Alkynes as masked ylides: Gold-catalysed intermolecular reactions of propargylic carboxylates with sulfides†

Paul W. Davies* and Sébastien J.-C. Albrecht

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The *in situ*-generation of sulfur ylides by the gold-catalysed rearrangement of propargylic carboxylates in the presence of sulfides has resulted in highly efficient and novel transformations.

The transition-metal-catalysed decomposition of diazo compounds is a well-established and powerful strategy to access metal carbenoids, which may then be used to generate reactive intermediates. A powerful example is the Doyle–Kirmse reaction, which generates new C–C and C–S bonds (Scheme 1), most notably under Rh(II) and Cu(I) catalysis.[1] In this process, an allyl sulfide **3** reacts with carbenoid **2** to give a sulfur ylide intermediate **4** that is capable of undergoing a [2,3]-sigmatropic rearrangement.[2] This overall strategy, however, is limited: first, by safety concerns associated with the handling and use of diazo compounds; second, by the synthetic impact associated with the introduction of a diazo functionality. With these factors in mind, we recently initiated a programme to explore the utility of reactive intermediates derived from metal carbenoids that are accessed *via* rearrangement processes. By bypassing the preparation and use of diazo compounds, this strategy should result in increased overall synthetic efficiency, whilst also decreasing potential operating risks.

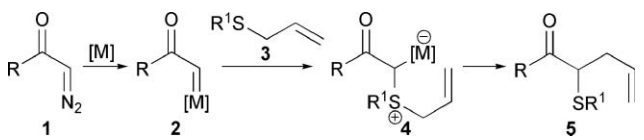
As a starting point, we studied the reaction between a propargylic carboxylate and an allyl sulfide (Scheme 2). Within the rapidly developing area of gold- and platinum-based homogeneous catalysis,[3,4] the propargylic carboxylate moiety has invited special interest owing to its propensity to act as an α-diazocarbonyl surrogate upon rearrangement to metal carbenoid **7**.[5] This reactivity has been successfully employed in a number of transformations, in particular through reaction with additional C–C π-systems.[6,7]

We questioned whether this mode of reactivity could therefore be used as an alternative strategy to access reactive intermediates, such as sulfur ylides. If successful, the combination of ylide chemistry and noble-metal-catalysed isomerisation processes would allow a plethora of valuable new transformations to be developed. However, several issues needed to be explored: first, whether these π-acid catalysts retain efficacy in intermolecular processes featuring reagents that may otherwise be considered as effective catalyst poisons;[8,9] second, whether the reactivity profile of the carbenoid and/or the ylide formed from it mimics that of species derived from α-diazocarbonyl compounds.

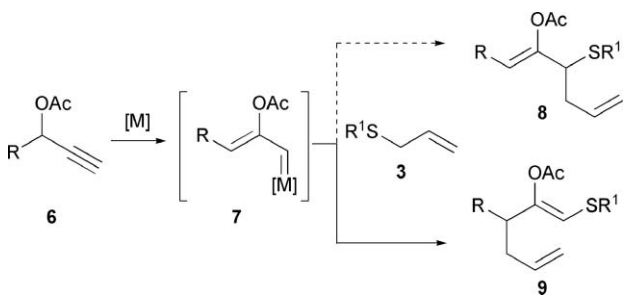
To this end, propargylic carboxylate **6** (R = Ph, 1.00 equiv.) and phenyl allyl sulfide **3** (R^1 = Ph, 1.05 equiv.) were reacted together in the presence of 5 mol% of a noble metal catalyst (Scheme 2, Table 1). While cationic gold species and $PtCl_2$ were ineffective, the simple AuCl salt afforded a new product in high yield. Analysis of this compound using extensive NMR studies showed it to be compound **9**. No traces of isomer **8**, expected from a Doyle–Kirmse type reaction,[10] or products resulting from cyclopropanation of the allyl unit were seen, and only the (*Z*)-isomer of **9** was observed (see ESI†).

