UC Santa Barbara

Title

A Non-Diazo Approach to α-Oxo Gold Carbenes via Gold-Catalyzed Alkyne Oxidation

Permalink

https://escholarship.org/uc/item/0pg244j3

Journal

Accounts of Chemical Research, 47(3)

ISSN

0001-4842

Author

Zhang, Liming

Publication Date
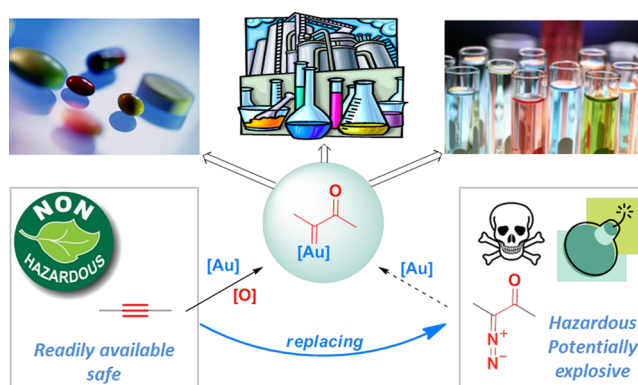
2014-03-18

DOI

10.1021/ar400181x

Peer reviewed

A Non-Diazo Approach to α-Oxo Gold Carbenes via Gold-Catalyzed Alkyne Oxidation

LIMING ZHANG

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States

RECEIVED ON JULY 30, 2013

CONSPECTUS

For the past dozen years, homogeneous gold catalysis has evolved from a little known topic in organic synthesis to a fully blown research field of significant importance to synthetic practitioners, due to its novel reactivities and reaction modes. Cationic gold(I) complexes are powerful soft Lewis acids that can activate alkynes and allenes toward efficient attack by nucleophiles, leading to the generation of alkenyl gold intermediates. Some of the most versatile aspects of gold catalysis involve the generation of gold carbene intermediates, which occurs through the approach of an electrophile to the distal end of the alkenyl gold moiety, and their diverse transformations thereafter. On the other hand, α-oxo metal carbene/carbenoids are highly versatile intermediates in organic synthesis and can undergo various synthetically challenging yet highly valuable transformations such as C—H insertion, ylide formation, and cyclopropanation reactions. Metal-catalyzed dediazotizations of diazo carbonyl compounds are the principle and most reliable strategy to access them. Unfortunately, the substrates contain a highly energetic diazo moiety and are potentially explosive. Moreover, chemists need to use energetic reagents to prepare them, putting further constrains on operational safety.

In this Account, we show that the unique access to the gold carbene species in homogeneous gold catalysis offers an opportunity to generate α-oxo gold carbenes if both nucleophile and electrophile are oxygen. Hence, this approach would enable readily available and safer alkynes to replace hazardous α-diazo carbonyl compounds as precursors in the realm of gold carbene chemistry.

For the past several years, we have demonstrated that alkynes can indeed effectively serve as precursors to versatile α-oxo gold carbenes. In our initial study, we showed that a tethered sulfoxide can be a suitable oxidant, which in some cases leads to the formation of α-oxo gold carbene intermediates. The intermolecular approach offers excellent synthetic flexibility because no tethering of the oxidant is required, and its reduced form is not tangled with the product. We were the first research group to develop this strategy, through the use of pyridine/quinolone N-oxides as the external oxidants. In this manner, we can effectively make a C—C triple bond a surrogate of an α-diazo carbonyl moiety in various gold catalyses. With terminal alkynes, we demonstrated that we can efficiently trap exclusively formed terminal carbene centers by internal nucleophiles en route to the formation of cyclic products, including strained oxetan-3-ones and azetidin-3-ones, and by external nucleophiles when a P,N-bidentate ligand is coordinated to gold. With internal alkynes, we generated synthetically useful regioselectivities in the generation of the α-oxo gold carbene moiety, which enables expedient formation of versatile enone products. Other research groups have also applied this strategy en route to versatile synthetic methods. The α-oxo gold carbenes appear to be more electrophilic than their Rh counterpart, which many chemists have focused on in a large array of excellent work on metal carbene chemistry. The ease of accessing the reactive gold carbenes opens up a vast area for developing new synthetic methods that would be distinctively different from the known Rh chemistry and promises to generate a new round of "gold rush".

Introduction

The recent explosive development in homogeneous gold catalysis[1,2] has rapidly transformed it from a little known "ugly duckling" at the turn of the new millennium to now a "beautiful golden swan". A large array of developed methods has greatly enriched the repertoire of synthetic practitioners, and examples of their applications in the synthesis of natural products[3,4] and complex molecules abound.

The rapid evolution of homogeneous gold chemistry, thanks to the contributions by many research groups around the globe, can be duly attributed to the potent and versatile reactivities of gold complexes. Besides the renown soft Lewis acidities of cationic gold(I) species toward alkynes and allenes, the ready access to gold carbene intermediates and their diverse transformations thereafter are arguably the most versatile aspect of gold catalysis, offering access to a diverse range of functional products from often simple substrates. Scheme 1 outlines a general approach to the generation of gold carbenes from alkynes. First, a nucleophilic attack at the C–C triple bond is greatly promoted upon the coordination of a Lewis acidic cationic gold complex to the π bond, resulting in the formation of an alkenyl gold intermediate **A**; while the Au–C(sp^2) bond in this intermediate can react (formally) with an approaching electrophile or proton (i.e., the α approach), the alternative attack by an electrophile at the alkene end distal to gold (i.e., the β approach) would then generate a gold-substituted carbocation (i.e., **B**). Back donation from the metal center would stabilize the electron-deficient trivalent carbon center and render a gold carbene intermediate (i.e., **C**). Though gold is the most electronegative metal in the Pauling's scale,[5] DFT calculations have suggested that such back-donation can occur to a similar extent as the stabilization offered by a directly substituted MeO group.[6]

It is interesting to note that the overall conversion of an alkyne to a gold carbene of type **C** is identical in a formal sense to that of a hypothetical α-carbene gold carbene **D** reacting consecutively with a nucleophile and an electrophile at its free carbene center. Hence, a gold-coordinated alkyne, if en route to a gold carbene intermediate, is formally equivalent to the provocative **D** (Scheme 1)! This formalism is useful as a model for envisioning bond formations en route to the generation of gold carbene and could also stimulate further reaction discovery.

It is important to point out that the initial nucleophilic attack and the subsequent approach of electrophile could occur as a single concerted step. This variant, in the form of

SCHEME 1. Generation of Gold Carbenes from Alkynes: A Formalism to α-Carbene Gold Carbenes
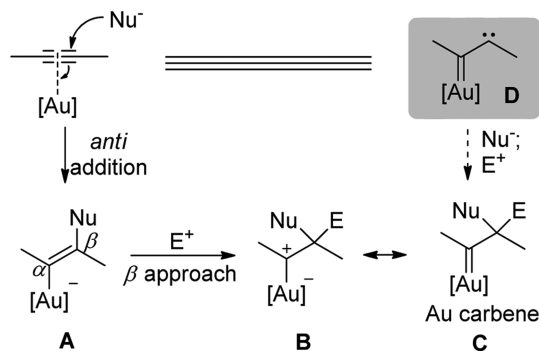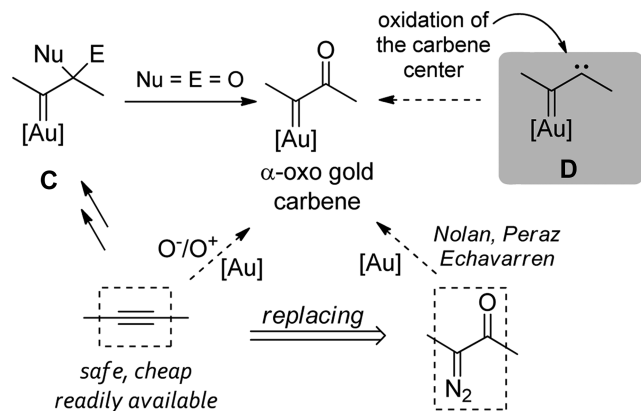

cyclopropanation, in fact, is the main theme of gold-catalyzed enyne cycloisomerizations (e.g., eq 1), which have been a rich "gold" mine for reactivity discovery.[7,8] In this case, the formalism between a gold-activated alkyne and α-carbene gold carbenes of type **D** is even more evident.

