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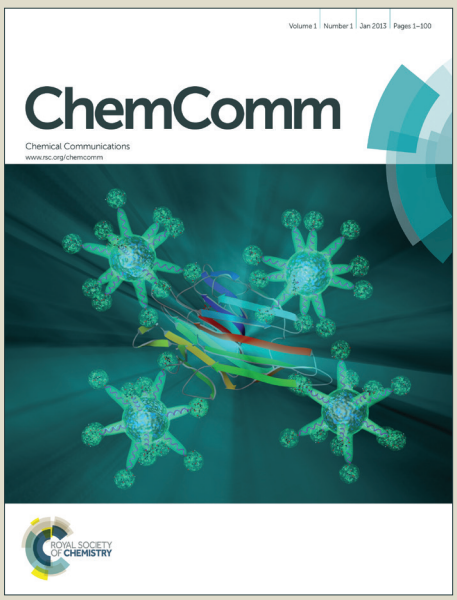

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ARTICLE TYPE

Stereoselective synthesis and reaction of gold(I) (*Z*)-enethiolate†

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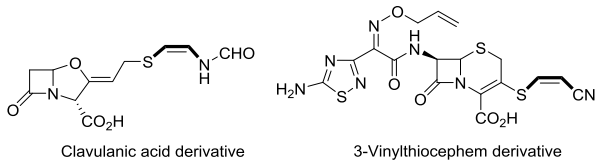
Bench-top-storable (Z)-enethiol reagent: gold (*Z*)-1-decenylthiolates were synthesized stereoselectively in high yields. They are stable on storage at room temperature without protection from light, and react smoothly with various alkyl halides, α,β-unsaturated ketones, and electron-deficient aryl halides with excellent stereoselectivity.

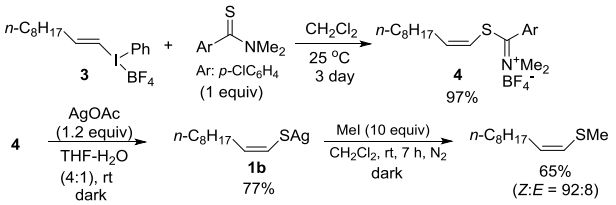
The (*Z*)-vinylthio moiety is an important functional group in organic synthesis and medicinal chemistry, being contained in many pharmaceutically important compounds (Scheme 1).[1] For example, a vinylthio functionality is present as a side chain in clavulanic acid derivatives, which show β-lactamase-inhibitory activity,[1a] and cephem derivatives, which exhibit broad-spectrum antibacterial activities.[1b] In both cases, the (Z)-isomers show greater activity than the (*E*)-isomers.



Clavulanic acid derivative 3-Vinylthiocephem derivative

Scheme 1 Biologically active β-lactam antibiotics containing a (*Z*)-vinylthio group.

The parent enethiols (RCH=CHSH) **1** are fairly tautomerically stable,[3] but in general, they are thermally unstable and readily undergo dimerization to give dithiohemiacetals or divinylsulfides even at room temperature.[4] Therefore, regio- and stereoselective synthesis of functionalized vinylthio moieties remains a challenging issue in organic synthesis, and only limited success has been achieved by using silyl vinyl sulfides as precursors.[5,6] In contrast, some heavier-metal enethiolates are less prone to dimerize. For example, cesium (*Z*)-enethiolate generated *in situ* at low temperature reacts with alkyl halides to afford (*Z*)-vinyl sulfides with high stereoselectivity (up to 98:2).[7] However, the use of a harder counter cation such as lithium ion results in configurational lability: enethiolate **1a** (R = *n*-Bu, M = Li) readily isomerizes even at –40 °C in THF.[8] In 2006, we developed a new type of configurationally stable (*Z*)-enethiol equivalent, silver(I) (*Z*)-β-alkylvinylthiolate **1b** by utilizing an unusual vinylic S_N2 reaction of (*E*)-β-alkylvinyl-λ^3-iodane with thiobenzamide, followed by hydrolysis with silver acetate (Scheme 2).[9,10]

