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Gold(I)-Catalyzed Synthesis of Highly Substituted 1,4-Dicarbonyl Derivatives via Sulfonium [3,3]-Sigmatropic Rearrangement

Weiping Zhou and Arnaud Voituriez*

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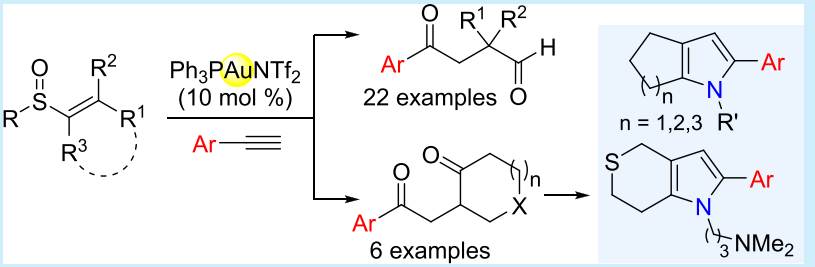

ABSTRACT: An efficient and straightforward gold-catalyzed protocol for the synthesis of 2-substituted 4-oxo-4-arylbutanal derivatives from commercially available or easily accessible alkynes and vinylsulfoxide substrates has been developed. Extension of the methodology to the use of 1-cycloalkenyl sulfoxides allowed the facile synthesis of five-, six-, and seven-membered-ring cycloalkyl-1-one backbone. Subsequently, the tetrahydrocycloalkyl[*b*]pyrrole derivatives, which are found in many active pharmaceutical ingredients, were isolated in good yields. Mechanistic investigation highlighted a [3,3]-sigmatropic rearrangement of a sulfonium intermediate in this process.

1,4-Dicarbonyl derivatives are widely present as structural motifs in natural products and bioactive molecules.[1] These compounds are also useful building blocks and starting materials for different reactions such as the Paal−Knorr synthesis, to easily prepare heterocycles (furan, thiophene, pyrrole, etc.) from the same key intermediate.[2] Many different strategies have been described for the synthesis of these valuable scaffolds, such as oxidative couplings[3] or umpolung processes,[4a−e] including enolate[4f−i] and radical-based transformations,[4j−o] and others.[5] However, each of these approaches is necessarily limited to specific substrates, and several methods failed to construct quaternary centers or to use easy-to-handle reagents. In the framework of this study, we proposed to develop a gold(I)-catalyzed sulfonium [3,3]-sigmatropic rearrangement for the synthesis of highly functionalized 1,4-dicarbonyls.

Indeed, in recent years cascade reactions, including [3,3]-sigmatropic rearrangement of sulfur-containing substrates, have emerged as powerful strategies for the synthesis of molecules of interest.[6,7] In 2007, Toste[7a] and Zhang[7b] independently described the intramolecular gold-catalyzed alkynyl arylsulfoxide transformation to furnish the seven-membered thiepinone ring (Scheme 1a). Initially it was proposed that the reaction intermediate was an α-oxo gold carbene, but it was demonstrated later that the reaction most certainly proceeded through a [3,3]-sigmatropic rearrangement via intermediate (**I**).[7c] The intermolecular version of this reaction was then exemplified with aryl sulfoxide substrates (Scheme 1b).[7d] In addition to these processes catalyzed by organometallic Lewis acids, other strategies have emerged with the development of interrupted Pummerer reaction/sigmatropic rearrangements using charge-accelerated [3,3]-rearrangement.[6,8,9] In this context, in 2018 Maulide developed a powerful methodology for the synthesis of functionalized 1,4-dicarbonyl compounds (Scheme 1c).[9e] In the presence of triflimide, the ynamide derivative is protonated to form a highly electrophilic keteniminium intermediate, which can undergo addition of the sulfoxide. The resulting key intermediate (**III**) could then perform a rearrangement to deliver after hydrolysis the corresponding γ-keto amide. Furthermore, starting with enantiopure sulfoxides led to enantioenriched products with a good chirality transfer. While ingenious, this methodology has some perfectible features, namely, (1) the use of ynamides as starting materials, whose syntheses can sometimes be challenging or are commercially very expensive; (2) the use of a strong Brønsted acid, which must be handled carefully; and (3) the use of mainly vinyl sulfoxides without aryl groups (R^3, $R^4 \neq$ Ar). To overcome these limitations, we hypothesized that cationic gold(I) complexes could activate simple alkynes **1** via formation of π complexes and allow the regioselective addition of the

