoles were examined in the coupling with diethyl 2-diazoacetate (2a). The introduction of various N-alkyl and -phenyl groups into the indole had marginal influence on the yield of the product (3aa–3fa, 79–96%). N-Pyridylindole and NH indole also reacted with 2a, giving a relatively lower yield of products (3ga, 64% and 3ha, 51%). In the case of a pyridyl group, the site selectivity remains dominated by the Piv DG (3ha). Indoles bearing halogen groups at the C5–C7 positions were fully compatible, affording the desired products in high yields (up to 98%). Furthermore, different ketone directing groups at the C3-position were also tolerated (3ia–ka). In contrast, poor reactivity and selectivity were observed for a 3-acetyl-substituted indole substrate. In addition, both electron-withdrawing and -donating groups at the C5–C7 positions were consistently tolerated, affording the alkylation products in moderate to excellent yields (3la–ta).

The coupling of indole 1a or 1h with various diazo esters was then examined under conditions A (Scheme 3). Various symmetrical or nonsymmetrical diazo malonates all coupled smoothly with such indoles in 50–93% yield. In the case of diazo esters having a larger alkyl group, decreased yields were observed as seen in 3ac–ae. Furthermore, 2-diazo-3-oxobutan-2-one (2f) and its derivatives (2g and 2h) also reacted successfully with 1a to afford the desired products (3af–ah) in 60–81% yields, which were isolated as two tautomers due to keto–enol tautomerization (see the SI). Unfortunately, a donor/acceptor diazo compound was not suitable for this alkylation. For example, coupling with isopropyl 2-diazopropanoate (2j) produced the C4-alkenylation product 3j as a result of 1,2-hydrogen shift to the carbene followed by C4-alkenylation.

Subsequently, the substrate scope of the C2-annulation reaction was investigated under conditions B (Scheme 4). Introduction of substituents such as methyl and methoxyl at the C6-position of the N-protected indole was tolerated, affording the corresponding annulated products 4b and 4c in moderate yields (51–63%). Furthermore, unprotected NH indoles were also amendable to the reaction conditions, giving the desired products 4d–g in moderate to good yields (32–81%). Besides, different ketone directing groups at the C3 position of indoles

Table 1. Optimization of Reaction Conditions<sup>a</sup>

<table>
<thead>
<tr>
<th>entry</th>
<th>additive (mol %)</th>
<th>acid</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>3aa</th>
<th>4a</th>
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<tr>
<td>1</td>
<td>AgSbF6 (10)</td>
<td>PivOH</td>
<td>DCE</td>
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<td>37</td>
<td>31</td>
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<tr>
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<td>PivOH</td>
<td>DCE</td>
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<td>0</td>
</tr>
<tr>
<td>3</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
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<td>PivOH</td>
<td>DCE</td>
<td>80</td>
<td>29</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
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<td>AcOH</td>
<td>DCE</td>
<td>80</td>
<td>9</td>
<td>48</td>
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<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AgNTf2 (10)/Zn(OTf)&lt;sub&gt;2&lt;/sub&gt; (50)</td>
<td>AcOH</td>
<td>DCE</td>
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<td>DCE</td>
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<td>trace</td>
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<td>PivOH</td>
<td>PhCl</td>
<td>40</td>
<td>87</td>
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</tr>
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</table>

<sup>a</sup>Reaction conditions: 1a (0.2 mmol), 2a (0.5 mmol), [Cp*RhCl]<sub>2</sub> (2.5 mol %), silver salt, acid (2.0 equiv), solvent (2 mL), 40–100 °C, 20 h. <sup>b</sup>Isolated yield. The reaction time was 10 h.

Scheme 2. Substrate Scope of Indoles for C4-Alkylation<sup>a</sup>

Scheme 3. Substrate Scope of Diazoo Compounds for C4-Alkylation<sup>a</sup>

<sup>a</sup>Reaction conditions: indole 1 (0.2 mmol), diazo 2a (0.5 mmol), [Cp*RhCl]<sub>2</sub> (2.5 mol %), AgSbF6 (10 mol %), and PivOH (2.0 equiv) in DCE (2 mL) at 40 °C for 20 h, isolated yield. <sup>b</sup>[Cp*RhCl]<sub>2</sub> (5 mol %) and AgSbF6 (20 mol %) were used.

