Published in final edited form as:

Angew Chem Int Ed Engl. 2020 September 28; 59(40): 17398–17402. doi:10.1002/anie.202003698.

Non-Diazo C-H Insertion Approach to Cyclobutanones via Oxidative Gold Catalysis

Zhitong Zheng^{a,†}, Youliang Wang^{a,†,‡}, Xu Ma^a, Yuxue Li^b, Liming Zhang^{*,a}

^aDepartment of Chemistry and Biochemistry, University of California Santa Barbara, CA 93106, USA

^bCAS Key Laboratory of Energy Regulation Materials, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China

Abstract

Cyclobutanones are synthetically versatile compounds that often requires extensive effort to access. Herein, we report a facile synthesis of cyclobutanones based on the C(sp³)-H insertion chemistry of oxidatively generated gold carbenes. A range of cyclobutanones was obtained in synthetically useful yields from substrates with minimal structural prefunctionalization. This discovery reveals new synthetic utilities of gold-catalyzed oxidative transformations of alkynones.

Graphical Abstract

Insertion into unactivated C(sp³)-H bonds by metal carbenes/carbenoids is a reaction of significant synthetic value. In this study, easily accessible alkynone substrates are converted to strained cyclobutanones via such an insertion by an oxidatively generated β -diketone- α -gold carbene. This reaction serves as a benign and more synthetically expedient alternative to diazo-based approaches.

* zhang@chem.ucsb.edu, Homepage: <http://www.chem.ucsb.edu/~zhang/index.html>.

†Current address: College of Science, Xi'an Jiaotong University, Xi'an 710049, P. R. China

‡These authors contributed equally.

Keywords

gold carbene; catalysis; cyclobutanone; oxidation; C-H insertion

We have previously reported facile access to 2-acylcyclopentanones^[1] via gold-catalyzed oxidative transformations of alkynones.^[2] Our preliminary mechanistic studies are consistent with the generation of a β -diketone- α -gold carbene (i.e., **A**, Scheme 1) as the reactive intermediate and its subsequent insertion into an unactivated C-H bond as the key ring formation step. This approach permits the use of C-C triple bonds instead of diazo compounds as precursors to gold carbenes in the context of synthetically highly valuable C-H insertions.^[3] During the catalyst optimization, we observed, as shown in Scheme 1, cyclobutanones **3a** and **3a'** were formed in combined yields that are substantially more than those of the intended cyclopentanone **4** when BrettPhos or ^tBuBrettPhos was used as the gold catalyst ligand. Moreover, the ratio of **3a** and **3a'**, the products of insertion into the C-H bonds of the methyl groups and the β -CH₂, respectively, and the combined yield increase as the ligand becomes bulkier. The apparent ease of forming the highly strained four-membered ring in this reaction and its tunability suggested that the gold carbene intermediate generated can be highly reactive yet could be coerced via ligand tuning and other condition optimization into achieving efficient constructions of cyclobutanones.

Of note is that cyclobutanones along with cyclobutanes are synthetically highly useful structures due to their high ring strain.^[4] Moreover, they are found in bioactive natural products, as represented in Figure 1.^[5] While cyclobutanones can be formed via Rh/Cu-catalyzed C-H insertive cyclization of diazo ketones, they are mostly side products along with the desired cyclopentanones.^[6] Consequently, the reaction yields are at best moderate, and the corresponding diazo substrates often demand tedious and hazardous preparation. Hence, there is a need for more efficient access to these strained cyclic ketones based on a safer and more efficient carbene C-H insertion strategy.

At the outset, instead of **1a**, the tert-butyl alkynyl ketone **1b** was used as the substrate for reaction optimization as the removal of regioselectivity issues significantly simplified the task at hand. With Ph₃PAuNTf₂, MorDalPhosAuNTf₂ or IPrAuNTf₂ as the gold catalyst, the desired cyclobutanone **3b** was nearly undetectable (entries 1–3). However, the gold catalysts derived from the Buchwald ligands were proven uniquely effective (entries 4–7). Among them, both BrettPhosAuNTf₂ and the sterically more hindered ^tBuBrettPhosAuNTf₂ enabled the highly efficient formation of **3b**, with the former affording an impressive 84% yield (entry 6). Control experiments with AgNTf₂ (entry 8) or HNTf₂ (entry 9) as the catalyst led to little or no reaction, respectively, confirming the indispensable role of gold in this catalysis. Varying the *N*-oxide revealed that 8-isopropylquinoline *N*-oxide **2b** is the best

oxidant (entry 10), while the pyridine-based ones, i.e., **2c** (entry 11) and **2d** (entry 12), are moderately effective at an elevated temperature. Other counter anions (entries 13–15) and different reaction solvents (entries 16–18) had mostly little impact on the reaction efficiency.

