Rhodium(III)-Catalyzed Isoquinolone Synthesis: The N–O Bond as a Handle for C–N Bond Formation and Catalyst Turnover

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The abundance of nitrogen-containing heterocycles in biologically active molecules has occasioned many efforts for their synthesis and functionalization.1 As a result, direct approaches toward their construction have become competitive with more traditional protocols based on substrate preactivation. Indeed, methods involving C–H bond cleavage and subsequent C–N bond formation are emerging as attractive alternatives (Scheme 1).2 However, such strategies generally require an external oxidant to account for the change in oxidation state of the C–H bond and to enable catalyst turnover. In a recent elegant report,3 Hartwig addressed this issue using a N–O bond contained in the substrate as a built-in oxidant.4 This indole formation was the first example of a non-nitrene-based5 redox neutral intramolecular amination achieved from C–H and N–X coupling partners. In this communication, we wish to disclose an intermolecular and mechanistically distinct process that affords the isoquinolone motif via Rh(III)-catalyzed annulation of benzhydroxamic acids with alkynes. This external-oxidant-free process strategically utilizes a N–O bond as an instrument for C–N bond formation and catalyst release.

Pursuing our interest in heterocycle formation, we sought to use an oxidative coupling approach analogous to those employed by Satoh and Miura2a,b as well as our group2c,d to gain entry to different nitrogen-containing heterocycles. We postulated that the isoquinolone motif could be accessed using a benzamide-derived starting material.6 Inspired by Yu’s work in direct amination,2n we reasoned that benzhydroxamic acids could serve as a directing group for C–H functionalization as well as predisposing the substrate toward C–N reductive elimination. However, initial attempts toward the formation of isoquinolone 3a resulted in product mixtures (Table 1, entry 1). Interestingly, the major product (4a) of the reaction had undergone N–O bond cleavage. Considering that an additional synthetic step is usually required to achieve this reduction,2n we decided to further explore this direct reaction path to obtain 4a in one step. To our delight, replacing Cu(OAc)2·H2O by a catalytic amount of base and using methanol as solvent revealed that 4a could be obtained in high yield (Table 1, entry 2–4).

Table 1. Selected Observations during Reaction Developmenta

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>additive (equiv)</th>
<th>1H NMR yield</th>
<th>1H NMR ratio 3a : 4a</th>
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<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>Cu(OAc)2·H2O (2)</td>
<td>89</td>
<td>1:1.1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>CsOAc (2)</td>
<td>38</td>
<td>1:20</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>CsOAc (2)</td>
<td>97 (92)b</td>
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a Isolated yield. b Reaction conducted in a sealed tube at 100 °C for 40 h.

With this set of conditions in hand, the scope of isoquinolone formation was demonstrated with a variety of substituted benzhydrazodic acids. As shown in Table 2, the reaction provides the desired isoquinolones regardless of the electron-donating or -withdrawing character of the benzhydrazodic acid substituents. Additionally, when meta-substituted benzhydrazodic acids are used, the arene rhodation occurs at the less hindered site, providing exclusively the C-7 substituted regioisomer (4e, 4f). Also, both symmetrical and unsymmetrical alkynes are tolerated as coupling partners.7 Moreover, the insertion of an aryl–alkyl disubstituted alkyne occurs regioselectively with the sp2 center being installed at the 3-position. Of note, these mild and copper-free conditions allow an alkyne bearing a pyridyl group to undergo the isoquinolone formation (4i).

Table 2. Reaction Scopea

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The absence of added oxidant and the loss of the N-methoxy substituent in the isoquinoline product prompted us to probe the mechanism of this redox neutral process. The role of the N-methoxy group was initially evaluated by carrying out two experiments in deuterated methanol, the first with 1a and the second with benzamide. In both cases, deuterium was incorporated exclusively ortho to the directing group (eqs 1 and 2). In addition, no cleavage of the N–O bond was observed with 1a. These results suggest that the first step of the mechanism is a reversible cyclometalation.8 Also, the integrity of the N-methoxy group is consistent with a mechanism involving N–O bond oxidative addition as has previously been demonstrated in Hartwig’s system.3 Next, a reaction starting from benzamide was run in the presence of 2a and 20 mol % of Rh(III) (eq 3). From this experiment, 71% of the starting product was recovered, along with 6% of the benzannulation product 5.9 No formation of isoquinoline 4a was observed, signifying that the N-methoxy group is a prerequisite for C–N bond formation. Lastly, to determine whether the N–O bond simply acts as an oxidant for Rh(I) after C–N bond reductive elimination, 1a and 2b were reacted in the presence of 3a. No formation of 4a from 3a was observed (eq 4), indicating that N–O bond cleavage happens intramolecularly with the substrate on which C–N bond formation occurs.

The postulated mechanism is presented in Scheme 2.10 The mechanistic information revealed above is consistent with the first step being a reversible aren e rhodation providing 6. The alkyne can then undergo an insertion into the Rh–C bond, forming intermediate 7. At this point, a concerted or stepwise C–N bond forming/N–O bond cleaving event can occur, affording the desired isoquinoline and releasing the catalyst. Computational and experimental studies are underway to further establish the nature of this last catalytic step.

Scheme 2. Postulated Mechanism

In conclusion, we have developed a conceptually new approach to C–N bond formation from benzhydroxamic acid precursors. This redox neutral isoquinolone synthesis operates under mild conditions, is not sensitive to air or moisture, and does not require an external oxidant. This interesting reactivity should find a broader use in the formation and functionalization of other heterocycles.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References


(2) For selected examples proceeding through cross-coupling/cyclization, see:


(6) For a review on recent isoquinolone synthesis, see: Glushkov, V. A.; Shklyaev, Y. V. Chem. Heterocycl. Compd. 2001, 37, 663.


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