(1)
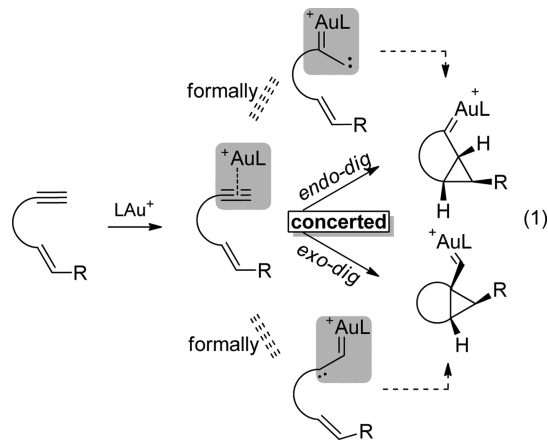
If both the nucleophile and the electrophile en route to the gold carbene **C** are oxygen, an α-oxo gold carbene is generated (Scheme 2). Formally, this particular scenario can be viewed as an oxidation of the carbene center of **D**.

Metal-catalyzed dediazotizations of diazo carbonyl compounds are the principle and most reliable strategy to access α-oxo metal carbenes/carbenoids, which are versatile intermediates that can undergo various synthetically challenging yet highly valuable transformations such as C–H insertion, ylide formation, and cyclopropanation reactions.[9] Of particular synthetic importance are those methods based on Rh catalysis, which permit enantioselective transformations with chiral coordinating ligands. Unfortunately, this strategy is hindered by the hazardous nature of the substrates, diazo carbonyl compounds, due to the highly energetic diazo moiety and hence the potential of explosion. Consequently, these reactions are advised to be performed in small scales, although large scale processes have been implemented with

SCHEME 2. Generation of α-Oxo Gold Carbenes via Alkynes Oxidation: Alkynes as Surrogates of α-Diazo Carbonyl Compounds

SCHEME 3. Gold-Catalyzed Intramolecular Alkyne Oxidation: An Alternative Mechanism[37]

engineering ingenuity.[10,11] Additionally, the preparations of these precursors typically require energetic reagents, hence putting further strain on operational safety, and often require multiple steps unless the methylene group is fairly acidic.[9] The development of safe surrogates of diazo carbonyl compounds while maintaining the ease of accessing the corresponding metal carbenes would address this debilitating issue and provide substantial benefit to synthetic practices.

While diazo carbonyl compounds have been used, albeit seldom, to access α-oxo gold carbene/carbenoid,[12–16] the oxidative variant of Scheme 1 (see Scheme 2) could generate the same intermediate from a C—C triple bond instead of an energetic diazo moiety. Hence, at least in the realm of gold catalysis, *the hazardous α-diazo carbonyl compounds in principle could be replaced with readily available and mostly benign alkynes.* Considering the largely unexplored reactivities of α-oxo gold carbenes and their potential ease of efficient access enabled by this oxidative strategy, we were drawn to the synthetic potential of the approach and have spent the past several years working on implementing it and exploring the versatile reactivities of these carbene intermediates en route to the development of versatile synthetic methods. In this Account, I will discuss our results based both on intramolecular alkyne oxidation and on intermolecular oxidation, with the latter being the focus. I am, however, obligated to point out here that many other researchers including Liu,[17–22] Toste,[23] Shin,[24,25] Zhang,[26–28] Davies,[29–31] Gagosz,[32] Hashmi,[33,34] Li,[35] and Liu[36] have also made outstanding contributions in this field, which will not be discussed due to the nature of this Account.
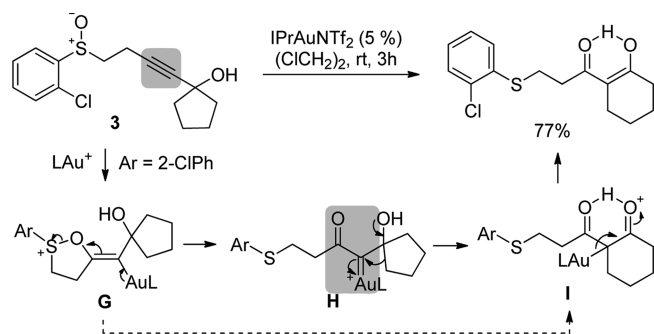
Intramolecular Alkyne Oxidation

With no precedent of this oxidative strategy being implemented, we envisioned that an intramolecular version with an oxidant tethered at an optimal distance to a C—C triple
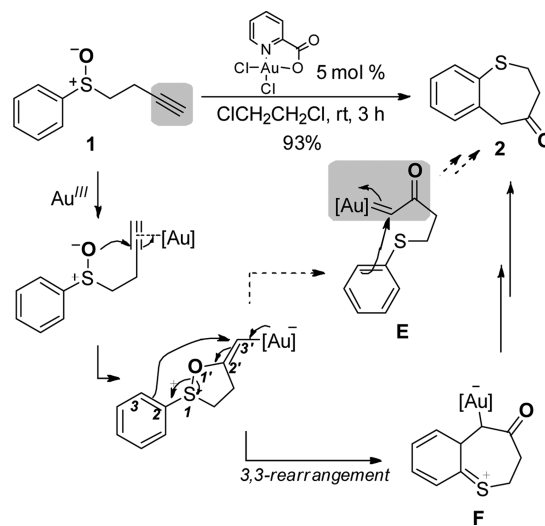
bond would present the best chance. Since the particular oxidant has to be first a nucleophile and then an electrophile, a nucleophilic one should be chosen. A sulfoxide, albeit considered a weak oxidant, came to our mind immediately. We quickly prepared the simple sulfoxide **1** and subjected it to various gold catalysts (Scheme 3). Much to our delight as well as to our surprise, the tetrahydrobenzothiepinone **2** was formed nearly quantitatively with a Au(III) salt as the catalyst.[37] The initially proposed mechanism largely followed that outlined in Scheme 2, where the α-oxo gold carbene **E** is generated upon an initial gold-catalyzed nucleophilic attack at the C—C triple bond by the sulfoxide oxygen followed by a gold-promoted heterolytic fragmentation of the S—O bond. It is notable in this process that the sulfoxide oxygen would act first as an O[−] and then as an O[+]. Subsequent intramolecular Friedel—Crafts-type alkylation would deliver the observed product. This mechanism, though, much to our delight, seemingly validating our design, is simply too good to be true as the final cyclization to form a seven-membered ring is just unbelievably efficient. Instead, our latest mechanistic studies via a combination of experiments and DFT calculations ruled out the intermediacy of **E** en route to **2**.[38] Instead, the initial cyclized product should undergo preferably a facile 3,3-sigmatropic rearrangement to construct the seven-membered ring directly.

This mechanistic twist, however, needs not to be generalized and is likely limited to the cases where other facile processes could interfere. It does not necessarily invalidate the general strategy outlined in Scheme 2. In fact, in the same original paper, we showed that a pinacol-type rearrangement

SCHEME 4. Tandem Gold Carbene Formation and Pinacol-Type Rearrangement[37]

SCHEME 5. Gold-Catalyzed Intermolecular Oxidation

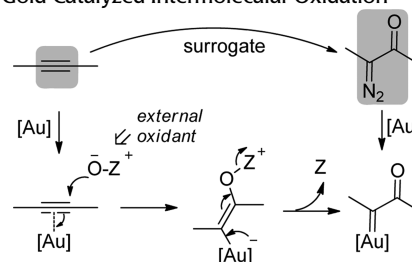**SCHEME 6.** Gold-Catalyzed Oxidative Cyclization of Homopropargylic Alcohol[42]

could be engineered into the reaction to harness the electrophilicity of the α-oxo-gold carbene **H** (Scheme 4), therefore offering circumstantial evidence of its formation. An important feature in the structure of the substrate is that the benzene ring is *ortho*-chlorinated, which helps curb the 3,3-sigmatropic rearrangement en route to the corresponding tetrahydrobenzothiepinone product. One, however, needs to be cautioned that a direct conversion of the initial cyclization intermediate **G** to the aurated diketone species **I** could not be ruled out.[18]

The reaction shown in Scheme 3 was independently reported by Toste and co-workers at around the same time.[23] Later studies by Davies,[29,30] Shin,[24,25,39] and Liu[17,40] using different tethered oxidants lent further support for the validity of this intramolecular strategy and led to the development of a plethora of useful synthetic methods.

