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Heer, Parmjit; Davies, Paul

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# Gold-catalysed cycloisomerisation of ynamides to access 2,2-disubstituted tetrahydrothiophene motifs

Parmjit Heer[a,1]
Paul W. Davies*[a]

[a] School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom; https://orcid.org/0000-0002-0340-2414.

p.w.davies@bham.ac.uk

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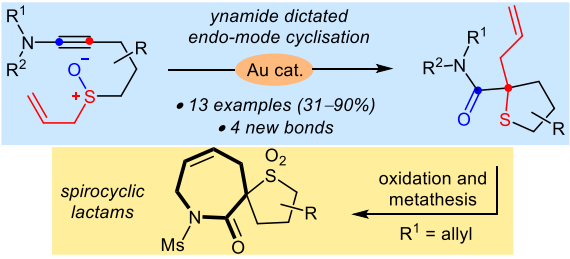


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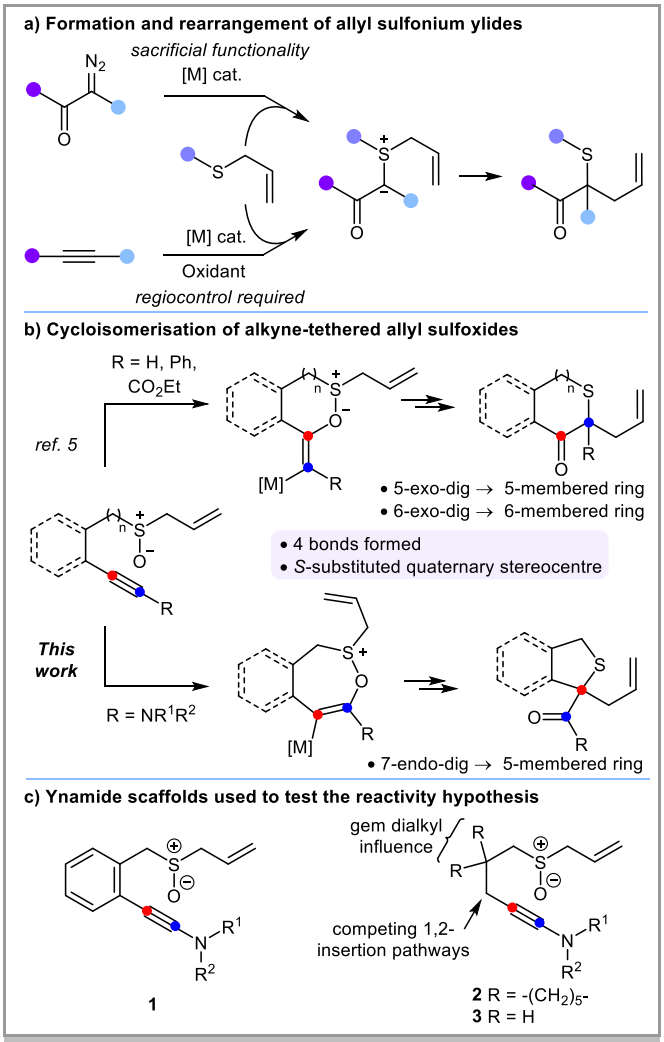
**Abstract** Ynamides bearing a tethered allyl sulfoxide undergo a gold-catalysed cycloisomerisation to afford 2-carboxylic amide tetrahydrothiophenes and their benzofused analogues. The reactions are initiated by a formal 7-*endo*-dig cyclisation and accommodate a range of different substituents. The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

**Key words** gold, ynamide, isomerisation, ylides, sulfur, regioselectivity,

The π-acid catalyzed cycloisomerisation of alkyne-bearing substrates has delivered a huge diversity of inherently efficient and complexity-building transformations.[1] Many such reactions illustrate π-acid catalysis' capacity to access metal carbene-like reactivity patterns.[2] Unlike diazocompounds 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 import of sulfur heterocycles in medicinal chemistry.[3] Cycloisomerisation reactions affording sulfur heterocycles by C-S bond formation are however relatively rare compared to C-O and C-N bond forming reactions.[4]

