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Gold(I)-Catalyzed Formation of 3-Pyrazolines through Cycloaddition of Diaziridine to Alkynes

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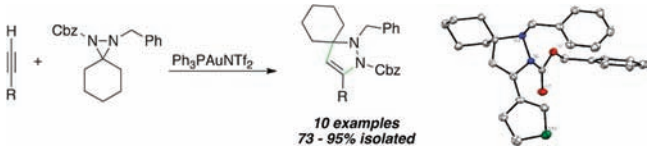
ABSTRACT



This work reports the high-yield formation of pyrazoline derivatives mediated by gold(I) catalysts. The reaction utilizes a diaziridine, which has seen only limited usage in organic methodology. Mechanistic studies suggest a gold-mediated opening of the diazridine ring, alkyne insertion, and finally an intramolecular hydroamination to furnish the product.

Pyrazolines have been heavily investigated due to their occurrence in a number of biologically active molecules. Various pyrazolines have exhibited antibacterial, anti-amoebic, antitumor, anti-inflammatory, antidepressant, and MAO-inhibitory activities.[1] It is therefore important to be able to access them through methods that are rapid, cost-effective, and atom-economical. Pyrazolines are typically synthesized by the condensation/addition of hydrazines onto α,β-unsaturated carbonyl compounds.[2,3] More recently, azomethine iminies have been used to form pyrazoline-containing scaffolds via cycloaddition onto alkynes.[4]

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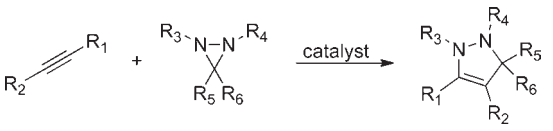
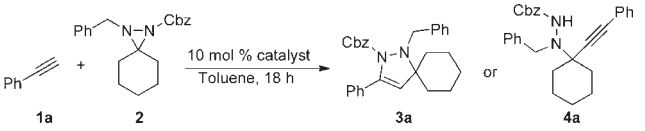
Scheme 1. Cycloaddition of Diaziridine to Alkynes To Construct 3-Pyrazolines



An intramolecular iodocyclization was also recently reported in which the use of propargylic hydrazides yielded 1-iodo-3-pyrazolines.[5] Even with recent developments, there are limited ways to synthesize the pyrazoline scaffold. We propose a different strategy of accessing pyrazolines through the use of diaziridines, the dinitrogen analogues of the more familiar three-membered aziridines. We envisioned either a tandem event wherein diaziridine would open and then react with an alkyne in a formal [3 + 2] cycloaddition or a concerted process to yield the same product (see Scheme 1). Metal catalysts, especially π-acids such as gold ions, may mediate such reactions. In addition, gold complexes have recently been established as superior catalysts for the addition of nitrogen and oxygen nucleophiles to unsaturated hydrocarbons.[6]

Reactivity reports of diaziridines are limited and most revolve around the use of activated substrates such as ketenes, cyclopropenones, isocyanates, maleimides, or highly tailored diaziridines.[7] There have also been a few reports of Lewis-acid-catalyzed cycloaddition reactions with similarly activated substrates.[8] Shi and co-workers have utilized diaziridinones, analogues of diaziridines, with palladium and copper catalysts to perform α-aminations and diaminations of dienes, esters, and ketones.[9] Compared to other systems, in our reaction system, the diaziridine is minimally modified and the alkynes are not activated by electronics, strain, etc.[4a,b] In this paper, we report the first gold(I)-catalyzed cycloaddition of this diaziridine onto alkynes, giving high yields of 3-pyrazolines. In our initial studies, we sought to utilize a diaziridine that is readily accessible and, under the right conditions, exhibits high reactivity. We employed diaziridine **2**, in which the two nitrogens are modified with benzyl and carbamate groups. **2** is readily synthesized in two high-yielding steps beginning from cheap and commercially available cyclohexanone and benzylamine and is column and air-stable. Initial optimizations were carried out between **2** and phenylacetylene **1a** (Table 1). Entries 1−3 in Table 1 ruled out both thermal and simple acid-catalyzed reactions. Entries 4 and 5 in Table 1 attempted to mimic conditions used to cyclize azomethine imine intermediates, but with no success.[4a,b]