With the optimal conditions (Table 1, entry 10) secured, we then varied the phenyl group of **1b**. As shown in Table 2, an *n*-butyl group was tolerated (entry 1), but the substrate with a cyclohexyl group underwent mostly the Wolff rearrangement,^[7] which upon subsequent hydrolytic decarboxylation led to the formation of the ketone **5** in 79% yield (entry 2). A cyclopropyl group, however, had little such side reaction (entry 3). When alkenyl groups were in the place of the phenyl group, the Wolff reaction interestingly occurred with a cyclohexen-1-yl (entry 4) but not with a propen-2-yl (entry 5). In addition, both the electron-donating 4-methoxy group (entry 6) and the electron-withdrawing 4-trifluoromethyl group (entry 7) were allowed on the phenyl ring, and the reaction yields were only slightly affected.

Next, we examined how the *t*-butyl group of **1b** could be varied. As shown in Table 3, entry 1, the ynone **1j** possesses the ethyl counterpart of *t*-butyl, i.e., 3-ethylpent-3-yl. Its reaction, optimally performed using ^tBuBrettPhosAuNTf₂ as the catalyst, was slow but delivered the cyclobutanone product **3j** in 89% yield. The cyclopentanone product **7**, the result of insertion into the methyl groups was barely detected. The good regioselectivity is anticipated in light of the results in Scheme 1, where **3a'** and **4** were formed in nearly equal amounts, and the well-precedented preference of carbene insertion into methylene C-H over methyl C-H. With the *t*-pentyl ketone **1k** as the substrate, AdBrettPhosAuNTf₂ was the optimal catalyst for a slightly improved yield (entry 2). The cyclobutanones **3k/3k'** were formed in a good combined yield, and **3k** is favored over **3k'** by a ratio of 4.5:1, which is slightly better than that of **3a'/3a** (1:1 and 1.75:1, Scheme 1) and readily understandable by the fact that ethyl is smaller than *n*-hexyl. Again, the cyclopentanone product **8** was barely formed. We then turned our attention to tertiary cycloalkyl ketone substrates. In the case of **1l**, two cyclobutanones **3l** and **3l'** were formed in a combined 79% yield and with a ratio of **3l/3l'** = 7:1. It is remarkable that the inductive deactivation of the ring C-H bonds β to the carbonyl group is largely inconsequential, despite literature precedents,^[8] while the absence of insertion into the more deactivated C-H bond α to the ring carbonyl group^[11] to afford a bicyclo[3.2.1]octadione could be readily understood. With the substrate **1m** possessing two 1,4-*cis*-substituted methyl groups on the cyclohexane ring, IMesAuNTf₂ turned out to be a better catalyst, and the bicyclo[4.2.0]octanedione **3m** was isolated in 62% yield. On the contrary, in the case of diastereomeric ketone substrate **1n** with *trans*-methyl groups, however, the reaction yields the cyclopentanone product **3n** as the major product. Such reactivity divergence must be due to conformational bias. In the case of **1n**, the β-diketone-α-gold carbene generated resides predominantly at the axial position in order to avoid positioning both methyl groups at axial positions and is primed to insert into a *cis* and axial C-H bond en route to the bridged cyclopentanone **3n**. On the other hand, in the case of **1m**, the methyl groups conformationally cancel each other and hence the carbene moiety prefers the equatorial position, which could only lead to cyclobutanone formation. In our previous work, the ynone **1o** derived readily from cyclohexanone was transformed into a bicyclo[3.2.1]octanones selectively in the presence of LAuNTf₂, where L is a *P,N*-bidentate

ligand; in contrast, when IPrAuNTf_2 is the catalyst, the cyclobutanone **3o** was formed in 45% yield, thereby highlighting the critical role of the ligand in deciding the reaction outcome. This chemistry is also applicable to the construction of five-membered ring fused cyclobutanones, and bicyclic ketone **3p** was isolated in a respectable 69% yield (entry 8).

