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A Desulfonylative Approach in Oxidative Gold Catalysis: Regiospecific Access to Donor-Substituted Acyl Gold Carbenes

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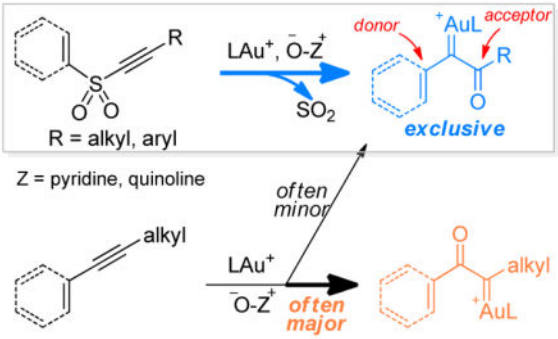
Abstract

Donor-substituted acyl gold carbenes are challenging to access selectively via gold-promoted intermolecular oxidation of internal alkynes as the opposite regioisomers frequently predominate. By using alkynyl sulfones or sulfonates as substrates, the oxidative gold catalysis in the presence of substituted pyridine N-oxides offers regiospecific access to acyl/aryl, acyl/alkenyl or acyl/alkoxy gold carbenes by in situ expulsion of sulfur dioxide. The intermediacies of these reactive species are established by their reactivities including undergoing further oxidation by the same oxidant, cyclopropanating styrenes, engaging a [3+2] cycloaddition with α-methylstyrene, and being converted into dienones.

Graphical Abstract

The regioselectivity in the generation of α-oxo gold carbenes via gold-catalyzed intermolecular oxidation of internal alkynes can be challenging and, for the realized cases, only one of the two regioisomers can be accessed selectively based on substrate structural bias and upon condition optimization. There is no viable strategy to gain access to the often minor regioisomers selectively, let alone with regiospecificity. A desulfonylative approach is developed in this work to regiospecifically access these underexplored species from alkynyl aryl/alkenyl sulfones or alkynesulfonate substrates. The reactivities of these donor- and acceptor-substituted carbenes are examined.



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Keywords

gold; carbene; cyclopropanation; desulfonylation; oxidation

Gold-catalyzed intermolecular oxidation of alkyne[1] has become an increasingly popular approach to accessing highly electrophilic α-oxo gold carbene intermediates since first reported in 2010[2] (Scheme 1A). This strategy permits ready explorations of these reactive intermediates without resorting to hazardous and potentially explosive diazo ketone precursor,[3] and thereby facilitates the development of various versatile synthetic methods.[2, 4],[5] While terminal alkynes are most frequently oxidized to terminal gold carbene intermediates, regioselective oxidations of internal alkynes can be challenging, and often only one regioisomer could be accessed selectively based on structural biases and upon optimizations of catalyst, oxidant and other reaction conditions. For example, in our previous work,[6] under optimal conditions, differences in steric bulk of the two alkyne ends were harnessed to achieve selective oxygen delivery to the less hindered C(sp) (e.g., **1**, Scheme 1B), and with electronically biased internal alkynes oxidation occurs selectively at the end most accommodating to positive charge development upon gold coordination, i.e., proximal to aryl, alkeny and *N*-amido (e.g., **2**–**3**,[7] Scheme 1B) [5l–o, 6] and distal to electron-withdrawing groups (e.g., **4**, Scheme 1B).[4f, 5e, 5f] There is, however, no viable approach to generating α-oxo gold carbenes selectively with regiochemistries opposite to the structurally preferred ones, let alone regiospecifically. Hence, the potential rich reactivities of those often minor regioisomeric gold carbenes could not be readily explored. Herein, we disclose a solution to this challenge with regard to arylalkynes, enyne and alkoxyalkyne substrates via on a desulfonylative strategy and explore the reactivities of these regiospecifically generated donor-substituted acyl carbenes including acyl/aryl, acyl/alkenyl and acyl/alkoxy gold carbenes. Notably, most of these carbenes[5a] studied so far are generated using the corresponding diazo precursors[3g, 3j]or the activated aryl/alkenyl-terminated ynamides instead of typical internal alkynes.[5b, 5o]

