

# Dimerization of ethynylaniline to a quinoline derivative using a ruthenium/gold heterobimetallic catalyst

Phillip A. Shelton, Casie R. Hilliard, Michael Swindling, and Lisa McElwee-White\*

*Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA.*

*E-mail: [lmwhite@chem.ufl.edu](mailto:lmwhite@chem.ufl.edu)*

**Dedicated to Dr Cynthia A. Maryanoff and Dr Bruce E. Maryanoff**

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## Abstract

Dimerization of 2-ethynylaniline in the presence of the Ru/Au complexes  $\text{CpRu}(\text{PPh}_3)\text{Cl}(\mu\text{-dppm})\text{AuCl}$  or  $\text{CpRu}(\text{PPh}_3)\text{I}(\mu\text{-dppm})\text{AuI}$  results in formation of a quinoline derivative. Monometallic model compounds for the Ru and Au centers did not catalyze the dimerization reaction. This transformation proceeds in higher yield in the absence of solvent.

**Keywords:** Homogeneous catalysis, heterobimetallic catalyst, quinoline, gold catalysis

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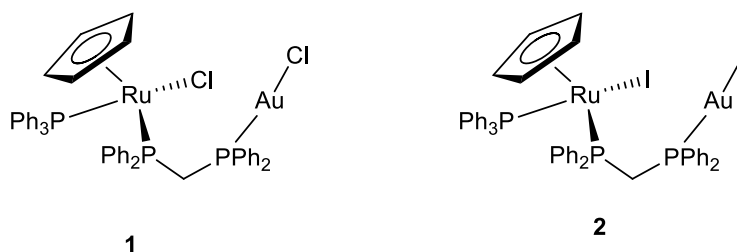
## Introduction

Bimetallic catalysts have recently been reported for a wide variety of applications,<sup>1-8</sup> including carbon-carbon bond forming reactions,<sup>9-11</sup> methanol oxidation,<sup>8</sup> molecular switching,<sup>12,13</sup> and polymerization of ethylene.<sup>14</sup> In these examples, the different metal centers in heterobimetallic catalysts provide advantages including the formation of products different from those obtained using mononuclear complexes.

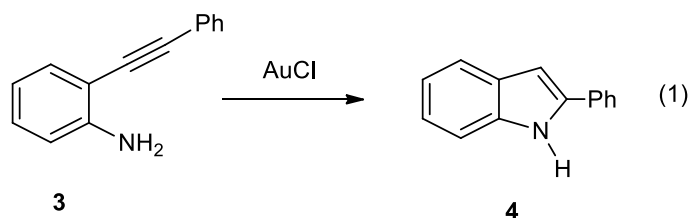
There has been much recent interest in the use of gold complexes as catalysts for synthetic transformations.<sup>15-26</sup> Many of these reactions take advantage of the alkynophilicity of gold. Coordination of an alkyne to the gold center increases the electrophilicity of the alkyne thereby allowing attack of weaker nucleophiles than would normally be reactive. We now report the utilization of the alkynophilicity of gold to induce dimerization of 2-ethynylaniline, catalyzed by Ru/Au heterobimetallic complexes.

## Results and Discussion

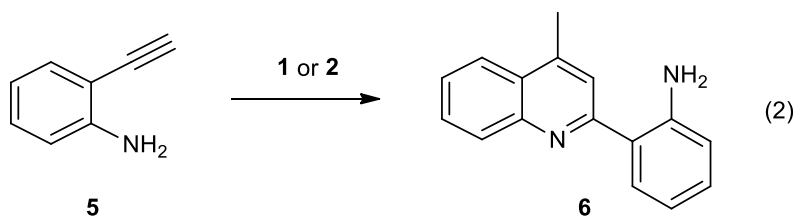
The heterobimetallic complexes  $\text{CpRu}(\text{PPh}_3)\text{Cl}(\mu\text{-dppm})\text{AuCl}$  **1** and  $\text{CpRu}(\text{PPh}_3)\text{I}(\mu\text{-dppm})\text{AuI}$  **2**<sup>27</sup> were investigated as possible catalysts for reactions that take advantage of the reactivity of gold with alkynes while simultaneously promoting reactivity at the proximate ruthenium center.



One such system was found when re-examining the cyclization of 2-ethynylaniline derivatives to indoles.



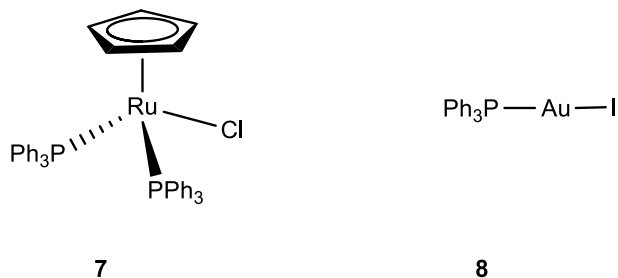
The conversion of the alkyne **3** to indole **4** has been previously reported to be catalyzed by gold(I) chloride (Equation 1).<sup>28</sup> In contrast, reaction of 2-ethynylaniline **5** in the presence of the heterobimetallic complex **1** or **2** did not afford the parent indole in a reaction analogous to the formation of compound **4**. Instead, reaction of **5** in the presence of **2** resulted in formation of quinoline derivative **6** in 20% isolated yield (Equation 2).



