Synthetic Methods

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Gold- or Platinum-Catalyzed Synthesis of Sulfur Heterocycles: Access to Sulfur Ylides without Using Sacrificial Functionality**

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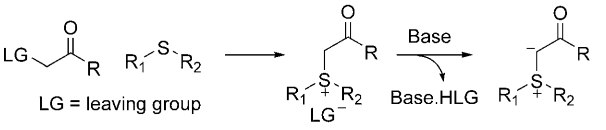
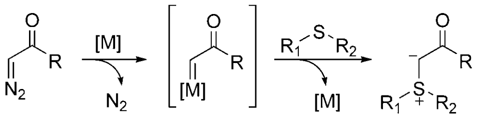
Sulfur ylides are potent reactive units which are utilized in synthetic chemistry for a variety of powerful carbon–carbon and carbon–heteroatom bond-forming reactions.[1] The classical preparation of ylides depend on the use of "sacrificial functionality": a leaving group is displaced by a sulfide with subsequent regioselective deprotonation of the resulting sulfonium salt [Eq. (1)];[2] or a sulfide is treated with a metal carbene, which is formed by the decomposition of a diazo compound with loss of molecular nitrogen [Eq. (2)].[3] The synthetic efficiency of such processes is also adversely affected by the manipulations required to introduce the precursor moiety. Consequently, the appeal of ylide chemistry is diminished by the negative implications of these strategies on reagent usage, waste production, and functional group tolerance.

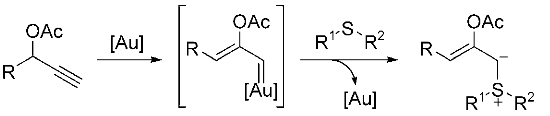


(1)



(2)

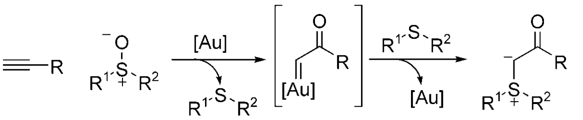
The preparation of sulfur ylides by methods which do not depend on the use of sacrificial functionality are therefore potentially attractive.[4] To this end, we recently established a program to explore direct access to ylides from alkynes under noble-metal catalysis. In our initial study we reported the intermolecular coupling of propargylic carboxylates and sulfides. A gold carbenoid was generated by a rearrangement process and led to an ylide on reaction with sulfide [Eq. (3); R^1 = allyl or propargyl, R^2 = aryl or allyl].[5,6] This established the principle of generating sulfur ylides through gold-catalyzed rearrangement, and also represented one of the few reactions involving low-valent sulfur in gold catalysis.[7]



(3)

However, the relative complexity of the propargylic carboxylate precursors is limiting. Additionally, the presence of an enol acetate adjacent to the metal carbenoid, which is formed in situ, diverts the course of the reaction away from that usually observed with allyl sulfonium ylides. We were therefore keen to identify an alternative strategy using alkynes as ylide precursors that could be used directly in place of the usual preparation methods. Herein, we report the successful fulfillment of this goal and its application in the synthesis of monocyclic and fused-bicyclic, functionalized sulfur heterocycles.

The research groups of Toste and Zhang have independently reported the gold-promoted reaction of a sulfoxide group with a tethered alkyne to generate α-keto gold carbenoids.[8] We considered that this approach might allow alkynes to be used directly as precursors for the ylide site. While the initial use of a sulfoxide group could reduce unfavorable gold–sulfur interactions, an internal redox process simultaneously generates the carbenoid and sulfide components required for ylide formation [Eq. (4)].[9]



(4)

To test this strategy we prepared a range of substrates **A** bearing allyl units tethered to the sulfoxide group. In our desired process, π-acid activation renders the alkyne moiety susceptible to attack by the nucleophilic sulfoxide (Scheme 1, **A**→**B**).[10] Evolution of the resulting intermediate **C** generates the α-carbonyl metal carbenoid **D** and concomitantly engenders the sulfide, thus providing the two units required for ylide formation.[11] The resulting allyl sulfonium ylide **E** should undergo a 2,3-sigmatropic rearrangement to complete