Our design is shown in Scheme 2. While arylalkynes and enynes would often lead to selective generation of the α-oxo gold carbene **A** over its regioisomer **B**, which is an acceptor- and donor-substituted gold carbene, it is envisioned that **B** could be generated exclusively from a different class of substrates, namely, alkynyl sulfones **5**. Hence, upon its coordination to a cationic gold(I) catalyst, the C-C triple bond, polarized by the electron-withdrawing sulfonyl group, should be attacked by a *N*-oxide regiospecifically at the β-C(sp). Such a process followed by redox rearrangement would lead to the dual acceptor-substituted gold carbene intermediate, i.e., **D**. Its carbene moiety are likely highly electrophilic, and could react intramolecularly with the aryl/alkenyl group on the other side of the sulfonyl group, leading to the formation of the episulfone intermediate **E**. Alternatively, this intermediate could be formed directly from the initial adduct **C**, i.e., the precursor to the carbene **D**, via a 3-*exo*-*trig* cyclization.[5p] The desulfonylative fragmentation of **E**[8] would then afford only the α-oxo gold carbene **B**. It is noteworthy that **B** is a donor-substituted acyl gold carbenes and should display reactivities characteristically different from those readily accessible yet without donor substitution.

As shown in Table 1, we set out to validate the above design and discover optimal reaction conditions by using the alkynyl sulfone **5a** as the substrate, which can be readily prepared.[9] It is anticipated that the gold carbene of type **B** generated could be simply further oxidized by the same *N*-oxide to deliver the corresponding 1,2-diketone **7a**. When the Gagosz catalyst $Ph_3PAuNTf_2$[10] was employed, DCE as the solvent, and 2,6-dichloropyridine *N*-oxide (**6a**) as the oxidant, the desired product **7a** was indeed formed, albeit in a low 15% yield (entry 1). Subsequent catalyst screenings revealed that the *N*-hetereocyclic carbene-based catalyst $IPrAuNTf_2$ performed noticeably better (entries 2–5). Concerned about potential chloride abstraction[11] of the solvent DCE by highly electrophilic gold carbene intermediates of type **C**, we used $PhCF_3$ instead. Much to our delight, the reaction yield was improved to a decent 72% (entry 6). Our ensuing screenings of the *N*-oxides revealed large variations of reaction efficiencies (entries 7–10). Among them, 2-*tert*-butyl-4-chloropyridine *N*-oxide, i.e., **6c**, first reported by Gagosz,[5i] proved to be the most effective (entry 8), and **7a** was isolated in 80% yield. It is notable that **7a** could not be generated cleanly via gold-catalyzed double oxidation[5k, 12] of the corresponding 1-methyl-4-(prop-1-yn-1-yl)benzene as facile 1,2-C-H insertions by the isomeric gold carbenes of type **A** would lead to the formation of enone side products.[6] [13]

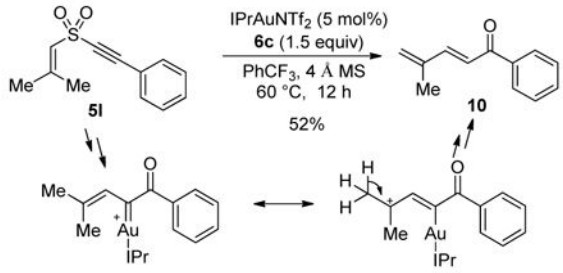
We explored the scope of this desulfonylative double oxidation chemistry. As shown in Table 2, the *p*-tolyl group of **5a** could be replaced with an electron-rich 4-methoxyphenyl (entry 1) or a slightly electron-deficient 4-bromophenyl (entry 2), and the reaction yields correlated well with the trend of the benzene ring reacting with electrophiles, which is consistent with the envisioned reaction mechanism. When the alkynyl terminal methyl group was replaced with a *n*-butyl group in **5d** (entry 3), the desired 1,2-diketone **7d** was formed in only 19% yield; instead, the sulfonylcyclopentanone **7d′** was isolated in 54% yield. This side product must be the result of C-H insertion[4h] by an acyl/sulfonyl-substituted gold carbene of type **D**. It was envisioned that a more electron-rich phenyl ring in **D** could accelerate its desulfonylatirve rearrangement, thereby minimizing side reactions. Indeed, with the anisyl sulfone substrate **5e**, the double oxidation displayed a much improved yield, while the C-H insertion product was formed in <5% yield (entry 4). Similarly, a cyclohexyl group at the alkyne terminus was allowed (entry 5). In addition, the alkyne terminus could accommodate a cyclopropyl (entry 6), a phenyl group (entry 7), or a furan-2-yl (entry 8), the last two of which allowed regiospecific generation of diaryl-substituted α-oxo gold carbenes by simply using appropriate aryl alkynyl sulfone substrates. Besides phenyl-based sulfones, a *trans*-*β*-styryl sulfone (i.e., **5j**, entry 9) and a furan-2-yl sulfone (i.e., **5k**, entry 10) underwent the reaction without incident, affording the diketone products **7j** and **7k** in 75% and 87% yield, respectively. Of note, in some cases (entries 5–6, 8–10), 2,6-dichloropyridine *N*-oxide (**6a**) was more efficient than **6c**.