Interestingly, dimerization of **5** to **6** has previously been reported to be catalyzed by the Lewis acid  $\text{InBr}_3$ .<sup>29,30</sup> Although gold-carbene complexes have been proposed as reactive intermediates in the reactions of terminal alkynes,<sup>21,31</sup> recent results suggest that gold(I) complexes can function as Lewis acids to generate dipolar intermediates during their catalytic reactions with alkynes.<sup>32,33</sup> These latter results are consistent with the reaction of **5** and  $\text{InBr}_3$  generating the same product **6** as the reactions of **5** with **1** or **2**.

Model catalysts **7** and **8** were studied in control experiments to investigate the possibility that the reaction proceeds at one metal center with no contribution from the other. Reaction of 2-ethynylaniline **5** in the presence of **7** or **8** in methylene chloride at 90 °C produced no detectable quantities of quinoline **6** (Table 1, Entries 1 and 2), nor was **6** produced when both **7** and **8** were present (Entry 3). If the gold centers of **1** and **2** are acting as simple Lewis acids in the

conversion of **5** to **6**, they must be more Lewis acidic than **8**. This seems particularly unlikely for the heterobimetallic gold iodide complex **2**, which does produce quinoline **6** from **5**.



When catalyst **1** was reacted with 2-ethynylaniline, a low yield of **6** was obtained (Entry 4), but the result was slightly improved in the absence of solvent (Entry 5). Use of catalyst **2** resulted in a 34% yield of **6** (Entry 6), but lengthening the reaction time further did not increase the yield. When this reaction was conducted in neat 2-ethynylaniline (Entry 7), an enhancement of the yield was observed. Our efforts to optimize the yields of **6** included reactions at three different temperatures: 25 °C, 45 °C and 90 °C. The formation of the quinoline **6** required the highest temperature. In the absence of substrate, catalyst **2** is stable at these temperatures – as established by control experiments in which  $\text{CDCl}_3$  solutions of **2** were monitored by  $^{31}\text{P}$ -NMR spectroscopy for three hours at 125 °C. No decomposition products were observed. Upon addition of one equivalent of 2-ethynylaniline, however, decomposition to an unidentifiable mixture occurred.

**Table 1.** Formation of the quinoline **6** catalyzed by monometallic and heterobimetallic catalysts

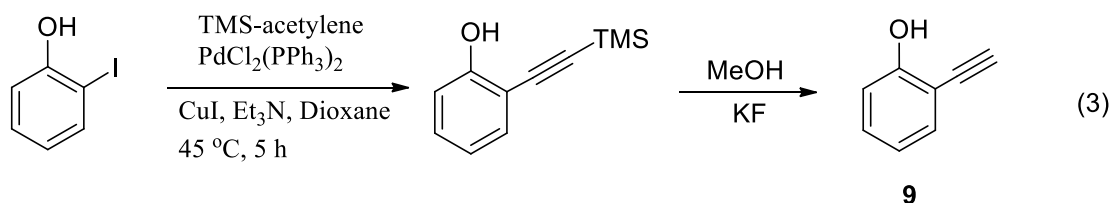
Entry	Catalyst	Solvent	Yield <sup>a,b</sup>
1	<b>7</b>	$\text{CH}_2\text{Cl}_2$	0%
2	<b>8</b>	$\text{CH}_2\text{Cl}_2$	0%
3	<b>7</b> and <b>8</b>	$\text{CH}_2\text{Cl}_2$	0%
4	<b>1</b>	$\text{CH}_2\text{Cl}_2$	7%
5	<b>1</b>	None	18%
6	<b>2</b>	$\text{CH}_2\text{Cl}_2$	34%
7	<b>2</b>	None	41%

<sup>a</sup> 5 mmol 2-ethynylaniline, 0.05 mmol catalyst, 5 mL solvent at 90 °C for 24 h under  $\text{N}_2$  atmosphere. <sup>b</sup>Yields determined by  $^1\text{H}$  NMR spectroscopy.

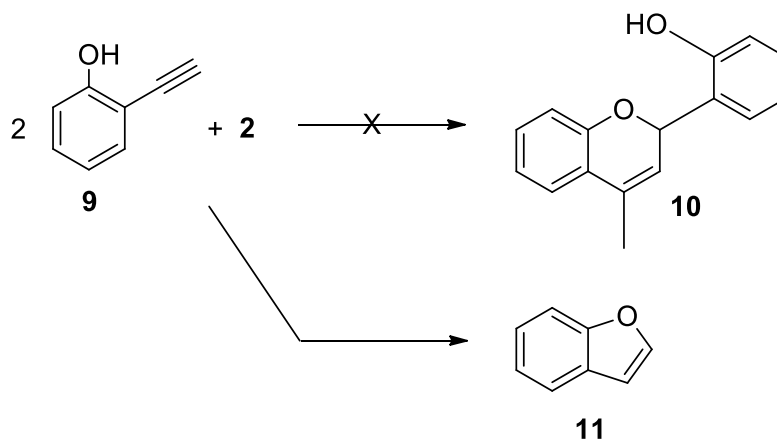
Various solvents were also used in efforts to optimize production of the quinoline **6**. Non-polar (hexane and toluene), polar (tetrahydrofuran, ether and ethanol), oxidizing- (nitromethane) and coordinating- solvents (dimethylformamide and acetonitrile) were examined with catalyst **2** as well as the model compounds **7** and **8**. The monometallic complexes **7** and **8**, either separately

