Title

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Gold-Catalyzed Oxidation of Propargylic Ethers with Internal C-C Triple Bonds: Impressive Regioselectivity Enabled by Inductive Effect

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Abstract

Inductive perturbations of C-C triple bonds are shown to dictate the regiochemistry of gold-catalyzed oxidation of internal C-C triple bonds in the cases of propargylic ethers, resulting in highly regioselective formation of β-alkoxy-α,β-unsaturated ketones (up to >50/1 selectivity) via α-oxo gold carbene intermediates. Ethers derived from primary propargylic alcohols can be reliably transformed in good yields, and various functional groups are tolerated. With substrates derived from secondary propargylic alcohols, the development of a new *P*,*N*-bidentate ligand enables the minimization of competing alkyl group migration to the gold carbene center over the desired hydride migration; the preferred migration of a phenyl group, however, results in efficient formation of a α-phenyl-β-alkoxy-α,β-unsaturated ketone. These results further advance the surrogacy of a propargyl moiety to synthetically versatile enone function with reliable and readily predictable regioselectivity.

Keywords

Gold; Oxidation; Enone; Inductive effect; Regioselectivity

1. Introduction

α,β-Unsaturated ketones (hereafter called enone) are essential substrates for organic synthesis due to their versatile reactivities. In a multi-step synthesis, however, the enone moiety, as it is prone to react with a wide range of reducing, oxidizing, and nucleophilic reagents, can often be problematic if carried over multi-step synthetic sequences. An ideal solution would be to have it masked as a relatively unreactive moiety and reveal it reliably and predictably when needed.

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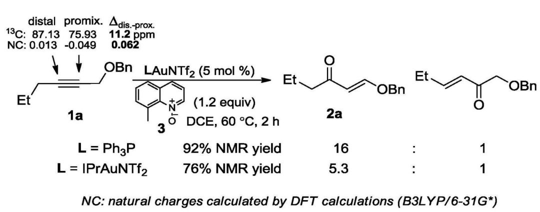
Appendix A. Supplementary data
Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.201xxxxx.

We [1] have previously showed that via gold-catalyzed [2] intermolecular oxidation [3] of internal alkynes a propargyl moiety can be converted into an enone moiety under exceptionally mild reaction conditions, thereby providing a solution for masking synthetically versatile enones. [1e] Scheme 1 shows a generic reaction with the proposed mechanism outlined. Hence, a gold-activated alkyne is initially attacked by a pyridine/quinoline *N*-oxide, which is a mild nucleophilic oxidant; driven by the weak O-N bond, the nascent alkenylgold intermediate **A** undergoes fragmentation, generating the α-oxo gold carbene **B**; this metal carbene is highly reactive and rapidly transformed into the enone **2** via a hydride migration/elimination sequence. A vital issue for the practicality of this strategy is controlling the regioselectivity in the generation of **B** or its regioisomer **B'**, which in general is challenging for intermolecular reactions [4] of internal alkynes [5] lack of direct electronic perturbation. [1e, 6] In our initial study,[1e] we reported that both steric differences between the groups at the opposite ends of the C-C triple bond and electronic delocalization (conjugation) found in arylalkynes and enynes permit predictable and often synthetically desirable regioselectivities. We also exploited the inductive effect [7] as it could polarize the C-C triple bond toward regioselective nucleophilic attack. [8] Indeed, propargylic carboxylates undergo highly regioselective alkyne oxidation, consistent with the inductive polarization of the alkynes by strongly electron-withdrawing carboxy groups (e.g., Scheme 2). [1k] Notably in this reaction, carboxy groups migrate preferentially over hydrogen to the carbene center, yielding α-acyloxyenone products. The same phenomenon is observed with propargylic carbonates.[3p]

To further exploit the inductive effect of other functional groups in facilitating regioselective gold-catalyzed oxidation of alkynes, we examined propargylic ethers, [9] which possess less electron-withdrawing alkoxy groups. Herein, we report that high regioselectivities could be achieved with this class of substrates, resulting in efficient formation of β-alkoxyenone products, which are synthetically versatile and can serve as precursor to the Danishefsky's diene [10] and its congeners, [11] functionalized tetrahydropyrans, [12] and enynones. [13]

