



**HAL**  
open science

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

Weiping Zhou, Arnaud Voituriez

► **To cite this version:**

Weiping Zhou, Arnaud Voituriez. Gold(I)-Catalyzed Synthesis of Highly Substituted 1,4-Dicarbonyl Derivatives via Sulfonium [3,3]-Sigmatropic Rearrangement. *Organic Letters*, 2021, 23 (1), pp.247-252. <10.1021/acs.orglett.0c04023>. <hal-03298007>

**HAL Id: hal-03298007**

**<https://hal.science/hal-03298007v1>**

Submitted on 23 Jul 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

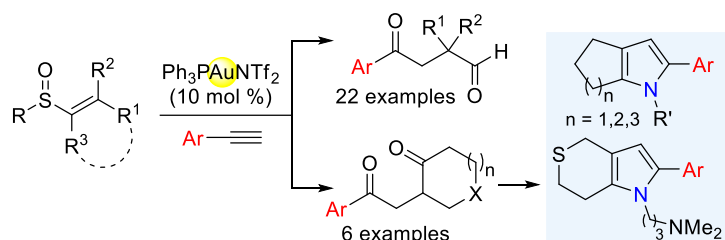


HAL Authorization

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

Weiping Zhou and Arnaud Voituriez\*

Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, UPR 2301, 91198, Gif-sur-Yvette, France.



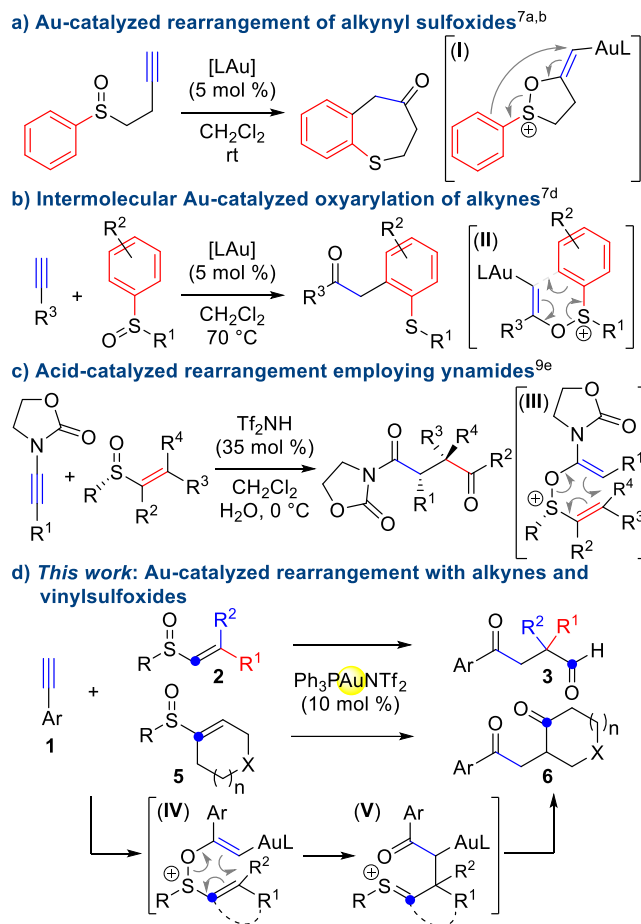
**ABSTRACT:** An efficient and straightforward gold-catalyzed protocol for the synthesis of 2-substituted-4-oxo-4-arylbutanal derivatives has been developed from commercially available or easily accessible alkynes and vinylsulfoxide substrates. Extension of the methodology to the use of 1-cycloalkenyl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

1,4-Dicarbonyl derivatives are widely present as structural motifs in natural products and bioactive molecules.<sup>1</sup> 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,...) from the same key intermediate.<sup>2</sup> Many different strategies have been described for the synthesis of these valuable scaffolds, such as oxidative couplings<sup>3</sup> or umpolung processes,<sup>4a-e</sup> including enolate<sup>4f-i</sup> and radical-based transformations,<sup>4j-o</sup> and others.<sup>5</sup> However, each of these approaches are 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 the recent years, cascade reactions including [3,3]-sigmatropic rearrangement of sulfur-containing substrates has emerged as powerful strategies for the synthesis of molecules of interest.<sup>6</sup> In 2007, Toste and Zhang independently described the intramolecular gold-catalyzed alkynyl arylsulfoxide transformation, to furnish the seven-membered thiepinone ring (Scheme 1a).<sup>7a-b</sup> Initially, it was proposed that the reaction intermediate was an  $\alpha$ -oxo gold carbene, but it was demonstrated later that the reaction most certainly proceeded through a [3,3]-sigmatropic rearrangement, *via* intermediate (**I**).<sup>7c</sup> The intermolecular version of this reaction was then exemplified with aryl sulfoxide substrates (Scheme 1b).<sup>7d</sup> 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.<sup>6,8,9</sup> In this context, Maulide developed in 2018 a powerful methodology for the synthesis of functionalized 1,4-dicarbonyl compounds (Scheme 1c).<sup>9e</sup> In the presence of triflimide, the ynamide derivatives are protonated to form a highly electrophilic keteniminium intermediate, which can undergo the addition of sulfoxides. The resulting key intermediate (**III**) could then perform a rearrangement to deliver after hydrolysis the corresponding  $\gamma$ -ketoamides. 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 material, whose syntheses can sometimes be challenging or are commercially very expensive; (2) the use of a strong Brønsted acid, which must be handled carefully; (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  $\pi$ -complexes and allow the regioselective addition of the oxygen atom of the sulfoxide partner **2**<sup>th</sup> (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.

