

# Intramolecular Insertions into Unactivated C(sp<sup>3</sup>)–H Bonds by Oxidatively Generated $\beta$ -Diketone- $\alpha$ -Gold Carbenes: Synthesis of Cyclopentanones

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**S** Supporting Information

**ABSTRACT:** Generation of reactive  $\alpha$ -oxo gold carbene intermediates via gold-catalyzed oxidation of alkynes has become an increasing versatile strategy of replacing hazardous diazo carbonyl compounds with benign and readily available alkynes in the development of efficient synthetic methods. However, one of the hallmarks of metal carbene/carbenoid chemistry, i.e., insertion into an unactivated C(sp<sup>3</sup>)–H bond, has not been realized. This study reveals for the first time that this highly valuable transformation can be readily realized intramolecularly by oxidatively generated  $\beta$ -diketone- $\alpha$ -gold carbenes using ynones as substrates. Substrate conformation control via the Thorpe–Ingold effect is the key design feature that enables generally good to excellent efficiencies, and synthetically versatile cyclopentanones including spiro-, bridged, and fused bicyclic ones can be readily accessed.

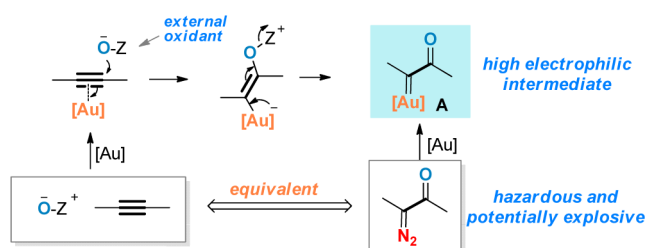
Insertions into unactivated C(sp<sup>3</sup>)–H bonds by reactive metal carbene/carbenoids are powerful synthetic strategies in the construction of complex functional structures, and diazo compounds are the most utilized precursors to these metal intermediates.<sup>1</sup> While many preparative methods have been developed,<sup>1a</sup> they remain as highly hazardous materials and are potentially explosive. Moreover, the reagents used for their synthesis tend to be energetic and thereby put further strain on operational safety.

A few years ago we<sup>2</sup> developed an intermolecular oxidative gold catalysis that permits facile access to  $\alpha$ -oxo gold carbenes (i.e., **A**) by using benign and readily available alkynes instead of diazo carbonyl compounds<sup>3</sup> (Scheme 1). This approach opens a readily accessible venue to probe the reactivities of these reactive intermediates and explore their synthetic utilities. Indeed, a range of useful synthetic methods has been developed by us<sup>4</sup> and

others<sup>5</sup> based on this nondiazo strategy. From all the documented reactivities,  $\alpha$ -oxo gold carbenes appear to be more electrophilic than their Rh carbenoid counterparts and react readily with various nucleophiles including solvents,<sup>6</sup> hence displaying more of the characteristics of gold-stabilized carbocations.<sup>7</sup> As a consequence, their insertions into C(sp<sup>3</sup>)–H bonds, hallmarks of carbene reactivities, have so far not been observed, despite a formal instance in the versatile gold-catalyzed oxidative formation of cyclopentenone reported by Liu,<sup>5j</sup> where the intermediacy of  $\alpha$ -oxo gold carbenes is deemed unlikely, and cases involving intramolecularly generated more electron-rich counterparts.<sup>8</sup> Notwithstanding, the gold carbenes/carbenoids generated from ethyl diazoacetate have been shown to be capable of inserting into the C–H bonds of alkanes (used as solvent).<sup>3a</sup> To reconcile these contrasting reaction outcomes, we reasoned that  $\alpha$ -oxo gold carbenes are capable of C–H insertions but prefer electrophilic reactions.<sup>3b</sup> In the cases of their oxidative generations, various nucleophiles present in the reaction mixture, such as the oxidants, the reduced counterparts, and even solvents,<sup>6,9</sup> can readily trap these highly electrophilic species and thereby divert them from significant and observable C–H insertions. We anticipated that by suitable substrate design and by optimization of reaction conditions, insertions into unactivated C(sp<sup>3</sup>)–H bonds by oxidatively generated  $\alpha$ -oxo gold carbenes can be realized. Herein we disclose our preliminary results.

