

# Catalytic C–H Functionalization Driven by CO as a Stoichiometric Reductant: Application to Carbazole Synthesis

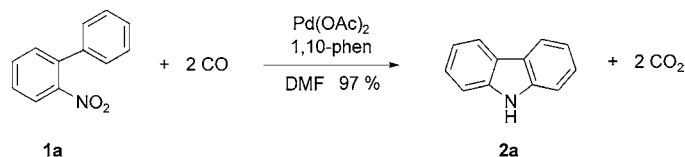
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## ABSTRACT



A palladium-catalyzed regioselective C–H bond functionalization driven by CO as the stoichiometric reductant is described. Nitrogen heterocycles, e.g., carbazoles, are accessible in good to excellent yields with use of palladium acetate and 70 psig of carbon monoxide at 140 °C.

The functionalization of unactivated C–H bonds represents a powerful approach to C–C and C–heteroatom bond formation and is currently receiving significant attention. Palladium-catalyzed processes using stoichiometric Cu(OAc)<sub>2</sub> or dioxygen have recently been developed for the formation of C–C,<sup>1</sup> C–N,<sup>2,3</sup> and C–O<sup>3</sup> bonds.<sup>4</sup> Rhodium-catalyzed formation of C–N bonds with PhI(OAc)<sub>2</sub> as the stoichiometric oxidant has also been reported<sup>5</sup> and exploited in complex molecule synthesis, e.g. (–)-tetrodotoxin.<sup>6</sup> These new methods introduce functionality at C–H bonds via a catalytic cycle driven by a terminal oxidative event.

Deoxygenation of nitroaromatics to give heterocycles was first realized by Waterman and Vivian in 1940 using stoichiometric iron oxalate at 200 °C.<sup>7</sup> The deoxygenative

cyclization of *o*-nitro arenes in refluxing triethyl phosphite as solvent remains the most common method to effect this transformation.<sup>8,9</sup> The widely accepted mechanism for this transformation involves exhaustive deoxygenation to a singlet nitrene that undergoes a downstream C–H insertion.<sup>10</sup> While broad in scope, the generation of a large amount of phosphorus waste detracts from this approach. In recent years, transition metal catalyzed variants of this reaction with CO as the stoichiometric reductant have been developed.<sup>11,12</sup> Palladium/phosphine catalysts are effective for the reductive

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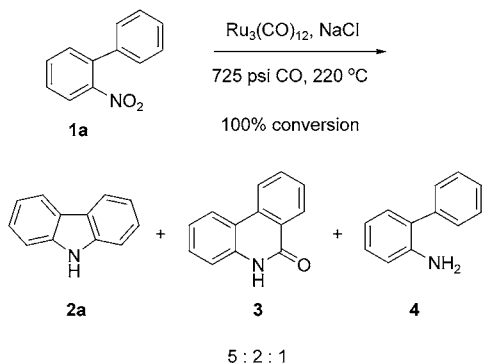
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cyclization of *o*-nitrostyrenes to indoles, but fail when applied to biaryl substrates.<sup>11</sup> A transition metal catalyzed reductive cyclization of nitrobiaryls uses Ru<sub>3</sub>(CO)<sub>12</sub> at 220 °C and 725 psi of CO (Scheme 1).<sup>13</sup> The moderate yields of carbazoles

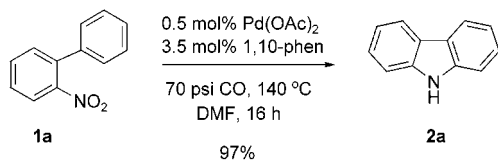
### Scheme 1. Ruthenium-Catalyzed Reductive Cyclization



obtained in this reaction due to competitive formation of products from CO insertion (**3**) and over-reduction (**4**), coupled with the harsh conditions, significantly limit the synthetic utility of this system.

The high reactivity of catalysts derived from palladium(II) salts and bidentate nitrogen ligands in the reduction of nitroarenes to isocyanates and carbamates<sup>14</sup> motivated us to investigate application of these systems to carbazole synthesis. Treatment of *o*-nitrobiphenyl **1a** with 2 mol % of palladium(II) acetate and 4 mol % of 1,10-phenanthroline in DMF at 60 psig of CO and 60 °C afforded carbazole **2a** in 53% yield. Comprehensive screening<sup>15</sup> revealed that conversion increased with both temperature and pressure. At 60 psig of CO and 120 °C the yield of **2a** increased to 84%, while at 15 psig of CO and 120 °C the yield of **2a** decreased to 32%. Optimal pressure and temperature conditions were determined to be 70 psig of CO at 140 °C and gave **2a** in 95% assay yield.