Scheme 4. Substrate Scope of Indoles for C2-Alkylation<sup>a</sup>

<sup>a</sup>Reaction conditions: indole 1a or 1i (0.2 mmol), diazo 2 (0.5 mmol), [Cp*RhCl]<sub>2</sub> (2.5 mol %), AgSbF6 (10 mol %), PivOH (2.0 equiv), and DCE (2 mL) at 40 °C for 20 h, isolated yield. <sup>b</sup>The products were isolated as a mixture of two keto–enol tautomers.
were also investigated, giving the target products (4h−j) in moderate yields (43−71%). In all cases, a small amount of the corresponding 4-alkylation product was also generated. In contrast, the electron-withdrawing group was not suitable for this transformation. For example, an ester-substituted indole at the C6 position produced the DG-removed C4-alkylated product 5a under the standard conditions as a result of C(4)-alkylation followed by in situ removal of the DG.

The synthetic utility of the alkylation system was next demonstrated in a scale-up reaction. Thus, a 5 mmol reaction of 1a and 2a afforded the alkylation product 3aa in 85% yield (Scheme 5a). Treatment of 3aa with KOH led to hydrolysis−decarboxylation to give product 6 in 83% yield (Scheme 5b). The carboxyl group in 6 should provide handles for further functionalization. The DG in 3aa was readily removed using a general method (Scheme 5b). Furthermore, when catalyzed by Pd/C, the annulated product 4a can be selectively hydrogenated together with decarboxylation to give a 2,3-dialkylated indole 8 in good yield, with aromatization being a driving force (Scheme 5c).

Several experiments have been conducted to briefly probe the mechanism of the alkylation system (Scheme 6). Two H/D-exchange experiments have been conducted between indoles 1a and CD3COOD (Scheme 6a). Under conditions A, only the C4-H was partially deuterated. In contrast, both the C2-H and C4-H underwent deuteration under conditions B. Besides the reversibility of the C−H activation (if any), these outcomes on H/D exchange are inconsistent with the site-selectivity of our C−H functionalization systems, and the C2-alkylation should carry a higher barrier likely due to steric effects. Thus, the C4-alkylation is the kinetic product, while the C2-alkylation product is likely the thermodynamic product. Furthermore, a competitive coupling between 1s and 1t with diazo ester 2a yielded a mixture of 3sa (Me) and 3ta (Br) in a ratio of 1.8:1 under conditions A, suggesting that the C−H alkylation reaction is kinetically favored for a more electron-rich indole (Scheme 6b).

On the basis of the literature reports,6,11 a plausible mechanism of the annulation reaction is proposed in Scheme 7. Starting from a Cp*RhX2 catalyst, a five-membered rhodacyclic intermediate I is generated via C2-H activation of indole 1a. Coordination of an incoming diazo ester (2a) is followed by denitrogenation to afford a metal−carbene species II. Subsequent migratory insertion of the Rh-aryl bond into the carbene moiety gives alkyl species III. Protonolysis of the intermediate III then generates a 2-alkylated intermediate IV, which could tautomerize to V.11c Finally, under assistance of the Rh or the zinc catalyst, the ester carbonyl group is activated toward nucleophilic attack to furnish the annulated product 4a, together with regeneration of the active Rh(III) catalyst.
In summary, we have developed the Rh(III)-catalyzed efficient and site-selective C–H activation systems of indoles with diazo esters as a coupling partner. A variety of indoles and diazo compounds are amenable to the coupling systems, affording the C4-alkylation or C2-annulation products in good selectivity. The selectivity is collectively controlled by reaction temperature and additives. This protocol features a relatively low catalyst loading and compatibility with diverse functional groups, thus providing a straightforward strategy to accessfunctionalized indoles. (a) Sandtory, A. H. Adv. Synth. Catal. 2015, 357, 2403.

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**Notes**

The authors declare no competing financial interest.