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Tempering the Reactivities of Postulated α-Oxo Gold Carbenes Using Bidentate Ligands: Implication of Tricoordinated Gold Intermediates and the Development of an Expedient Bimolecular Assembly of 2,4-Disubstituted Oxazoles

Yingdong Luo,[†] Kegong Ji,[†] Yuxue Li,[‡] and Liming Zhang*[,†]

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

[‡]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, China

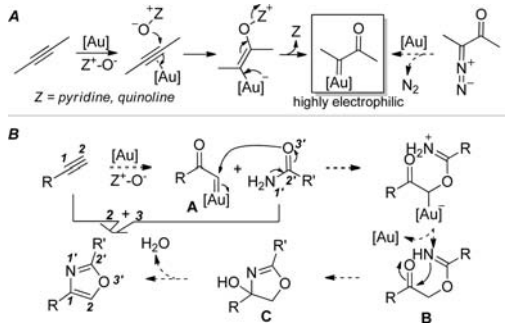
Supporting Information

ABSTRACT: 2,4-Oxazole is an important structural motif in various natural products. An efficient modular synthesis of this structure has been achieved via a [3 + 2] annulation between a terminal alkyne and a carboxamide using a gold-catalyzed oxidation strategy. The postulated reactive intermediate, a terminal α-oxo gold carbene, previously known to be highly electrophilic and hence unlikely to be trapped by stoichiometric external nucleophiles, is coerced to react smoothly with the carboxamide en route to the oxazole ring by a P,N- or P,S-bidentate ligand such as MorDalPhos; in stark contrast, often-used ligands such as monodentate phosphines and N-heterocyclic carbenes are totally ineffective. The role of these bidentate phosphines in this reaction is attributed to the formation of a tricoordinated gold carbene intermediate, which is less electrophilic and hence more chemoselective when reacting with nucleophiles. The success in using bidentate phosphine ligands to temper the reactivities of in situ-generated gold carbenes is likely to open many new opportunities to apply oxidative gold catalysis to the development of novel methods, and the implication of tricoordinated gold intermediates in homogeneous gold catalysis should stimulate further advances in gold catalysis.

2,4-Disubstituted oxazole is a structural motif found in many bioactive natural products, including (−)-hennoxazole A[1] and phorboxazoles.[2] Biosynthetically, it is formed via post-translational modifications of serine-containing peptides via sequential cyclization, dehydration, and oxidative aromatization. Chemical syntheses[3] of this functionality can often be achieved via sequential dehydrative cyclization[4] and dehydrogenation[5] of substituted *N*-(2-hydroxyethyl)amides. Though this approach is reliable, constructing this important motif through a one-step bimolecular annulation[6] would offer excellent step economy and desirable synthetic convergence. Several elegant protocols of this nature,[7] however, have their own limitations. Herein we disclose a new approach featuring gold-catalyzed oxidative [3 + 2] annulations between readily available terminal alkynes and carboxamides under mild conditions. A key intermediate implicated in the catalytic cycle is a tricoordinated Au(I) complex, which is rare in gold catalysis.[8]

We recently developed a strategy for gold-catalyzed intermolecular alkyne oxidation[6b,9,10] in which α-oxo gold carbenes were postulated to be key reactive intermediates (Scheme 1A). A range of versatile synthetic methods based on this design have been developed by us[6b,9] and others,[11] offering strong support for the intermediacy of these gold carbenes and revealing their potent electrophilicities. While α-oxo metal carbenes/carbenoids can typically be generated via metal-catalyzed dediazotization of α-diazo ketones,[12,13] this strategy provides a safe, step-economic, and scalable alternative in the case of gold that uses readily available alkynes as substrates. Unfortunately, all of the reactions developed to date have relied on rapid trapping of the gold carbene either via facile intramolecular processes or by the reaction solvent.[6b] In the latter case, we developed a rapid synthesis of 2,5-disubstituted oxazoles in a [2 + 2 + 1] manner using nitrile as both the solvent and the trapping reagent.[6b] Otherwise, the reaction tends to be messy, perhaps due to a lack of chemoselectivity by the α-oxo gold carbene intermediate because of its high electrophilicity. This rationale was further corroborated by the observation that the intermediate can abstract chloride from dichloroethane solvent.[9d] The highly electrophilic nature of α-oxo gold carbenes, especially those without additional substitutions at the carbene