While these results are consistent with the desulfonylative generation of the donor-substituted acyl gold carbene intermediates of type **B**, the fact that the C-C triple bond is oxidized into a symmetric 1,2-dicarbonyl moiety prevented us from unequivocally establishing the regiochemistry of these carbenes, despite our difficulty in formulating an alternative mechanism for the formation of its isomer **A**. Liu and co-worker[14] have previously demonstrated that that donor-substituted acyl gold carbenes related to **B**,

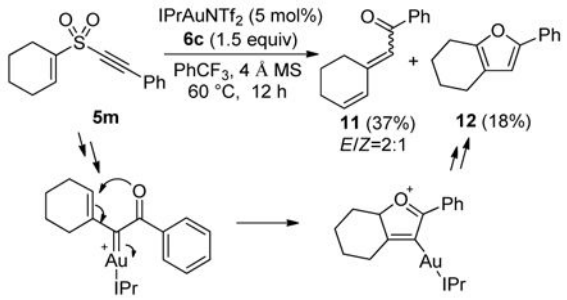
generated via intramolecular alkyne oxidation, can undergo cyclopropanation reactions with styrenes. When the oxidation of the alkynyl sulfone **5a** was performed in the presence of styrene, the intended cyclopropanation reaction indeed occurred, and the cyclopropyl ketone **8a** was formed selectively in 80% isolated yield (Table 3, entry 1). This result offers strong support for the regiospecific generation of gold carbenes of type **B**, and reveals that the pyridine byproduct does not interfere the intermolecular cyclopropanation. The reaction scope was then examined. As shown in entries 2–5, the aryl sulfones **5** with different aryl groups including furan-2-yl (entry 4) were allowed. The substrate alkyne terminal substituents could be a phenyl (entry 5) or a cyclopropyl (entry 6). Our attempt to vary the styrene was successful with 4-bromostyrene (entry 7) and 4-tert-butylstyrene (entry 8) but not in the case of 4-methoxystyrene, which underwent apparent polymerization during the reaction. Other electron-rich alkenes such as ethyl vinyl ether were also not suitable.

With α-methylstyrene used as solvent, a step-wise, formal [3+2] cycloaddition occurred, affording the dihydrofuran **9** in a serviceable yield (entry 9).[5a] This divergent reactivitiy can be understood by considering that the benzylic position of the styrene can better accommodate positive charge and has increased steric hindrance, which disfavour the expected concerted cyclopropanation reaction.

The success with the *β*-styryl sulfone **5j** (Table 2, entry 9) encouraged us to examine other alkenyl sulfones. As shown in Eq. 1, the 2-methylprop-1-en-1-yl sulfone **5l** did undergo the gold-catalyzed oxidative desulfonylation, but the isolated product was the *trans*-dienone **10** instead of the corresponding diketone. Our attempt to trap the alkenyl acyl gold carbene intermediate with styrene was futile. These results highlight the facile nature of the carbene to undergo E1-type elimination under the reaction conditions, as outlined in the equation. With the cyclohexen-1-yl sulfone **5m** as the substrate, besides the expected dienone product **11**, a bicyclic furan, i.e., **12**, was isolated (Eq. 2). The formation of the latter product should involve a 4π electrocyclic ring closure, in line with the related work by Liu[5b] and us.[15]

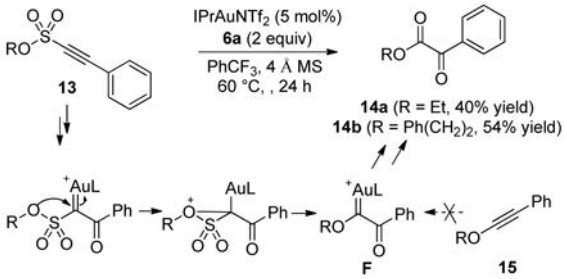


(1)



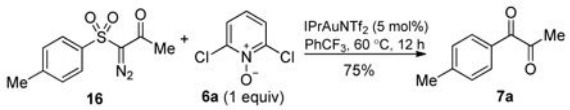
(2)

To further investigate the desulfonylative carbene rearrangement, we surmised that instead of an aryl or alkenyl group an alkoxy might behave in a similar manner, thereby leading to the generation of a new type of donor/acceptor-substituted gold carbenes, i.e., acyl/alkoxy gold carbenes **F** (Eq. 3). When the alkynesulfonates **13** were subjected to the reaction, the α-ketoesters **14**, apparently resulting from further oxidation of the gold carbene intermediates, were indeed formed, albeit with moderate yields in both cases. In these cases, **6a** was a better oxidant than **6c** as slower reactions and lower yields were observed with the latter (e.g., 2 days, ~14% yield). It is worthy to point out that the carbene intermediate **F** could not be possibly derived from the alkynyl ethers **15** via direct oxidative gold catalysis due to their opposite polarized nature, despite the same diketone products might be formed from these electron-rich alkyne under the same gold catalysis via the isomeric gold carbene intermediates.