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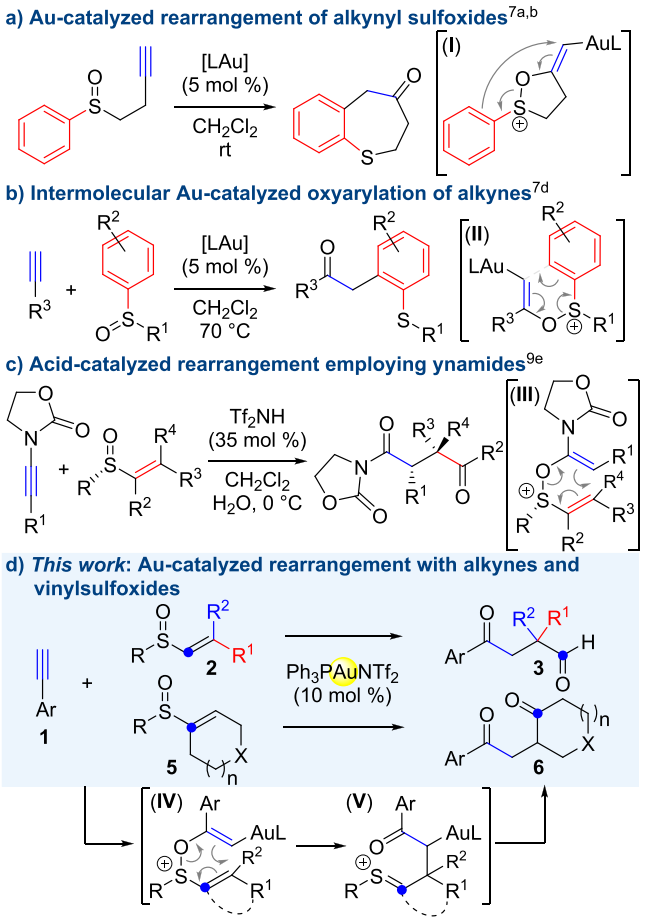
Scheme 1. Sigmatropic Rearrangement of Sulfonium Intermediates for the Synthesis of Carbonyl-Containing Compounds

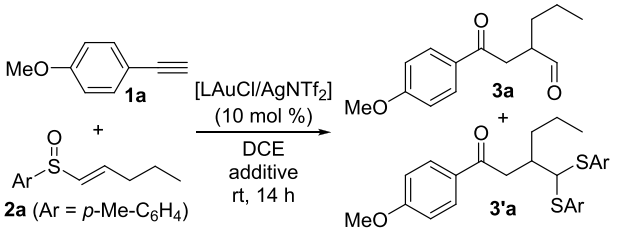


oxygen atom of the sulfoxide partner **2**[7h] (Scheme 1d). Subsequently, the sulfonium intermediate (**IV**) should perform a [3,3]-sigmatropic rearrangement to deliver a thionium ion (**V**). After hydrolysis, the corresponding 1,4-keto aldehydes **3** should be isolated.

In this paper, we report our efforts in this direction and the extension of this methodology to the use of 1-cycloalkenyl sulfoxides **5** as starting materials, whose potential has been underexploited to date. The corresponding highly functionalized cycloalkyl ketones **6** have also been used as key building blocks for the rapid synthesis of five active pharmaceutical ingredients (APIs).

Our study was initiated by reacting 1-ethynyl-4-methoxybenzene (**1a**) and sulfoxide **2a** in the presence of a 10 mol % loading of different gold(I) precatalysts in dichloroethane at room temperature (Table 1). After activation with silver bis(trifluoromethanesulfonyl)imide, the corresponding cationic gold catalysts without ligand (entry 1) or coordinated with structurally diverse ligands such as an N-heterocyclic carbene (entry 2), triphenyl phosphite (entry 3), or phosphine ligands (entries 4−6) furnished the desired 2-(2-aryl-2-oxoethyl)-pentanal (**3a**) in moderate yields. The formation of the bis(arylsulfane) byproduct **3′a** was also observed. Slight differences in both conversion and product selectivity (**3a**/**3′a**) were ascertained depending on the catalyst used. We decided to continue our study with commercially available Ph_3PAuCl as the catalyst (entry 6). After verifying that it was