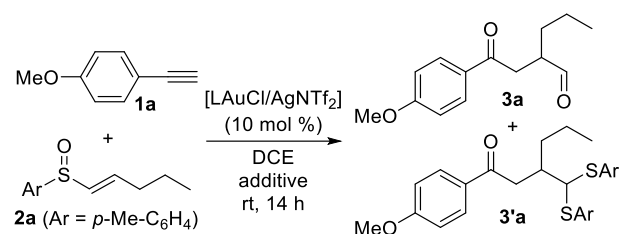
**Scheme 1. Sigmatropic rearrangement of sulfonium intermediates for the synthesis of carbonyl-containing compounds**



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 so far been underexploited. The corresponding highly functionalized cycloalkyl ketones **6** have also been used as key building blocks for the rapid synthesis of five APIs.

Our study was initiated by reacting 1-ethynyl-4-methoxybenzene **1a** and sulfoxide **2a**, in the presence of 10 mol % 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) by-product **3'a** was also observed. A slight difference both in conversion and product selectivity **3a/3'a** was ascertained, depending on the catalyst used. We decided to continue our study with the commercially available Ph<sub>3</sub>PAuCl catalyst (entry 6). After verifying that it was necessary to form the cationic gold catalyst (entry 7), we added some water in 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, since the yield of **3a** increased from 48 to 72%.

**Table 1. Optimization of the Reaction Conditions**



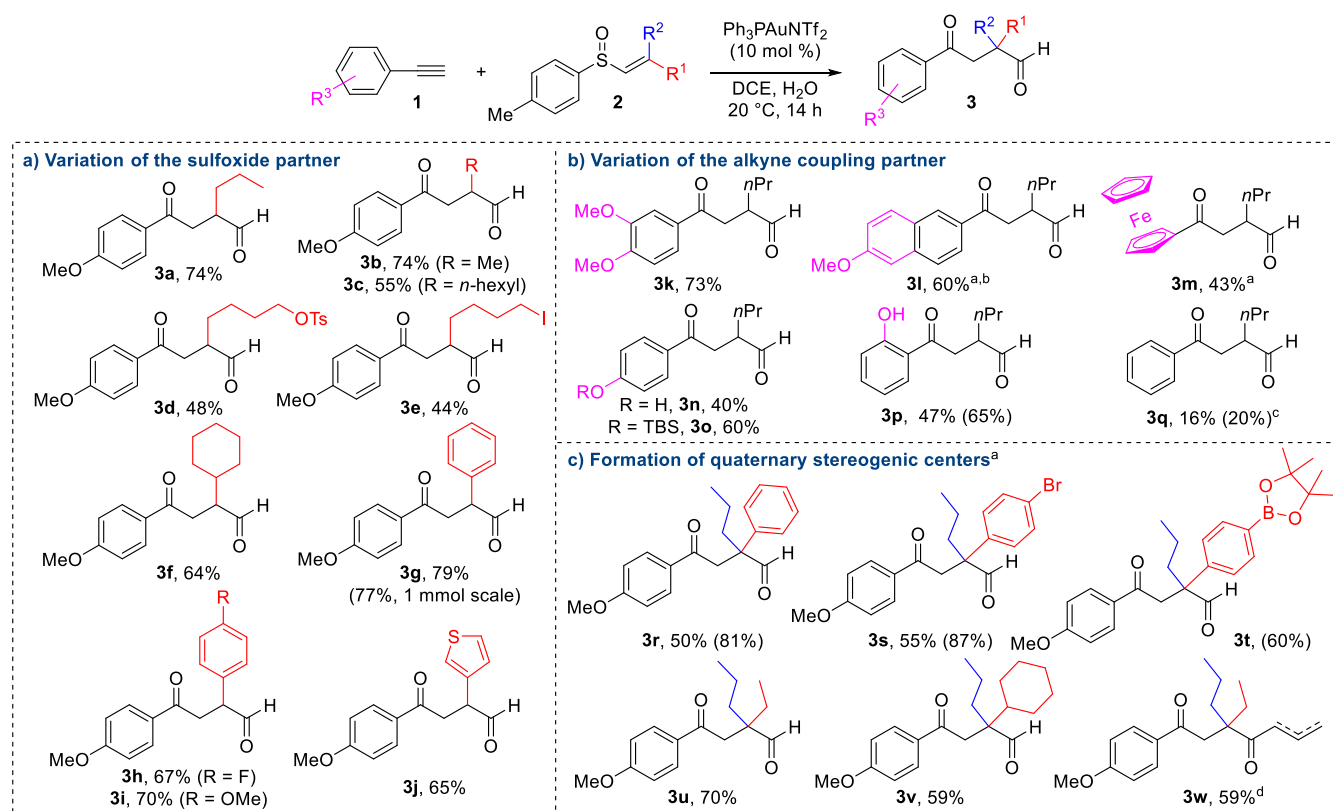
entry	[Au]	Additive	Conv. (%)	<b>3a/3'a</b> ratio <sup>a</sup>	<b>3a</b> yield (%) <sup>a</sup>
1	AuCl	-	90 (1/1.1)	37	
2	IPrAuCl	-	90 (1/1)	43	
3	(PhO) <sub>3</sub> PAuCl	-	>98 (1/1)	50	
4	L <sub>1</sub> AuCl	-	90 (1.1/1)	47	
5	L <sub>2</sub> AuCl	-	83 (1.8/1)	53	
6	Ph <sub>3</sub> PAuCl	-	>98 (1/1)	48	
7 <sup>b</sup>	Ph <sub>3</sub> PAuCl	-	<5	nd	
8	Ph <sub>3</sub> PAuCl	H <sub>2</sub> O <sup>c</sup>	>98 (7/1)	72	
9 <sup>d</sup>	-	H <sub>2</sub> O <sup>c</sup>	50 (1/1)	25	
10	Ph <sub>3</sub> PAuNTf <sub>2</sub>	H <sub>2</sub> O <sup>c</sup>	>98 (10/1)	76 (74) <sup>e</sup>	

<sup>a</sup>Conversion, **3a/3'a** ratio and yield of **3a** were determined by <sup>1</sup>H NMR analysis of the crude reaction mixture, with an internal standard. <sup>b</sup>No silver salt was added. <sup>c</sup>3.0 equiv of H<sub>2</sub>O was added. <sup>d</sup>Only the silver salt AgNTf<sub>2</sub> was used. <sup>e</sup>Isolated yield. L<sub>1</sub> = di(1-adamantyl)-2-morpholinophenylphosphine; L<sub>2</sub> = tris(4-methoxyphenyl)phosphine.