Our group previously reported the preparation of dihydrothiophen-3(2H)-one and dihydro-2H-thiopyran-3(4H)-one derivatives from allyl sulfoxide-tethered alkynes under Pt(II) or Au(III) catalysis.[5] This cycloisomerisation makes four new bonds via 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 endo-dig cyclisation were observed in only two examples and as minor products, with the exo-pathway dominating. We questioned whether an initial endo-mode



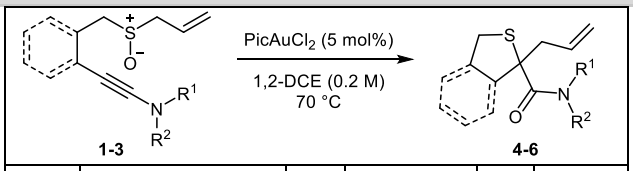

**Scheme 1** The formation and rearrangement of allyl sulfonium ylides and accessing them by cycloisomerisation of alkyne-tethered allyl sulfoxides.

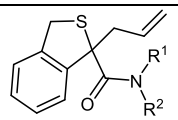
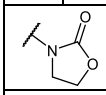
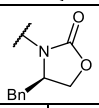
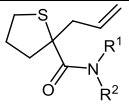
cyclisation could be enforced to achieve the same type of cycloisomerisation, and herein we report our studies using an ynamide strategy.

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 realized across numerous intermolecular processes,[8] including those accessing sulfonium ylides.[9] Our group have previously used ynamides to favour 6-endo-dig cyclisation over a 5-exo-dig pathway.[10] In the proposed transformation, a more challenging 7-endo-dig outcome is however required in order to obtain a 5-membered sulfur heterocycle (Scheme 1b). If achievable, then, as ynamides are accessible directly from terminal alkynes,[11] different types of sulfur-heterocycles 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 forming adjacent to either an aryl (**1**) or alkyl (**2**, **3**) substituent. The latter situation introduces a competing 1,2-CH insertion pathway over sulfonium ylide formation.[8a] Scaffolds **2** and **3** are differentiated by gem-dialkyl substitution affecting the relative rate of cyclisation both pre- and post-carbenoid formation. The required ynamides were prepared using a modified version of Stahl's oxidative coupling approach (see ESI).[11]

**Table 1** Gold-catalysed cycloisomerisation reactions of ynamides to prepare 2,2-disubstituted tetrahydrothiophene derivatives.[a]