(3)

To further corroborate the initial oxidative generation of the gold carbene **D** and its subsequent desulfonylative rearrangement into **B** (cf. Scheme 2), we prepared the α-sulfonyl-α-diazoacetone **16** and subjected it to the optimal conditions with the exception of only 1 equiv. of **6a**. Indeed, the diketone **7a** was formed smoothly in 75% yield (Eq. 4), slightly higher than that of our oxidative gold catalysis (see Table 1, entry 6). However, the desulfonylative cyclopropanation reaction with **16** was not successful.



(4)

In summary, we have implemented a novel approach to achieving regiospecific generation of donor-substituted acyl gold carbenes. These intermediates are often formed as minor isomers or could not be generated at all from the corresponding donor-substituted alkynes as the polarization of the π bonds upon coordination to gold often leads to the opposite regioisomers. With alkynyl sulfones or alkynesulfonates as substrates, the oxidative gold catalysis by using substituted pyridine *N*-oxides as oxidants provide regiospecific access to acyl/aryl, acyl/alkenyl or acyl/alkoxy gold carbenes via expulsion of sulfur dioxide. These underexplored carbenes can readily undergo further oxidation by the same oxidant, cyclopropanate styrenes, undergo [3+2] cycloaddition with α-methylstyrene, and be converted into dienones. With the establishment of their access and their basic reactivities, the synthetic utilities of these intermediates will soon be explored in ring-forming intramolecular processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

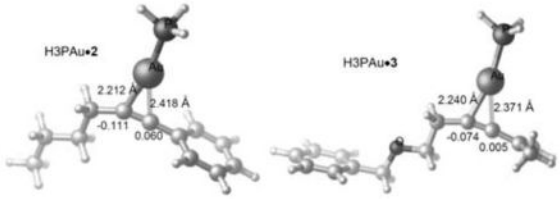
1. Zhang L. Acc Chem Res. 2014; 47:877–888. [PubMed: 24428596]
2. Ye L, Cui L, Zhang G, Zhang L. J Am Chem Soc. 2010; 132:3258–3259. [PubMed: 20166668]
3. (a) Doyle, MP., McKervey, MA., Ye, T. Modern catalytic methods for organic synthesis with diazo compounds: from cyclopropanes to ylides. Wiley; New York: 1998. (b) Fructos MR, Belderrain TR, de Fremont P, Scott NM, Nolan SP, Diaz-Requejo MM, Perez PJ. Angew Chem Int Ed. 2005; 44:5284–5288.(c) Prieto A, Fructos MR, Mar Díaz-Requejo M, Pérez PJ, Pérez-Galán P, Delpont N, Echavarren AM. Tetrahedron. 2009; 65:1790–1793.(d) Pawar SK, Wang CD, Bhunia S, Jadhav AM, Liu RS. Angew Chem, Int Ed. 2013; 52:7559–7563.(e) Pagar VV, Jadhav AM, Liu RS. J Org Chem. 2013; 78:5711–5716. [PubMed: 23641859] (f) Jadhav AM, Pagar VV, Liu RS. Angew Chem, Int Ed. 2012; 51:11809–11813.(g) Yu Z, Ma B, Chen M, Wu HH, Liu L, Zhang J. J Am Chem Soc. 2014; 136:6904–6907. [PubMed: 24779511] (h) Briones JF, Davies HML. J Am Chem Soc. 2012; 134:11916–11919. [PubMed: 22770434] (i) Cao ZY, Wang X, Tan C, Zhao XL, Zhou J, Ding K. J Am Chem Soc. 2013; 135:8197–8200. [PubMed: 23697751] (j) Xi Y, Su Y, Yu Z, Dong B, McClain EJ, Lan Y, Shi X. Angew Chem, Int Ed. 2014; 53:9817–9821.
4. (a) Ji K, Zhao Y, Zhang L. Angew Chem, Int Ed. 2013; 52:6508–6512.(b) Wang Y, Ji K, Lan S, Zhang L. Angew Chem, Int Ed. 2012; 51:1915–1918.(c) Luo Y, Ji K, Li Y, Zhang L. J Am Chem Soc. 2012; 134:17412–17415. [PubMed: 23039251] (d) Ye L, He W, Zhang L. Angew Chem, Int Ed. 2011; 50:3236–3239.(e) He W, Li C, Zhang L. J Am Chem Soc. 2011; 133:8482–8485. [PubMed: 21563762] (f) Ye L, He W, Zhang L. J Am Chem Soc. 2010; 132:8550–8551. [PubMed:

20521793] (g) Lu B, Li C, Zhang L. J Am Chem Soc. 2010; 132:14070–14072. [PubMed: 20853846] (h) Wang Y, Zheng Z, Zhang L. J Am Chem Soc. 2015; 137:5316–5319. [PubMed: 25835372] (i) Ji K, Zheng Z, Wang Z, Zhang L. Angew Chem, Int Ed. 2015; 54:1245–1249.