Silver salt alone does not efficiently catalyze the reaction (entry 9). It is noteworthy that the use of HNTf<sub>2</sub> as catalyst gave the same disappointing results (38% yield). Among all the different solvents and counteranion tested, AgNTf<sub>2</sub> proved to be the best silver salt and DCE the best solvent (see Table S1). *In fine*, the optimal result was obtained with the use of Ph<sub>3</sub>PAuNTf<sub>2</sub> preformed 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<sup>1</sup> = alkyl, R<sup>2</sup> = H; Scheme 2a). The products **3a,e** 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-aryl-vinylsulfoxide substrates **2g-i** (R<sup>1</sup> = aryl, R<sup>2</sup> = H). The 4-(4-methoxyphenyl)-4-oxo-2-phenylbutanal **3g** was synthesized in 77% yield on 1 mmol scale. Regardless of the electron-donating *para*-methoxy- and electronegative *p*-fluoro-substituents, the corresponding products **3h-3i** were obtained in 67-70% yields. A heteroaryl substituent such as a thiophene group is 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 **1a**. Indeed, 1,2-dimethoxybenzene, 6-methoxynaphthalen and ferrocene-alkynes reacted smoothly to give the 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,p** under air atmosphere.

## Scheme 2. Reaction Scope of the catalytic transformation for the formation of 1,4-dicarbonyl derivatives 3



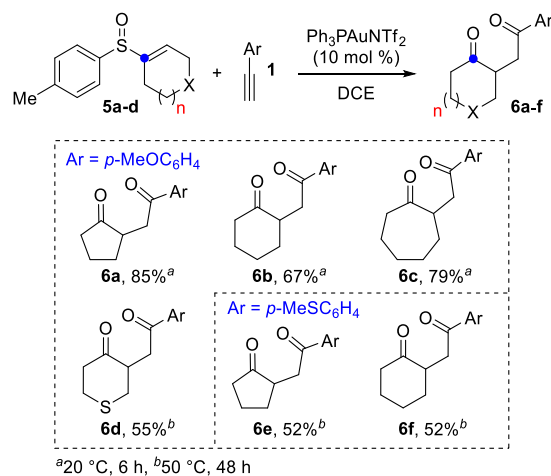
Isolated yield after purification by column chromatography on silica gel. NMR yields in parentheses. <sup>a</sup>The presence of water was not required to improve yields. <sup>b</sup>After 14 h reaction time, addition of chloreal, AgNO<sub>3</sub> and CdCO<sub>3</sub>. <sup>c</sup>(Johnphos)AuCl/AgNTf<sub>2</sub> catalyst, 60 h at rt. <sup>d</sup>(*Z*)-1-((5-Ethyl-octa-1,4-dien-4-yl)sulfinyl)-4-methylbenzene was used as the sulfoxide substrate; mixture of two isomers of **3w**, in a 1/0.8 ratio.

The use of TBS-protecting group increased the isolated yield to 60% (compound **3o**). For the alkyne partner, electron-rich alkyne would appear to be necessary, since the use of ethynylbenzene provides the corresponding product **3q** in only 20% yield. It is noteworthy that with this substrate, the use of HNTf<sub>2</sub> did not furnish any conversion in the desired product. In a general way, with substrates having various substituents and/or electronic effects, the *bis*(aryltio)methyl derivatives **3'** were rarely obtained in more than 10% yield and were easily separated from the target product with a simple purification step. Finally, six compounds possessing quaternary stereogenic centers were isolated in 50-70% yields (compounds **3r-w**, Scheme 2c). These last examples highlight the versatility of our methodology to access complex molecules in a single step. This 1,4-dicarbonyl derivative was next transformed into various useful disubstituted heterocycles such as pyrrole **4a**, furan **4b** and thiophene **4c** derivatives through Paal-Knorr reactions (Scheme S2).<sup>2</sup>

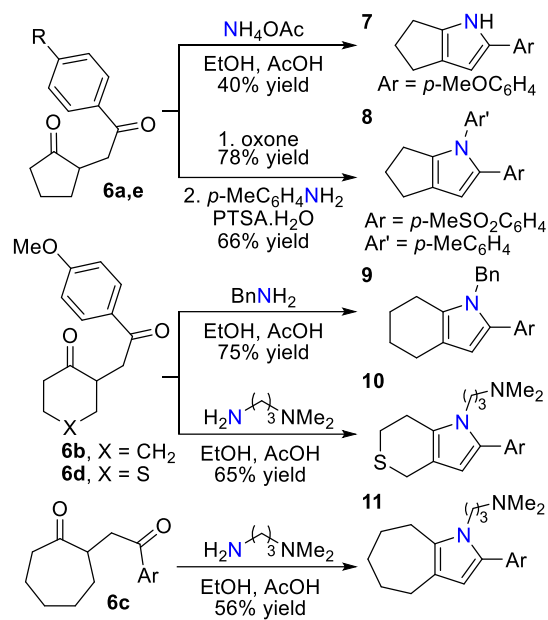
In the following of this work, we have considered 1-cycloalkenyl sulfoxides **5a-d**<sup>10</sup> as potential substrates for this transformation (Scheme 3). These substrates have been scarcely used in [3,3]-sigmatropic rearrangements. Reaction of **5a-c** with **1a**, in the presence of Ph<sub>3</sub>PAuNTf<sub>2</sub> (10 mol %) led to compounds **6a-c** in 67-85% yields, possessing respectively a five, six and seven-membered cyclo-alkyl-1-one backbone. These skeletons have already been synthesized, but using less direct synthetic pathways and/or more complex procedures.<sup>11</sup> 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 was extended to the use of the (4-ethynylphenyl)(methyl)sulfane, to produce compounds **6e-f** in 52% yield. We next envisioned the application of our methodology to the synthesis of API's (Scheme 4). The tetrahydrocyclopenta-*b*]pyrrole backbone is present in many bioactive molecules, as demonstrated by the known anti-inflammatory activity<sup>12a-b</sup> of compound **7** or the inhibiting properties of compound **8** on the cyclooxygenase 2 (COX-2).<sup>12b</sup>

