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Cyclopropanation of Benzene Rings by Oxidatively Generated α -Oxo Gold Carbene: One-Pot Access to Tetrahydropyranone-Fused Cycloheptatrienes from Propargyl Benzyl Ethers

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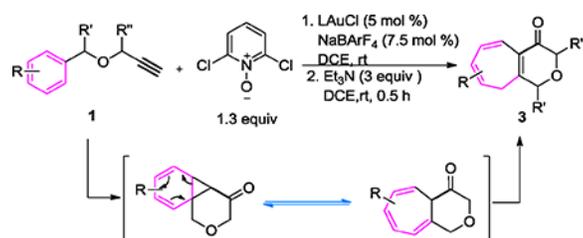
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Abstract

Cyclopropanations of benzene rings by oxidatively generated α -oxo gold carbenes are for the first time demonstrated in a Buchner reaction, in which readily available propargyl benzyl ethers are converted in one-pot to tetrahydropyranone-fused cycloheptatrienes *via* sequential oxidative gold catalysis and base-promoted isomerization. Additional examples of arene cyclopropanations without fragmentation of the cyclopropane ring are also realized.

Graphical Abstract



Keywords

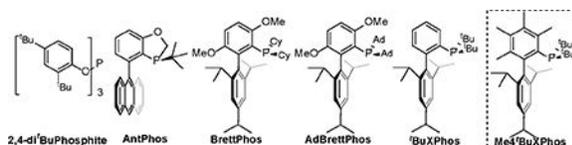
Cyclopropanation; Gold Carbene; Oxidation; Buchner reaction; Cycloheptatriene

Gold-catalyzed intermolecular oxidation of alkynes^[1] has become a valuable synthetic strategy since the original report in 2010,^[2] owing to the efficient and expedient access to α -oxo gold carbene intermediates and/or their precursors and their exceptional reactivities and synthetic versatility. A diverse range of functional structures of significant synthetic utilities have been developed.^[2–4] Comparing to the Rh/Cu carbene chemistry based on diazo carbonyl compounds,⁵ this chemistry employs benign and readily available alkynes substrates and hence circumvents the use of hazardous and potentially explosive α -diazo

ketone precursors (Scheme 1A). These α -oxo gold carbene intermediates typically display exceptional electrophilicities, and can be trapped by tethered or external nucleophiles, including cyclopropanation of tethered alkenes.^[3e, 3g, 4a, 4n, 6] However, cyclopropanation of the more challenging benzene ring,^[7] owing to the loss of aromaticity, has so far not been demonstrated in the oxidative gold catalysis, despite the reports of Rh/Cu catalysis based on hazardous diazo carbonyl substrates.^[5b, 8]

We surmised, as shown in Scheme 1B, that a readily available benzyl propargyl ether **1** could enable us to study cyclopropanations of arenes by α -oxo gold carbenes of type **A**. Our prior studies have revealed that the gold carbene generated from propargylic ethers^[9] can readily undergo cyclization. The norcaradiene intermediate **4** would then be formed and undergo known reversible electrocyclic ring opening to afford the tetrahydropyranone-fused cycloheptatriene **3'** in the form of a Buchner reaction,^[10] which could isomerize to the conjugated enone **3**, or undergo alternative ring opening under acidic conditions to afford the Friedel-Crafts products **5**. Notably, the related Rh-catalyzed Buchner reaction using the related diazo ketone counterpart of **1** (Scheme 1C) has only been reported once,^[11] where the tetrahydropyranone-fused cycloheptatriene product was formed in a low yield.

Herein, we report the implementation of our design, which results in rapid access to the bicyclic heptatrienes.