Intermolecular Oxidation of Terminal Alkynes Followed by Intramolecular Trapping

While tethering an oxidant to an alkyne greatly facilitated the initial gold-promoted nucleophilic attack at the C—C triple bond, the very bondage between the two reacting partners significantly hinders further application of the oxidative gold catalysis due to the following issues: first of all, a suitable functional group, being a sulfur or nitrogen atom or an alkene, needs to be present in order to deliver an oxygen atom; second, such a functional group has to be optimally positioned so that the initial cyclization forms a five- or six-membered cyclic intermediate; third, unless the oxygen-delivering group is an integral part of the final target, its installation and later removal would significantly diminish the overall efficiency of any synthetic endeavor; last, the C—C triple bond is arguably not a strict surrogate of a diazo carbonyl moiety because the oxidant part is reduced in the process.

These problems, however, could be overcome readily if effective external oxidants could be discovered (Scheme 5). Importantly, this approach, without the entanglement of the
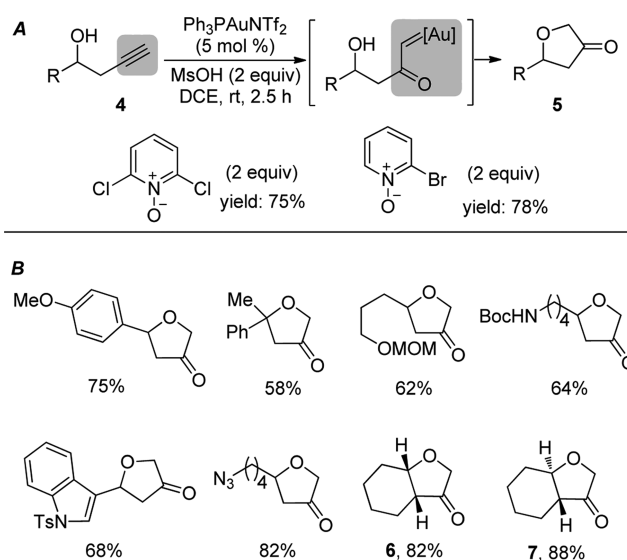
oxidant, would make a C—C triple bond in the presence of an oxidant as a true surrogate of the hazardous α-diazo carbonyl moiety in gold catalysis.

The initial attempt by Ujaque, Asensio, and co-workers to achieve this intermolecular oxidation using aryl sulfoxides was not successful due to a facile competing 3,3-sigmatropic rearrangement.[41] A similar phenomenon was observed later by Liu.[18]

Not discouraged, we screened a variety of nucleophilic oxidants for the model reaction shown in Scheme 6A. The substrate **4**, a homopropargyl alcohol, was chosen because we anticipated that the optimally positioned hydroxyl group could efficiently trap the generated gold carbene species. While an array of sulfoxides were not effective, pyridine *N*-oxides in general and 2,6-dichloropyridine *N*-oxide and 2-bromopyridine *N*-oxide in particular were found to be suitable oxidants for the gold catalysis at ambient temperature. With MsOH (2 equiv) as an additive, the anticipated dihydrofuranone **5** was formed in good yields.[42] The role of the acid is to protonate the pyridine byproduct so that it

SCHEME 7. One-Step Synthesis of Oxetan-3-Ones from Readily Accessible Propargyl Alcohols[43]
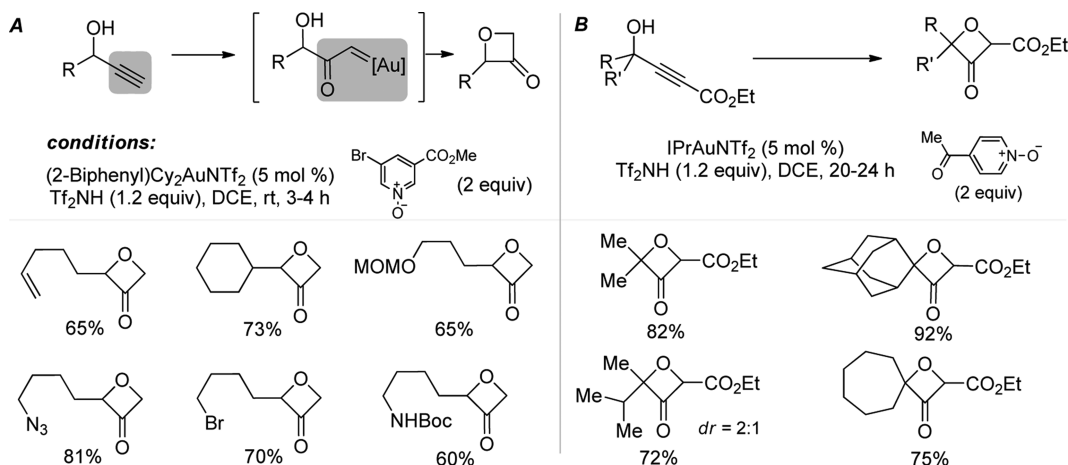

would not deactivate the gold catalyst, Ph_3PAu^+, via coordination. Some selected examples of this chemistry are shown in Scheme 6B. Various functional groups and different substitution patterns in the substrates are allowed. The tolerance of acid-sensitive MOMO and NHBoc groups in the presence of superstoichiometric amount of MsOH is particularly notable and can be ascribed to the buffering effect by the basic N-oxide. The product with the best yield (88%) among all the studied cases is the bicyclic ketone **7**, the 5,6-*trans*-fused skeleton of which is strained and less stable than that of the lower yielding isomer **6**. The result is unexpected but can be readily understood by invoking the generation of a highly reactive intermediate (i.e., an α-oxo gold carbene), which would command an early transition state for the cyclization, and hence the reaction efficiency has little to do with the product stability but more with the kinetics of the HO trapping.

This first realization of generating α-oxo gold carbenes via gold-catalyzed intermolecular alkyne oxidation opens a new area for exploring gold catalysis. While contemplating synthetically useful transformations, we also sought to gather additional experimental evidence of the gold carbene formation. To this end, we chose to examine the direct conversion of propargyl alcohols to oxetan-3-ones (Scheme 7) because the highly strained small ring in the products permits reasonable exclusion of other potential mechanism alternatives.

Much to our delight, the oxidation strategy worked with both secondary alcohols with a terminal alkyne (Scheme 7A) and tertiary alcohols with an electron-withdrawing group at the alkyne terminus (Scheme 7B), affording various functionalized oxetan-3-ones in acceptable to good yields. In the latter case, the electron-withdrawing ester group is essential because in its absence the

reaction was messy. We attributed the failure to the instability of the nonsubstituted tertiary alcohol under the acidic conditions. While the optimized conditions in these two cases differ in terms of the gold catalysts and the oxidants, the reactions proceeded better with Tf_2NH as the acid additive than MsOH, presumably due to the less nucleophilic nature of its counteranion (note that the N-oxide buffers the acidity of the reaction).

The oxetane ring has recently been advocated as a better alternative than *gem*-dimethyl for protecting metabolically labile methylene groups in medicinal chemistry,[44,45] and the parent oxetan-3-one is the necessary precursor for the incorporation of this strained heterocycle. Compared with the conventional, multistep preparative methods, our approach needs only one step from the commodity chemical propargyl alcohol (eq 2).

$$(2)$$
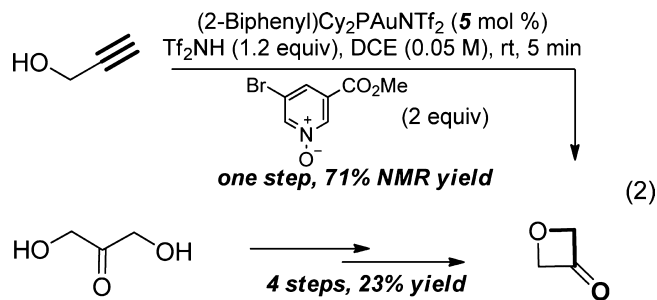
This very strategy was also applied successfully to the one-step synthesis of azetidin-3-ones from propargylic amides (Scheme 8).[46] The *t*-butylsulfonyl group was chosen as the amine protecting group because it could be easily accessed by oxidation of a *t*-butylsulfinyl group, which in a chiral form in turn allowed highly stereoselective construction of the stereogenic propargylic position by utilizing Ellman's chemistry.[47] The bulky amide group, in contrast

