STUDYING THE SYNTHESIS AND REACTIVITY OF SULFONIUM YLIDES DERIVED VIA GOLD CATALYSIS

THOMAS BAKER

A thesis submitted to the

University of Birmingham

for the degree of

DOCTOR OF PHILOSOPHY

School of Chemistry

University of Birmingham

September 2013

Abstract

This thesis details the development of a gold-catalysed, ketone-stabilised ylide synthesis and the intermolecular reaction of this ylide. The reaction of this ylide with butenone proceeds via a novel, three-component coupling. This represents the first intermolecular reaction of a gold-derived ylide.

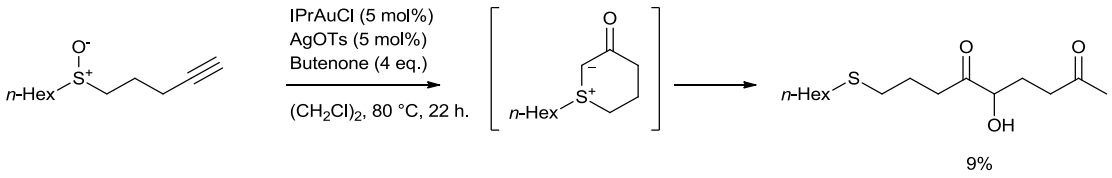


Figure 1: Intermolecular reaction of a gold-derived ylide

The development of a novel, gold-catalysed, amide-stabilised ylide synthesis was also successful. The ylides underwent 2,3-sigmatropic rearrangements and Stevens 1,2-shifts. The Stevens rearrangement has previously not been reported for gold-derived ylides. These ylide transformations gave a range of novel, polysubstituted thiomorpholinones, which are difficult to access via classical approaches. The amide-stabilised ylides were found to be unsuitable for intermolecular reaction.

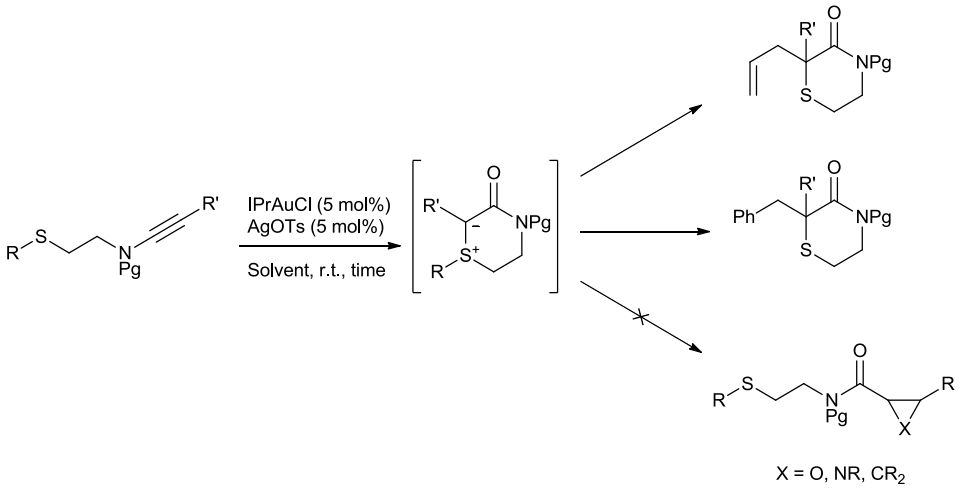


Figure 2: Intermolecular reaction of gold-derived thiomorpholinone ylides

Thioynol ethers were also investigated as triple-bonded substrates for gold-catalysed reactions.

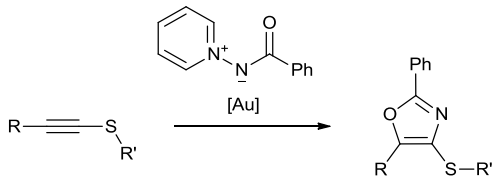


Figure 3: Thioynol ethers as triple bonds for gold catalysis

While the thioynol ethers were found to be significantly less reactive than the equivalent alkyne or ynamide, it was possible employ them for the synthesis of oxazoles in comparable yield to ynol ethers.

For Laura

Firstly I must thank all the kind people who assisted with the preparation of this thesis: Laura Totterdell, Andy Gillie, Elli Chatzopoulou, Holly Adcock, Peter Elliott, Steve Cooper, Dr Jonathan Knowles, Dr Tom Parsons and Dr Paul Davies.

School of Chemistry analytical staff: Peter Ashton, Nick May, Chi Tsang and Dr Neil Spencer provided mass spectrometry, often of unpleasant compounds and at short notice.

I would particularly like to thank Dr Neil Spencer for NMR spectra and, more importantly, for all his kind words and support.

Funding and support for this project was provided by the School of Chemistry and the EPSRC. Johnson Matthey PLC and Advantage West Midlands kindly provided equipment and catalysts.

Lastly, I would like to thank all the members of the Davies, Snaith, Cox, Grainger, Simpkins and Tucker groups for making Birmingham such a pleasant place to work.

List of abbreviations

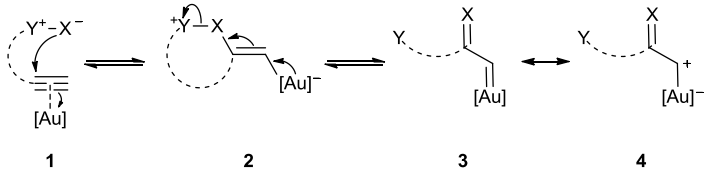
Ac	acetyl
Au-**I**	dichloro(2-pyridinecarboxylato)gold (III)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BrettPhos	2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
Bs	benzenesulfonyl
Bu	butyl
C	Celsius
DCD	Dewar–Chatt–Duncanson
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DMF	*N*,*N*-dimethylformamide
e.e.	enantiomeric excess
EI	electron impact
ES	electrospray
Et	ethyl
h	hours
Hex	hexyl
HRMS	high resolution mass spectrometry
IAd	1,3-Bis(2,6-adamantyl-imidazol-2-ylidene)
IMes	1,3-Bis(2,4,6-trimethylphenyl-imidazol-2-ylidene)
IPr	1,3-Bis(2,6-diisopropylphenyl-imidazol-2-ylidene)
m-CPBA	*meta*-chloroperbenzoic acid
Ms	methanesulfonyl

NBO	natural bond order
NMR	nuclear magnetic resonance
Ns	*para*-nitrobenzenesulfonyl
Pg	protecting group
Ph	phenyl
Piv	pivaloyl
PMP	*para*-methoxyphenyl
Py	pyridine
r.t.	room temperature
t.	time
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	*N*,*N*,*N*,*N*-tetramethylethylenediamine
TMS	trimethylsilyl
TMS	tetramethylsilane
Ts	*para*-methylbenzenesulfonyl

Chapter 1: Introduction

Oxidative synthesis of gold carbenoids from triple bonds via precious metal catalysis

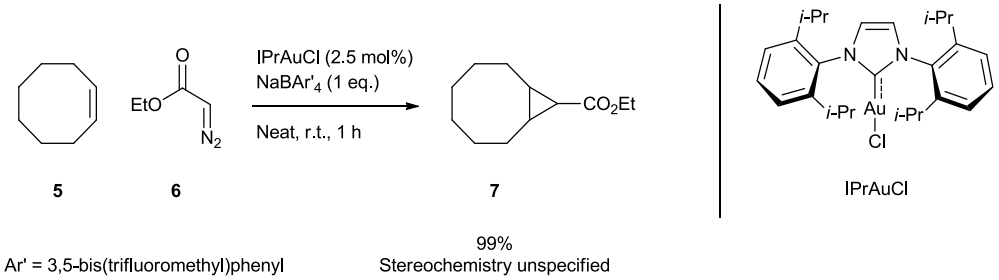
This chapter aims to review the development of the field of catalytic α-keto and α-imido gold carbenoid synthesis and to introduce the recent developments in ylide synthesis via these gold carbenoids. These carbenoids are obtained by a gold-catalysed redox cascade, where X and Y are heteroatoms, such as sulfoxides or *N*-oxides (Scheme 1).



