A gold-catalysed fully intermolecular oxidation and sulfur-ylide formation sequence on ynamides†

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An efficient C–O, C–S and C–C bond-forming sequence leads to functionalised compounds bearing sulfur-substituted quaternary carbons. Ynamides are employed as diazo-equivalents to access the [2,3]-sigmatropic rearrangements of allyl sulfonium ylides by a three-component chemoselective oxidation and intermolecular ylide formation.

The [2,3]-sigmatropic rearrangement of allyl sulfonium ylides is a potent method for the formation of Csp³–Csp³ bonds. A significant hydrocarbon functionalisation process is achieved when the rearrangement is coupled with in situ ylide formation through reaction of a sulfide with a metal carbene, formed in situ from a sacrificial functionality such as the diazo-group (Doyle–Kirmse reaction, Scheme 1).4,5 We and others4 have been engaged in efforts to access the synthetic potential of these ylides using methods to generate carbenoids that avoid the pre-installation and use of potentially hazardous high-energy diazo groups. Our initial studies established that sulfur ylides can be prepared from the intermolecular reaction of sulfides with gold-carbenes (Scheme 2).4,4a,4d However, the use of propargylic carboxylates as carbenoid precursors impacted on the subsequent ylide rearrangements to generally afford products isomeric to those from [2,3]-sigmatropic pathways. More-congested centres and synthetically valuable sulfur-substituted quaternary carbons were inaccessible as terminal alkynes and unsubstituted allyl groups on the sulfide7 were required.4a,d We subsequently established that sigmatropic-rearrangements of sulfur ylides were accessible through an intramolecular gold or platinum catalysed cycloisomerisation of alkynyl allyl sulfoxides.4b,a Here we report a diazo-free oxidation-ylide formation sequence to access sulfur-ylide rearrangements by a selective and efficient fully intermolecular transformation of ynamides.

In light of our,4 and others10 studies into gold-catalysed intermolecular atom/group-transfer onto ynamides,11 we questioned whether ynamides could be used to replace diazo compounds in intermolecular sulfonium ylide formation to form quaternary carbons (Schemes 1 and 3). Significant transformations have resulted from 2-oxo-gold carbene formation by intermolecular oxidation of a C–C triple bond.9,10,12 While these predominantly feature subsequent intramolecular cyclisations, there are striking exceptions in the terminal alkyne series where the mono-substituted gold carbene is trapped with intermolecular oxygen-, nitrogen- and halide nucleophiles other than the oxidant.13 Similar three-component couplings have not however been reported in the ynamide series and it is notable that the resulting 1,1-disubstituted organogold species C/D appears prone to oxidation even when intramolecular pathways are available.9,10,14 A successful outcome therefore requires a high level of reagent-compatibility and selectivity: the sulfide must not affect...
activation or oxidation of the ynamide (A → B → C).\textsuperscript{15} Ylide formation must then compete successfully with cyclopropanation (G) and oxidation (H) of organogold species C and/or D.

After exploring a variety of parameters including catalyst, solvent and oxidant with various ynamides (see ESI†), reaction conditions were found to effect the complexity-increasing cascade from ynamides 1 into the functionalised tertiary thiocarbonyl D (Scheme 4). Competing double-oxidation to form imido-ketones (E) or imido-ynamides (F) of organogold species to react preferentially with the polarisable sulfur was avoided. This preference was maintained throughout the study in order to explore the extent and influences on the observed chemoselective preference for sulfide attack at the organogold intermediate.\textsuperscript{15,16}

Ynamides bearing N-phenyl and N-methyl groups reacted similarly (4ba vs. 4a) while an N-benzyl equivalent was less suited affording a lower yield of 4ca with competing oxidation observed.\textsuperscript{17} The trend between N-phenyl and N-methyl was maintained in the p-tolysulfonamide series, albeit with slightly higher yields (Scheme 4, 4da and 4ea). In both cases, products from cyclisation of C/D onto the N-substituent were not observed. An ynamide prepared from imidazole was unreactive.

The sulfonamide-derived ynamides were used throughout the remainder of this study into structural effects on the relative efficacy of the standard conditions. The reaction remained effective in the presence of S-aryl, S-benzyl- and S-alkyl allyl sulfides 2b–e as well as bisallylsulfide 2f (Scheme 5). Unsurprisingly, a more electron-deficient aryl bromide substituent renders the ylide pathway less competitive against oxidation with ~30% yield of the over-oxidation product determined from the crude reaction mixture.