### Scheme 3. Au-catalyzed rearrangement of 1-cycloalkenyl sulfoxides **5a-d**.



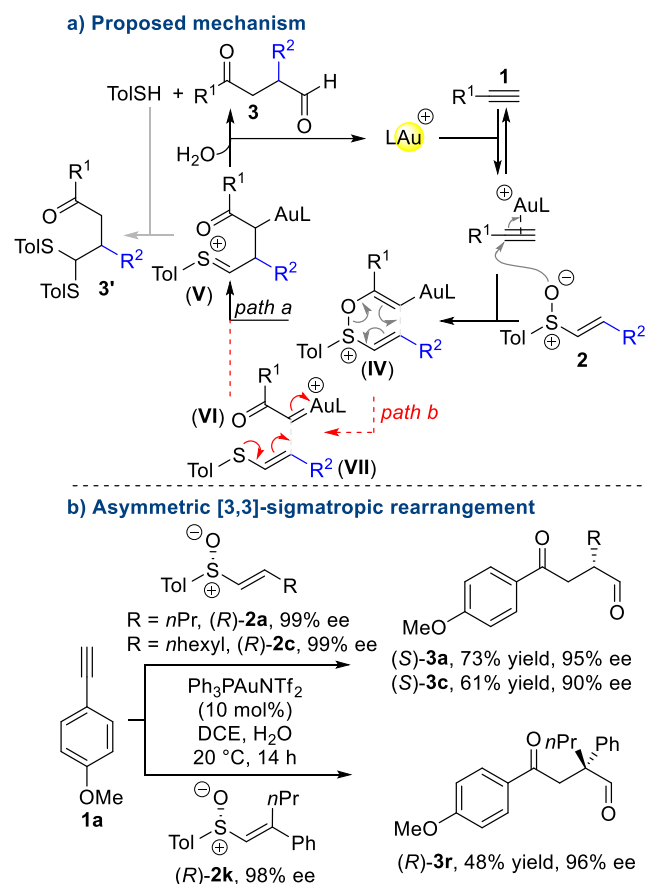
#### Scheme 4. Application of the methodology to the synthesis of API's



Using our methodology, we prepared easily **7** in 40% yield from diketone **6a** (R = OMe) and **8** from diketone **6e** (R = SMe, 66% yield), which was first oxidized to the corresponding sulfone. Starting from cyclohexanone **6b** (X = CH<sub>2</sub>), the Paal-Knorr reaction with benzylamine gave access to a potent anti-hepatitis C virus agent **9** in 75% yield.<sup>13</sup> Finally, compounds **10** and **11** possess interesting properties as phosphodiesterase (PDE7) inhibitors, involved in inflammatory processes.<sup>13d</sup> They were synthesized in 56–65% yield using dimethylpropane-1,3-diamine and substrates **6d** and **6c**.

Concerning the mechanism of this transformation, the cationic Au(I)-complex activates the alkyne **1** toward the addition of the vinylsulfoxide **2**, to form the intermediate (IV) (Scheme 5a). Then, the sulfonium (IV) could perform a [3,3]-sigmatropic rearrangement, to deliver the thionium ion (V) (*path a*). After hydrolysis and 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 the dithioacetal **3'**. Different reaction conditions were screened to *in situ* convert the small amounts of **3'** into **3**. The addition after 14 h reaction time of chloreal, AgNO<sub>3</sub> and CdCO<sub>3</sub> allowed in some cases to increase the yield of **3** (see for instance compound **3l** in Scheme 2). In a next step, we excluded a mechanism involving the *in situ* formation of  $\alpha$ -oxo gold carbenes (VI)<sup>14</sup> and *in situ* generation of *p*-tolyl(vinyl)sulfane (VII) as potential nucleophile (*path b*, in red and Scheme S3). Finally, enantiopure sulfoxide (*R*)-**2a** was engaged in the reaction with **1a** under the optimized reaction conditions, leading to product **3a** in 73% yield and 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.<sup>9e</sup>

#### Scheme 5. Mechanistic proposal and control experiments



In summary, we have developed an efficient synthesis of 1,4-dicarbonyl derivatives using simple alkyne substrates and vinylsulfoxides. Furthermore, this gold-catalyzed sulfonium [3,3]-sigmatropic rearrangement furnished an easy two-steps access to tetrahydrocycloalkyl[b]pyrroles, which is a pattern present in many bioactive molecules. Efforts are ongoing to expand the synthetic potential of this transformation, particularly in total synthesis of natural products.

#### AUTHOR INFORMATION

##### Corresponding Author

[arnaud.voituriez@cnrs.fr](mailto:arnaud.voituriez@cnrs.fr)

##### ACKNOWLEDGMENT

We thank the CSC (China Scholarship Council) for PhD grant to W. Z. and CNRS for financial support.

##### REFERENCES

- (1) (a) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. Design and Therapeutic Application of Matrix Metalloproteinase Inhibitors. *Chem. Rev.* **1999**, *99*, 2735–2776. (b) DeMartino, M. P.; Chen, K.; Baran, P. S. Intermolecular Enolate Heterocoupling: Scope, Mechanism, and Application. *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560. (c) Valot, G.; Regens, C. S.; O'Malley, D. P.; Godineau, E.; Takikawa, H.; Fürstner, A. Total Synthesis of Amphidinolide F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9534–9538. (d) Gavai, A. V. *et al.* Discovery of Clinical Candidate BMS-906024: A Potent Pan-Notch Inhibitor for the Treatment of Leukemia and Solid Tumors. *ACS Med. Chem. Lett.* **2015**, *6*, 523–527.