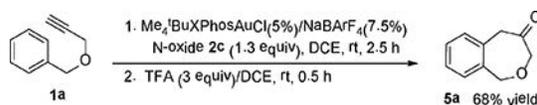


At the outset, we employed the parent propargyl benzyl ether, i.e., **1a**, for reaction discovery and condition optimization, some results of which are shown in Table 1. Initially, the sterically highly hindered Me₄tBuXPhos was employed as the ligand as it was previously proved to be highly effective in promoting cyclization of α -oxo gold carbenes to tethered benzene rings and C-C triple bonds.^[9] With NaBARF (7.5 mol %) as the chloride scavenger and 2-bromopyridine *N*-oxide (**2a**, 1.3 equiv) as the oxidant, the reaction was carried out in 1,2-dichloroethane (DCE) at room temperature for 2.5 h, and the resulting mixture was then treated with triethylamine (3 equiv) in order to isomerize **3'** into **3** (see Scheme 1B) and hence abolish the equilibrium between **4** and **3'**. To our delight, the desired bicyclic heptatriene **3a** was indeed formed in 7 % NMR yield (entry 1). Screening of various other pyridine/quinoline *N*-oxides (entries 2–6)^[12] revealed that sterically hindered oxidants derived from electron-deficient pyridine ring, i.e., 2,6-dichloropyridine *N*-oxide (**2c**, entry 3), 2,6-dibromopyridine *N*-oxide (**2d**, entry 4) and the Hantzsch ester *N*-oxide **2g** (entry 6)^[3c] are among the most effective, with the halogenated ones being the best and equally effective and affording the desired product **3a** in around 72% NMR yield. A range of other gold catalysts derived from typical ligands such as Ph₃P, IPr, JohnPhos (entry 7) and tBuXPhos (entry 8) were ineffective, affording trace amount (<5%) of **3a**. Sterically demanding BrettPhos (entry 9) and AdBrettPhos (entry 10) fared better, but are still substantially inferior to even more hindered Me₄tBuXPhos, attesting the importance of ligand bulkiness in this chemistry. AntPhosAuCl/NaBARF₄ was also tested but led to no

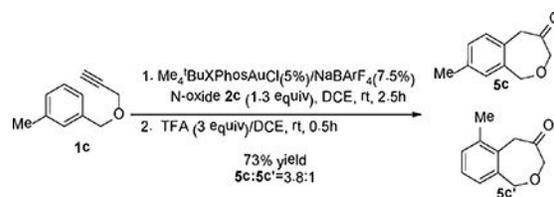
reaction (entry 11). Deviation from the best conditions in entry 3 by lowering the reaction temperature to 0 °C led to a lower yield (entry 12), and by changing the chloride scavenger from NaBARF₄ to AgNTf₂ resulted in predominant formation of the Friedel-Crafts product **5a** (entry 13). In this latter case, the slightly excess of acidic AgNTf₂ is likely enough to promote the alternatively cyclopropane ring opening during the gold catalysis (Scheme 1B, from **4** to **5**).

With the optimal conditions (Table 1, entry 3) in hand, the reaction scope was examined. As shown in Table 2, entries 1 and 3, benzylic ethers possessing an electron-donating 4-Me or 4-MeO group at the benzene ring reacted as expected, despite exhibiting moderate yields. A poor regioselectivity along with a low yield was detected in the case of a *meta*-methyl group (entry 2). On the other hand, electron-withdrawing arene substituents are detrimental to the gold catalysis and, for example, little desired product was formed with an *ortho*-Br and *para*-CN. This can be attributed to the decreased nucleophilicity of the benzene ring. Interestingly, aliphatic substitutions at the substrate benzyl position including methyl (entry 4), phenethyl (entry 5) and the sterically demanding isopropyl (entry 6) and cyclohexyl group (entry 7) are readily accommodated and moreover, the corresponding gold catalyses afforded the bicyclic cycloheptatrienes (i.e., **3e-h**) in good yields. An allyl and a benzyl group are also readily tolerated at the benzyl position (entries 8 and 9), and their π bonds do not noticeably interfere with the desired cyclopropanation, likely due to the formation of larger rings and hence slower cyclization kinetics. Moreover, double substitutions at the benzyl position with aliphatic, aromatic and/or allyl group were uneventful (entries 10–12). On the other hand, a methyl substitution at the propargylic position, as in entry 13, led to **3n** in only 40% yield.

As the norcaradiene intermediate **4** (Scheme 1B) can undergo alternative cyclopropane ring opening under acidic conditions, we treated the resulting mixture of **1a** upon the oxidative gold catalysis with trifluoroacetic acid (3 equiv) instead of Et₃N. As expected, the 1,5-dihydrobenzo[*c*]oxepin-4(3*H*)-one **5a**^[13] was formed in 68% isolated yield. On the other hand, treatment of **3a** with trifluoroacetic acid for much longer 10 h expectedly resulted in no formation of **5a**. Likewise, substrate **1c** with a *meta*-methyl substitution on the benzene ring also led to the oxepinones **5c/5c'** in 73% combined yield [Eqn (2)]. However, the inferred cyclopropanation regioselectivity, i.e., *para:ortho* = 3.8:1, is higher than that observed upon base treatment (1.7:1, Table 2, entry 2). Considering the difference in yields, it is likely that the base treatment decomposed some of the *para*-norcaradiene isomer.

