

Gold-Catalyzed Highly Regioselective Oxidation of C–C Triple Bonds without Acid Additives: Propargyl Moieties as Masked α,β -Unsaturated Carbonyls

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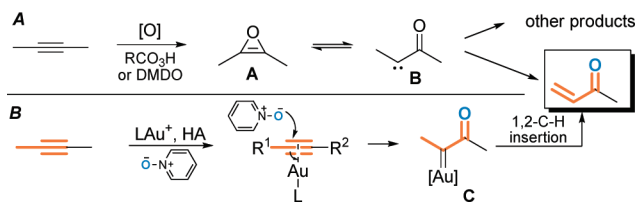
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Abstract: Gold-catalyzed intermolecular oxidations of internal alkynes have been achieved with high regioselectivities using 8-alkylquinoline *N*-oxides as oxidants and in the absence of acid additives. Synthetically versatile α,β -unsaturated carbonyls are obtained in good to excellent yields and with excellent *E*-selectivities. A range of functional groups such as THP, MOMO, N_3 , OTBS, and *N*-Boc are tolerated. This reaction allows α,β -unsaturated carbonyls to be masked as propargyl moieties, thus offering a practical solution to compatibility issues with these functional groups likely encountered in syntheses of complex structures.

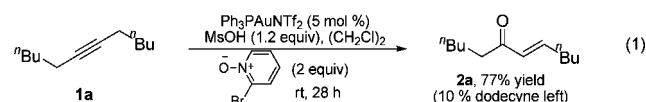
Although alkene epoxidation is a classic and versatile reaction in organic synthesis, epoxidation of C–C triple bonds¹ with DMDO or peracids has little synthetic utility except with electronically biased ynamide substrates,² as often multiple products including α,β -unsaturated ketones were formed with little chemoselectivity and regioselectivity. Many of the product formations could be rationalized via an initial rearrangement of oxirene **A**³ into highly reactive α -oxocarbene **B** (Scheme 1A). In the cases of alternative metal-mediated/catalyzed intermolecular alkynes oxidation, further oxidation is unavoidable,⁴ leading to α,β -epoxy ketones⁵ or 1,2-dicarbonyl or carboxylic products;⁶ hence, regioselectivity has not been studied nor achieved. Herein, we report a rare, highly regioselective single oxidation of internal alkynes via gold catalysis under exceedingly mild conditions, and synthetically versatile α,β -unsaturated carbonyls are directly formed from propargyl moieties for the first time in good yields and with high to excellent regioselectivities.

Scheme 1. Oxidation of C–C Triple Bonds: Conversion of a Propargyl Moiety into an α,β -Unsaturated Carbonyl Moiety



We have recently reported that terminal alkynes or alkynoates can be oxidized intermolecularly into α -oxo gold carbene **C**,⁷ which could be trapped efficiently by tethered OH groups.⁸ We envisioned such a gold carbene intermediate, if generated from internal alkynes, might undergo facile 1,2-C–H insertions, thus avoiding further oxidation and forming highly valuable α,β -unsaturated carbonyls (Scheme 1B). This gold catalysis would make a propargyl moiety a masked α,β -unsaturated carbonyl;⁹ however, the challenge is how to achieve high regioselectivities¹⁰ without much bias in the substrate structure.

To our delight, the oxidation of symmetric 6-dodecyne indeed afforded α,β -unsaturated ketone **2a** in 77% yield, albeit a sluggish reaction (eq 1). In contrast to *cis*-C–C double bonds formed in



Rh-catalyzed decomposition of α -diazo carbonyl compounds,¹¹ only *trans*-**2a** was observed, reflecting a unique aspect of gold carbene reactivities.

Table 1. Screening Gold Catalyst and Reaction Conditions for High Regioselectivity^a

