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Atom-Efficient Gold(I)-Chloride-Catalyzed Synthesis of α-Sulfenylated Carbonyl Compounds from Propargylic Alcohols and Aryl Thiols: Substrate Scope and Experimental and Theoretical Mechanistic Investigation

Srijit Biswas,[a] Christian Dahlstrand,[a] Rahul A. Watile,[a] Marcin Kalek,[b] Fahmi Himo,*[b] and Joseph S. M. Samec*[a]

Abstract: Gold(I)-chloride-catalyzed synthesis of α-sulfenylated carbonyl compounds from propargylic alcohols and aryl thiols showed a wide substrate scope with respect to both propargylic alcohols and aryl thiols. Primary and secondary aromatic propargylic alcohols generated α-sulfenylated aldehydes and ketones in 60–97% yield. Secondary aliphatic propargylic alcohols generated α-sulfenylated ketones in yields of 47–71%. Different gold sources and ligand effects were studied, and it was shown that gold(I) chloride gave the highest product yields. Experimental and theoretical studies demonstrated that the reaction proceeds in two separate steps. A sulfenylated allylic alcohol, generated by initial regioselective attack of the aryl thiol on the triple bond of the propargylic alcohol, was isolated, evaluated, and found to be an intermediate in the reaction. Deuterium labeling experiments showed that the protons from the propargylic alcohol and aryl thiol were transferred to the 3-position, and that the hydride from the alcohol was transferred to the 2-position of the product. Density functional theory (DFT) calculations showed that the observed regioselectivity of the aryl thiol attack towards the 2-position of propargylic alcohol was determined by a low-energy, five-membered cyclic protodeauration transition state instead of the strained, four-membered cyclic transition state found for attack at the 3-position. Experimental data and DFT calculations supported that the second step of the reaction is initiated by protonation of the double bond of the sulfenylated allylic alcohol with a proton donor coordinated to gold(I) chloride. This in turn allows for a 1,2-hydride shift, generating the final product of the reaction.

Keywords: gold · homogeneous catalysis · reaction mechanisms · sulfenylation · synthetic methods

Introduction

Formation of C–S bonds is a fundamental transformation in organic synthesis. Sulfur-containing compounds have biological activity and thus have applications in the pharmaceutical and agrochemical industries.[1] Compounds with a thio group in the position alpha to a carbonyl group are referred to as α-thio- or α-sulfenylated carbonyl compounds and can be found in anti-infective, anti-tumor, anti-inflammatory, and nervous-system agents.[2,3]

The carbonyl group of α-sulfenylated carbonyl compounds can easily be transformed into other functional groups such as alcohol, imine, amine, and cyanohydrin. Alternatively, the sulfur atom can be oxidized, producing the corresponding β-carbonyl sulfoxides, which are important starting materials for biotransformation to produce chiral β-

[a] Dr. S. Biswas, Dr. C. Dahlstrand, R. A. Watile, Prof. Dr. J. S. M. Samec
Department of Chemistry, BMC, Uppsala University
Box 576, 75123, Uppsala (Sweden)
Fax: (+46) 018-471-3818
E-mail: joseph.samec@kemi.uu.se

[b] Dr. M. Kalek, Prof. Dr. F. Himo
Department of Organic Chemistry, Stockholm University
10691, Stockholm, Sweden
E-mail: himo@organ.su.se

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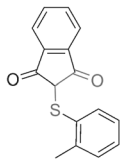
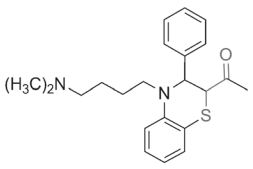
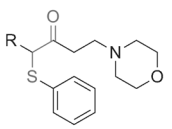


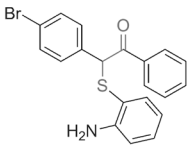
anti-infective agent[2a]



anti-inflamatory agent[2d]

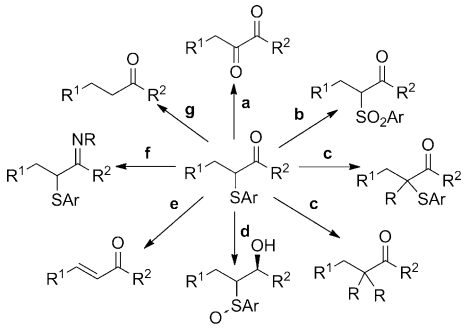


substituted 4-morpholino-1-phenylthio-2-butanone (anti-cancer agent)[3]



anti-tumor agent[2c]

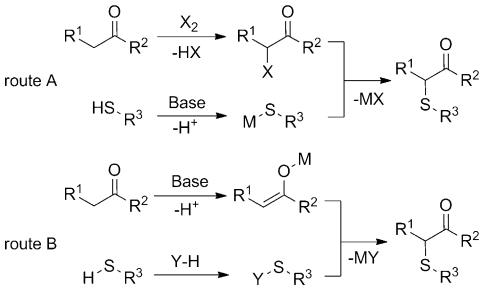
hydroxy sulfoxides.[4] These types of sulfone derivatives have potential anti-infective activity.[5] Various β-amino thioether compounds, which could easily be synthesized by functional group interconversion of α-sulfenylated carbonyl compounds, are reported to be apoptosis promoters;[6] their enantiomerically pure isomers are also widely employed as chiral ligands in asymmetric catalysis.[7] Moreover, in synthesis, α-sulfenylated carbonyl compounds[8] are used for the mono- and dialkylation of carbonyl compounds,[8d] preparation of 1,2-dicarbonyl compounds by disulfenylation,[8f] 1,2-carbonyl transposition,[8g] and for the synthesis of α,β-unsaturated carbonyl compounds (Scheme 1).[8h] These classes of



Scheme 1. α-Sulfenylated carbonyl compounds as important synthetic intermediates. a) Preparation of 1,2-dicarbonyl compounds by disulfenylation (ref. [8f]); b) traditional sulfur oxidation; c) mono- and dialkylation (ref. [8d]); d) biotransformation to chiral β-hydroxy sulfoxides (ref. [4]); e) synthesis of α,β-unsaturated carbonyl compounds (ref. [8f]); f) traditional imine formation through carbonyl–imine condensation; g) reductive removal of sulfur substituent (ref. [8i]).

compounds are employed as starting materials to synthesize butenolides[9] as well as in silyl carbonyl chemistry for regio- and stereoselective synthesis of the corresponding enol silyl ethers[10] and oxetanes.[11] The sulfur substituent alpha to the carbonyl group can be reductively removed, making these compounds convenient precursors for acylations and alkylations.[8f] Substituted α-sulfenylated carbonyl compounds also serve as starting materials for the synthesis of 2-halobenyl-3-arylbenzo[b]thiophene ethers, which act against breast cancer MCF7 cells, indicating antiproliferative activity against estrogen-dependent neoplasms.[12] Moreover, these types of compounds are used as starting materials for the preparation of therapeutically useful tumor-necrosis-factor-α-converting enzyme (TACE)-inhibitors, such as imidazolidinedione,[13] and photochromic compounds, such as thieno-2*H*-chromene derivatives.[14]