Scheme 1: General gold-catalysed redox cascade

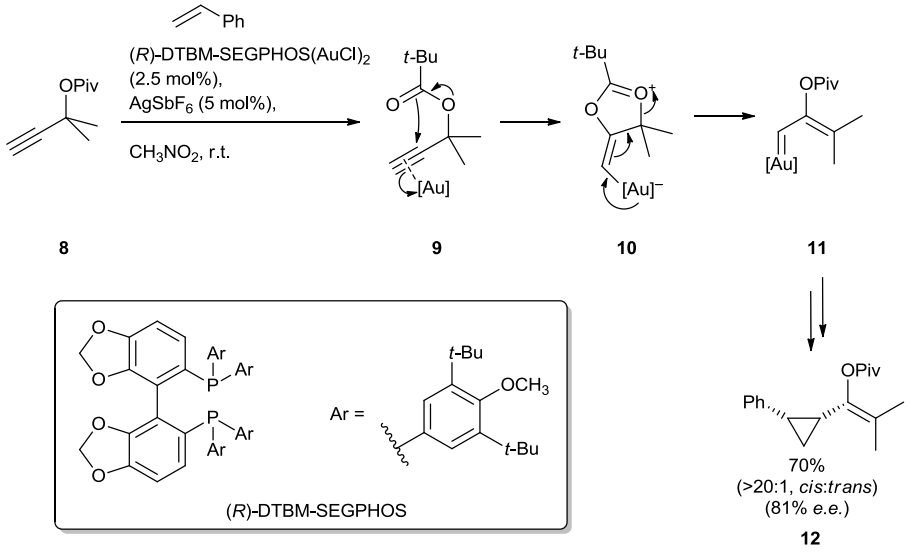
The general process for these reactions occurs via the intra- or intermolecular nucleophilic addition of a dipolar nucleophile to a gold-activated triple bond **1**. The cationic portion of the dipole is eliminated from the resulting zwitterionic gold complex **2**, resulting in an α-keto or α-imido gold carbenoid complex (**3** & **4**), which may be harnessed to access further reactivity.

Gold catalysis is typified by mild reaction conditions and exceedingly selective catalyst reactivity which, combined with the reactivity of a carbene, gives a powerful synthetic tool.[1, 2] Gold carbenoid complexes have been known since 1973,[3, 4] however their application was limited to stoichiometric processes and it was not until the advent of catalytic carbenoid syntheses, that they were employed in reactions with real synthetic utility. Over the last eight years, gold carbenoids have been accessed in a number of ways, the classic approach of metal-catalysed decomposition of a diazo compound being the most straightforward. For example, in 2005, Nolan, Pérez and co-workers demonstrated that NHC-ligated gold complexes can catalyse these reactions, reporting a range of simple cyclopropanations with their newly developed IPrAuCl catalyst (Scheme 2).[5]



Scheme 2: Gold-catalysed cyclopropanation with ethyl diazoacetate

The use of diazo derivatives is not attractive however, given their toxicity and instability.[6-8] More elegantly, carbenoids may be accessed via the rearrangement of an alkynyl ester or during enyne cyclisation reactions. These rearrangements are well explored and have been applied to a variety of different metal carbenoids.[9-16] For example in 2005 Toste and co-workers demonstrated that the gold-catalysed rearrangement of propargyl pivalate **8**, could access the desired carbenoid moiety **11.** The carbenoid was subsequently trapped with good stereocontrol, difficult to achieve with a gold catalyst (Scheme 3).[17]



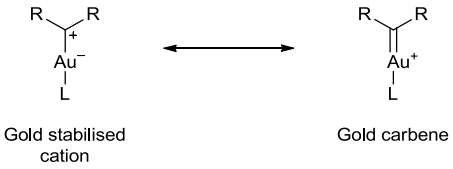
Scheme 3: Toste's pivaloyl rearrangement

This carbenoid was subsequently trapped by a range of alkenes and use of a suitable chiral ligand gave control over the stereochemistry of the resulting cyclopropane **12**. These early approaches

allowed access to the desired carbenoid functionality; however they have a significant drawback, requiring the pre-installation of a migrating group, cyclising group or sacrificial diazo moiety.

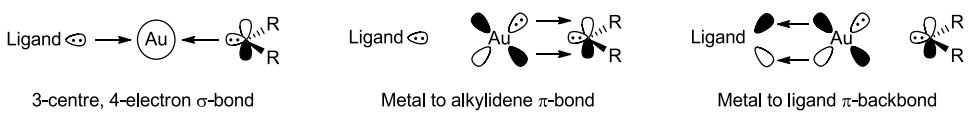
Bonding in gold carbenoids

Despite the widespread application of gold catalysis, the exact nature of the Au-C bonding in gold carbenoid complexes remains unclear. Whether these complexes exist as gold-stabilised carbocations or gold carbenes has been a matter of considerable debate.[18-21]



Scheme 4: Cation vs. Carbene

NMR spectroscopic observation of gold complexes by Fürstner's group suggested that the complexes typically have a bond order approximately equal to or less than one, although the complexes studied were limited to phosphine-ligated gold catalysts.[18, 22] DFT and NBO studies by Toste's and Hashmi's groups agree with this value, but also indicate the Au-C bond may possess both σ and π-bonding character, allowing it to function as a gold carbene (Scheme 5).[23, 24] The degree of π-bonding is dependent upon the substrate and ligand, suggesting that carbenoid character is a tuneable property.[25] These gold complexes cannot be described as purely "carbene"- or "cation"-like and in their review of π-acid catalysis, Fürstner and Davies recommend that the bonding of these complexes be considered as a continuum, with the carbene and cation at the two extremes (Scheme 4).[20]



Scheme 5: Toste's DCD model for Au(I) carbenoid bonding

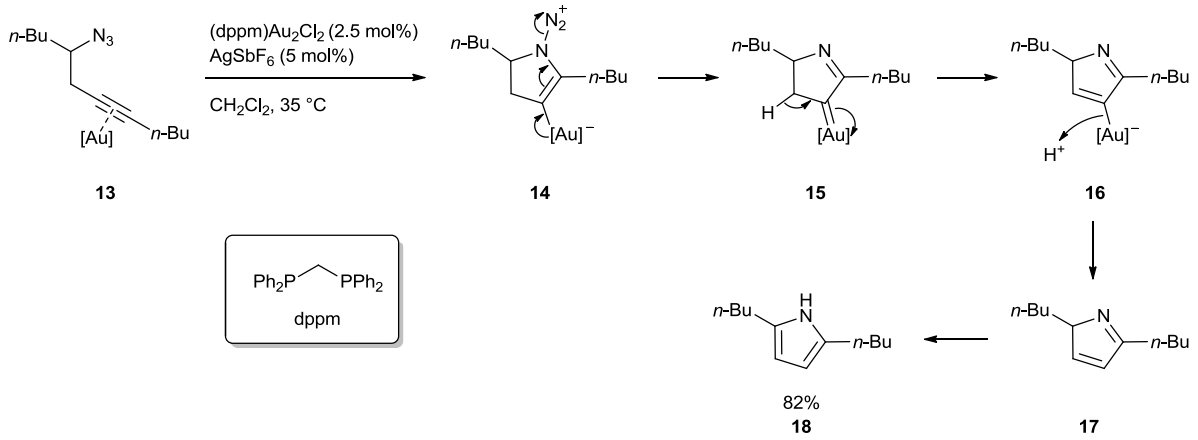
Toste's and Hashmi's models describe the ligand and alkylidene σ-interactions with the gold as a 3 centre, 4-electron hyperbond, as the Au(I) only possesses one free valence orbital. Strong σ-donor

ligands therefore weaken the overall σ-bond, leading to an increase in the Au-C bond length. The gold centre can also π-bond to the alkylidene, however, this is in competition with backbonding to the ligand. Strongly π-acidic ligands, reduce the π component of the Au-C bond leading to an increase in Au-C bond length and a decrease in carbenoid character. To maximise carbenoid character in the Au-C complex, therefore, a ligand would be strongly σ-donating to weaken the σ component of the Au-C bond and display minimal π-acidity to maximise the π component, although maximising π-acidity of the alkylidene substrate is also key.[23, 24]