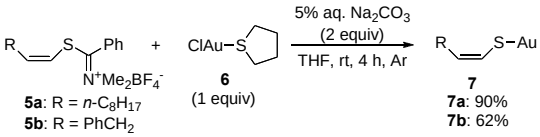


Scheme 2 Synthesis and reaction of (*Z*)-silver enethiolate **1b**

Enethiolate **1b** is stable on storage in a refrigerator (4 °C) for 3 months, but it is light-sensitive, and its reactivity is only moderate. For example, 1) 50% degradation of **1b** was observed at room temperature after 5 days without light protection; 2) slow isomerization of **1b** occurs in solution in the absence of a radical scavenger; 3) with less reactive substrates, addition of *n*-Bu_4NI or LiI is necessary to increase the nucleophilicity of sulfur and/or to activate electrophiles, and this may lead to side-reactions (*vide infra*). Herein, we report the first synthesis and characterization of gold(I) enethiolates. These are the most robust and practically convenient enethiolates currently available, and enable straightforward installation of a (*Z*)-enethiol unit in functional molecules. Furthermore, PPh_3- and N-heterocyclic carbene (NHC)-coordinated gold(I) enethiolates function as much better nucleophiles than the corresponding silver(I) enethiolates. Gold(I) enethiolates are thermally stable, photostable, and show high reactivity towards alkyl halides, cyclic enones, and electron-deficient aryl halides under mild reaction conditions.

The key to success in the preparation of gold(I) enethiolates **7** was the use of AuCl-tetrahydrothiophene complex **6**.[11] Exposure of *S*-vinylthiobenzimidonium salt **5a** (1 equiv) to gold(I) complex **6** in the presence of sodium carbonate (2 equiv) in THF at room temperature under argon resulted in selective hydrolysis to afford gold(I) enethiolate **7a** stereoselectively in 90% yield, along with *N*,*N*-dimethylbenzamide (94%) (Scheme 3). Gold(I) enethiolate **7a** is soluble in various solvents including dichloromethane, chloroform, benzene, and THF, but exhibits poor solubility in more polar solvents such as methanol, ethyl acetate, DMF, DMSO, and water. Gold(I) thiolates intrinsically adopt an oligomeric structure through intermolecular S···Au interactions.[12] ESI-MS spectra indicated that **7a** is prone to

adopt dimer and trimer forms (Figure S1), which might account for the reduced solubility in polar solvents.



Scheme 3 Synthesis of gold (Z)-enethiolate **7**

It is noteworthy that **7a** showed much higher photostability than silver enethiolate **1b**, and was stable on bench-top storage for at least 20 days without protection from light (Figure 1). The bond of Au(I) ion with thiolate anion is much stronger than that of Ag(I) ion (the bond dissociation energy of Au-S is 100 kcal mol^{-1} and that of Ag-S is 51.9 kcal mol^{-1}),[13] which is consistent with the higher stability of gold(I) thiolate **7a**.

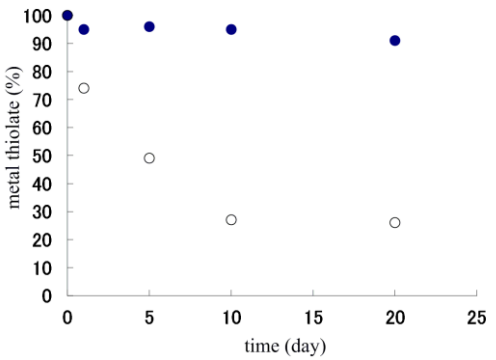
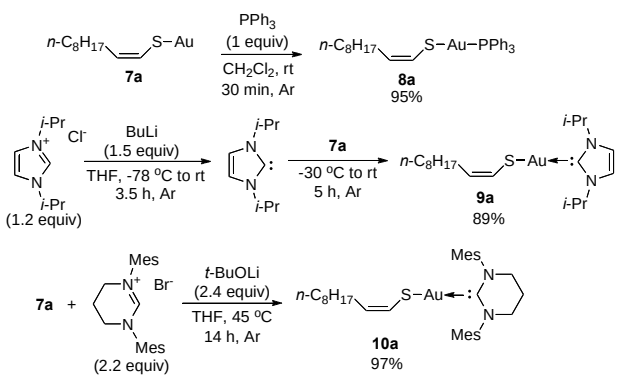


Figure 1 Stability differences between silver(I) enethiolate **1b** (open circle) and gold(I) enethiolate **7a** (filled circle).