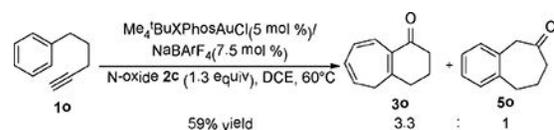


(1)



(2)

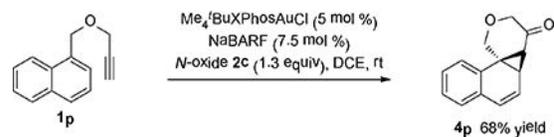
We attempted to extend the chemistry to the all-carbon counterpart of **1a**, i.e., **1o**. As shown in Eqn (3), the desired Buchner product **3o** and the Friedel-Crafts benzocycloheptanone **5o** were formed in a combined 59% isolated yields with a moderate regioselectivity.^[14] Notably, the reaction required heating (60 °C) and no acid or base treatment was needed.



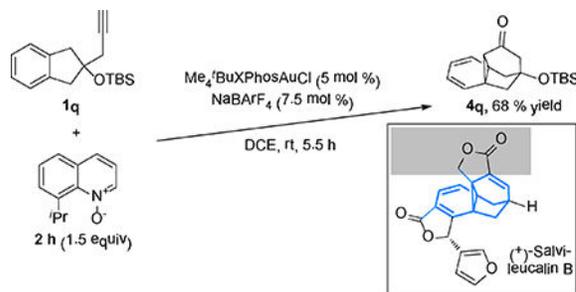
(3)

We are interested in systems where the electrocyclic ring opening of the norcaradiene **4** is retarded. As such, the cyclopropanation of a benzene ring by in situ-generated α -oxo gold carbenes can be confirmed beyond doubt. We examined the propargyl 1-naphthylmethyl ether **1p**. It is known in metal carbene chemistry^[15] that *vicinal*-benzene-fused norcaradienes (i.e., the benzene ring next to the cyclopropane ring) do not readily undergo electrocyclic ring-opening due to the necessity of loss of aromaticity in the process. Indeed, our gold catalysis cleanly affords the cyclopropane product **4p** [Eqn (4)]. With the substrate **1q** easily prepared from 2-indanone, the benzene cyclopropanation product **4q** was readily formed in a decent yield [Eqn (5)], the stability of which can be readily attributed to the avoidance of bridgehead double bonds in the ring open form. Interestingly, **4q** possesses the core structure of salvileucalin B,^[16] thus revealing the synthetic potential of the oxidative gold catalysis.

These experimental results point to^[17] a reaction mechanism consistent with that shown in Scheme 1B, where α -oxo gold carbenes readily cyclopropanate benzene rings.



(4)



(5)

In summary, we have realized cyclopropanations of benzene rings by oxidatively generated α -oxo gold carbene intermediates. From readily available propargyl benzyl ethers, this chemistry enables an expedient synthesis of various tetrahydropyranone-fused cycloheptatrienes upon basic treatment, while avoiding the use of hazardous diazo carbonyl substrates. Alternative acidic workup provides rapid access to 3, 5-dihydrobenzo[*c*]oxepin-4(*1H*)-ones. We have also demonstrated that some norcaradiene intermediates, e.g. **4p** and **4q**, can be isolated, thereby confirming the arene cyclopropanation in these oxidative gold catalysis.

