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Rearrangements

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Gold-Catalyzed Rearrangement of Allylic Oxonium Ylides: Efficient Synthesis of Highly Functionalized Dihydrofuran-3-ones**

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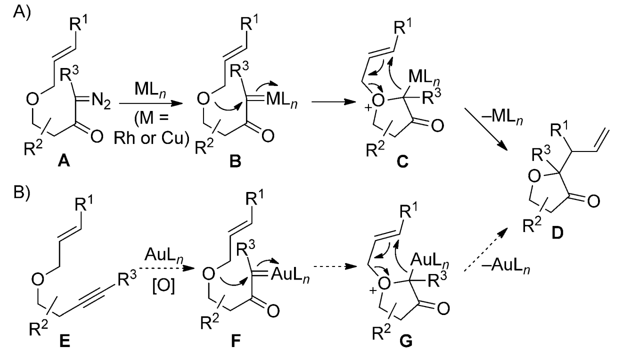
Rearrangements of allylic oxonium ylides have been recognized as powerful tools for the syntheses of oxygenated carbocycles.[1] This type of transformation typically proceeds through a cascade carbenoid generation/oxonium ylide formation/[2,3]-sigmatropic rearrangement. The most common method to generate an oxonium ylide is the decomposition of an α-carbonyl diazo compound with a metal catalyst to form the metallocarbenoid, which is then trapped by the oxygen atom of an allylic ether (**A**→**C**, Scheme 1 A).[2] Given that diazo compounds are usually hazardous and explosive, and their preparation and handling are not trivial, the synthetic utility of this type of transformation has been somewhat limited. In this context, the search for a system that is free of diazo compounds and thus less hazardous to promote the rearrangement of allylic oxonium ylides is of great value.[3]



Scheme 1. A) [2,3]-Sigmatropic rearrangement promoted by a metallocarbenoid that was derived from a diazo carbonyl compound. B) Proposed mechanism for the [2,3]-sigmatropic rearrangement promoted by an α-oxo gold carbenoid.

Recently, α-oxo gold carbenoids have received considerable attentions because they were assumed to be the key intermediates in a range of intriguing transformations,[4] such as gold-catalyzed C−H insertion,[5] O−H insertion,[6] cyclopropanation,[7] dipolar cycloaddition[8] and others.[9] Readily generated through intra- or intermolecular oxidation of gold-activated alkynes, α-oxo gold carbenoids display versatile reactivity, analogous to that of metallocarbenoids derived from diazo carbonyl compounds. For instance, Davies and Albrecht reported a gold-catalyzed [2,3]-sigmatropic rearrangement of sulfur ylides through an internal redox-combination strategy.[10] More recently, Zhang and co-workers developed a facile synthesis of dihydrofuran-3-one derivatives from the readily available homopropargylic alcohols through a gold-catalyzed intramolecular O−H insertion.[6a] Inspired by these seminal contributions, we envisioned that a similar strategy could be used in the [2,3]-sigmatropic rearrangement of oxonium ylides, as rationalized by the transformations from **E**→**D** (Scheme 1 B). The proposed strategy would enable the [2,3]-sigmatropic rearrangement of oxonium ylides to proceed with readily available, diazo-free precursors under exceptionally mild conditions and with an operationally simple procedure. Moreover, the resulting product **D** features a highly functionalized dihydrofuran-3-one scaffold, which could be further elaborated into the core structures of various bioactive natural products, such as that of griseofulvin.[1c]

To test the hypothesis, we initiated our studies by treatment of model substrate **1** with the conditions employed by Zhang and co-workers in their studies (Scheme 2).[6a] The reaction was completed in three hours and led to the formation of two major products, one of which was the by-product resulting from direct deallylation of **1** (product structure not shown), and the other was the benzofuran allylic ether **2**. Although the expected [2,3]-sigmatropic rearrangement product **3** was not observed, we were pleased to find that **2** was converted almost quantitatively into **3** upon standing for 72 hours in $CDCl_3$. The structure of **3** was unambiguously confirmed by X-ray crystallography.[11] Subsequently, the conversion of **1** to **3** could be effected in one pot simply by increasing the reaction temperature to 60 °C. The observations indicated that the transformation of **1** to **3**, albeit formally a [2,3]-sigmatropic rearrangement, may indeed proceed through a mechanism distinctly different from the