entry	catalyst	<i>N</i> -oxide (equiv)	MsOH (equiv)	reaction conditions	yield % (% 1b left) ^b	2b/4
1	Ph ₃ PAuNTf ₂	3a (2)	1.2	DCE, rt, 12 h	45 (50)	2.1
2	Ph ₃ PAuNTf ₂	3b (2)	1.2	DCE, rt, 12 h	53 (37)	2.6
3	Ph ₃ PAuNTf ₂	3c (2)	1.2	DCE, rt, 18 h	46 (20)	2.3
4	Ph ₃ PAuNTf ₂	3d (2)	1.2	DCE, rt, 40 min	88	2.8
5	Ph ₃ PAuNTf ₂	3e (2)	1.2	DCE, rt, 40 min	82	3.1
6	Ph ₃ PAuNTf ₂	3f (2)	1.2	DCE, rt, 40 min	85	3.4
7	Ph ₃ PAuNTf ₂	3f (1.2)	no	DCE, rt, 40 min	87	3.2
8	Et ₃ PAuNTf ₂	3f (1.2)	no	DCE, rt, 40 min	71	3.8
9	LAuNTf ₂ ^c	3f (1.2)	no	DCE, rt, 40 min	83	3.1
10	IPrAuNTf ₂	3f (1.2)	no	DCE, rt, 15 min	85	6.4
11	IPrAuNTf ₂	3f (1.2)	no	DCE, –20 °C, 14 h	89	9.1
12	IPrAuNTf ₂	3f (1.2)	no	toluene, –20 °C, 14 h	80	12
13	IPrAuNTf ₂	3f (1.2)	no	THF, –20 °C, 14 h	90 ^d	13

^a In vial; [**1b**] = 0.1 M. ^b Estimated by ¹H NMR using diethyl phthalate as internal reference. ^c L = (4-CF₃Ph)₃P. ^d 83% isolated yield.

With this encouraging result, we then chose nonsymmetric aliphatic alkyne **1b** to study regioselectivity by tuning the steric and electronic properties of gold catalysts and *N*-oxides. Table 1 shows some of the results. Several trends can be readily concluded: (1) the oxygen atom was selectively delivered to the less hindered alkyne end, suggesting that the oxidant approach was the regio-determining event; (2) the bulkier the *N*-oxide was, the more selective the oxidation (comparing entries 1, 2 and entries 3–6); (3) 8-alkylquinoline *N*-oxides (i.e., **3d–f**) oxidized alkynes much more rapidly than the unsubstituted one (i.e., **3c**) and pyridine *N*-oxides; and (4) the less Lewis acidic the gold catalyst was, the better the selectivity (comparing entries 8–11). To our surprise, no acid was needed when **3f**¹² was used as the oxidant, and the reaction rate was not affected at all! This is a major improvement over the conditions used in our previous studies,⁸ and as a result, acid-labile groups could be completely tolerated (vide infra). With only a slight excess of **3f** (1.2 equiv) and 5 mol % of IPrAuNTf₂,

a high selectivity was achieved when the reaction was run at -20°C in THF (entry 13), and the isolated yield was 83%.

With the optimized, exceedingly mild reaction conditions (Table 1, entry 13) in hand, we then examined a range of aliphatic alkynes, and the results are shown in Table 2. All the alkynes were oxidized efficiently and without any observable overoxidation; importantly, regioselectivities were high with nonsymmetric substrates ($\geq 10:1$), and the oxygen was always selectively delivered to the less hindered end of the C–C triple bond. A range of sensitive functional groups (entries 4–9) were allowed, and without acid additive the reaction conditions were so mild that even THP (entry 9) was tolerated. Notably, 6-*exo-dig* cyclizations in the cases of entries 8 and 9 did not compete. Somewhat to our surprise, cyclopentylalkyne **1k** led mostly to ring enlargement, presumably due to the release of the cyclopentane ring strain (6.2 kcal/mol,¹³ entry 10).

Table 2. Reaction Scope Studies of Aliphatic Alkynes^{a,b}

1 2a , 91% rt; 1 h	2 2c , 91%, (>50:1) 0 °C; 3 h	3 2d , 71% (11:1) -20 °C; 48 h	4 2e , 90% (14:1) -20 °C; 14 h
5 2f , 84% (11:1) -20 °C; 24 h	6 2g , 78%, (10:1) 0 °C; 48 h	7 2h , 88% (16:1) -20 °C; 24 h	8 2i , 83% (17:1) -20 °C; 36 h
9 2j , 82% (12:1) -20 °C; 48 h	10 2k* (64%) 2k (15%)		

^a In vial; [alkyne] = 0.1 M. Oxidant, **3f** (1.2 equiv); catalyst, IPrAuNTf₂ (5 mol %); solvent, THF. ^b Isolated yields; the regioselectivity (defined as **2/4**) is shown in parentheses, and the bold bond is the original C–C triple bond.

