Gold Catalysis

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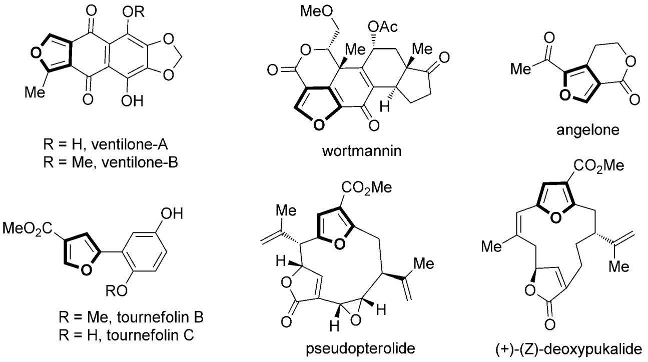
Gold-Catalyzed Synthesis of Furans and Furanones from Sulfur Ylides**

*Xueliang Huang, Bo Peng, Marco Luparia, Luis F. R. Gomes, Luís F. Veiros, and Nuno Maulide**

Polysubstituted furan derivatives are fundamental building blocks in organic synthesis. The plethora of natural products, agrochemicals, and pharmaceuticals that contain a di-, tri-, or tetrasubstituted furan moiety attests to this fact (Scheme 1).[1] A cursory examination of the compounds depicted in Scheme 1 reveals a notable incidence of 3-carboxy-functionalized polysubstituted furans in the natural product cores, including furofuranone and -pyranone moieties (such as in angelone).



Scheme 1. Selected examples of natural products containing a furan core.[1]

Herein we report a simple and flexible gold-catalyzed[2,3] synthesis of densely functionalized 3-carboxyfuran derivatives that hinges on a key cross-coupling between sulfonium ylides and alkynes.[4–6] We further disclose an intriguing reactivity switch that allows the synthesis of furanones containing a quaternary center as well as computational data on the mechanism of these transformations.[7]

Initial studies focused on the alkynyl sulfonium ylide **1a**, readily available by direct ylide transfer[8] to the corresponding ketoester. Exposure of this compound to diverse gold(I) promoters led to sharply contrasting results (see the Supporting Information for details), and it was found that the simple combination of commercially available PPh_3AuCl and $AgSbF_6$ led to quantitative conversion into the furofuranone **2a** at room temperature within 3 h.[9]

We then examined the scope of this simple yet highly effective procedure for the intramolecular preparation of bicyclic furans. Importantly, all the alkynyl sulfonium ylides employed as substrates could be readily accessed by direct ylide transfer in very high yields according to our previously reported procedure.[8] Their stability towards chromatography and recrystallization along with their crystallinity renders them easily handled substrates for subsequent transformations.

As shown in Table 1, a variety of bicyclofurans could be readily prepared by simply stirring the ylide precursors in the presence of the gold catalyst at room temperature. Importantly, the preparation of the furopyranone **2i** (Table 1, entry 9) required slightly modified conditions and the use of a different, more electron-poor phosphine, once again suggesting that less facile cyclizations of sulfonium ylides onto alkynes may be favored by the use of more electron-deficient gold(I) species. Various alkyl and aryl moieties were tolerated by the procedure, and furopyrrolones such as **2k** could also be prepared by employing an amide-tethered alkyne. All-carbon tethers are also suitable for this transformation (Table 1, entry 12). To the best of our knowledge, this constitutes the first intramolecular synthesis of furans from stabilized sulfonium ylides.[9a]

We then turned our interest to an intermolecular version of the same reaction.[10] The double stabilization of our sulfonium ylides made some optimization of this process necessary,[11] and some key results obtained are compiled in Scheme 2.

The use of *t*BuXPhos as a ligand was required to obtain synthetically useful yields of product **5a**, particularly with regard to preventing excessive polymerization of phenylacetylene (**4a**; Scheme 2a). The very high regioselectivity of this reaction is noteworthy, as only trace amounts of other regioisomers could be detected. Additionally, and in complementary fashion to the recent elegant report by Skyrdstrup et al. employing singly stabilized sulfonium ylides,[4g] we

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[*] Dr. X. Huang, Dr. B. Peng,[+] Dr. M. Luparia,[+] L. F. R. Gomes,[+]
Dr. N. Maulide
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
E-mail: maulide@mpi-muelheim.mpg.de
Homepage: http://www.kofo.mpg.de/maulide
Prof. Dr. L. F. Veiros
Centro de Química Estrutural, Complexo I
Instituto Superior Técnico, Universidade Técnica de Lisboa
Av. Rovisco Pais 1, 1049-001 Lisbon (Portugal)

[+] These authors contributed equally to this work.