Table 1. Optimization of the Reaction Conditions



entry	[Au]	additive	Conv. (%) (**3a**/**3′a**)[a]	yield of **3a** (%)[a]
1	AuCl	–	90 (1/1.1)	37
2	IPrAuCl	–	90 (1/1)	43
3	$(PhO)_3PAuCl$	–	>98 (1/1)	50
4	L_1AuCl[b]	–	90 (1.1/1)	47
5	L_2AuCl[c]	–	83 (1.8/1)	53
6	Ph_3PAuCl	–	>98 (1/1)	48
7[d]	Ph_3PAuCl	–	<5	nd
8	Ph_3PAuCl	H_2O[e]	>98 (7/1)	72
9[f]	–	H_2O[e]	50 (1/1)	25
10	$Ph_3PAuNTf_2$	H_2O[e]	>98 (10/1)	76 (74[g])

[a]Conversions, **3a**/**3′a** ratios, and yields of **3a** were determined by ^1H NMR analysis of the crude reaction mixtures with an internal standard. [b]L_1 = di-1-adamantyl-2-morpholinophenylphosphine. [c]L_2 = tris(4-methoxyphenyl)phosphine. [d]No silver salt was added. [e]3.0 equiv of H_2O was added. [f]Only the silver salt $AgNTf_2$ was used. [g]Isolated yield.

necessary to form the cationic gold catalyst (entry 7), we added some water to the reaction mixture to facilitate the hydrolysis of the thionium ion and to favor the formation of **3a** (entry 8). The expected effect was verified, as the yield of **3a** increased from 48 to 72%. Silver salt alone did not efficiently catalyze the reaction (entry 9). It is noteworthy that the use of $HNTf_2$ as the catalyst gave the same disappointing results (38% yield). Among all of the different solvents and counteranion tested, $AgNTf_2$ proved to be the best silver salt and DCE the best solvent (see Table S1). Finally, the optimal result was obtained with the use of preformed $Ph_3PAuNTf_2$ complex (10 mol %) in the presence of water at room temperature for 14 h (entry 10). The desired compound **3a** was isolated in pure form in 74% yield.

Under the optimized reaction conditions, we next examined the substrate scope, and the results are summarized in Scheme 2. We started our study with the use of various substrates **2a**−**e** (R^1 = alkyl, R^2 = H) (Scheme 2a). The products **3a**−**3e** were isolated in 44−74% yield. Product **3f**, with a cyclohexyl group, was isolated in 64% yield. Interestingly, the methodology could be efficiently extended to the 2-arylvinyl sulfoxide substrates **2g**−**i** (R^1 = aryl, R^2 = H). 4-(4-Methoxyphenyl)-4-oxo-2-phenylbutanal (**3g**) was synthesized in 77% yield on a 1 mmol scale. Regardless of the electron-donating *p*-methoxy and electronegative *p*-fluoro substituents, the corresponding products **3h** and **3i** were obtained in 67−70% yield. A heteroaryl substituent such as a thiophene group was also well-tolerated (compound **3j**, 65% yield). The second step was then to expand the substrate scope to various aryl alkynes **1b**−**h** (Scheme 2b). Seven different aryl-substituted alkynes reacted with vinyl sulfoxide **2a**. Indeed, 1,2-dimethoxybenzene, 6-methoxynaphthalene, and ferrocene alkynes reacted smoothly to give compounds **3k**−**m** in up to 73% yield. Substrates possessing hydroxyl groups exhibited moderate yields in this transformation because of the instability of both the alkyne substrates and the compounds **3n** and **3p** under air atmosphere. The use of a TBS protecting group