2. Results and discussion

At the outset, we subjected the propargyl benzyl ether **1a** to the gold-catalyzed oxidation (Eq. 1). Much to our delight, an excellent regioselectivity (16/1) was observed by using 8-methylquinoline *N*-oxide (**3**) [1e] as the oxidant and $Ph_3PAuNTf_2$ [14] as the gold catalyst. Moreover, the β-benzyloxyenone **2a** was formed in 92% NMR yield. This outstanding selectivity can be rationalized by inductive polarization of the C-C triple bond by the electronegative ethereal oxygen. Since natural charges (NC) obtained via natural population analysis [15] have been



(1)

shown to correlate well with properties such as pK_a [16] and 13C NMR, [17] we calculated the natural charges at the sp-hybridized carbons using Density Functional Theory (B3LYP/6-31G*, Spartan06). The NC is 0.013 for the distal carbon and −0.049 for the proximal carbon to the oxygen atom, revealing that the distal alkyne end is more electron-deficient. These data are consistent with their ^{13}C NMR shifts and can explain the observed regioselectivity. Notably, a recently published Pt-catalyzed hydrosilylation on a similar substrate showed only a 3.2:1 regioselectivity. [8d] This unexpectedly high selectivity is attributed to the augmentation of the electronic bias of the C-C triple bond by the gold activation. Indeed, when IPrAuNTf$_2$, a less Lewis acidic catalyst, was used, the selectivity decreased substantially.

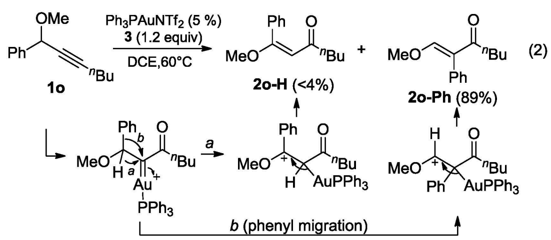
The scope of this gold-catalyzed oxidation was then probed. First, we examined the substrates with no propargylic substitution. As shown in Table 1, besides the benzyl group, other ethereal protecting groups such as Me (**1b**), MOM (**1c**), and TIPS (**1d**) were readily allowed, and the reactions all proceeded with good yields and excellent regioselectivities. With the sterically biased methyl ether **1e**, the electronic bias easily overrode the opposing steric preference, [1e] when bulky Me$_4$*t*BuXPhosAuNTf$_2$ [1g] was used. An even higher selectivity was observed with the phenyl ether **1f**, consistent with the fact that phenoxy as a group is more electron-withdrawing than methoxyl. The use of bulky Me$_4$*t*BuXPhosAuNTf$_2$ enhanced the regioselectivities in both cases of **1e** and **1f** as Ph$_3$PAuNTf$_2$ rendered ratios of **2**/**2'** as 5.3/1 and 20/1, respectively. This ligand effect can be attributed to the preference of a bulkier gold complex residing at the less hindered alkyne end, thereby augmenting the desired regioselectivity. As the inductive effect is inversely correlated to distance, the regio preference with the bisether **1g** and the ethereal acetate **1h** were expected; however, the high selectivities observed in both cases were pleasingly surprising. Interestingly, the 1,6-enyne substrate **1i** did not undergo the typically facile enyne cycloisomerization; [2c, 2e, 18] instead, the oxidation proceeded smoothly, affording the allyl vinyl ether **2i** in 80% yield.

For the methyl ether **1j** with a Me group substituted at the propargylic position (Scheme 3), the steric bias and the inductive effect worked in sync, and the gold-catalyzed oxidation exhibited expectedly excellent regioselectivities (>25). However, the gold carbene intermediate apparently, upon generation, underwent competing 1,2-H and 1,2-Me migrations, leading to the formation of **2j-H** and **2j-Me**, respectively. When Ph$_3$PAuNTf$_2$ was the catalyst, **2j-Me** was formed in 50% yield. By using the much bulkier ^{t}BuXPhos as the ligand, the desired **2l-H** became the major product, although the migration selectivity was still poor.