Intramolecular oxidation systems

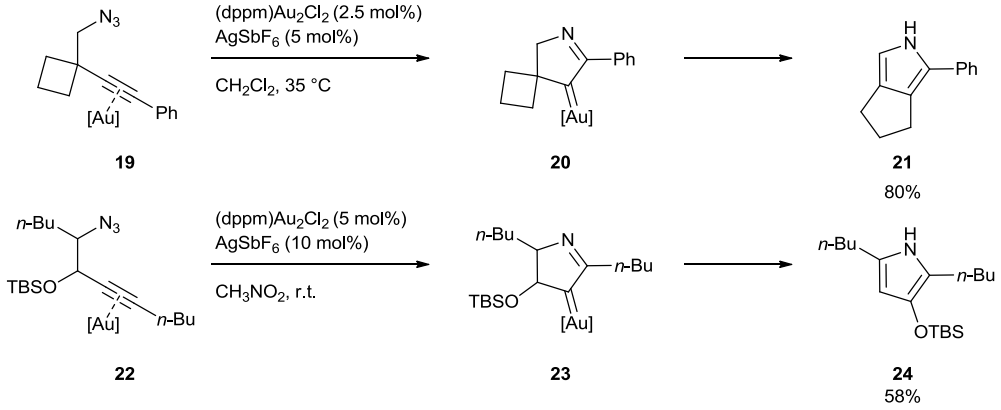
Early azide-based carbenoid synthesis

In 2005, Toste's group published the synthesis of a variety of pyrroles from the cyclisation of alkynyl azides. These pyrroles were obtained via nucleophilic attack of the azide onto the gold-activated alkyne **13**. Subsequent loss of nitrogen generated gold carbenoid **15**. Elimination of a proton, proto-demetallation and then prototropy gave the final pyrrole **18** (Scheme 6).[26]



Scheme 6: Toste's pyrrole synthesis

Toste reasoned that the intermediate gold carbenoid could tolerate other modes of carbenoid reactivity and was able to successfully expand the reactivity to include to silyl ether migrating groups and ring expansions (Scheme 7).

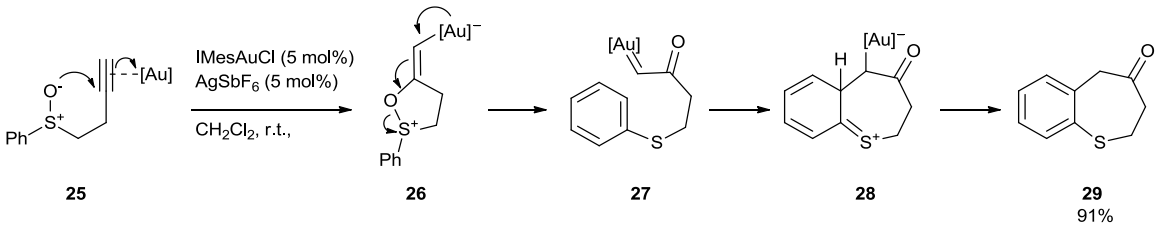


Scheme 7: Expanded carbenoid reactivity

Hiroya *et al* subsequently demonstrated that this transformation could also be performed with platinum (IV) chloride to obtain trisubstituted pyrroles.[27]

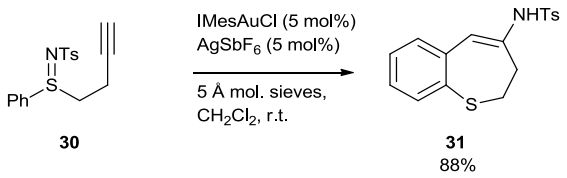
Sulfur-based oxidants

In 2007, Shapiro and Toste reported the synthesis of α-keto carbenoids using a gold-catalysed redox cascade (Scheme 8). It was postulated that the resulting carbenoids were rapidly trapped in an electrophilic aromatic substitution. This protocol allowed an alkyne moiety to function as a masked α-keto gold carbenoid.[28]



Scheme 8: Toste's carbenoid synthesis

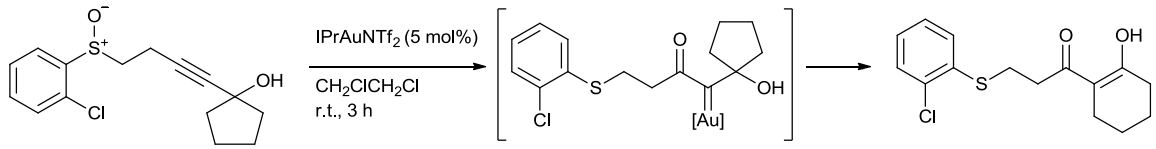
Toste expanded upon this approach, showing that the oxidant is not limited to sulfoxides; sulfonimines also proved viable oxidants, leading to sulfonenamides (Scheme 9).



30 **31** 88%

Scheme 9: Sulfonamide synthesis

Shortly after Toste, L. Zhang's group published a paper with similar findings, however they also demonstrated that electrophilic aromatic substitution could be disfavoured by tuning the sulfoxide substituent (Scheme 10).

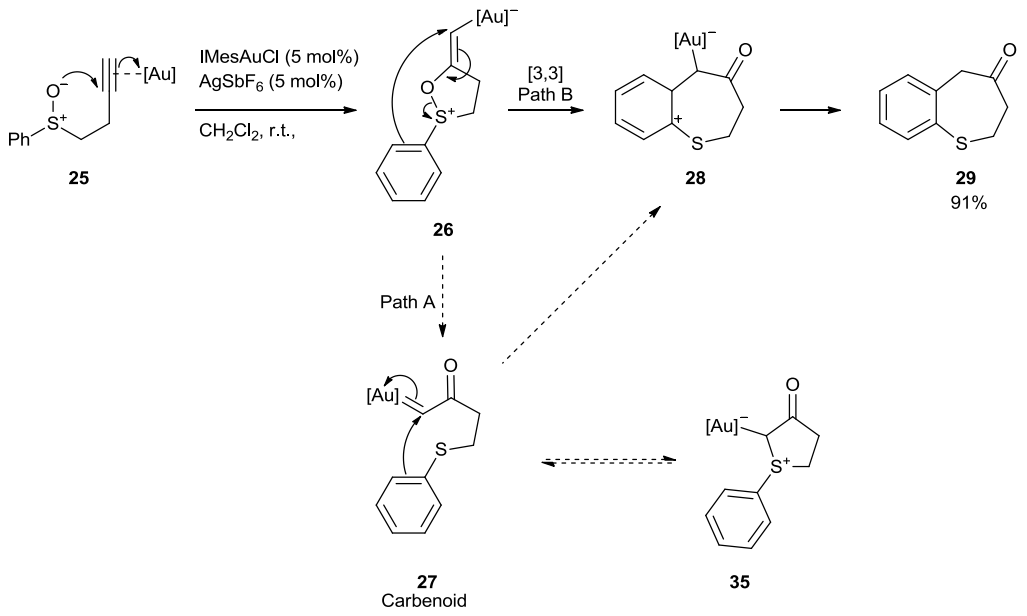


32 **33** **34** 77%

Scheme 10: Tuning carbenoid reactivity

By exploiting the competing reactivity of o-chlorophenyl and cyclopentyl alcohol substituents, Zhang was able to competitively access alternative carbenoid reactivity, in this case ring expansion.[29] Toste's and Zhang's combined work demonstrated that redox cascades of these kinds had the potential to access diverse carbenoid functionality from a variety of oxidants. Crucially, the pendant sulfoxide, responsible for oxidant delivery during Zhang's carbenoid formation, was placed significantly further from the reacting alkyne than in Toste's propargyl migrations (Scheme 3 *vs.* Scheme 8). This increased the synthetic flexibility considerably, allowing the resulting sulfide to be easily cleaved or used for further transformations.