Table 1. Catalyst Screen for Pyrazoline Formation[a]



entry	catalyst	temp	equiv **1a**	yield (%)[b]
1	none	100 °C	5.0	no reaction[c]
2	TfOH	rt	5.0	no reaction
3	TfOH	50 °C	5.0	degradation
4	CuCl	70 °C	5.0	no reaction
5	CuI	70 °C	5.0	no reaction[d]
6	AgOTf	70 °C	5.0	41 (**4a**)
7	$AuCl_3$	70 °C	5.0	30 (**4a**)
8	$Zn(OTf)_2$	70 °C	5.0	23 (**4a**)
9	$Cu(OTf)_2$	70 °C	5.0	20 (**4a**)
10	$Ph_3AuCl/AgOTf$	70 °C	5.0	89 (**3a**)
11	$Ph_3AuCl/AgOTf$	50 °C	5.0	85 (**3a**)
12	$Ph_3AuCl/AgOTf$	rt	1.0	35 (**3a**)
13	$Ph_3AuCl/AgOTf$	70 °C	1.0	58 (**3a**)
14	$Ph_3AuCl/AgOTf$	70 °C	2.0	85 (**3a**)
15	Ph_3AuNTf_2	70 °C	5.0	85 (**3a**)
16	Ph_3AuNTf_2	70 °C	2.0	85 (**3a**)

[a] Reactions performed with 0.25 mmol **2**. [b] Yield of isolated product. [c] Reaction was run for five days. [d] Reaction run with 0.5 equiv of Cy_2NMe.

Surprisingly, the use of copper, zinc, silver, and gold(III) catalysts (Table 1, entries 6−9) led to insertion of the alkyne into the ring-opened diaziridine (product **4a**). We reason that, due to the presence of the carbamate group on one of the nitrogen atoms of the diaziridine **2**, the C−N bond is polarized which may facilitate thermal ring opening followed by metal-catalyzed insertion of an acetylide species. Further optimization showed that $Ph_3PAuNTf_2$ provided a cleaner reaction and slightly higher yields in comparison to the $Ph_3PAuCl/AgOTf$ system.[10]

With the reaction conditions optimized, we studied the scope of the reaction. As shown in Table 2, both aryl and aliphatic alkynes react, but it is clear that electron-poor

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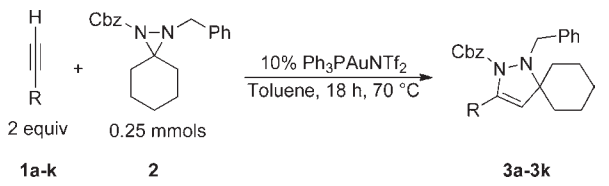
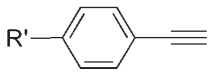
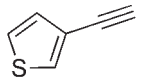
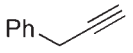
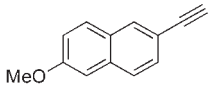
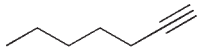
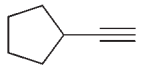
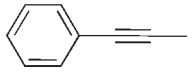
(10) For a description of metal triflimidates as catalysts in organic synthesis, see:Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7860–7888.

Table 2. Substrate Scope for Pyrazoline Formation

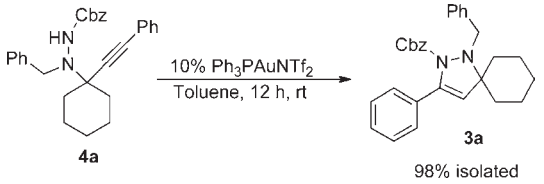


1a-k 2 3a-3k

entry	substrate		product	yield (%)[a]
1		R' = H (**1a**)	**3a**	85
2		R' = Me (**1b**)	**3b**	89
3		R' = Br (**1c**)	**3c**	95
4		R' = OMe (**1d**)	**3d**	73[b]
5		R' = Ph (**1e**)	**3e**	95
6		R' = CF_3 (**1f**)	**3f**	85
7		**1g**	**3g**	73
8		**1h**	**3h**	84
9		**1i**	**3i**	85
10		**1j**	**3j**	83
11		**1k**	**3k**	78
12		**1l**	**3l**	0

[a] Yields are from isolated products. [b] Reaction run at room temperature.

Scheme 2. Gold-Catalyzed Cyclization of Compound **4a**



substrates give higher yields (Table 2, entries 1–6). As we hypothesized, gold(I) performed the cycloaddition reaction leading to the target product **3a**. Thiophene does not poison the catalyst, and good yields were seen with 3-ethynylthiophene (entry 7). Entry 12 shows that so far our reaction is limited to terminal alkynes. One possible argument is that steric hindrance might come into play for this reactivity pattern; however, even the use of 2-butyne as substrate gave no yield of pyrazoline. This requirement of a terminal alkyne for the reaction suggests a mechanism with a terminal alkyne insertion step followed by cyclization. We speculated that product **4a** is an intermediate to the

