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A gold(I)-catalyzed route to α-sulfenylated carbonyl compounds from propargylic alcohols and aryl thiols†‡

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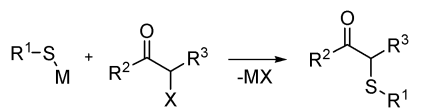
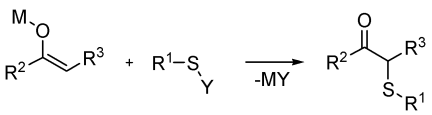
A one-step atom efficient gold(I)-catalyzed route to α-sulfenylated ketones and aldehydes from propargylic alcohols and aryl thiols is described.

α-Sulfenylated carbonyl compounds and their derivatives are important in agrochemicals and pharmaceuticals.[1] The traditional synthesis of α-sulfenylated carbonyl compounds involves substitution of the corresponding α-halogenated precursor by sulphide anions (eqn (1)).[2] These intermediates are toxic, difficult to handle, and generate a stoichiometric amount of chemical waste. Alternatively, the α-sulfenylated carbonyl compounds can be synthesized by the reaction of a carbonyl compound with sulfenylating agents (eqn (2)).[3] However, these sulfenylating agents have to be prepared in a separate step and also generate a stoichiometric amount of waste.



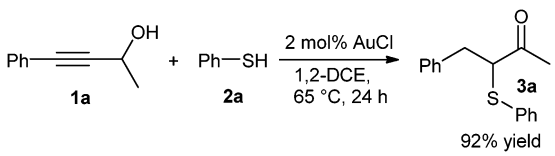
(1)



(2)

We found that gold(I) chloride catalyzed[4] a chemo- and regioselective reaction with thiophenol (**2a**) and 4-phenyl-3-butyn-2-ol (**1a**) to generate α-sulfenylated carbonyl compound **3a**. Other metal catalysts, such as rhenium(I), bismuth(III) or iron(III), allowed direct substitution of the hydroxyl group to generate the corresponding propargylic thioether.[5] The lack of an efficient, atom-economical[6] and sustainable route to synthesize α-sulfenylated carbonyl compounds motivated us to explore this novel transformation and study the reaction mechanism (Scheme 1).[7]

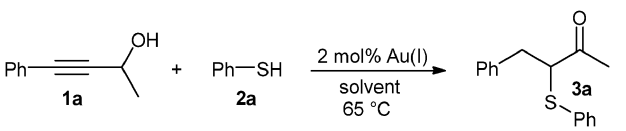
Thiophenol **2a** is known to reduce tetrachloro aureate(III) to generate gold(I) benzenethiolate.[8] Gold(I) chloride and **2a** may generate gold(I) benzenethiolate under the reaction conditions



Scheme 1 α-Sulfenylation of propargylic alcohol **1a**.

employed. An interesting question to ask is whether gold(I) benzenethiolate or gold(I) chloride operates as the true catalyst in the α-sulfenylation reaction. Therefore, the two gold complexes were evaluated in generating **3a** from **1a** and **2a** (Table 1). In the presence of gold(I) chloride (2 mol%), 62% conversion to **3a** was observed (Table 1, entry 1). In the presence of gold(I) benzenethiolate (2 mol%), 25% conversion to **3a** was observed after 15 h performing the reaction at 65 °C (Table 1, entry 2). This is consistent with gold(I) chloride being responsible for the observed reactivity. The reaction proceeds to yield the desired product in polar solvents such as 1,2-dichloroethane (1,2-DCE), chloroform or nitromethane (Table 1, entries 1, 3 and 4). An excess of thiophenol **2a** (1.5 equivalent) was required for completion of the reaction (Table 1, entries 1, 5 and 6). To inhibit the competing disulfide formation, the reaction was performed in an inert atmosphere (Table 1, entries 1 and 7). Under the optimized reaction conditions, the reaction was run in 1,2-DCE at 65 °C for 24 hours to generate **3a** in 92% yield (Table 1, entry 8).