Experimental Section

General procedure for one-pot gold-catalyzed oxidative propargyl benzyl ethers to tetrahydropyranone-fused cycloheptatrienes **3**:

2, 6-dichloropyridine N-oxide **2c** (42.4 mg, 0.26 mmol), and $\text{Me}_4^t\text{BuXPhosAuCl}$ (7.1 mg, 0.010 mmol, 5 mol %) and NaBARF_4 (13 mg, 0.015 mmol, 7.5 mol %) were added sequentially to a solution of the propargyl benzyl ethers **1** (0.20 mmol) in DCE (4 mL, 0.05M) at room temperature. The resulting reaction mixture was stirred at RT, and the progress of the reaction was monitored by TLC. The reaction typically took 1–3 h. Upon completion, the reaction mixture was added 3 equiv. Et_3N and stirred for 0.5 h at room temperature. The reaction mixture was concentrated under vacuum. The residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired products **3**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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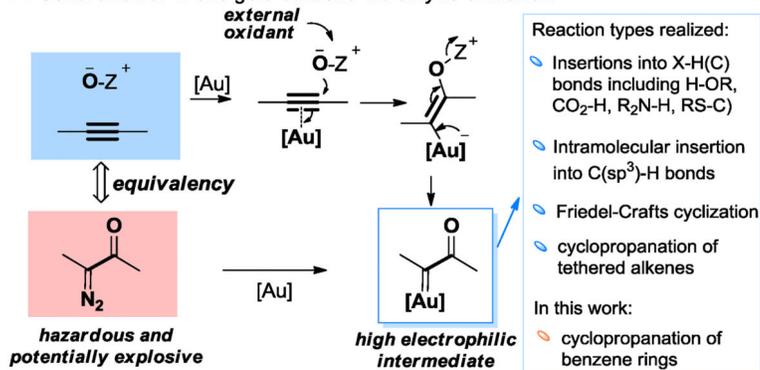
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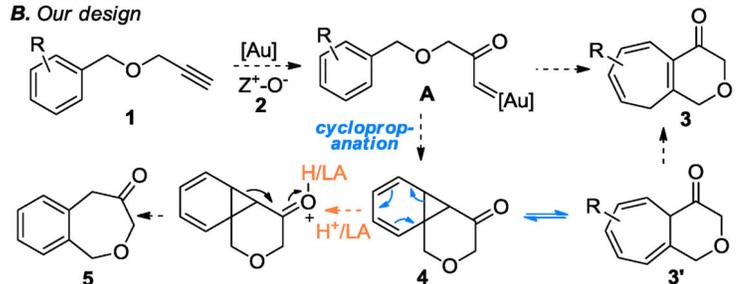
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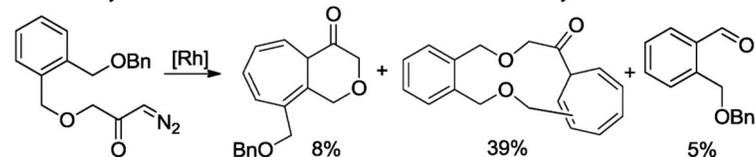
A. Generation of α -oxo gold carbene via alkyne oxidation



B. Our design

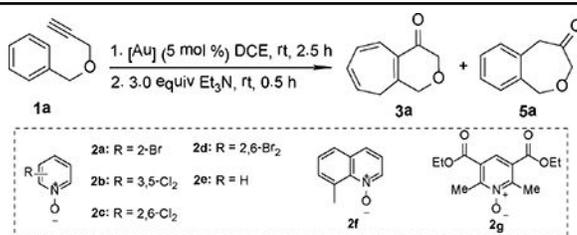


C. Rh-catalyzed intramolecular Buchner reaction with benzyl ether substrate



Scheme 1.
Background and Design.

Table 1.

Initial discovery of gold-catalyzed oxidation of benzyl aryl ether **1a** and screening of reaction conditions. ^[a]

Entry	N-oxide	Gold catalyst (5 mol %)	Additives (7.5mol %)	Yield ^[b]	
				3a	5a
1	2a	Me ₄ ^t BuXPhosAuCl	NaBAR ^F ₄	7%	<2%
2	2b	Me ₄ ^t BuXPhosAuCl	NaBAR ^F ₄	15%	<2%
3	2c	Me₄^tBuXPhosAuCl	NaBAR^F₄	72% ^[c]	<2%
4	2d	Me ₄ ^t BuXPhosAuCl	NaBAR ^F ₄	71%	<2%
5	2f	Me ₄ ^t BuXPhosAuCl	NaBAR ^F ₄	5%	<2%
6	2g	Me ₄ ^t BuXPhosAuCl	NaBAR ^F ₄	52%	<2%
7	2c	JohnPhosAuCl	NaBAR ^F ₄	3%	<2%
8	2c	^t BuXPhosAuCl	NaBAR ^F ₄	4%	<2%
9	2c	BrettPhosAuCl	NaBAR ^F ₄	32%	<2%
10	2c	AdBrettPhosAuCl	NaBAR ^F ₄	25%	<2%
11	2c	AntPhosAuCl	NaBAR ^F ₄	nr ^[d]	
12 ^[e]	2c	Me ₄ ^t BuXPhosAuCl	NaBAR ^F ₄	65%	<2%
13 ^[f]	2c	Me ₄ ^t BuXPhosAuCl	AgNTf ₂	<2%	49%