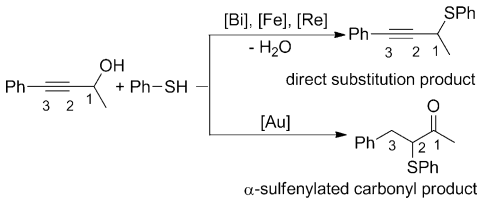
Traditionally, α-sulfenylated carbonyl compounds are prepared by S_N2 displacement of the corresponding α-halogenated carbonyl compounds by sulfide anions (Scheme 2, route A).[8] These reactive intermediates must be prepared in separate reaction steps. This is often associated with the generation of stoichiometric amounts of chemical waste both in the preparation of the α-halogenated carbonyl compounds and in the subsequent substitution reaction to generate the α-sulfenylated carbonyl products. Moreover, the reactive α-halo carbonyl intermediates are known warfare agents, for example, tear gas.[15] Alternatively, α-sulfenylated carbonyl compounds are synthesized by the reaction of a carbonyl compound or a preformed enolate with sulfenylating agents such as disulfides, *N*-(phenylsulfanyl)succinimides, and sulfenyl chlorides (Scheme 2, route B).[16] This alternative route also suffers from severe limitations of multiple reaction steps, toxicity, difficulty in handling intermediates, and low atom efficiency.



Scheme 2. Traditional synthesis of α-sulfenylated carbonyl compounds.

In recent years, stoichiometric versions of electrophilic asymmetric α-sulfenylation,[17] as well as catalytic asymmetric transformations employing organocatalysts[18] and enantiopure titanium(IV) or nickel(II) complexes,[19] have been reported. These synthetic methods generally suffer from stoichiometric use of toxic and expensive catalysts, waste generation, long reaction times, and/or low product yields with limited substrate scope. Therefore, an efficient, atom-economical,[20] and sustainable method to synthesize α-sulfenylated carbonyl compounds from readily available, simple starting materials is desirable.

During a study on catalytic substitution of propargylic alcohol with thiophenol[21] all screened catalysts except gold gave the expected thioether product by direct substitution of the hydroxyl group. Surprisingly, a different reactivity was observed in the presence of Au catalyst. Instead of the expected thioether, the corresponding α-sulfenylated carbonyl product was observed (Scheme 3). The initial findings on this transformation were published in a recent communication.[22] As an extension of this work, we herein report on the detailed scope and limitations of the regioselective sulfenylation of propargylic alcohols with gold catalysts. An experimental and theoretical mechanistic study on this transformation was also performed.

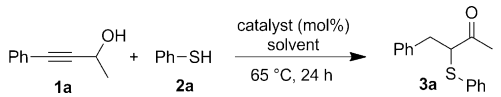


Scheme 3. Unique reactivity of gold catalyst.

Results and Discussion

For optimization of the reaction conditions, 4-phenylbut-3-yn-2-ol (**1a**) and thiophenol (**2a**) were chosen as model substrates. Different gold sources and additives were screened in the transformation of **1a** and **2a** into the α-sulfenylated carbonyl product **3a** in different solvents at 65 °C (Table 1).

Table 1. Optimization of reaction conditions.[a]



1a 2a 3a

Entry	Catalyst ([mol %])	Equiv of **2a**	Solvent	Yield[b] [%]
1	$AuBr_3$ (5)	1	DCE[c]	11
2	AuI (5)	1	DCE[c]	32
3	AuSPh (5)	1	DCE[c]	29
4	$(PPh_3)AuCl$ (5)	1	DCE[c]	21
5	$(PPh_3)AuCl$ (5) + $AgSbF_6$ (10)	1	DCE[c]	0[e]
6	AuCl (5) + NHC (5)[d]	1	DCE[c]	29
7	AuCl (5) + NHC (5)[d]	1	$MeNO_2$	47
8	AuCl (5) + NHC (5)[d] + Ag(OTf) (10)	1	$MeNO_2$	0[e]
9	AuCl (5) + NHC (5)[d] + $AgSbF_6$ (10)	1	$MeNO_2$	0[e]
10	Ag(OTf) (5)	1	$MeNO_2$	0[e]
11	$NaAuCl_4 \cdot 2H_2O$ (5)	1	DCE[c]	65
12	AuCl (10)	1	DCE[c]	69
13	AuCl (2)	1	DCE[c]	69
14	AuCl (2)	1.2	DCE[c]	79
15	AuCl (2)	1.5	DCE[c]	93
16	AuCl (2)	2	DCE[c]	92
17	AuCl (2)	1.5	$MeNO_2$	97
18	AuCl (2)	1.5	$CHCl_3$	40
19	AuCl (2)	1.5	MeCN	42
20	AuCl (2)	1.5	$PhCH_3$	0

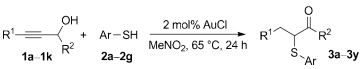
[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), and the catalyst were heated at 65 °C in 2.5 mL of solvent for 24 h. [b] NMR yield with toluene as internal standard. [c] DCE: 1,2-dichloroethane. [d] NHC: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [e] Formation of a new product resulting from Meyer–Schuster rearrangement followed by Michael addition of thiophenol was observed.

When a 1:1 mixture of **1a** and **2a** reacted in the presence of 5 mol % of gold(III) bromide, only 11 % product formation was observed after 24 h (Table 1, entry 1), whereas, gold(I) iodide and gold(I) thiophenolate[23] gave 32 and 29 % product, respectively (Table 1, entries 2 and 3) in 1,2-dichloroethane. Attempts to increase the efficiency of the catalysis by adding different ligands to the reaction mixture were unsuccessful (Table 1, entries 4–9). No α-sulfenylated product **3a** was formed on addition of $AgSbF_6$ to the $(PPh_3)AuCl$ catalyst (Table 1, entry 5). Instead, a different product resulted from Meyer–Schuster rearrangement of **1a** followed by Michael addition of **2a**.[24] Also, an *N*-heterocyclic carbene ligand and silver additives were tested, but gave poor results (Table 1, entries 6–9). Using only silver(I) trifluoromethanesulfonate as catalyst also led to Meyer–Schuster rearrangement followed by Michael addition (Table 1, entry 10). Increased conversion to **3a** was observed when the reaction was performed with 2 mol % of gold(I) chloride catalyst and 1.5 equivalents of **2a** with respect to **1a** (Table 1, entry 15).[22] A further increase in the amount of **2a** to two equivalents did not increase the conversion to **3a** (Table 1, entry 16). Substituting 1,2-dichloroethane (DCE) by nitromethane ($MeNO_2$) increased the efficiency of the reaction to generate 97 % of **3a** (Table 1, entry 17). Moreover, nitromethane is a nonhalogenated solvent having a higher boiling point than 1,2-dichloroethane. In contrast to the previous report, we chose nitromethane as solvent in the present study instead of 1,2-dichloroethane to obtain a better yield of the product, especially when aliphatic propargylic alcohols were employed as substrates at higher reaction temperature.[26] Chloroform and acetonitrile gave poor results (Table 1, entries 18–19), and no reaction was observed in toluene (Table 1, entry 20).

