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A Novel Palladium-Catalyzed Synthesis of 1,2-Dihydroquinoxalines and 3,4-Dihydroquinoxalinones

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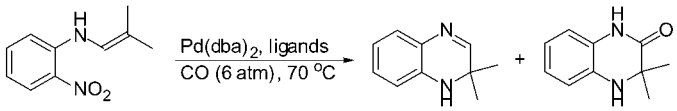
ABSTRACT



Reactions of enamines, derived from 2-nitroanilines and α-substituted aldehydes, with carbon monoxide (6 atm) in the presence of a catalytic amount of bis(dibenzylideneacetone)palladium(0) (Pd(dba)$_2$) and 1,3-bis(diphenylphosphino)propane (dppp) afford readily separated mixtures of 1,2-dihydroquinoxalines and 3,4-dihydroquinoxalinones. Addition of a catalytic amount of 1,10-phenanthroline to the reaction mixture substantially improved the yield of products.

A variety of nitrogen-containing heterocyclic compounds have been prepared by transition metal-catalyzed reductive *N*-heteroannulation of ortho-substituted nitrobenzenes in the presence of carbon monoxide. Examples of heterocycles obtained in this fashion include indoles,[1] 2(1*H*)-indazoles,[1f,2] quinolines,[1f] 4(1*H*)-quinolones,[3] quinazolines,[4] 4(3*H*)-quinazolinones,[5] pyrrolines,[6] benzimidazoles,[1g,7] 2(1*H*)-benzimidazolones,[7] benzotriazoles,[8] 2,1-benzoisoxazole,[1f] benzo[*c*]-cinnoline,[9] 1,4-dihydro-(2*H*)-3,1-benzoxazine-2-ones,[10] and 2(1*H*)-benzoxazolone.[11] Palladium complexes have predominantly been used as the catalyst for reductive *N*-heteroannulations, but a number of other transition metals, such as iron, manganese, cobalt, ruthenium, platinum, selenium, and rhodium, have successfully been employed.

Reductive *N*-heteroannulations of 2-nitro-*N*-(arylmethylene)benzenamines have previously been reported by Cenini et al. to afford 2-arylbenzimidazoles.[1g,7a] For example, reaction of 2-nitro-*N*-(phenylmethylene)benzeneamine (**1**) with carbon monoxide (50 atm, 220 °C), in the presence of a catalytic amount of triruthenium dodecacarbonyl, gave 2-phenylbenzimidazole (**2**) in 86% yield (Scheme 1). A palladium-based catalyst system has been developed, by the

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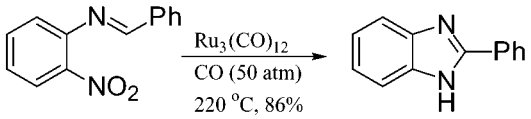
Scheme 1



1 **2**

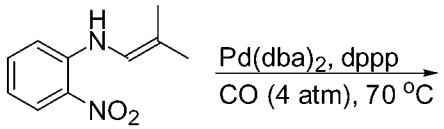
same group, for the transformation of in situ formed imines to benzimidazoles.[1g] In addition, potassium tetracarbonylhydridoferrate ($KHFe(CO)_4$) has been reported to mediate the transformation of **1** to **2** in low isolated yield.[12]

In a systematic effort to expand our milder palladium-catalyzed methodology[1e] to the synthesis of benzimidazoles and other heterocycles containing two or more nitrogen atoms, we turned our attention to reactions of imines. 2-Nitro-*N*-(4-nitrophenylmethylene)benzenamine, formed by condensation between 2-nitrobenzenamine and 4-nitrobenzaldehyde, was reacted with carbon monoxide (4 atm, 70 °C) in the presence of a catalytic amount of palladium diacetate and triphenylphosphine. Somewhat to our disappointment, no benzimidazole was produced under the reaction conditions; only recovered imine and hydrolysis products thereof were isolated. We have previously noted that some substituted 2-nitrostyrenes do not undergo annulation to form indoles under the above conditions but could be cyclized using a catalytic amount of $Pd(dba)_2$, dppp, and 1,10-phenanthroline in DMF under 6 atm of carbon monoxide at temperatures between 70 and 120 °C. However, the latter conditions also failed to produce the expected benzimidazole.