SCHEME 8. Expedient Synthesis of Chiral Azetidin-3-Ones[a46]
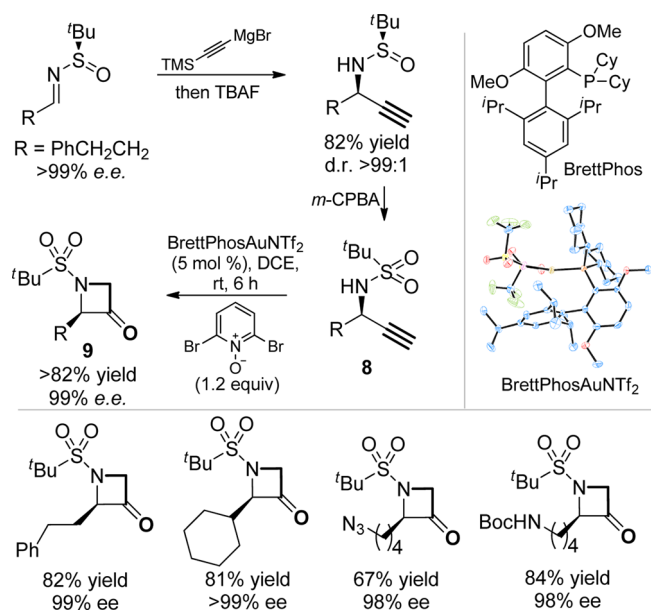
[a]Yields are calculated based on sulfinamides.

to the much smaller HO group in our previous work,[43] did require extensive catalyst optimization. We found BrettPhos, a bulky ligand developed by Buchwald,[48] affords the most effective cationic gold complex. Coupled with a bulky N-oxide (i.e., 2,6-dibromopyridine N-oxide), the model substrate **8** was converted into the azetidin-3-one **9** in >82% yield at ambient temperature. Notably, no acid additive is required, which is attributed to the difficulty in coordinating bulky and weakly basic 2,6-dibromopyridine to bulky BrettPhosAu$^+$. This reaction permits an expedient access to various chiral azetidin-3-ones and tolerates sensitive functional groups such as azido and NHBoc due to the exceedingly mild conditions,

With the generation of α-oxo gold carbenes from intermolecular alkyne oxidation firmly established, we probed the feasibility of other types of internal nucleophiles including carbonucleophiles. The easily prepared phenyl propargyl ether **10** was chosen as the model substrate due to the synthetic importance of the constructed structural motif, chroman-3-one (Scheme 9). Optimization of reaction conditions revealed that the sterically highly demanding Me$_4$^{t}-BuXPhos is the best ligand for this reaction, and the isolated yield was 78%.[49] In comparison, the bulky but yet smaller BrettPhos led to a lower 65% yield, and the much less congested CyJohnPhos resulted in only 9% yield. These data highlight the benefit of steric hindrance around the metal gold to the reaction efficiency, which can be attributed to minimizing intermolecular side reactions.

Another notable feature of this chemistry is the use of the N-oxide derived from Hantzsch ester, which fared better than 2,6-dibromopyridine N-oxides and other oxidants.
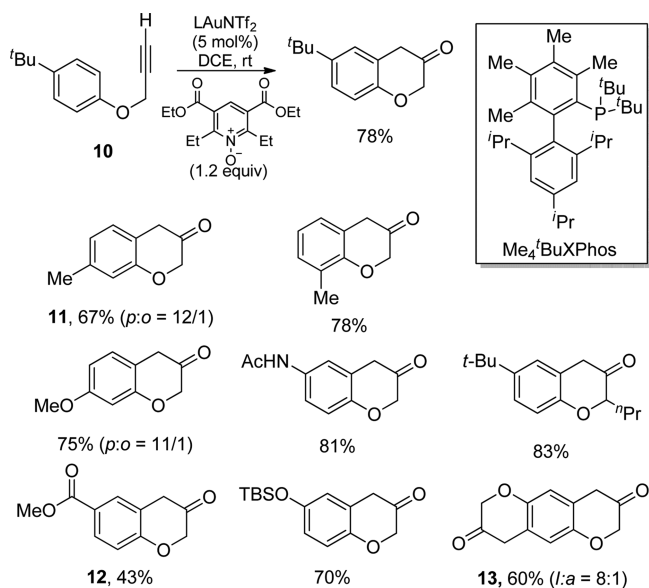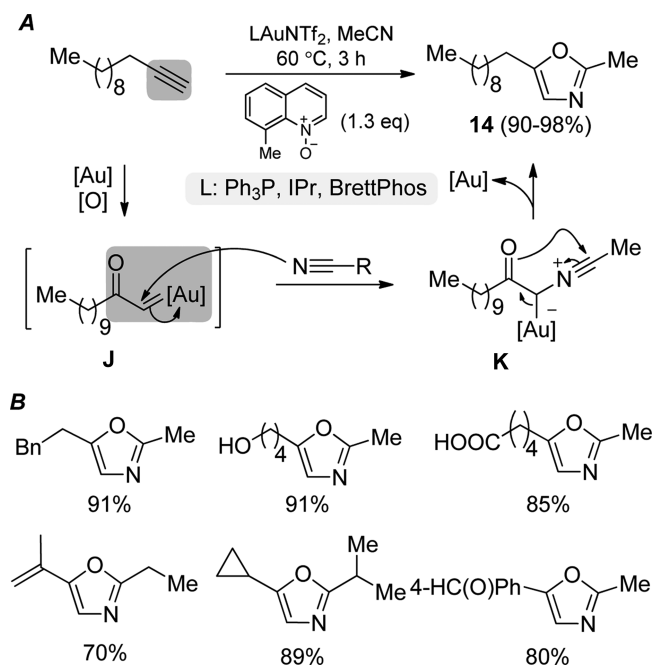
The reaction worked with substituents of varying nature and at different positions albeit to a less degree with an electron-withdrawing group (e.g., **12**). A synthetically valuable feature of this reaction is the good regioselectivity observed with the products **11** and **13**.

While other research groups have shown the α-oxo gold carbene generated via the intermolecular oxidation strategy could undergo cyclopropanation with tethered alkenes in special cases,[21,28] the carbene center appears to be highly electrophilic and behaves mostly as a carbocation. As a result, the venerable C−H insertions by Rh carbenes/carbenoids have not been realized with the gold counterpart.[22] In addition, its electrophilicity is evident in the observed chloride abstraction from the reaction solvent, 1,2-dichloroethane, under acidic conditions (eq 3). In comparison, similar chloride abstractions were observed with Rh carbenes/carbenoids flanked by two electron-withdrawing acyl groups. The more electrophilic nature of the gold carbene species could be understood by considering that the metal is most electronegative in the Pauling's scale.
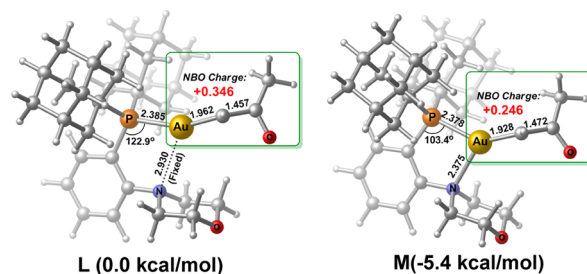

$$(3)$$
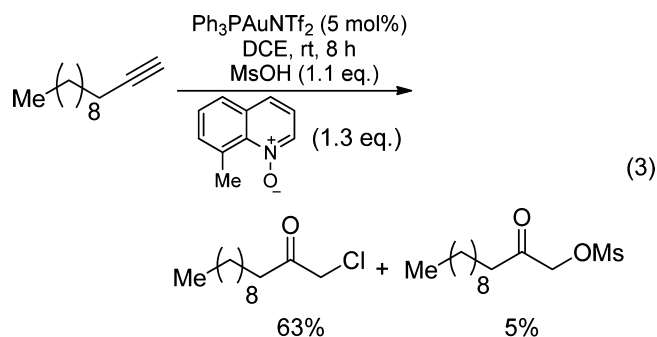
Intermolecular Oxidation of Terminal Alkynes Followed by Intermolecular Trapping

The strong electrophilicity of the α-oxo gold carbene moiety poses a stern challenge to its intermolecular trapping, which on the other hand is synthetically highly desirable and offers many new synthetic opportunities. In our first successful attempt using nitriles as the external reacting partner, instead of optimizing reaction conditions to avoid side reactions with solvents (vide supra), we embraced them and used nitriles as solvent. For example, by running the oxidation in acetonitrile, the 2,5-disubstituted oxazole **14** was formed in nearly quantitative yields with different gold catalysts (Scheme 10A).[50] The optimal oxidant is 8-methylquinoline N-oxide, which was developed early in the reactions of

**SCHEME 9.** Rapid Access to Chroman-3-Ones via Gold-Catalyzed Oxidation of Propargyl Aryl Ethers[49]

FIGURE 1. The partially optimized structure of bis-coordinated gold carbene **L** with fixed Au–N distance of 2.930 Å and the fully optimized tris-coordinated gold carbene **M**. The relative energies are in kcal/mol. Calculated at PBE1PBE/6-311+G** level.[53]

expensive to be used as solvent, we found that the chemistry could still afford a serviceable yield if a moderate excess of the nitrile (3 equiv) is used in the absence of any solvent (eq 4). In addition, the excess nitrile could be recovered.