We have recently reported that gold complexes with P, N/P,S bidentate ligands such as Mor-DalPhos[19] can stabilize carbene and make it less electrophilic via the formation of tri-coordinated structures. [1i-k] We reasoned that such a gold carbene intermediate (i.e., **C**, Scheme 3) would be less reactive and hence more selective in the formation of **2j-H** or **2j-Me**. To our delight, when Mor-DalPhosAuNTf$_2$ was used, the reaction was highly selective toward the 1,2-H migration, affording **2j-H** was in 71% yield. The selectivity over the methyl migration was >30. The reaction yield was improved by the use of pyrrolidine-containing ligand **L1**. This new ligand can be readily prepared following the known preparative procedure for Mor-DalPhos, [19a] and should find broad application in gold carbene chemistry.

With **L1**$AuNTf_2$ as the catalyst, the reaction scope was briefly examined. As shown in Table 2, the R group can be a sterically more demanding isopropyl group (entry 1) or even a *t*-butyl group (entry 2), the substrate can be an allyl ether (entry 3), and the R'' can be a cyclohexyl group. All the reactions proceeded with acceptable efficiencies and showed excellent regioselectivities and group migration selectivities. The products, however, are mixtures of double bond geometric isomers, the ratios of which appear to be dictated by both sterics and dipole-dipole repulsion.

The hydride migration by a gold carbene of type **B**, however, becomes the minor process when in competition with a phenyl group. As shown in Eq. 2, α-phenyl-β-methoxyenone **2o-Ph** was formed selectively in 89% yield, while the hydride migration product **2o-H** was negligible. Notably, this method can serve as a useful approach to α-aryl-β-alkoxy-α,β-unsaturated ketones.



3. Conclusions

In summary, we have examined inductive effects in controlling the regioselectivities of gold catalyzed oxidation of propargylic ethers. Though often considered minor or ignored, the electronic perturbations of the C-C triple bond by α-alkoxy groups are capable of imparting surprisingly excellent regioselectivities, with ratios typically ranging from 10 to >50. The broad scope with general tolerance of functional groups and good efficiency of this oxidative gold catalysis make readily accessible propargyl ethers as reliably masked β-alkoxy-α,β-unsaturated ketones. This new way of functional group transformation provides a valuable retrosynthetic tool for synthetic design, especially considering the synthetic versatility of this enone moiety.

4. Experiment section

Gold-catalyzed oxidation of propargyl ethers to β-alkoxy/aryloxy-α,β-unsaturated ketones

8-methylquinoline-*N*-oxide (0.36 mmol, 1.2 eq) and $LAuNTf_2$ (11 mg, 0.015 mmol, 5 mol %) were added in this order to a solution of the propargyl ethers **1** (0.3 mmol) in DCE (6 mL) at room temperature. The resulting reaction mixture was stirred at the indicated temperature until the substrate was completely consumed. The reaction mixture was concentrated under vacuum. The residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired β-alkoxy/aryloxy-α,β-unsaturated ketones **2**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

[1]. a) Ye L, He W, Zhang L. J. Am. Chem. Soc. 2010; 132:8550–8551. For our own work, see: [PubMed: 20521793] b) Ye L, Cui L, Zhang G, Zhang L. J. Am. Chem. Soc. 2010; 132:3258–3259. [PubMed: 20166668] c) He W, Li C, Zhang L. J. Am. Chem. Soc. 2011:8485–8485.d) Ye L, He W, Zhang L. Angew. Chem., Int. Ed. 2011; 50:3236–3239.e) Lu B, Li C, Zhang L. J. Am. Chem. Soc. 2010; 132:14070–14072. [PubMed: 20853846] f) Li Z, Brouwer C, He C. Chem. Rev. 2008; 108:3239–3265. [PubMed: 18613729] g) Wang Y, Ji K, Lan S, Zhang L. Angew. Chem., Int. Ed. 2012; 51:1915–1918.h) He W, Xie L, Xu Y, Xiang J, Zhang L. Org. Biomol. Chem. 2012; 10:3168–3171. [PubMed: 22419033] i) Luo Y, Ji K, Li Y, Zhang L. J. Am. Chem. Soc. 2012; 134:17412–17415. [PubMed: 23039251] j) Ji K, Zhao Y, Zhang L. Angew. Chem., Int. Ed. 2013; 52:6508–6512.k) Ji K, Nelson J, Zhang L. Beilstein Journal of Organic Chemistry. 2013; 9:1925–1930. [PubMed: 24204402] l) Li J, Ji K, Zheng R, Nelson J, Zhang L. Chem. Commun. 2014; 50:4130–4133.m) Zhang L. Acc. Chem. Res. 2014; 47:877–888. [PubMed: 24428596] n) Wu G, Zheng R, Nelson J, Zhang L. Adv. Synth. Catal. 2014; 356:1229–1234.o) Ji K, Zhang L. Org. Chem. Front. 2014; 1:34–38.