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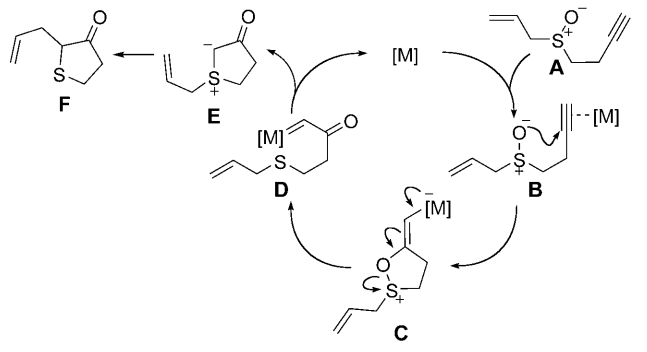
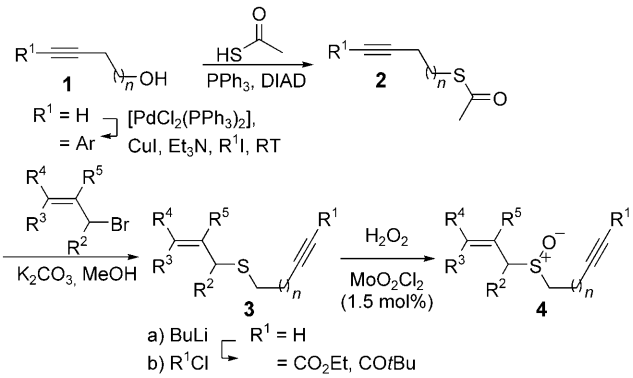


Scheme 1. Proposed reaction mechanism.



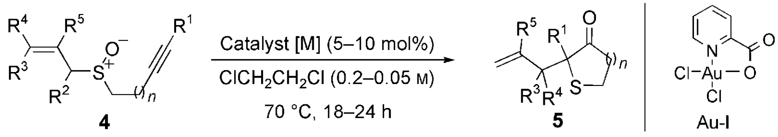
Scheme 2. General synthesis of sulfoxide tethered enynes **4**. See the Supporting Information for experimental details. DIAD = diisopropylazodicarboxylate.

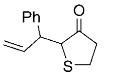
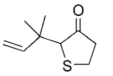
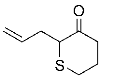
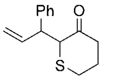
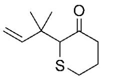
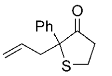
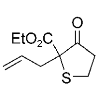
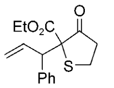
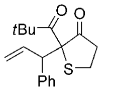
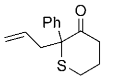
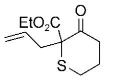
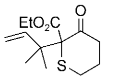
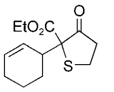
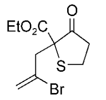
the synthesis of heterocycle **F**.[12,13] The overall transformation (**A**→**F**) leads to the formation of new carbon–carbon, carbon–oxygen, and carbon–sulfur bonds.

Substrates **4**, which are based on motif **A**, bearing a range of substituents on the sulfur center and the alkyne group were synthesized through standard substitution strategies. Chemoselective oxidation of sulfide **3** was performed using hydrogen peroxide under molybdenum catalysis (Scheme 2).[14] The polarity of the sulfoxide unit provides practical benefit by rendering purification at the final stage facile. Indeed, all substrates **4** bearing terminal alkyne groups were purified only after the final stage. By using standard strategies, the sensitive moieties of the immediate precursors for the ylide sites are only introduced in the final stages of the ylide preparation [Eqs. (1) and (2)]. In contrast, the alkyne precursor to the ylide can be introduced earlier, thus allowing more flexible retrosynthetic analyses to be applied.

Pleasingly, the desired ylide formation and rearrangement process proceeded smoothly when the substrates were treated with a platinum or gold π-acidic species (Table 1). The use of catalytic quantities of $PtCl_2$ in $ClCH_2CH_2Cl$ under mild heating was found to be the most effective activation system

Table 1: Platinum- or gold-catalyzed cyclizations.[a]

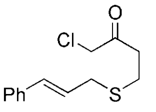


Entry	Substrate	Catalyst [M]	Product	Yield [%][b]	d.r.[c]
1	(*E*)-**4a**	$PtCl_2$	 **5a**	61[d]	2.6:1
2	**4b**	$PtCl_2$	 **5b**	51	–
3	**4c**	$PtCl_2$	 **5c**	62	–
4	(*E*)-**4d**	$PtCl_2$	 **5d**	55–64	4.8:1
5	**4e**	$PtCl_2$	 **5e**	44	–
6	**4f**	$PtCl_2$	 **5f**	24	–
7	**4f**	Au-I		69	–
8	**4g**	$PtCl_2$	 **5g**	60	–
9	**4g**	Au-I		85	–
10	(*E*)-**4h**	$PtCl_2$	 **5h**	53	1.45:1
11	**4h**	Au-I		78	1.45:1
12	(*E*)-**4i**	Au-I	 **5i**	83	1.06:1
13	**4j**	Au-I	 **5j**	55	–
14	**4k**	Au-I	 **5k**	84	–
15	**4l**	Au-I	 **5l**	60	–
16	**4m**	Au-I	 **5m**	83	1.2:1
17	**4n**	Au-I	 **5n**	83	–

[a] Catalyst (5–10 mol %) was added to a solution of **4** in 1,2-dichloroethane (0.2–0.05 M), the flask was sealed and heated at 70 °C for 18 h. [b] Yield of isolated product after flash column chromatography. [c] Diastereomeric ratio determined from by ^1H NMR spectroscopy. [d] 11 % of **6** was isolated.

for terminal alkynes (Table 1, entries 1–5).[15] Variously substituted allyl fragments can be tolerated in the formation of dihydrothiophenone and dihydrothiopyranone structures. The reactions proceed with allylic inversion (for example, Table 1, entries 1–2).