Maulide's group suggested that the proposed carbenoid **27** in Zhang's and Toste's intramolecular transformations does not form (Path A) and that the resulting bicycle could be explained by a [3,3]-sigmatropic rearrangement of the vinyl gold intermediate **26** to give the final bicycle **29** (Path B).[30] Very recent studies by L. Zhang's group have confirmed this hypothesis (Scheme 11).[31]



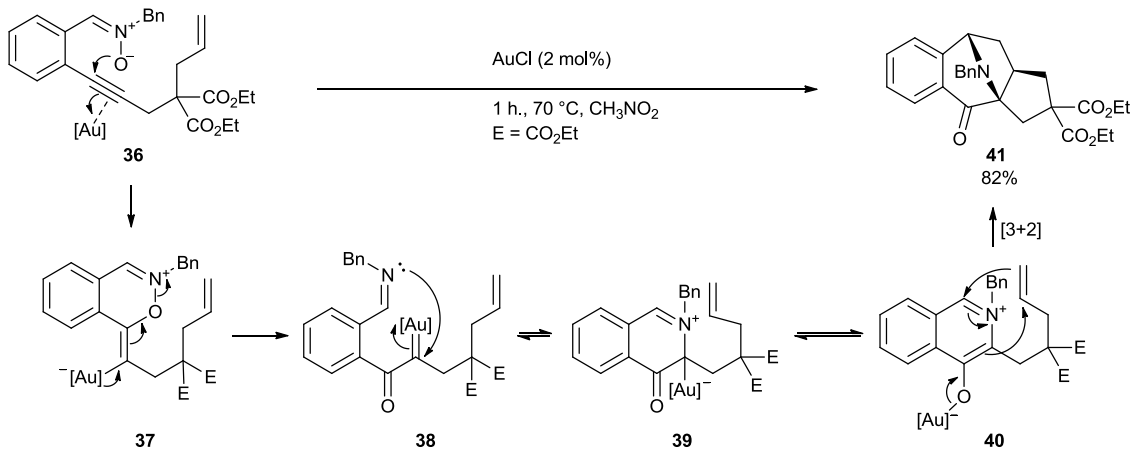
Scheme 11: Alternative [3,3]-sigmatropic rearrangement

Zhang's DFT study and comparison with intermolecularly oxidised systems indicate that the [3,3] sigmatropic rearrangement of **26** (Path B) is favoured compared to the relatively high energy barrier for carbenoid **27** formation (Path A).

While Toste's and Zhang's sulfoxide protocols ultimately were determined to proceed via a rearrangement, rather than a gold "carbene" complex, these reactions, and Toste's azide protocol, introduced the concept that an alkyne could function as a masked α-keto or α-imido gold carbenoid and inspired what has become a rapidly advancing field within gold catalysis.

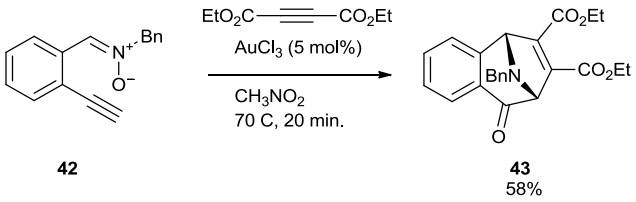
Nitrogen-based oxidants

Shin's group reported the first nitrogen-based oxidant system in 2008 and went on to explore their reactivity in great depth. In place of the sulfoxide, Shin's system used a nitrone (**36**) which performed the redox cascade necessary to generate a carbenoid (**38**). The resulting imine was not redundant after performing the initial oxygen delivery and Shin demonstrated that it could be employed further in the cascade reaction, both as a nucleophile and an electrophile (Scheme 12).



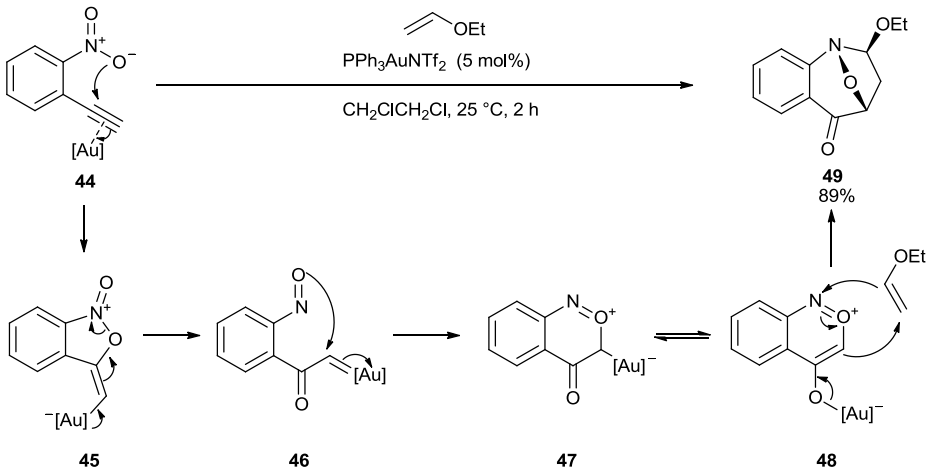
Scheme 12: Shin's intramolecular nitrone-based [3+2] cycloaddition

In Shin's first example the generated imine re-trapped the carbenoid, generating a 1,3 dipole (**40**) which underwent Huisgen-type 3+2 cycloaddition with the tethered alkene. This approach allows complex polycyclic structures to be readily assembled, typically as single diastereomers. Shin also demonstrated that the dipole could be trapped with an intermolecular dipolarophile, eliminating the need for a tethered alkene (Scheme 13).[32]



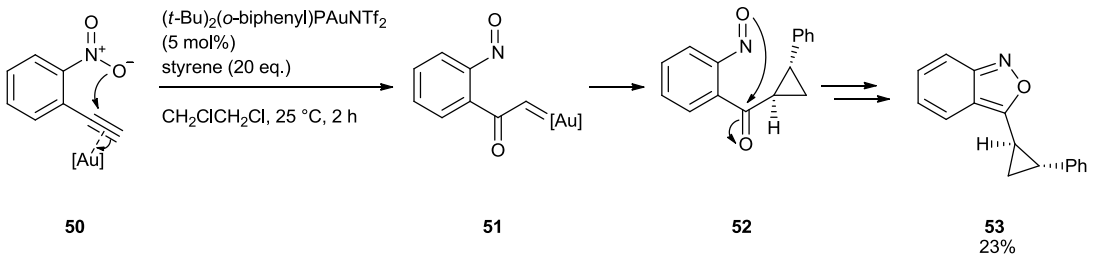
Scheme 13: Shin's intermolecular nitrone-based [2+3] cycloaddition

Liu's group further developed this concept, reporting an intermolecular 3+2 cycloaddition between a 1,3 dipole (**48**) derived from an *o*-nitrophenylacetylene (**44**), and an electron-rich alkene. High diastereoselectivity was observed again, Liu obtaining only single diastereomers (Scheme 14).[33]



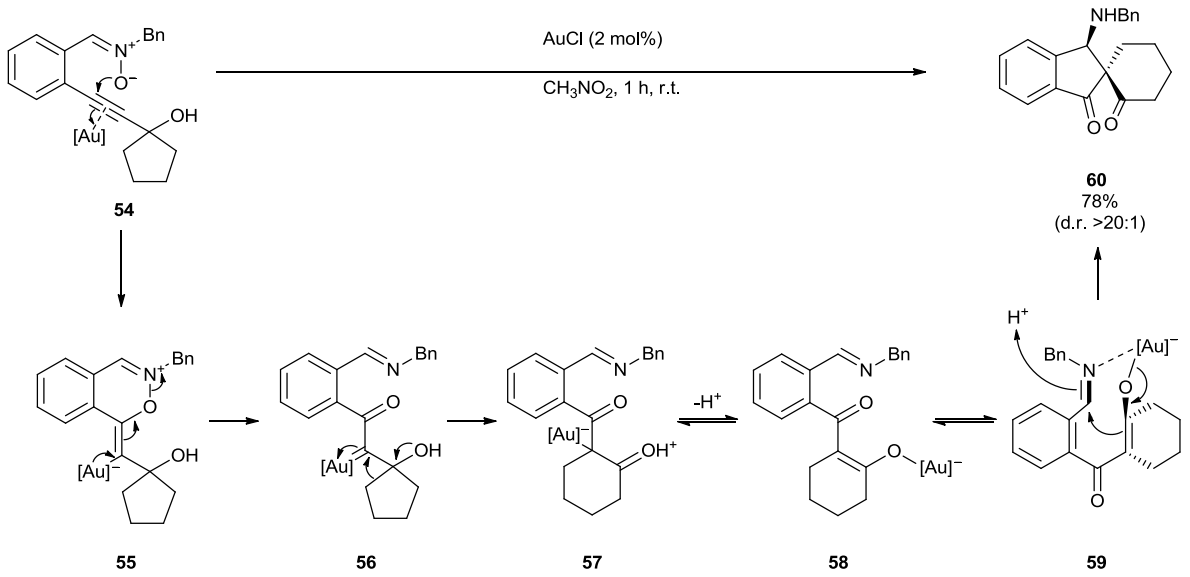
Scheme 14: Liu's intermolecular nitroalkyne-based [2+3] cycloaddition

The reaction tolerated a range of dipolarophiles and substituents, providing the product typically in yields of 60 to 80%. Crucially, cyclopropanation of the intermediate carbenoid **46** was not observed; however Liu was able to trap this intermediate by varying the ligand and introducing a large excess of styrene (Scheme 15).