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The role of the ynamide C-substituent was next tested under the standard conditions (Scheme 6). None of the desired product from ylide formation was observed when anisole-derived ynamide 1g was reacted with sulfides 2a or 2b with the over-oxidation product 5 instead predominating. A preference for over-oxidation against an intramolecular reaction has recently been reported when using p-anisole derived ynamide.\textsuperscript{10f} In contrast, both inductively and mesomerically electron-withdrawing groups were well tolerated (4ib and 4ih). Alkyl-substituted gold carbenoids are prone to 1,2-insertion\textsuperscript{9a} and this intramolecular pathway was indeed preferred, affording 6 with low conversion of the hexyne-derived ynamide 1j. A conjugated enyne-ynamide 1k did not follow a recently reported 4-π-electrocyclisation pathway\textsuperscript{10d} instead reacting productively to afford functionalised tertiary allylic thioether 4la.

By analogy to the effects encountered in diazo-derived metal carbone chemistry, changing the ynamide C-substituent was expected to influence the reactivity of the resulting carbenoid.\textsuperscript{2} However, the impact of the electronic influence on the chemoselectivity of these ynamide-based reactions is informative: the formation of the desired compound 4 requires the active organogold species to react preferentially with the polarisable sulfur nucleophile 2 in preference to the dipolar oxygen-nucleophile 3.

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Scheme 3 A gold-catalysed intermolecular oxidation – intermolecular trapping manifold for ynamides.

Scheme 4 The ynamide-based Doyle–Kirmse type reaction.

Scheme 5 Effect of the non-migrating group on the allyl sulfide.
Nucleophilic attack can occur either alongside- or after elimination of methylyphoxinate (Scheme 3, C → E vs. C → D → E).\textsuperscript{8,10,12,13} Considering the contrasting natures of the nucleophiles, a favourable attack of the sulfide on the vinyl gold carbenoid C, bearing a relatively-uncharged carbon centre, appears more likely than on the cationic carbon of gold carbene D. The strongly p-acidic phosphite ligand affords significant cationic character to D by decreasing the ability of gold to donate electron density.\textsuperscript{18} However, these same electronic characteristics should aid the desired chemoselectivity by disfavouring the elimination of methylyphoxinate required to form D. On this basis, the reactivity of electron-rich ynamide 1g (R² = p-MeOC₆H₄) can be explained by the mesomeric contribution from the anisole MeO-group aiding elimination of the nucleofuge to form D and disfavouring ylide formation.

Sulfides with substituted allyl units were then explored to ascertain if a [2,3]-sigmatropic rearrangement was operative. Pleasingly, and in contrast with other systems,\textsuperscript{7} both 2-vinyl- and cinnamyl derivative 2h underwent clean reactions. The functionalised 8-membered sulfur heterocycle 4eg and the tertiary thioether bearing a vicinal tertiary mesomeric contribution from the anisole MeO-group aiding elimination of the nucleofuge to form D and disfavouring ylide formation.

Scheme 6 Effect of the ynamide C-substituent on the reaction outcome.

reaction of substituted allyl sulfides 2h with metal carbenes derived from donor-acceptor diazocompounds.\textsuperscript{6,15} The relative stereochemistry of the major diastereoisomer was confirmed by X-ray analysis (Scheme 7) and is consistent with a preference for the cinnamyl phenyl group to be positioned anti to the amide group across an envelope transition state. Rapid access to these N,N-disubstituted amide derivatives by the ynamide strategy may therefore provide additional synthetic advantages.

In conclusion, a gold-catalysed cascade reaction is reported for the practical complexity-increasing synthesis of functionalised tertiary thioethers directly from ynamides. Selectivity for sulfur ylide formation over competing processes is rationalised and can be achieved when all reagents are added at the start of the process with a near-stoichiometric reagent loading. The products are consistent with those expected from [2,3]-sigmatropic rearrangement of allyl sulfonium ylides. This report demonstrates that ynamides can be used as synthetically attractive replacements to 1,1-disubstituted diazocompounds in intermolecular processes.

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Notes and references


7 Cyclopropanation not ylide formation was observed when allyl sulfides bearing more substituted alkenes were employed, see ref. 4d.

Ynamide preparations: (a) For the first report and then representative examples from other groups: (a) Y. Zhang, R. P. Hsung, Angew. Chem., Int. Ed., 2011, 50, 8931.  
14 For two-component intermolecular metathesis, see ref. 10b.  
16 Regular portionwise addition of 3 affords 81% (by 1H NMR) by maintaining a low concentration of oxidant relative to the sulfide.  
17 Co-elution prevented accurate yields of over-oxidised product.  