Scheme 1. (A) Alkynes as Surrogates of Hazardous α-Diazo Ketones in the Generation of α-Oxo Gold Carbene Intermediates; (B) Application in the Synthesis of 2,4-Disubstituted Oxazoles via [3 + 2] Annulations



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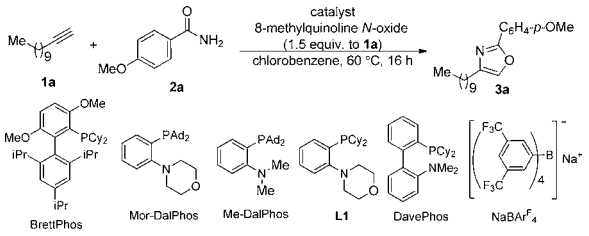
center, can be understood by invoking the relatively weak back-donation by the electronegative gold atom.[14] Trapping these highly electrophilic gold carbenes with stoichiometric external nucleophiles is difficult.

Not deterred, we set out to discover catalysts and conditions that would overcome this daunting challenge. The targeted reaction was a [3 + 2] annulation between a terminal alkyne and a carboxamides for the formation of 2,4-disubstituted oxazoles. The design is rationalized in Scheme 1B: the α-oxo gold carbene intermediate **A** could be attacked by an amide through its carbonyl oxygen, yielding imidate **B** upon protodeauration; cyclization of **B** would generate oxazolinol **C**, in situ dehydration of which would afford the desired product.

Table 1 shows the reaction discovery and subsequent optimization of conditions. We chose chlorobenzene as the solvent to avoid solvent participation.[6b,9d] Initially, no desired reaction was detected with various typical gold catalysts with a range of electronic and steric characteristics (entries 1−4). The only exception was BrettPhosAuNTf$_2$,[9c] but the expected oxazole **3a** was formed in a pitiful 4% yield (entry 5). These results highlighted the low selectivities associated with the highly reactive α-oxo gold carbenes. By expanding the types of ligands examined, we fortuitously came upon Mor-DalPhos, a P,N-bidentate ligand developed by Stradiotto.[15] With Mor-DalPhosAuNTf$_2$ as the catalyst, the reaction yield, to our amazement, jumped to 58% (entry 6). The effect of the counteranion was examined. While SbF_6^- (entry 7) and OTf^- (entry 8) fared worse, $[BAr^F{}_4]^-$, a noncoordinating, lipophilic anion developed by Kobayashi,[16] improved the reaction yield by a significant 6% (entry 9). The reactive catalyst in this case can be readily generated in situ, driven by the precipitation of insoluble NaCl in PhCl. Other ligands with substituted amino groups were also tested. Me-DalPhos,[15] a ligand in the same series as Mor-DalPhos, gave identical results (entry 10), and **L1**,[15a] a ligand that differs from Mor-DalPhos by having smaller cyclohexyl groups on the P atom, led to a lower yet acceptable yield (entry 11); however, DavePhos was completely ineffective (entry 12). These data suggested that the position of the amino group is critical, steric congestion is beneficial, and the morpholine oxygen is inconsequential. A much higher yield (87%) was achieved when the carboxamide was the limiting reagent and 1.5 equiv of the alkyne was used (entry 13). Other more conventional solvents such as DCE (entry 14) and toluene (entry 15) were less conducive to this reaction, presumably because of side reactions involving the solvent. Also, to avoid further oxidation of the gold carbene intermediate by the remaining 8-methylquinoline *N*-oxide to form an α-ketoaldehyde, the oxidant had to be introduced into the reaction flask slowly using a syringe pump to keep its concentration low during the reaction.