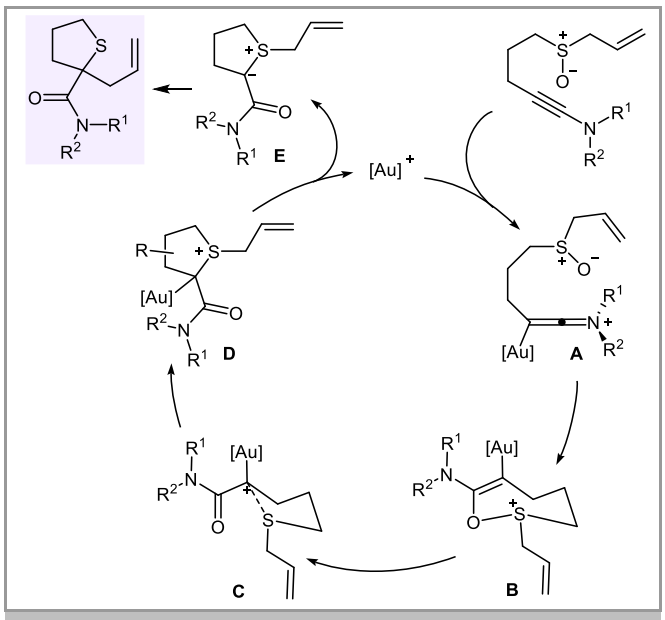

| Entry | Products | R¹ | R² | 4-6 | Yield[b] |
|---|---|---|---|---|---|
| 1 |  4a-e | Ms | Ph | **4a** | 74% |
| 2 | | Ms | Bn | **4b** | 81% |
| 3 | | Ms | *n*Bu | **4c** | 88% |
| 4 | |  | | **4d** | 74% |
| 5 | |  | | **4e** | 85% (dr 1:1) |
| 6 |  5a-d | Ms | Ph | **5a** | 69% |
| 7 | | Ms | Br | **5b** | 49% |
| 8 | | Ms | *n*Bu | **5c** | 69% |
| 9 | |  | | **5d** | 47% |
| 10 |  3a-b | Ms | Bn | **6a** | 31%[c] |
| 11 | | Ms | Bn | **6a** | 63%[d] |
| 12 | | Ts | $CH_2CH_2OTBS$ | **6b** | 40%[d] |

[a] Reactions were carried out at 0.2 M in 1,2-dichloroethane (0.2 M) using $PicAuCl_2$ (5 mol%) at 70 °C. [b] Isolated yields after flash column chromatography. [c] The ynamide hydration product was isolated in 16% isolated yield. [d] Reactions carried out with freshly distilled 1,2-dichloroethane.

Ynamides **1-3** underwent rearrangement to give *S*-heterocyclic products **4-6** on heating in the presence of $PicAuCl_2$ (Table 1).[12] Lower conversions and less clean outcomes were obtained using gold(I) complexes. Variously substituted *N*-sulfonyl and oxazolidinone ynamides **1a-e** underwent cycloisomerisation to give the 1,3-dihydrobenzo[c]thiophenes **4a-e** in high yield (Table 1, Entries 1-5). No transfer of chiral information to the sulfur-substituted quaternary centre was observed from a chiral oxazolidinone **1e** (Entry 5).

Effective cycloisomerisation occurred with scaffolds **2** and **3** affording heterocycles **5a-d** and **6a-b** under the same reaction conditions, despite the presence of $sp^3$-CH bonds adjacent to the gold carbenoid.[13] Products from competing ynamide hydration were observed with substrate **3a**, lacking a gem-dialkyl substitution pattern between the reacting centres when using undried solvent. However, the yield of **6a** doubled on using freshly distilled solvent (Table 1, entry 11). A silyl ether **6b** was also tolerated (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 coordination of the active gold catalyst to the ynamide (**A**) enforces an overall endo-dig addition: Sulfoxide attack generates the vinyl gold carbenoid **B** which then evolves to ylide **D** and subsequently the observed products with release of the gold catalyst and [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, aligning that bond with the alkene π-system in **B**, positioning the sulfur to interact with the electrophilic carbon in **C**.




**Scheme 2** Mechanistic outline for the observed transformation.

Representative examples of the sulfur-heterocycle motifs were subjected to oxidation in order to assess the potential of the cycloisomerisation method to access novel cyclic sulfones. High yields were observed for **7a** and **7b**, from **4b** and **6b**, respectively, using ammonium heptamolybdate and hydrogen peroxide (Figure 1).

