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Gold-Catalysed Cycloisomerisation of Ynamides To Access 2,2-Disubstituted Tetrahydrothiophene Motifs

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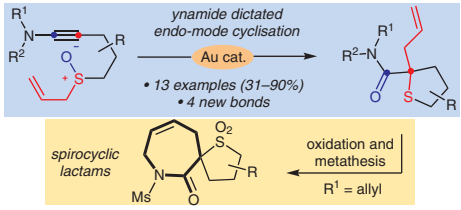

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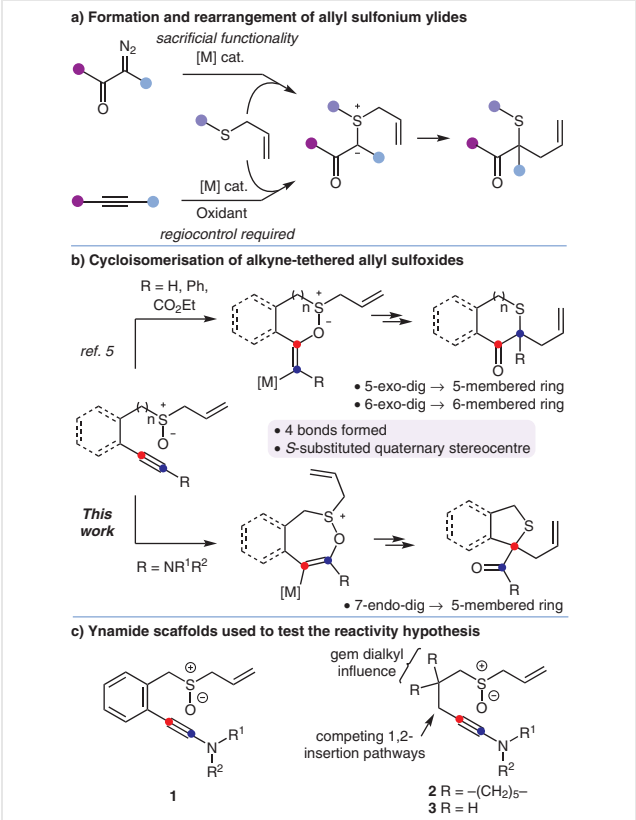
Abstract Ynamides bearing a tethered allyl sulfoxide undergo a gold-catalysed cycloisomerisation to afford tetrahydrothiophene-2-carboxamides and their benzo-fused analogues. The reactions are initiated by a formal 7-*endo-dig* cyclisation and accommodate a range of different substituents. The use of *N*-allyl ynamides provided a route into novel spirocyclic ε-lactam structures.

Key words gold, ynamides, isomerization, ylides, regioselectivity, thiophenecarboxamides

The π-acid-catalysed cycloisomerisation of alkyne-bearing substrates has delivered a huge diversity of inherently efficient and complexity-building transformations.[1] Many such reactions illustrate the capacity of π-acid catalysis to access metal carbene-like reactivity patterns.[2] Unlike diazo compounds and other carbene precursors that use a sacrificial functionality to direct the site of carbene formation, alkynes offer two sites for metal carbene formation and, hence, the possibility for divergent reaction outcomes if effective regiocontrol can be achieved (Scheme 1a).

The ability to access new S-heterocyclic motifs under the mild and functional-group-tolerant conditions associated with gold catalysis is appealing, given the importance of sulfur heterocycles in medicinal chemistry.[3] Cycloisomerisation reactions affording sulfur heterocycles by C–S bond formation are, however, relatively rare compared with C–O and C–N bond-forming reactions.[4]

Our group previously reported the preparation of dihydrothiophen-3(2*H*)-one and dihydro-2*H*-thiopyran-3(4*H*)-one derivatives from allyl sulfoxide-tethered alkynes under Pt(II) or Au(III) catalysis.[5] This cycloisomerisation creates four new bonds through the [2,3]-sigmatropic rearrangement of an α-oxo allyl sulfonium ylide formed in situ. Initially, the reactions involve a 5- or 6-*exo-dig* cyclisation, leading to an internal redox transfer of an oxygen atom from sulfur onto the alkyne (Scheme 1b).[6] Products from an



Scheme 1 The formation and rearrangement of allyl sulfonium ylides and access to them by cycloisomerisation of alkyne-tethered allyl sulfoxides

endo-dig cyclisation were observed only as minor products in just two examples, with the *exo*-pathway dominating. We questioned whether an initial *endo*-mode cyclisation could be enforced to achieve the same type of cycloisomerisation, and here we report our studies using an ynamide strategy.

