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Alkynes as “masked” ylides under noble-metal catalysis*

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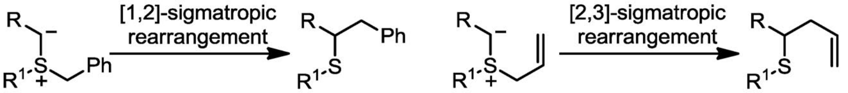
Abstract: Our development of noble-metal-catalyzed reactions that involve the preparation of sulfur ylides directly from alkynes, without employing sacrificial functionality, is reviewed.

Keywords: atom efficiency; catalysis; gold; platinum; sulfur ylides.

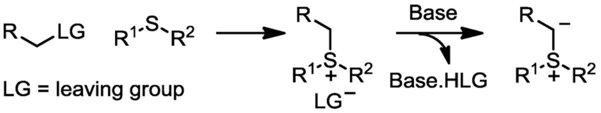
INTRODUCTION

Sulfonium ylide rearrangements are a useful class of reactions for making new carbon–carbon bonds (Scheme 1). Since the initial discovery of 1,2- and 2,3-sigmatropic rearrangements with sulfur ylides there has been expansive progress in the field [1–3].



Scheme 1 1,2- and 2,3-sigmatropic rearrangements of sulfonium ylides.

Traditionally, the ylides are prepared by the deprotonation of sulfonium salts, which are in turn synthesized by alkylation of sulfides with alkyl halides or equivalent carbon electrophiles (Scheme 2). Limitations of this approach include regioselectivity issues within the deprotonation of salts containing more than one acidic site, functional group incompatibility with the required basic conditions, and dealkylative side reactions.



Scheme 2 Classical synthetic approach for ylide formation.

Many of these issues can be addressed by an alternative ylide preparation through the reaction of a sulfide with a diazocompound (Scheme 3). The use of a catalytic quantity of a metal species is generally beneficial, resulting in effective reactions which proceed under mild conditions. Ylide formation

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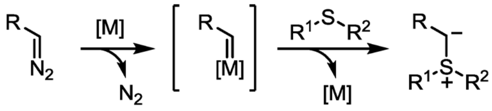


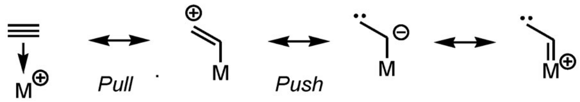
Scheme 3 Use of diazocompounds as ylide precursors.

proceeds by reaction of a sulfide with an intermediate metal carbene, which is formed in situ on elimination of molecular nitrogen from the diazocompound in the presence of a metal species [4]. Practically, the potentially dangerous diazocompounds must often be introduced into the reaction media over a prolonged period of time to minimize undesirable dimerization reactions [5].

Both of the strategies described above depend on the use of "sacrificial functionality" [6], be it an alkyl halide or diazo unit, to introduce the desired sulfonium ylide. This dependence has a significantly deleterious impact on both the applicability and attractiveness of such reactions in synthesis. While the loss of such moieties affects the atom-economy of a process, the need to introduce such moieties in the first place is intrinsically inefficient and can require several undesirable synthetic manipulations. This is particularly problematic in the synthesis of more complex species where functional group compatibility becomes increasing important.

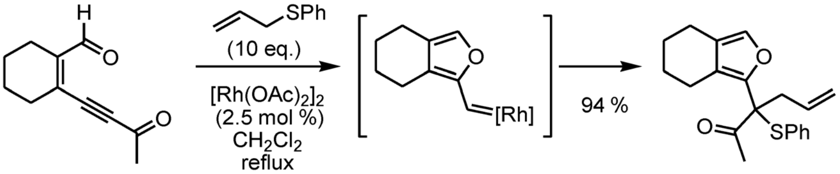
Alternative methods to make sulfonium ylides that do not depend upon the use of such sacrificial functionality are therefore attractive, with potential benefits for both step and atom economy. Furthermore, such approaches may lead to alternative retrosynthetic analyses.