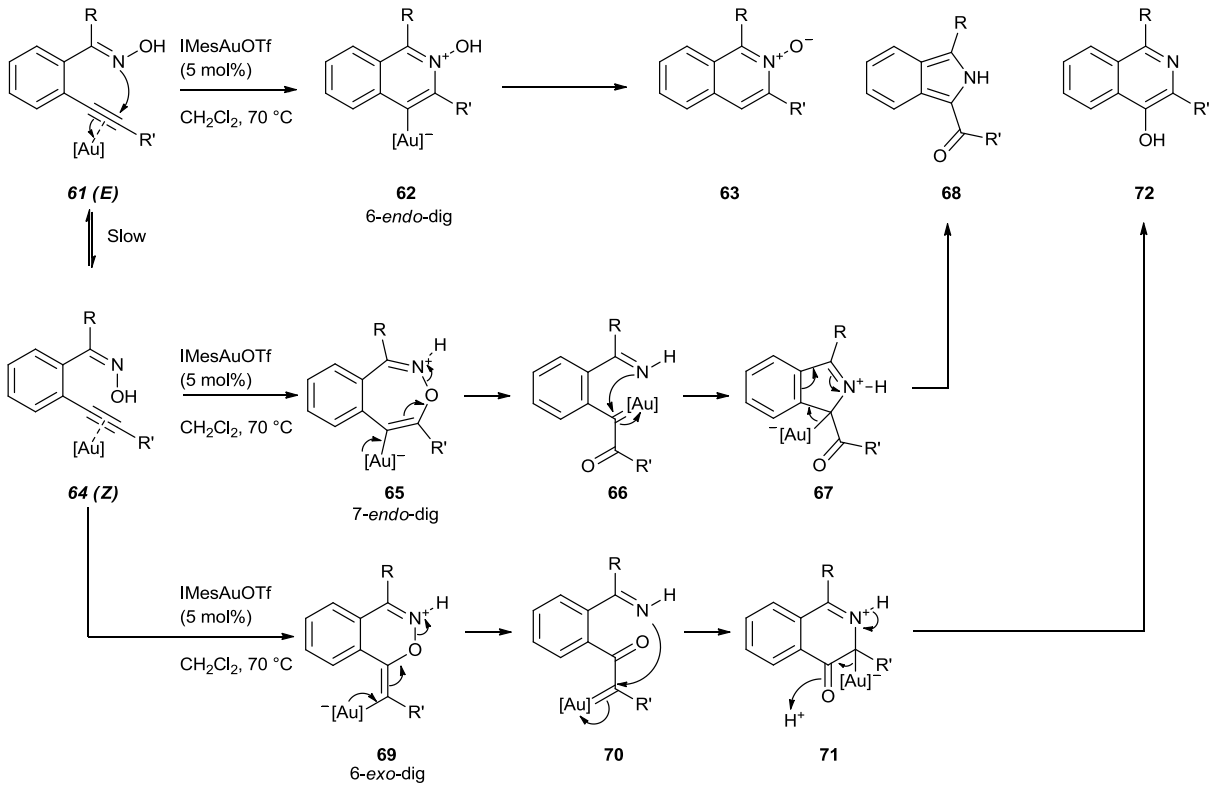
Scheme 15: Liu's carbene intermolecular trap

Shin's group further expanded the reactivity of the nitrone-derived carbenoid system, to one that disfavoured trapping of the carbenoid **56** by the imine; instead undergoing a 1,2-alkyl shift. The resulting gold enolate **58** then attacked the imine to give a variety of spirocycles, in most cases as a diastereomer. This further demonstrated the utility of nitrones as oxidant moieties, the intermediate imine now functioning as an electrophile (Scheme 16).[34]



Scheme 16: Shin's spirocycle synthesis

Shin rationalised the high diastereoselectivity by suggesting that coordination of the gold catalyst to the imine and enolate (**59**) controls the resulting geometry. Low catalyst loading was also tolerated. The work of Shin's and Liu's groups demonstrated the level of control that can be exercised over these cascades, which possess multiple nucleophilic and electrophilic sites, potentially resulting in competing reaction pathways (Scheme 17).



Scheme 17: Regiochemistry in Shin's ketoxime-based cyclisation

Shin subsequently illustrated the complexity involved in optimising such transformations. By replacing the nitrone with an oxime, Shin was able to use oxidants with fixed geometry which, combined with careful tuning of the substrate, allowed a variety of isomeric products to be obtained selectively.[35] In this case, controlling the regioselectivity of nucleophilic attack onto the alkyne was key, given the ketoxime's dual nucleophilic positions and possibility of cyclisation onto either of the alkyne carbons.

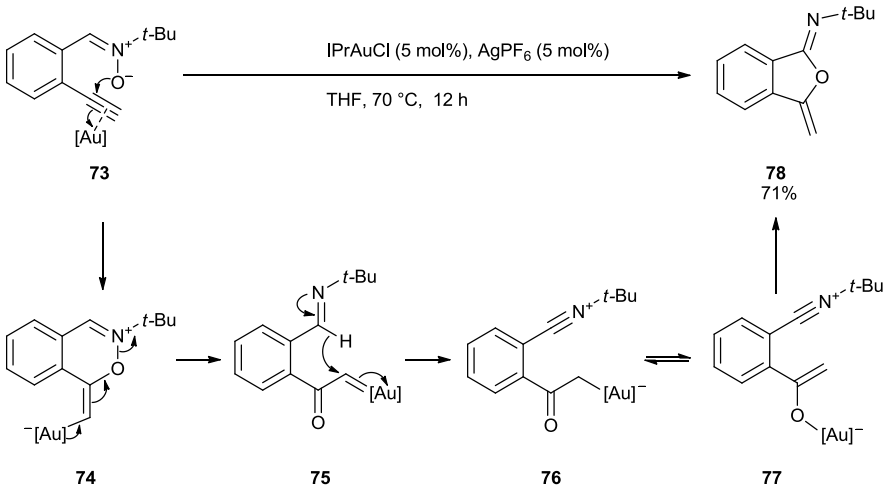
Table 1: Effect of ketoxime geometry and substitution upon product distribution

			Yield (%)		
Ketoxime geometry	**R**	**R'**	**63**	**68**	**72**
E	CH_3	CH_3	82	-	-
Z	CH_3	CH_3	-	66	-
Z	CH_3	Ph	-	30	41
Z	*n*-Pr	CH_3	-	94*	-

* 10 mol% catalyst

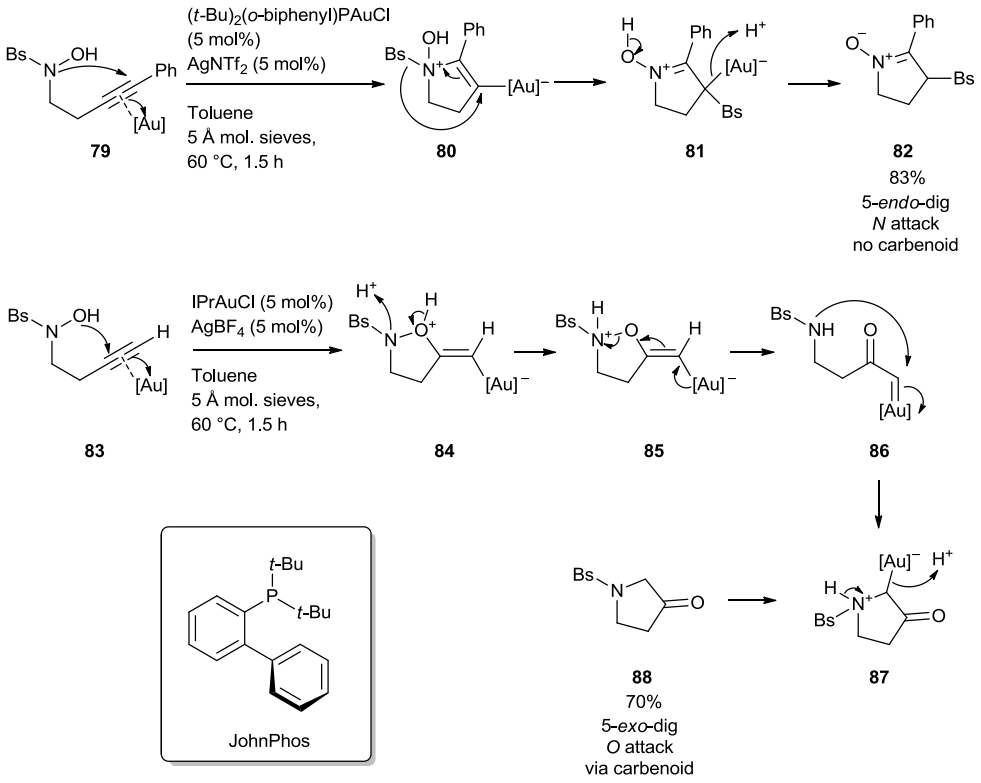
The *E* ketoxime **61** gave only isoquinoline *N*-oxide **63**, without carbenoid formation, due to the proximity of the ketoxime oxygen to the alkyne. *O* attack upon the alkyne was obtained with *Z* ketoxime **64**, however, controlling the regioselectivity of attack on the alkyne proved difficult (Table 1). Tuning the substrate and increasing catalyst loading allowed Shin to obtain **68** in almost quantitative yield. 7-*endo* attack was more favourable with alkyl substituents, owing to favourable carbenoid stabilisation by the adjacent aromatic ring. Unfortunately, substitution of the alkyne with a second phenyl ring gave mixtures of **68** and **72**, as the carbenoid is stabilised in both positions. Shin's protocol highlights the precise conditions required for complex gold cascades to achieve a given outcome, which can limit the scope for substrate elaboration.