[2]. a) Fürstner A, Davies PW. Angew. Chem., Int. Ed. 2007; 46:3410–3449. For selected reviews on gold catalysis, see: b) Hashmi ASK. Chem. Rev. 2007; 107:3180–3211. [PubMed: 17580975] c) Zhang L, Sun J, Kozmin SA. Adv. Synth. Catal. 2006; 348:2271–2296.d) Arcadi A. Chem. Rev. 2008; 108:3266–3325. [PubMed: 18651778] e) Jiménez-Núñez E, Echavarren AM. Chem. Rev. 2008; 108:3326–3350. [PubMed: 18636778] f) Gorin DJ, Sherry BD, Toste FD. Chem. Rev. 2008; 108:3351–3378. [PubMed: 18652511] g) Abu Sohel SM, Liu R-S. Chem. Soc. Rev. 2009; 38:2269–2281. [PubMed: 19623349] h) Sengupta S, Shi X. Chemcatchem. 2010; 2:609–619.i) Wang S, Zhang G, Zhang L. Synlett. 2010:706–706.j) Rudolph M, Hashmi ASK. Chem. Soc. Rev. 2012; 41:2448–2462. [PubMed: 22182942]

[3]. a) Li C-W, Pati K, Lin G-Y, Sohel SMA, Hung H-H, Liu R-S. Angew. Chem., Int. Ed. 2010; 49:9891–9894. For selected work by other researchers, see: b) Wang T, Zhang JL. Dalton Trans. 2010; 39:4270–4273. [PubMed: 20379602] c) Xu C-F, Xu M, Jia Y-X, Li C-Y. Org. Lett. 2011; 13:1556–1559. [PubMed: 21332143] d) Qian D, Zhang J. Chem. Commun. 2011; 47:11152–11154.e) Vasu D, Hung H-H, Bhunia S, Gawade SA, Das A, Liu R-S. Angew. Chem., Int. Ed. 2011:6914–6914.f) Davies PW, Cremonesi A, Martin N. Chem. Commun. 2011; 47:379–381.g) Bhunia S, Ghorpade S, Huple DB, Liu R-S. Angew. Chem., Int. Ed. 2012:2942–2942.h) Yuan W, Dong X, Wei Y, Shi M. Chem. Eur. J. 2012; 18:10501–10505. [PubMed: 22807410] i) Xu M, Ren T-T, Li C-Y. Org. Lett. 2012; 14:4902–4905. [PubMed: 22954390] j) Murai M, Kitabata S, Okamoto K, Ohe K. Chem. Commun. 2012; 48:7622–7624.k) Qian D, Zhang J. Chem. Commun. 2012; 48:7082–7084.l) Dateer RB, Pati K, Liu R-S. Chem. Commun. 2012; 48:7200–7202.m) Wang L, Xie X, Liu Y. Angew. Chem., Int. Ed. 2013; 52:13302–13306.n) Nösel P, dos Santos Comprido LN, Lauterbach T, Rudolph M, Rominger F, Hashmi ASK. J. Am. Chem. Soc. 2013; 135:15662–15666. [PubMed: 24050384] o) Henrion G, Chavas TEJ, Le Goff X, Gagosz F. Angew. Chem., Int. Ed. 2013; 52:6277–6282.p) Sun, N.; Chen, M.; Liu, Y. 2014.