Our interest in this area developed from studies using π-acid catalysis for the activation of alkynes, during which it had been demonstrated that the alkyne could be employed as an α-alkylidene carbenoid synthon (Scheme 4). The resulting processes show excellent chemoselectivity under mild and straight-forward reaction conditions [7]. We hypothesized that an alkyne could therefore be used as a direct precursor to a sulfur ylide if we could employ this type of gold activation in the presence of a sulfide. If successful, this would provide an alternative access to ylides without the need for sacrificial functionality.



Scheme 4 Fundamental processes in the activation of alkynes by π-acids.

A diazoalkane-free ylide formation was reported by Ohe, Uemura, and co-workers in 2003 [8]. The transformation centered on a rhodium-promoted rearrangement of conjugated ene-yne-carbonyl compounds affording (2-furyl)carbenoids. In the presence of 10 equiv of an allyl sulfide, *S*-ylide formation occurred with subsequent 2,3-sigmatropic rearrangement, in analogy to the Doyle–Kirmse reaction of allyl sulfides with diazocompounds (Scheme 5) [9]. The overall coupling products were obtained in good to excellent yields, with the additional benefit that there was no need for slow addition of the carbene precursor. When diallyl sulfide was used, running the reaction at a higher temperature provided access to subsequent Diels–Alder reaction with significant generation of complexity under mild reaction conditions.

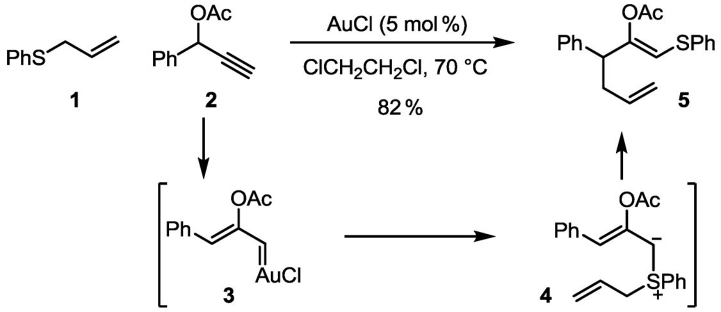


Scheme 5 Diazo-free Doyle–Kirmse type reaction.

RESULTS AND DISCUSSION

Gold-catalyzed coupling of propargylic carboxylates and sulfides

Our initial foray into the use of alkynes as "masked" ylides centered on the intermolecular coupling of an allyl aryl sulfide **1** with a propargylic carboxylate **2** (Scheme 6). The propargylic carboxylate moiety has been established as a favored motif in gold and platinum catalysis, and is used in a variety of rearrangement processes [10,11]. We were interested in the gold-promoted 1,2-rearrangement of these units as a means to access the gold carbenoid **3**. We reasoned that if the rearrangement proceeded in the presence of an allyl sulfide then this might provide access to a sulfonium ylide **4**, which would then undergo sigmatropic rearrangement with the formation of a new carbon–carbon bond. After initial screening, we found that an effective coupling reaction could be achieved using catalytic quantities of gold(I)chloride in chlorinated solvent under mild heating [12]. The reaction product appeared to confirm that sulfur ylides could be prepared through a gold-promoted rearrangement-coupling. Intriguingly, however, the final result is not that of a 2,3-sigmatropic rearrangement of an allyl sulfonium ylide. Instead carbon–carbon bond formation occurs at the position initially occupied by the acetate moiety in the starting material. From the sulfonium ylide **4**, plausible pathways for the formation of **5** remain under study and include: sequential 2,3- then 3,3-rearrangement; direct 1,4-rearrangement; and either stepwise or concerted mechanisms involving migration of an allyl cation to the C-nucleophilic position adjacent to the phenyl group.



Scheme 6 Gold-catalyzed coupling of propargylic carboxylates and allyl sulfides.

The coupling product **5** was isolated as a single isomer. Our study highlighted a requirement for an aryl substituent in the propargylic position, but otherwise the reaction tolerates a range of functionality on both reaction partners (Chart 1).

