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Three-Component Gold(I)-Catalyzed Alkoxyvinylation

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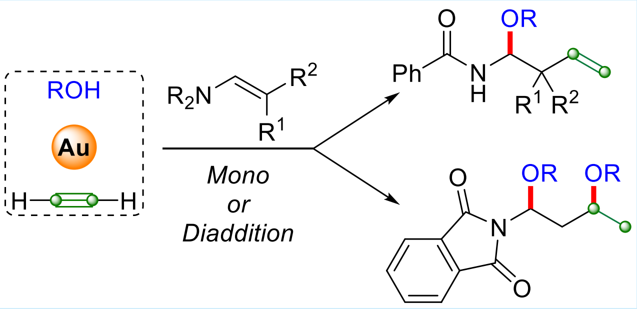
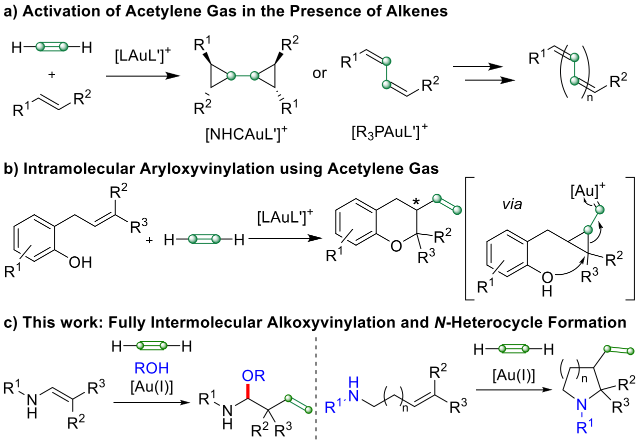
ABSTRACT: Acetylene has been underexploited despite being a highly valuable feedstock for chemical synthesis. We have developed the first true gold(I)-catalyzed intermolecular three-component reaction between acetylene, alkenes, and alcohols to afford β-vinyl hemiaminal scaffolds from *N*-vinyl amides. Unusual biscyclopropyl and 3-vinyl *N*-heterocyclic scaffolds were obtained through the incorporation of a second *N*-vinyl unit or tethered alkene into the starting material.



Due to its high abundance and high reactivity, acetylene has become one of the major chemical feedstocks in chemical synthesis.[1−4] Another important aspect of the utilization of acetylene gas in organic synthesis is its high atom economical potential, well suited for growing demands for green and financially viable synthetic protocols to tackle current environmental and economic challenges.[2] In spite of these highly desired attributes of acetylene, the current industrial applications encompass uncatalyzed vinylation[3] and hydrochlorination processes.[4] Despite recent advances in the development of transition metal mediated methodologies,[5−7] more examples are desired for the full utilization of the intriguing properties of acetylene.

Gold(I)-catalysts have been shown to be highly efficient in the electrophilic activation of alkynes, which has been applied in a wide variety of organic transformations.[8] One example is the reaction of alkenes with alkynes, known to proceed via a well-established cyclopropyl gold(I)-carbene intermediate following initial reaction between the two reagents.[9] Even though there are several intermolecular examples in the literature (such as the [2 + 2] cycloaddition of alkenes and alkynes),[8,10] a majority of the reported examples are intramolecular (such as the cyclization of 1,n-enynes).[8,11] We have previously reported the successful gold(I)-catalyzed reaction between acetylene gas and alkenes to perform (*Z*,*Z*)-1,3-diene formations and biscyclopropanations, through ligand-controlled product distribution (Scheme 1a).[6] Additionally, we recently showed that, by including an *O*-nucleophile tethered to the alkene, the corresponding cyclopropyl gold(I)-carbene intermediate could be trapped to afford 3-vinyl chromane scaffolds, including one of the first examples of enantioselective catalysis using acetylene gas (Scheme 1b).[7] In these studies we found that overactivity toward polymerization was a major issue to overcome, as the products of the reaction also contain alkenes which can again partake in the reaction to generate oligomeric products. This has been the major hindrance toward the development of a truly intermolecular three-component protocol where none of the alkynes, alkenes, and nucleophiles are covalently linked.