To probe the reaction mechanism, we subjected the phenyl alkynyl ketone **1b'**, which differs from **1b** by swapping the ynone moiety substituents, to the optimized reaction conditions. The reaction was very slow, which could be attributed to the steric hindrance caused by the bulky *t*-butyl group in the initial oxidant nucleophilic attack, but the reaction yield was comparable to that of **1b**, suggesting that a locally symmetric β -diketone- α -gold carbene moiety of type **A** is formed. We also prepared the corresponding α -diazo- β -diketone **9**. While its reaction in the presence of $\text{Rh}_2(\text{TFA})_4$ required a much longer time, the yield is nearly identical to that in the presence of BrettPhosAuNTf_2 and the oxidative gold catalysis of **1b**. A similar outcome was observed with α -diazo- β -diketone **10** related to the ynone **11**. Comparing with our oxidative gold catalysis of **11**, Rh-catalyzed transformation of **10** gave very similar regioselectivity and a lower yield at 60 °C and required a longer reaction time. The reaction at room temperature was, however, sluggish. These results strongly suggest that the gold carbene of type **A** is the reactive intermediate in this gold catalysis. In addition, these comparisons reveal that the oxidative gold catalysis, in general, undergoes substantially faster generation of the β -diketone- α -metal carbene intermediate than dediazotization by Rh complexes.

To have a better understanding on how the bulky ligands control the regioselectivity of the C-H bond insertion, we performed a DFT^[9–13] study of the case of the *tert*-pentyl ketone **1k** (Table 3, entry 2) by using M06^[10] and SMD^[12] methods (DCE as solvent). The SDD basis set with an Effective Core Potential (ECP)¹³ was used for the Au atom, the 6–311+G** basis set for the P atom, and the 6–31+G** basis set for the other atoms. As shown in Figure 2, the C-H insertion starts from the β -diketone- α -gold carbene intermediate **A-3k**. The calculated transition state, i.e., **TS-Ins-3k**, for the formation of the cyclobutanone **3k** is 6.9 kcal/mol higher in free energy. This number is 1.1 kcal/mol more favorable than **TS-Ins-8**, which is 8.0 kcal/mol higher in free energy than **A-3k** and leads to the formation of the cyclopentanone **8**. This result is in line with the experiment observation, in which **8** is barely formed.

In **A-3k**, there are steric repulsions between the carbene fragment and the large AdBrettPhos ligand, which are at least in part responsible for the compressed angle of P-Au-C1. This angle is measured at 150.66° and substantially bended and deviated from typical ~180°. In the transition states, the Au carbene bond (i.e., Au=C1) length increases from 2.015 Å in **A-3k** to 2.076 Å in **TS-Ins-3k** and 2.073 Å in **TS-Ins-8**, which are concurrent to the relaxation of the $\angle\text{P-Au-C1}$ bending but to different extents. The angle in **TS-Ins-3k** expands to 156.66°, but to a notably smaller 152.41° in **TS-Ins-8**. This difference reflects that the C-H insertion to form the cyclobutanone **3k** is less sterically demanding than that leading to the cyclopentanone **8** and hence experiences less steric repulsion from the bulky ligand 2,4,6-triisopropylphenyl group. It is also in line with the difference in the distance between C6, i.e., the *para*-carbon on the ligand pendant benzene ring, and the carbene

carbon. In **TS-Ins-3k**, the distance is 4.339 Å, while in **TS-Ins-8**, it is 4.686 Å. The more bended $\angle$ P-Au-C1 in **TS-Ins-8** is consistent with its being higher in energy, which in turn support the role of ligand bulk in enabling regioselective C-H insertions, leading to preferential formation of cyclobutanone products via a sterically less demanding transition state.

In summary, we have exploited the C(sp^3)-H insertion chemistry of oxidatively-generated gold carbenes for the generation of strained cyclobutanones. The method avoids the use of diazo precursors and can be highly efficient and applied to the synthesis of fused bicyclic cyclobutanes. Comparative studies with rhodium-catalyzed decomposition of α -diazo- β -diketones strongly suggested the key role of β -diketone- α -gold carbene in this transformation and reveal that this oxidative gold catalysis is, in general, more facile. DFT studies lend further support to the carbene pathway and shed lights on how bulky ligands are essential to achieve regioselective C-H insertions. By forming these highly strained cycles, this chemistry confirms the exceptional reactivity of these carbene species and offers facile access to synthetically valuable cyclobutanones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The experimental work by Z. Z., Y. W. And L.Z. was supported by NIGMS R01GM123342 and NIH shared instrument grant S10OD012077 for the purchase of a 400 MHz NMR spectrometer. The DFT studies by Y.-X. L. is supported by the Natural Science Foundation of China (Grant No. 21672247).