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The gold-keteneiminium character generated from gold-activation of an ynamide has proven to be remarkably useful for the discovery of efficient new synthetic methods under gold catalysis.[7] Superb regiocontrol has been realised across numerous intermolecular processes,[8] including those leading to sulfonium ylides.[9] Our group has previously used ynamides to favour 6-*endo*-*dig* cyclisation over a 5-*exo*-*dig* pathway.[10] In the proposed transformation, however, a more-challenging 7-*endo*-*dig* outcome is required to produce a five-membered sulfur heterocycle (Scheme 1b). If achievable, then, because ynamides are accessible directly from terminal alkynes,[11] various types of sulfur heterocycle might be prepared from the same late-stage precursors (Scheme 1b).

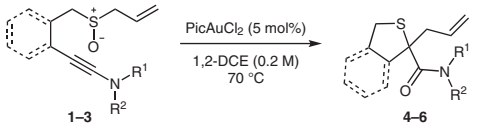
Our study centred on three substrate scaffolds **1**–**3** (Scheme 1c), in which the putative α-amido gold carbenoid is formed adjacent to either an aryl (**1**) or an alkyl (**2** and **3**) substituent. The latter situation introduces a 1,2-CH insertion pathway that competes with sulfonium ylide formation.[8a] Scaffolds **2** and **3** are differentiated by *gem*-dialkyl substitution, which affects the relative rates of cyclisation both before and after carbenoid formation. The required ynamides were prepared by using a modified version of Stahl's oxidative coupling approach [see the Supporting Information (SI)].[11]

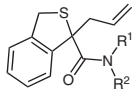
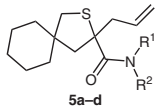
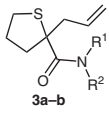
On heating in the presence of dichloro(2-pyridinecarboxylato)gold (PicAuCl$_2$), ynamides **1**–**3** underwent rearrangement to give the corresponding S-heterocyclic products **4**–**6** (Table 1).[12] Lower conversions and less-clean outcomes were obtained by using gold(I) complexes. Various substituted *N*-sulfonyl and oxazolidinone ynamides **1a**–**e** underwent cycloisomerisation to give the corresponding 1,3-dihydro-2-benzothiophenes **4a**–**e** in high yields (Table 1, entries 1–5). No transfer of chiral information to the sulfur-substituted quaternary centre from the chiral oxazolidinone **1e** was observed (Entry 5).

Effective cycloisomerisation occurred with scaffolds **2** and **3**, affording heterocycles **5a**–**d** and **6a**–**b**, respectively, under the same reaction conditions, despite the presence of C(sp^3)–H bonds adjacent to the gold carbenoid.[13] Products from competing ynamide hydration were observed when an undried solvent was used with substrate **3a**, which lacks a *gem*-dialkyl substitution pattern between the reacting centres (entry 10); however, the yield of **6a** doubled on using freshly distilled solvent (entry 11). A silyl ether was also tolerated (**6b**; entry 12).

The observed products are consistent with the broad mechanism previously proposed for terminal and internal alkynes (Scheme 2).[5] In this case, however, the gold-keteneiminium character resulting from the coordination of the active gold catalyst to the ynamide **A** forces an overall *endo*-*dig* addition. Sulfoxide attack generates the vinyl gold carbenoid **B**, which then evolves to ylide **D** and, subsequently, to the observed products through the release of the gold catalyst and a [2,3]-sigmatropic rearrangement. The absence of products from potentially available and fast pathways such as 1,2-CH insertion[8a] indicates ready C–S bond formation. Within the constraints of a cyclic system, the stereoelectronic requirement for S–O bond cleavage align that bond with the alkene π-system in **B**, positioning the sulfur to interact with the electrophilic carbon in **C**.

Table 1 Gold-Catalysed Cycloisomerisation Reactions of Ynamides to Prepare 2,2-Disubstituted Tetrahydrothiophene Derivatives[a]



Entry	Product	R^1	R^2	4–6	Yield[b] (%)
1	 4a–e	Ms	Ph	**4a**	74
2		Ms	Bn	**4b**	81
3		Ms	Bu	**4c**	88
4				**4d**	74
5				**4e**	85 (dr 1:1)
6	 5a–d	Ms	Ph	**5a**	69
7		Ms	Br	**5b**	49
8		Ms	Bu	**5c**	69
9				**5d**	47
10	 3a–b	Ms	Bn	**6a**	31[c]
11[d]		Ms	Bn	**6a**	63
12[d]		Ts	$(CH_2)_2OTBS$	**6b**	40

