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Au(I)-catalyzed intramolecular oxidative cyclopropanation of 1,6-enynes derived from propiolamides with diphenyl sulfoxide†

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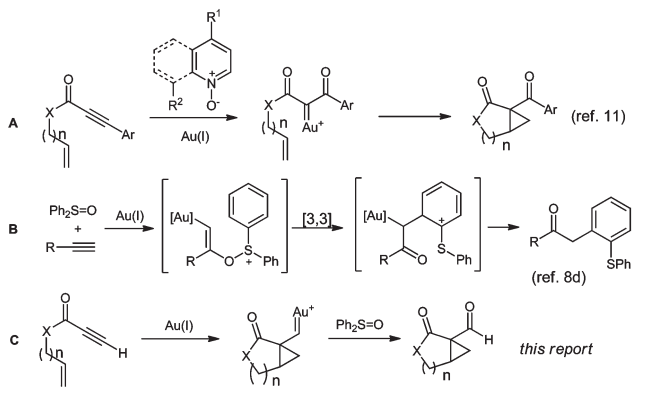
We have developed gold(I)-catalyzed oxidative cyclopropanation of 1,6-enynes derived from propiolamides employing diphenyl sulfoxide as an oxidant. 1,6-Enynes having a terminal alkyne and a propiolamide tether efficiently transformed into cyclopropane carboxaldehyde derivatives.

Cyclopropane rings are highly strained but nonetheless frequently found in a wide range of natural products, such as terpenes, fatty acid metabolites and amino acids, as well as medicinal agents.[1] Due to the inherent ring strain, they also serve as useful synthons for diverse organic reactions.[2] Therefore, there has been a large amount of effort toward efficient synthesis of the cyclopropane unit. Traditional approaches employing Simmons–Smith reagent ($RZnCH_2I$)[3] or sulfonium (sulfoxonium or phosphonium) ylides,[4] although effective, have poor atom-economy and involve highly basic conditions. Metal catalyzed decomposition of diazoacetates has been known to generate metal carbenoids that form cyclopropanes in the presence of olefins.[5] However, the use and preparation of non-stabilized diazo compounds involve explosion hazards, thus limiting their widespread applications. Therefore, much attention has been paid to the diazo-free access to metal carbenoids in the past decades.[6]

Recently, we have introduced a new method of generating α-oxo gold carbenoid synthons by oxidation of alkynes with nitrones and hydroxylamines (N–O bond oxidants),[7] based on the seminal reports by Toste and coworkers employing sulfoxides.[8] Since then, Zhang and coworkers have introduced pyridine-*N*-oxides as intermolecular oxidants.[9] This method provides for a convenient and benign route to α-oxo gold carbenoids and diverse transformations have been realized, including X–H (X = O, N) insertion,[10a] ylide formation/cycloaddition,[10b] C–H insertion[10c] and 1,2-alkyl (or H) shift.[10d]

In 2011, Zhang and coworkers reported cyclopropanation of 1,6-enyne scaffolds employing Au(I) catalyst and pyridine-*N*-oxides (quinolone-*N*-oxides) as oxidants (Scheme 1A).[11,12] They proposed that the alkyne is initially oxidized by pyridine-*N*-oxides to form an α-oxo gold carbenoid followed by cyclopropanation with the pendant olefin. Replacing pyridine-*N*-oxides with $Ph_2S{=}O$ in this case turned out to be ineffective, presumably because $Ph_2S{=}O$ is a weaker oxidant and/or the S–O cleaving redox process is known to occur through concerted 3,3-sigmatropic rearrangement to produce α-arylated carbonyl compounds, as supported by DFT computational study (Scheme 1B).[8d,e] Furthermore, neither the Pd(II) catalyzed cyclopropanation with $PhI(OAc)_2$[12] nor the Au(I) catalyzed oxidative cyclopropanation by pyridine-*N*-oxides[11] could accommodate terminal alkyne substrates (*vide infra*, eqn (1)). In contrast to these precedents, we have found that the corresponding *terminal* alkyne substrates underwent efficient oxidative cyclopropanation with $Ph_2S{=}O$ oxidants (Scheme 1C) and details of this study are presented herein.[13]

We recently reported that acceptor-polarized alkynes are highly efficient substrates for intermolecular coupling reactions with alkenes.[14] To further probe the effect of acceptor-substituents on alkynes, we examined the intramolecular



Scheme 1 Intramolecular oxidative cyclopropanation.