5. (a) Li CW, Lin GY, Liu RS. Chem Eur J. 2010; 16:5803–5811. [PubMed: 20379977] (b) Dateer RB, Pati K, Liu RS. Chem Commun. 2012; 48:7200–7202.(c) Ghorpade S, Su MD, Liu RS. Angew Chem, Int Ed. 2013; 52:4229–4234.(d) Bhunia S, Ghorpade S, Huple DB, Liu RS. Angew Chem, Int Ed. 2012; 51:2939–2942.(e) Qian D, Zhang J. Chem Commun. 2012; 48:7082–7084.(f) Qian D, Zhang J. Chem Commun. 2011; 47:11152–11154.(g) Davies PW. Pure Appl Chem. 2010; 82:1537–1544.(h) Davies PW, Cremonesi A, Martin N. Chem Commun. 2011; 47:379–381.(i) Henrion G, Chavas TEJ, Le Goff X, Gagosz F. Angew Chem, Int Ed. 2013; 52:6277–6282.(j) Xu M, Ren TT, Li CY. Org Lett. 2012; 14:4902–4905. [PubMed: 22954390] (k) Shi S, Wang T, Yang W, Rudolph M, Hashmi ASK. Chem Eur J. 2013; 19:6576–6580. [PubMed: 23576273] (l) Wang T, Shi S, Hansmann MM, Rettenmeier E, Rudolph M, Hashmi ASK. Angew Chem, Int Ed. 2014; 53:3715–3719.(m) Pan F, Liu S, Shu C, Lin RK, Yu YF, Zhou JM, Ye LW. Chem Commun. 2014; 50:10726–10729.(n) Wang L, Xie X, Liu YH. Angew Chem, Int Ed. 2013; 52:13302–13306.(o) Li L, Shu C, Zhou B, Yu YF, Xiao XY, Ye LW. Chem Sci. 2014; 5:4057–4064.(p) Chen M, Chen Y, Sun N, Zhao J, Liu Y, Li Y. Angew Chem, Int Ed. 2015; 1200–1204

6. Lu B, Li Y, Wang Y, Aue DH, Luo Y, Zhang L. J Am Chem Soc. 2013; 135:8512–8524. [PubMed: 23731178]

7. DFT calculations were performed with the alkynes 2 and 3 coordinated to PH_3Au^+ at the B3LYP/6–311G(d,p)/SDD(Au) level. The optimized structures are shown below. The gold atom slightly slides away from the Ph or 2-isopropenyl group, and the NBO analysis of the alkyne carbons promixal to these groups show that they are more electron-deficient than their distal counterparts. These results are consistent with the experimental outcomes.



8. Nájera C, Yus M. Tetrahedron. 1999; 55:10547–10658.

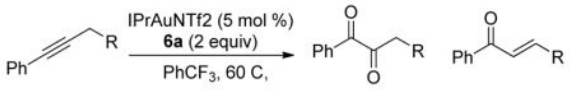
9. Eisch JJ, Behrooz M, Dua SK. J Organomet Chem. 1985; 285:121–136.