References:

- [1]. Wang Y, Zheng Z, Zhang L, J. Am. Chem. Soc 2015, 137, 5316–5319. [PubMed: 25835372]
- [2]. (a)Zhang L, Acc. Chem. Res 2014, 47, 877–888; [PubMed: 24428596] (b)Zheng Z, Wang Z, Wang Y, Zhang L, Chem. Soc. Rev 2016, 45, 4448–4458; [PubMed: 26781300] (c)Zhang L, in Contemporary Carbene Chemistry (Eds.: Moss RA, Doyle MP), John Wiley & Sons, 2013; (d)Xiao J, Li X, Angew. Chem., Int. Ed 2011, 50, 7226–7236.
- [3]. (a)Doyle MP, McKervy MA, Ye T, Modern catalytic methods for organic synthesis with diazo compounds: from cyclopropanes to ylides, Wiley, New York, 1998;(b)Dörwald FZ, Metal carbenes in organic synthesis, Wiley-VCH, Weinheim; New York, 1999;(c)Davies HML, Dai X, in Comprehensive Organometallic Chemistry III (Eds.: Mingos DMP, Crabtree RH), Elsevier, Oxford, 2007, pp. 167–212;(d)Taber DF, in Carbon-Carbon σ -Bond Formation, Vol. 3 (Ed.: Pattenden G), Pergamon Press, Oxford, England; New York, 1991, pp. 1045–1062.
- [4]. (a)Seiser T, Saget T, Tran DN, Cramer N, Angew. Chem. Int. Ed 2011, 50, 7740–7752;(b)Mack DJ, Njardarson JT, ACS Catal 2013, 3, 272–286;(c)Matsuo J.-i., Tetrahedron Lett 2014, 55, 2589–2595.
- [5]. (a)Marrero J, Rodríguez AD, Baran P, Raptis RG, Sánchez JA, Ortega-Barria E, Capson TL, Org. Lett 2004, 6, 1661–1664; [PubMed: 15128261] (b)Tanaka N, Okasaka M, Ishimaru Y, Takaishi Y, Sato M, Okamoto M, Oshikawa T, Ahmed SU, Consentino LM, Lee K-H, Org. Lett 2005, 7, 2997–2999. [PubMed: 15987189]
- [6]. (a)Wenkert E, Davis LL, Mylari BL, Solomon MF, Da Silva RR, Shulman S, Warnet RJ, Ceccherelli P, Curini M, Pellicciari R, J. Org. Chem 1982, 47, 3242–3247;(b)Cane DE, Thomas PJ, J. Am. Chem. Soc 1984, 106, 5295–5303;(c)Hashimoto S.-i., Shinoda T, Shimada Y, Honda T, Ikegami S, Tetrahedron Lett 1987, 28, 637–640;(d)Sonawane HR, Bellur NS, Ahuja JR, Kulkarni DG, J. Org. Chem 1991, 56, 1434–1439;(e)Ceccherelli P, Curini M, Marcotullio MC,

- Rosati O, Tetrahedron 1991, 47, 7403–7408;(f)Padwa A, Kinder FR, J. Org. Chem 1993, 58, 21–28;(g)Mander LN, Wells AP, Tetrahedron Lett 1997, 38, 5709–5712;(h)Huang H-X, Jin S-J, Gong J, Zhang D, Song H, Qin Y, Chem. Eur. J 2015, 21, 13284–13290. [PubMed: 26239744]
- [7]. Zheng Y, Zhang J, Cheng X, Xu X, Zhang L, Angew. Chem., Int. Ed 2019, 58, 5241–5245.
- [8]. (a)Stork G, Kazuhiko N, Tetrahedron Lett 1988, 29, 2283–2286;(b)Chen J-H, Levine SR, Buegler JF, McMahon TC, Medeiros MR, Wood JL, Org. Lett 2012, 14, 4531–4533. [PubMed: 22913575]
- [9]. (a)Hohenberg P; Kohn W Phys. Rev 1964, 136, B864–B871.(b)Kohn W; Sham LJ Phys. Rev 1965, 140, A1133–A1138.
- [10]. (a)Zhao Y; Truhlar DG J. Phys. Chem. A 2006, 110, 13126. [PubMed: 17149824] (b)Zhao Y; Truhlar DG J. Chem. Phys 2006, 125, 194101; [PubMed: 17129083] (c)Zhao Y; Truhlar DG Theor. Chem. Acc 2008, 120, 215.
- [11]. Frisch MJ; Trucks GW; Schlegel HB; Scuseria GE; Robb MA; Cheeseman JR; Scalmani G; Barone V; Mennucci B; Petersson GA; Nakatsuji H; Caricato M; Li X; Hratchian HP; Izmaylov AF; Bloino J; Zheng G; Sonnenberg JL; Hada M; Ehara M; Toyota K; Fukuda R; Hasegawa J; Ishida M; Nakajima T; Honda Y; Kitao O; Nakai H; Vreven T; Montgomery JA Jr.; Peralta JE; Ogliaro F; Bearpark M; Heyd JJ; Brothers E; Kudin KN; Staroverov VN; Kobayashi R; Normand J; Raghavachari K; Rendell A; Burant JC; Iyengar SS; Tomasi J; Cossi M; Rega N; Millam NJ; Klene M; Knox JE; Cross JB; Bakken V; Adamo C; Jaramillo J; Gomperts R; Stratmann RE; Yazyev O; Austin AJ; Cammi R; Pomelli C; Ochterski JW; Martin RL; Morokuma K; Zakrzewski VG; Voth GA; Salvador P; Dannenberg JJ; Dapprich S; Daniels AD; Farkas Ö; Foresman JB; Ortiz JV; Cioslowski J; Fox DJ Gaussian 09, revision A. 02; Gaussian, Inc. Wallingford, CT 2009.
- [12]. Marenich AV; Cramer CJ; Truhlar DG J. Phys. Chem. B 2009, 113, 6378. [PubMed: 19366259]
- [13]. Fuentealba P; Preuss H; Stoll H; Von Szentpály L Chem. Phys. Lett 1982, 89, 418–422.