or together, did not produce the quinoline **6** in any of the solvents. In each of the solvents, the heterobimetallic complex **2** afforded trace amounts of quinoline **6**, as detected in the NMR spectra of reaction mixtures. These yields were, however, lower than those of the reaction in methylene chloride and the neat reaction reported above.

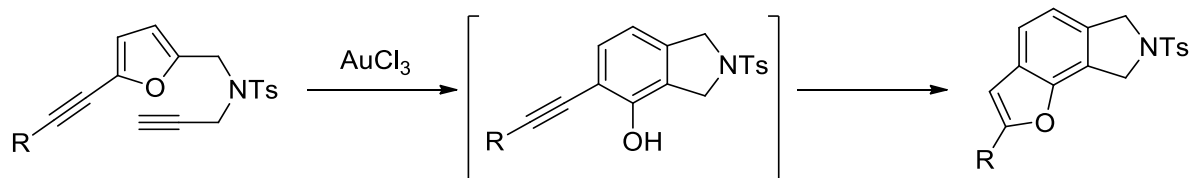
Attempts were also made to perform a similar dimerization reaction with 2-ethynylphenol. The starting material was synthesized according to Equation 3.<sup>34</sup> Addition of TMS-acetylene to *o*-iodophenol in a Sonogashira reaction was followed by deprotection of the alkyne to form **9** in 69% yield. The compound was used immediately after preparation, due to its lability.



Reaction of **9** with the heterobimetallic catalyst **2** produced a mixture of compounds, as observed by GC/MS, in which the only identifiable product was the indole analogue, benzofuran **11**. None of the dimerization product **10** was obtained (Scheme 1). Cyclization of **9** to **11** is analogous to the formation of indole from **5** in the presence of AuCl (Equation 1). A related benzofuran formation has been previously catalyzed with AuCl<sub>3</sub> to generate similar products (Scheme 2).<sup>35</sup>



**Scheme 1.** Formation of benzofuran from 2-ethynylphenol.



**Scheme 2.** Benzofuran derivative generated with AuCl<sub>3</sub> catalysis.

## Conclusions

Dimerization of 2-ethynylaniline to form the quinoline derivative **6** occurs in moderate yields in the presence of the heterobimetallic complexes **1** and **2**. Control experiments confirm that the heterobimetallic catalysts afford a product different from the monomeric model compounds. Solvent-free reactions afforded higher yields than those obtained in the presence of solvent. Formation of a product with the heterobimetallic catalysts that is different than that obtained using the monometallic model compounds is consistent with prior studies where the synergistic effect of two metal centers controls the reactivity.

## Experimental Section

**General.** <sup>1</sup>H- and <sup>13</sup>C- NMR spectra were obtained on Varian Gemini 300, VXR 300 and Mercury 300 spectrometers. Infrared spectra were measured on a Perkin-Elmer Spectra One FTIR. Mass spectrometry was performed by the University of Florida analytical service. All chemicals were purchased from Sigma-Aldrich except for metal-containing reagents which were purchased from Strem in reagent grade and used with no further purification unless stated otherwise. Solvents were passed through an MBraun MB-SP solvent purification system prior to use. The bimetallic catalysts, **1**<sup>36</sup> and **2**,<sup>27</sup> and 2-ethynylphenol **9**<sup>34</sup> were prepared according to literature reports. Compounds **1**,<sup>36</sup> **2**,<sup>27</sup> and **9**<sup>34</sup> were characterized by comparison to literature data. Benzofuran **11** was characterized by comparison to an authentic sample purchased from Sigma-Aldrich.

**Formation of 2-(4-methylquinolin-2-yl)aniline 6 from 2-ethynylaniline 5.** The heterobimetallic catalyst **2** (0.0500 mmol, 0.0586 g) was placed into a 50 mL Schlenk flask and allowed to stand under vacuum for 20 minutes. While under nitrogen, 5 mL of dry methylene chloride was then added, followed by 2-ethynylaniline (5.00 mmol, 0.569 mL), and the solution was allowed to stir under reflux for 24 h at 90 °C. The reaction mixture was extracted with hexane, and the solvent was evaporated under reduced pressure. An off-white powder was isolated in 20% yield after column chromatography on silica gel (10% EtOAc/hexane). The compound, m.p. 74.3-76.0 °C, was identified by comparison with literature data.<sup>30</sup>

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