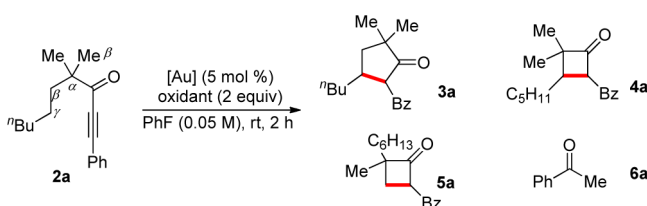
At the outset, we chose the alkyne **2a** as the substrate (Table 1) for the following considerations: (a) the likely generated  $\beta$ -diketone- $\alpha$ -gold(I) carbene (i.e., **B**, Scheme 2) should be even more electrophilic than the  $\alpha$ -oxo gold carbene counterpart **A** and thereby more reactive toward C–H insertion; (b) the additional acyl group would provide extra steric bulk to hinder intermolecular side reactions; and (c) the *gem*-dimethyl groups would provide beneficial conformation control of the carbon backbone due to the Thorpe–Ingold effect. Much to our delight, C–H insertions occurred even with Ph<sub>3</sub>PAuNTf<sub>2</sub> as catalyst and 8-methylquinoline *N*-oxide (**1a**) as oxidant, and three different products, i.e., **3a–5a**, were formed, albeit only in a 30% combined yield as mixtures of tautomers and diastereomers at the  $\beta$ -diketone moieties<sup>10</sup> (entry 1). In addition, acetophenone (**6a**) was also formed in 7% yield. These results indicate that the gold carbene generated is indeed highly reactive and very capable of inserting into unactivated C(sp<sup>3</sup>)–H bonds including those of

**Scheme 1. Oxidative Generation of  $\alpha$ -Oxo Gold Carbenes**



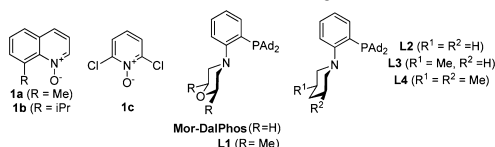
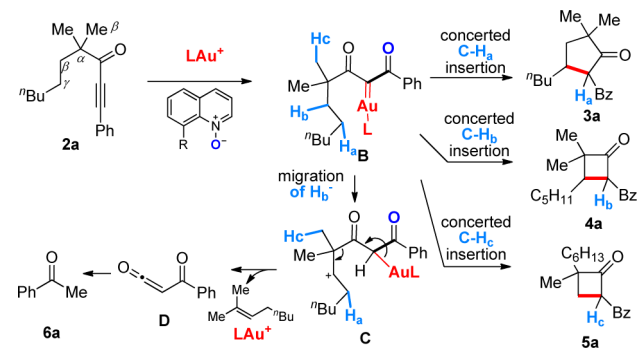
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**Table 1. Initial Reaction Discovery and Conditions Optimization<sup>a</sup>**

entry	catalyst (5 mol %)	N-oxide	yield <sup>b</sup>	
			3a/4a/5a <sup>c</sup>	6a
1	Ph <sub>3</sub> PAuNTf <sub>2</sub>	1a	30% (9.5/1/1.1)	7%
2	BrettPhosAuNTf <sub>2</sub>	1a	61% (1.1/1/1)	20%
3	IPrAuNTf <sub>2</sub>	1a	63% (7.9/1/0)	11%
4	IMesAuCl/AgNTf <sub>2</sub>	1a	57% (15.7/1/0)	7%
5	MorDalPhosAuNTf <sub>2</sub>	1a	70% (6.7/1/0)	12%
6	L1AuCl/AgNTf <sub>2</sub>	1a	59% (7.7/1/0)	7%
7	L2AuCl/AgNTf <sub>2</sub>	1a	65% (10.0/1/0)	10%
8	L3AuCl/AgNTf <sub>2</sub>	1a	68% (11.0/1/0)	8%
9	L4AuCl/AgNTf <sub>2</sub>	1a	72% (13.2/1/0)	7%
10	L4AuCl/AgOTf	1a	67% (12.8/1/0)	12%
11	L4AuCl/AgSbF <sub>6</sub>	1a	67% (12.2/1/0)	10%
12 <sup>d</sup>	L4AuCl/NaBAF <sub>4</sub> (10 mol %)	1a	71% (9.5/1/0)	5%
13	L4AuCl/AgNTf <sub>2</sub>	1b	84% <sup>e</sup> (13.7/1/0)	8%
14 <sup>f</sup>	L4AuCl/AgNTf <sub>2</sub>	1c	75% (13.0/1/0)	6%
15	IMesAuCl/AgNTf <sub>2</sub>	1b	74% (13.8/1/0)	10%

<sup>a</sup>[2a] = 0.05 M. <sup>b</sup>Estimated by <sup>1</sup>H NMR using diethyl phthalate as the internal reference. <sup>c</sup>As mixtures of tautomers and diastereomers. <sup>d</sup>12 h; isolated yield. <sup>e</sup>77% isolated yield. <sup>f</sup>Overnight.

