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Alkynes as Equivalents of α-Diazo Ketones in Generating α-Oxo Metal Carbenes: A Gold-Catalyzed Expedient Synthesis of Dihydrofuran-3-ones

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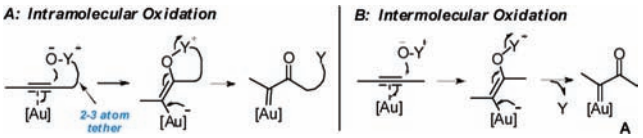
Late transition metal carbenes are versatile intermediates and can undergo a wide range of highly valuable and often difficult transformations, including C−H insertion/functionalization, cyclopropanation, and formation of reactive ylides.[1] It is not surprising that the generation of these species has been subjected to intensive studies. Of particular practical importance are methods that are highly reliable and do not require the assistance/participation of a tethered functional group.[2] The most useful method of this kind is metal-catalyzed decomposition of diazo compounds, especially relatively stable α-diazo carbonyl compounds, and a plethora of versatile synthetic transformations based on this method have been developed.[3] However, diazo compounds are (a) hazardous and potentially explosive and (b) mostly prepared from carbonyl precursors without much enhancement of molecular complexity, leading to diminished synthetic efficiency.

Recent rapid development in gold catalysis offers alternative approaches[4] for generating α-oxo metal carbenes (with gold as the metal) via intramolecular oxidation of alkynes. While several versatile synthetic methods based on this strategy have been developed, the required oxidants had to be tethered to the C≡C triple bond at optimal distances (Scheme 1A).[5] This requirement of intramolecularity imposes significant structural constraints on both substrates and products and severely limits the synthetic potential of this chemistry. To date, no success has been reported with external oxidants (Scheme 1B).[6] *Significantly, the intermolecular approach makes alkynes equivalent to hazardous α-diazo ketones and, moreover, offers much synthetic flexibility in comparison with the intramolecular approach*. Herein, we report the first example of accessing α-oxo gold carbenes via intermolecular oxidation of terminal alkynes under mild reaction conditions and its application in a simple but efficient preparation of dihydrofuran-3-ones. Notably, the existing synthetic methods for this useful class of O-heterocycles[7] typically require multiple steps and/or rather functionalized substrates.[8]

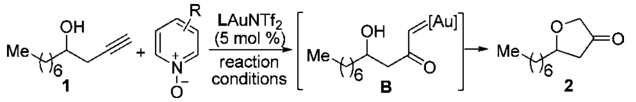
We began by using homopropargylic alcohol **1** as a substrate, anticipating that an intramolecular O−H insertion by the gold carbene moiety in **B** would be facile and productive (Table 1). After limited success using various sulfoxides as external oxidants, we turned to pyridine *N*-oxides, hoping to limit the known 3,3-rearrangement.[6] To our delight, dihydrofuran-3-one **2** was indeed formed using the parent pyridine *N*-oxide, albeit in only 9% yield (entry 1). We suspected that basic pyridine formed during the reaction might deactivate IPrAuNTf$_2$.[9] The addition of acids indeed substantially improved the reaction (entries 2−6), and the yields were 50−56% using strong acids (entries 3−6); moreover, the stronger the acid, the faster the reaction proceeded. Consequently, the reaction could be performed conveniently at room temperature (entries 4−6) with acceptable reaction times. We chose MsOH to further optimize the reaction conditions, hoping to balance the reaction time and the acidity of the reaction system. A range of substituted pyridine *N*-oxides were examined, some of which are shown in entries 7−10. 3,5-Dichloropyridine *N*-oxide and 2-bromopyridine *N*-oxide turned out to work equally well. The reaction conditions were further improved by lowering the amount of acid without sacrificing much of the yield (entry 11). Surprisingly, Ph$_3$PAuNTf$_2$ performed better than IPrAuNTf$_2$ (entries 13 and 14), which was advantageous because of its lower cost. Notably, PtCl$_2$ and AuCl$_3$ led to poor results (13 and 15%, respectively), and no reaction was observed in the absence of a metal catalyst.

Scheme 1. Access to α-Oxo Gold Carbenes: Intra- versus Intermolecular Oxidation



The reaction scope was then promptly studied. As shown in Table 2, this reaction proceeded well with various substrates, and the yields ranged from 55% (entry 12) to 88% (entry 18); moreover, many functional groups were tolerated. Several conclusions can be drawn from these studies: (a) This gold-catalyzed oxidation strategy is a reliable method for accessing α-oxo gold carbenes and may allow predictable synthetic designs; the exceptions were terminal alkynes that can undergo facile cyclization by tethered nucleophiles (e.g., 5-exo-dig cyclization in the case of bishomopropargylic alcohols, which led to low efficiency). (b) The reaction system was mildly acidic, and both Boc and MOM groups were tolerated (entries 5−6); although MsOH (pK_a = −2.6) is a strong acid, the excess pyridine *N*-oxide (pK_a =

Table 1. Optimization of Reaction Conditions[a]