(4)

64% based on alkyne
81% based on recovered nitrile
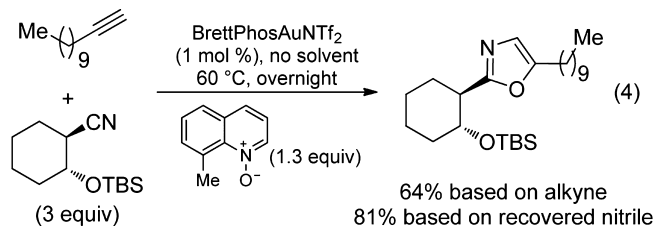
Trapping the gold carbene intermediate with various stoichiometric external nucleophiles, however, always led to abysmal results (<4% yield). Serendipitously, we came upon Mor-DalPhos, a ligand developed by Stradiotto and used mostly in Pd catalysis[51] and in one case for gold catalysis.[52] To our delight, it led to, after optimization, a much improved yield (87%) of the expected 2,4-disubstituted oxazole using a primary amide as the reacting partner (Scheme 11A).[53] The net result of this reaction is an oxidative [3 + 2] annulation between an amide and a terminal alkyne. Considering the frequent occurrence of this type of oxazole in natural products, this method would likely prove to be useful. The reaction scope is general to terminal alkynes but limited to conjugated carboxamides (Scheme 11B).

The unique role of Mor-DalPhos in promoting this reaction was attributed to its P,N-bidentate nature and hence its ability to use both coordinating heteroatoms to enable the formation of a tris-coordinated gold carbene (e.g., the DFT optimized structure **M**, Figure 1). This species should be less electrophilic due to the additional donating N atom and hence react more selectively. As a result, the interference of solvents and other weak nucleophiles are minimized, and much higher yields could be achieved. DFT calculations support this rationale as the additional coordination makes the

SCHEME 10. Gold-Catalyzed [2 + 2 + 1] Annulation to 2,5-Disubstituted Oxazoles[50]

internal alkynes (vide infra) and allows omission of an acid additive in the reaction. A nitrile ylide **K**, proposed as the key intermediate for the formation of the versatile heteroaromatic ring, reflects again the strong electrophilicity of the α-oxo gold carbene precursor (i.e., **J**).

This formally [2 + 2 + 1] annulation worked well with various terminal alkynes and a range of cheap nitriles (Scheme 10B). When the desired nitrile is too scarce or

SCHEME 11. Ligand-Enabled Efficient Intermolecular Trapping: One-Step [3 + 2] Annulation toward 2,4-Disubstituted Oxazole Synthesis[53]
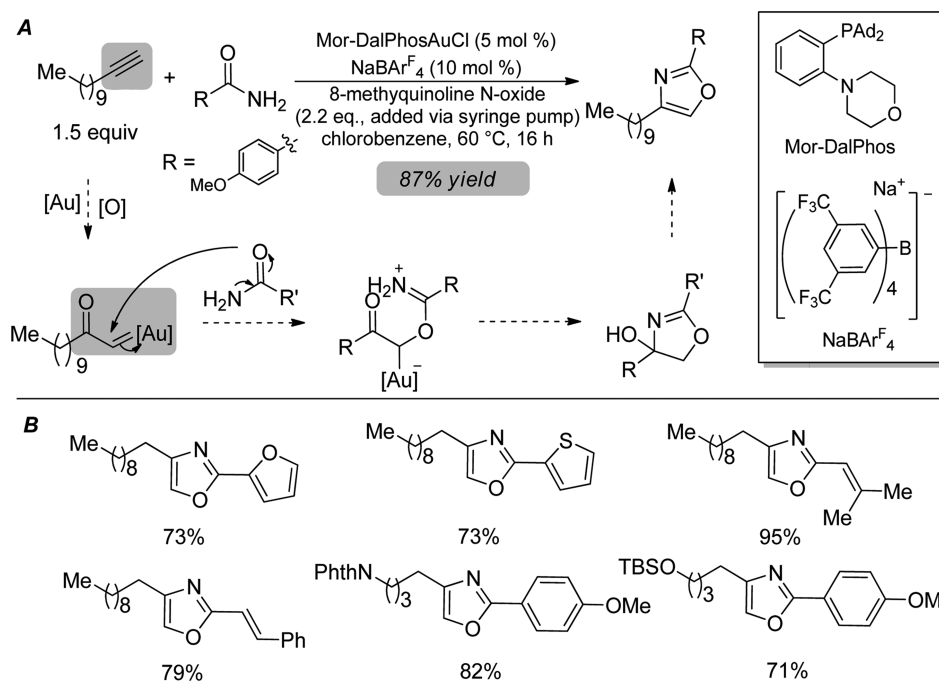
SCHEME 12. Ligand-Enabled Efficient Intermolecular Trapping by Carboxylic Acid[56]
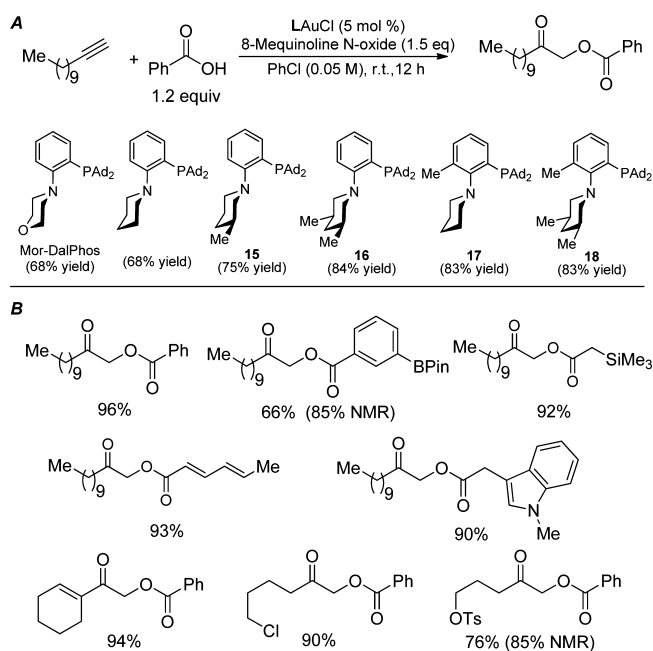
gold carbene more stable. It is important to point out that even though tris-coordinated gold complexes are well-known, their involvements in gold catalysis are rare.[54,55]

While our efforts to extend this intermolecular trapping to carbonucleophiles have so far been unsuccessful, carboxylic acids were found to be suitable trapping reagents

for the in situ generated α-oxo gold carbenes. As shown in Scheme 12A,[56] a serviceable 68% yield was obtained by using Mor-DalPhos as the metal ligand. Not satisfied, we undertook extensive ligand optimization by modifying the pendant morpholine ring. The results shown in Scheme 12A established that the better ligands (i.e., **16**−**18**) all have their pendant piperidine ring adopting the indicated rather fixed chair conformation. This conformation offers better steric shielding to the highly electrophilic gold carbene center so that the intermolecular trapping is more selective and efficient.

The reaction worked well with various functionalized carboxylic acids including those containing a Bpin, an α-silyl, an electron-rich indole ring, and conjugated dienes (Scheme 12B). Similarly, different terminal alkynes participated in the reaction with high efficiencies.