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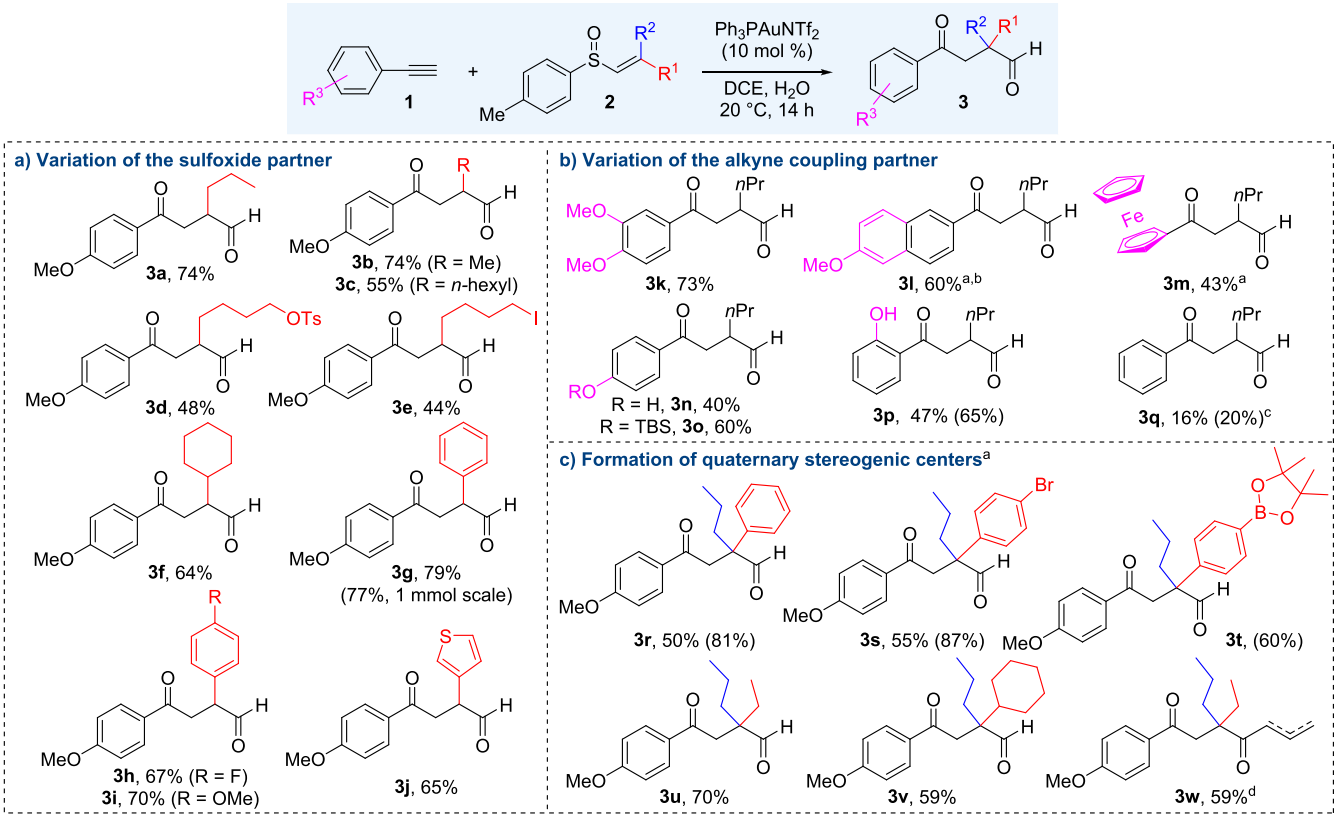
Scheme 2. Reaction Scope of the Catalytic Transformation for the Formation of 1,4-Dicarbonyl Derivatives 3[e]

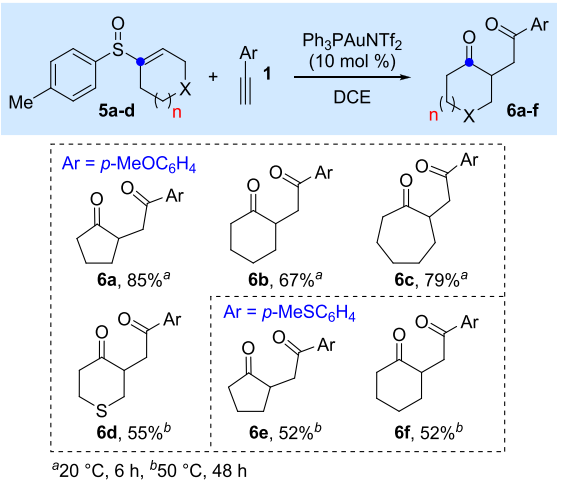


[a]The presence of water was not required to improve the yield. [b]After 14 h of reaction time, chloreal, $AgNO_3$, and $CdCO_3$ were added. [c](Johnphos)AuCl/$AgNTf_2$ catalyst, 60 h, rt. [d](*Z*)-1-((5-Ethylocta-1,4-dien-4-yl)sulfinyl)-4-methylbenzene was used as the sulfoxide substrate; a mixture of two isomers of **3w** was obtained in a 1/0.8 ratio. [e]Isolated yields after purification by column chromatography on silica gel are shown. NMR yields are given in parentheses.