The optimized reaction conditions were applied to different substrates having an aromatic group in the R^1 position (Table 2). The reaction was general with respect to the aromatic propargylic alcohols. Both primary and secondary propargylic alcohols were employed to produce the desired α-sulfenylated ketones and aldehydes in high yields. Secondary alcohols with different aliphatic groups at the R^2 position reacted smoothly to produce the corresponding α-sulfenylated products (Table 2, entries 1–4). The reactions also showed high generality for the aryl group at the R^1 position of the alcohol. Excellent yields of the products were observed for alcohols with a 1-naphthyl group at the R^1 position (Table 2, entries 7 and 10). The effect of substituents of the phenyl ring at the R^1 position of the alcohol was investigated. Electron-withdrawing substituents such as 4-phenyl and 3,4-dichloro resulted in 89 and 95 % of **3f** and **3h**, respectively (Table 2, entry 6 and 8), whereas a 4-methyl substituent led to **3e** in 87 % yield (Table 2, entry 5). 1,3-Diphenylprop-2-yn-1-ol with a phenyl ring in both R^1 and R^2 positions did not react with thiophenol to yield the desired product under the present reaction conditions. Aryl thiols with different substituents in the *para* position of the aryl group were studied (Table 2, entries 12–25). 4-Chlorobenzenethiol (**2b**) and 4-bromobenzenethiol (**2c**) reacted smoothly with different primary and secondary propargylic alcohols to form the products in high yields (Table 2, entries 12–17). Carrying out the reaction at reflux for 48 h was required for reactions involving aryl thiols with electron-withdrawing substituents at the *para* position of the phenyl ring. Thus, 4-fluorobenzenethiol (**2d**) gave 80–86 % yield of product (Table 2, entries 18–20,) whereas *N*-(4-mercaptophenyl)acetamide (**2e**) generated **3u** in a 67 % yield (Table 2, entry 21). Aryl thiols with electron-donating groups such as 4-methoxyl (**2f**) and 4-isopropyl (**2g**) gave the products **3v**–**3y** in lower yields (Table 2, entries 22–25), whereby significant formation of disulfides as side products was observed.[25] Attempts to use aliphatic thiols were unsuccessful under the present reaction conditions, and no product formation was observed.

Propargylic alcohols with different aliphatic groups at the R^1 positions were also studied (Table 3, entries 1–6). Aliphatic alcohols generally showed lower reactivity than aromatic alcohols, and an increased catalyst loading to 5 mol %

Table 2. α-Sulfenylated carbonyl compounds from aromatic propargyl alcohols.[a]



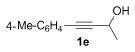
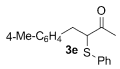
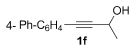
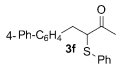
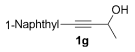
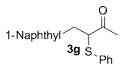
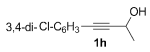
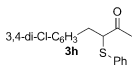
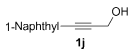
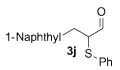
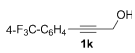
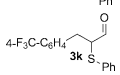
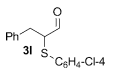
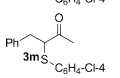
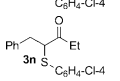
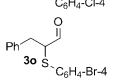
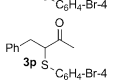
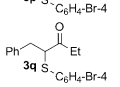
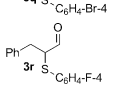
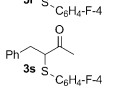
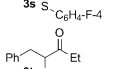
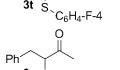
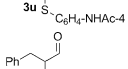
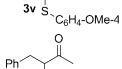
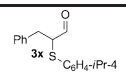
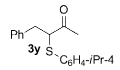
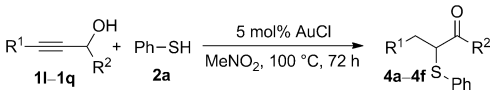
Entry	Alcohol **1**	Thiol **2**	Product **3**	Yield[b] [%]
1		Ph-SH **2a**		94
2		**2a**		93
3		**2a**		92
4		**2a**		88
5		**2a**		87
6		**2a**		89
7		**2a**		97
8		**2a**		95[c]
9		**2a**		95
10		**2a**		97
11		**2a**		89
12	**1i**	4-Cl-C_6H_4-SH **2b**		92
13	**1a**	**2b**		90
14	**1b**	**2b**		90
15	**1i**	4-Br-C_6H_4-SH **2c**		88
16	**1a**	**2c**		85
17	**1b**	**2c**		81
18	**1i**	4-F-C_6H_4-SH **2d**		86[c]
19	**1a**	**2d**		80[c]
20	**1b**	**2d**		81[c]
21	**1a**	4-AcNH-C_6H_4-SH **2e**		67[c]
22	**1i**	4-MeO-C_6H_4-SH **2f**		62
23	**1a**	**2f**		60

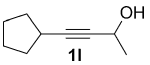
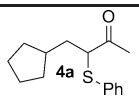
Table 2. (Continued)

Entry	Alcohol **1**	Thiol **2**	Product **3**	Yield[b] [%]
24	**1i**	4-*i*Pr-C_6H_4-SH **2g**		78
25	**1a**	**2g**		73

[a] Reaction conditions: **1** (1 mmol), **2** (1.5 mmol), and AuCl (2 mol%) were heated at 65 °C in 2.5 mL of nitromethane for 24 h. [b] Yield of isolated product. [c] Reactions at 100 °C for 48 h.

Table 3. α-Sulfenylated carbonyl compounds from aliphatic propargyl alcohols.[a]



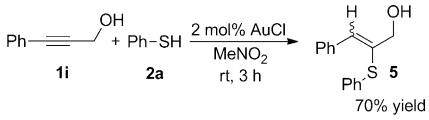
Entry	Alcohol **1**	Product **4**	Yield[b] [%]
1			71
2			70
3			63[c]
4			71
5			67
6			47

[a] Reaction conditions: **1** (1 mmol), **2** (3 mmol), and AuCl (5 mol%) were heated at 100 °C in 2.5 mL of nitromethane for 72 h. [b] Yield of isolated product. [c] Three equivalents of **1n** were used with respect to **2a**.

was required. The reactions were also performed for 72 h with an excess (3 equiv) of thiophenol with respect to the alcohol at 100 °C oil bath temperature.[26] Propargylic alcohols with cyclopentyl (**1l**) and cyclohexyl (**1m**) groups at the R^1 position generated the products in 71 and 70% yields, respectively (Table 3, entries 1 and 2). Due to the low boiling point of alcohol **1n** with an ethyl group at the R^1 position, three equivalents were used to yield the product **4c** in 63% (Table 3, entry 3), whereas 71% yield of product was observed for alcohol **1o** with a 2-phenylethyl substituent (Table 3, entry 4). Importantly, alcohols with functional groups such as an olefinic double bond (**1p**) or ester (**1q**) at the R^1 position gave the products **4e** and **4f** in 67 and 47% yield, respectively (Table 3, entries 5 and 6).