Intermolecular Oxidation of Internal Alkynes: Control of Regiochemistry

While the gold carbene moiety is invariably positioned at the terminus upon oxidation of terminal alkynes, regioselectivity with internal alkyne substrates becomes a major challenge to efficient catalysis. We first examined a sterically biased substrate (i.e., **19**), in which one end of the C−C triple bond is substituted by a primaryl alkyl group and the other by a secondary one (Scheme 13A). After extensive search for the optimal conditions, we discovered that the combination of IPrAuNTf$_2$ (5 mol %) and 8-isopropylquinoline N-oxide

SCHEME 13. Gold-Catalyzed Regioselective Oxidation of Internal Alkynes: Steric Control[57]

SCHEME 14. Gold-Catalyzed Regioselective Oxidation of Propargylic Carboxylates: Inductive Effect in Controlling Regioselectivity
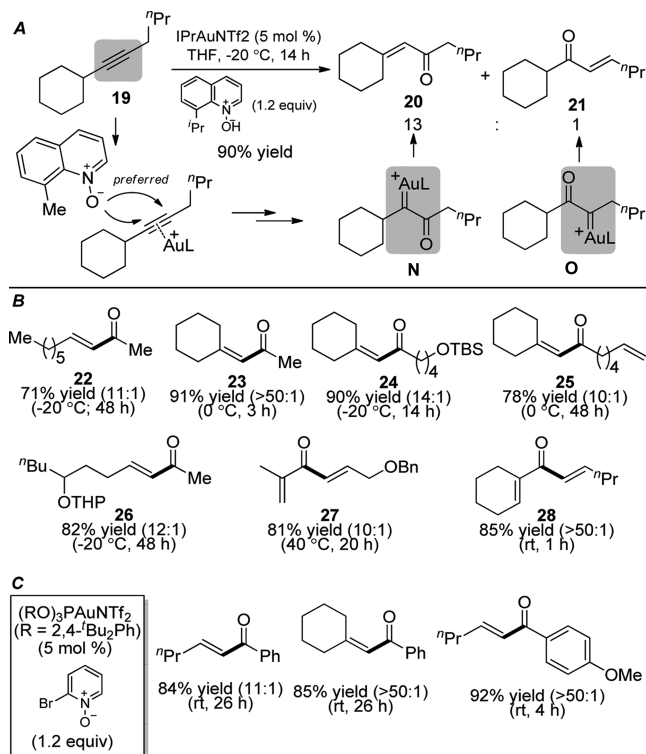
(1.2 equiv) in THF at −20 °C led to a pleasingly selective formation of the enone **20** over its regioisomer **21**.[57] These enones are formed upon 1,2-C−H insertions by the isomeric α-oxo gold carbenes **N** and **O**, respectively. The regioselectivity is attributed to the preferred approach of the oxidant to the less hindered end of the C−C triple bond. Notably, the minor product **21**, as in the other cases of the scope study, was isolated as the exclusive *E*-isomer, in contrast to the Rh carbene/carbenoid chemistry,[58,59] where *cis*-enones are formed selectively upon decomposition of α-diazo carbonyl compounds. Another notable discovery during the optimization is that 8-substituted quinoline *N*-oxides are highly efficient oxidants. Due to the steric congestion around the nitrogen atom, these oxidants can exclude the use of acid additive regardless of the gold catalyst, offering desirable synthetic flexibility. Although in most cases of this chemistry 8-isopropylquinoline *N*-oxide was the best oxidant, the more readily available 8-methylquinoline *N*-oxide has become our favoriate oxidants for further exploring the gold carbene chemistry.

Similar regioselectivities were observed in the cases of Me vs primary alkyl groups (e.g., **22** and **26**), and functionalized primary groups vs cyclohexyl (**24** and **25**). When a methyl group is put against a much bigger cyclohexyl group (i.e., in

the case of **23**), the regioselectivity, as expected, jumped to >50:1. With enyne substrates, the high ratio in the case of **28** suggests the synergistic effect of conjugation, although the ratio in the case of **27** is comparably low. In these two cases, 8-ethylquinoline *N*-oxide was used as the oxidant.

For the less reactive aryl alkynes, the above conditions, however, were ineffective. By using the much more Lewis-acidic phosphite gold complex and 2-bromopyridine *N*-oxide as the oxidant, electronic control became predominant, and these substrates were again regioselectively oxidized, offering efficient access to unsaturated aryl ketones (Scheme 13C).

Our further probe into the regioselectivity with internal alkynes has lately revealed the importance of inductive effect. When the propargylic acetate **29** was subjected to oxidative gold catalysis, the enones **30-H** and **30-OAc** were isolated in 11% and 82% yield, respectively (Scheme 14A). Both products are formed via an initial attack by the oxidant at the alkyne end distal to the acetoxy group. To our surprise, the product derived from the regioisomeric attack was not detected. This excellent regioselectivity is attributed to the inductive effect by the electron-withdrawing acetoxy moiety. Indeed, as shown in Figure 2, the C−C triple bond is polarized substantially as revealed by the natural charges calculated by density functional theory (B3LYP/6-31G*, Spartan06); the alkyne end distal to the carboxy group is significantly more electron-deficient than the proximal end, therefore inviting preferential attack by the approaching nucleophilic oxidant. This revelation is consistent with the ^{13}C NMR chemical shifts of the alkynyl carbons. It is important
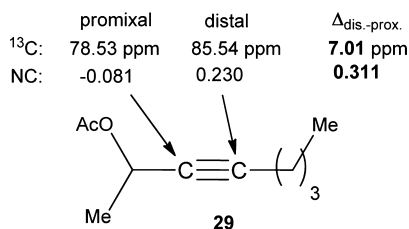
FIGURE 2. Natural charges and ^{13}C chemical shifts of the alkynyl carbons in **29**.
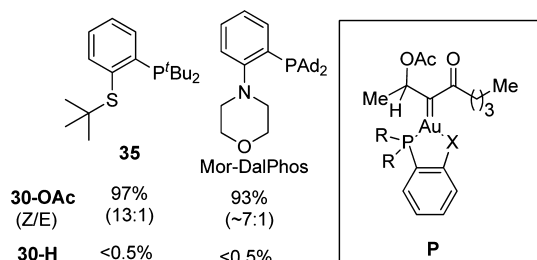

FIGURE 3. The impact of ligands on the ratio of **30-OAc** and **30-H** in the gold-catalyzed oxidation of **29** (reaction conditions 5 mol % gold catalyst, 1.5 equiv of 8-methylquinoline N-oxide, DCE, rt, 3 h).

to note that a recently published Pt-catalyzed hydrosilylation on a similar substrate showed a 3.7:1 regioselectivity.[60] This unexpectedly high selectivity with gold catalysis is ascribed to the augmentation of the electronic bias of the C−C triple bond via the gold activation.

This reaction offers reliable access to α-acetoxy α,β-unsaturated enones. Some selected examples are shown in Scheme 14B. For most cases, the enone side products due to regioisomeric oxidation were not detected, confirming the excellent control by the inductive effect. An exception is the product **31**, the oxidative regioisomer of which was formed in a 23% yield. The low regioselectivity, however, can be readily explained again by the polarization caused by the inductive effect, which in this case was attenuated by the opposing inductive polarization by the BnO group. The improved regioselectivity in the methyl homologue **32** is due to the additional synergistic steric bias. For the cases leading to the products **32−34**, as well as **30**, the selectivities of the 1,2-acetoxy migrations over competing 1,2-C−H insertions are mostly <10:1. To improve the ratios, we screened other catalysts and found that the P,N-bidentate ligand, Mor-DalPhos improved it in the case of **30-OAc/30-H** to >150 (Figure 3). Likewise, the P,S-bidentate ligand **35** that we previously developed gave a similar improvement; moreover, it gave better Z/E ratio. The results with the products **32−34** in Scheme 14B reflect the improvement offered by the P,S-bidentate ligand. The enhanced preference of AcO migration over the 1,2-C−H insertion is attributed to

attenuation of the electrophilicity of the gold carbene moiety via the formation of a tris-coordinated gold complex (i.e., **P**).[53]

Conclusion

For the past several years, we have advanced the strategy of generating α-oxo gold carbenes via gold-catalyzed alkyne oxidation. While our initial approach of tethering a nucleophilic sulfoxide to an alkyne enabled the implementation of the general strategy, the development of the intermolecular version using pyridine/quinoline-based N-oxides opens a fertile field for developing efficient catalysis. Compared with the typical approach of accessing metal carbenes/carbenoids from α-diazo carbonyl substrates, this intermolecular strategy allows the substitution of the hazardous, energetic, and potentially explosive diazo compounds with readily accessible and comparably much safer alkynes in gold carbene chemistry. As such, we achieved intramolecular trappings of the carbene intermediates by using heteronucleophiles and carbonucleophiles, resulting in novel and efficient access to oxetan-3-ones, aziridin-3-ones, and chroman-3-ones. For the challenging intermolecular trapping, we discovered that P,N- or P,S-bidentate ligands help attenuate the electrophilicity of these gold carbenes via the formation of tris-coordinating catalytically relevant variants, which permit efficient trapping by primary amides and even weak nucleophilic carboxylic acids. We were able to achieve good regioselectivities with internal alkyne substrates by harnessing steric or electronic differences and developed rapid access to synthetically versatile α,β-unsaturated carbonyl compounds.