Li's group subsequently showed that further control over imine-forming redox cascades could be exerted, employing a *t*-butyl-substituted nitrone (**73**) to sterically disfavour nucleophilic attack by the imine intermediate (Scheme 18).[36]



Scheme 18: Li's regioselectivity switch

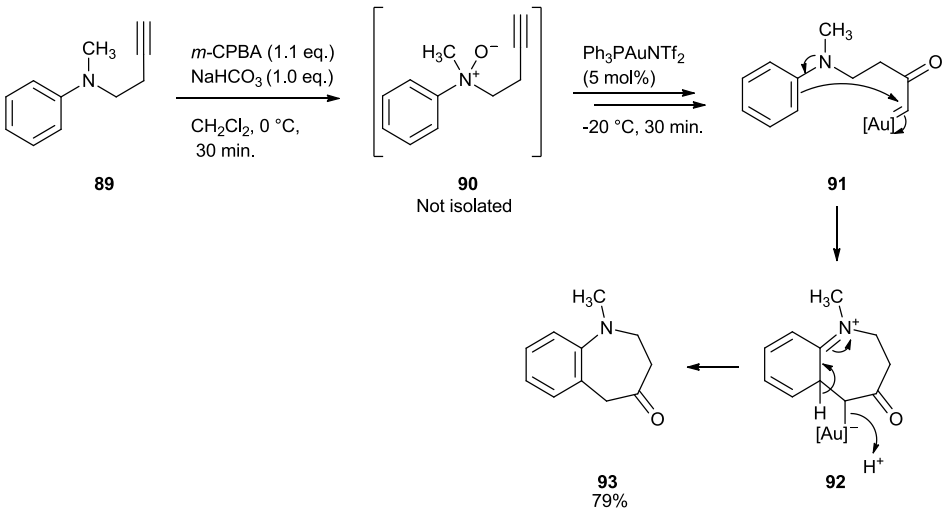
Instead, Li's system underwent a hydride shift to generate a gold enolate and nitrilium (**77**), to give a substituted iminoisobenzofuran (**78**). Shi's group also expanded the scope of control over competing *N* and *O* attack by elegantly tuning the catalyst systems (Scheme 19).[37]



Scheme 19: Favouring *O* or *N* attack by catalyst selection

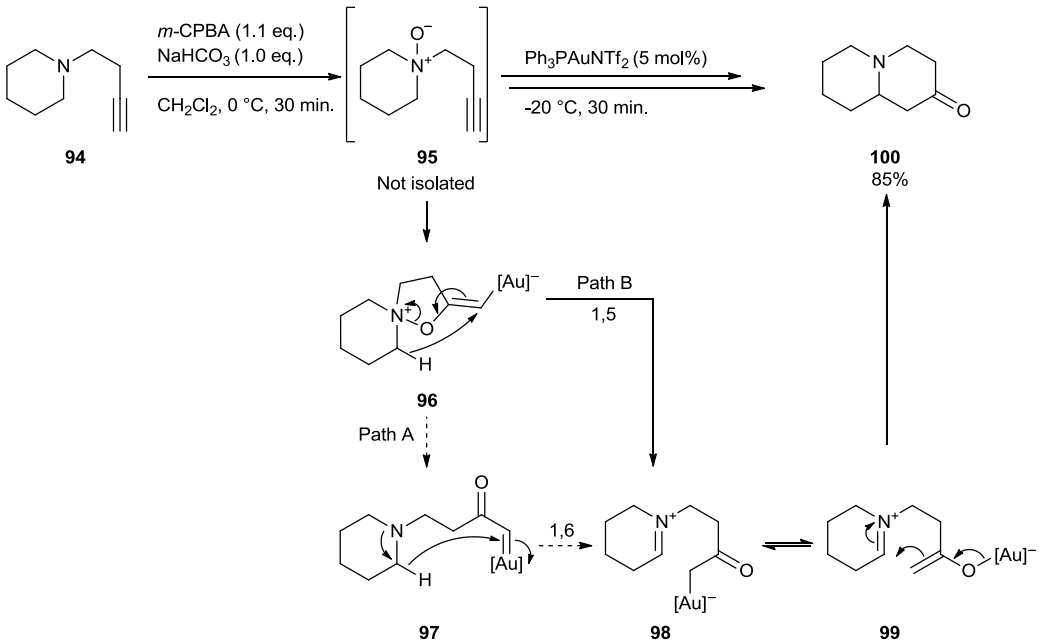
Shin was able to select the nucleophilic region of the hydroxylamine and control the regiochemistry of nucleophilic attack onto the alkyne. JohnPhos ((2-biphenyl)di-tert-butylphosphine) was observed to lead to a vinyl gold species (**80**) rather than a carbenoid, however the complex subsequently underwent a 1,3 sulfonyl migration, resulting in nitrone formation (**82**). However, the NHC-ligated IPrAuCl was shown to favour carbenoid formation (**86**) via *O* attack and subsequent redox cascade, as is typical of this catalyst, leading to a 3-pyrrolidinone (**88**).

L. Zhang's group reported a similar *N*-oxide system (Scheme 20), using an *N*-oxide generated *in situ* (**90**) to perform a redox cascade analogous to his and Toste's previous sulfur systems (Scheme 8 and Scheme 9).[38]



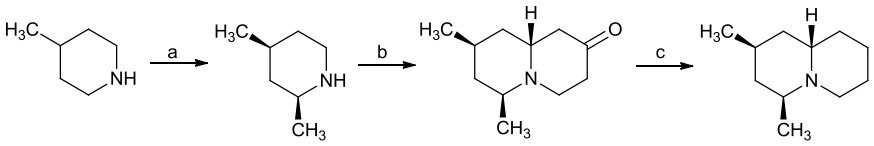
Scheme 20: Zhang's *in situ N*-oxide formation and electrophilic aromatic substitution

Expansion of this protocol to non-aromatic substrates was also successful, proceeding via a formal 1,5-hydride shift to form iminium **98**, gold enolate **99** and ultimately piperidinone **100** (Scheme 21).[39] Zhang's initial publication suggested the reaction proceeded via the formation of gold carbenoid **97** (Path A), followed by a 1,6 shift to give **98**. However, Zhang's subsequent DFT study indicated that ring-opening of the vinyl gold species **96** and hydride shift are a concerted process. Ammonium **96** leads directly to iminium **98** via a 1,5 shift, without formation of the free carbenoid **97** (Path B).[40]



Scheme 21: *In situ N*-oxide formation followed by hydride shift

Zhang demonstrated the applicability of these gold-catalysed cascades to the synthesis of complex structures, synthesising (+/-)-cermizine C (Scheme 22).