**Scheme 2. A Proposed Mechanism for the Reaction of 2a**

methyl groups. With the bulky and electron-rich BrettPhos as ligand, the combined yield of the C–H insertion products was much improved, despite a low regioselectivity (entry 2). When the N-heterocyclic carbene IPr was used as ligand, the reaction yield was moderate but with serviceable regioselectivity (entry 3). Notable in this case is that there was no insertion into the methyl C–H bond, indicating the gold carbene intermediate is less reactive than those generated in entries 1 and 2, consistent with the fact that IPr is a stronger  $\sigma$ -donor than phosphines. This was also the case with IMes, another frequently used NHC, despite an even better selectivity of the cyclopentanone 3a over

the cyclobutanone 4a (15.7:1) was realized (entry 4). We have previously reported that P,N-bidentate ligands can attenuate the reactivity of  $\alpha$ -oxo gold carbenes via the formation of tris-coordinated gold centers.<sup>4b–c</sup> Indeed, when Mor-DalPhos<sup>11</sup> was used, the insertion into methyl C–H bonds likewise did not occur, and the reaction yield was improved while the ratio of 3a over 4a was moderate (entry 5). Other P,N-bidentate ligands, i.e., L1–L4, were also examined. In all the cases, no cyclobutanone 5a was detected (entries 6–9). A good regioselectivity of 13.2/1 was achieved with L4<sup>4d</sup> as ligand (entry 9), along with an acceptable 72% yield. Replacing NTf<sub>2</sub><sup>–</sup> with other counteranions led to lower selectivities and/or decreased reaction yields (entries 10–12). The oxidant was then varied. 8-Isopropylquinoline N-oxide (1b),<sup>4f</sup> a more hindered oxidant, led to an improved 84% yield (entry 13), while others including 2,6-dichloropyridine N-oxide (entry 14) were not as effective. Finally, replacing L4 with IMes led to a similar ratio but a lower yield (comparing entry 15 with entry 13). In all these cases, acetophenone was detected as a side product.

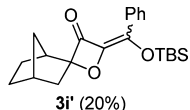
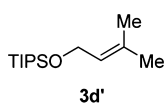
A plausible mechanism is proposed in Scheme 2. Based on the ease of insertion into unactivated C(sp<sup>3</sup>)–H bonds including those of methyl, it is likely that the  $\beta$ -diketone- $\alpha$ -gold carbene B is generated as the key reactive intermediate upon gold-promoted regioselective oxidation of the ynone 2a and, moreover, the C–H insertions are concerted. On the other hand, a competitive hydride abstraction<sup>12</sup> of the  $\beta$ -methylene group would lead to the formation of the carbocation intermediate C, which would then undergo C–C bond fragmentation to deliver the acylketene D. This intermediate could then undergo hydrative decarboxylation to yield 6a during the reaction and/or upon workup. In addition, the formation of the other side product, i.e., 2-methyl-2-octene, in the process is supported by GC-MS analysis of one of the reaction mixtures.<sup>10</sup>