[4]. a) Miller KM, Jamison TF. J. Am. Chem. Soc. 2004; 126:15342–15343. For examples of intramolecular control of regioselectivity, see: [PubMed: 15563136] b) Bahadoor AB, Flyer A, Micalizio GC. J. Am. Chem. Soc. 2005; 127:3694–3695. [PubMed: 15771493]

[5]. Malik HA, Sormunen GJ, Montgomery J. J. Am. Chem. Soc. 2010; 132:6304–6305. For a case of ligand-controlled regiodivergent reaction, see: [PubMed: 20394367]

[6]. a) Engel DA, Dudley GB. Org. Lett. 2006; 8:4027–4029. For selected examples of gold catalysis using electronically directly poloarized internal alkynes, see: [PubMed: 16928065] b) Hashmi A, Rudolph M, Huck J, Frey W, Bats J, Hamzić M. Angew. Chem., Int. Ed. 2009; 48:5848–5852.c) Zhang G, Zhang L. J. Am. Chem. Soc. 2008; 130:12598–12599. [PubMed: 18754587]

[7]. Wang Y, Liu L, Zhang L. Chem. Sci. 2013; 4:739–746.

[8]. a) Matsumoto H, Hoshino Y, Nagai Y. Chem. Lett. 1982:1666–1666. For selected examples, see: b) Tsipis CA. J. Organometallic Chem. 1980; 187:427–446.c) Rubin M, Trofimov A, Gevorgyan V. J. Am. Chem. Soc. 2005; 127:10243–10249. [PubMed: 16028935] d) Rooke DA, Ferreira EM. Angew. Chem., Int. Ed. 2012:3230–3230.

[9]. Hashmi ASK, Wang T, Shi S, Rudolph M. J. Org. Chem. 2012:7761–7767. A study on tertiary propargylic alcohol was reported by Hashmi. The regioselectivity, albeit not rationalized, is likely controlled synergistically by steric and induction. For reference, see: [PubMed: 22877083]

[10]. Danishefsky S, Kitahara T. J. Am. Chem. Soc. 1974; 96:7807–7808.

[11]. a) Danishefsky S, Yan C-F, Singh RK, Gammill RB, McCurry PM, Fritsch N, Clardy J. J. Am. Chem. Soc. 1979; 101:7001–7008. For selected examples, see: b) Kusama H, Karibe Y, Imai R, Onizawa Y, Yamabe H, Iwasawa N. Chem. Eur. J. 2011; 17:4839–4848. [PubMed: 21425366]

[12]. Kozmin SA. Org. Lett. 2001; 3:755–758. [PubMed: 11259054]

[13]. Negishi, E-I.; Idacavage, MJ. Formation of Carbon-Carbon and Carbon-Heteroatom Bonds via Organoboranes and Organoborates. John Wiley & Sons, Inc.; 2004. p. 1-246.in: Organic Reactions

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

[15]. Reed AE, Weinstock RB, Weinhold F. J. Chem. Phys. 1985; 83:735–746.

[16]. Gross KC, Seybold PG, Hadad CM. Int. J. Quant. Chem. 2002; 90:445–458.

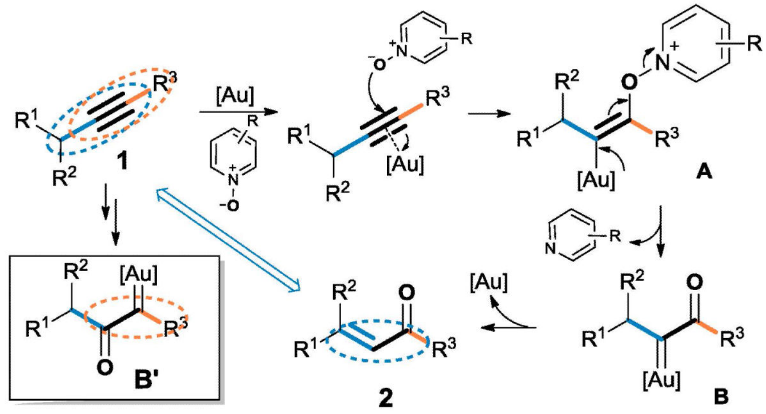
[17]. Levy JB. Struct. Chem. 1999; 10:121–127.