Scheme 1. Use of Acetylene Gas in Gold(I)-Catalyzed Transformations



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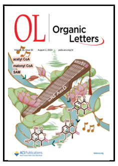

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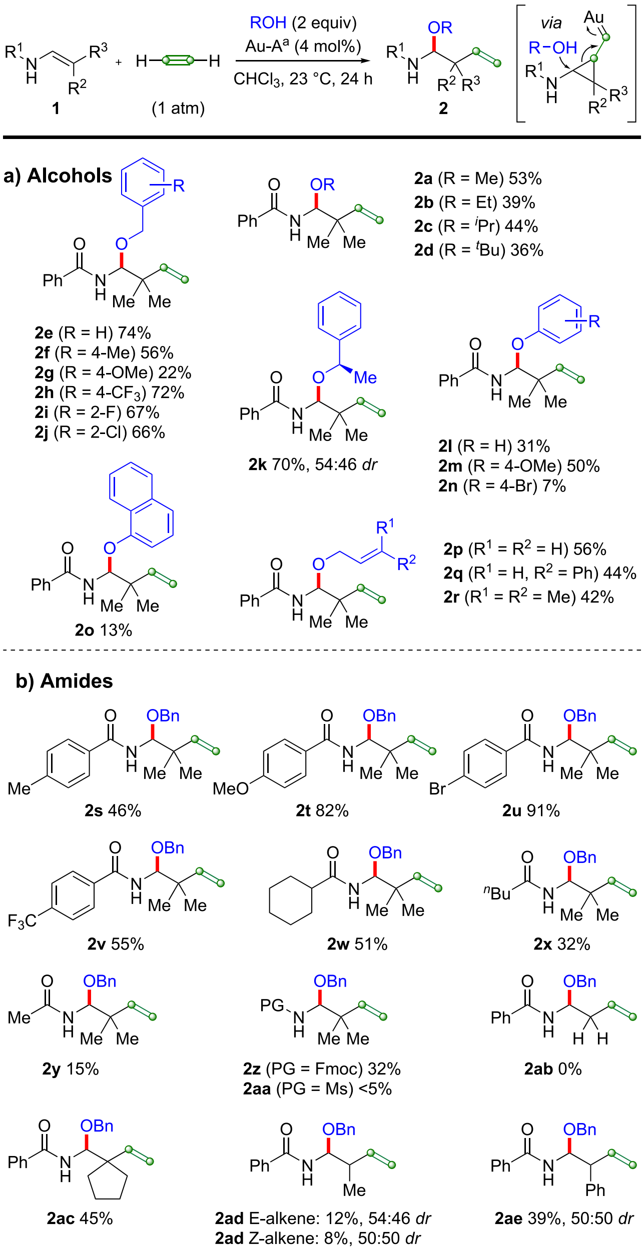
Herein we report the first three-component gold(I)-catalyzed intermolecular acetylene/alkene/nucleophile three-component reaction in the formation of β-vinyl hemiaminal products from the corresponding *N*-vinyl amides (Scheme 1c). Hemiaminals are widely present in bioactive natural products and pharmaceuticals, and are also utilized as *N*-heterocyclic carbene and ionic liquid precursors.[12] We also report the synthesis of pyrrolidine and piperidine derivatives through the biscyclopropanation of *N*,*N*-divinyl amide and aminovinylation of amine-tethered alkenes. Pyrrolidines and piperidines are some of the most sought-after organic scaffolds in the development of new pharmaceutical and agrochemical molecules.[13]

Through our initial attempts to achieve a three-component intermolecular gold(I)-catalyzed alkoxyvinylation between acetylene, alkenes, and alcohols, we encountered a significant hurdle of undesired oligomerization/polymerization in the screening of suitable alkenes. *N*-Vinyl amides were pleasingly found to be promising substrates, due to an apparent disfavored formation of these side-products. We performed an optimization of the reaction parameters for the standard reaction between *N*-vinyl benzamide **1a** and methanol under an acetylene atmosphere to afford the corresponding hemiaminal product (Tables S1−S4). It was found that commercially available [JohnPhosAu(NCMe)]SbF$_6$ (**Au-A**) was the most efficient catalyst for the reaction, chloroform was the best solvent, and an excess of alcohol improved the yield of the reaction, leading to the conditions used for the reaction scope (Scheme 2).