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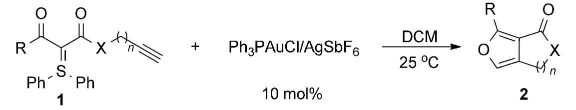
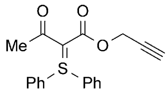
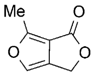
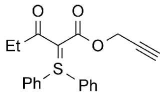
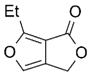
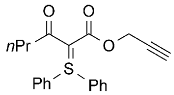
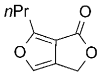
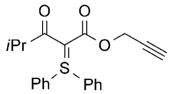
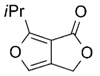
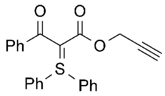
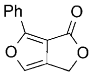
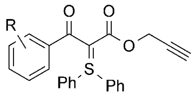
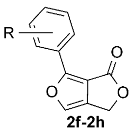
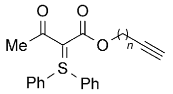
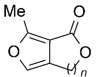
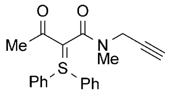
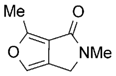
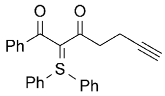
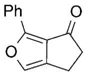
Table 1: Scope of the intramolecular synthesis of bicyclofurans.

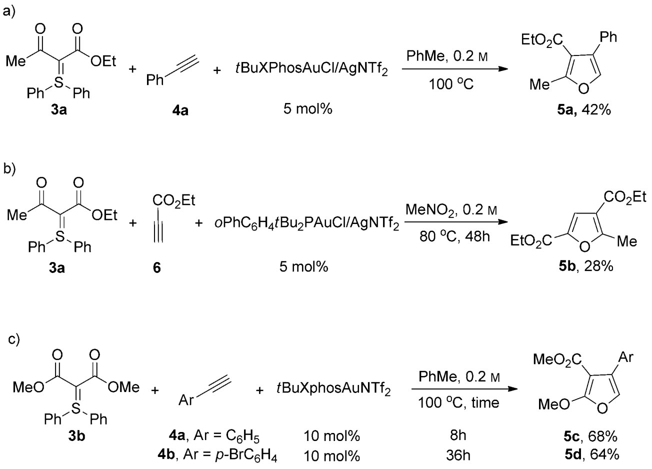


Entry	Ylide	t [h]	Product	Yield [%][a]
1	 **1a**	3	 **2a**	99
2	 **1b**	3	 **2b**	90
3	 **1c**	3	 **2c**	87
4	 **1d**	3	 **2d**	63
5	 **1e**	4	 **2e**	60
6[b] 7[b] 8[b]	 **1f-1h**	7	 **2f-2h**	**2f**, R = *p*-Me, 66 **2g**, R = *p*-Cl, 49 **2h**, R = *m*-(2-Naph), 46
9[c] 10	 **1i-1j**	24	 **2i-2j**	**2i**, $n=2$, 80 **2j**, $n=3$, 0
11[b]	 **1k**	13	 **2k**	50
12	 **1l**	20	 **2l**	45

[a] See the Supporting Information for detailed reaction conditions. Yields refer to isolated products after chromatography. [b] 5 mol% of $Ph_3PAuCl/AgSbF_6$ was employed. [c] 5 mol% of $[3,5\text{-}(CF_3)_2C_6H_3]_3PAuCl$ was used instead of Ph_3PAuCl.

found that arylalkynes are the most successful triple-bond partners. Best results are obtained when the ylide partner is the limiting reagent and the alkyne is employed in excess.

We subsequently realized that this intermolecular furan synthesis is particularly sensitive to the substitution pattern of both the sulfur ylide and the alkyne partner (Scheme 2b). While the use of electron-poor alkynes (such as propiolate derivatives) leads to low yields of product **5b**, it was interesting to note that a malonate-derived sulfonium ylide provided 2-methoxyfuran **5c** in reasonable efficiency (Scheme 2c). Again, this observation seems to nicely complement the recent report on an efficient stoichiometric silver-mediated furan synthesis from active methylene compounds, for which malonate esters were not competent substrates.[9b] The ability to access 2-methoxyfuran products is noteworthy owing to their synthetic versatility.[12]



Scheme 2. Intermolecular synthesis of furans.