increased the isolated yield to 60% (compound **3o**). For the alkyne partner, an electron-rich alkyne would appear to be necessary, since the use of ethynylbenzene provided the corresponding product **3q** in only 20% yield. It is noteworthy that with this substrate, the use of $HNTf_2$ did not furnish any conversion to the desired product. In a general way, with substrates having various substituents and/or electronic effects, the bis(arylthio)methyl derivatives **3′** were rarely obtained in more than 10% yield and were easily separated from the target products with a simple purification step. Finally, six compounds possessing quaternary stereogenic centers (compounds **3r**–**w**) were isolated in 50–70% yield (Scheme 2c). These last examples highlight the versatility of our methodology to access complex molecules in a single step. These 1,4-dicarbonyl derivatives can be transformed into various useful disubstituted heterocycles. For example, product **3g** was converted into pyrrole **4a**, furan **4b**, and thiophene **4c** through Paal–Knorr reactions (Scheme S2).[2]

Next, we considered 1-cycloalkenyl sulfoxides **5a**–**d**[10] as potential substrates for this transformation (Scheme 3). These substrates have been scarcely used in [3,3]-sigmatropic rearrangements. Reaction of **5a**–**c** with **1a** in the presence of $Ph_3PAuNTf_2$ (10 mol %) led to compounds **6a**–**c** possessing five-, six-, and seven-membered cycloalkyl-1-one backbones, respectively, in 67–85% yield. These skeletons have already been synthesized, but using less direct synthetic pathways and/or more complex procedures.[11] 3,6-Dihydro-2*H*-thiopyran sulfoxide **5d** was also engaged in the same transformation, and product **6d** was isolated in 55% yield. Finally, the substrate scope

Scheme 3. Au-Catalyzed Rearrangement of 1-Cycloalkenyl Sulfoxides 5a–d



[a]20 °C, 6 h, [b]50 °C, 48 h

was extended to the use of (4-ethynylphenyl)(methyl)sulfane, producing compounds **6e** and **6f** in 52% yield.

We next envisioned the application of our methodology to the synthesis of APIs (Scheme 4). The tetrahydrocyclopenta-[*b*]pyrrole backbone is present in many bioactive molecules,[12] as demonstrated by the known anti-inflammatory activity[12a,b] of compound **7** and the inhibitory activity of compound **8** toward cyclooxygenase 2 (COX-2).[12b] Using our methodology, we

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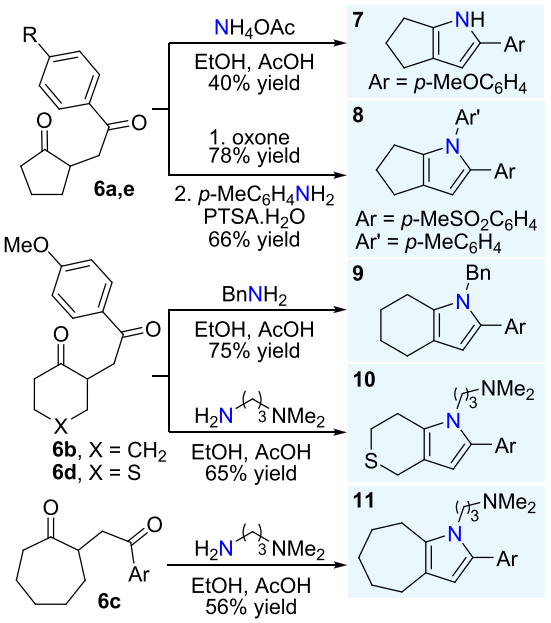
Scheme 4. Application of the Methodology to the Synthesis of APIs