For the reaction scope, we screened a variety of alcohols (Scheme 2a) for the β-vinyl hemiaminal formation, and the reaction was found to tolerate primary, secondary, and tertiary alcohols (**2a**−**d**). Benzylic alcohols (**2e**−**k**) performed particularly well both with electron-withdrawing (**2h**, **2j**) and -neutral substituents (**2e**, **2i**, **2k**). Electron-donating substituents could also be employed, though the stronger *para*-methoxy substituent led to a diminished yield of the product **2g**. Phenol nucleophiles (**2l**−**o**) were also successfully used, and in contrast to the benzylic alcohols, the more electron-rich phenols afforded higher yields. We were delighted to find that allylic alcohols (**2p**−**r**) also were tolerated under the reaction conditions, despite containing substituted alkenes, which could react further with acetylene themselves.

When exploring the scope of the *N*-vinyl amides (Scheme 2b) it was found that electron-withdrawing and -donating substituents on the benzamide afforded the β-vinyl hemiaminal products (**2s**−**v**) in moderate to excellent yields. Both alkyl amides (**2w**−**y**) and protected *N*-vinyl enamines (**2y**−**aa**) could be employed, though at slightly diminished yields compared with the aryl amide derivatives. The modification of the alkene substituents to a cyclopentyl group afforded spirocyclic product **2ac** in good yield, while removal of the alkene substituents (**2ab**) led to only products of polymerization. Removal of a single methyl substituent did allow for the formation of product **2ad** in poor yield for both the *E*- and *Z*-alkenes. Employing an *E*-phenyl substituted *N*-vinyl benzamide afforded product **2ae** in moderate yield.

Scheme 2. Synthesis of Hemiaminals by Gold(I)-Catalyzed Three-Component Reaction with Acetylene Gas

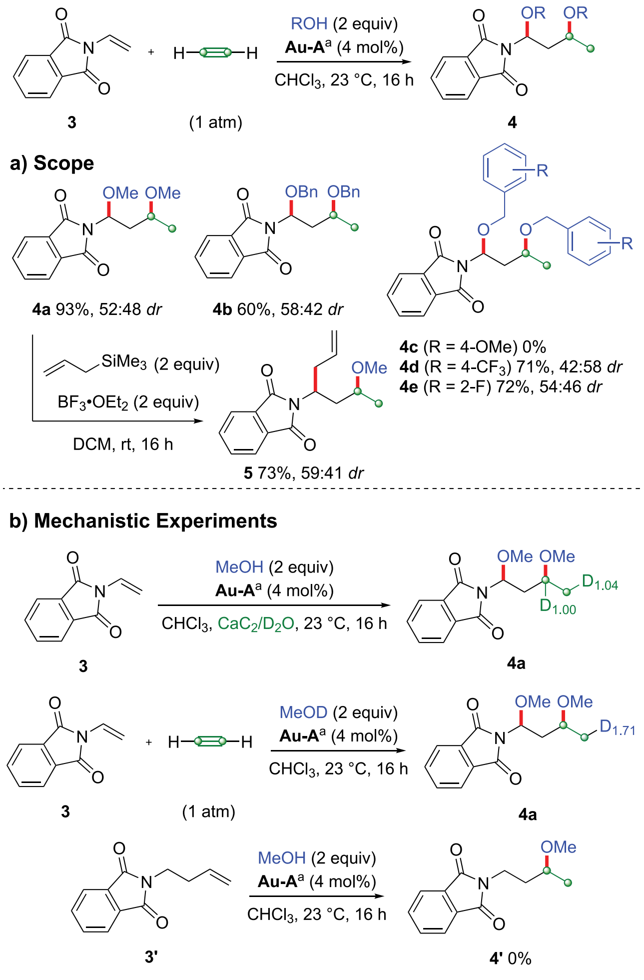


[a]**Au-A** = [JohnPhosAuNCMe]SbF$_6$.

Despite not yielding any desired product **2ab** (derived from *N*-vinylbenzamide), it was found that *N*-vinyl phthalimide **3** did afford an hemiaminal product, though with the addition of two units of the alcohol (Scheme 3a). In this case, stoichiometric methanol could be used to afford hemiaminal **4a** in excellent yield. Electron neutral and poor benzylic alcohols (**4b**, **4d**, **4e**) again performed well in the reaction, though with no formation of the desired product **4c** using an electron-donating *para*-methoxy substituent. To highlight the versatility of the products, the hemiaminal of **4a** was activated by a Lewis acid in the presence of a nucleophile to yield the allylated product **5** in good yield.