[18]. Echavarren AM, Nevado C. Chem. Soc. Rev. 2004; 33:431–436. For selected reviews, see: [PubMed: 15354224]

[19]. a) Lundgren RJ, Peters BD, Alsabeh PG, Stradiotto M. Angew. Chem., Int. Ed. 2010; 49:4071–4074.b) Hesp KD, Stradiotto M. J. Am. Chem. Soc. 2010; 132:18026–18029. [PubMed: 21133383]

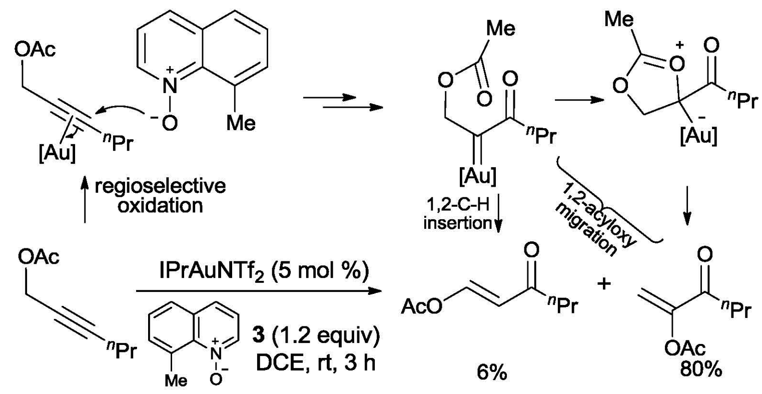
Highlights

- Inductive perturbation of C-C triple bond permits its regioselective oxidation.
- Regioselectivities up to >50/1 are achieved.
- Propargylic ethers are converted into β-alkoxy-enones reliably in good yields.
- A new *P*,*N*-bidentate ligand enables selective hydride migration.

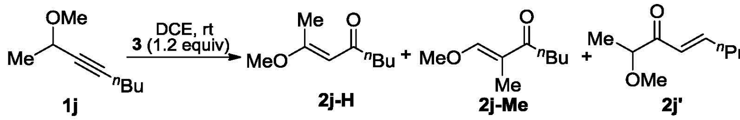


Scheme 1.

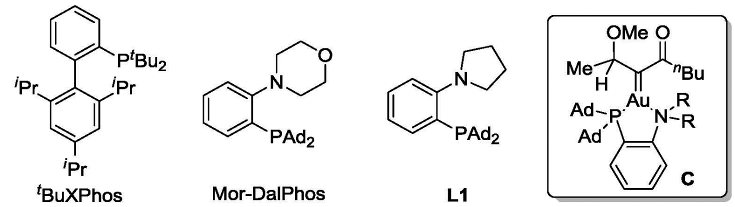
Using propargyl moieties as masked enones.



Scheme 2.
Au-catalyzed regioselective oxidation of propargylic carboxylates.



Catalyst	2j-H	2j-Me	2j'
$Ph_3PAuNTf_2$ (5 mol %)	30%	50%	<3%
(^{t}BuXPhos)$AuNTf_2$ (5 mol %)	53%	29%	4%
(Mor-DalPhos)$AuNTf_2$ (5 mol %)	71%	2%	<2%
L_1AuNTf_2 (5 mol %)	82%	2%	<3%



Scheme 3.

Ligand optimization for highly selective hydride migration.