Considering the extensive work on carbenes and carbenoids of other metals, we and other researchers in the field have really just scratched the surface of the synthetic potential of α-oxo gold carbenes. Coupled with the efficient access by our intermolecular oxidation strategy, one could anticipate a blossoming area in gold catalysis that explores their synthetic potential. To materialize this prospect, breakthroughs in several fronts are desirable: (a) the development of more atom-economic and greener oxidants; ideally oxygen or nitrous oxide could be used; (b) extending intermolecular trapping to a broad range of nucleophiles; (c) better understanding of the elementary reaction steps via extensive DFT calculations; (d) lowering the catalyst loading so that operations of industrial scale could become affordable.

BIOGRAPHICAL INFORMATION

Liming Zhang was born in Pingxiang, China, on May 11, 1972, and received his Ph. D. degree from the University of Michigan in 2003. He was a postdoctoral fellow at the University of Chicago before joining the University of Nevada, Reno, as an assistant professor in 2005. He moved to UCSB in 2009 and is currently a full professor. He was an Alfred P. Sloan Fellow during 2009−2011. His research focus is transition metal catalysis with applications in natural product synthesis, materials research, and medicinal chemistry.

FOOTNOTES

The authors declare no competing financial interest.

REFERENCES

1 Hashmi, A. S. K. Gold-Catalyzed Organic Reactions. *Chem. Rev.* **2007**, *107*, 3180–3211.

2 Fürstner, A.; Davies, P. W. Catalytic Carbophilic Activation: Catalysis by Platinum and Gold π Acids. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449.

3 Hashmi, A. S. K.; Rudolph, M. Gold Catalysis in Total Synthesis. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775.

4 Rudolph, M.; Hashmi, A. S. K. Gold Catalysis in Total Synthesis-an Update. *Chem. Soc. Rev.* **2012**, *41*, 2448–2462.

5 Pauling, L. *The Nature of the Chemical Bond and the Structure of Molecules and Crystals; an Introduction to Modern Structural Chemistry*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960.

6 Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A., III; Toste, F. D. A Bonding Model for Gold(I) Carbene Complexes. *Nat. Chem.* **2009**, *1*, 482–486.

7 Zhang, L.; Sun, J.; Kozmin, S. A. Gold and Platinum Catalysis of Enyne Cycloisomerization. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296.

8 Jimenez-Nunez, E.; Echavarren, A. M. Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective. *Chem. Rev.* **2008**, *108*, 3326–3350.

9 Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998.

10 Archibald, T. G. Large-Scale Use of Diazomethane in Pharmaceutical Production. *Chim. Oggi* **2000**, *18*, 34–38.

11 Rossi, E.; Woehl, P.; Maggini, M. Scalable in Situ Diazomethane Generation in Continuous-Flow Reactors. *Org. Process Res. Dev.* **2012**, *16*, 1146–1149.

12 Fructos, M. R.; Belderrain, T. R.; de Fremont, P.; Scott, N. M.; Nolan, S. P.; Diaz-Requejo, M. M.; Perez, P. J. A Gold Catalyst for Carbene-Transfer Reactions from Ethyl Diazoacetate. *Angew. Chem., Int. Ed.* **2005**, *44*, 5284–5288.

13 Prieto, A.; Fructos, M. R.; Mar Díaz-Requejo, M.; Pérez, P. J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A. M. Gold-Catalyzed Olefin Cyclopropanation. *Tetrahedron* **2009**, *65*, 1790–1793.

14 Pawar, S. K.; Wang, C.-D.; Bhunia, S.; Jadhav, A. M.; Liu, R.-S. Gold-Catalyzed Formal Cycloaddition of 2-Ethynylbenzyl Ethers with Organic Oxides and A-Diazoesters. *Angew. Chem., Int. Ed.* **2013**, *52*, 7559–7563.

15 Pagar, V. V.; Jadhav, A. M.; Liu, R.-S. Gold-Catalyzed Reactions between Alkenyldiazo Carbonyl Species and Acetals. *J. Org. Chem.* **2013**, *78*, 5711–5716.

16 Jadhav, A. M.; Pagar, V. V.; Liu, R.-S. Development of a Povarov Reaction/Carbene Generation Sequence for Alkenyldiazocarbonyl Compounds. *Angew. Chem., Int. Ed.* **2012**, *51*, 11809–11813.

17 Li, C.-W.; Lin, G.-Y.; Liu, R.-S. Construction of 2,3-Dihydrofuran Cores through the [3 + 2] Cycloaddition of Gold A-Carbonylcarbenoids with Alkenes. *Chem.—Eur. J.* **2010**, *16*, 5803–5811.

18 Li, C.-W.; Pati, K.; Lin, G.-Y.; Sohel, S. M. A.; Hung, H.-H.; Liu, R.-S. Gold-Catalyzed Oxidative Ring-Expansions and Ring-Cleavages of Alkynylcyclopropanes by Intermolecular Reactions Oxidized by Diphenylsulfoxide. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891–9894.

19 Dateer, R. B.; Pati, K.; Liu, R.-S. Gold-Catalyzed Synthesis of Substituted 2-Aminofurans via Formal 4 + 1 -Cycloadditions on 3-En-1-Ynamides. *Chem. Commun.* **2012**, *48*, 7200–7202.

20 Ghorpade, S.; Su, M.-D.; Liu, R.-S. Gold-Catalyzed Oxidative Cyclizations on 1,4-Enynes: Evidence for a γ-Substituent Effect on Wagner−Meerwein Rearrangements. *Angew. Chem., Int. Ed.* **2013**, *52*, 4229–4234.

21 Vasu, D.; Hung, H.-H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R.-S. Gold-Catalyzed Oxidative Cyclization of 1,5-Enynes Using External Oxidants. *Angew. Chem., Int. Ed.* **2011**, 6911–6914.

22 Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R.-S. Gold-Catalyzed Oxidative Cyclizations of cis-3-En-1-ynes to Form Cyclopentenone Derivatives. *Angew. Chem., Int. Ed.* **2012**, 2939–2942.

23 Shapiro, N. D.; Toste, F. D. Rearrangement of Alkynyl Sulfoxides Catalyzed by Gold(I) Complexes. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161.

24 Yeom, H. S.; Lee, J. E.; Shin, S. Gold-Catalyzed Waste-Free Generation and Reaction of Azomethine Ylides: Internal Redox/Dipolar Cycloaddition Cascade. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040–7043.

25 Yeom, H. S.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J. E.; Lee, S. S.; Shin, S. Stereoselective One-Pot Synthesis of 1-Aminoindanes and 5,6 Fused Azacycles Using a Gold-Catalyzed Redox-Pinacol-Mannich-Michael Cascade. *Angew. Chem., Int. Ed.* **2010**, *49*, 1611–1614.

26 Qian, D.; Zhang, J. Catalytic Oxidation/C-H Functionalization of N-Arylpropiolamides by Means of Gold Carbenoids: Concise Route to 3-Acyloxindoles. *Chem. Commun.* **2012**, *48*, 7082–7084.

27 Qian, D.; Zhang, J. Gold/Brønsted Acid Relay Catalysis for Enantioselective Construction of Spirocyclic Diketones. *Chem.—Eur. J.* **2013**, *19*, 6984–6988.

28 Qian, D.; Zhang, J. A Gold(I)-Catalyzed Intramolecular Oxidation-Cyclopropanation Sequence of 1,6-Enynes: A Convenient Access to [N.1.0]Bicycloalkanes. *Chem. Commun.* **2011**, *47*, 11152–11154.