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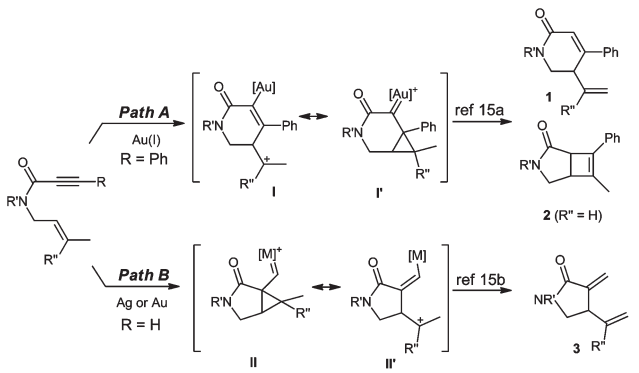


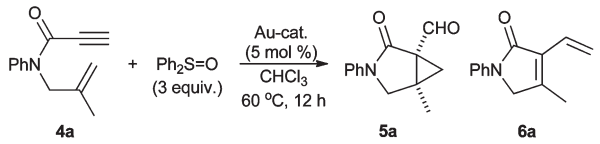
Scheme 2 6-*endo*-dig or 5-*exo*-dig cyclization.

reaction of 1,6-enynes having propiolamide tether.[15] Chung and coworkers proposed that the cyclization of propiolamide-derived 1,6-enynes proceeds with 6-*endo*-dig pathway to form **1** and **2** (σ-bond reorganization) based on the experimental and computational study (Path A, Scheme 2).[15a] In contrast, we have found that the reaction of terminal alkyne substrates predominantly proceed through 5-*exo*-dig pathway leading to an Alder-ene type cycloisomerization **3** either with Ag(I) or Au(I) catalyst (Path B, Scheme 2).[15b] Along this line, we projected that trapping the intermediates **II** with $Ph_2S{=}O$ might lead to oxidative intramolecular cyclopropanation.

Our study commenced with the *N*-methallyl substrate **4a** employing various Au(I) catalysts and 3 equiv. of Ph_2SO in chloroform (0.1 M) at 60 °C (Table 1). Gratifyingly, we were able to isolate oxidative cyclopropanation product **5a** along with a small amount of enyne metathesis product **6a**. The efficiency as well as the selectivity toward **5a** was affected tremendously by the catalyst used. Buchwald ligands having *ortho*-biphenyl group generally performed better than NHC ligands, while $P(C_6F_5)_3$ or ligandless $AuCl_3$ were not effective at all (entries 1–10). From the screening of counter-anion, NTf_2 anion was proved optimal for cationic Au(**L3**) complex (entries 11–15).

The selectivity between **5a** and **6a** was also highly dependent on the solvent used: 1,4-dioxane tends to give more metathesis product **6a** and the use of 1,2-dichloroethane predominantly gave oxidative cyclopropanation product **5a**, further improving the yield to 64% in 2 h (entries 2 and 5, Table 2). A decrease in the amount of $Ph_2S{=}O$ to 2 equivalent did not affect the reaction much (entry 11), but the reactions run at lower temperature took much longer time (entries 12–13). We also examined other oxidants (pyridine-*N*-oxide derivatives, DMSO, *m*CPBA, H_2O_2, *t*BuOOH, oxone and air): while DMSO (80 °C/24 h, 34% of **5a**), H_2O_2 (60 °C/9 h, 35% of **5a**), *t*BuOOH (60 °C/3 h, 17% of **5a**) were somewhat inferior, *m*CPBA (epoxidation as a side reaction), oxone and air were completely inactive as oxidants. Importantly, 2-bromo pyridine-*N*-oxide was incompatible with the terminal alkyne substrate **4a** and predominantly gave conjugate addition adduct

Table 1 Optimization of ligands and counter-anions[a]



