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Homogeneous Catalysis

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Gold in Total Synthesis: Alkynes as Carbonyl Surrogates

*William E. Brenzovich Jr.**

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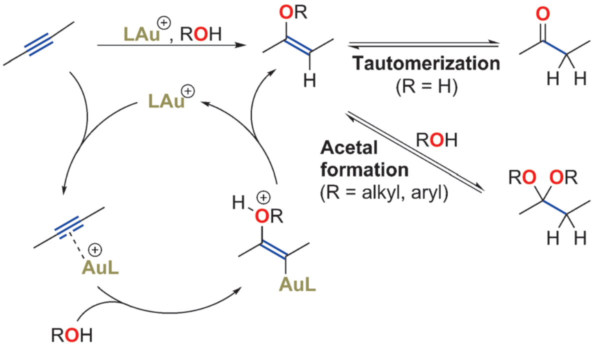
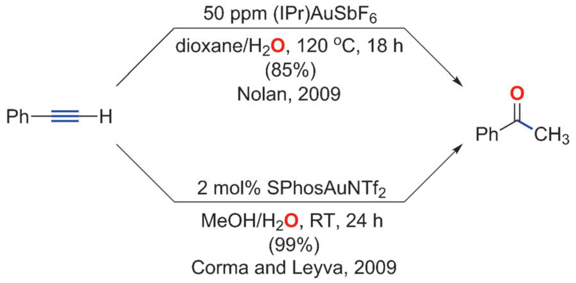
Alkyne hydration, or the addition of an equivalent of water across a carbon–carbon triple bond, is a valuable transformation in the context of chemical synthesis. The stability and ease of installation of the alkyne allows a chemist to mask the reactivity of a carbonyl moiety, thus providing greater flexibility in synthetic planning. As taught to first year organic chemists, an alkyne can be transformed into a ketone by a variety of means, most notably by the use of an electrophilic mercury salt.[1] Given the toxicity of mercury, a range of alternate transition-metal catalysts have been developed, with gold complexes taking a leading role.[2] The general mechanism of this transformation is shown in Scheme 1, and in many cases, alcohols can be used in place of water to provide enol ether or acetal products, depending on the conditions and the substrate.[3]



Scheme 1. Proposed mechanism of the gold-catalyzed hydration and hydroalkoxylation of unactivated alkynes.

Arguably, it was the work of Teles and co-workers in 1998 on the hydration of alkynes by cationic gold(I) complexes that has led to the current activity in gold catalysis.[3,4] Following these initial reports, many groups sought to improve the reaction, and recently there have been several interesting breakthroughs (Scheme 2).[5] In 2009, Nolan and co-workers published a report of the hydration of alkynes by N-heterocyclic carbene (NHC) gold complexes under essentially acid-free conditions. The extremely high stability and activity of the catalyst complex provides a turnover number in excess of 84000, thus allowing extremely low catalyst loadings ($\delta =$ 50 ppm or lower).[6] In 2009, Corma and Leyva made further improvements, reporting a series of isolable gold bistrifluoromethylsulfonimide complexes which can catalyze alkyne hydration at room temperature.[7] This method provides extremely mild access to a variety ketones, though the selectivity on unsymmetric internal alkynes remains problematic. In 2012, Xu and co-workers performed a systematic study of ligand selection on the rate of various gold-catalyzed reactions, thus clearly demonstrating the impact of the electronics and sterics of the catalyst on the pathway of a reaction.[8] This study underscores the unexpected complexity of the established gold hydration mechanism, while providing insight into the further improvement of the catalyst design.



Scheme 2. Recent advances in the development of general alkyne hydrations by cationic gold catalysts.

In chemical synthesis, great care must be taken with highly complex late stage intermediates to prevent unwanted side reactions while maintaining good conversions. Therefore, there are ample possibilities to utilize the exceptional chemoselectivity observed for the reaction of cationic gold with alkynes. While the direct alkyne hydration to provide ketones has been employed several times with great success in total synthesis,[9] the real power of this technology lies in the direct transformation of alkynes into the derivatives of carbonyls, such as acetals and enol ethers. These acid-sensitive functionalities are typically formed from carbonyls under dehydrating conditions that are often destructive to highly complex synthetic intermediates.[10] The gold-catalyzed addition of an alcohol or carboxylic acid across a triple bond can circumvent these problems and provide elegant routes to sensitive and complex natural products. This method had been applied by a variety of groups, including Forsyth, Trost, Fürstner, Dudley, and Floreancig, en route to a variety of complex natural products, selected examples of which are shown in