(2) General review on the Paal-Knorr reaction : Khaghaninejad, S.; Heravi, M. M. *Adv. Heterocycl. Chem.* **2014**, *111*, 95–146.

(3) (a) Ito, Y.; Konoike, T.; Saegusa, T. Synthesis of 1,4-diketones by the reaction of silyl enol ether with silver oxide. Regiospecific formation of silver(I) enolate intermediates. *J. Am. Chem. Soc.* **1975**, *97*, 649-651. (b) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. Synthesis of 1,4-diketones by oxidative coupling of ketone enolates with copper(II) chloride. *J. Am. Chem. Soc.* **1977**, *99*, 1487-1493. (c) Baran, P. S.; DeMartino, M. P. Intermolecular Oxidative Enolate Heterocoupling. *Angew. Chem. Int. Ed.* **2006**, *45*, 7083-7086. (d) Clift, M. D.; Taylor, C. N.; Thomson, R. J. Oxidative Carbon–Carbon Bond Formation via Silyl Bis-enol Ethers: Controlled Cross-Coupling for the Synthesis of Quaternary Centers. *Org. Lett.* **2007**, *9*, 4667-4669. (e) Ref 1b. (f) Amaya, T.; Maegawa, Y.; Masuda, T.; Osafune, Y.; Hirao, T. Selective Intermolecular Oxidative Cross-Coupling of Enolates. *J. Am. Chem. Soc.* **2015**, *137*, 10072-10075. For reviews, see : (g) Csáky, A. G.; Plumet, J. Stereoselective coupling of ketone and carboxylate enolates. *Chem. Soc. Rev.* **2001**, *30*, 313-320. (h) Guo, F.; Clift, M. D.; Thomson, R. J. Oxidative Coupling of Enolates, Enol Silanes, and Enamines: Methods and Natural Product Synthesis. *Eur. J. Org. Chem.* **2012**, 4881-4896.

(4) (a) Enders, D.; Han, J.; Henseler, A. Asymmetric intermolecular Stetter reactions catalyzed by a novel triazolium derived N-heterocyclic carbene. *Chem. Commun.* **2008**, 3989-3991. (b) Liu, Q.; Perreault, S.; Rovis, T. Catalytic Asymmetric Intermolecular Stetter Reaction of Glyoxamides with Alkylidenemalonates. *J. Am. Chem. Soc.* **2008**, *130*, 14066-14067. (c) Jousseau, T.; Wurz, N. E.; Glorius, F. Highly Enantioselective Synthesis of  $\alpha$ -Amino Acid Derivatives by an NHC-Catalyzed Intermolecular Stetter Reaction. *Angew. Chem. Int. Ed.* **2011**, *50*, 1410-1414. (d) Wilde, M. M. D.; Gravel, M. Bis(amino)cyclopropenylidenes as Organocatalysts for Acyl Anion and Extended Umpolung Reactions. *Angew. Chem. Int. Ed.* **2013**, *52*, 12651-12654. (e) Chen, X.-Y.; Enders, D., Radical Umpolung: Efficient Options for the Synthesis of 1,4-Dicarbonyl Compounds. *Angew. Chem. Int. Ed.* **2019**, *58*, 6488-6490. (f) Kise, N.; Tokioka, K.; Aoyama, Y.; Matsumura, Y. Enantioselective Synthesis of 2,3-Disubstituted Succinic Acids by Oxidative Homocoupling of Optically Active 3-Acyl-2-oxazolidones. *J. Org. Chem.* **1995**, *60*, 1100-1101. (g) Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. Cross-Coupling Reaction of  $\alpha$ -Chloroketones and Organotin Enolates Catalyzed by Zinc Halides for Synthesis of  $\gamma$ -Diketones. *J. Am. Chem. Soc.* **2002**, *124*, 7440-7447. (h) Luo, J.; Jiang, Q.; Chen, H.; Tang, Q. Catalyst-free formation of 1,4-diketones by addition of silyl enolates to oxallyl zwitterions in situ generated from  $\alpha$ -haloketones. *RSC Advances* **2015**, *5*, 67901-67908. (i) Kaiser, D.; Teskey, C. J.; Adler, P.; Maulide, N. Chemoselective Intermolecular Cross-Enolate-Type Coupling of Amides. *J. Am. Chem. Soc.* **2017**, *139*, 16040-16043. (j) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. Enantioselective Organocatalytic Singly Occupied Molecular Orbital Activation: The Enantioselective  $\alpha$ -Enolation of Aldehydes. *J. Am. Chem. Soc.* **2007**, *129*, 7004-7005. (k) Yasu, Y.; Koike, T.; Akita, M. Sunlight-driven synthesis of  $\gamma$ -diketones via oxidative coupling of enamines with silyl enol ethers catalyzed by  $[\text{Ru}(\text{bpy})_3]^{2+}$ . *Chem. Commun.* **2012**, *48*, 5355-5357. (l) Zhang, F.; Du, P.; Chen, J.; Wang, H.; Luo, Q.; Wan, X. Co-Catalyzed Synthesis of 1,4-Dicarbonyl Compounds Using TBHP Oxidant. *Org. Lett.* **2014**, *16*, 1932-1935. (m) Morack, T.; Mück-Lichtenfeld, C.; Gilmour, R. Bioinspired Radical Stetter Reaction: Radical Umpolung Enabled by Ion-Pair Photocatalysis. *Angew. Chem. Int. Ed.* **2019**, *58*, 1208-1212. (n) Goti, G.; Bieszczad, B.; Vega-Peñaloza, A.; Melchiorre, P. Stereocontrolled Synthesis of 1,4-Dicarbonyl Compounds by Photochemical Organocatalytic Acyl Radical Addition to Enals. *Angew. Chem. Int. Ed.* **2019**, *58*, 1213-1217. (o) Kuang, Y.; Wang, K.; Shi, X.; Huang, X.; Meggers, E.; Wu, J. Asymmetric Synthesis of 1,4-Dicarbonyl Compounds from Aldehydes by Hydrogen Atom Transfer Photocatalysis and Chiral Lewis Acid Catalysis. *Angew. Chem. Int. Ed.* **2019**, *58*, 16859-16863.