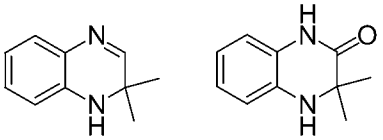
Enamines were next examined as potential substrates for reductive annulation. Reaction of enamine **3a**, formed by condensation of 2-nitrobenzenamine with 2-methylpropanal in the presence of molecular sieves, with carbon monoxide (4 atm, 70 °C) in the presence of $Pd(dba)_2$ and dppp in acetonitrile produced a mixture of 1,2-dihydroquinoxaline **4a** and 3,4-dihydroquinoxalinone **5a** (Scheme 2). The products were readily separated by column chromatography on silica gel.

Metal-catalyzed *N*-heteroannulations in many cases closely resemble reactions wherein a nitrene or nitrenoid intermediate can be invoked.[13] For example, benzimidazole **2** has been prepared by reductive annulation of **1** with triethyl phosphite although in substantially lower yield compared to the metal-catalyzed reactions.[14] To the best of our knowledge, annulation of enamines to give dihydroquinoxaline derivatives is a novel reaction which does not have a counterpart in more classical nitrene type chemistry.

Scheme 2



3a



4a (71%) **5a** (11%)

Probably the most widely used method for the preparation of quinoxaline derivatives is the Hinsberg condensation of 1,2-diaminobenzenes with 1,2-dicarbonyl compounds.[15] A disadvantage of this type reaction is the formation of isomeric products using unsymmetrically substituted reactants. In our case, the cyclization is inherently regioselective and may be a viable alternative to the Hinsberg condensation reaction.

A selection of additional enamines was examined, and the results thereof are summarized in Table 1.[16] For all reactions in the table, unless otherwise stated, a 0.7−1.2 M solution of the enamine in DMF was reacted with carbon monoxide (6 atm, 70 °C) in the presence of $Pd(dba)_2$ (6 mol %), dppp (6 mol %), and 1,10-phenanthroline (12 mol %). Although acetonitrile worked well as the solvent in our initial reaction using **3a**, DMF was found to be a superior solvent for the functionalized enamines. For example, no product was obtained from **3c**, using the conditions shown in Scheme 2. Addition of phenanthrolines, or related chelating nitrogen donor ligands, has been shown to accelerate a number of reductive *N*-heteroannulation and carbonylation reactions of nitroaromatic compounds.[10] This was also the case in some but not all of our reactions. For example, reaction of the methoxy-substituted enamine **3b** in the presence of 1,10-phenanthroline gave 57% of **4b** and 40% of **5b** (entry 2). In sharp contrast, reaction in the absence of 1,10-phenanthroline gave a 7% total yield of **4b** + **5b** (entry 1). As seen in Table 1, aromatic rings having electron-donating and moderately electron-withdrawing substituents readily undergo the annulation reaction. Enamines substituted with a strong electron-withdrawing substituent on the benzene ring apparently do not participate in the annulation reaction. For example, the enamine derived from 2,4-dinitrobenzenamine and 2-methylpropanal was completely consumed under standard reaction conditions; however, no major product was identified.

Heteroaromatic enamines can also be used as substrates for the palladium-catalyzed annulation reaction. For example, reaction of the pyridine-derived enamine **3i** gave the expected products **4i** and **5i**, albeit in somewhat lower yield compared

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(13) For a review, see: Söderberg, B. C. G. *Curr. Org. Chem.* **2000**, *4*, 727.