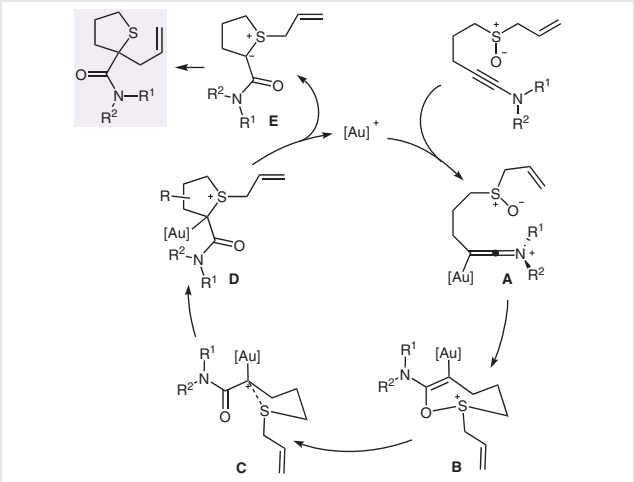
[a] Reactions were carried out at 0.2 M in DCE using PicAuCl$_2$ (5 mol%) at 70 °C.
[b] Isolated yields after flash column chromatography.
[c] The ynamide hydration product was also obtained in 16% isolated yield.
[d] Reaction in freshly distilled DCE.

Representative examples of the sulfur-heterocycle motifs were oxidised to assess the potential of the cycloisomerisation method to access novel cyclic sulfones. Oxidation of **4b** and **6b** by using ammonium heptamolybdate and hydrogen peroxide gave high yields of **7a** and **7b**, respectively (Figure 1).

We envisaged that the formation of α-allyl amide motifs in this cycloisomerisation could be harnessed in a preparation of new and usefully functionalized structures containing reactive groups that might be introduced through the ynamide nitrogen. Spirocyclic compounds are desirable motifs for drug discovery due to their conformationally

well-defined and three-dimensional character.[14] Ynamides with *N*-allyl substituents were therefore prepared to test whether spirocyclic lactams might be obtainable by using a post-cycloisomerisation ring-closing metathesis. Ynamides **8** and **11** underwent gold-catalysed reactions to give the sulfur heterocycles **9** and **12**, respectively (Scheme 3). No products from cyclopropanation were observed. Diene **9** was oxidised to the sulfone and subjected to metathesis conditions using either the first- or second-generation Grubbs catalyst, with the latter giving an excellent yield of the dispirocycle **10**.[15] The same sequence was then applied to ynamide **11**, affording the benzo-fused spirocycle **14** in excellent yield.[16]

In summary, ynamides with tethered allyl sulfoxide moieties undergo gold-catalysed cycloisomerisation to form 2,2-disubstituted tetrahydrothiophenes. The reaction works well when the ynamide is connected to the allyl sulfoxide through either an aromatic or an aliphatic linking group. As the ynamides are prepared directly from terminal alkynes, two distinct sulfur heterocycles are accessible from a common alkyne intermediate by π-acid-catalysed cycloisomerisation. This study highlights the potential of ynamides in controlling π-acid-catalysed reaction pathways, in this case imposing an initial 7-*endo*-*dig* cyclisation outcome. In addition to providing a regiocontrol element, the ynamide unit can also be used to introduce useful functionality that can be combined with that assembled during the cycloisomerisation reaction, as demonstrated by the ready formation of sp^3-rich spirocyclic lactams.



Scheme 2 Mechanistic outline for the observed transformation

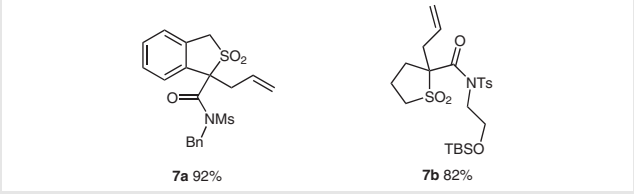
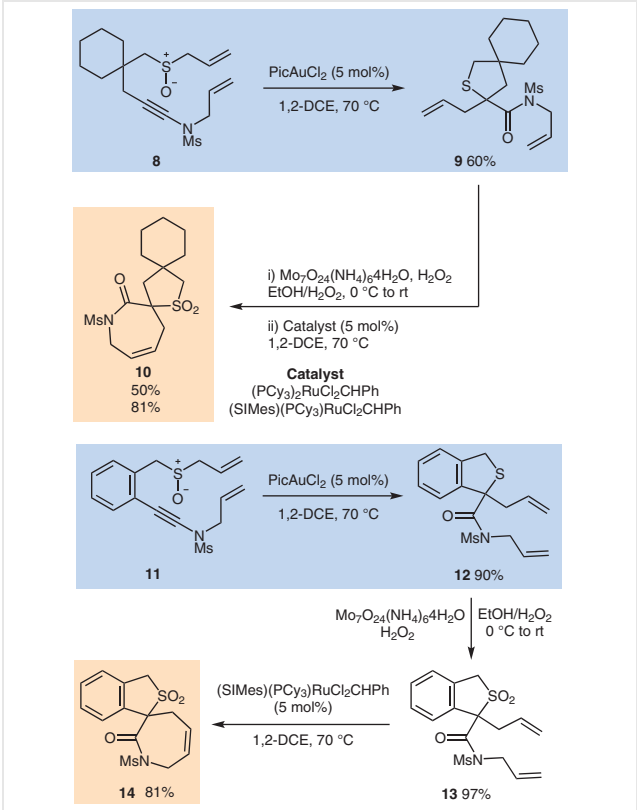