### Scheme 2. Palladium-Catalyzed Reductive Cyclization



The scope of the reaction was investigated by using the Pd(OAc)<sub>2</sub>/phen catalyst system optimized for **1a** (Table 1).

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**Table 1.** Reductive Cyclization of Substituted *o*-Nitrobiaryl Substrates<sup>a</sup>

entry	substrate	product	yield <sup>b</sup>
1			96
2			59 (70) <sup>c</sup>
3			22
4			45 (91) <sup>d</sup>
5			75
6			81 <sup>e,f</sup>
7			74 <sup>f,g</sup>

<sup>a</sup> Reaction conditions: 2 mol % of Pd(OAc)<sub>2</sub>, 4 mol % of phen, 70 psig of CO, 140 °C for 16 h in DMF. <sup>b</sup> Isolated yield unless otherwise noted.

<sup>c</sup> HPLC assay yield. <sup>d</sup> Yield based on recovered starting material. <sup>e</sup> Product obtained as a 93:7 ratio of regioisomers as determined by <sup>1</sup>H NMR spectroscopic analysis of the unpurified reaction mixture. <sup>f</sup> Yield reported for major isomer isolated by flash chromatography. <sup>g</sup> Product obtained as an 85:15 ratio of regioisomers as determined by <sup>1</sup>H NMR spectroscopic analysis of the unpurified reaction mixture.

The reductive conditions tolerate a wide range of functional groups, e.g. amides and aromatic chlorides (entries 1 and 5). The C–H functionalization of pyridines and thiophenes occurs in good yield with good regioselectivity (entries 6 and 7). The regioselectivity is reminiscent of that obtained with nitrenes.<sup>16</sup> Yields for electron-rich *o*-nitrobiphenyls **1c** and **1d** were lower due to nonproductive formation of the corresponding anilines.

Further optimization of the reaction of **1a** revealed that catalyst loading can be reduced by increasing the ligand/

(15) Optimization was accomplished by using a 6 × 8 module parallel pressure reactor system.

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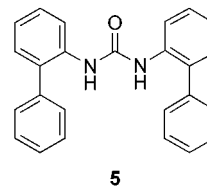
palladium ratio.<sup>17</sup> At 0.5 mol % of Pd(OAc)<sub>2</sub>, a high yield (94%) was obtained in 16 h at a 7:1 ligand/palladium ratio. The yield decreased (57%) at a 5:1 ligand/palladium ratio due to lower conversion. At 0.1 mol % of Pd(OAc)<sub>2</sub>, the reaction did not occur at a synthetically useful rate, with 50% conversion after 16 h. In a preparative run in an autoclave, reaction of **1a** with 0.5 mol % of Pd(OAc)<sub>2</sub> and 3.5 mol % of phen afforded **2a** in 97% yield (Scheme 2).

Changing the catalyst system to palladium(II) trifluoroacetate [Pd(TFA)<sub>2</sub>] and 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) drastically affected the reaction. For the reductive carbonylation of nitroarenes to afford isocyanates, increased catalytic activity is obtained with palladium(II) salts with noncoordinating counterions and electron-rich phenanthrolines.<sup>14b,c,18,19</sup> Reaction of **1a** under the optimized conditions with 2 mol % of Pd(TFA)<sub>2</sub> and 4 mol % of tm-phen surprisingly afforded primarily aniline **4** (54%) and none of the expected cyclization product. Submission of **4** to standard reaction conditions afforded recovered starting material, verifying that **4** is not on the reaction pathway to **2a**. Aniline **4** and urea **5** were produced as low-level impurities under optimal cyclization conditions by using the palladium acetate/phen catalyst system.

(17) In the synthesis of oxazines from nitroarenes with a similar catalyst system, a 16:1 ligand/palladium ratio is optimal: Ragaini, F.; Cenini, S.; Brignoli, D.; Gasperini, M.; Gallo, E. *J. Org. Chem.* **2003**, *68*, 460–466.

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(19) For counterion effects in Pd-catalyzed C–H functionalization reactions, see ref 3.



In conclusion, we have developed a palladium-catalyzed reduction of biphenyls to afford nitrogen heterocycles in good to excellent yield. This method forms a nitrogen–carbon bond at an unactivated sp<sup>2</sup> C–H bond via a catalytic cycle driven by a terminal reductive event. With use of CO as the stoichiometric reductant and 0.5 mol % of palladium acetate, CO<sub>2</sub> is the only stoichiometric byproduct, which offers significant economic and environmental advantages over the standard triethyl phosphite deoxygenation procedure. Speculation on the identity of reactive intermediates at this stage would be premature; however, detailed investigations into the mechanism are currently in progress.

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**Supporting Information Available:** 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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