101 | **102** 41% | **103** 63% (d.r. >50:1) | **104** 43% (+/-)-cermizine C

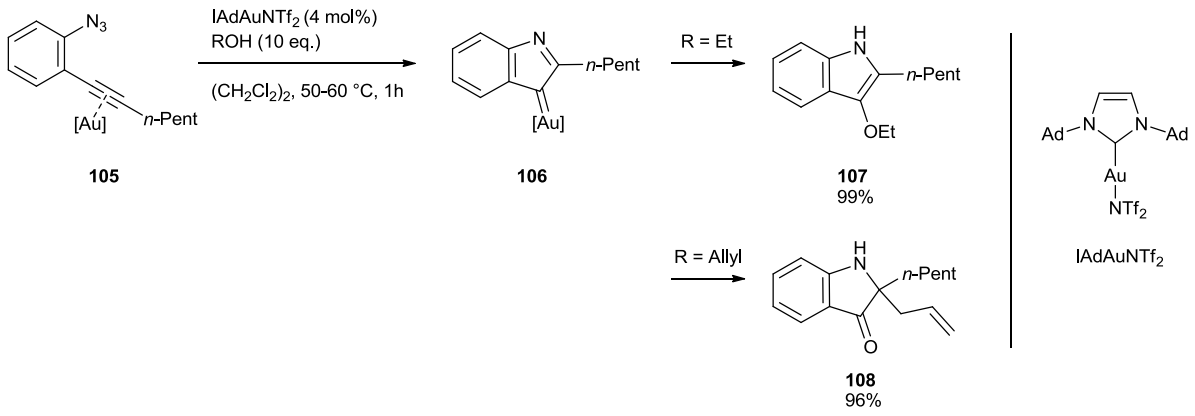
Reagents and conditions:
(a) (i) $(Boc)_2O$, THF/H_2O, NaOH (1N); (ii) $RuO_2.xH_2O$ (20 mol%), $NaIO_4$ (5 eq.), $EtOAc/H_2O$;
(iii) CH_3MgBr; (iv) CF_3CO_2H, then NaOH; (v) $Pd(OH)_2/C$, H_2 (45 psi);
(b) (i) 3-Butynyl tosylate, NaI, Cs_2CO_3, CH_3CN, reflux; (ii) *m*-CPBA, (1 eq.), 0 °C, 1 h., then $Ph_3PAuNTf_2$ (5 mol%), 0 °C, 1 h.;
(c) (i) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$; Raney Nickel, MeOH, reflux.

Scheme 22: Zhang's (+/-)-cermizine C synthesis

The dimethylpiperidine precursor **102** was assembled via sequential Boc protection, oxidation, nucleophilic ring opening with methyl magnesium bromide, deprotection, re-cyclisation and reduction. The key gold catalysed cyclisation was accomplished using a one-pot procedure. The necessary alkyne was installed using butynyl tosylate, the *N*-oxide formed with *m*-CPBA and cyclised using Zhangs's gold catalysed process to give bi-cycle **103**. Lewis acid-catalysed thioacetal formation and reduction using Raney nickel gave the target (+/-)-cermizine C.

Recently, Gagosz's and L. Zhang's groups utilised Toste's and Hiroya's early azide-based carbenoid syntheses (Scheme 6), with the specific aim of exploiting the α-imino carbenoids. These azides may be considered to be umpolung equivalents of the previously discussed *O*- and *S*- oxides, as the tether is attached at the nucleophilic, anionic position of the oxidant, rather than at the cationic leaving group. This arrangement is unique for intramolecular oxidants, as the leaving group is therefore not incorporated into the final structure and this allows the construction of interesting polycyclic products.

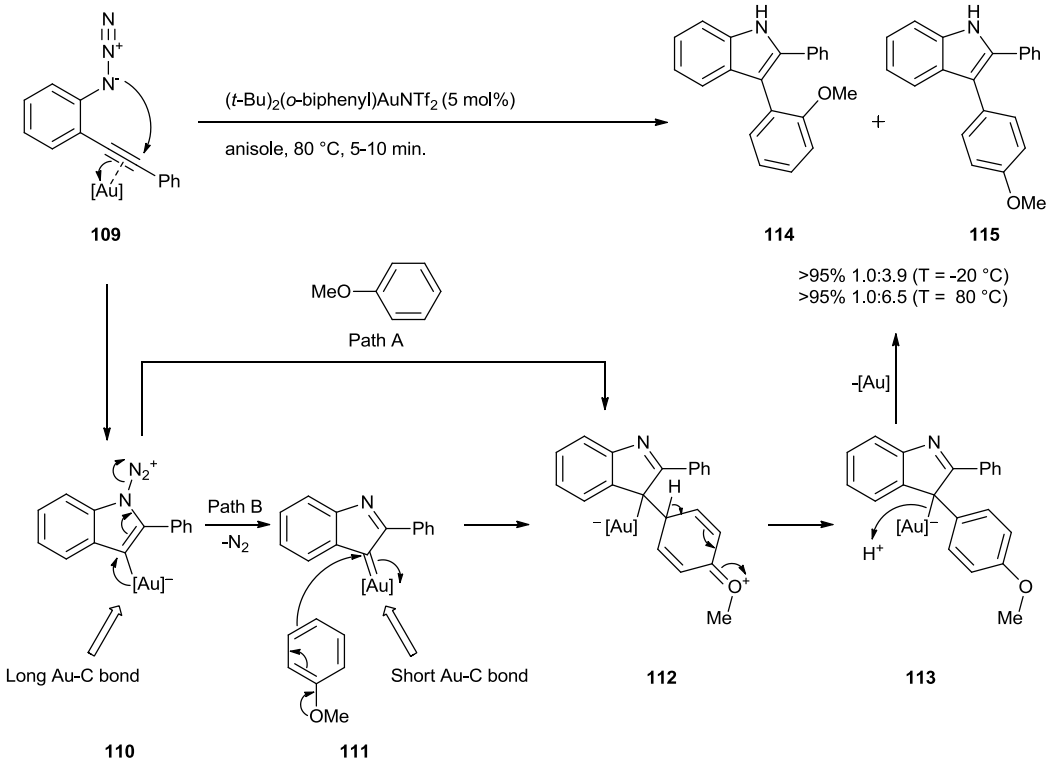
Wetzel and Gagosz employed a phenyl azide (**105**), which allowed access to a gold-indole carbenoid (**106**). The presence of a carbenoid allowed the indole to display umpolung reactivity, subject to nucleophilic attack at the normally nucleophilic 3-position (Scheme 23).[41]



Scheme 23: Gagosz's indole synthesis

The carbenoid **106** was successfully trapped with a range of alcohol nucleophiles, allyl alcohol subsequently undergoing a Cope rearrangement to give **108**.

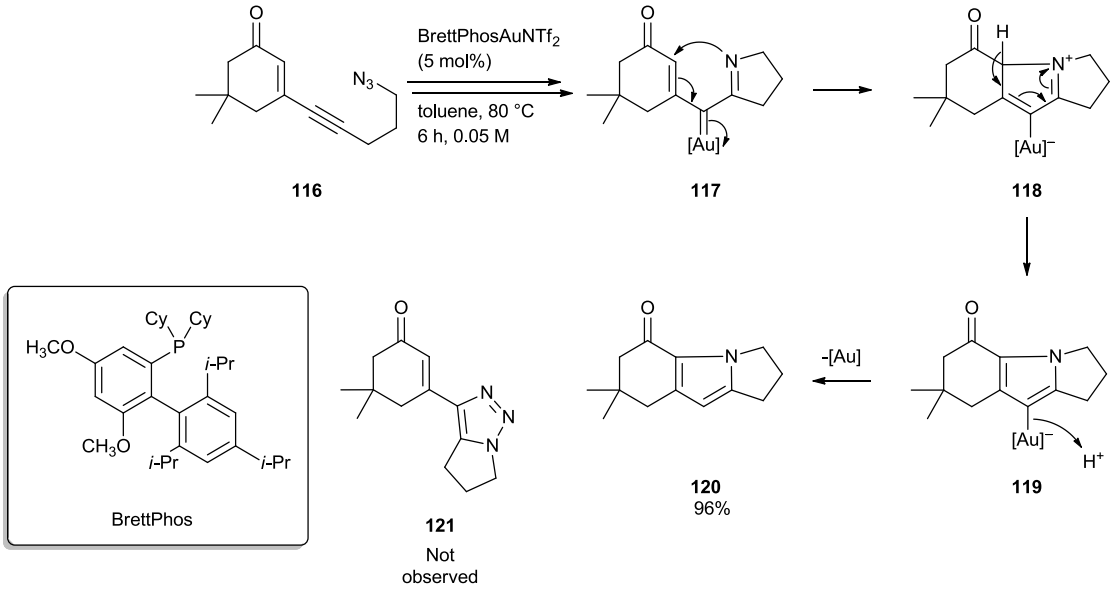
Zhang's first example also generated a gold-indole complex, which was subsequently trapped by the anisole solvent via an intermolecular electrophilic aromatic substitution. This trapping can occur at the vinyl gold intermediate **110**, as a concerted process with loss of nitrogen (Path A), or after carbenoid **111** formation (Path B). [42]