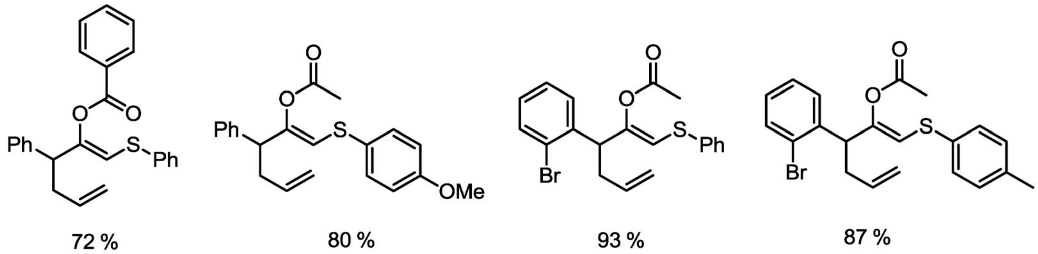
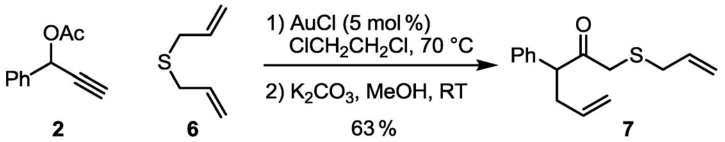


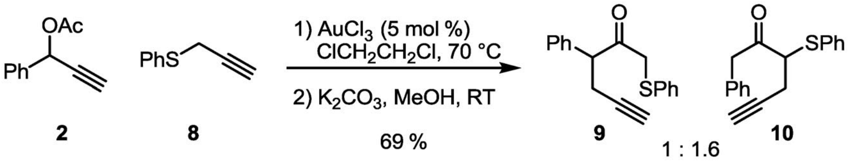
Chart 1 Representative examples of the gold-catalyzed coupling reaction.

Diallyl sulfide **6** could also be employed in the reaction, although a larger excess of the sulfide was required for complete conversion (Scheme 7). Hydrolysis of the initially formed enol acetate was performed for ease of purification, resulting in formation of the diene **7** in 63 % over two steps.



Scheme 7 Use of diallyl sulfide in the coupling reaction.

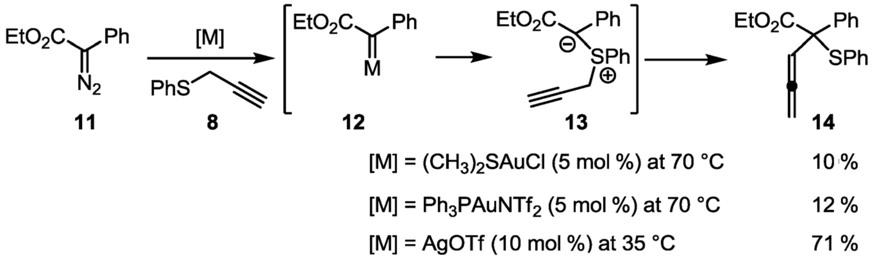
The use of phenyl propargyl sulfide **8** in the gold-catalyzed reaction resulted in the isolation of two isomers **9** and **10** in a combined 69 % yield after hydrolysis of the enol acetate (Scheme 8). Both products contain the intact alkyne unit, with migration of the propargylic unit onto either of the two termini of the intermediate anionic allyl species. This was unexpected for two reasons; first, the divergence with the allyl sulfides, in which only one isomer was observed with the new carbon–carbon bond formed adjacent to the aromatic unit of the propargyl acetate. Second, in the Doyle–Kirmse reaction of propargylic sulfides, 2,3-sigmatropic rearrangement results in the formation of allenes [13].



Scheme 8 Use of a propargyl sulfide.

Silver-catalyzed Doyle–Kirmse reaction of allyl and propargyl sulfides

To probe this outcome, we investigated the gold-catalyzed Doyle–Kirmse reaction of propargyl sulfide **8** with a diazocompound **11**. The sole-observed product was the allene **14** in low yield (Scheme 9). Based on this result, the products we previously observed from gold-catalyzed coupling of propargylic carboxylates and propargyl sulfides do not result from a 1,2-shift of a propargyl unit in the intermediate sulfur ylide, implicating a more complex process that remains under study. During this process, we discovered that a simple silver salt was an effective catalyst for the Doyle–Kirmse reaction, under the simple protocol of mixing both reagents and catalyst with mild heating (Scheme 9). This reaction represents one of only a few examples of atom-transfer reactions using silver catalysis [14]. Both propar-



Scheme 9 Gold- and silver-catalyzed Doyle–Kirmse reaction.