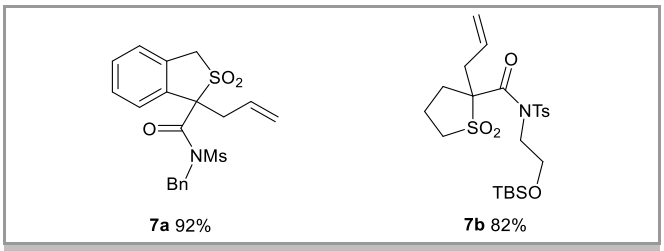
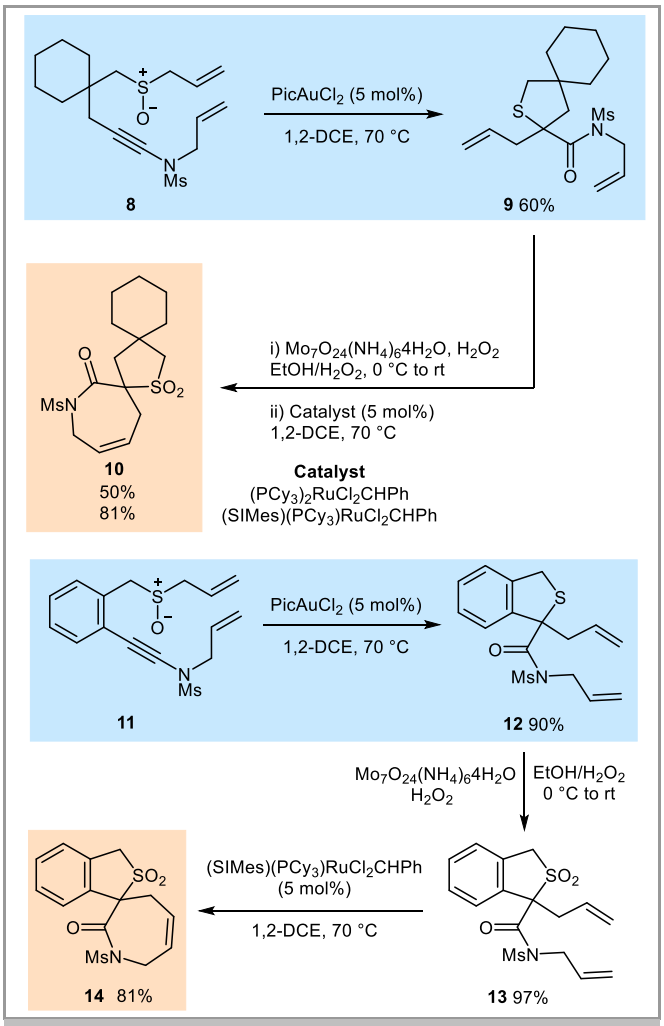



**Figure 1** The formation of cyclic sulfones by ammonium heptamolybdate catalysed oxidation of the analogous sulfides with hydrogen peroxide in ethanol (see ESI for conditions). Isolated yields following flash column chromatography. Yield in parenthesis determined by analysis of the crude reaction mixture against an internal standard using $^1$H NMR spectroscopy.

We envisaged that the formation of α-allyl amide motifs in this cycloisomerisation could be harnessed for the preparation of new and usefully-functionalized structures in combination with reactive groups that might be introduced via 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 in order to test whether spirocyclic lactams might be achievable using a post-cycloisomerisation ring-closing metathesis. Ynamides **8** and **11** underwent gold catalysis to give the sulfur heterocycles **9** and **12** (Scheme 3). No products from cyclopropanation were observed. Diene **9** was oxidized to the sulfone and subjected to metathesis conditions, using either the 1st and 2nd generation Grubbs catalysts, 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 will undergo gold-catalysed cycloisomerisation into 2,2-disubstituted tetrahydrothiophenes. The reaction works well whether the ynamide is connected to the allyl sulfoxide through 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 catalyzed cycloisomerisation. This study highlights the potential of ynamides in controlling π-acid catalyzed reaction pathways, here enforcing an initial 7-*endo* dig cyclisation outcome. In addition to providing the regiocontrol element, the ynamide unit an also be used to introduce useful functionality that can be combined with that assembled during the cycloisomerisation reaction, as demonstrated in the ready formation of sp$^3$-rich spirocyclic lactams.




**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

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## Supporting Information

YES (this text will be updated with links prior to publication)

## Primary Data

NO (this text will be deleted prior to publication)

## References and Notes

(1) (a) Lee, Y.-C.; Kumar, K., *Isr. J. Chem.* **2018**, *58*, 531; (b) Quiros, M. T.; Munoz, M. P., *Top. Heterocycl. Chem.* **2016**, *46*, 117.