^[a] [1a] = 0.05M, and 1.3 equiv of the oxidant.

^[b] NMR yield using diethyl phthalate as the internal reference.

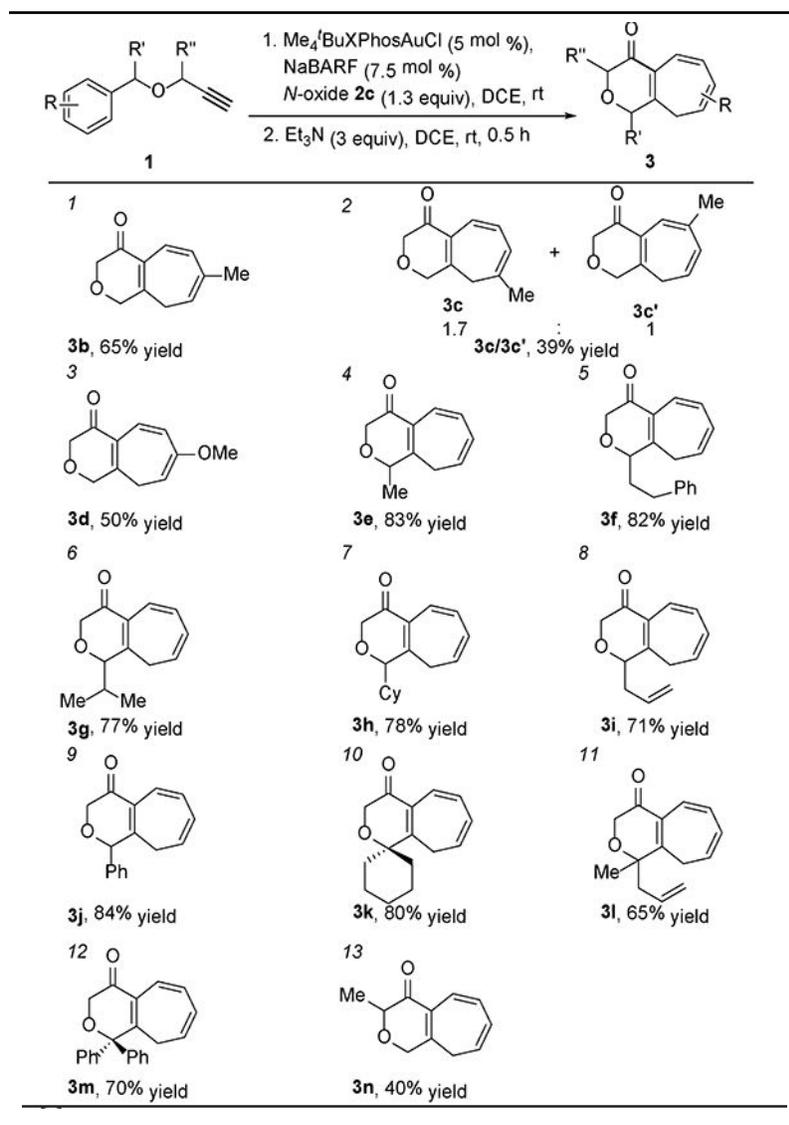
^[c] Isolated yield is 69%. DCE = 1,2-dichloroethane.

^[d] 95% of SM was recovered.

^[e] The reaction was carried out at 0°C for 6 h.

^[f] 49% of **4a** was isolated after 2.5 h.

Table 2.

Reaction scope.^[a, b]

^[a]The reactions were run in a vial without exclusion of air and moisture, and the substrate concentration was 0.05 M.

^[b]Yields of isolated products are reported.