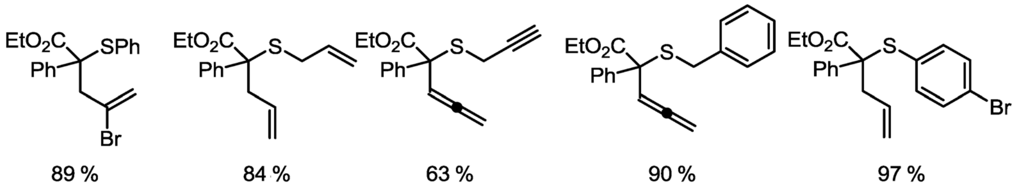
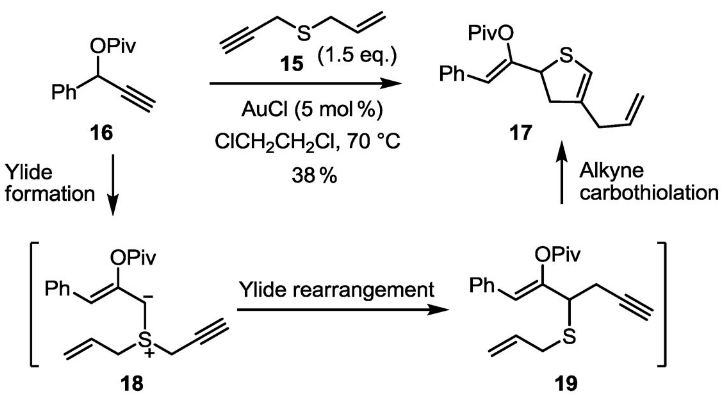


Chart 2 Representative products from the silver-catalyzed Doyle–Kirmse reaction.

gyl and allyl sulfides bearing a range of functionality were subjected to the silver-catalyzed conditions to afford the coupling products from formation of sulfur ylide intermediates in high yields (Chart 2) [15].

Gold-catalyzed cascade reaction

An unexpected outcome was observed when allyl propargyl sulfide **15** was employed in the coupling reaction with propargylic carboxylate **16**. Further demonstrating the potential of gold catalysis in generating complexity, the sole isolated product was dihydrothiophene **17** (Scheme 10) [12]. Formation of **17** can be explained by formation of ylide **18** in the usual manner followed by an overall "1,2-migration" of the propargylic unit. Intramolecular gold-catalyzed carbothiolation of the alkyne in **19** results in formation of the sulfur heterocycle through 5-*endo*-dig cyclization and S → C migration of the allyl unit [16].

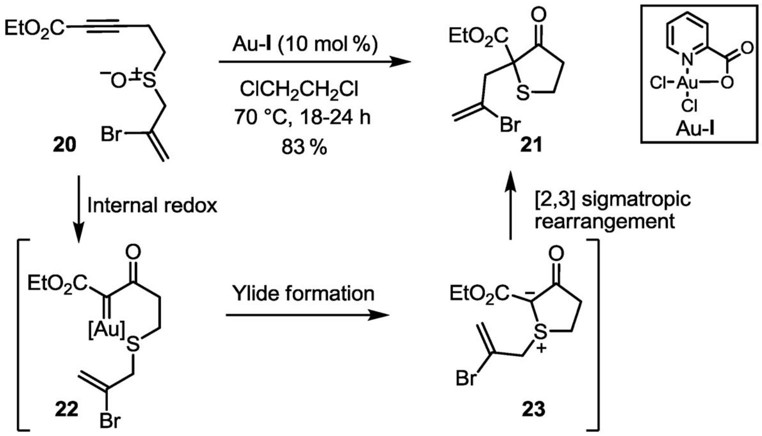


Scheme 10 Gold-catalyzed cascade reaction.