10. Mézailles N, Ricard L, Gagosz F. Org Lett. 2005; 7:4133–4136. [PubMed: 16146370]

11. He W, Xie L, Xu Y, Xiang J, Zhang L. Org Biomol Chem. 2012; 10:3168–3171. [PubMed: 22419033]

12. Xu C-F, Xu M, Jia Y-X, Li C-Y. Org Lett. 2011; 13:1556–1559. [PubMed: 21332143]

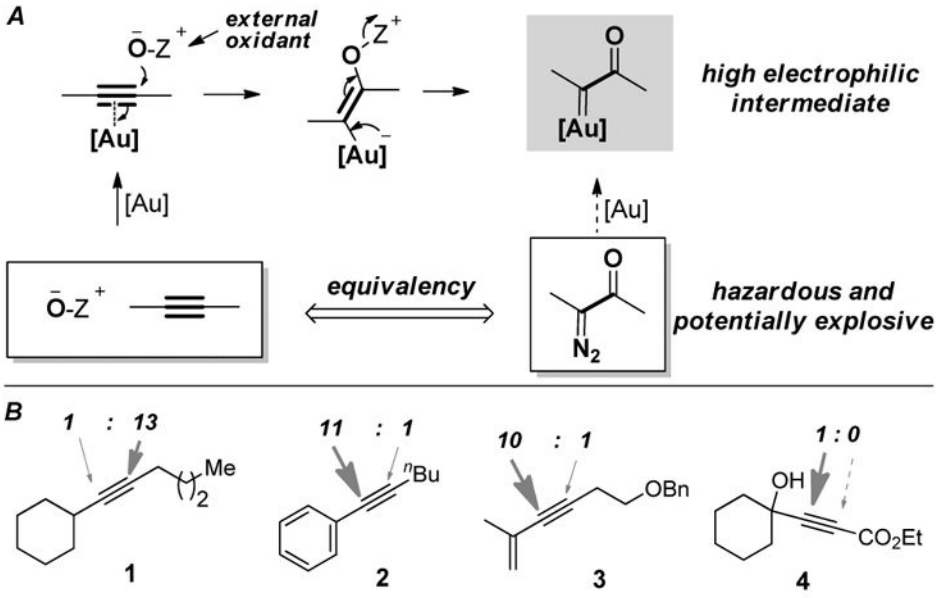
13. Indeed when the related 1-phenyl-1-alkynes were subjected to the reaction, the enones were formed as side products. With R = H, the diketone was the major product due to the contrasting regioselectivity bestowed by sterics (i.e., Me is small).



R	reaction time	conversion	yield	
H	overnight	86%	60%	20%
Bu	8 h	50%	16%	24%

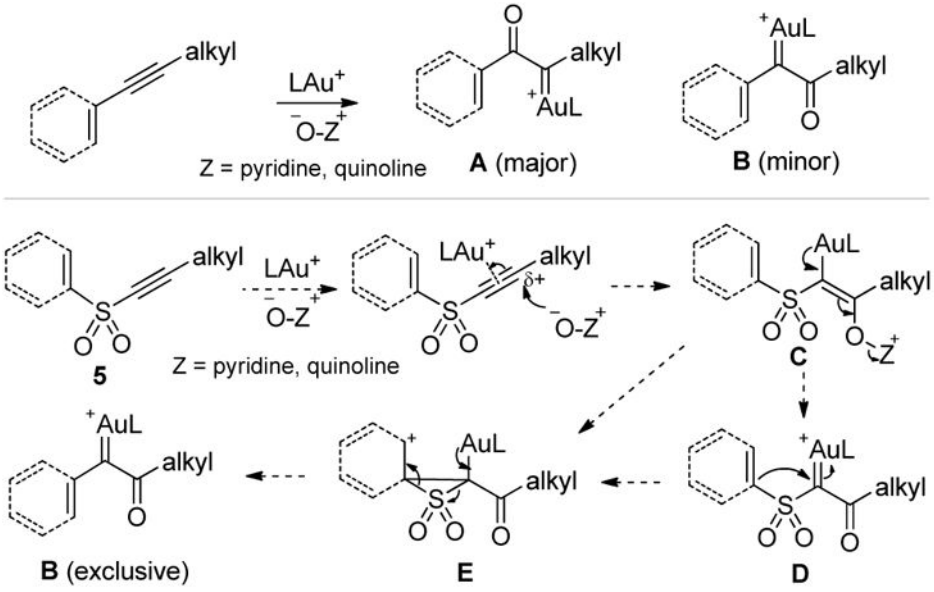
14. Lin G-Y, Li C-W, Hung S-H, Liu R-S. Org Lett. 2008; 10:5059–5062. [PubMed: 18855406]

15. Yan ZY, Xiao Y, Zhang L. Angew Chem, Int Ed. 2012; 51:8624–8627.



Scheme 1.

(A) Oxidative gold catalysis: a facile, non-diazo access to α-oxo gold carbenes; (B) Examples of regioselective oxidative gold catalysis with the optimized ratios shown.



Scheme 2.

A desulfonylative approach toward exclusive generation of the typically minor α-oxo gold carbene intermediates: design.

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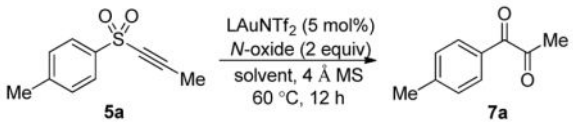
Table 1

Optimization of reaction conditions for double oxidation[a,b].