For arylalkyne substrates, the combination of IPrAuNTf₂ and **3f**, however, led to poor regioselectivity,¹⁴ which was expected as in these cases the resonance stabilization by the aryl group worked against the expected regio preference (assuming aryl is bigger than ⁿBu). Catalyst and oxidant screening led to [(2,4-^tBu₂PhO)₃P]AuNTf₂ and **3b** as the optimal combination, and the regioselectivities were opposite to those of aliphatic alkynes. Apparently, resonance stabilization became the controlling factor with arylalkynes, and more Lewis acidic [(2,4-^tBu₂PhO)₃P]AuNTf₂ led to better regioselectivities. As shown in Table 3, entries 1–6, activated benzene rings (entries 2, 3) led to better regioselectivities over the parent benzene ring, in line with the electronic effect. While a slight deactivation (entry 4) did not diminish the selectivity, strong deactivation proved to be detrimental (e.g., 4-MeO₂CPh, 3.5:1¹⁴). Notably, when electronics and sterics worked in sync, an excellent selectivity was observed (entry 6). Again, no acid additive was needed in these reactions.¹²

For other types of conjugated alkynes, the regioselectivity is again dictated by resonance stabilization.¹⁵ For example, α,β -unsaturated *N*-acyloxazolidinone **2r** was obtained from the corresponding ynamide in 92% yield in 1 h (entry 7); notably, the regioselectivity was opposite to those observed upon DMDO oxidation.² The combination of IPrAuNTf₂ and **3e** worked the best in this case. Under similar conditions (oxidant, **3f**, entry 8), cyclopropyl enone **2s** was obtained in 83% yield.

Table 3. Reaction Scope Studies of Conjugated Alkynes^{a,b}

1 2l , 84% (11:1) rt; 26 h	2 2m , 92%, (>50:1) rt; 4 h	3 2n , 72% (16:1) rt; 26 h
4 2o , 75% (11:1) rt; 26 h	5 2p , 78%, (12:1) rt; 26 h	6 2q , 85% (>50:1) rt; 26 h
7 ^d 2r , 92% (>50:1) rt; 1 h	8 ^e 2s , 83%, (10:1) rt; 1 h	9 ^d 2t , 81% (10:1) 40 °C; 20 h
10 ^d 2u , 85% (>50:1) rt; 1 h	11 ^d 2v , 87% (>50:1) rt; 1 h	12 ^d 1w low regioselectivity side reactions

^a In vial; [alkyne] = 0.1 M. Oxidant, **3b** (1.2 equiv); catalyst, [(2,4-^tBu₂PhO)₃P]AuNTf₂ (5 mol %); solvent, THF. ^b Isolated yields; the regioselectivity (defined as **2/diketone**) is shown in parentheses, and the bold bonds are the original C–C triple bonds. ^d Oxidant, **3e**; catalyst, IPrAuNTf₂. ^e Oxidant, **3f**; catalyst, IPrAuNTf₂.

Divinyl ketones are highly useful compounds. While they could be prepared via Pd/Ni-catalyzed carbonylative Stille or Nigishi reaction,¹⁶ the use of toxic alkenylstannanes or reactive alkenylzincs is synthetically limiting. This intermolecular alkyne oxidation reaction would provide an exceedingly mild and safe approach to this important class of compounds from easily available enynes. For example, divinyl ketone **2t** was obtained in 81% yield and with a 10:1 regioselectivity (entry 9). With cyclohexene as the ene part, the reactions proceeded to completion in 1 h, and the desired products were obtained in high yields and without the detection of any diketone isomer¹⁴ (entries 10, 11); notably, the *N*-Boc group was readily tolerated. Surprisingly, enyne **1w** (entry 12) did not work well, indicating that the alkene internal end needs to be fully substituted in order to achieve efficient reactions.

In conclusion, a rare single oxidation of internal alkynes with high to excellent regioselectivity was achieved via gold catalysis, leading to synthetically versatile α,β -unsaturated carbonyls in good to excellent yields and with excellent *E*-selectivities. The exceedingly mild reaction conditions (mostly room temperature or below, no N₂ protection, no acid additive, and mild oxidants) readily tolerate a range of sensitive functional groups. This reaction provides an efficient masking of α,β -unsaturated carbonyls as propargyl moieties, offering a practical solution to compatibility issues involving α,β -unsaturated carbonyls, which are likely encountered in many multistep syntheses. Moreover, the identification of 8-alkylquinoline *N*-oxides as facile oxidants and the abolishment of acid additives should unveil many exciting opportunities to apply this mild alkyne oxidation to the development of various novel synthetic methods.