The strong Au–S interaction enhances the thermal stability and photostability of enethiolate ion, but might cause a decrease in the reactivity. We envisioned that addition of electron-donating ligands such as triphenylphosphine (PPh_3) and NHCs, which form stable 1:1 complexes simply upon mixing with **7a** at ambient temperature, would increase the nucleophilicity via *trans* influence and stereoelectronic effects (Scheme 4).[14]



Scheme 4. Synthesis of gold(I) (*Z*)-enethiolate-ligand complexes

Complexes **8a**-**10a** showed higher solubility than parent **7a** in common organic solvents, such as ethyl acetate and methanol. The increased solubility can be attributed to inhibition of aggregation via intermolecular Au···S interaction. The 1:1 complex between **7a** and PPh_3 is predominant in $CDCl_3$ solution, as indicated by a Job plot of the ^{13}C NMR data (Figure S2). The binding constant was measured as K_a = 1.8 x 10^4 M^{-1} by means of ^{13}C NMR spectroscopic titration at room temperature (Figure S3). Complexation clearly increases the configurational stability of these compounds, and no isomerization of (*Z*)-enethiolate **8a** was observed even after 20 days in $CDCl_3$ at room temperature in the presence of TEMPO (0.1 equiv).[15] The formation of NHC adduct **10a** was unambiguously confirmed by X-ray diffraction analysis (Figure 2).[16] The structure contains one carbene ligand on the gold(I) center at the opposite side to the sulfur atom of **10a**, with a near-linear S1–Au1–C11 triad (178.26°). The thiolate ligand in **10a** is tightly bound to the gold(I) center with an Au1–S1 distance of 2.2883 Å, which is slightly longer than the predicted sum of covalent radii (2.27 Å). The C_{NHC}-Au bond length of 2.018 Å in **10a** is slightly longer than that observed in the corresponding chloride complex (1.993 Å), which probably reflects stronger *trans* influence of the thiolate anion. The Au–S and Au–C bond lengths are comparable to those observed in thioglucoside–Au(I)–NHC complex.[17] It is noteworthy that no intermolecular gold···gold interaction (< 3.2 Å) was observed in the crystal packing structure of **10a**.[18]

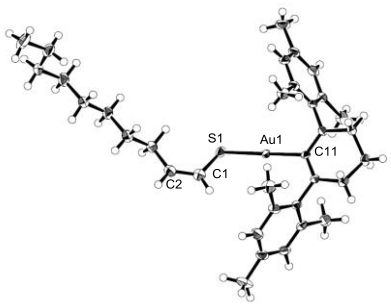
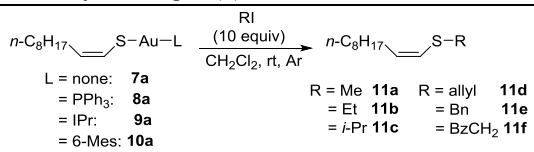


Figure 2 ORTEP drawing of gold enethiolate-6-Mes complex **10a** with thermal ellipsoids at 50% probability. Selected bond lengths (Å) and angles (deg): Au1-S1 2.2883(12), Au1-C11 2.018(2), S1-C1 1.774(5), C1-C2 1.354(7), S1-Au1-C11 178.26(11), Au1-S1-C1 102.21(15), S1-C1-C2 123.5(4).