Mindful of the beneficial Thorpe–Ingold effect in facilitating the C–H insertion, we first probed the reaction scope using ynones possessing fully substituted  $\alpha$ -carbons under the optimal conditions outlined in Table 1, entry 13. As shown in Table 2, the phenyl group of 2a can be replaced with an *n*-butyl in the case of the ynone substrate 2b, and the gold catalysis was highly efficient and regioselective (entry 1). Insertion into a sterically more hindered C–H bond, as in the case of 2c, was more efficient and selective with IMesAuCl/AgNTf<sub>2</sub> (5 mol %) as catalyst (entry 2); moreover, in this case no product derived from insertion into the more labile methine C–H bond was detected, indicating a strong preference of forming five-membered rings. The expected insertion into an etheral and hence activated C–H bond in the case of 2d, however, did not occur. With IPrAuNTf<sub>2</sub> as catalyst, the cyclic acetal 3d was isolated in 60% yield along with 12% of 3d' (entry 3). The former product must be formed via an initial hydride abstraction<sup>12</sup> at the CH<sub>2</sub>  $\alpha$  to the etheral oxygen followed by nucleophilic attack by the gold enolate oxygen, and the latter via the same process as 2-methyl-2-octene in Scheme 2. It is important to point out that the absence of any product of type 3d in the prior cases as well as in the ensuing cases suggests that insertions into nonactivated C–H bonds by  $\beta$ -diketone- $\alpha$ -gold carbenes might not involve similar hydride abstractions and hence likely be concerted. Entries 4–6 show the reactions of ynone substrates possessing a cyclohexane ring at the  $\gamma$ -,  $\beta$ -,  $\alpha$ -carbon and the formed cyclopentanone products featured spiro-, fused, and bridged bicyclic skeletons, respectively, in good to excellent yields. Of note is that 3f was formed predominantly as the 5,6-*trans*-fused isomer and the high efficiency of forming 3g, despite the strained nature of the bicyclo[3.2.1]octane ring. The

Table 2. Scope with Ynones Featuring Fully Substituted  $\alpha$ -Carbons<sup>a</sup>

entry	substrate <b>2</b>	product <b>3</b>	yield <sup>b</sup>
1			94% (>25/1) <sup>c</sup>
2 <sup>d,e</sup>			78% (15/1) <sup>c</sup>
3 <sup>f</sup>			60%
4			96% (18.2/1) <sup>c</sup>
5			72% (trans/cis :>20/1)
6			85%
7			75%
8 <sup>f</sup>			76%

<sup>a</sup>Reaction conditions: **2** (0.05 M in PhF), L4AuCl/AgNTf<sub>2</sub> (5 mol %), **1b** (2 equiv), rt, 2 h. <sup>b</sup>Isolated yield. <sup>c</sup>Ratio of 3/4. <sup>d</sup>IMesAuCl/AgNTf<sub>2</sub> (5 mol %) as catalyst. <sup>e</sup>58% yield and 3/4 = 2/1 with L4AuCl/AgNTf<sub>2</sub> as catalyst. <sup>f</sup>IPrAuNTf<sub>2</sub> (5 mol %) as catalyst.



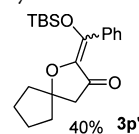
TIPS-protected hydroxylalkynone **2h**, readily accessible from cyclohexanone in three steps by using Katritzky's alkynylacyl anion equivalent,<sup>13</sup> also underwent the oxidative gold catalysis in good efficiency (entry 7). By following the same 4-step sequence with the exception of the gold catalyst, the TBSO-substituted hexahydro-1,4-methanopentalen-2(1H)-one **3i** was prepared from norcamphor in a good yield (entry 8). Also isolated in the reaction was the side product **3i'**, the formation of which can be ascribed to silyloxy oxygen trapping of the carbene center followed by silyl migration. This finding suggests the importance of properly masking a competing nucleophilic site in order to facilitate the desired C–H insertion process.

To further explore the synthetic utility of this C–H insertion chemistry, we turned our attention to substrates offering access to fused bicyclic cyclopentanones, as in the case of **2f** (cf. Table 2, entry 5). For the cases examined in Table 3, IPrAuNTf<sub>2</sub> turned out to be the optimal catalyst, and in some cases (entries 3–5) the oxidant loadings were lowered to 1.5 equiv. In the absence of

Table 3. Constructions of Fused Bicyclic Cyclopentanones<sup>a</sup>

entry	substrate <b>2</b>	cyclopentanone <b>3</b>	yield <sup>b</sup>
1 <sup>c</sup>			40% (trans/cis: >8/1)
2			48%
3 <sup>d</sup>			83% (cis/trans: 3.5/1)
4 <sup>d</sup>			75% (cis only)
5 <sup>d</sup>			75% (cis only)
6			67% (cis only)
7			67% (cis only)
8			40%