Entry	Catalyst[b]	5a	6a	SM(4a)
1	$Au(PPh_3)SbF_6$	—	—	84%
2	[Au(**L1**)]SbF_6	52%	15%	—
3	[Au(**L2**)]SbF_6	10%	12%	64%
4	[Au(**L3**)]SbF_6	54%	16%	—
5	[Au(**L4**)]SbF_6	17%	16%	76%
6	[Au(**L5**)]SbF_6	53%	22%	—
7	[Au(IMes)]SbF_6	—	—	95%
8	[Au(IPr)]SbF_6	10%		26%
9	$[AuP(C_6F_5)_3]SbF_6$	—	—	90%
10	$AuCl_3$	—	—	65%
11	[Au(**L3**)]OTf	23%	22%	—
12	[Au(**L3**)]NTf_2	57%	17%	—
13	[Au(**L3**)]BF_4	33%	29%	—
14	[Au(**L3**)]ClO_4	3%	—	91%
15	[Au(**L3**)]OTs	—	—	>97%

[a] [Au(L)]X catalyst was generated *in situ* from an equimolar mixture of Au(L)Cl (5 mol%) and AgX (5 mol%); the yields of **4a–6a** are crude yields based on ^{1}H NMR spectra (1,3,5-tri-MeO-C_6H_3 as an internal standard); the remaining mass balance was unselective decomposition. [b] See below for ligand structures.

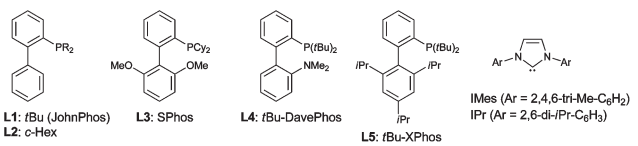
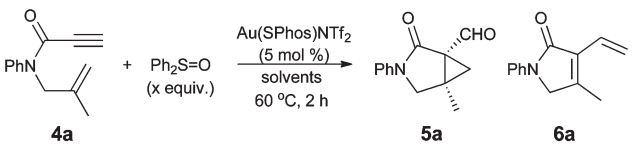


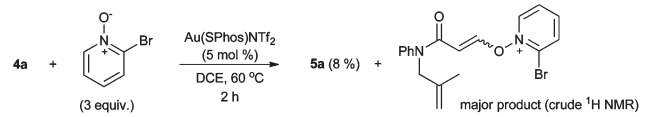
Table 2 Optimization of solvents and the amount of Ph_2SO[a]



Entry	Solvent	*x* equiv.	5a	6a	SM (4a)
1	CH_2Cl_2	3	38%	8%	48%
2	1,2-DCE	3	64%	10%	—
3	CH_3CN	3	5%	—	93%
4	CH_3NO_2	3	51%	14%	—
5	1,4-Dioxane	3	30%	43%	—
6	Toluene	3	50%	11%	—
7	DME	3	38%	13%	35%
8	DMF	3	—	—	>97%
9	1,2-DCE	1	37%	11%	27%
10	1,2-DCE	1.5	45%	11%	15%
11	1,2-DCE	2	59%	13%	—
12	1,2-DCE	2[b]	50%	6%	—
13	1,2-DCE	2[c]	12%	—	62%

[a] [Au(SPhos)]NTf_2 catalyst was generated *in situ*; the yields of **4a–6a** are crude yields based on ^{1}H NMR spectra (1,3,5-tri-MeO-C_6H_3 as an internal standard); the remaining mass balance was unselective decomposition. [b] 24 h at 40 °C. [c] 72 h at rt.

(crude ^{1}H NMR) along with only a small amount of **5a** (8%) (eqn (1)).



(1)

Employing the above optimized conditions (Au(SPhos)NTf_2 (5 mol%) and $Ph_2S{=}O$ (2 equiv.) in 1,2-DCE at 60 °C), we next investigated the scope of this transformation as in Table 3. Except for a few cases where a small amount of competitive formation of metathesis product **6** (entries 1 and 3) is seen, most 1,6-enynes with a terminal alkyne provided oxidative cyclopropanation products **5** as the major respective products. A notable feature of this transformation is that diverse substitutions on the allyl unit could be accommodated. For example, methallyl (entries 1, 2, 7 and 8), allyl (entries 3 and 6), crotyl (entry 4) and cinnamyl (entry 9) substrates all provided the corresponding **5**'s as exclusive products. Of particular relevance is substrate **4e** with electron-rich tri-substituted olefin, since this substrate was known to undergo Alder-ene type cycloisomerization leading to **7e** exclusively both under Au(I) or Ag(I) catalysis.[15b,16] Intriguingly, **4e** afforded predominant formation of **5e** (55%) under the current optimized conditions, along with only a small amount of **7e** (17%). Thus, the examples in Table 3 exemplify the excellent generality, especially considering that the reaction manifolds of 1,6-enyne cycloisomerization depend highly on the subtle structural variations on the allyl unit.[16]