To gain some insight into why the second addition of the alcohols occurred, we performed a few mechanistic experiments (Scheme 2b). No deuterium scrambling was observed when the reaction was performed using deuterated acetylene (formed from CaC$_2$ and D$_2$O)[6] or methanol with only the expected incorporation on the two terminal carbons. These experiments support a mechanism in which the intermediate cyclopropyl gold(I)-carbene is trapped by the alcohol before a second addition occurs to the resulting terminal alkene.

Scheme 3. Gold(I)-Catalyzed Double Addition of Alcohol to *N*-Vinyl Phthalimide and Mechanistic Experiments



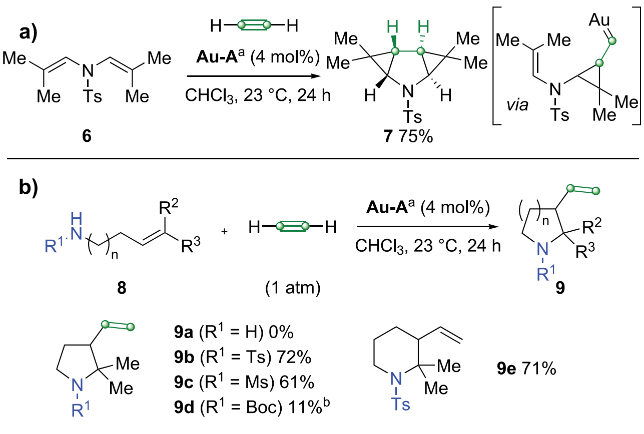
[a]**Au-A** = [JohnPhosAu(NCMe)]SbF$_6$.

However, when substrate **3′** was submitted to the reaction conditions, the expected product of addition methanol **4′** was not observed. The exact reason for the second alcohol addition to *N*-vinyl phthalimide is currently under further investigation.

Next, we decided to investigate the reaction with acetylene after the second addition of an *N*-vinyl unit (Scheme 4a). Pleasingly, the reaction of *N*,*N*-bisvinyl amine **6** with acetylene in the presence of [JohnPhosAuNCMe]SbF$_6$ led to biscyclopropanation to give biscyclopropyl pyrrolidine **7** in excellent yield.

Inspired by the formation of pyrrolidine **7** and our previous synthesis of chromanes,[7] we attempted the intramolecular trapping of the cyclopropyl gold(I)-carbene by an amine nucleophile to afford 3-vinyl *N*-heterocycles (Scheme 4b). We decided to screen *N*-protecting groups as the reaction of free amine **8a** did not yield any desired reactivity. *N*-Tosyl derivative **8b** afforded the corresponding 3-vinyl pyrrolidine **9b** very efficiently, as did mesyl-derivative **8c**. Moving away from the sulfonamide protecting groups, Boc-substituted amine **8d** yielded minor quantities of the corresponding pyrrolidine **9d**. The carbon-linker could be extended by one carbon to afford 3-vinyl piperidine derivative **9f** in very good yield.

Scheme 4. Synthesis of *N*-Heterocycles via Biscyclopropanation (a) or Cyclization of Amine-Tethered Alkenes (b)



[a]**Au-A** = [JohnPhosAuNCMe]SbF$_6$. [b]Determined by ^{1}H NMR spectroscopy using 1,4-diacetylbenzene as internal standard.

In summary, we have developed the first gold(I)-catalyzed intermolecular three-component reaction between acetylene, alkenes, and alcohols to afford *β*-vinyl hemiaminals. A range of alcohol and *N*-vinyl amide substrates could be employed in the reaction, with the use of alkene-containing allylic alcohols being particularly noteworthy. The use of *N*-vinyl phthalimide **3** surprisingly led to a second addition of an alcohol, the exact mechanism of which is currently unknown. Additionally, biscyclopropyl and 3-vinyl pyrrolidine scaffolds could be obtained from the corresponding *N*,*N*-bisvinyl or alkene-tethered amines, highlighting the potential for the rapid synthesis of interesting organic scaffolds from cheap and readily available acetylene gas.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c02102.

General remarks, optimization of the reaction conditions, general procedures and compound data, deuterium labeling experiments, X-ray structure, and NMR spectra (PDF)

Accession Codes

CCDC 2360638 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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