(2) (a) Gorin, D. J.; Toste, F. D., *Nature* **2007**, *446*, 395; (b) Fürstner, A.; Davies, P. W., *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; (c) Adcock, H. V.; Davies, P. W., *Synthesis* **2012**, *44*, 3401; (d) Zhang, L., *Acc. Chem. Res.* **2014**, *47*, 877; (e) Yeom, H.-S.; Shin, S., *Acc. Chem. Res.* **2014**, *47*, 966; (f) Wang, Y.; Muratore, M. E.; Echavarren, A. M., *Chem. Eur. J.* **2015**, *21*, 7332; (g) Harris, R. J.; Widenhoefer, R. A., *Chem. Soc. Rev.* **2016**, *45*, 4533; (h) Ye, L. W.; Zhu, X. Q.; Sahani, R. L.; Xu, Y.; Qian, P. C.; Liu, R. S., *Chem Rev* **2020**, DOI:

10.1021/acs.chemrev.0c00348; (i) Wang, T.; Hashmi, A. S. K., *Chem. Rev.* **2020**, DOI: 10.1021/acs.chemrev.0c00811.

(3) (a) Pathania, S.; Narang, R. K.; Rawal, R. K., *Eur. J. Med. Chem.* **2019**, *180*, 486; (b) Minghao, F.; Bingqing, T.; Steven, H. L.; Xuefeng, J., *Curr. Top. Med. Chem.* **2016**, *16*, 1200.

(4) Early examples: (a) Morita, N.; Krause, N., *Angew. Chem., Int. Ed.* **2006**, *45*, 1897; (b) Nakamura, I.; Sato, T.; Yamamoto, Y., *Angew. Chem. Int. Ed.* **2006**, *45*, 4473; Review: (c) Debrouwer, W.; Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V., *Adv. Synth. Catal.* **2015**, *357*, 2975.

(5) Davies, P. W.; Albrecht, S. J. C., *Angew. Chem. Int. Ed.* **2009**, *48*, 8372.

(6) (a) Lu, B.; Li, Y.; Wang, Y.; Aue, D. H.; Luo, Y.; Zhang, L., *J. Am. Chem. Soc.* **2013**, *135*, 8512; (b) Shapiro, N. D.; Toste, F. D., *J. Am. Chem. Soc.* **2007**, *129*, 4160; (c) Li, G.; Zhang, L., *Angew. Chem. Int. Ed.* **2007**, *46*, 5156.

(7) (a) Hong, F.-L.; Ye, L.-W., *Acc. Chem. Res.* **2020**, *53*, 2003; (b) Campeau, D.; Leon Rayo, D. F.; Mansour, A.; Muratov, K.; Gagosz, F., *Chem. Rev.* **2020**, DOI: 10.1021/acs.chemrev.0c00788; (c) Evano, G.; Lecomte, M.; Thilmany, P.; Theunissen, C., *Synthesis* **2017**, *49*, 3183; (d) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P., *Acc. Chem. Res.* **2014**, *47*, 560; (e) De Korver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P., *Chem. Rev.* **2010**, *110*, 5064.

(8) For early examples see: (a) Davies, P. W.; Cremonesi, A.; Martin, N., *Chem. Commun.* **2011**, *47*, 379; (b) Li, C.; Zhang, L., *Org. Lett.* **2011**, *13*, 1738; (c) Davies, P. W.; Cremonesi, A.; Dumitrescu, L., *Angew. Chem., Int. Ed.* **2011**, *50*, 8931; (d) Kramer, S.; Odabachian, Y.; Overgaard, J.; Rottlaender, M.; Gagosz, F.; Skrydstrup, T., *Angew. Chem., Int. Ed.* **2011**, *50*, 5090; (e) Mukherjee, A.; Dateer, R. B.; Chaudhuri, R.; Bhunia, S.; Karad, S. N.; Liu, R.-S., *J. Am. Chem. Soc.* **2011**, *133*, 15372; (f) Dateer, R. B.; Shaibu, B. S.; Liu, R.-S., *Angew. Chem., Int. Ed.* **2012**, *51*, 113; (g) Rettenmeier, E.; Schuster, A. M.; Rudolph, M.; Rominger, F.; Gade, C. A.; Hashmi, A. S. K., *Angew. Chem., Int. Ed.* **2013**, *52*, 5880; (h) Li, L.; Shu, C.; Zhou, B.; Yu, Y.-F.; Xiao, X.-Y.; Ye, L.-W., *Chem. Sci.* **2014**, *5*, 4057; For reviews, see ref 7.

