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Isoquinoline Synthesis via Rhodium-Catalyzed Oxidative Cross-Coupling/ Cyclization of Aryl Aldimines and Alkynes

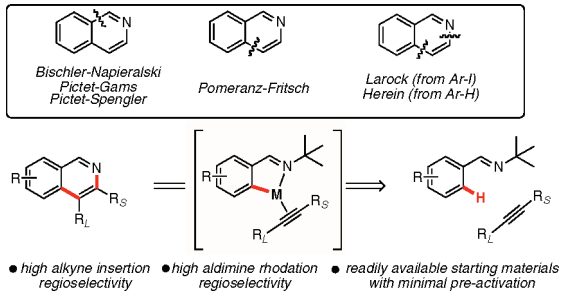
Nicolas Guimond and Keith Fagnou*

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Canada K1N 6N5

Received May 29, 2009; E-mail: keith.fagnou@uottawa.ca

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

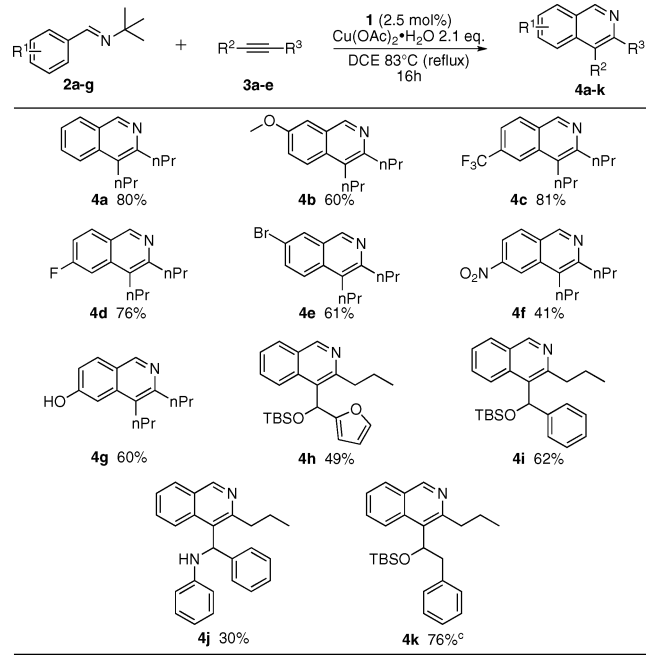


A number of challenges are inherent in this approach. Colby, Bergman, and Ellman[6] have described a Rh(I)-catalyzed C−H enimine vinylation that can be followed by electrocyclization/ oxidation steps to generate functionalized pyridines. However, application of a similar approach in quinoline synthesis by Jun and co-workers[7] necessitated the use of highly elevated temperatures (150 °C) because of the loss of aromaticity during the electrocyclization and resulted in product mixtures and diminished yields. To avoid this unfavorable second step, we envisioned a catalytic process where the metal catalyst would be involved in both the C−C and C−N bond-forming steps.[8,9] As a precedent, Jones and co-workers[10,11] recently reported that isoquinolinium salts can be generated under mild conditions in three steps: (1) stoichiometric Rh(III)-induced C−H bond cleavage of 2-phenylpyridine, benzo[*h*]quinoline, or *N*-benzilidenemethylamine; (2) alkyne carbometalation; and (3) Cu(II)-induced C−N reductive elimination. In the last step, the Cu(II) was proposed to engage in single-electron transfer to form a Rh(IV) intermediate more pre-disposed to reductive elimination.[10]

Herein we describe the realization of this goal by showing that $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (**1**) catalyzes the formation of isoquinoline compounds from readily available and minimally functionalized starting materials. These reactions occur under mild reaction conditions [83 °C, refluxing 1,2-dichloroethane (DCE)] with high regioselectivity. We also present preliminary mechanistic studies that point to the involvement of the rhodium catalyst in each of the C−H bond-breaking and C−C/C−N bond-forming steps and show that while a copper(II) terminal oxidant is employed, its use is not a prerequisite for the C−N reductive elimination with these substrates.[10] In view of the importance of the isoquinoline motif, particularly in medicinal chemistry, these results should find wide use in the preparation of these compounds.