Table 1. Optimization of the Reaction Conditions[a]



entry	**1a**/**2a**	catalyst	yield[b]
1	1:1.2	$Ph_3PAuNTf_2$ (5 mol %)	0[c]
2	1:1.2	Cy-JohnPhosAuNTf$_2$ (5 mol %)	0[c]
3	1:1.2	IPrAuNTf$_2$ (5 mol %)	0[c]
4	1:1.2	(4-CF_3Ph)$_3$PAuNTf$_2$ (5 mol %)	0[c]
5	1:1.2	BrettPhosAuNTf$_2$ (5 mol %)	4%[c]
6	1:1.2	Mor-DalPhosAuNTf$_2$ (5 mol %)	58%
7	1:1.2	Mor-DalPhosAuCl (5 mol %)/$AgSbF_6$ (5 mol %)	37%
8	1:1.2	Mor-DalPhosAuCl (5 mol %)/AgOTf (5 mol %)	30%
9	1:1.2	Mor-DalPhosAuCl (5 mol %)/NaBAr$^F_4$ (10 mol %)	64%
10	1:1.2	Me-DalPhosAuCl (5 mol %)/NaBAr$^F_4$ (10 mol %)	64%
11	1:1.2	**L1**AuCl (5 mol %)/NaBAr$^F_4$ (10 mol %)	52%
12	1:1.2	DavePhosAuCl (5 mol %)/NaBAr$^F_4$ (10 mol %)	0[c]
13	1.5:1	Mor-DalPhosAuCl (5 mol %)/NaBAr$^F_4$ (10 mol %)	87%[d]
14	1.5:1	Mor-DalPhosAuCl (5 mol %)/NaBAr$^F_4$ (10 mol %)	59%[e]
15	1.5:1	Mor-DalPhosAuCl (5 mol %)/NaBAr$^F_4$ (10 mol %)	78%[f]

[a]The reaction was run with everything except the oxidant in a vial capped with a septum, and the oxidant was introduced into the reaction mixture slowly using a syringe pump. Initially, [**1a**] = 0.1 M. [b]Measured by ^{1}H NMR analysis using diethyl phthalate as the internal standard. [c]<20% of 1-dodecyne was left, and the crude ^{1}H NMR spectrum was mostly messy. [d]81% isolated yield. [e]DCE was used as the solvent. [f]Toluene was used as the solvent.

With the optimized reaction conditions in hand, we examined the reaction scope (Table 2). First, a range of carboxamides were tested using 1-dodecyne as the alkyne component (entries 1−10). Benzamides with electron-donating (i.e., in the cases of **3a** and entry 1) or weakly electron-withdrawing (entries 3−5) para substituents or no substitution (entry 2) underwent the reaction smoothly, affording 2,4-disubstituted oxazoles in acceptable to good yields. Furan-2-carboxamide and thiophene-2-carboxamide gave the corresponding biheteroaryl products **3g** and **3h** uneventfully in coincidently the same 73% yield (entries 6 and 7). The reaction also worked with α,β-unsaturated carboxamides. While **3j** was isolated in only 55% yield using crotonamide (entry 9), the reaction proceeded efficiently with cinnamamide (entry 8) and especially well with 3,3-dimethylacrylamide (95% yield; entry 10). The reaction did not work with aliphatic carboxamides,[17] and poor yields (<30%) were observed with benzamides bearing strongly electron-withdrawing para substituents such as acetyl and nitro or ortho substituents such as Me and F because of their lower nucleophilicities and/or steric hindrance.

With respect to the alkyne, both cyclohexylacetylene (entry 11) and cyclopropylacetylene (entry 12) were suitable substrates. In the former case, **3l** was isolated in a good 83% yield. In contrast, its analogue with the anisyl group replaced by a phenyl group was obtained in only 18% yield[7h] using the Blümlein−Lewy method.[18] Linear aliphatic terminal alkynes with remote functional groups such as NPhth (entry 13), TIPS-protected HO (entry 14), chloro (entry 15), and acetoxy (entry 16) were also allowed. When these groups were placed at propargyl or homopropargyl positions, the reaction became much less efficient because of their interference with the gold carbene moiety. Nevertheless, when a weakly nucleophilic phenyl group was present (entry 17), the reaction still afforded an acceptable yield. Phenylacetylene without (entry 18) and with (entries 19 and 20) electron-donating para substituents gave the triaryl products in serviceable yields. On the other hand, *p*-nitrophenylacetylene led to a mere ∼30% yield of the expected oxazole product (R′ = anisyl; data not shown).