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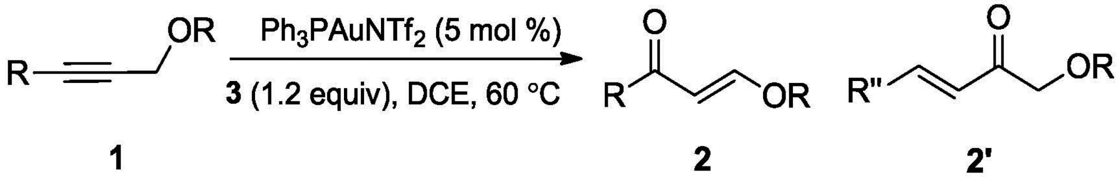
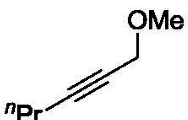
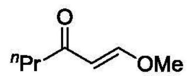
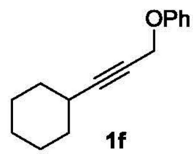
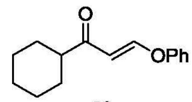
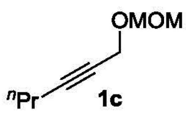
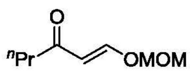
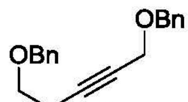
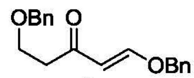
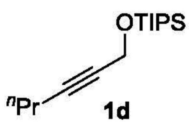
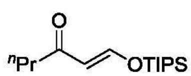
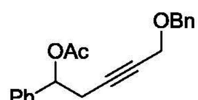
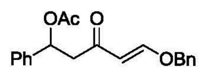
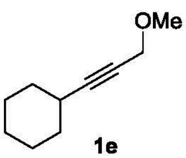
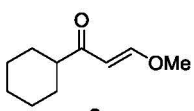
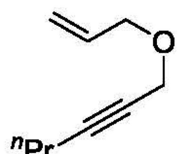
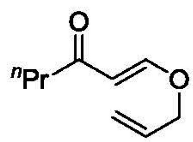
Table 1

Highly regioselective gold-catalyzed oxidation of propargyl ethers: access to *β*-alkoxy/aryloxy-*α*,*β*-unsaturated ketones.[a].



1	2	yield/ 2/2’	1	2	yield/ 2/2’
 **1b**	 **2b**	86% >50	 **1f**	 **2f**	81% >35[b],[d]
 **1c**	 **2c**	86% >18	 **1g**	 **2g**	79% 15
 **1d**	 **2d**	81% >19	 **1h**	 **2h**	72% 10[b],[d]
 **1e**	 **2e**	83% >15[b],[c]	 **1i**	 **2i**	80% 16

[a][**1**] = 0.05 M; isolated yields shown.

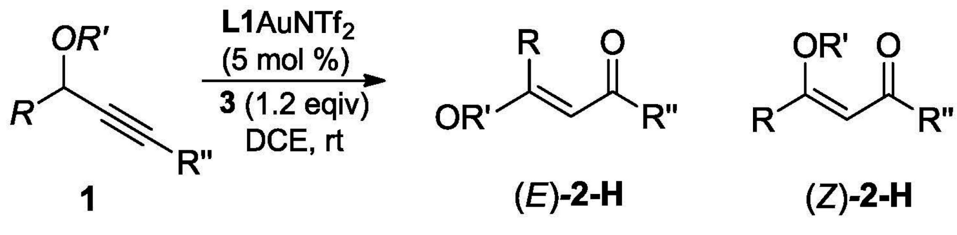
[b]$Me_4{}^tBuXPhosAuNTf_2$ was used as the catalyst.

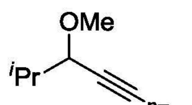
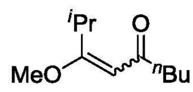
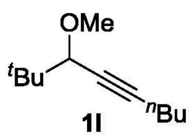
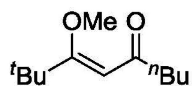
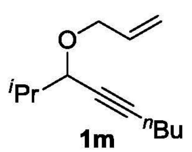
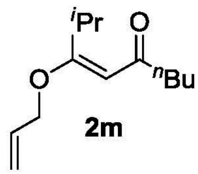
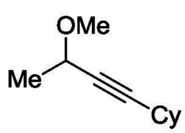
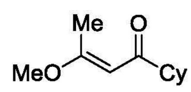
[c]**2/2’** = 5.3/1 with $Ph_3PAuNTf_2$ as the catalyst.

[d]**2/2’** = 20/1 with $Ph_3PAuNTf_2$ as the catalyst.

Table 2

Gold-catalyzed oxidation of ethers of secondary propargyl alcohols: excellent regioselectivities.[a]



entry	1	2	Yield[b]	E/Z[c]
1	 **1k**	 **2k**	74%	7:1
2	 **1l**	 **2l**	67%	1:4
3	 **1m**	 **2m**	70%	2:1
4	 **1n**	 **2n**	70%	10:1

[a][1] = 0.05 M;

[b]The combined Isolated yield of **2-H** shown. The yields of the R migration product or the oxidative regioisomer was <2%.

[c]Ratio determined by ^{1}H NMR.