We found that treatment of a variety of *N-tert*-butylbenzaldimines[12] **2** with an internal alkyne **3**, 2.5 mol % **1**, and 2.1 equiv of $Cu(OAc)_2 \cdot H_2O$[13] in refluxing DCE provides the corresponding isoquinoline products **4** in good yield (Table 1). A variety of substituents may be employed on the aldimine coupling partner, including electron-donating and -withdrawing groups. An aryl bromide substituent remains intact during the reaction (**4e**), providing a useful handle for further elaboration, and a phenolic OH group does not need protection, as illustrated by the formation of **4g**.

Table 1. Reaction Scope[a,b]



[a] Conditions: benzaldimine (1 equiv), alkyne (1.2 equiv), **1** (2.5 mol %), and $Cu(OAc)_2 \cdot H_2O$ (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

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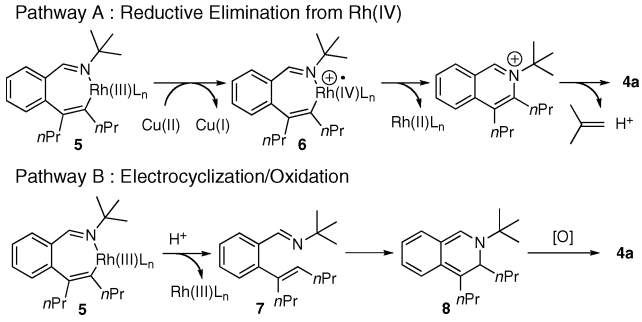
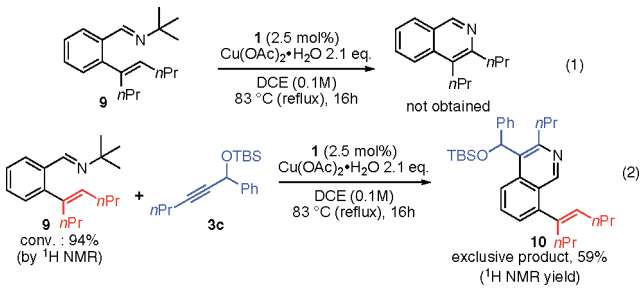
the nitrogen atom. For example, isoquinolines **4h**−**j** are all formed as the exclusive regioisomers. In the case of **4k**, the two isomers are produced in an 11:1 ratio.

Scheme 2. Potential Reaction Pathways



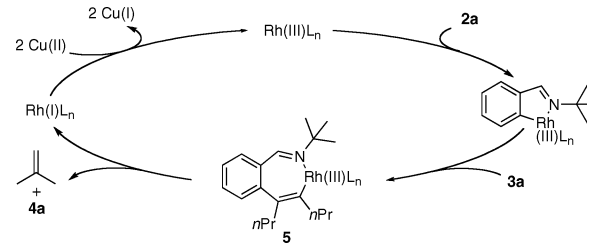
In addition to the electrocyclization/oxidation[6] and the Rh(IV)[10] pathways described earlier and illustrated in Scheme 2, C−N reductive elimination may also potentially occur directly from the Rh(III) intermediate **5** (Scheme 3). To probe the nature of the reaction mechanism, the reaction of **2a** was performed in the presence of 20 mol % **1** in the absence of added $Cu(OAc)_2 \cdot H_2O$. In this case, **4a** was obtained in 18% yield. Similarly, when the reaction was performed with 2.5 mol % **1** without added $Cu(OAc)_2 \cdot H_2O$, **4a** was generated in 2.2% GC−MS yield after 16 h. After this time, addition of 2.1 equiv of $Cu(OAc)_2 \cdot H_2O$ 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 aldimine **9** bearing an alkene substituent was subjected to the standard reaction conditions, no reaction was observed (eq 1).



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 alkynes should not only find application in the preparation of other isoquinoline molecules

Scheme 3. Proposed Mechanism



but also serve as a useful point of departure for the development of other novel rhodium(III)-catalyzed transformations in heterocycle synthesis.

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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.

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(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%), PhI(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 alkyne dimerization.

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