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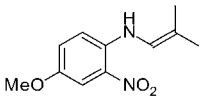
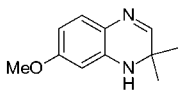
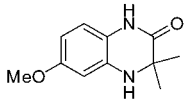
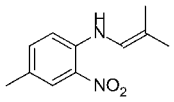
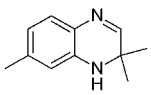
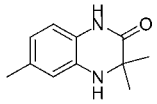
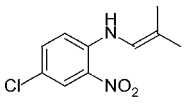
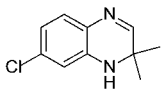
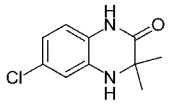
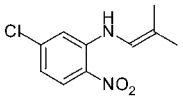
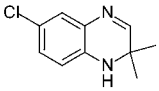
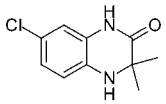
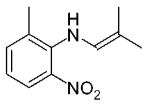
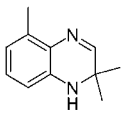
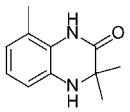
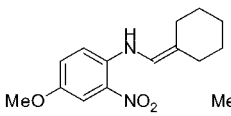
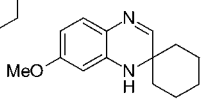
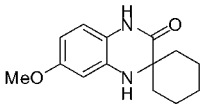
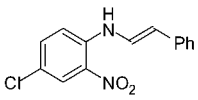
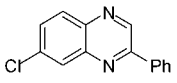
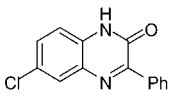
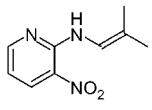
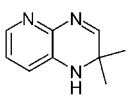
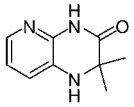
(16) **Typical experimental procedure:** To an ACE-Glass pressure tube were added **3b** (107 mg, 0.48 mmol), $Pd(dba)_2$ (18 mg, 0.031 mmol), dppp (13 mg, 0.032 mmol), 1,10-phenanthroline (10 mg, 0.055 mmol), and DMF (5 mL). A pressure head was attached; the reaction mixture was pressurized to 6 atm of carbon monoxide and heated at 70 °C for 4 h. A slow change in color from deep purple to brown was observed. Extractive workup with dichloromethane and brine followed by flash chromatography (98:2, hexanes:ethyl acetate) gave 57% of **4b** and 40% of **5b**.

Table 1. Synthesis of 1,2-Dihydroquinoxalines and 3,4-Dihydroquinoxalinones

Entry	Enamine[a]	Quinoxaline[b]	Quinoxalinone[b]
1[c]	 **3b** (95%)	 **4b** (1%)	 **5b** (6%)
2		**4b** (57%)	**5b** (40%)
3	 **3c** (89%)	 **4c** (50%)	 **5c** (45%)
4	 **3d** (100%)	 **4d** (56%)	 **5d** (16%)
5	 **3e** (88%)	 **4e** (29%)	 **5e** (45%)
6	 **3f** (5%)	 **4f** (29%)	 **5f** (45%)
7	 **3g** (88%)	 **4g** (70%)	 **5g** (13%)
8	 **3h** (85%)[d]	 **4h** (25%)	 **5h** (14%)
9	 **3i** (20%)	 **4i** (34%)	 **5i** (6%)

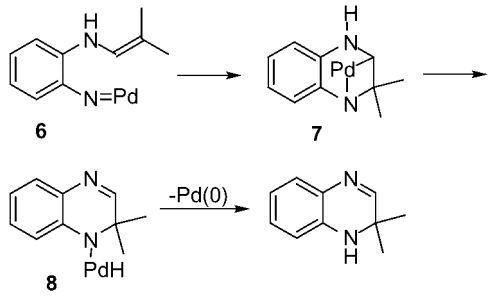
[a] Isolated yield of enamine from the corresponding 2-nitroaniline and aldehyde. [b] Isolated yield of pure 1,2-dihydroquinoxaline or 3,4-dihydroquinoxalinone. [c] In the absence of 1,10-phenanthroline. [d] Isolated as a 1:1 *cis*:*trans* mixture.

to aniline derived enamines (entry 9). A spirocyclic 1,2-dihydroquinoxaline and 3,4-dihydroquinoxalinone were obtained upon reaction of a cyclohexane-substituted enamine (entry 7). Finally, substrates having only one β-substituent on the enamine moiety underwent the cyclization (entry 8). The overall yield of products was low; however, interestingly, a fully aromatic quinoxaline (**4h**) was obtained. The annulation reaction is apparently restricted to enamines that can be isolated and, at least partially, purified. Attempted palladium-catalyzed cyclization of enamines formed in situ from aldehydes and anilines was unsuccessful. An additional restriction is the unfavorable imine−enamine equilibrium observed using α-unsubstituted aldehydes and the complete lack of reaction between ketones and 2-nitroanilines.