Table 1 Optimisation of the reaction conditions[a]



Entry	Catalyst	Equiv. of **2a**	Solvent	Yield[b] (%)
1	AuCl	1.5	1,2-DCE	62
2	AuSPh	1.5	1,2-DCE	25
3	AuCl	1.5	$CHCl_3$	31
4	AuCl	1.5	$MeNO_3$	54
5	AuCl	1.0	1,2-DCE	48
6	AuCl	2.0	1,2-DCE	62
7	AuCl	1.5	1,2-DCE	39[c]
8	**AuCl**	**1.5**	**1,2-DCE**	**92**[d]

[a] Reaction conditions: **1a** (1 mmol), **2a** (X mmol) and Au (2 mol%) were run at 65 °C in 2.5 mL 1,2-DCE solvent for 15 h under an argon atmosphere. [b] Yields refer to isolated yields. [c] The reaction was performed open to air. [d] Reaction run for 24 h.

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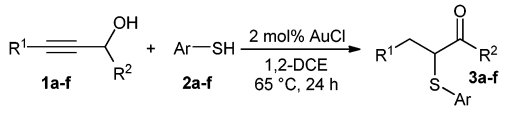
† Dedicated to Professor Robert H. Grubbs on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data, and copy of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c2cc32042h

The optimized reaction conditions were employed on a variety of propargylic alcohols **1a–f** and aromatic thiols **2a–f** (Table 1). Secondary aromatic propargylic alcohols **1a–c** reacted smoothly with **2a** to produce the corresponding α-thio ketones **3a–c** in good to excellent yields (Table 1, entries 1–3). Also, secondary aliphatic propargylic alcohol **1d** generated the corresponding α-sulfenylated ketone **3d** albeit in a lower yield (Table 1, entry 4). Primary propargylic alcohols were also transformed to generate the corresponding α-thio aldehydes **3e** and **3f** in high yields (Table 1, entries 5 and 6). Alcohols with a terminal triple bond were unreactive under the employed reaction conditions. Reactions using thiophenols having halogen substituents at the *para*-position (**2b–d**) were studied. In the case of *para*-bromo (**2b**) and chloro (**2c**) thiophenol the reaction with **1f** proceeded to generate the products **3g** and **3h** in comparable yields to **2a** (Table 1, entries 7 and 8). However, the use of *para*-fluoro thiophenol leads to a decrease in the yield of the desired product **3i** even when the reaction was run at 90 °C for 48 h (Table 1, entry 9). Thiophenols having electron donating isopropyl and methoxy groups at the *para*-position lead to a decrease in reactivity. The isopropyl substituted thiophenol **2e** reacted with **1f** to generate **3j** in 76% yield and the methoxy substituted thiophenol **2f** generated **3k** in 43% yield (Table 2, entries 10 and 11). Aliphatic propargylic alcohol **1g** having a cyclopentyl ring also reacted with thiophenol to produce **3l** (Table 2, entry 12). Attempts to employ aliphatic thiol under the same reaction conditions were unsuccessful.

Table 2 α-Sulfenylation of propargylic alcohols by aryl thiols[a]

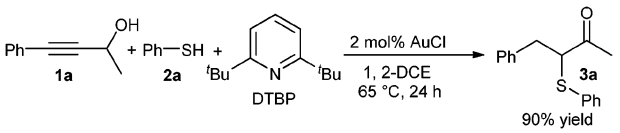


Entry	1	R^1	R^2	2	Ar	3	Yield[b]
1	**1a**	Ph	Me	**2a**	Ph	**3a**	92
2	**1b**	Ph	Pr	**2a**	Ph	**3b**	89
3	**1c**	Ph	^{i}Pr	**2a**	Ph	**3c**	88
4	**1d**	Et	Me	**2a**	Ph	**3d**	50[c]
5	**1e**	1-Naph	H	**2a**	Ph	**3e**	90
6	**1f**	Ph	H	**2a**	Ph	**3f**	93
7	**1f**	Ph	H	**2b**	*p*-Br-Ph	**3g**	88
8	**1f**	Ph	H	**2c**	*p*-Cl-Ph	**3h**	92
9	**1f**	Ph	H	**2d**	*p*-F-Ph	**3i**	48[d]
10	**1f**	Ph	H	**2e**	*p*-^{i}Pr-Ph	**3j**	76
11	**1f**	Ph	H	**2f**	*p*-OMe-Ph	**3k**	43
12	**1g**	Cyclopentyl	Me	**2a**	Ph	**3l**	48[d]

[a] Reaction conditions: **1** (1 mmol), **2** (1.5 mmol) and AuCl (2 mol%) 1,2-DCE (2.5 mL) for 24 h at 65 °C. [b] Yields refer to isolated yields. [c] 3 Equiv. of **1d** was used. [d] The reaction was run at 90 °C for 48 h.