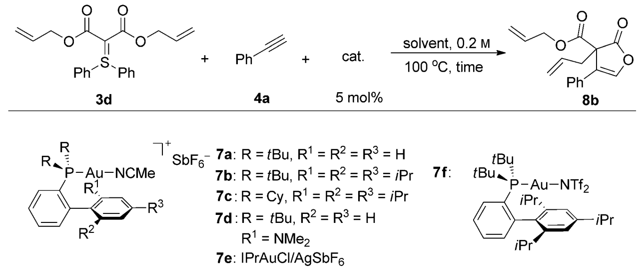
During our screening of diversely decorated ylide substrates, we hypothesized that modification of one or both alkoxycarbonyl moieties might unlock new reactivity. In the event, the reaction of the readily available allyloxyester **3c** with phenylacetylene, promoted by Echavarren's catalyst **7**,[13] afforded the C-allylated 2-furanone **8a**, which contains a quaternary center, along with the expected furan product.[14] As polysubstituted γ-lactones are common structural motifs in bioactive natural compounds,[15,16] we decided to investigate this transformation further.[17]

We thus prepared the diallylmalonate-derived ylide **3d** and briefly studied its reaction with phenylacetylene. Under conditions similar to those described above, the reaction proceeded to completion within 2 h, giving lactone **8b** in high yield (Table 2, entry 2). Other ligands led to slower reactions with marginally lower yields (Table 2, entries 1 and 3–6). A screening of different solvents revealed dichloroethane to be superior (Table 2, entries 2 and 7–10). Interestingly, switching to a more coordinating counteranion led to a lower yield of **8b** (Table 2, entry 6). After establishing optimized conditions for this transformation, we investigated its scope (Scheme 3).

As depicted, a variety of different alkynes can be employed, and best results are obtained with aromatic alkynes. The use of an aliphatic alkyne (cf. **8i**) leads to lower yield of the furanone product.

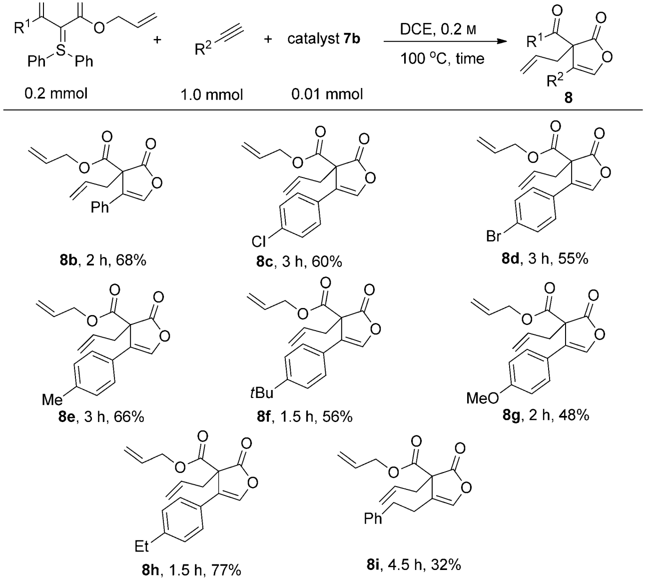
The outcome observed upon exposure of allyloxycarbonyl substrates to an alkyne and a gold(I) catalyst presumably results from allylic rearrangement of that ester moiety. To determine whether the metal catalyst might be involved in this rearrangement event, we prepared the tetradeuterated diester **3d** and subjected it to the reaction conditions (Scheme 4). In the event, the rearranged furanone was formed with complete transfer of the deuterated label to the vinyl position, a hallmark of highly concerted allylic transfers characteristic of [3,3]-sigmatropic events.[16]

Table 2: Optimization of the γ-lactone synthesis from sulfonium ylides and alkynes.[a]



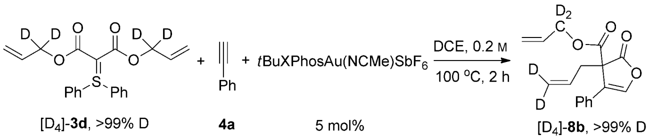
Entry	Cat.	Solvent	Time [h]	Yield [%][b]
1	**7a**	DCE	7	64
2	**7b**	**DCE**	**2**	**68**
3	**7c**	DCE	2	65
4	**7d**	DCE	5	65
5	**7e**	DCE	5	32
6	**7f**	DCE	3	63
7	**7b**	PhMe	3	50
8	**7b**	PhH	3	36
9	**7b**	MeCN	8	45
10	**7b**	$MeNO_2$	2	48

[a] Reaction was conducted on a 0.2 mmol scale; ratio of **3d** to **4a** is 1:5. [b] Yield of isolated product after column chromatography. DCE = dichloroethylene.