Further optimisation showed the use of chlorinated solvents at 0.1 M concentration to be most effective (Table 1, entry 5). Although good results were achieved using CH_2Cl_2 at room temperature, the reaction time was significantly reduced when performed in $ClCH_2CH_2Cl$ at 70 °C (Table 1, entry 10).

The same reaction conditions were applied across a number of substrates (Table 2). Pivaloyl, acetyl and benzoyl esters may be employed (Table 2, entries 1–3); however, the use of a *para*-nitrobenzoate ester led to decomposition. Electron-rich and electron-poor aromatic units were accommodated on the sulfide (Table 2, entries 4–8).[11] In the latter cases, 2 equiv. of sulfide were employed to achieve good yields (Table 2, entries 5–7), and the enol acetates were hydrolysed to the ketones **10** before being isolated, in order to aid purification. The propargylic acetate may also be modified, and a high yield was observed using the *ortho*-bromo substituent (Table 2, entry 9). The use of halide substituents



Scheme 1 The Doyle–Kirmse reaction.



Scheme 2 The rearrangement–coupling–rearrangement reaction between propargylic carboxylates and allyl sulfides.

School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT. E-mail: p.w.davies@bham.ac.uk; Fax: +44 (0)121 414 4403; Tel: +44 (0)121 414 4408

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Table 1 Screening of reaction conditions (Scheme 2)[a]

Entry	Catalyst	Solvent	T/°C	Time/h	Yield **9** (%)[b]
1	PPh_3AuSbF_6[c]	CH_2Cl_2	23	40	—[d]
2	Me_2SAuCl	CH_2Cl_2	23	40	12
3	PPh_3AuNTf_2	CH_2Cl_2	23	40	—[e]
4	$PtCl_2$	$PhCH_3$	60	40	—[d]
5	AuCl	CH_2Cl_2	23	40	85
6	AuCl	CH_2Cl_2	23	40	44[f]
7	AuCl	MeCN	23	40	24
8	AuCl	$PhCH_3$	23	40	43
9	AuCl	$PhCH_3$	70	18	50
10	AuCl	$ClCH_2CH_2Cl$	70	6	95

[a] For the reaction of **6** (R = Ph, 1.00 equiv.) with phenyl allyl sulfide **3** (R^1 = Ph, 1.05 equiv.) at 0.1 M concentration. [b] Yields determined by NMR against a known quantity of benzaldehyde. [c] Formed by mixing equimolar quantities of PPh_3AuCl and $AgSbF_6$. [d] No reaction was observed. [e] Degradation. [f] At 0.5 M concentration.

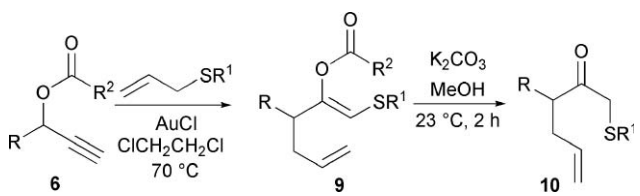
Table 2 Scope of the Au(I)-catalysed cascade reaction (Scheme 3)[a]

Entry	R	R^1	R^2	Time/h	Product (yield (%))[b]
1	Ph	Ph	Me	6	**9a** (82)
2	Ph	Ph	^{t}Bu	6	**9b** (72)
3	Ph	Ph	Ph	4	**9c** (72)
4	Ph	*p*-$MeOC_6H_4$	Me	6	**9d** (80)
5	Ph	*p*-MeC_6H_4	Me	5	**9e** (82)
6	Ph	*p*-BrC_6H_4	Me	9	**10f** (64)[c]
7	Ph	*o*-BrC_6H_4	Me	9	**10g** (54)[c]
8	Ph	*p*-$CF_3C_6H_4$	Me	9	**10h** (58)[c]
9	*o*-BrC_6H_4	Ph	Me	5	**9i** (93)
10[d]	*o*-BrC_6H_4	*p*-MeC_6H_4	Me	24	**9j** (87)
11	Ph	Allyl	Me	42	**10k** (63)[e]