To rule out AuCl is operating as a HCl generator, the reaction between **1a** and **2a** was performed in the presence of 30 mol% 2,6-di-*t*-butyl pyridine (DTBP) (Scheme 2). The reaction was found to proceed with equal efficiency (90% yield) compared to running the reaction in the absence of DTBP (92% yield). As a control, the α-sulfenylation reaction was attempted using HCl in ether (20 mol%) as catalyst, where below 15% conversion of **1a** was observed after 24 hours and no **3a** was observed. This supports that the gold(I) and not HCl generated from the metal salt is acting as the catalyst in the α-sulfenylation reaction.

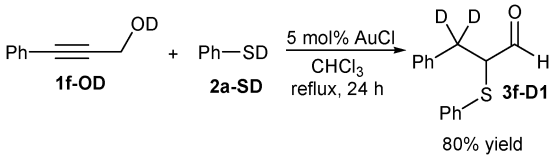
The α-sulfenylation is an atom efficient reaction where all the atoms of the reacting alcohol and thiol end up in the



Scheme 2 The α-sulfenylation proceeds in the presence of DTBP.

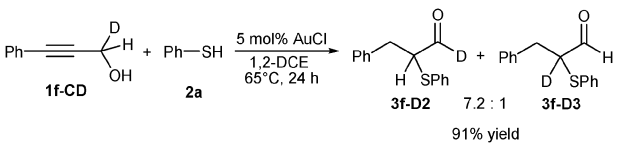
α-sulfenylated carbonyl product. The α-hydrogen of the alcohol and the protons of the alcohol and thiol are transferred to the triple bond of **1** during the course of the reaction. We wanted to determine where the individual hydrogens are transferred. Therefore, a series of reactions were carried out with deuterium labelled **1f-OD** (D in the protic position), **1f-CD** (D in the hydridic position) and **2a-SD** (D in the protic position).

The reaction between **1f-OD** and **2a-SD** (80% deuterium purity) was run for 24 hours in $CHCl_3$ at reflux using 5 mol% gold(I) chloride and the product was isolated in 80% yield (Scheme 3). ^{1}H NMR and ^{2}H NMR spectroscopic studies of the purified product revealed that the total deuterium content was 75%, of which deuterium incorporation at the benzylic position (**3f-D1**) was 90% (Scheme 3).[9] This labelling experiment shows that the protons from both the OH of **1f** and the SH of **2a** are transferred to the benzylic position of **3f**.



Scheme 3 Deuterium incorporation using labelled **1f-OD** and **2a-SD**.

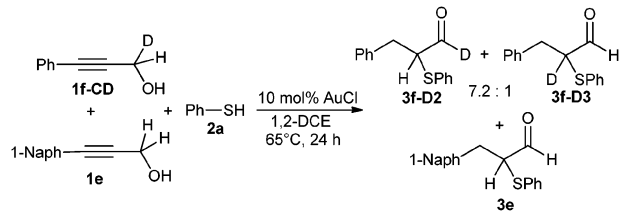
Alcohol **1f-CD** (90% deuterium purity) labelled by one deuterium in the hydridic position was used as the substrate in the α-sulfenylation reaction. The reaction was run for 24 hours and the product was isolated in 91% yield (Scheme 4). ^{1}H NMR and ^{2}H NMR spectroscopic studies of the purified product show that the total deuterium content of the product was 90%, of which deuterium incorporation at the aldehyde position (**3f-D2**) was 79% and the remaining 11% deuterium was incorporated at the α-position of the product (**3f-D3**). The labelling study shows that the hydride or deuteride of **1f-CD** is transferred to the α-position of the product.



Scheme 4 Deuterium incorporation using labelled **1f-CD**.