We have reported that silver(I) enethiolate shows moderate reactivity towards various alkyl halides. For example, silver(I) enethiolate **1b** underwent nucleophilic substitution with methyl iodide (10 equiv) in dichloromethane at room temperature to give a regioisomeric mixture of methyl vinyl sulfide **11a** (R = Me, *Z*:*E* = 92:8) in 65% yield.[10] In contrast, gold(I) enethiolate **7a** was inert under similar conditions (Table 1, entry 1). However, phosphine and NHC-treated **8a**-**10a** reacted smoothly with alkyl iodide to afford (*Z*)-vinyl sulfide **11** in high yields (entries 2-11). The *Z*-selectivity was generally very high (>91%), and the use of TEMPO as an additive improved the yield and/or selectivity (entries 5, 6, 8, and 11).[20]

Table 1 Alkylation of gold (Z)-enethiolates

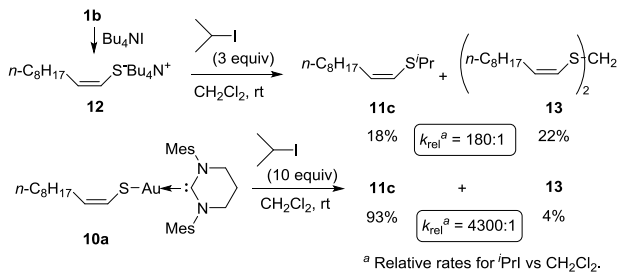


Entry	thiolate	RI	time (h)	yield[b] (%)	11 *Z*:*E*[b]
1	**7a**	MeI	7	0 **11a**	-
2	**8a**	MeI	3	77 **11a**	96:4
3	**9a**	MeI	0.5	79 **11a**	99:1
4	**10a**	MeI	0.5	79 **11a**	>99:1
5[c]	**9a**	MeI	0.5	95 **11a**	98:2
6[c]	**10a**	MeI	0.5	93 **11a**	99:1
7	**8a**	EtI	24	73 **11b**	78:22
8[c]	**8a**	EtI	24	82 **11b**	94:6
9	**8a**	*i*-PrI	48	33 **11c**	91:9
10	**10a**	*i*-PrI	48	63 **11c**	92:8
11[c]	**10a**	*i*-PrI	48	93 **11c**	91:9
12	**8a**	CH_2=$CHCH_2Br$	12	97 **11d**	96:4
13	**8a**	$PhCH_2Br$	4	77 **11e**	95:5
14	**8a**	$PhCOCH_2Br$	4	89 **11f**	94:6

[a] Isolated yields. [b] Determined by ^{1}H NMR analyses. [c] 0.1 equiv of TEMPO was added.

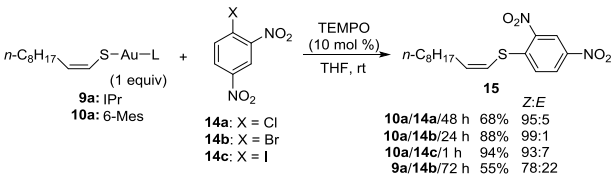
Complexes **9a** and **10a** with stronger *trans*-influencing NHC ligands showed higher reactivity toward nucleophiles than phosphine complex **8a**. For example, branched isopropyl iodide underwent nucleophilic substitution smoothly with **10a** in high yield (entry 10), while **8a** was less reactive under similar conditions (entry 9). Allyl/benzyl bromide and 2'-bromoacetophenone could be employed in these reactions (entries 12-14), and the yields and stereo-/regioselectivities of (*Z*)-vinyl sulfides **11d-f** were very high.

It should be noted that gold(I) enethiolate **10a** serves as highly selective nucleophile for alkyl iodide. In contrast, ammonium (*Z*)-vinylthiolate **12** generated *in situ* from silver(I) enethiolate **1a** undergoes S_N2 reaction with isopropyl iodide to form the corresponding sulfide **11c** in low yield, accompanied with formation of dithioacetal **13** (22%) from solvent dichloromethane (Scheme 5).[10] However, gold(I) enethiolate **10a** selectively reacted with isopropyl iodide to afford sulfide **11c** in high yield (93%), and the formation of dithioacetal **13** was negligibly small. The superior reactivity of gold(I) enethiolate with isopropyl iodide is probably due to the more favorable Au(I)···I interaction, which increases the leaving group ability of the iodine atom in isopropyl iodide.[21]



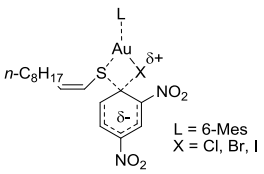
Scheme 5. Competitive alkylation of metal thiolates between isopropyl iodide and dichloromethane.

