Recognizing the industrial value of nitrogen-containing heterocyclic compounds,\(^1\) chemists continue to devise novel methods for their synthesis.\(^2\) The preparative chemistry of isoquinolines is illustrative, where traditional routes for azine ring fusion typically involve intramolecular cyclizations of highly functionalized substrates at elevated temperatures under strongly acidic reaction conditions (Scheme 1).\(^3\) More recently, metal-catalyzed approaches\(^4\) have begun to address some of these issues, as exemplified by the Larock isoquinoline synthesis that couples o-iodoaldimines and alkynes in the presence of a palladium catalyst.\(^5\) Our interest in the minimization of substrate preactivation in metal-catalyzed processes led us to question whether a similar reaction mode in which the aryl C–I functional group of the o-iodobenzimine is replaced by a simple C–H bond might be possible.

**Scheme 1. Retrosynthetic Disconnections of the Isoquinoline Core**

A number of challenges are inherent in this approach. Colby, Bergman, and Ellman\(^6\) have described a Rh(I)-catalyzed C–H reductive elimination.\(^7\) The preparative chemistry of isoquinolines is illustrative, where traditional routes for azine ring fusion typically involve intramolecular cyclizations of highly functionalized substrates at elevated temperatures under strongly acidic reaction conditions (Scheme 1).\(^3\) More recently, metal-catalyzed approaches\(^4\) have begun to address some of these issues, as exemplified by the Larock isoquinoline synthesis that couples o-iodoaldimines and alkynes in the presence of a palladium catalyst.\(^5\) Our interest in the minimization of substrate preactivation in metal-catalyzed processes led us to question whether a similar reaction mode in which the aryl C–I functional group of the o-iodobenzimine is replaced by a simple C–H bond might be possible.

### Table 1. Reaction Scope\(^a,b\)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2a-g</strong></td>
<td><strong>3a-e</strong></td>
<td>(2.5 mol%) Cu(OAc)(_2)·H(_2)O (2.1 equiv) in DCE at 83 °C (reflux) 16 h.</td>
</tr>
<tr>
<td>4a</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>4c</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>4e</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>4f</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>4g</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>4h</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>4i</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>4j</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>4k</td>
<td>76% (^c)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Conditions: benzaldimine (1 equiv), alkylne (1.2 equiv), Cu(OAc)\(_2\)·H\(_2\)O (2.1 equiv) in DCE at 83 °C (reflux), 16 h.

\(^{b}\) Isolated yields are reported. \(^{c}\) Isolated as a 11:1 mixture of regioisomers.

When unsymmetrical alkynes are employed,\(^14\) the larger substituent is regioselectively placed at the benzylic position away from
the nitrogen atom. For example, isoquinolines 4h–j are all formed as the exclusive regioisomers. In the case of 4k, the two isomers are produced in an 11:1 ratio.

**Scheme 2. Potential Reaction Pathways**

**Pathway A**: Reductive Elimination from Rh(IV)

![Scheme 2 - Pathway A](image1)

**Pathway B**: Electrocyclization/Oxidation

![Scheme 2 - Pathway B](image2)

In addition to the electrocyclization/oxidation and the Rh(IV) pathways described earlier and illustrated in Scheme 2, C–N reductive elimination may also potentially occur directly from the Rh(III) intermediate 5 (Scheme 3). To probe the nature of the reaction mechanism, the reaction of 2a was performed in the presence of 20 mol % 1 in the absence of added Cu(OAc)$_2$·H$_2$O. In this case, 4a was obtained in 18% yield. Similarly, when the reaction was performed with 2.5 mol % 1 without added Cu(OAc)$_2$·H$_2$O, 4a was generated in 2.2% GC-MS yield after 16 h. After this time, addition of 2.1 equiv of Cu(OAc)$_2$·H$_2$O induced catalyst turnover, resulting in a 79% GC–MS yield after 24 h. These results indicate that Cu(II) is not essential for C–N bond formation (Scheme 2, pathway A). Moreover, when aldinone 9 bearing an alkenyl substituent was subjected to the standard reaction conditions, no reaction was observed (eq 1).

\[ \text{Scheme 2} \]

In a similar fashion, when 9 was reacted in the presence of alkyne 3c, the only product detected in the crude reaction mixture was 10 (eq 2). The absence of cyclization with the preinstalled olefinic moiety in either the absence or the presence of added alkyne strongly indicates that an electrocyclization/oxidation pathway does not account for product formation (Scheme 2, pathway B). In light of these studies, we currently favor the reaction pathway outlined in Scheme 3, in which the rhodium catalyst is implicated in each of the bond-breaking/bond-forming steps and C–N reductive elimination may occur directly from Rh(III).

The ability of rhodium(III) to catalytically induce C–H bond cleavage, C–C bond formation, and, importantly, C(sp$^2$)–N(sp$^2$) bond reductive elimination under relatively mild reaction conditions with a range of different aldimines and alkyynes should not only find application in the preparation of other isoquinoline molecules but also serve as a useful point of departure for the development of other novel rhodium(III)-catalyzed transformations in heterocycle synthesis.

**Acknowledgment.** We thank NSERC, the University of Ottawa, Eli Lilly, Amgen, Astra Zeneca, and the Sloan Foundation (fellowship to K.F.). N.G. thanks NSERC for a graduate student scholarship.

**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**


12. Other N substituents, such as methyl or p-methoxybenzyl, resulted in lower yields (8% and 49%, respectively).

13. Other oxidants, such as AgOAc (50%), PhH(OAc)$_2$ (22%), and p-benzoquinone (5%), led to lower conversion (values in parentheses).

14. Under the current conditions, the use of terminal alkynes resulted in alkylene dimerization.

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