Mechanistic studies

Experimental studies: During the course of the reaction between primary propargyl alcohol **1i** and thiophenol **2a**, we observed the appearance of new ^{1}H NMR signals in the crude reaction mixture which did not correspond to the starting materials or the product. In a control experiment, a new compound was isolated. After structural elucidation, we concluded that the new compound was an *E*/*Z* mixture (2/7)[27] of sulfenylated allylic alcohol **5** (Scheme 4),[28] which

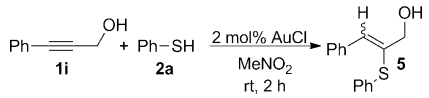


Scheme 4. Intermediate **5** formed in the AuCl-catalyzed reaction of **1i** and **2a**.

was found to be the true intermediate of this reaction (see below). Such intermediates were observed during the course of all reactions of propargylic alcohols and aryl thiols.

The hydrothiolation reaction to generate **5** from **1i** and **2a** without a catalyst has recently been reported.[29] The effect of a gold catalyst on the formation of allylic alcohol **5** was therefore investigated. Three separate reactions between **1i** and **2a** to generate **5** were carried out with and without the AuCl (2 mol%) catalyst at room temperature in nitromethane. The gold-catalyzed reaction produced 60% of **5**, whereas only a trace amount of **5** (<10%) was observed in the uncatalyzed reaction after 2 h (Table 4). We also

Table 4. Effect of AuCl on the formation of **5** from **1i** and **2a**.[a]



Entry	Mol% of AuCl	Additive ([mol%])	Conversion to **5**
1	2	–	60%
2	0	–	<10%
3	2	proton sponge (30)	58%

[a] Reaction conditions: **1i** (1 mmol), **2a** (1.5 mmol), AuCl, and additive were stirred at room temperature in nitromethane (2.5 mL) for 2 h.

tested whether addition of a proton sponge affects the formation of compound **5** in the presence of AuCl, but there was no difference to the reaction in the absence of the proton sponge (Table 4, entry 3 vs. entry 1).

Since the experimental data showed that sulfenylated allylic alcohol **5** is an intermediate in the overall reaction, we studied the conversion of **5** to the final product **3i** separately. Compound **5** was stable in nitromethane at 65 °C, and no conversion was observed (Table 5, entry 1). Also, addition of thiophenol **2a** did not result in any conversion to **3i**, and compound **5** remained intact under these reaction conditions (Table 5, entry 2). On the other hand, quantitative formation of aldehyde **3i** was observed in 8 h in the presence of

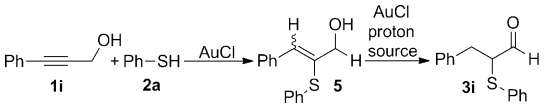
Table 5. Formation of product **3i** from intermediate **5**.[a]

Entry	Catalyst	Equiv of **2a**	Additive	Yield[b] [%]
1	–	0	–	0
2	–	1.5	–	0
3	AuCl	0	–	99
4	AuCl	0	proton sponge[c]	0
5	AuCl	0	molecular sieves[d]	0
6	AcOH	0	–	0
7	AuCl	1.5	proton sponge[c]	93
8	AuSPh	0	–	10

[a] Reaction conditions: **5** (1 mmol) and AuCl (2 mol%) were heated at 65 °C in 2.5 mL of nitromethane for 8 h. [b] NMR yield. [c] 30 mol% of 1,8-bis(dimethylamino)naphthalene was used. [d] Activated (4 Å).

2 mol% of AuCl (Table 5, entry 3). However, no conversion of **5** to **3i** was observed when 30 mol% of proton sponge or molecular sieves was used together with AuCl (Table 5, entries 4 and 5, respectively). The above results suggest that the reaction may be catalyzed by a protic acid. To verify this, compound **5** was treated with acetic acid, but no conversion to **3i** was observed (Table 5, entry 6). Interestingly, the reaction took place in the presence of the proton sponge (30 mol%) if a combination of 2 mol% of AuCl with 1.5 equiv of thiophenol **2a** was used (Table 5, entry 7). Moreover, application of Au^I thiophenolate[23] led only to a low conversion (Table 5, entry 8). These experiments support that the presence of both AuCl and a proton source (e.g., HCl or thiophenol) is necessary for the reaction to proceed efficiently.

The above experiments also confirmed that the overall reaction is indeed a two-step process and identified sulfenylated allylic alcohol **5** as the true intermediate. The first step is a regioselective AuCl-catalyzed addition of thiophenol **2a** to the triple bond of alcohol **1i**, and the second step is a rearrangement of the resulting intermediate **5** into the final product **3i** (Scheme 5). Efficient transformation of **5** into **3i** requires both AuCl and a proton source.

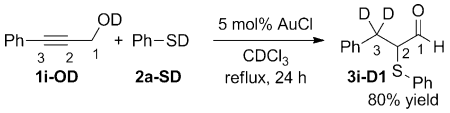


Scheme 5. The overall reaction between **1i** and **2a** to form product **3i** via intermediate allylic alcohol **5**.

Formation of the α-sulfenylated carbonyl compound is atom-efficient, since all atoms of the reacting alcohol and thiol end up in the α-sulfenylated carbonyl product. The α-hydrogen atom at the 1-position of the alcohol and the protons of the alcohol and thiol are transferred to the triple bond of the alcohol during the course of the reaction. To determine the positions to which the individual hydrogen atoms are transferred, reactions were carried out with deu-

terium-labeled **1i-OD** (D in the protic position), **1i-CD** (D in the hydridic position), and **2a-SD** (D in the protic position).

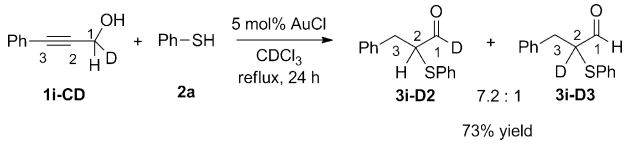
First, the OH proton of alcohol **1i** and SH proton of thiophenol **2a** were exchanged for deuterium atoms. The reaction between **1i-OD** and **2a-SD** (80% deuterium purity) was carried out for 24 h in $CDCl_3$ at reflux with 5 mol% of gold(I) chloride, and the product was isolated in a 80% yield (Scheme 6). ^1H and ^2H NMR spectroscopic studies on



Scheme 6. Deuterium incorporation with labeled **1i-OD** and **2a-SD**.

the purified product revealed that the total deuterium content was 75%, of which deuterium incorporation at the benzylic 3-position (**3i-D1**) was 90% (Scheme 6).[30] No deuterium incorporation was observed at the 2-position of the product. This labeling experiment shows that the protons from both the OH group of **1i** and the SH group of **2a** are transferred to the benzylic 3-position of **3i**.