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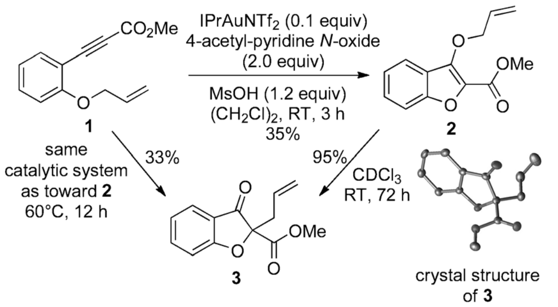
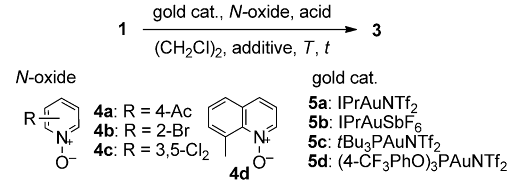


Scheme 2. Initial results of the gold-catalyzed rearrangement of allylic oxonium ylide **1**. In the crystal structure, hydrogen atoms have been omitted for clarity. Thermal ellipsoids drawn at 30% probability.

Table 1: Screening of reaction conditions for the gold-catalyzed rearrangement of allylic oxonium ylides.[a]



Entry	Cat.	*N*-oxide	Acid	Addit.	*T* [°C]	*t* [h]	Yield of **3** [%][b]
1	**5a**	**4a**	MsOH		60	12	33
2	**5a**	**4b**	MsOH		60	12	trace
3	**5a**	**4c**	MsOH		60	12	41
4	**5a**	**4d**	MsOH		60	12	37
5	**5a**	**4c**	MsOH	4 Å MS	60	12	42
6	**5a**	**4c**	MsOH	$MgSO_4$	60	12	50
7	**5a**	**4c**	MsOH	$MgSO_4$	80	3	54
8	–	**4c**	MsOH	$MgSO_4$	80	3	0
9	**5b**	**4c**	MsOH	$MgSO_4$	80	3	47
10	**5c**	**4c**	MsOH	$MgSO_4$	80	3	20
11	**5d**	**4c**	MsOH	$MgSO_4$	80	3	trace
12	**5a**	**4c**	CF_3CO_2H	$MgSO_4$	80	3	54
13	**5a**	**4c**	CCl_3CO_2H	$MgSO_4$	80	3	67
14	**5a**	**4c**	$BF_3\cdot Et_2O$	$MgSO_4$	80	3	70
15	**5a**	**4c**	$Sc(OTf)_3$	$MgSO_4$	80	3	65
16	**5a**	**4c**	**$Yb(OTf)_3$**	**$MgSO_4$**	**80**	**3**	**76**

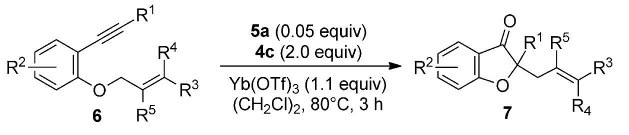
[a] Reaction conditions: **1** (0.30 mmol), gold catalyst (0.05 equiv), pyridine *N*-oxide (2.0 equiv), and acid (1.1 equiv) in $(CH_2Cl)_2$ (2.0 mL). [b] Yields of isolated products. IPr = 1,3-bis(2,6-diisopropyl-phenyl)imidazolidene, Ms = methanesulfonyl, Tf = trifluoromethylsulfonyl, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

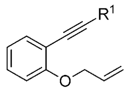
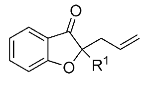
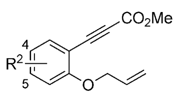
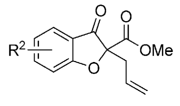
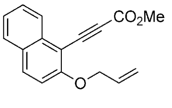
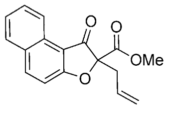
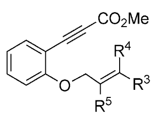
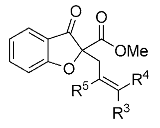
one proposed (Scheme 1B) and from those reported previously.[10,12]

To improve the efficiency of the transformation, we performed a systematic screening of the reaction parameters, including the choice of pyridine *N*-oxide, gold catalyst, and co-catalyst (Table 1). Among the several pyridine *N*-oxides that were examined (**4a–d**, entries 1–4), **4c** afforded the best result. Addition of 4 Å molecular sieves or anhydrous $MgSO_4$ had a beneficial effect on the reaction (entries 5 and 6). Raising the reaction temperature to 80°C dramatically shortened the reaction time, but had little influence on the yield (entry 7). The crucial role of the gold catalyst was proven with a control reaction that was conducted without a gold catalyst and failed to give even a trace of product **3** (entry 8). To our disappointment, efforts to improve the reaction by employing other gold catalysts (**5b–d**) did not lead to satisfactory outcomes (entries 9–11). In addition to MsOH, we also evaluated some other Brønsted and Lewis acids as co-catalysts (entry 12–16), among which $Yb(OTf)_3$ showed superior reactivity to afford **3** in 76% yield.[13] Notably, this reaction represents one of few examples of the use of a rare-earth metal salt as co-catalyst in a gold-catalyzed reaction.[14]