To investigate the intramolecularity of the hydride migration, a cross-over experiment was carried out using **1f-CD**, **1e** and **2a** (Scheme 5). ^{1}H and ^{2}H NMR spectral studies of the purified products showed no deuterium incorporation in **3e**, whereas deuterium incorporation in **3f** was obtained in similar ratios as mentioned in Scheme 4.

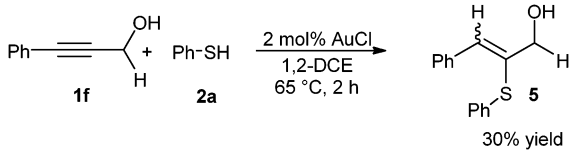
The ratio of **3f-D2** to **3f-D3** (7.2 : 1) in Scheme 4 is the ratio of the rate constants from the primary and secondary kinetic isotope effects of the 1,2-hydride or deuteride migration from the α-position of the **1f** to the α-position of the product **3f-D2** or **3f-D3**. Because the observed rates are a combination of a primary



Scheme 5 Investigation of intramolecularity of the hydrogen migration by cross-over experiment.

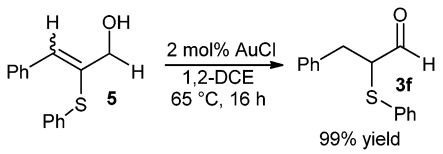
and a secondary isotope effect, the kinetic isotope effect was determined indirectly (see ESI‡ for experimental details and determination of the KIE). Given this, the observed primary deuterium kinetic isotopic effect was determined to be k_H/k_D = 8.4 ± 0.2 and the observed secondary deuterium kinetic isotopic effect was determined to be k_H/k_D = 1.17 ± 0.1.[10]

During the course of the reaction a diastereomeric mixture of **5** ($Z : E$ = 7 : 1) was observed in the reaction mixture (Scheme 6).[11] We were able to isolate and fully characterise intermediate **5** in 30% yield.[12]



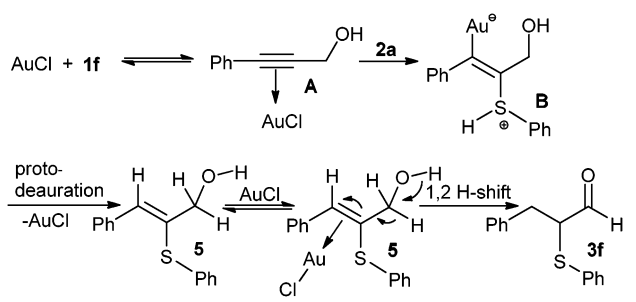
Scheme 6 Intermediate **5** formed in the AuCl catalysed reaction of **1a** and **2a**.

Compound **5** was tested as an intermediate in the transformation to **3f** (Scheme 7). Gold(I) chloride transformed **5** to generate **3f** in full conversion within 16 hours using standard reaction conditions. Attempts to perform this reaction step using acetic acid or **2a** as Brønsted acids were not successful.



Scheme 7 Testing **5**, as an intermediate to generate **3f**.

We propose a mechanism where gold(I) coordinates to the triple bond of **1a** and thiophenol attacks regioselectively the triple bond in the β-position of the alcohol **1a**. Protodeauration generates **5** as an intermediate in the reaction. A rate-limiting gold(I)-mediated 1,2-hydride migration[13] generates **3f** from **5** (Scheme 8).



Scheme 8 Proposed mechanism for the gold chloride catalysed α-sulfenylation of propargylic alcohols.

In conclusion, a novel gold-catalyzed route to α-sulfenylated carbonyl compounds from propargylic alcohols and aromatic thiols has been reported. In this protocol, primary, secondary, aromatic, and aliphatic alcohols are transformed to generate the α-sulfenylated carbonyl compounds in good to excellent yields. When a secondary alcohol is used, an α-sulfenylated ketone is generated and when a primary alcohol is used, an α-sulfenylated aldehyde is obtained. Mechanistic studies showed that gold(I) chloride is the active catalyst. The reaction proceeds through an initial regioselective thiol attack at the triple bond β to the alcohol. Protodeauration generates an alkene as a mixture of diastereomers. A rate-limiting gold(I)-catalyzed 1,2-hydride migration generates the α-sulfenylated carbonyl compounds.

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