(9) (a) Dos Santos, M.; Davies, P. W., *Chem. Commun.* **2014**, *50*, 6001; (b) Baker, T.; Davies, P. W., *Eur. J. Org. Chem.* **2019**, *2019*, 5201.

(10) Adcock, H. V.; Langer, T.; Davies, P. W., *Chem. Eur. J.* **2014**, *20*, 7262.

(11) Hamada, T.; Ye, X.; Stahl, S. S., *J. Am. Chem. Soc.* **2008**, *130*, 833.

(12) Experimental procedure: $AuPicCl_2$ (5.0 mol%, 5 μmol) was added to a solution of the ynamide (0.1 mmol) in 1,2-DCE (0.2 M) in a flame-dried Schlenk tube under an Ar atmosphere. Upon completion of the reaction (monitored by TLC) the crude mixture was passed through a small plug of silica to remove gold residue. The solvent was evaporated and the residue was purified by column chromatography.

1-Allyl-*N*-benzyl-*N*-(methylsulfonyl)-1,3-dihydrobenzo[c]thiophene-1-carboxamide (**4b**). Obtained after purification (7:3 hexane:EtOAc) as a yellow viscous oil; $\nu_{max}$ (neat) 2925 (w), 1679 (s), 1351 (s), 1162 (s); $\delta_H$ (300 MHz, $CDCl_3$) 2.92 (3H, s), overlaps with 3.01-2.95 (1H, m), 3.10 (1H, dd, *J* = 14.2, 7.4 Hz), 4.19 (1H, d, *J* = 14.2 Hz), 4.33 (1H, d, *J* = 16.0 Hz), 4.41 (1H, d, *J* = 14.2 Hz), 4.83 (1H, d, *J* = 16.0 Hz), 4.92-5.05 (2H, m), 5.46-5.64 (1H, m), 7.14-7.31 (9H); $\delta_C$ (101 MHz, $CDCl_3$) 38.0, 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; m/z (TOF MS ES$^+$) $[M+Na]^+$ 410 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{20}H_{21}NO_3S_2Na$ 410.0861, found 410.0859.

*N*,3-Diallyl-*N*-(methylsulfonyl)-2-thiaspiro[4.5]decane-3-carboxamide (**9**). Obtained after purification (7:3 hexane:EtOAc) as a colourless viscous oil (21.3 mg, 60%); $\nu_{max}$(neat) 2924 (s), 2852 (m), 1681 (s), 1352 (s), 1165 (s); $\delta_H$ (300 MHz, $CDCl_3$) 1.21-1.63 (10H), overlaps with 1.53 (1H, d, *J* = 13.6 Hz), 2.55 (1H, dd, *J* = 14.4, 7.2 Hz), 2.70 (1H, dd, *J* 14.4, 5.8 Hz), 2.69 (1H, d, *J* = 10.7 Hz), 2.77 (1H, d, *J* = 10.7 Hz), 2.96 (1H, d, *J* = 13.6 Hz), 3.28 (3H, s), 4.39-4.56 (2H, m), 5.05-5.20 (2H, m), 5.25-5.42 (2H, m), 5.63-5.81 (1H, m), 5.86-6.03 (1H, m); $\delta_C$ (101 MHz, $CDCl_3$) 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; m/z (TOF MS ES$^+$) $[M+Na]^+$ 380 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{17}H_{27}NO_3S_2Na$ 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 (ref. 5) providing access to a 2-thiaspiro[5.5]undecan-4-one motif (see ESI).

(14) (a) Zheng, Y.; Tice, C. M.; Singh, S. B., *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673; (b) Zheng, Y.-J.; Tice, C. M., *Expert Opin. Drug Discov.* **2016**, *11*, 831.

(15) Spagnol, G.; Heck, M.-P.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2002**, *4*, 1767

(16) Attempts to extrude sulfur dioxide from **15** were unsuccessful with no conversion even in diphenyl ether at 280 °C.