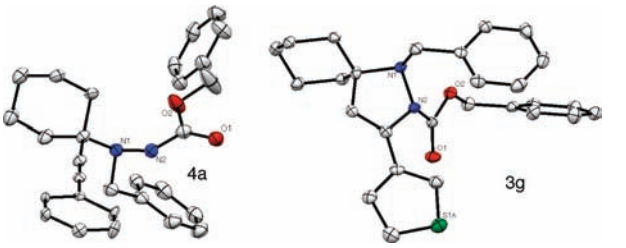
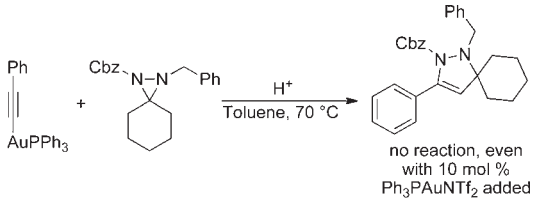


Figure 1. ORTEP representations of **4a** and **3g**.

final cycloaddition product **3a** in the gold-catalyzed process, but further proof was warranted.

The structure and connectivity of the product was demonstrated conclusively by an X-ray structure of **3g** (Figure 1), the thiophene-functionalized pyrazoline. We also obtained a crystal structure of insertion product **4a**, which can be isolated when other catalysts are used (vide supra).[11] This led us to hypothesize that the alkyne insertion product was possibly an intermediate in the catalytic reaction. Treatment of **4a** with 10 mol % of $Ph_3PAuNTf_2$ at room temperature afforded **3a** in near quantitative yield (Scheme 2). Postulating that a gold-acetylide species may be involved in the reaction, we synthesized the (phenylethynyl)(triphenylphosphine)gold species. We expected this intermediate to react stoichiometrically with **2** and lead to product. Much to our surprise, we only recovered the original gold-acetylide species, even with the addition of catalytic $Ph_3PAuNTf_2$ (Scheme 3).[12] This ruled out the role of a discrete metal-acetylide species in the reaction.

Scheme 3. Alkynyl–Gold Intermediate Does Not Participate in the Cycloaddition Reaction

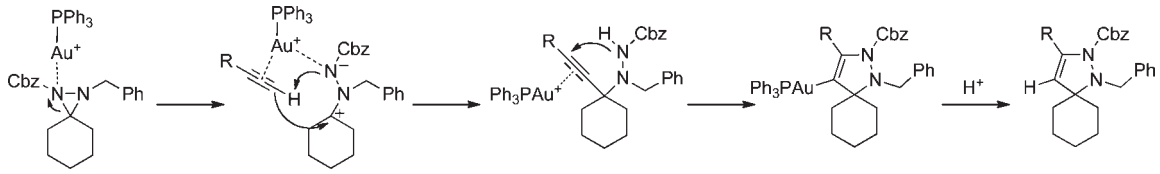


Surveying the reactivity pattern in Table 1, we hypothesized that the addition of a metal salt may facilitate the opening of the diaziridine ring. The existence of product **4a** as well as the ability of gold to cyclize product **4a** to yield product **3a** led us to the proposed mechanism shown in Scheme 4. In this case, gold facilitates the low-temperature opening of the diaziridine intermediate, followed by insertion of the alkyne into the cationic carbon center. While the second species is drawn with the gold center in a trigonal

(11) See Supporting Information for details on both crystal structures.

(12) See Supporting Information for further details on the conditions tested.

Scheme 4. Mechanistic Proposal for the Cycloaddition Reaction



geometry, it may also be a linear complex along the P–Au–alkyne axis with minor interaction with the diaziridine motif. The linear geometry is by far the most popular gold coordination motif; however, the trigonal geometry has been shown to be a valid structure in a number of coordination environments.[13] Finally, the gold(I) center performs an intramolecular hydroamination reaction between the alkyne and the hydrazine fragment, leading to the pyrazoline product. It explains why other metal salts do not yield the pyrazoline framework but instead intermediate **4**.

We have shown in this study that diaziridines are valuable synthons for the formation of nitrogen heterocycles, and that gold(I) is a superior catalyst to mediate the reaction. Diaziridines can be readily prepared and are reactive under the appropriate conditions. With more investigation, we believe that this organic motif could be used for various intra- and intermolecular additions to unsaturated substrates, leading to a variety of valuable nitrogen-containing heterocycles.

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Supporting Information Available. Experiment details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) For examples of trigonal gold complexes, see: (a) Pérez-Galán, P; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem.—Eur. J.* **2010**, *16*, 5324–5332. (b) Khin, C.; Hashmi, A. S. K.; Rominger, F. *Eur. J. Inorg. Chem.* **2010**, 1063–1069. (c) Dias, H. V. R.; Flores, J. A.; Wu, J.; Kroll, P. *J. Am. Chem. Soc.* **2009**, *131*, 11249–11255. (d) Gimeno, M. C.; Laguna, A. *Chem. Rev.* **1997**, *97*, 511–522. (e) Schmidbaur, H.; Schier, A. *Organometallics* **2010**, *29*, 2–23.