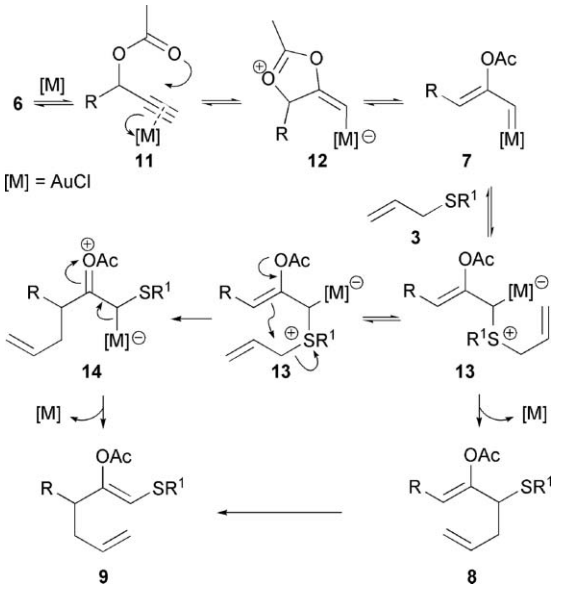
[a] For the reaction of carboxylates **6** (0.29 mmol) with sulfides **3** (0.30 mmol) in $ClCH_2CH_2Cl$ (0.1 M) using 5 mol% of AuCl. [b] Isolated yields after chromatographic purification. [c] 2 equiv. of sulfide and 10 mol% AuCl. [d] On a 1.0 mmol scale using 10 mol% AuCl. [e] 3 equiv. of diallylsulfide.

further exemplifies the chemoselectivity of gold catalysts toward alkynes and allows synthetic handles to be introduced for future manipulation (Table 2, entries 6, 7, 9, 10). Bis-allyl sulfide also undergoes the reaction cleanly, and the product was isolated as a ketone (Table 2, entry 11).

A proposed mechanistic scenario for the formation of **9** is shown in Scheme 4. Nucleophilic attack of the carbonyl unit onto gold-activated alkyne **11** is followed by back-donation from the metal to generate gold carbenoid **7**.[3,5] Subsequent reaction with a thioether generates ylide **13**, which may or may not be associated with AuCl. The subsequent evolution of **13** may then proceed through one of two pathways: a 1,2-shift or a [2,3]-sigmatropic rearrangement of the allyl fragment affording **8**, as per the Doyle–Kirmse process, followed by Cope rearrangement to **9**; or an overall oxygen-assisted 1,4-shift affording betaine **14**, and subsequent elimination of AuCl.[12]



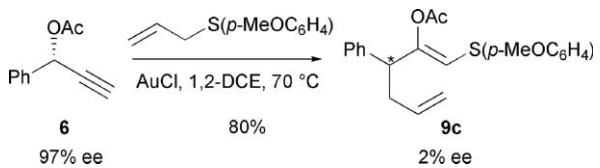
Scheme 3 Gold-catalysed rearrangement–addition reactions.



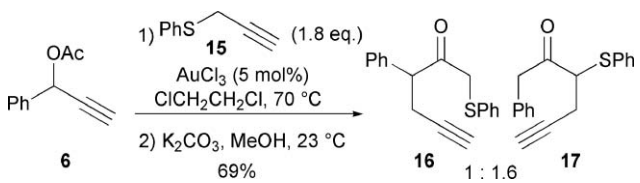
Scheme 4 Potential reaction pathways.