Adventitious water in the solvent, or in the carbon monoxide, was initially considered a possible source of the 3,4-dihydroquinoxalinone oxygen. However, reaction of enamine **3a** in a 1:1 DMF−water mixture gave only 1,2-dihydroquinoxaline **4a** in 37% isolated yield in addition to a small amount of starting material. No trace of 3,4-dihydroquinoxalinone **5a** was observed. Oxidation of the 1,2-dihydroquinoxaline to the 3,4-dihydroquinoxalinone was not observed under standard reaction conditions. For example, 1,2-dihydroquinoxaline **4e** was recovered unchanged from the reaction mixture. The reverse reaction, i.e., reduction of 3,4-dihydroquinoxalinone to 1,2-dihydroquinoxaline, was also disproved under the same conditions. These results suggest that the 3,4-dihydroquinoxalinone oxygen is derived from the nitro group.

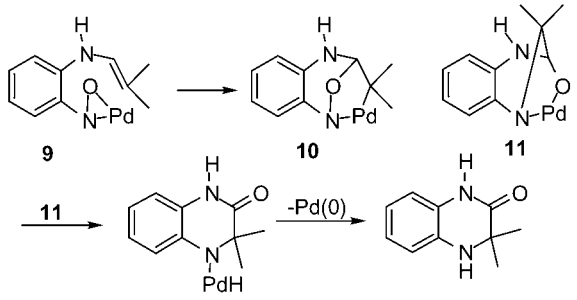
The mechanism of the annulation reaction is presently unclear; however, a few possible sequences of events are outlined in Schemes 3 and 4. Transition metal catalyzed

Scheme 3



deoxygenation of organic nitro compounds has been proposed to proceed via the formation of nitrene, or nitrenoid, intermediates. Carbon monoxide is crucial for the reaction

Scheme 4



to proceed, functioning as a reducing agent to give a putative metal-bound nitrene and carbon dioxide. Metal-bound nitrenes have been reported; for example, a ruthenium-bound nitrene derived from 2-nitrosobiphenyl has been isolated and characterized by X-ray crystallography.[17] Decomposition of this complex gave carbazole, the expected nitrene insertion product.

A formal, intramolecular, [2 + 2] cycloaddition between the intermediately formed palladium-bound nitrene **6** and the alkene would furnish the bicyclic compound **7**. Sequential β-hydride elimination, at least formally, to give **8** followed by reductive elimination would produce the 1,2-dihydroquinoxaline and regenerate the active palladium(0) catalyst. The regioselectivity of the cycloaddition parallels the selectivity observed for intramolecular ketene−alkene cycloadditions of terminally disubstituted alkenes. A related mechanism has been suggested for thermal decompositions of arylamino-substituted Fischer carbene complexes forming quinolines.[18]

The formation of 3,4-dihydroquinoxalinones presents, to our knowledge, an unknown reaction path. It is plausible that, prior to complete deoxygenation to give the palladium-bound nitrene **7**, insertion of the alkene into the intermediately formed metallacyclopropane **9** (a metal-bound nitrosarene)[19] occurs (Scheme 4). Two different metallacyclopentane insertion products having a bond between the oxygen and the vinylic CH carbon of the enamine can be envisioned (**10**−**11**). Complex **11** appears to be the more likely candidate since a simple β-hydride elimination−reductive elimination sequence would furnish a 3,4-dihydroquinoxalinone. Intramolecular insertions of alkenes into metal-bound nitrosarenes, the first step in Scheme 4, have been proposed.[20]

In summary, we have developed a novel palladium-catalyzed *N*-heteroannulation of enamines, formed by condensation of 2-nitrobenzenamines with aldehydes, to afford readily separated 1,2-dihydroquinoxalines and 3,4-dihydroquinoxalinones. The annulation reaction is inherently regioselective. An in-depth study of the scope, limitation, and mechanism of this reaction is underway in our laboratories.

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Supporting Information Available: Synthetic procedures and full 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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