To explain the effectiveness of Mor-DalPhos and the related Me-DalPhos and the role of the neighboring amino group, we first thought that H-bonding might be at play.[15b] However, inspection of the X-ray structure of Mor-DalPhosAuCl[15b] show that the N atom, with its lone electron pair pointing to and thereby shielded by the gold center, is too congested to be a H-

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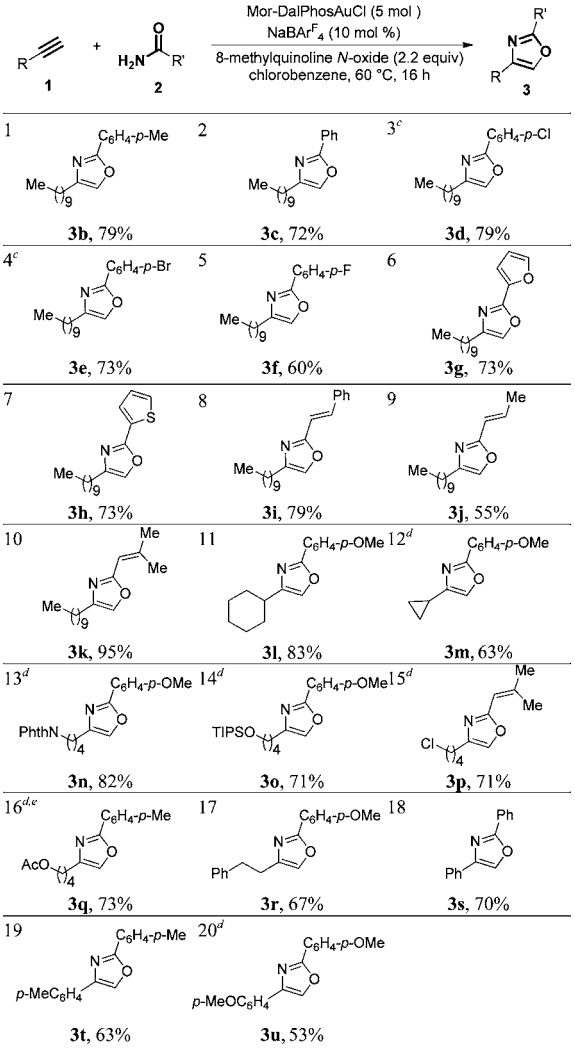
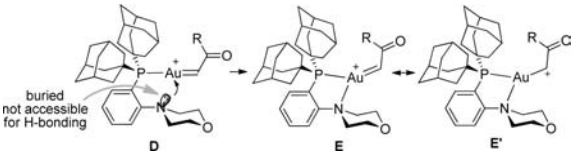
Table 2. Reaction Scope[a,b]



[a] **1**/**2** = 1.5/1; initially [**2**] = 0.1 M; the oxidant was introduced to the reaction vial using a syringe pump. [b] Isolated yields are shown. [c] 2 equiv of the alkyne and 3 equiv of the oxide were used. [d] The alkyne was added along with the oxide using a syringe pump. [e] At 100 °C.

bond acceptor (Scheme 2). The ineffectiveness of DavePhos provided some circumvential evidence for this conclusion. In addition, we prepared the related P,S-bidentate ligands **L2** and **L3** (Figure 1). To our delight, the corresponding gold complexes promoted the oxazole formation with efficiencies close to that of Mor-DalPhos (see Figure 1). As sulfides are not considered to be H-bond acceptors, these results effectively ruled out the participation of the ortho heteroatoms via H-bonding. The dramatic impact of these heteroatoms (N or S) suggests that instead they might be involved in coordination[19] to the formally cationic gold center in the postulated metal carbene moiety. As shown in Scheme 2, such a tricoordinated gold center in **E**/**E**′ should be less electron-deficient than the dicoordinated one in **D**, making it more capable of back-donating electrons to the carbene center. Consequently, the carbene center would be less cationic because of the decreased contribution by the mesomeric cationic form **E**′. This tempering of the electrophilicity of the gold carbene is likely the key to achieving its chemoselective trapping by carboxamides for the formation of 2,4-disubstituted oxazoles. The slightly higher yields in the cases of **L3** versus **L2** (Figure 1) and Mor-DalPhos versus **L1** are consistent with tricoordinated gold carbene intermediates, as their formation would be further facilitated by the bigger substituents on the heteroatoms of **L3** and Mor-DalPhos via steric coercion.[9e]