With the optimal conditions established, we surveyed the scope of the reaction by employing various homopropargylic allylic ethers as substrates (Table 2). Substrates bearing an electron-withdrawing group (ester, amide, or Cl, **6a–d**) on the alkyne unit underwent the reactions smoothly to afford the corresponding products in good to acceptable yields (entries 1–4).[15] Comparably, the yield of **6e**, which contains a terminal alkyne, dropped

Table 2: Gold-catalyzed rearrangement of allylic oxonium ylides with aromatic moieties.[a]



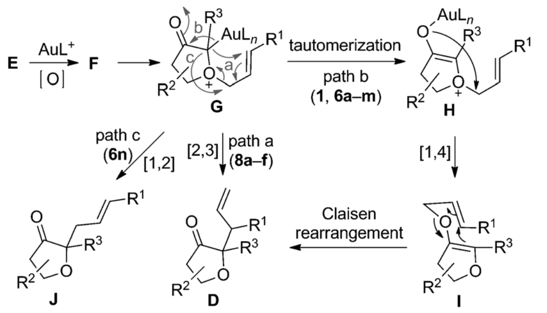
Entry	Substrate		R	Product		Yield[b] [%]
1		**6a**	$R^1 = CO_2Et$		**7a**	81
2		**6b**	$R^1 = CO_2Bn$		**7b**	66
3		**6c**	$R^1 = CONEt_2$		**7c**	63
4		**6d**	$R^1 = Cl$		**7d**	58
5		**6e**	$R^1 = H$		**7e**	45
6		**6f**	$R^2 = 4$-*t*Bu		**7f**	75
7		**6g**	$R^2 = 4$-Me		**7g**	71
8		**6h**	$R^2 = 5$-Me		**7h**	66
9		**6i**	$R^2 = 5$-MeO		**7i**	48
10		**6j**	$R^2 = 5$-F		**7j**	55
11		**6k**	$R^2 = 5$-Cl		**7k**	65
12		**6l**			**7l**	80
13		**6m**	$R^3 = R^4 = H$; $R^5 = Me$		**7m**	57
14[c]		**6n**	$R^3 = Me$; $R^4 = R^5 = H$		**7n**	52

[a] Reactions were performed as described in Table 1. [b] Yields of isolated products. [c] Both **6n** and **7n** consist of a mixture of *Z/E* isomers (*Z*:*E* = 1:4), and only the major *E* isomer is shown.

to 45 % (entry 5). The effect of substituents on the phenyl ring was also evaluated. Both electron-donating (*t*Bu-, Me-, or MeO-, **6 f–i**) and electron-withdrawing (F- or Cl-, **6 j** and **6 k**) groups were tolerated well (entries 6–11). Naphthalene-derived compound **6 l** also turned out to be a good substrate for the reaction (entry 12). The reactions also worked with **6 m** and **6 n**, which bear a 2,2- and 1,2-disubstituted alkene, respectively (entries 13 and 14). Notably, we observed the corresponding benzofuran allylic ether intermediates in the reactions with **6 a–m**, suggesting that these reactions follow a stepwise process similar to that of compound **1**. In contrast, no such intermediate was detected for the reaction with **6 n**. Moreover, both the substitution pattern and *E*/*Z* ratio of the alkene unit were fully preserved in the transformation from **6 n** to **7 n**, thus indicating that it proceeds through a [1,2] rearrangement, rather than a [2,3] rearrangement.

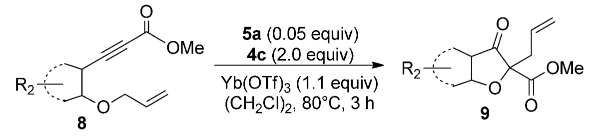
In order to further extend the scope of the reaction, various aliphatic substrates were examined (Table 3). The reactions of **8 a–c**, in which the alkene and alkyne units are incorporated into a cyclic framework with either *cis* or *trans* configuration, proceeded smoothly to afford the corresponding products **9 a–c** in excellent yields (entries 1–3). Notably, **9 a** and **9 b** were obtained as a single diastereoisomer, whereas **9 c** was obtained as a mixture of C2 diastereoisomers (1:1 ratio). Interestingly, both diastereoisomers are *cis*- rather than *trans*-configured at the ring junction.[16] This result might be attributed to a thermodynamically less stable 5–6 *trans*-fused product, which upon formation gradually epimerizes into the corresponding *cis*-fused product. Furthermore, substrates with linear tethers were examined. To our delight, all of the reactions furnished the corresponding products in good yields (entries 4–6). Notably, unlike for the reactions with **6 a–m**, the corresponding vinyl allylic ether intermediates were not observed in the reactions listed in Table 3.