Quaternary carbon centers could be formed using this method, although the yield does begin to drop off as the center that forms becomes more highly congested (Table 1, entries 2 and 5). Small amounts of a side product were occasionally observed in these reactions. From the cyclization of **4a**, the side product was isolated and identified as the α-chloroketone **6**. A likely pathway for the formation of **6** involves the reaction of electrophilic platinum carbenoid **D** with chlorinated solvent, in analogy to the reactions observed with other metal carbenes.[16]



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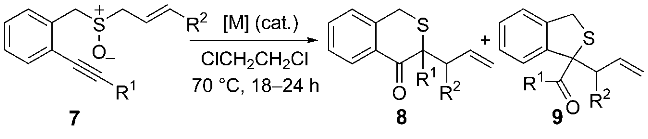
Substrates incorporating an internal alkyne unit (**4f**–**4n**) gave the desired cyclized products in only modest yield under platinum(II) catalysis (Table 1, entries 6, 8, and 10). However, a significant improvement was observed upon switching to the dichloro(pyridine-2-carboxylato)gold(III) species (Au-**I**; Table 1, entries 7, 9, and 11).[17] With this method aromatic and electron-withdrawing groups such as esters and ketones are readily incorporated.[18] The resulting cycloisomerizations allow highly congested and functionalized systems to be built up rapidly in high yield from simply constructed precursors (for example, Table 1, entries 7, 11–13, and 15). Both acyclic and cyclic units can be incorporated into the sigmatropic rearrangement (Table 1, entry 16). Additionally, the synthetically useful vinyl bromide functionality remains unscathed under the reaction conditions (Table 1, entry 17).

Isothiochroman-4-ones **8** were prepared from cyclization precursors **7** that incorporate an aromatic unit between the alkyne and sulfoxide groups (Table 2). Under the standard conditions, terminal alkynes **7a** and **7b** led to **8a** and **8b** as the major products respectively, through an initial 6-*exo*-dig cyclization of sulfoxide unit onto the alkyne group (Table 2, entries 1 and 2). Only small amounts of the 1,3-dihydrobenzo[c]thiophene products, **9a** and **9b**, were isolated from the analogous process starting with 7-*endo*-dig cyclization. When the electronic bias on the alkyne group was increased by substitution with an ester moiety (Table 2, entry 3), the isothiochroman-4-one product **8c** was formed exclusively under gold catalysis.

Table 2: Formation of fused heterocycles.



Entry	7	R1	R2	[M]	Product	Yield [%][b]
1	**7a**	H	H	$PtCl_2$	**8a** **9a**	55 8
2	**7b**	H	Ph	$PtCl_2$	**8b** **9b**	53[c] 11[d]
3	**7c**	CO_2Et	H	Au-**I**	**8c**	64

[a] Catalyst (10 mol%) was added to a solution of **7** in 1,2-dichloroethane (0.2 M), the flask was sealed and heated at 70 °C for 18 h. [b] Yield of isolated product after flash column chromatography. [c] As a 2.8:1 mixture of diastereomers. [d] as a 1.3:1 mixture of diastereomers.

In summary, we have shown that the simple and robust alkyne functionality can be used as a direct precursor to a sulfur ylide using gold or platinum catalysis. An internal redox-combination strategy bypasses the need to employ sacrificial functionality to access sulfur ylide chemistry, and enables non-standard retrosynthetic approaches to be employed. A range of functionalized sulfur heterocycles have been synthesized by novel cycloisomerization reactions of readily prepared sulfoxide tethered enynes. The study of this reaction and wider applications of the practical principle of using alkynes as immediate ylide precursors is under investigation in our laboratory and will be reported in due course.

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Keywords: alkynes · gold · homogeneous catalysis · sulfur heterocycles · ylides

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[15] A survey of catalysts and reaction conditions for the challenging cyclization precursor **4b** is provided in the Supporting Information.

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[18] No reaction was observed when substrate **4k**, bearing an activated alkyne, was treated under the usual reaction conditions with amberlyst-15, toluene-*p*-sulfonic acid, or silver triflate in place of the platinum or gold catalyst. The use of two equivalents of $BF_3.OEt_2$ resulted in the formation of a temporary complex which returned **4k** upon treatment with silica gel.