Entry	L	Solvent	N-Oxide	yield	Conv.
1	PPh_3	DCE	**6a**	15%	57%
2	$(2,4\text{-}^tBu_2PhO)_3P$	DCE	**6a**	8%	40%
3	Mor-DalPhos	DCE	**6a**	10%	100%
4	t-BuMe_4XPhos	DCE	**6a**	17%	93%
5	IPr	DCE	**6a**	22%	45%
6	IPr	$PhCF_3$	**6a**	72%	100%
7	IPr	$PhCF_3$	**6b**	32%	61%
8	**IPr**	**$PhCF_3$**	**6c**	**80%**[c]	**100%**
9	IPr	$PhCF_3$	**6d**	8%	91%
10	IPr	$PhCF_3$	**6e**	20%	96%

[a]All the reactions were run in the sealed vials.

[b]NMR yields using diethyl phthalate as internal reference.

[c]Isolated yield.

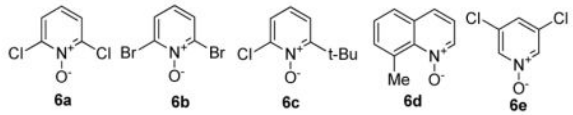
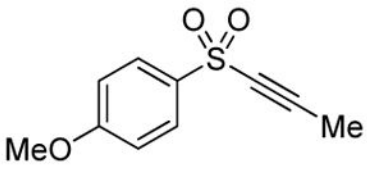
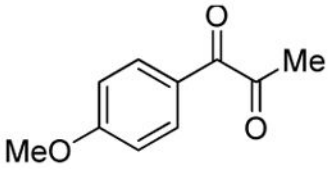
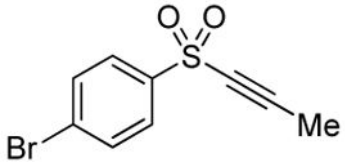
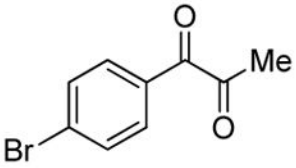
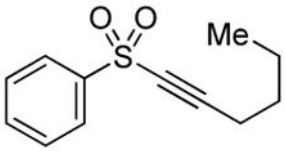
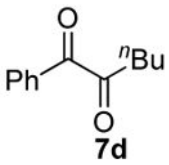
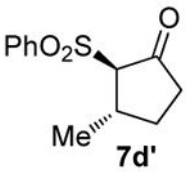
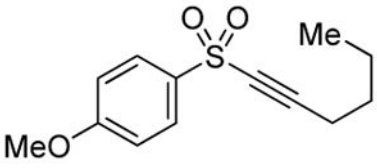
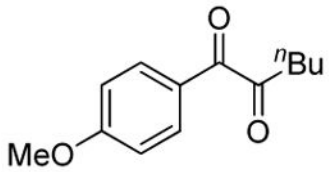
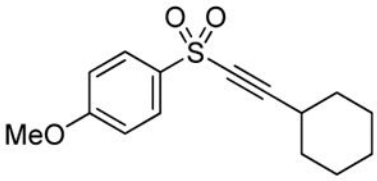
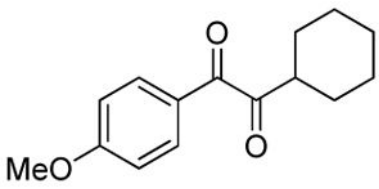
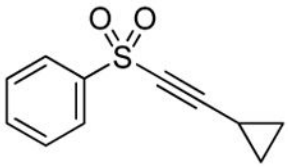
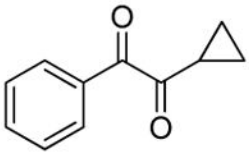
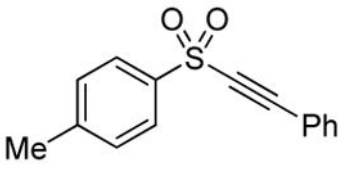
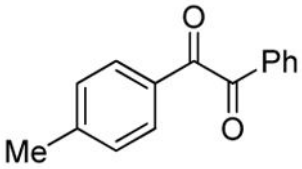
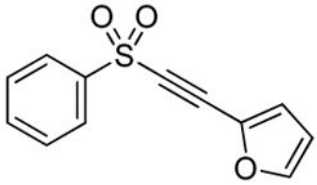
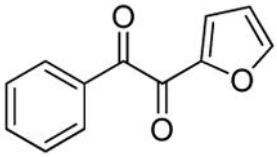
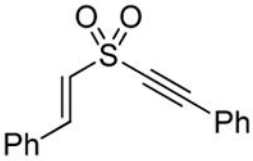
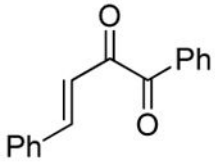
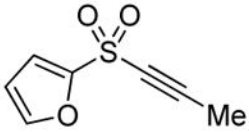
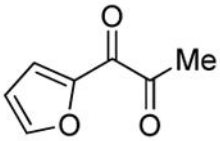