Figure 1.
Bioactive natural products featuring cyclobutanoid core structures.

Figure 2.

The calculated carbene intermediate **A-3k** and the C-H bond insertion transition states that leading to product **3k** and **8**, respectively. Selected bond lengths are in angstroms, and bond angles in degrees. Calculated on M06/SDD(Au)/6-311+G**(P)/6-31+G** level in DCE.

Scheme 1.

Our previous studies forming cyclobutanones as side products.

Scheme 2.
Mechanistic studies.

Table 1.

Initial reaction discovery and optimization.

entry	catalyst	N-oxide	conditions	yield ^[a]
1	Ph ₃ PAuNTf ₂	2a	DCE, rt, 2 h	2% ^[b]
2	MorDalPhosAuNTf ₂	2a	DCE, rt, 2 h	<1%
3	IPrAuNTf ₂	2a	DCE, rt, 2 h	< 1%
4	CyJohnPhosAuNTf ₂	2a	DCE, rt, 2 h	33%
5	XPhosAuNTf ₂	2a	DCE, rt, 2 h	65%
6	BrettPhosAuNTf ₂	2a	DCE, rt, 2 h	84%
7	^t BuBrettPhosAuNTf ₂	2a	DCE, rt, 2 h	81%
8	AgNTf ₂ (10 mol %)	2a	DCE, rt, 24 h	7% ^[c]
9	HNTf ₂ (10 mol %)	2a	DCE, rt, 24 h	0% ^[d]
10	BrettPhosAuNTf₂	2b	DCE, rt, 2 h	92%
11	BrettPhosAuNTf ₂	2c	DCE, 60°C, 7 h	64%
12	BrettPhosAuNTf ₂	2d	DCE, 60°C, 7 h	60%
13	BrettPhosAuCl/AgOTf	2b	DCE, rt, 2 h	92%
14	BrettPhosAuCl/AgPF ₆	2b	DCE, rt, 2 h	87%
15	BrettPhosAuCl/NaBARF	2b	DCE, rt, 4 h	87%
16	BrettPhosAuNTf ₂	2b	PhF, rt, 2 h	90%
17	BrettPhosAuNTf ₂	2b	PhcF ₃ , rt, 2 h	79%
18	BrettPhosAuNTf ₂	2b ^[e]	DCE, rt, 2 h	90% ^[f]

^[a] Determined by ¹H NMR using diethyl phthalate as internal reference.

^[b] 72% of **1b** remained.

^[c] 56% of **1b** remained.

^[d] Most **1b** remained.

^[e] 1.5 equiv.

^[f] 82% isolated yield.

Table 2.

Scope of different alkyne substituents.^[a]

^[a] Reactions were run under the optimal conditions from Table 1, entry 10. All yields are isolated ones except **3d**.

Table 3.

Reaction scope of different alkyl ketones.^[a]

Entry	Ynone	product(s)	catalyst/yield
1			^t BuBrettPhosAuNTf ₂ 24 h 89% 3j:7 > 16:1
2			AdBrettPhosAuNTf ₂ 2 h 86% 3k:3k':8 = 4.5:1:<0.1
3			AdBrettPhosAuNTf ₂ 2 h 80% 3l:3l' = 7:1
4			IMesAuNTf ₂ 7 h 62%
5			IMesAuNTf ₂ 7 h 42%
6			IPrAuNTf ₂ 5 h 45%
7			BrettPhosAuNTf ₂ 4h 69%

^[a]Reactions were run with the optimal conditions from Table 1. All yields are isolated yields.