Alcohol **1i-CD** (90% deuterium purity) labeled with a deuterium atom in the hydridic 1-position was prepared and used as substrate in the α-sulfenylation reaction. The reaction was run for 24 h and the product was isolated in a 73% yield (Scheme 7). ^1H NMR and ^2H NMR spectro-

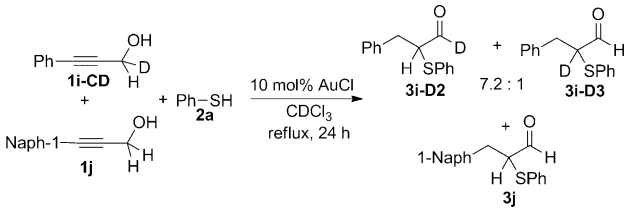


Scheme 7. Deuterium incorporation with labeled **1i-CD**.

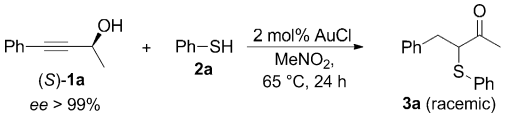
scopic studies on the purified product showed that the total deuterium content of the product was 90%, of which deuterium retention at the aldehyde 1-position (**3i-D2**) was 79% and the remaining 11% deuterium was incorporated at the 2-position of the product (**3i-D3**). This labeling study shows that the hydride or deuteride of **1i-CD** is transferred to the 2-position of the product.

To investigate the intramolecularity of the hydride migration, a crossover experiment was carried out with **1i-CD**, **1j**, and **2a** (Scheme 8). ^1H and ^2H NMR spectral studies on the purified products showed no deuterium incorporation in **3j**, whereas deuterium incorporation in **3i** was obtained in similar ratios to Scheme 7. This points to a mechanism involving an intramolecular 1,2-hydride transfer.

To study the scope of chirality transfer of the present reaction, optically pure (*S*)-**1a** was used as substrate in the gold(I)-catalyzed α-sulfenylation reaction (Scheme 9). No chirality transfer was observed when (*S*)-**1a** reacted with



Scheme 8. Crossover experiment to investigate the intramolecularity of the hydride shift.



Scheme 9. Investigation of chirality transfer for the conversion of (*S*)-**1a** into **3a**.

thiophenol **2a** under the optimized reaction conditions, and *rac*-**3a** was generated.

Theoretical studies: To gain further insight into the reaction mechanism, a theoretical study was performed with the DFT functional M06[31] (see Experimental Section). First, formation of the experimentally observed sulfenylated allylic alcohol intermediate **5** by gold-catalyzed regioselective addition of thiophenol **2a** to the triple bond of propargylic alcohol **1i** was studied. Second, gold-catalyzed rearrangement of compound **5** to the final product **3i** was investigated. While the gold-catalyzed additions of various nucleophiles to triple and double bonds have been the subject of both experimental and theoretical mechanistic studies,[32] the corresponding reaction with aryl thiol nucleophiles has been less studied. The present calculations on the gold-catalyzed hydrothiolation reaction complement our experimental results and increase the mechanistic understanding of this class of reactions.

The experimental results presented above point to AuCl being the true catalyst of the reaction (Tables 1 and 4). Therefore, we considered several different complexes of AuCl with thiophenol **2a** and propargylic alcohol **1i** as the starting point for the catalytic cycle of the hydrothiolation reaction. The lowest-energy complex is formed between AuCl and thiophenol **2a** (**INT0**, Figure 1) with a binding energy of 22.1 kcal mol^{-1}. Therefore, **INT0** serves as the zero point in the free-energy plots below. The catalytically relevant AuCl complex with propargylic alcohol **1i** (**INT1**, Figure 1) is, however, only 1.4 kcal mol^{-1} less stable (see Figure 1 for the calculated free-energy profile).[33]

The first step in the mechanism is nucleophilic attack of thiophenol on the triple bond of the propargylic alcohol bound to AuCl.[34] Thiophenol can attack at the 2- or 3-position with formation of isomeric products. Furthermore, both the *syn* addition of thiophenol and AuCl (which can be termed inner-sphere) and *anti* addition (outer-sphere) pathways are possible. These options were evaluated by calcula-

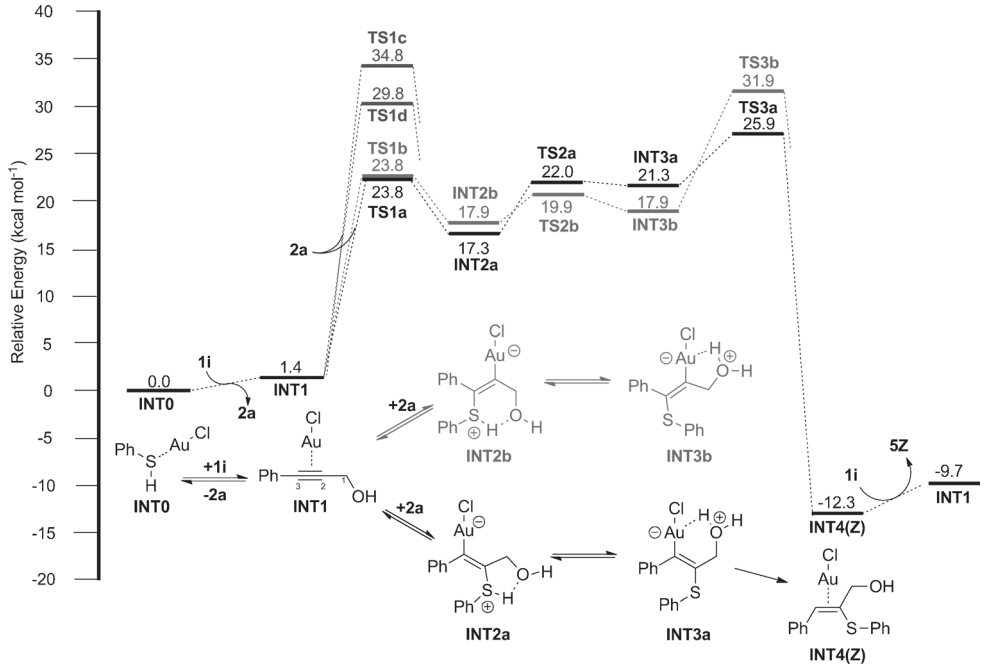


Figure 1. Free-energy profile for the regioselective gold-catalyzed addition of thiophenol **2a** to the triple bond of propargylic alcohol **1i**.