(5) Representative publications : (a) Moriarty, R. M.; Prakash, O.; Duncan, M. P. Carbon–carbon bond formation using hypervalent iodine under Lewis acid conditions: 1,4-diarylbutane-1,4-diones. *J. Chem. Soc., Chem. Commun.* **1985**, 420-420. (b) Aoki, S.; Nakamura, E. Synthesis of 1,4-dicarbonyl compounds and 4-keto pimelates by

palladium-catalyzed carbonylation of siloxycyclopropanes. *Tetrahedron* **1991**, *47*, 3935-3946. (c) Echavarren, A. M.; Pérez, M.; Castano, A. M.; Cuerva, J. M. Palladium-Catalyzed Reductive Coupling of Acid Chlorides with  $\beta$ -Stannyl Enones: Synthesis of 1,4-Diketones and Mechanistic Aspects. *J. Org. Chem.* **1994**, *59*, 4179-4185. (d) Yin, H.; Nielsen, D. U.; Johansen, M. K.; Lindhardt, A. T.; Skrydstrup, T. Development of a Palladium-Catalyzed Carbonylative Coupling Strategy to 1,4-Diketones. *ACS Catalysis* **2016**, *6*, 2982-2987. (e) Rong, J.; Li, H.; Fu, R.; Sun, W.; Loh, T.-P.; Jiang, Y. Cleavage and Reassembly C=C Bonds of Ynones to Access Highly Functionalized Ketones. *ACS Catalysis* **2020**, *10*, 3664-3669.

(6) (a) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. Beyond the Pummerer Reaction: Recent Developments in Thionium Ion Chemistry. *Angew. Chem. Int. Ed.* **2010**, *49*, 5832-5844. (b) Huang, X.; Klimczyk, S.; Maulide, N., Charge-Accelerated Sulfonium [3,3]-Sigmatropic Rearrangements. *Synthesis* **2012**, *44*, 175-183. (c) Pulis, A. P.; Procter, D. J. C–H Coupling Reactions Directed by Sulfoxides: Teaching an Old Functional Group New Tricks. *Angew. Chem. Int. Ed.* **2016**, *55*, 9842-9860. (d) Yorimitsu, H. Cascades of Interrupted Pummerer Reaction-Sigmatropic Rearrangement. *Chem. Rec.* **2017**, *17*, 1156-1167. (e) Yanagi, T.; Nogi, K.; Yorimitsu, H. Recent development of ortho-C–H functionalization of aryl sulfoxides through [3,3] sigmatropic rearrangement. *Tetrahedron Lett.* **2018**, *59*, 2951-2959. (f) Kaiser, D.; Klose, I.; Oost, R.; Neuhaus, J.; Maulide, N. Bond-Forming and -Breaking Reactions at Sulfur(IV): Sulfoxides, Sulfonium Salts, Sulfur Ylides, and Sulfinate Salts. *Chem. Rev.* **2019**, *119*, 8701-8780.

(7) (a) Shapiro, N. D.; Toste, F. D. Rearrangement of Alkynyl Sulfoxides Catalyzed by Gold(I) Complexes. *J. Am. Chem. Soc.* **2007**, *129*, 4160-4161. (b) Li, G.; Zhang, L. Gold-Catalyzed Intramolecular Redox Reaction of Sulfinyl Alkynes: Efficient Generation of  $\alpha$ -Oxo Gold Carbenoids and Application in Insertion into R-CO Bonds. *Angew. Chem. Int. Ed.* **2007**, *46*, 5156-5159. (c) Lu, B.; Li, Y.; Wang, Y.; Aue, D. H.; Luo, Y.; Zhang, L. [3,3]-Sigmatropic Rearrangement versus Carbene Formation in Gold-Catalyzed Transformations of Alkynyl Aryl Sulfoxides: Mechanistic Studies and Expanded Reaction Scope. *J. Am. Chem. Soc.* **2013**, *135*, 8512-8524. (d) Cuenca, A. B.; Montserrat, S.; Hossain, K. M.; Mancha, G.; Lledós, A.; Medio-Simón, M.; Ujaque, G.; Asensio, G. Gold(I)-Catalyzed Intermolecular Oxyarylation of Alkynes: Unexpected Regiochemistry in the Alkylation of Arenes. *Org. Lett.* **2009**, *11*, 4906-4909. (e) Li, C.-W.; Pati, K.; Lin, G.-Y.; Soheli, S. M. A.; Hung, H.-H.; Liu, R.-S. Gold-Catalyzed Oxidative Ring Expansions and Ring Cleavages of Alkynylcyclopropanes by Intermolecular Reactions Oxidized by Diphenylsulfoxide. *Angew. Chem. Int. Ed.* **2010**, *49*, 9891-9894. (f) Barrett, M. J.; Davies, P. W.; Grainger, R. S. Regioselective functionalisation of dibenzothiophenes through gold-catalysed intermolecular alkyne oxyarylation. *Org. Biomol. Chem.* **2015**, *13*, 8676-8686. (g) Murakami, K.; Imoto, J.; Matsubara, H.; Yoshida, S.; Yorimitsu, H.; Oshima, K., Copper-Catalyzed Extended Pummerer Reactions of Ketene Dithioacetal Monoxides with Alkynyl Sulfides and Ynamides with an Accompanying Oxygen Rearrangement. *Chem. Eur. J.* **2013**, *19*, 5625-5630. For general reviews on gold-catalysis, see : (h) Dorel, R.; Echavarren, A. M. Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity. *Chem. Rev.* **2015**, *115*, 9028-9072. (i) Wei, Y.; Shi, M. Divergent Synthesis of Carbo- and Heterocycles via Gold-Catalyzed Reactions. *ACS Catalysis* **2016**, *6*, 2515-2524.