Similar gold(I)-halogen interaction-assisted enhancement of the reactivity of gold(I) enthiolate **10a** was observed in arylation with 2,4-dinitrohalobenzenes (Scheme 6). Reaction of equimolar 2,4-dinitrohalobenzenes **14a-c** and enethiolate **10a** at room temperature resulted in aromatic nucleophilic substitution (S_NAr) at the halogen *ipso* position, affording the corresponding aryl vinyl sulfide **15** in high yield with excellent stereoselectivity, while **9a** was less reactive.[22]



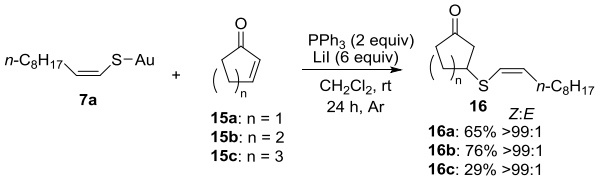
Scheme 6. S_NAr reaction of 2,4-dinitrohalobenzenes with gold(I) enethiolates.

In the S_NAr reaction of 2,4-dinitrohalobenzene with ammonium thiophenoxide ($PhS^-Bu_4N^+$), the reactivity of halobenzenes has been reported to decrease monotonically in the order F > Cl > Br > I.[23] Interestingly, the present S_NAr reaction with gold(I) enthiolate showed completely the opposite reactivity in terms of halogen leaving ability. The difference is due, at least in part, to the coordination of Au(I) ion to the halogen atom, increasing the positive charge on the *ipso* carbon atom of **14** (Scheme 7).[24] A similar mechanism has been proposed in diaryl ether synthesis by the reaction of alkali metal phenoxide with haloarenes.[25] These observations suggest that the Au(I) ion can transform the intrinsic reactivity of "(naked) thiolate anion" with electrophiles.



Scheme 7 A possible transition structure for S_NAr reaction of enethiolate **10a**.

We have reported that silver(I) enethiolate **1b** smoothly undergoes Michael addition with 2-cyclohexen-1-one **15b**, and the reaction is accelerated by the presence of lithium iodide.[10] *In situ*-generated gold(I) enethiolate **8a** could also be used in Michael addition with cyclic enones **15a-c** in the presence of lithium iodide. In these reactions, lithium cation functions as a Lewis acid; the use of *n*-Bu_4NI or NaI instead of lithium iodide did not afford **16b** at all.



Scheme 8. Michael addition of enethiolate **8a** generated *in situ* toward cycloalkenone

In conclusion, we have developed an efficient method for the synthesis of a bench-top-stable (*Z*)-enethiol equivalent, i.e., gold(I) (*Z*)-enethiolates, which serve as efficient nucleophiles for S_N2 reaction, S_NAr reaction, and Michael addition, affording a variety of (Z)-vinyl sulfides. Thus, gold(I) ion not only tames the configurationally labile enethiolate moiety, but also changes its reactivity toward electrophiles such as alkyl halides and aryl halides.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, figures, and spectral data. CCDC 1026924 (**10a**). For ESI and crystallographic data in CIF or other electronic format see DOI: xxx

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16 Crystal data for **10a**: $C_{32}H_{47}AuN_2S$, colorless prisms with dimensions of 0.20 X 0.20 X 0.10 mm^3, monoclinic, P-1 (No. 2), a = 9.6005(4), b = 11.3245(5), c = 15.2126(7) Å, α = 74.934(2), β = 82.830(2), γ = 77.842(2)° V = 1556.9(2) $Å^3$, Z = 2, D_{calcd} = 1.469 g cm^{-3}. Data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with MoK_α radiation (λ = 0.71075 Å) at T = 93 K, $2\theta_{max}$ = 54.9°, 24548 reflections measured, of which 7077 were unique (R_{int} = 0.0321), μ = 48.296 cm^{-1}. The structure was solved by heavy-atom Patterson methods[26a] and expanded using Fourier techniques,[26b] R = 0.027, R_w = 0.1063. Hydrogen atoms were included but not refined. CCDC-1026924 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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