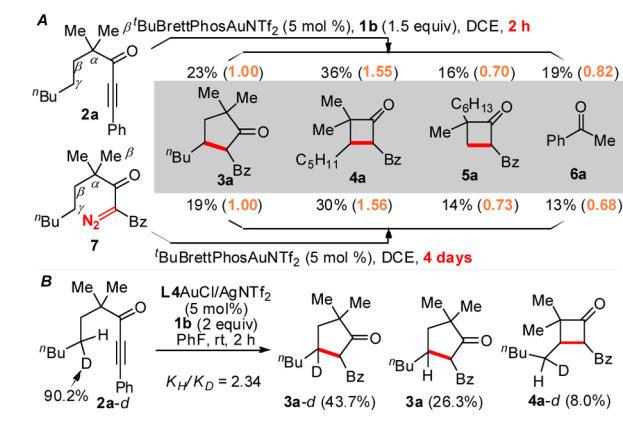
<sup>a</sup>Reaction conditions: **2** (0.05 M in PhF), IPrAuNTf<sub>2</sub> (5 mol %), **1b** (2 equiv), rt, 2 h. <sup>b</sup>Isolated yield. <sup>c</sup>DCE as solvent. <sup>d</sup>1.5 equiv of **1b**.



the Thorpe–Ingold effect, the cyclohexyl-containing alkynone **2j** still underwent the desired reaction, affording mainly the *trans*-fused product **3j** albeit in 40% yield (entry 1). The use of a C–C double bond to limit conformational flexibility in the case of **2k** did improve the reaction to some extent (entry 2).<sup>5j</sup> Much to our delight, the Thorpe–Ingold effect again significantly facilitates the reaction, and as shown in entries 3–4, the bicyclic cyclopentanones **3l** and **3m** were both formed in good yields. Different from the cases of **3f** and **3j**, they are mainly or exclusively *cis*-fused, likely the result of the gold carbene moiety mostly or completely residing at the cyclohexane ring axial position. The symmetric nature of the 1,3-diketone-2-gold carbene generated in these oxidative gold catalysis suggests that **3m** should be accessible from the isomeric phenyl alkynyl ketone **2m'**. Indeed, the reaction of **2m'** proceeded with an identical yield and the same exclusive *cis*-selectivity (entry 5). This catalysis was also conducive to the construction of 5,5-fused cyclopentanones, which are exclusive *cis*-fused (entries 6–8). Again, the phenyl alkynyl ketones **2o** and **2p** were suitable substrates. The low yield of the latter (entry 8) again reflected the



## Scheme 3. Mechanistic Studies



importance of sterically shielding of the HO group as the side product **3p'**, owing to the competing oxygen attack, was formed in an equal amount.

To gain additional insights into the reaction mechanism, we examined the gold-catalyzed reactions of the  $\alpha$ -diazo  $\beta$ -diketone **7** (Scheme 3A). While too slow with either  $\text{IPrAuNTf}_2$  or  $\text{L4AuNTf}_2$ , the reaction in the presence of  ${}^t\text{BuBrettPhosAuNTf}_2$  (5 mol %) proceeded to completion in 4 days. In comparison, the corresponding oxidative gold catalysis using the same catalyst took only 2 h and, moreover, afforded higher yields, highlighting the additional advantages of our oxidative gold catalysis over the diazo approach. Importantly, the nearly identical ratios of **3a/4a/5a** corroborate the likely formation of a common reactive intermediate (i.e., **B**) in both cases. The C–H insertion step was probed by deuterium kinetic isotope effect (KIE). As shown in Scheme 3B, in the internal competition a KIE of 2.34 was observed.<sup>14</sup> This value indicates that the C–H bond is significantly elongated in the insertion transition state. In contrast, inverse KIEs were observed with donor-substituted gold carbenes.<sup>8c</sup>

In summary, we have discovered for the first time that oxidatively generated gold carbenes in the form of  $\beta$ -diketone- $\alpha$ -gold carbenes can easily insert intramolecular into unactivated  $\text{C}(\text{sp}^3)\text{--H}$  bonds in likely concerted manners. Substrate conformation control via the Thorpe–Ingold effect is the key design feature that enables the generally good to excellent efficiencies in the examined cases. This novel reactivity offers efficient access to synthetically versatile cyclopentanones including spiro-, bridged, and fused bicyclic ones from readily available ynone substrates. This study represents a remarkable advance in replacing toxic and potentially explosive diazo ketones with benign and easily available alkynes in achieving one of the hallmark and most valuable transformations of metal carbenes/carbenoids, i.e., insertions into unactivated  $\text{C}(\text{sp}^3)\text{--H}$  bonds.

## ■ ASSOCIATED CONTENT

### Supporting Information

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

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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