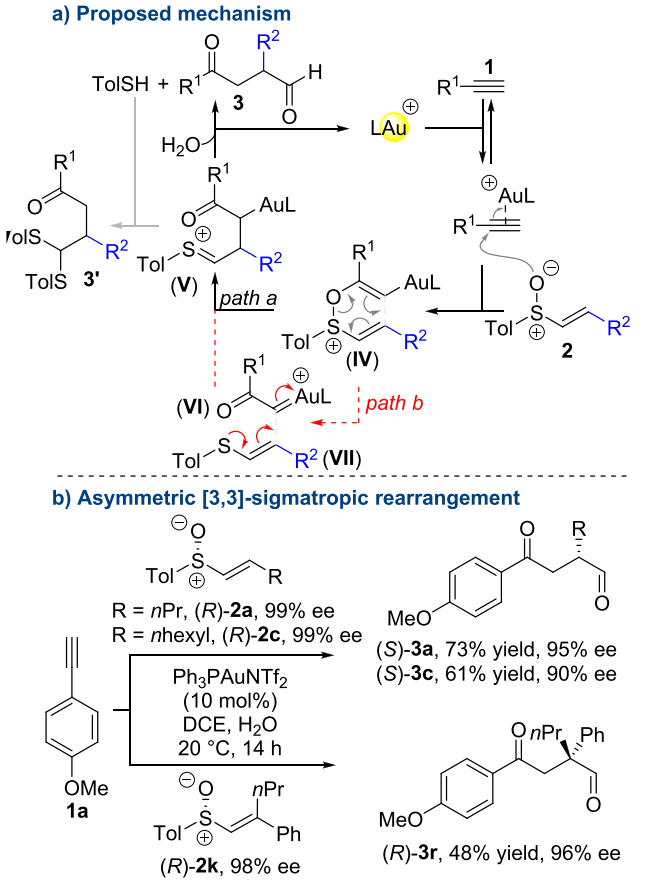


easily prepared **7** in 40% yield from diketone **6a** (R = OMe) and **8** in 66% yield from diketone **6e** (R = SMe), which was first oxidized to the corresponding sulfone. Starting from cyclohexanone **6b** (X = CH_2), the Paal–Knorr reaction with benzylamine gave access to the potent antihepatitis C virus agent **9** in 75% yield.[13] Finally, compounds **10** and **11** possess interesting properties as phosphodiesterase (PDE7) inhibitors, involved in inflammatory processes.[13d] They were synthesized in 56–65% yield using dimethylpropane-1,3-diamine and substrates **6d** and **6c**, respectively.

Concerning the mechanism of this transformation, the cationic Au(I) complex activates alkyne **1** toward the addition of vinyl sulfoxide **2** to form intermediate (**IV**) (Scheme 5a). Then sulfonium (**IV**) can perform a [3,3]-sigmatropic rearrangement to deliver thionium ion (**V**) (path a). After hydrolysis and a protodemetalation step, the corresponding 1,4-dicarbonyls **3** are formed in the presence of 4-methylbenzenethiol (TolSH). If the hydrolysis of (**V**) is not fast enough, the latter can do an addition on (**V**) to form dithioacetal **3′**. Different reaction conditions were screened to convert the small amounts of **3′** into **3** in situ. The addition of chloreal, $AgNO_3$, and $CdCO_3$ after 14 h of reaction time in some cases allowed the yield of **3** to increase (see, e.g., compound **3l** in Scheme 2). In a next step, we excluded a mechanism involving the in situ formation of α-oxo gold carbenes (**VI**)[14] and in situ generation of *p*-tolyl(vinyl)sulfane (**VII**) as potential nucleophile (path b, shown in red and in Scheme 5 and in Scheme S3). Finally, enantiopure sulfoxide (*R*)-**2a** was reacted with **1a** under the optimized reaction conditions, leading to product **3a** in 73% yield with 95% ee (Scheme 5b). Starting from (*R*)-**2c**, **3c** was isolated with 90% ee. Interestingly, this asymmetric transformation can be extended to the synthesis of enantioenriched products possessing quaternary stereogenic centers (product **3r**, 96% ee). This excellent chirality transfer from sulfur to carbon attests that the reaction mechanism evolves most probably via a [3,3]-sigmatropic rearrangement.[9e]

In summary, we have developed an efficient synthesis of 1,4-dicarbonyl derivatives using simple alkyne substrates and vinyl

Scheme 5. Mechanistic Proposal and Control Experiments



sulfoxides. Furthermore, this gold-catalyzed sulfonium [3,3]-sigmatropic rearrangement furnishes easy two-step access to tetrahydrocycloalkyl[*b*]pyrroles, a pattern present in many bioactive molecules. Efforts are ongoing to expand the synthetic potential of this transformation, particularly in the total synthesis of natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04023.

General information, experimental procedures, NMR spectra (^{1}H, and ^{13}C NMR), and HPLC data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Arnaud Voituriez − *Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette, France;* orcid.org/0000-0002-7330-0819; Email: arnaud.voituriez@cnrs.fr

Author

Weiping Zhou − *Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette, France*

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Notes

The authors declare no competing financial interest.

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