tions. The barriers for the two outer-sphere attacks via **TS1a** and **TS1b** (see Figure 2 for optimized structures) were both calculated to be 23.8 kcal mol^{-1} relative to **INT0**. In both **TS1a** and **TS1b**, and also in the resulting intermediates **INT2a** and **INT2b**, a hydrogen bond is present between the thiol proton and the oxygen atom of the hydroxyl group. The calculations show that the transition states for the alternative inner-sphere additions (**TS1c** and **TS1d**) have significantly higher energies than those of the outer-sphere additions (6-11 kcal mol^{-1}, see Figure 1 for energy diagram and Figure 2 for optimized structures). This result is in line with previous findings on gold-catalyzed additions to double and triple bonds, which were shown to take place preferentially by an outer-sphere mechanism.[35] Therefore, the subsequent steps of the inner-sphere addition pathways were not further evaluated in the present study. The outer-sphere course of thiophenol addition implies that the reaction will afford only the *Z* isomer of allylic alcohol **5**. However, since a mix-

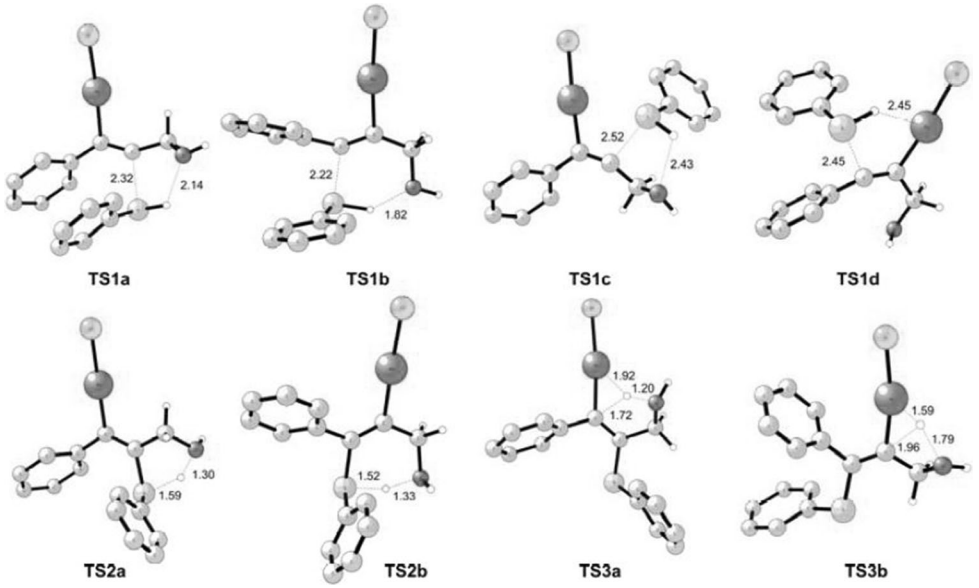


Figure 2. Optimized transition-state structures for the key steps of the gold-catalyzed hydrothiolation of propargylic alcohol **1i**. The phenyl hydrogen atoms have been omitted for clarity.

ture of *E* and *Z* isomers of **5** was observed experimentally, some other process must be responsible for the formation of the *E* isomer. This is indeed the case (see below).

The next step in the gold-catalyzed addition of thiophenol to propargylic alcohol is a protodeauration. This reaction cannot take place directly from **INT2a** or **INT2b**, because that would require transferring the proton from the sulfur atom to a distant carbon atom. Instead, this step is facilitated by the adjacent hydroxyl group, which can transfer the proton intramolecularly in a stepwise fashion.[36] Hence, an initial proton transfer from sulfur to oxygen takes place (**TS2a** and **TS2b**, Figure 2), followed by protodeauration (**TS3a** and **TS3b**). Transition states **TS3a** and **TS3b** are the highest points in the free-energy profiles of the respective pathways, and their relative energies therefore determine the overall regioselectivity of the addition. Protodeauration via **TS3a** is calculated to be favored by 6.0 kcal mol^{-1} compared to **TS3b** (25.9 versus 31.9 kcal mol^{-1} relative to **INT0**, respectively). This difference in energy corresponds well to the experimental finding that only α-sulfenylated carbonyl compounds were observed. The difference in barriers can be explained by the fact that the **TS3b** contains a strained, four-membered cyclic structure, while **TS3a** has a more relaxed, five-membered cyclic structure. Thus, according to the calculations, the hydroxyl group of the reactant plays an important role in controlling the regioselectivity of the reaction.

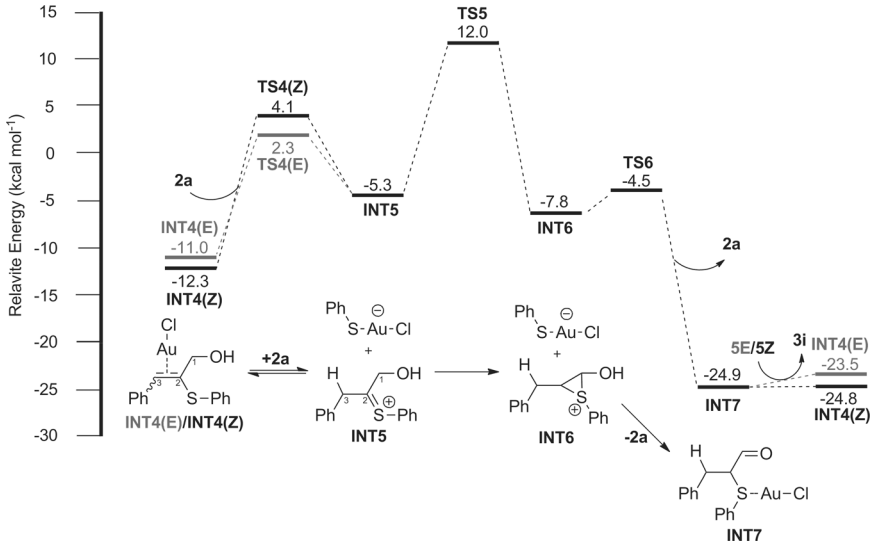


Figure 3. Free-energy profile for the gold-catalyzed isomerization of allylic alcohol **5** to aldehyde **3i**.

The protodeauration was found to be very exergonic and thus irreversible, and it results in the formation of complex **INT4(Z)**, with AuCl coordinated to the double bond of intermediate **5Z**. To close the catalytic cycle for thiophenol addition, compound **5Z** is released by **1i** to regenerate **INT1**. Overall, the formation of intermediate **5Z** is calculated to be exergonic by 11.1 kcal mol^{-1}.

In the second part of the reaction, intermediate **5** rearranges to the final product, aldehyde **3i**. The isomerization of allylic alcohols to the corresponding ketones is known to be catalyzed by complexes of transition metals such as Ru, Rh, and Fe.[37] However, to the best of our knowledge, no examples of gold-catalyzed isomerization of allylic alcohols have been reported. Interestingly, the above-mentioned reactions usually follow a redox pathway involving intermediate formation of metal hydride and α,β-unsaturated ketone, and result in an intra- or intermolecular 1,3-hydride transfer to the 3-position of the product. In contrast, the gold-catalyzed process described here results in a selective intramolecular 1,2-hydride shift (Schemes 7 and 8). The dissimilarity in hydride transfer and the fact that this process requires the presence of both AuCl and a proton source (Table 5) suggests that this gold-catalyzed isomerization of **5** to **3i** follows a different mechanistic route compared with previous reactions catalyzed by other metals.