Figure 1 Cyclic sulfones formed by ammonium heptamolybdate-catalysed oxidation of the analogous sulfides with hydrogen peroxide in ethanol (see SI for the conditions). Isolated yields following flash column chromatography are reported. Yields in parenthesis were determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy with an internal standard.



Scheme 3 Use of the ynamide-based cycloisomerisation to access novel functionalised α-spirocyclic lactam structures. SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1434-4273.

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(12) **Cycloisomerisation of Ynamides: General Procedure**
AuPicCl2 (5.0 mol%, 5 μmol) was added to a 0.2 M solution of the appropriate ynamide in DCE (0.1 mmol) in a flame-dried Schlenk tube under argon, and the mixture was heated at 70 °C. Upon completion of the reaction (TLC), the crude mixture was passed through a small plug of silica to remove gold residues. The solvent was then evaporated, and the residue was purified by column chromatography (hexanes–EtOAc).
1-Allyl-*N*-benzyl-*N*-(methylsulfonyl)-1,3-dihydro-2-benzothiophene-1-carboxamide (4b)
Purified by column chromatography [silica gel, hexanes–EtOAc (7:3)] as a yellow viscous oil; yield: 31 mg (81%). IR (neat): 2925 (w), 1679 (s), 1351 (s), 1162 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.92 (s, 3 H) overlaps with 3.01–2.95 (m, 1 H), 3.10 (dd, *J* = 14.2, 7.4 Hz, 1 H), 4.19 (d, *J* = 14.2 Hz, 1 H), 4.33 (d, *J* = 16.0 Hz, 1 H), 4.41 (d, *J* = 14.2 Hz, 1 H), 4.83 (d, *J* = 16.0 Hz, 1 H), 4.92–5.05 (m, 2 H), 5.46–5.64 (m, 1 H), 7.14–7.31 (m, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 238.0, 43.3, 47.2, 50.6, 69.0, 120.1, 125.2, 125.3, 127.8, 127.9, 128.4, 128.5, 128.6, 132.2, 135.6, 140.2, 141.0, 175.1. MS (TOF ES$^+$): *m/z* = 410 (100%) $[M + Na]^+$. HRMS (TOF ES$^+$): *m/z* calcd for $C_{20}H_{21}NNaO_3S_2$: 410.0861; found: 410.0859.
***N*,3-Diallyl-*N*-(methylsulfonyl)-2-thiaspiro[4.5]decane-3-carboxamide (9)**
Colourless viscous oil; yield: 21.3 mg (60%); IR (neat): 2924 (s), 2852 (m), 1681 (s), 1352 (s), 1165 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.63 (m, 10 H), overlaps with 1.53 (d, *J* = 13.6 Hz, 1 H), 2.55 (dd, *J* = 14.4, 7.2 Hz, 1 H), 2.70 (dd, *J* = 14.4, 5.8 Hz, 1 H), 2.69 (d, *J* = 10.7 Hz, 1 H), 2.77 (d, *J* = 10.7 Hz, 1 H), 2.96 (d, *J* = 13.6 Hz, 1 H), 3.28 (s, 3 H), 4.39–4.56 (m, 2 H), 5.05–5.20 (m, 2 H), 5.25–5.42 (m, 2 H), 5.63–5.81 (m, 1 H), 5.86–6.03 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.0, 24.0, 26.1, 34.6, 37.8, 43.3, 44.5, 45.8, 46.5, 47.7, 62.3, 119.5, 132.5, 132.8, 174.6. MS (TOF ES$^+$): *m/z* = 380 (100%). HRMS (TOF ES$^+$): *m/z* calcd for $C_{17}H_{27}NNaO_3S_2$: 380.1330; found: 380.1338.

(13) To complement the 2-thiaspiro[4.5]decane motif **5** accessed from ynamides **2**, their alkyne precursor was tested under the conditions previously developed for the reaction of terminal alkynes (see ref. 5), providing access to a 2-thiaspiro[5.5]undecan-4-one motif (see SI).

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(16) Attempts to extrude sulfur dioxide from **13** were unsuccessful with no conversion even in diphenyl ether at 280 °C.