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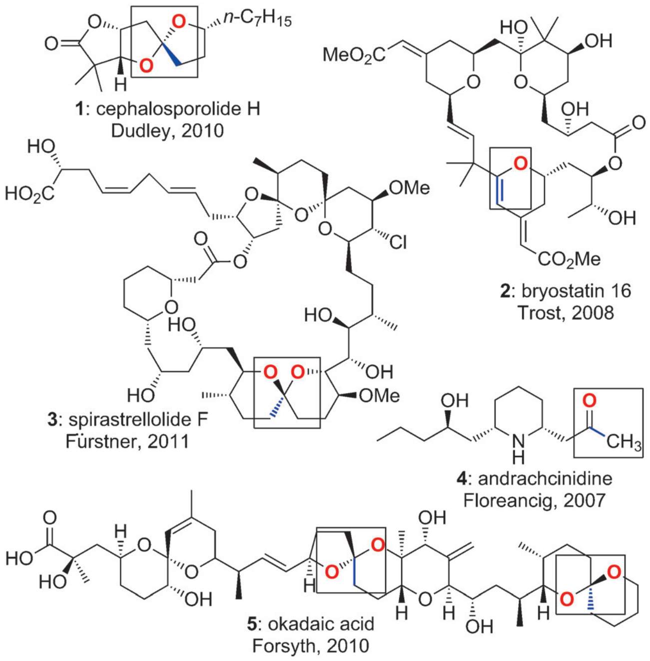
[*] Dr. W. E. Brenzovich Jr.
Department of Chemistry, Roanoke College
221 College Lane, Salem, VA 24153 (USA)
E-mail: brenzovich@roanoke.edu

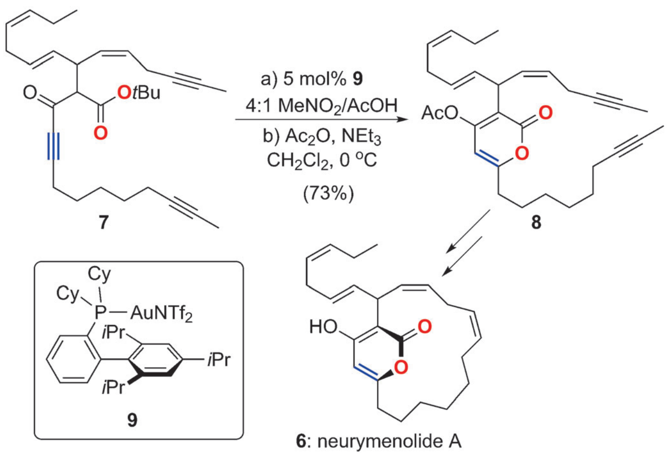


Scheme 3. Selected natural products synthesised by a gold(I)-catalyzed hydration or hydroalkoxylation of an alkyne.[10]

Scheme 3.[10] In one noteworthy example, the 2010 synthesis of okadaic acid (**5**) by Forsyth and co-workers, contained two gold-catalyzed spiroacetal formations.[10g] In their 2011 second-generation synthesis of spirastrellolide F, Fürstner and co-workers were able to utilize the gold-catalyzed acetal formation on a highly advanced intermediate where the macrolactone had already been synthesized.[10j] These cyclizations and spiroketalizations typically proceed without unwanted isomerizations, eliminations, or side reactions which can plague other methods.

In a true testament to the nature of the reaction, Fürstner and co-workers very recently disclosed the total synthesis of the highly sensitive pyrone-containing cyclophane, neurymenolide A (**6**; Scheme 4).[10k] Aside from the conformational instability, neurymenolide A also contains a series of sensitive skipped *cis* dienes which have a high propensity for isomerization. Synthesis of this compound in a biomimetic fashion would require the dehydration of a 1,3,5-tricarbonyl unit under reactions conditions which are likely to disrupt a carefully prepared advanced intermediate. In recognizing the relationship between alkynes and carbonyls, Fürstner and co-workers developed a synthesis of hydroxypyrones from corresponding alkynyl ketoesters through a gold-catalyzed hydroacyloxylation. Treatment of the polyenyne **7** with 5 mol% of the catalyst **9** led to the facile formation of the desired pyrone core (**8**), while the stereochemistry and position of the remaining unsaturation remains unchanged in this high-yielding process. This transformation represents a further demonstration of the potential of gold-catalyzed transformations, especially in the presence of sensitive functionality.

While the use of alkynes as carbonyl surrogates is not a new concept in the context of total synthesis, the advent of gold catalysis has revolutionized its use. The mild and chemoselective nature of the gold complexes have opened the door for interesting late-stage conversions of alkynes into carbonyl derivatives, thus providing additional flexibility in the design of complicated synthetic routes. With the significant advances that have been made in the development of new and more active catalysts, and the recent illustrations of its utility, we are likely to see gold continue its rise in total synthesis.



Scheme 4. Key gold-catalyzed step of Fürstner's total synthesis of neurymenolide A (**6**).

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