We have evaluated theoretically a number of possible mechanisms for the isomerization of **5** to **3i** which comply with the results of the experimental investigations discussed above. The calculations show that the only pathway that has plausible barriers is initiated by protonation of allylic alcohol **5** by an external proton source activated with AuCl (Figure 3). All of the other alternative mechanisms tested, such as those involving hydride shift promoted by coordination of AuCl to the double bond of **5** or intramolecular protonation of the double bond by the AuCl-activated hydroxyl group, were found to proceed via high-energy routes with barriers exceeding 30 kcal mol^{-1} (see Supporting Information for details).

The catalytic cycle for the rearrangement of **5Z** into **3i** starts with complex **INT4(Z)**. Under the normal reaction conditions thiophenol **2a** is present in the reaction mixture in excess and may act as a proton donor. Thus, in the first step of the reaction, **2a**, acidified by coordination of AuCl to the sulfur atom, protonates the double bond of allylic alcohol **5Z** at the 3-position (**TS4(Z)**, see Figure 4 for the optimized structure). The calculated barrier is 16.4 kcal mol^{-1} relative to **INT4(Z)**, and the resulting dissociated ion-pair intermediate **INT5** lies 7.0 kcal mol^{-1} higher than **INT4(Z)** (see Figure 3 for the free-energy diagram). Since the transition state for the following step of the catalytic cycle (**TS5**) is higher in energy than **TS4(Z)**, the protonation is reversible.

Importantly, the intermediate **INT5** can undergo rotation around the C−C single bond and a subsequent reprotonation via **TS4(E)**, which results in the formation of the isomeric

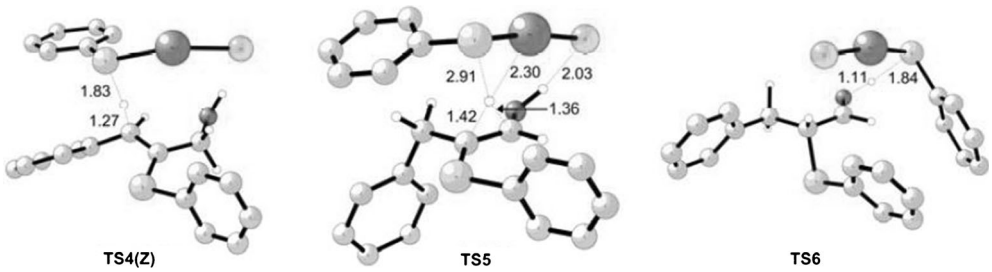


Figure 4. Optimized transition-state structures for the key steps of the gold-catalyzed isomerization of allylic alcohol **5** to aldehyde **3i**.

INT4(E). Hence, although the preceding hydrothiolation reaction delivers the *Z*-configured allylic alcohol **5Z** exclusively, as discussed above, it may interconvert with **5E** under the reaction conditions to afford the experimentally observed mixture of isomers. The calculated energy difference between free **5E** and **5Z** is 0.5 kcal mol^{-1} in favor of **5E**. This corresponds to a **5E**:**5Z** ratio of about 2:1, which differs slightly from the experimentally observed 2:7 mixture, which corresponds to 0.8 kcal mol^{-1} in favor of **5Z**. This discrepancy may be ascribed to the errors of the theoretical methodology.

The subsequent step of the reaction is the key 1,2-hydride shift (**TS5**), driven by the electron-deficient character at the 2-position in **INT5**. This takes place via **TS5** with an overall barrier of 24.3 kcal mol^{-1} relative to **INT4(Z)**. Interestingly, although both **INT5** preceding **TS5** and the resulting **INT6** were found to be more stable as dissociated ion pairs, the transition state has slightly lower energy as an associated ion pair. This is due to the interaction between the gold center and the hydride (Figure 4), that is, gold assists the hydride shift.

After the hydride shift, the proton is returned to the thiophenol (**TS6**, see Figure 4 for the optimized structure) and a complex of AuCl with the product is formed (**INT7**). The calculated barrier for this is very low, only 3.3 kcal mol^{-1} relative to **INT6**. To close the catalytic cycle, product **3i** is released and **INT4** regenerated. The latter ligand exchange is slightly endergonic (by 0.1 and 1.4 kcal mol^{-1} for **INT4(Z)** and **INT4(E)**, respectively). This means that **INT4(Z)** and **INT7** are the most stable gold complexes present in the reaction mixture.

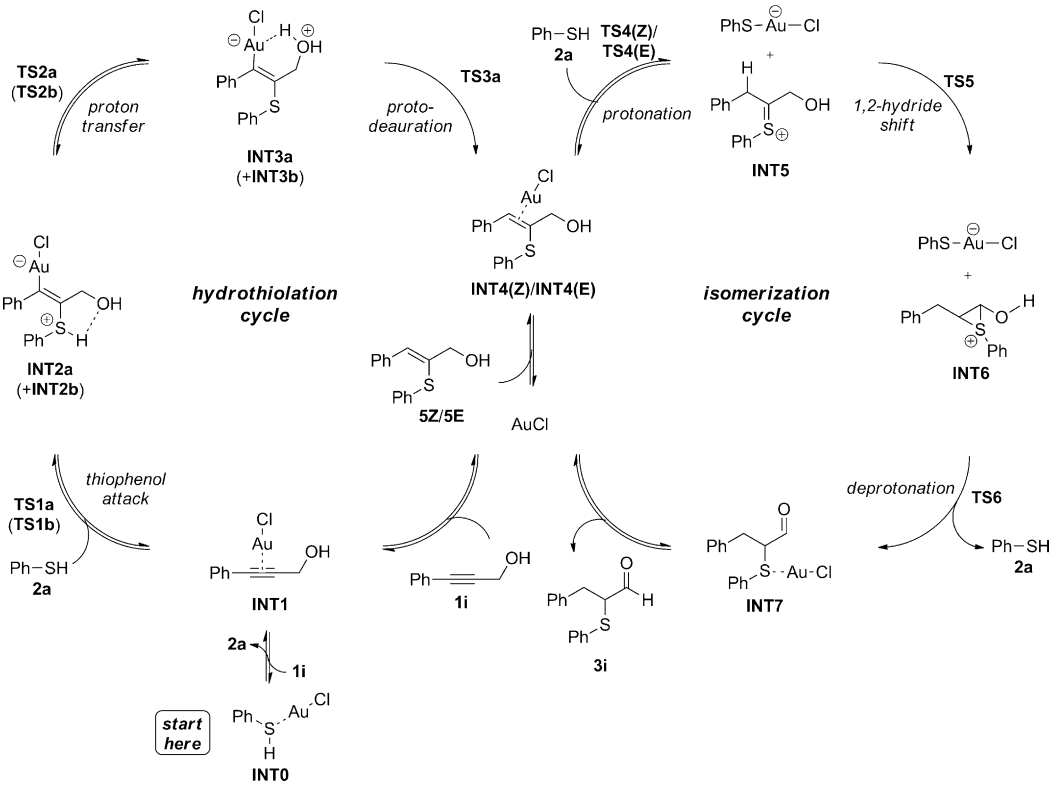
As discussed above, it was experimentally shown that AuCl can promote the isomerization of allylic alcohol **5** to aldehyde **3i** even in the absence of the thiophenol (Table 5, entry 3). The reaction was, however, inhibited by the addition of 30 mol% of proton sponge (Table 5, entry 4) or molecular sieves (Table 5, entry 5). From these results, we concluded that the role of the proton donor may also be played by HCl, which could be present in AuCl or might be generated under the reaction conditions. Therefore, we also calculated the free-energy profile for the reaction involving HCl as the proton source instead of thiophenol. The results indicated that such process is indeed feasible and in fact more energetically favorable than that with thiophenol (see Supporting Information). However, from the calculations it is difficult to say which of the two alternative pathways is operational under the normal reaction conditions, due to the much higher concentration of **2a** compared to HCl in the reaction mixture.