29 Davies, P. W.; Albrecht, S. J. C. Gold- or Platinum-Catalyzed Synthesis of Sulfur Heterocycles: Access to Sulfur Ylides without Using Sacrificial Functionality. *Angew. Chem., Int. Ed.* **2009**, *48*, 8372–8375.

30 Davies, P. W. Alkynes as "Masked" Ylides under Noble-Metal Catalysis. *Pure Appl. Chem.* **2010**, *82*, 1537–1544.

31 Davies, P. W.; Cremonesi, A.; Martin, N. Site-Specific Introduction of Gold-Carbenoids by Intermolecular Oxidation of Ynamides or Ynol Ethers. *Chem. Commun.* **2011**, *47*, 379–381.

32 Henrion, G.; Chavas, T. E. J.; Le Goff, X.; Gagosz, F. Biarylphosphonite Gold(I) Complexes as Superior Catalysts for Oxidative Cyclization of Propynyl Arenes into Indan-2-Ones. *Angew. Chem., Int. Ed.* **2013**, *52*, 6277–6282.

33 Hashmi, A. S. K.; Wang, T.; Shi, S.; Rudolph, M. Regioselectivity Switch: Gold(I)-Catalyzed Oxidative Rearrangement of Propargyl Alcohols to 1,3-Diketones. *J. Org. Chem.* **2012**, *77*, 7761–7767.

34 Shi, S.; Wang, T.; Yang, W.; Rudolph, M.; Hashmi, A. S. K. Gold-Catalyzed Synthesis of Glyoxals by Oxidation of Terminal Alkynes: One-Pot Synthesis of Quinoxalines. *Chem.—Eur. J.* **2013**, *19*, 6576–6580.

35 Xu, M.; Ren, T.-T.; Li, C.-Y. Gold-Catalyzed Oxidative Rearrangement of Homopropargylic Ether Via Oxonium Ylide. *Org. Lett.* **2012**, *14*, 4902–4905.

36 Wang, L.; Xie, X.; Liu, Y. Gold-Catalyzed Oxidative Rearrangement Involving 1,2-Acyl Migration: Efficient Synthesis of Functionalized Dihydro-γ-Carbolines from α-(2-Indolyl) Propargylic Alcohols and Imines. *Angew. Chem., Int. Ed.* **2013**, *52*, 13302–13306.

37 Li, G.; Zhang, L. Gold-Catalyzed Intramolecular Redox Reaction of Sulfinyl Alkynes: Efficient Generation of A-Oxo Gold Carbenoids and Application in Insertion into R-Co Bonds. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156–5159.

38 Noey, E. L.; Luo, Y.; Zhang, L.; Houk, K. N. Mechanism of Gold(I)-Catalyzed Rearrangements of Acetylenic Amine-N-Oxides: Computational Investigations Lead to a New Mechanism Confirmed by Experiment. *J. Am. Chem. Soc.* **2012**, *134*, 1078–1084.

39 Yeom, H.-S.; Lee, Y.; Lee, J.-E.; Shin, S. Geometry-Dependent Divergence in the Gold-Catalyzed Redox Cascade Cyclization of O-Alkynylaryl Ketoximes and Nitrones Leading to Isoindoles. *Org. Biomol. Chem.* **2009**, *7*, 4744–4752.

40 Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. Diversity in Gold- and Silver-Catalyzed Cycloisomerization of Epoxide−Alkyne Functionalities. *Org. Lett.* **2008**, *10*, 5059–5062.

41 Cuenca, A. B.; Montserrai, S.; Hossain, K. M.; Mancha, G.; Lledos, A.; Medio-Simon, M.; Ujaque, G.; Asensio, G. Gold(I)-Catalyzed Intermolecular Oxyarylation of Alkynes: Unexpected Regiochemistry in the Alkylatioin of Arenes. *Org. Lett.* **2009**, *11*, 4906–4909.

42 Ye, L.; Cui, L.; Zhang, G.; Zhang, L. Alkynes as Equivalents of a-Diazo Ketones in Generating a-Oxo Metal Carbenes: A Gold-Catalyzed Expedient Synthesis of Dihydrofuran-3-Ones. *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259.

43 Ye, L.; He, W.; Zhang, L. Gold-Catalyzed One-Step Practical Synthesis of Oxetan-3-Ones from Readily Available Propargylic Alcohols. *J. Am. Chem. Soc.* **2010**, *132*, 8550–8551.

44 Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. Oxetanes as Promising Modules in Drug Discovery. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736–7739.

45 Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. Oxetanes as Versatile Elements in Drug Discovery and Synthesis. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052–9067.

46 Ye, L.; He, W.; Zhang, L. A Flexible and Stereoselective Synthesis of Azetidin-3-Ones through Gold-Catalyzed Intermolecular Oxidation of Alkynes. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236–3239.

47 Robak, M. T.; Herbage, M. A.; Ellman, J. A. Synthesis and Applications of tert-Butanesulfinamide. *Chem. Rev.* **2010**, *110*, 3600–3740.

48 Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. A Highly Active Catalyst for Pd-Catalyzed Amination Reactions: Cross-Coupling Reactions Using Aryl Mesylates and the Highly Selective Monoarylation of Primary Amines Using Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 13552–13554.

49 Wang, Y.; Ji, K.; Lan, S.; Zhang, L. Rapid Access to Chroman-3-Ones through Gold-Catalyzed Oxidation of Propargyl Aryl Ethers. *Angew. Chem., Int. Ed.* **2012**, *51*, 1915–1918.

50 He, W.; Li, C.; Zhang, L. An Efficient [2 + 2 + 1] Synthesis of 2,5-Disubstituted Oxazoles via Gold-Catalyzed Intermolecular Alkyne Oxidation. *J. Am. Chem. Soc.* **2011**, *133*, 8482–8485.

51 Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. A P,N-Ligand for Palladium-Catalyzed Ammonia Arylation: Coupling of Deactivated Aryl Chlorides, Chemoselective Arylations, and Room Temperature Reactions. *Angew. Chem., Int. Ed.* **2010**, *49*, 4071–4074.

52 Hesp, K. D.; Stradiotto, M. Stereo- and Regioselective Gold-Catalyzed Hydroamination of Internal Alkynes with Dialkylamines. *J. Am. Chem. Soc.* **2010**, *132*, 18026–18029.

53 Luo, Y.; Ji, K.; Li, Y.; Zhang, L. Tempering the Reactivities of Postulated A-Oxo Gold Carbenes Using Bidentate Ligands: Implication of Tricoordinated Gold Intermediates and the Development of an Expedient Bimolecular Assembly of 2,4-Disubstituted Oxazoles. *J. Am. Chem. Soc.* **2012**, *134*, 17412–17415.

54 Ito, H.; Takagi, K.; Miyahara, T.; Sawamura, M. Gold(I)-Phosphine Catalyst for the Highly Chemoselective Dehydrogenative Silylation of Alcohols. *Org. Lett.* **2005**, *7*, 3001–3004.

55 Ito, H.; Saito, T.; Miyahara, T.; Zhong, C.; Sawamura, M. Gold(I) Hydride Intermediate in Catalysis: Dehydrogenative Alcohol Silylation Catalyzed by Gold(I) Complex. *Organometallics* **2009**, *28*, 4829–4840.

56 Ji, K.; Zhao, Y.; Zhang, L. Optimizing P,N-Bidentate Ligands for Oxidative Gold Catalysis: Efficient Intermolecular Trapping of A-Oxo Gold Carbenes by Carboxylic Acids. *Angew. Chem., Int. Ed.* **2013**, *52*, 6508–6512.

57 Lu, B.; Li, C.; Zhang, L. Gold-Catalyzed Highly Regioselective Oxidation of C–C Triple Bonds without Acid Additives: Propargyl Moieties as Masked α,β-Unsaturated Carbonyls. *J. Am. Chem. Soc.* **2010**, *132*, 14070–14072.

58 Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. Catalyzed Insertion Reactions of Substituted [Alpha]-Diazoesters. A New Synthesis of cis-Enoates. *Tetrahedron Lett.* **1981**, *22*, 4163–4166.

59 Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. A Convenient Method for the Preparation of (Z)-α,β-Unsaturated Carbonyl Compounds. *J. Org. Chem.* **1996**, *61*, 2908–2910.

60 Rooke, D. A.; Ferreira, E. M. Platinum-Catalyzed Hydrosilylations of Internal Alkynes: Harnessing Substituent Effects to Achieve High Regioselectivity. *Angew. Chem., Int. Ed.* **2012**, 3225–3230.