An absence of chirality transfer was demonstrated in the reaction of enantioenriched (*R*)-**6** (Scheme 5), thus suggesting the intermediacy of an achiral species, such as **7**. Similar results were found in intermolecular cyclopropanation processes mediated by cationic gold species.[7b]

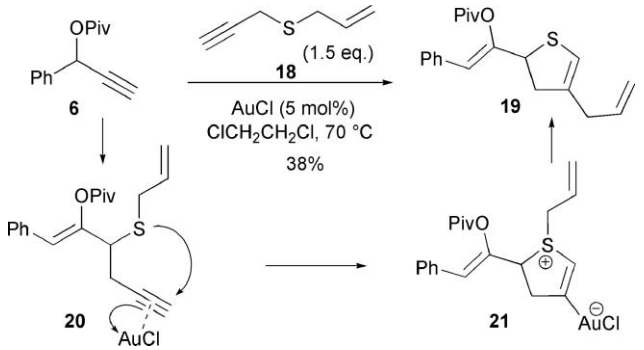
In contrast to reactions with allyl thioethers, the use of propargyl thioether **15** gave a mixture of isomeric products, **16** and **17**, after hydrolytic work-up (Scheme 6). Although similar ratios were observed with AuCl, $AuCl_3$ was found to be most efficacious for this process. Minor isomer **16** is analogous to the products derived from the reaction of allyl thioethers, whereas major isomer **17** matches that expected from direct 1,2-transfer of the propargylic fragment from the ylide intermediate. Despite the mixture of isomers, the reaction displays excellent chemoselectivity with respect to the two terminal alkyne units available for reaction. The reaction funnels cleanly through the activation of the propargylic carboxylate rather than the reaction of the propargylic sulfide. The reason for the shift in selectivity is, as yet, unclear. However, the formation of **17** contrasts with the Cu(I)-catalysed



Scheme 5 Use of an enantioenriched substrate.



Scheme 6 Use of propargylic sulfide.



Scheme 7 A cascade rearrangement–coupling–rearrangement–cycloisomerisation reaction.

Doyle–Kirmse reactions of propargylic sulfides, which afford allene products *via* a [2,3]-sigmatropic rearrangement.[2a]

In order to explore the relative proclivities of allyl and propargyl fragments to undergo the shift process, **6** was reacted with allyl propargyl sulfide **18** (Scheme 7). The major product of the reaction was dihydrothiophene **19** (with <10% by mass of a complex mixture of other products). A likely reaction pathway involves the preferential formation of **20** through a shift of the propargylic fragment. Subsequent gold-catalysed carbothiolation sees the formation of a dihydrothiophene core with a S → C shift of the allyl unit. While endocyclic carboheteroatom additions have previously been used to prepare benzothiophenes and other fused aromatic systems, to the best of our knowledge, this is the first report of an endo-mode 1,2-carbothiolation of an alkyne to afford semi-saturated heterocycles.[8a,13] Overall, this process involves three key stages: gold-catalysed rearrangement, ylide formation and rearrangement, and gold-catalysed cycloisomerisation. Although the overall yield of **19** is modest, the large number of bond forming processes and the very significant increase in molecular complexity from the simple starting materials renders this cascade process attractive, especially when considering the numerous selectivity issues at play.

In summary, the use of gold-catalysed isomerisations to access reactive sulfur ylide intermediates has been shown to be a viable intermolecular strategy. A highly efficient rearrangement–coupling–rearrangement process has been developed that utilises simple, readily constructed precursors to access highly functionalised materials under mild conditions. This study demonstrates that the gold carbenoids derived from propargylic carboxylates can show a complementary mode of reactivity to carbenoids derived from α-diazo carbonyl compounds, with the propargylic carboxylate reacting as an overall 1,3-dipolar synthon rather than a 1,1-dipolar species. Further exploration of the reactivity of ylides derived from gold carbenoids and a study into the mechanism of this process is under way, and will be reported in due course.

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Notes and references

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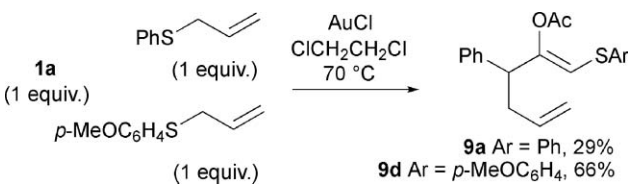

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