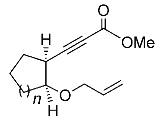
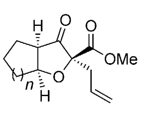
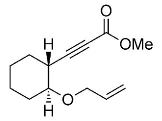
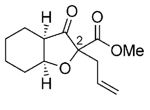
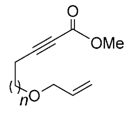
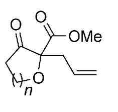
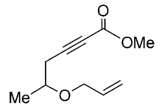
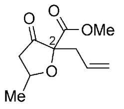
To gain deeper insight into the gold-catalyzed rearrangement of allylic oxonium ylides, we performed deuterium-labeling experiments (Scheme S1, see Supporting Information), which, combined with the aforementioned experimental results, allowed us to propose a plausible mechanism (Scheme 3). Oxonium ylide **G**, which is generated from **E** via α-oxo gold carbenoid **F**, may undergo three different pathways to give dihydrofuran-3-one **D** or its isomer **J**, depending on the nature of the substrates. The first pathway features a concerted [2,3]-sigmatropic rearrangement (path a), and is most likely involved in the reactions with **8 a–f**, considering that 1) no vinyl allylic ether intermediates were observed in these reactions, and 2) inversion of the allyl moiety was observed in the deuterium-labeling experiment. In contrast, a stepwise mechanism may account for the reactions with **1** and **6 a–m**, in which **G**, once generated, could rapidly tautomerize into the thermodynamically more stable intermediate **H**. Compound **H** undergoes a 1,4-allyl migration to afford **I**,[17] which is readily converted into **D** through a Claisen rearrangement (path b).[18] Moreover, a [1,2] rearrangement (path c) that leads to the formation of **J** cannot be completely ruled out in certain cases. Indeed, the transformation from **6 n** to **7 n** may follow this pathway.



Scheme 3. Proposed mechanisms for the gold-catalyzed rearrangement of allylic oxonium ylides.

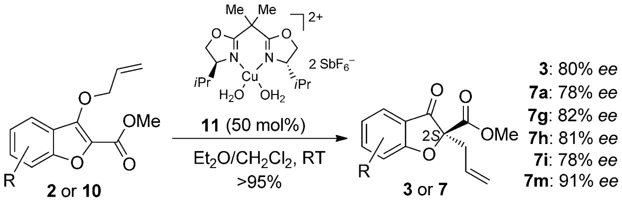
Table 3: Gold-catalyzed rearrangement of allylic oxonium ylides with aliphatic moieties.[a]



Entry	Substrate		*n*	Product		Yield[b] [%]
1		**8 a**	1		**9 a**	65
2		**8 b**	2		**9 b**	84
3[c]		**8 c**			**9 c**	84
4		**8 d**	1		**9 d**	85
5		**8 e**	2		**9 e**	65
6[c]		**8 f**			**9 f**	67

[a] Reactions were performed as described in Table 1. [b] Yields of isolated products. [c] The diastereoselectivity was determined by ^{1}H NMR spectroscopy. [d] d.r. = 1:1 (at C2). [e] d.r. = 3:2 (at C2).

To highlight the synthetic utility of the new reaction, we finally attempted to realize its asymmetric version. Significant efforts have been devoted to the asymmetric synthesis of dihydrofuran-3-ones through a [2,3]-sigmatropic rearrangement of oxonium ylides,[19] however, only modest successes have been achieved. For instance, **1** was frequently employed as model substrate in the previous studies,[19a–c] however, to date the highest *ee* value reported for **3** was 62 %.[19b] We envisioned that the unique mechanism of the gold-catalyzed rearrangement of allylic oxonium ylides may offer an opportunity to address the challenge. Indeed, for those reactions proceeding through path b (Scheme 3), it is feasible to attempt the enantioselective synthesis of **D** through an asymmetric Claisen rearrangement.[20] As expected, after extensive screening of reaction conditions with **2** as model substrate (Table S1, Supporting Information), we were pleased to find that the desired transformation could be achieved by employing chiral bis(oxazoline)copper(II) complex **11** as the catalyst and CH_2Cl_2/Et_2O (1:1) as the solvent.[21] Thus, **3** could be obtained almost quantitatively and with good enantioselectivity (80 % *ee*, Scheme 4). The absolute configuration at C2 of **3** was assigned as S by comparison of the rotation of a derivative with reported data (for details, see the Supporting Information).[22] Moreover, the asymmetric reaction could be applied to several other benzofuran allylic ethers (**10**, Scheme 4), all of which afforded the corresponding products with high yields (> 95 %) and good enantioselectivity (78–91 % *ee*). Thus, our method offers an alternative to the existing repertoire of asymmetric [2,3]-sigmatropic rearrangements of oxonium ylides for the enantioselective synthesis of benzofuranone-3-one derivatives that bear an oxygenated chiral quaternary carbon atom.