Scheme 2. Rationale for the Role of Mor-DalPhos



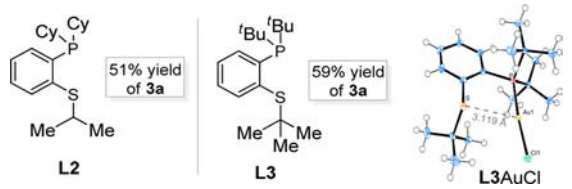


Figure 1. New, efficacious S-functionalized phosphine ligands **L2** and **L3** and ORTEP plot of **L3**AuCl (50% probability ellipsoids).

Further support for the involvement of the tricoordinated gold carbene **E** was provided by DFT calculations. The dicoordinated gold carbene **D**-**Me** (**D** with R = Me) was partially optimized by fixing the distance between Au and N at 2.930 Å (the Au−N distance in the X-ray structure of Mor-DalPhosAuCl),[15b] and the tricoordinated species **E**-**Me** (**E** with R = Me) was fully optimized (Figure 2). The latter is 5.4 kcal/mol more stable than the former, strongly supporting the role of **E** in the catalysis. Moreover, the sum of the natural bond order (NBO) charges for all of the atoms in the indicated box decreased from +0.346 to +0.246 upon N coordination, which supports our reasoning that the electrophilicity of the carbene center might be attenuated in the process. An additional notable change upon the formation of **E**-**Me** is that the Au−C bond was shortened by 0.034 Å, suggesting increased back-donation by the gold center.

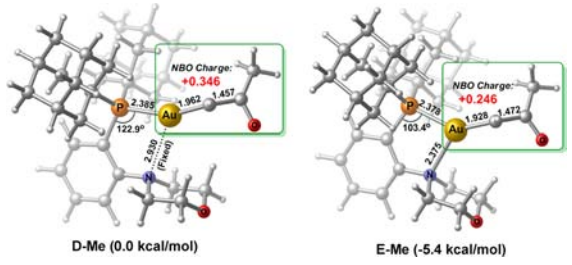


Figure 2. Partially optimized structure of **D**-**Me** with a fixed Au−N distance of 2.930 Å and the fully optimized structure of **E**-**Me**, calculated at the PBE1PBE/6-311+G** level. Selected bond lengths (in Å), bond angles, and relative energies Δ*E* are shown.

Tricoordinated Au complexes such as $(Ph_3P)_2AuCl$[20] and XantPhosAuCl,[21] though amply documented in the literature, have had surprisingly little relevance in homogeneous Au(I) catalysis; we are aware of only one such example, a dehydrogenative silylation of alcohols with R_3SiH involving XantPhosAuCl.[21,22] In view of the vast majority of Au catalyses involving π systems, our discovery that tricoordinated Au(I) species can attenuate the electrophilicity of carbene centers and hence enable new reactions will likely spur further development of homogeneous Au(I) catalysis via the use of designed efficacious bidentate ligands.

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In summary, we have developed a Au(I)-catalyzed modular synthesis of 2,4-disubstituted oxazoles via [3 + 2] annulations between readily available terminal alkynes and aromatic/alkenic carboxamides under mild conditions. The postulated key reaction intermediate, an α-oxo gold carbene, is generated via gold-promoted oxidation of a terminal alkyne and appears to be highly electrophilic, but the use of a P,N- or P,S-bidentate ligand, especially Mor-DalPhos, significantly tempers its reactivity, thereby permitting its efficient trapping by a carboxamide en route to the formation of the oxazole ring. This reactivity modulation is attributed to the formation of a tricoordinated gold carbene species through coordination of the non-phosphorus heteroatom, which is supported by DFT calculations. The rare involvement of tricoordinated gold complexes in homogeneous gold catalysis and their role in modulating the reactivities of cationic gold intermediates should stimulate new advances in this intensely researched field.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*zhang@chem.ucsb.edu

Notes

The authors declare no competing financial interest.

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L.Z. dedicates this work to Professor Masato Koreeda on the occasion of his 70th birthday. We thank NIH (R01 GM084254) and NSF (CAREER CHE-0969157 and PIRE-ECCI OISE-0968399) for general financial support.

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