Table 2

Scope of desulfonylative doube oxidation.[a]

entry	5	7	yield
1	 **5b**	 **7b**	96%
2	 **5c**	 **7c**	59%
3	 **5d**	 **7d**  **7d'**	19% (54%)[b]
4	 **5e**	 **7e**	69%[c]
5[d]	 **5f**	 **7f**	65%[c]
6[d]	 **5g**	 **7g**	67%

entry	5	7	yield
7	 **5h**	 **7h**	78%
8[d]	 **5i**	 **7i**	60%
9[d]	 **5j**	 **7j**	75%
10[d]	 **5k**	 **7k**	87%

[a]The reactions were run using the optimized conditions (i.e., Table 1, entry 8), and the isolated yield is reported.

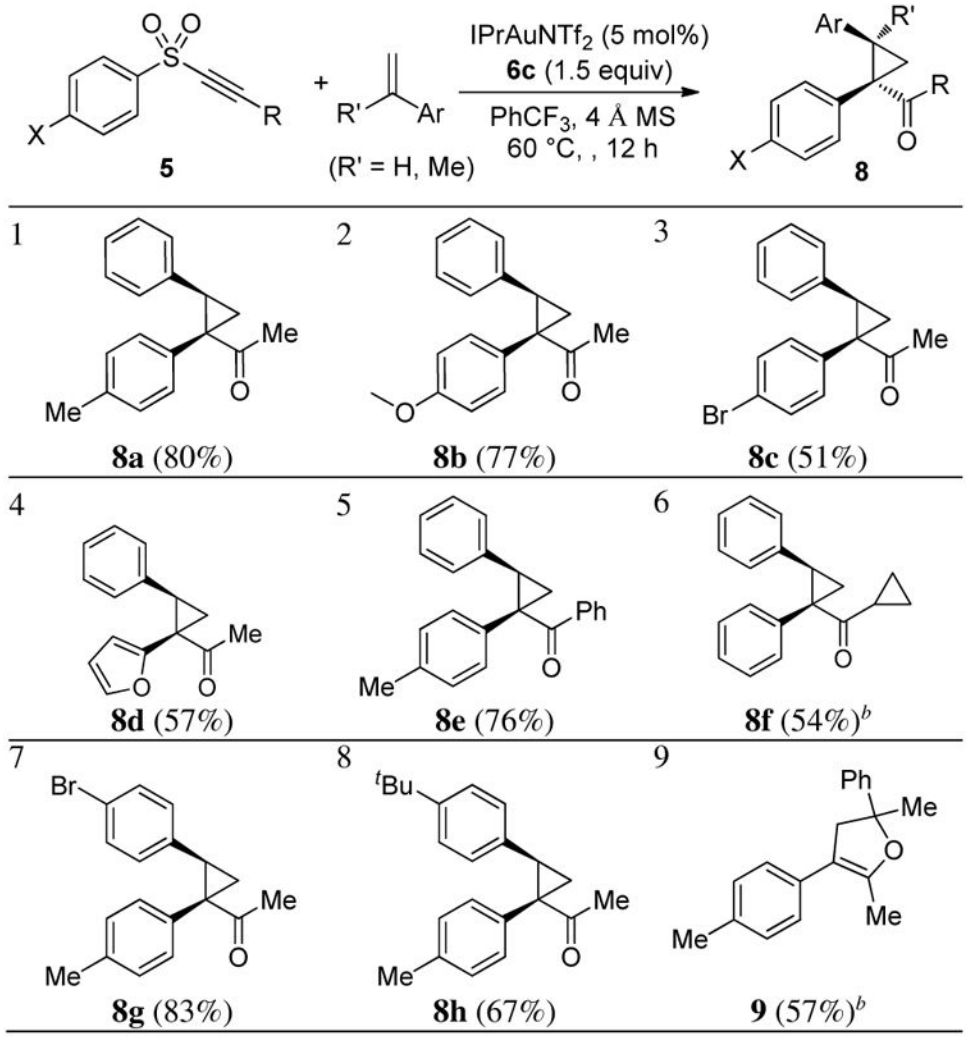
[b]The yield of the C-H insertion product **7g′**.

[c]C-H insertion product <5%.

[d]**6a** used as oxidant.

Table 3

Cyclopropanation with styrenes: scope[a]



[a] All the reactions run in vials, the oxidant introduced by syringe pump over a 12 h period, and the product d. r. >95:5.

[b] **6b** used as the oxidant, and α-methylstyrene as solvent.