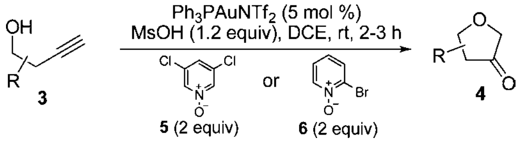


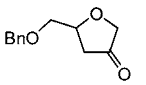
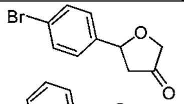
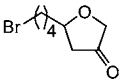
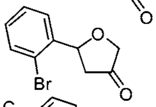
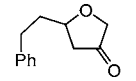
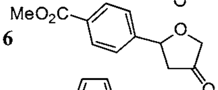
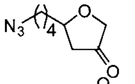
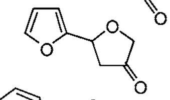
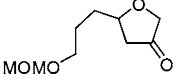
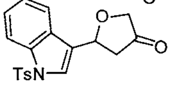
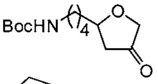
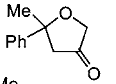
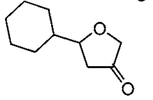
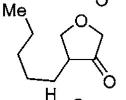
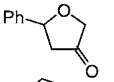
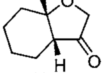
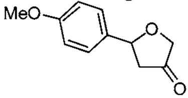
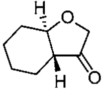
entry	L	R[b]	acid[b]	conditions	yield[c]
1	IPr	H	−	DCE, 60 °C, 10 h	9%[d]
2	IPr	H	Cl$_3$CCO$_2$H	DCE, 60 °C, 10 h	32%[e]
3	IPr	H	F$_3$CCO$_2$H	DCE, 60 °C, 5.5 h	56%
4	IPr	H	F$_3$CCO$_2$H	DCE, rt, 8 h	53%
5	IPr	H	MsOH	DCE, rt, 4.5 h	51%
6	IPr	H	TfOH	DCE, rt, 2 h	54%
7	IPr	3-Br	MsOH	DCE, rt, 2.5 h	64%
8	IPr	3,5-Cl$_2$	MsOH	DCE, rt, 2.5 h	68%
9	IPr	2-Br	MsOH	DCE, rt, 3.5 h	68%
10	IPr	4-Ac	MsOH	DCE, rt, 8 h	52%
11	IPr	2-Br	MsOH[f]	DCE, rt, 3.5 h	65%
12	Et$_3$P	2-Br	MsOH[f]	DCE, rt, 3.5 h	64%
13	**Ph$_3$P**	**2-Br**	**MsOH**[f]	**DCE, rt, 2.5 h**	**78%**[g]
14	**Ph$_3$P**	**3,5-Cl$_2$**	**MsOH**[f]	**DCE, rt, 2.5 h**	**75%**

[a] [**1**] = 0.05 M; DCE = 1,2-dichloroethane. [b] Unless otherwise specified, 2 equiv was used. [c] Estimated by ^{1}H NMR analysis using diethyl phthalate as an internal reference. [d] 75% conversion. [e] 68% conversion. [f] 1.2 equiv. [g] 76% isolated yield.

10.1021/ja100041e

Table 2. Reaction Scope[a]



entry	*N*-oxide	product	4/yield[b]	entry	*N*-oxide	product	4/yield[b]
1	**5**		**4a** 68%	10	**6**		**4j** 66%
2	**5**		**4b** 80%	11	**6**		**4k** 65%
3	**5**		**4c** 68%	12	**6**		**4l** 55%
4	**5**		**4d** 82%	13	**6**		**4m** 76%
5	**5**		**4e** 62%	14	**6**		**4n** 68%
6	**5**		**4f** 64%	15[c]	**5**		**4o** 58%
7	**5**		**4g** 72%	16	**5**		**4p** 65%
8	**6**		**4h** 63%	17[d]	**5**		**4q** 82%
9	**6**		**4i** 75%	18[e]	**5**		**4r**[f] 88%

[a] [**3**] = 0.05 M. [b] Isolated yields. [c] Time = 6 h. [d] Time = 4 h. [e] Temperature = 0 °C; time = 5 h. [f] About 4% of **4q** was formed upon silica gel column purification.

0−1)[10] acted as a base and tempered the reaction acidity, and the mild acidity of the reaction was also evident with furan and indole substrates (entries 13 and 14). (c) A general trend can be deduced on the basis of the results of a series of aryl substrates (e.g., entries 8, 9, 12, and 13): the more nucleophilic the OH group, the more efficient the reaction; this is in agreement with the fact that better yields were frequently obtained with R = an aliphatic or functionalized aliphatic group (entries 2, 5, 17, and 18). (d) For the furan (entry 13) and indole (entry 14) substrates, no 5-exo-dig or 6-endo-dig[11] cyclization of the arene ring to the C≡C triple bond was observed, reflecting the facile nature of the oxidation. (e) Finally, the efficient formation of strained 5,6-trans-fused **4r** suggests the synthetic potential of this chemistry and again the mild nature of the reaction, as its epimerization was observed during purification using either neutral alumina or silica gel columns.

The formation of gold carbenes was supported by the isolation of mesylate **7**[12] and the observation of pyridium **8** by crude ^{1}H NMR and ESI$^+$ MS analyses (Figure 1A). In fact, side products of these types counted for most of the remaining substrates. Although their formation could also be rationalized by an S_N2' process (Figure 1B), the formation of **2** would require a disfavored 5-endo-trig cyclization;[13] furthermore, the efficient and easy formation of **4r** argues against this alternative kinetically. Notably, our attempts to convert **7** or **8** to **2** did not succeed, even under basic conditions.

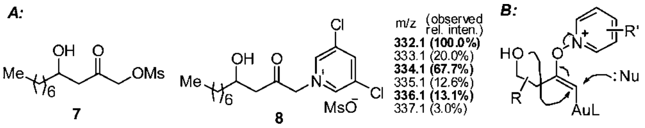


Figure 1

In summary, we have developed a convenient and reliable method to access reactive α-oxo gold carbenes via gold-catalyzed intermolecular oxidation of terminal alkynes under mild reaction conditions. This intermolecular strategy provides much improved synthetic flexibility in comparison with the intramolecular version and offers a safe and economical alternative to those based on diazo substrates. Its synthetic potential has been demonstrated by expedient preparation of dihydrofuran-3-ones containing a broad range of functional groups.

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

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