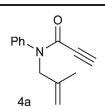
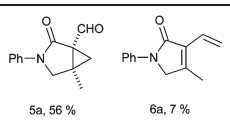
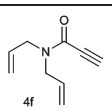
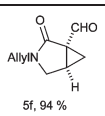
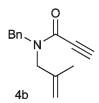
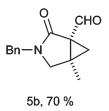
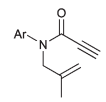
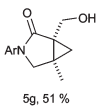
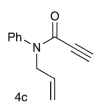
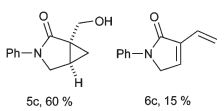
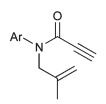
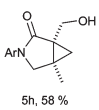
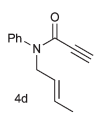
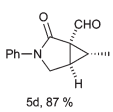
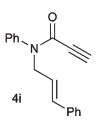
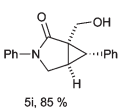
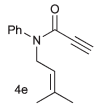
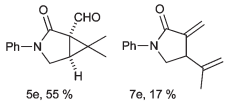
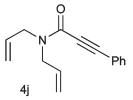
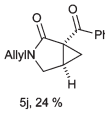
Finally, for the aryl substituted enyne **4j**, the efficiency toward oxidative cyclopropanation **5j** was significantly diminished, in contrast to the reactions with pyridine-*N*-oxide derivatives.[11]

Based on the regioselectivity of propiolamide-derived 1,6-enynes in the cyclization by Au(I) catalysts (Scheme 2), a plausible mechanism of the gold-catalyzed oxidative cyclopropanation may involve initial formation of cyclopropyl gold carbenoid **II**/**II′** (Path B, Scheme 2) followed by rapid trapping of the resulting highly reactive carbenoid by sulfoxides.[8g–i] In the alternative scenario, **4** could evolve through initial oxidation of the alkyne to form gold carbenoids (Scheme 1A) followed by intramolecular cyclopropanation. The latter possibility seems less likely for Ph_2SO mediated oxidation, considering that the sulfoxide redox tends to occur through a 3,3-sigmatropic rearrangement pathway to afford α-aryl carbonyl compounds rather than through a gold carbenoid.

In summary, we have developed intramolecular oxidative cyclopropanation of 1,6-enynes having propiolamide tethers. Substrates with terminal alkyne were first employed in the oxidative cyclopropanation to afford cyclopropane carboxaldehydes that would have distinct applications due to aldehyde functionality.[11,12] For this type of substrate, diphenyl sulfoxide, rather than pyridine-*N*-oxides, performed as an excellent oxidant and thus a wide generality in terms of alkenes has been demonstrated.

We thank the National Research Foundation of Korea (NRF-2011-0023686 and NRF-2012-015662) and also nano material technology development program (NRF-2012M3A7B4049653) for support.

Table 3 The scope of oxidative cyclopropanation[a]

Entry	Substrate	Product[b]	Entry	Substrate	Product[b]
1	 4a	 5a, 56 % 6a, 7 %	6	 4f	 5f, 94 %
2	 4b	 5b, 70 %	7[c]	 4g, Ar = 4-MeO-C_6H_4	 5g, 51 %
3[c]	 4c	 5c, 60 % 6c, 15 %	8[c]	 4h, Ar = 4-F-C_6H_4	 5h, 58 %
4	 4d	 5d, 87 %	9[c]	 4i	 5i, 85 %
5	 4e	 5e, 55 % 7e, 17 %	10	 4j	 5j, 24 %

[a] [Au(SPhos)]Cl (5 mol%) and $AgNTf_2$ (5 mol%) were mixed in 1,2-dichloroethane followed by addition of substrate **4** (0.1 M in DCE) and 2 equiv. of $Ph_2S{=}O$; the reaction mixture was stirred at 60 °C for 2–8 h. [b] Isolated yields after chromatographic separation. [c] The products were inseparable with excess $Ph_2S{=}O$; in this case, the crude reaction mixture was treated with 2 equiv. of $NaBH_4$ in MeOH before isolation.

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