(8) Representative examples : (a) Yoshida, S.; Yorimitsu, H.; Oshima, K., 2-(2,2,2-Trifluoroethylidene)-1,3-dithiane Monoxide as a Trifluoromethylketene Equivalent. *Org. Lett.* **2009**, *11* 2185-2188. (b) Kobatake, T.; Yoshida, S.; Yorimitsu, H.; Oshima, K., Reaction of 2-(2,2,2-Trifluoroethylidene)-1,3-dithiane 1-Oxide with Ketones under Pummerer Conditions and Its Application to the Synthesis of 3-Trifluoromethyl-Substituted Five-Membered Heteroarenes. *Angew. Chem. Int. Ed.* **2010**, *49*, 2340-2343. (c) Huang, X.; Maulide, N., Sulfoxide-Mediated  $\alpha$ -Arylation of Carbonyl Compounds. *J. Am. Chem. Soc.* **2011**, *133*, 8510-8513. (d) Eberhart, A. J.; Imbriglio, J. E.; Procter, D. J., Nucleophilic Ortho Allylation of Aryl and Heteroaryl Sulfoxides. *Org. Lett.* **2011**, *13*, 5882-5885. (e) Yanagi, T.; Otsuka, S.; Kasuga, Y.; Fujimoto, K.; Murakami, K.; Nogi, K.; Yorimitsu, H.;