Platinum- or gold-catalyzed synthesis of sulfur heterocycles

The next stage of our studies moved away from propargylic carboxylates toward simpler precursor sites for sulfur ylides. Prior art had shown that a sulfoxide could be employed as intramolecular nucleophiles for alkynes activated by gold. The resulting oxygen transfer process afforded α-keto gold carbenoids, which were employed in effective aromatic substitution or hydride shift reactions [17]. As the internal redox process generates both of the components required for ylide formation, a gold carbenoid and a sulfide, we considered that such a reaction might allow us to employ simple alkynes as direct precursors to sulfur ylides. Having observed how the relative complexity of the propargylic carboxylate influenced the subsequent evolution of the sulfonium ylide down an unexpected route, we thought that this simple system could provide a more direct replacement for classical ylide preparations. During the course of this study, azomethine ylides were prepared by the internal redox reaction between a nitrone and an alkyne and subsequently employed in cycloaddition reactions [18].

We tested the veracity of this approach in an intramolecular cyclization reaction. Allyl sulfoxides, such as **20**, bearing tethered alkynes were subjected to π-acid catalysis and found to undergo cycloisomerization affording functionalized sulfur heterocycles **21** under mild conditions (Scheme 11). The reaction proceeds with an internal redox reaction generating the α-ketocarbenoid and releasing the sulfide in **22**. Coupling of these units results in an allyl sulfonium ylide **23**, which on 2,3-sigmatropic rearrangement gives dihydrothiophenone **21** [6].



Scheme 11 Gold-catalyzed synthesis of sulfur heterocycles.

This reaction was applied to the synthesis of dihydrothiophenone and dihydrothiopyranone products (Chart 3). The reaction tolerates precursor alkynes capped with a proton, aryl unit, or electron-withdrawing group. $PtCl_2$ was used as catalyst with terminal alkynes, whereas the dichloro(pyridine-2-carboxylato)gold(III) precatalyst was employed for internal alkynes. Allylic inversion was observed and the reaction tolerated vinyl halides, ketones, and aromatic moieties. Crucially, this strategy allows the

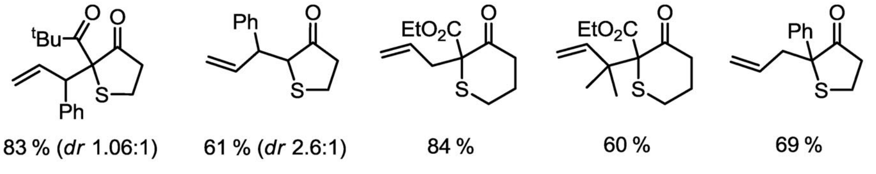
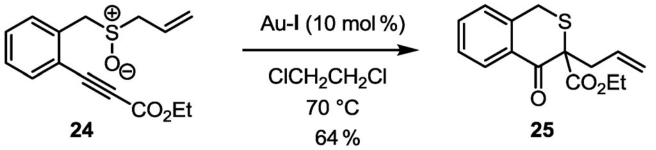


Chart 3 Representative cycloisomerization products.

immediate precursor to the ylide site to be incorporated into a molecule at an early stage of the synthesis, rather than immediately prior to the ylide formation as is the case with standard approaches, thus providing greater synthetic flexibility.

Incorporation of an aromatic unit in the linker between alkyne and sulfoxide allowed isothiochroman-4-ones **25** to be synthesized following the same strategy (Scheme 12).



Scheme 12 Gold-catalyzed synthesis of isothiochroman-4-ones.

SUMMARY

We have developed a range of new transformations based on the concept of using alkynes as direct precursors to sulfur ylides. These approaches bypass many of the problems associated with the usual methods for introduction of an ylide. In particular, we can avoid the use of sacrificial functionality. Two approaches have been demonstrated: the intermolecular coupling between a propargylic carboxylate and a sulfide, and the intramolecular reaction of alkyne-tethered allyl sulfoxides. These reactions allow a rapid build-up of molecular complexity from accessible molecules under mild reaction conditions.

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