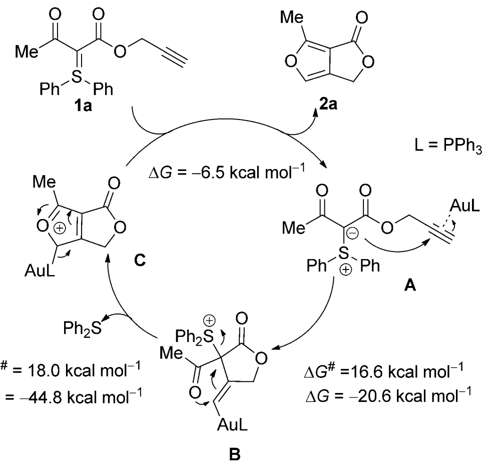


Scheme 3. Scope of the furanone synthesis. Yields reported are for pure, isolated compounds.

The mechanism of the intramolecular formation of bicyclofurans was studied by exploratory DFT calculations,[18] using ylide **1a** as a case study. The resulting path is depicted in Scheme 5 along with the free energy values calculated for the relevant steps (the energy profile for the reaction is given in Figure S1 in the Supporting Information). The reaction starts with activation of the $C{\equiv}C$ bond through π-coordination to the gold catalyst, as shown in intermediate **A**. From **A**, intramolecular attack of the ylidic carbon on the internal alkyne C-atom results in the gold–vinyl complex **B**, in which the five-membered lactone ring is already formed. In the subsequent steps, loss of SPh_2 and nucleophilic attack of the acyl oxygen onto the carbon coordinated to the metal result in complex **C**. Finally, from **C**, ligand exchange with release of the product **2a** and addition of a new molecule of ylide substrate **1a** regenerates the π-complex **A**, thus closing the catalytic cycle. All steps of the mechanism are thermodynamically favorable (Scheme 5) and the rate-limiting step is the formation of the furan ring, although the corresponding barrier is only 1.4 kcal mol^{-1} higher than that calculated for the initial C–C bond-formation event.



Scheme 4. Labeling experiment for the gold-catalyzed furanone synthesis.



Scheme 5. Mechanism calculated for the intramolecular formation of bicyclofurans.

It is important to stress that a hypothetical gold carbene intermediate[4g,19] without a neighboring SPh_2 substituent could not be optimized, despite numerous attempts. In all cases, there was spontaneous formation of the furan ring and intermediate **C**.[20] In fact, in the second part of the mechanism the intermediates formed after SPh_2 loss (**B1**–**B3**, see Figure S1) are stabilized by strong S–C or C–C interactions involving that leaving group.

It is conceivable that when an allyloxycarbonyl ester moiety is present in the substrate, the elimination of gold to form the 2-allyloxyfuran product is followed by a [3,3]-sigmatropic rearrangement (see Scheme S2 in the Supporting Information);[11] this is also in agreement with the labeling experiment.

In summary, we have developed a gold-catalyzed synthesis of heterocyclic products from doubly stabilized sulfonium ylides. This transformation is amenable to a reactivity switch triggered by the modification of the electron-withdrawing moieties of the ylide partner (delivering either furan products or furanone products having a quaternary center). Preliminary calculations support the mechanism proposed and point towards the noninvolvement of a gold carbene intermediate.

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Keywords: alkynes · DFT calculations · furans · gold · rearrangement · sulfonium ylides

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[7] During the preparation of this manuscript, Skrydstrup et al. reported an efficient gold-catalyzed furan synthesis from singly stabilized sulfonium ylides and alkynes, prompting us to report our own results herein. See reference [4g].

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[14] The original observation is shown below:
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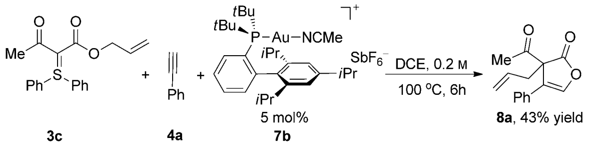

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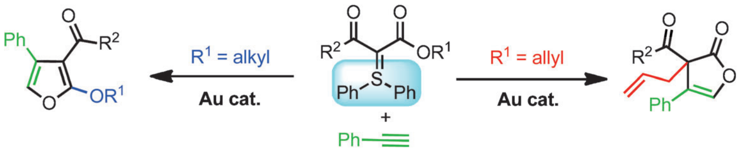
Communications

Gold Catalysis

X. Huang, B. Peng, M. Luparia,
L. F. R. Gomes, L. F. Veiros,
N. Maulide* ________ ■■■■–■■■■

Gold-Catalyzed Synthesis of Furans and Furanones from Sulfur Ylides



A golden switch: Doubly stabilized sulfonium ylides can be coupled with alkynes in a gold-catalyzed synthesis of heterocycles. This method hinges on a switch in the reactivity of the sulfur ylide resulting from the simple modification of the electron-withdrawing moieties and leads to either furans or furanones bearing a quaternary center (see scheme).