- Osuka, A. Metal-Free Approach to Biaryls from Phenols and Aryl Sulfoxides by Temporarily Sulfur-Tethered Regioselective C–H/C–H Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 14582–14585. (f) Fernández-Salas, J. A.; Eberhart, A. J.; Procter, D. J. Metal-Free CH–CH-Type Cross-Coupling of Arenes and Alkynes Directed by a Multifunctional Sulfoxide Group. *J. Am. Chem. Soc.* **2016**, *138*, 790–793. (g) Shrivs, H. J.; Fernández-Salas, J. A.; Hedtke, C.; Pulis, A. P.; Procter, D. J. Regioselective synthesis of C3 alkylated and arylated benzothiophenes. *Nat. Commun.* **2017**, *8*, 14801. (h) He, Z.; Shrivs, H. J.; Fernández-Salas, J. A.; Abengózar, A.; Neufeld, J.; Yang, K.; Pulis, A. P.; Procter, D. J. Synthesis of C2 Substituted Benzothiophenes via an Interrupted Pummerer/[3,3]-Sigmatropic/1,2-Migration Cascade of Benzothiophene S-Oxides. *Angew. Chem. Int. Ed.* **2018**, *57*, 5759–5764.
- (9) (a) Peng, B.; Huang, X.; Xie, L.-G.; Maulide, N. A Brønsted Acid Catalyzed Redox Arylation. *Angew. Chem. Int. Ed.* **2014**, *53*, 8718–8721. (b) Kaiser, D.; Veiros, L. F.; Maulide, N. Brønsted Acid-Mediated Hydrative Arylation of Unactivated Alkynes. *Chem. Eur. J.* **2016**, *22*, 4727–4732. (c) Kaiser, D.; Veiros, L. F.; Maulide, N. Redox-Neutral Arylations of Vinyl Cation Intermediates. *Adv. Synth. Catal.* **2017**, *359*, 64–77. (d) Kaldre, D.; Maryasin, B.; Kaiser, D.; Gajsek, O.; González, L.; Maulide, N. An Asymmetric Redox Arylation: Chirality Transfer from Sulfur to Carbon through a Sulfonium [3,3]-Sigmatropic Rearrangement. *Angew. Chem. Int. Ed.* **2017**, *56*, 2212–2215. (e) Kaldre, D.; Klose, I.; Maulide, N. Stereodivergent synthesis of 1,4-dicarbonyls by traceless charge-accelerated sulfonium rearrangement. *Science* **2018**, *361*, 664–667. For related studies, see: (f) Hu, L.; Gui, Q.; Chen, X.; Tan, Z.; Zhu, G. HOTf-Catalyzed, Solvent-Free Oxyarylation of Ynol Ethers and Thioethers. *J. Org. Chem.* **2016**, *81*, 4861–4868.
- (10) (a) Marino, J. P.; Perez, A. D. Enantiospecific lactonizations of chiral 1-(arylsulfinyl)cyclohexenes with chloro ketenes. *J. Am. Chem. Soc.* **1984**, *106*, 7643–7644. (b) Kunio, H.; Nobuhiko, M. A Novel and Useful Synthetic Way to Chiral  $\alpha$ -Sulfinyl Cyclic Ketones by the Acid-Catalyzed Reaction of Enol Silyl Ethers of Cyclic Ketones with Chiral Sulfinates. *Chem. Lett.* **1986**, *15*, 65–68. (c) Iwata, C.; Maezaki, N.; Kurumada, T.; Fukuyama, H.; Sugiyama, K.; Imanishi, T. New carbon–carbon bond formation by the Pummerer-type reaction of vinylic sulphoxides with allylmagnesium bromide. *J. Chem. Soc., Chem. Commun.* **1991**, 1408–1409. (d) Maezaki, N.; Izumi, M.; Yuyama, S.; Iwata, C.; Tanaka, T. Intramolecular alkylation of an  $\alpha$ -sulfinyl vinylic carbanion without loss of optical purity: a novel access to chiral cyclic vinylic sulfoxides. *Chem. Commun.* **1999**, 1825–1826. (e) Maezaki, N.; Izumi, M.; Yuyama, S.; Sawamoto, H.; Iwata, C.; Tanaka, T. Studies on Intramolecular Alkylation of an  $\alpha$ -Sulfinyl Vinylic Carbanion: a Novel Route to Chiral 1-Cycloalkenyl Sulfoxides. *Tetrahedron* **2000**, *56*, 7927–7945. (f) Díaz Buezo, N.; de la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. Sulfoxides as Stereochemical Controllers in Intermolecular Heck Reactions. *Chem. Eur. J.* **2001**, *7*, 3890–3900.
- (11) For representative examples, see: (a) Li, Y.; Shang, J.-Q.; Wang, X.-X.; Xia, W.-J.; Yang, T.; Xin, Y.; Li, Y.-M. Copper-Catalyzed Decarboxylative Oxyalkylation of Alkynyl Carboxylic Acids: Synthesis of  $\gamma$ -Diketones and  $\gamma$ -Ketonitriles. *Org. Lett.* **2019**, *21*, 2227–2230. (b) Arceo, E.; Bahamonde, A.; Bergonzini, G.; Melchiorre, P. Enantioselective direct  $\alpha$ -alkylation of cyclic ketones by means of photo-organocatalysis. *Chem. Sci.* **2014**, *5*, 2438–2442. (c) Sun, H.; Yang, C.; Gao, F.; Li, Z.; Xia, W., Oxidative C–C Bond Cleavage of Aldehydes via Visible-Light Photoredox Catalysis. *Org. Lett.* **2013**, *15*, 624–627. (d) Yasu, Y.; Koike, T.; Akita, M. Sunlight-driven synthesis of  $\gamma$ -diketones via oxidative coupling of enamines with silyl enol ethers catalyzed by [Ru(bpy)<sub>3</sub>]<sup>2+</sup>. *Chem. Commun.* **2012**, *48*, 5355–5357. (e) Xie, J.; Huang, Z.-Z. The cascade carbo-carbonylation of unactivated alkenes catalyzed by an organocatalyst and a transition metal catalyst: a facile approach to  $\gamma$ -diketones and  $\gamma$ -carbonyl aldehydes from arylalkenes under air. *Chem. Commun.* **2010**, *46*, 1947–1949. (f) Fujii, T.; Hirao, T.; Ohshiro, Y. Oxovanadium-induced oxidative desilylation for the selective synthesis of 1,4-diketones. *Tetrahedron Lett.* **1992**, *33*, 5823–5826.
- (12) (a) Xu, X.-T.; Mou, X.-Q.; Xi, Q.-M.; Liu, W.-T.; Liu, W.-F.; Sheng, Z.-J.; Zheng, X.; Zhang, K.; Du, Z.-Y.; Zhao, S.-Q.; Wang, S.-H. Anti-inflammatory activity effect of 2-substituted-1,4,5,6-tetrahydrocyclopenta[b]pyrrole on TPA-induced skin inflammation in mice. *Bio. Med. Chem. Lett.* **2016**, *26*, 5334–5339. (b) Zhong, B. H.; Li, M. Y. *China Pat.* **2007** CN 1995163A. (c) Mou, X.-Q.; Xu, Z.-L.; Wang, S.-H.; Zhu, D.-Y.; Wang, J.; Bao, W.; Zhou, S.-J.; Yang, C.; Zhang, D. An Au(I)-catalyzed rearrangement/cyclization cascade toward the synthesis of 2-substituted-1,4,5,6-tetrahydrocyclopenta[b]pyrrole. *Chem. Commun.* **2015**, *51*, 12064–12067. (d) François, B.; Eberlin, L.; Berrée, F.; Whiting, A.; Carboni, B. Access to Fused Pyrroles from Cyclic 1,3-Dienyl Boronic Esters and Arylnitroso Compounds. *J. Org. Chem.* **2020**, *85*, 5173–5182.
- (13) (a) Andreev, I. A.; Manvar, D.; Barreca, M. L.; Belov, D. S.; Basu, A.; Sweeney, N. L.; Ratmanova, N. K.; Lukyanenko, E. R.; Manfroni, G.; Cecchetti, V.; Frick, D. N.; Altieri, A.; Kaushik-Basu, N.; Kurkin, A. V. Discovery of the 2-phenyl-4,5,6,7-Tetrahydro-1H-indole as a novel anti-hepatitis C virus targeting scaffold. *Eur. J. Med. Chem.* **2015**, *96*, 250–258. (b) Andreev, I. A.; Belov, D. S.; Kurkin, A. V.; Yurovskaya, M. A. Synthesis of 4,5,6,7-Tetrahydro-1H-indole Derivatives Through Successive Sonogashira Coupling/Pd-Mediated 5-endo-dig Cyclization. *Eur. J. Org. Chem.* **2013**, 649–652. (c) Anderson, V. B.; Agnew, M. N.; Allen, R. C.; Wilker, J. C.; Lassman, H. B.; Novick, W. J. Carboxyarylindoles as nonsteroidal antiinflammatory agents. *J. Med. Chem.* **1976**, *19*, 318–325. (d) Jpn. Kokai Tokkyo Koho **2006**, JP 2006290791.
- (14) (a) Li, J.; Ji, K.; Zheng, R.; Nelson, J.; Zhang, L. Expanding the horizon of intermolecular trapping of *in situ* generated  $\alpha$ -oxo gold carbenes: efficient oxidative union of allylic sulfides and terminal alkynes via C–C bond formation. *Chem. Commun.* **2014**, *50*, 4130–4133. (b) Santos, M. D.; Davies, P. W. A gold-catalysed fully intermolecular oxidation and sulfur-ylide formation sequence on ynamides. *Chem. Commun.* **2014**, *50*, 6001–6004. (c) Zhang, L. A Non-Diazo Approach to  $\alpha$ -Oxo Gold Carbenes via Gold-Catalyzed Alkyne Oxidation. *Acc. Chem. Res.* **2014**, *47*, 877–888. (d) Stow, C. P.; Widenhofer, R. A. Synthesis, Structure, and Reactivity of Gold(I)  $\alpha$ -Oxo Carbenoid Complexes. *Organometallics* **2020**, *39*, 1249–1257.