Acknowledgment. We thank NSF (CAREER award CHE-0969157), NIGMS (R01 GM084254), and UCSB for generous financial support.

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

References

- (1) (a) McDonald, R. N.; Schwab, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 4866–4871. (b) Stille, J. K.; Whitehurst, D. D. *J. Am. Chem. Soc.* **1964**, *86*, 4871–4876. (c) Curci, R.; Fiorentino, M.; Fusco, C.; Mello, R.; Ballistreri, F. P.; Failla, S.; Tomaselli, G. A. *Tetrahedron Lett.* **1992**, *33*, 7929–7932.
- (2) (a) Couty, S.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2819–2822. (b) Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661–663.
- (3) Lewars, E. G. *Chem. Rev.* **1983**, *83*, 519–534.
- (4) For an exception, see: Sun, S.; Edwards, J. O.; Sweigart, D. A.; D'Accolti, L.; Curci, R. *Organometallics* **1995**, *14*, 1545–1547.
- (5) Ishii, Y.; Sakata, Y. *J. Org. Chem.* **1990**, *55*, 5545–5547.
- (6) (a) Ren, W.; Xia, Y.; Ji, S.-J.; Zhang, Y.; Wan, X.; Zhao, J. *Org. Lett.* **2009**, *11*, 1841–1844. (b) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28–29. (c) Srinivasan, N. S.; Lee, D. G. *J. Org. Chem.* **1979**, *44*, 1574–1574. (d) Muller, P.; Godoy, J. *Helv. Chim. Acta* **1981**, *64*, 2531–2533. (e) Zhu, Z. L.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 7728–7732.
- (7) For gold-catalyzed intramolecular oxidations of alkynes, see: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161. (b) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156–5159. (c) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394–8395. (d) Cui, L.; Ye, L.; Zhang, L. *Chem. Commun.* **2010**, 46, 3351–3353. (e) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225–1228. (f) Yeom, H. S.; Lee, Y.; Lee, J. E.; Shin, S. *Org. Biomol. Chem.* **2009**, *7*, 4744–4752. (g) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040–7043. (h) Yeom, H.-S.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J.-E.; Lee; Shim, S.; Shin, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1611–1614. (i) Davies, P. W.; Albrecht, S. J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 8372–8375. (j) Li, C. W.; Lin, G. Y.; Liu, R. S. *Chem. Eur. J.* **2010**, *16*, 5803–5811. (k) Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059–5062. (l) Hashmi, A. S. K.; Buehrle, M.; Salathe, R.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 2059–2064.
- (8) (a) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259. (b) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550–8551.
- (9) (a) Ye, L.; Zhang, L. *Org. Lett.* **2009**, *11*, 3646–3649. (b) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147–2150. (c) Yu, M.; Li, G.; Wang, S.; Zhang, L. *Adv. Synth. Catal.* **2007**, *349*, 871–875. (d) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029. (e) Marion, N.; Carlqvist, P.; Gealageas, R.; de Fremont, P.; Maseras, F.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 6437–6451. (f) Wang, D.; Ye, X.; Shi, X. *Org. Lett.* **2010**, *12*, 2088–2091.
- (10) Malik, H. A.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2010**, *132*, 6304–6305.
- (11) (a) Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4163–4166. (b) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908–2910.
- (12) For the results with other *N*-oxides in the absence of acid, see the Supporting Information.
- (13) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry. Part A: Structure and Mechanisms*, 5th ed.; Springer: New York, 2007; p 88.
- (14) 1,2-Diketones were formed as the regioisomer. This overoxidation is due to the lack of α -hydrogens and thus the 1,2-C–H insertion pathway.
- (15) Hashmi, A.; Rudolph, M.; Huck, J.; Frey, W.; Bats, J.; Hamzić, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5848–5852.
- (16) (a) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417–6422. (b) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500–7506. (c) Wang, Q.; Chen, C. *Tetrahedron Lett.* **2008**, *49*, 2916–2921.

JA1072614