Proposed reaction mechanism: On the basis of the experimental and computational studies the following reaction mechanism is proposed[38] for the gold-catalyzed reaction between propargylic alcohols and thiophenols producing α-sulfenylated carbonyl compounds. The mechanism consists of two catalytic cycles (Scheme 10), corresponding to the two sequential processes taking place in the course of the reaction: 1) hydrothiolation of propargylic alcohol **1i** and 2) isomerization of sulfenylated allylic alcohol **5** to the final aldehyde **3i**.

For the hydrothiolation cycle (Scheme 10, left part), it was established that the initial addition of the thiophenol to the triple bond of the propargylic alcohol proceeds by an outer-sphere mechanism and can occur at both the 2- and 3-positions (**TS1a** and **TS1b**), affording both **INT2a** and **INT2b**. However, this step and the subsequent proton transfer (**TS2a** and **TS2b**) were found to be reversible, and thus the final regioselectivity is determined by the protodeauration. According to the calculations, protodeauration is favored for the α-adduct (**TS3a**), in agreement with the experimental results.

Once formed, the intermediate sulfenylated allylic alcohol **5** can undergo isomerization to the final product, following the second catalytic cycle (Scheme 9, right part). The first step of the cycle involves protonation of the double bond of **5** by a proton donor (e.g., thiophenol **2a**), acidified by coordination to AuCl. The protonation step was found to be reversible, and this may account for the *Z*–*E* isomerization of allylic alcohol **5**, which is produced in the hydrothiolation step as the *Z* isomer exclusively, whereas a mixture of **5Z** and **5E** was observed experimentally. From **INT5** a 1,2-hydride shift takes place (**TS5**), which is driven by the electron-deficient character at the 2-position. In the final step of the cycle, the proton donor is regenerated.

The gold-catalyzed pathway described here is a new mechanism for the isomerization of allylic alcohols and is distinct from those followed in the presence of other transition metal catalysts.[37]



Scheme 10. Proposed reaction mechanism.

Conclusion

An atom-efficient, gold-catalyzed route to α-sulfenylated carbonyl compounds from propargylic alcohols and aromatic thiols was studied. By utilizing this protocol, primary aromatic, secondary aromatic, and secondary aliphatic propargylic alcohols were transformed into α-sulfenylated carbonyl compounds in good to excellent yields. When a secondary alcohol was used, an α-sulfenylated ketone was generated, and when a primary alcohol was used, an α-sulfenylated aldehyde was obtained. The protocol was found to be general with respect to a variety of substituents on the aromatic ring of the alcohols and thiols. Aliphatic propargylic alcohols were also successfully employed to produce the desired α-sulfenylated ketones. Experimental and theoretical investigations were performed to elucidate the mechanism and the source of regioselectivity of the reaction. The initial thiol attack at the 2-position of the propargylic alcohol was suggested to be due to a favored protodeauration step via an energetically favored five-membered cyclic transition state, instead of the unfavorable four-membered cyclic transition state found for attack at the 3-position of the triple bond. Furthermore, experimental data and calculations showed that protonation of the double bond of the sulfenylated allylic alcohol intermediate in the next step was promoted by a proton-transfer mediator coordinated to gold chloride. The protonation was required for the 1,2-hydride shift that generated the final product.

Experimental Section

4-Phenyl-3-(phenylthio)butan-2-one (3a): AuCl (5 mg, 2 mol%) was transferred to a 5 mL microwave vial with a small magnet in a glove box under nitrogen atmosphere. The cap of the vial was closed tightly and the vial was removed from the glove-box. Dry nitromethane (2.5 mL), alcohol **1a** (145 μL, 1 mmol), and benzenethiol (**2a**, 154 μL, 1.5 mmol) were added to the vial by syringe and the mixture was stirred with a magnetic stirrer at 65 °C for 24 h. After completion of the reaction (shown by TLC or crude NMR spectroscopy), the solvent was evaporated under reduced pressure and the residue was purified by silica-gel (100–200 mesh) column chromatography with 3 vol% ethyl acetate/pentane as eluent to yield the desired product **3a** as a pale yellow oil (240 mg, 0.94 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.20$ (s, 3H, H-1), 3.00 (dd, $J =$ 6.9 Hz, 14.4 Hz, 1H, H-4), 3.19 (dd, $J = 8.4$ Hz, 14.1 Hz, 1H, H-4), 3.90 (dd, $J = 6.9$ Hz, 8.4 Hz, 1H, H-3), 7.18–7.37 ppm (m, 10H, H-arom). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.1$, 36.9, 59.0, 127.1, 128.5, 128.8, 129.4, 133.0, 133.3, 138.3, 204.5 ppm.

Computational details: The calculations were performed with the M06 functional[31] as implemented in the Gaussian 09 package.[39] Geometries were optimized by using the def2-SVP double-ζ basis set with polarization functions on all atoms.[40] Relativistic effects were accounted for by using the relativistic SDD effective core potential for gold.[41] The stationary points were characterized by frequency calculations to confirm their character as minima (no imaginary frequencies) or transition states (one imaginary frequency corresponding to the reaction coordinate). The solvation energies were calculated as single-point energy corrections at the same level of theory as the geometry optimization by using the conductor-like polarizable continuum model (CPCM) formalism[42] with the parameters for nitromethane ($\varepsilon = 36.562$). Thermal corrections to Gibbs free energies were calculated for 338.15 K, which is the temperature at which the reactions were performed experimentally. The final Gibbs free energies reported in this article were obtained from single-point calculations with the larger 6-311+G(2d,2p) basis set for H, C, O, S, and Cl, and

SDD for Au, corrected for zero-point and thermal effects, as well as solvation.[43]

For comparison, we also reoptimized all of the structures using the B3LYP functional and recalculated the energies with all corrections, including dispersion. Some differences were observed, but the results were in general consistent with the M06 results presented here (see Supporting Information for details).

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