Scheme 4. Asymmetric Claisen rearrangement with vinyl allylic ether intermediates.

In summary, we developed a novel gold-catalyzed rearrangement of allylic oxonium ylides, allowing the rapid access of highly functionalized dihydrofuran-3-ones from readily available precursors in one pot. Mechanistically, the rearrangement of oxonium ylides may proceed through a concerted [2,3]-sigmatropic rearrangement or stepwise 1,4-allyl migration followed by Claisen rearrangement. We also succeeded in developing an efficient approach to the enantioselective synthesis of benzofuranone-3-one derivatives through a Cu^{II}-catalyzed asymmetric Claisen rearrangement. Owing to the absence of diazo compounds and the operationally simple and step-economical nature, this variant of the rearrangement of allylic oxonium ylides is not only conceptually novel, but also synthetically useful. Further mechanistic studies and applications of this methodology to the total synthesis of natural products are in progress and will be communicated in due course.

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Keywords: Claisen rearrangement · gold · carbenoids · oxonium ylide · sigmatropic rearrangement

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[1] For leading reviews, see: a) D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev.* **2001**, *30*, 50 – 61; b) J. S. Clark, in *Nitrogen, Oxygen and Sulfur Ylide Chemistry: A Practical Approach*, Oxford University Press, Oxford, **2002**; for representative examples, see: c) M. C. Pirrung, W. L. Brown, S. Rege, P. Laughton, *J. Am. Chem. Soc.* **1991**, *113*, 8561 – 8562; d) F. P. Marmsäter, F. G. West, *J. Am. Chem. Soc.* **2001**, *123*, 5144 – 5145; e) J. S. Clark, T. C. Fessard, C. Wilson, *Org. Lett.* **2004**, *6*, 1773 – 1776; f) J. S. Clark, S. T. Hayes, C. Wilson, L. Gobbi, *Angew. Chem.* **2007**, *119*, 441 – 444; *Angew. Chem. Int. Ed.* **2007**, *46*, 437 – 440; g) J. S. Clark, C. A. Baxter, A. G. Dossetter, S. Poigny, L. L. Castro, W. G. Wittingham, *J. Org. Chem.* **2008**, *73*, 1040 – 1055; h) D. M. Hodgson, D. Angrish, S. P. Erickson, J. Kloesges, C. H. Lee, *Org. Lett.* **2008**, *10*, 5553 – 5556; i) J. S. Clark, R. Berger, S. T. Hayes, L. H. Thomas, A. J. Morrison, L. Gobbi, *Angew. Chem.* **2010**, *122*, 10063 – 10066; *Angew. Chem. Int. Ed.* **2010**, *49*, 9867 – 9870; j) J. S. Clark, D. Vignard, A. Parkin, *Org. Lett.* **2011**, *13*, 3980 – 3983.

[2] For selected examples, see: a) M. C. Pirrung, J. A. Werner, *J. Am. Chem. Soc.* **1986**, *108*, 6060 – 6062; b) E. J. Roskamp, C. R. Johnson, *J. Am. Chem. Soc.* **1986**, *108*, 6062 – 6063; c) F. P. Marmsäter, J. A. Vanecko, F. G. West, *Org. Lett.* **2004**, *6*, 1657 – 1660; d) K. J. Quinn, N. A. Biddick, B. A. DeChristopher, *Tetrahedron Lett.* **2006**, *47*, 7281 – 7283; e) J. S. Clark, S. B. Walls, C. Wilson, S. P. East, M. J. Drysdale, *Eur. J. Org. Chem.* **2006**, 323 – 327; f) J. S. Clark, C. Guerot, C. Wilson, A. Blake, *Chem. Commun.* **2007**, 4134 – 4136.

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