Scheme 24: Zhang's azide-based carbenoid synthesis and intermolecular trap

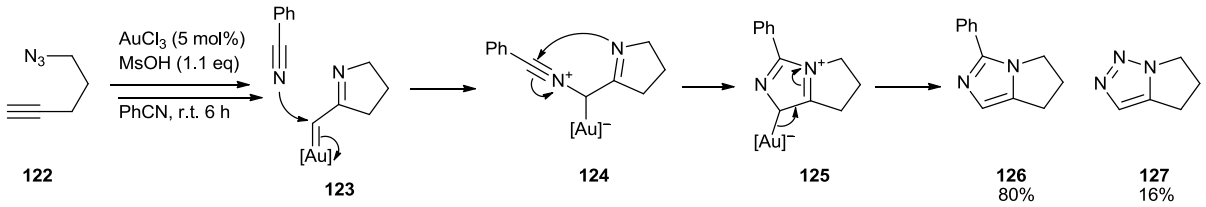
Zhang observed an inverse correlation of the observed isomers with temperature, elevated temperature improving the yield of the less sterically-demanding *para*-methoxy isomer **115**. Zhang rationalised this by suggesting that elevated temperature facilitates the loss of N_2, leading to increased carbenoid **111** formation (Path B). The gold-carbon carbenoid bond is shorter than that in the vinyl gold complex **110** (Path A), leading to increased steric demands on the orientation of the anisole during its attack by interference with the bulky JohnPhos ligand.[23]

Zhang's group further expanded this protocol, synthesising 2,3-dihydro-1*H*-pyrrolizines (120), by addition of an electron-deficient alkene adjacent to the alkyne (116).[43] By careful tuning of the reaction conditions, Zhang was able to obtain **120** in almost quantitative yield and avoid Huisgen type 1,3 dipolar addition of the azide over the alkyne, which was observed as a side-product during optimisation (**121**).



Scheme 25: Intramolecular rearrangement of the imino carbenoid

Xioa and Zhang further explored solvent traps for the α-imino carbenoid, reporting the synthesis of bicyclic imidazoles (**126**) from nitriles. Using benzonitrile, the nitrilium cation (**124**) generated by nucleophilic attack onto the carbenoid (**123**) was subsequently attacked by the imine.[44]



Scheme 26: Nitrile carbenoid trap

In this case Zhang was unable to eliminate the Huisgen side product (**127**), although it could be readily removed chromatographically due to its higher polarity.

Intermolecular oxidation systems

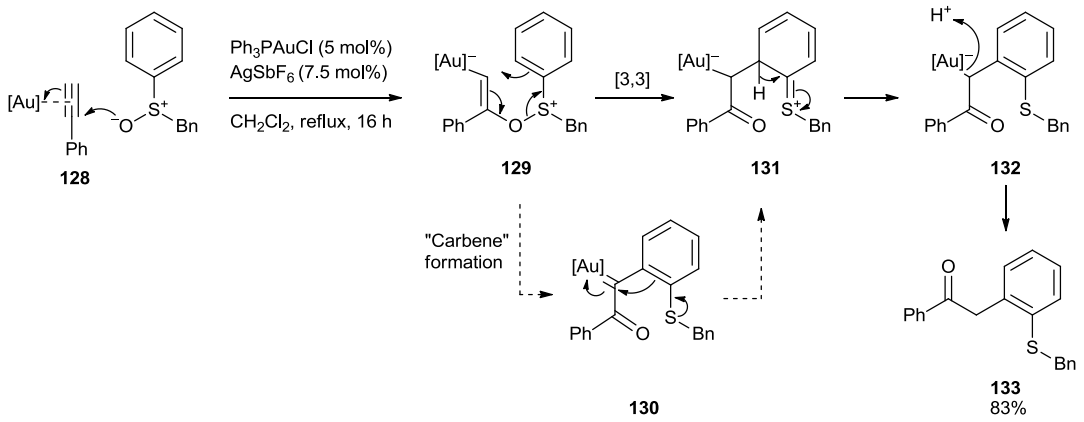
A wide range of intramolecular carbenoid syntheses have been reported, however the necessity for a tethered oxidant limits the overall synthetic utility of these reactions. While the intramolecular protocol had been applied to obtain valuable polycycles, removal of the tethered oxidant would allow much greater flexibility in the structure of carbenoid intermediates. It would also allow simple triple bonds to act directly as α-keto carbenoid equivalents without requiring any further elaboration of the substrate molecule.

Intramolecular carbenoid syntheses possess advantageous regiochemical and reaction rate controls. Regiocontrol of the oxidant delivery, and therefore carbenoid formation, may be determined by the geometry of cyclisation. Moreover, the rate of intramolecular carbenoid formation is typically more rapid than intermolecular trapping of the gold-activated alkyne, minimising intermolecular side reactions. Equivalent intermolecular processes lack these innate controls, with regiochemical control of carbenoid formation and ensuring correct reaction order being much more complex.

Early attempts

Asensio's group reported an attempted carbenoid formation via an intermolecular oxidant. Analogous to Zhang's and Toste's sulfoxide-based intramolecular electrophilic aromatic substitution (Scheme 8 and Scheme 10), Asensio's system utilised an intermolecular sulfoxide trap (Scheme 27).[45] The regioselectivity of substitution was exclusively *ortho* to the sulfide, irrespective of any directing

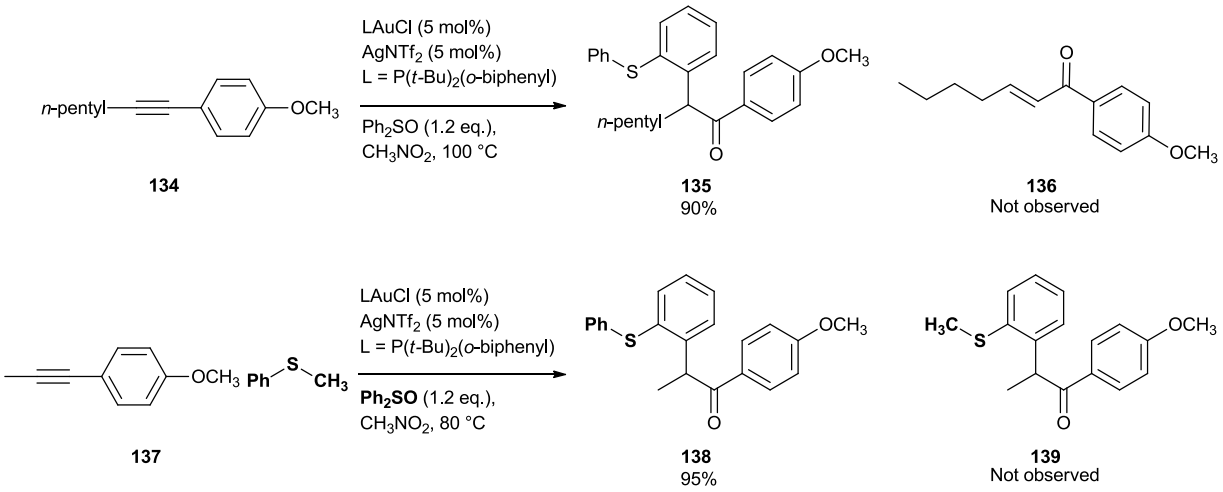
groups appended to the ring, leading Asensio to suggest that a [3,3] sigmatropic rearrangement pathway is responsible, instead of stepwise carbenoid (**130**) formation and substitution.



Scheme 27: Alternative reaction pathways in Asensio's redox cascade

A DFT study of the reaction pathway appeared to confirm the sigmatropic rearrangement, owing to the vinyl gold intermediate's (**129**) orientation during the catalytic cycle giving a particularly low activation barrier for sigmatropic rearrangement, compared to carbenoid formation.[46]

While investigating carbenoid ring expansions, Liu's group observed similar reactivity to Asensio, noting regioselective substitution of the oxidant (**135**) instead of the expected carbenoid reactivity, in this case via a 1,2-hydride shift to give **136** (Scheme 28).[47]



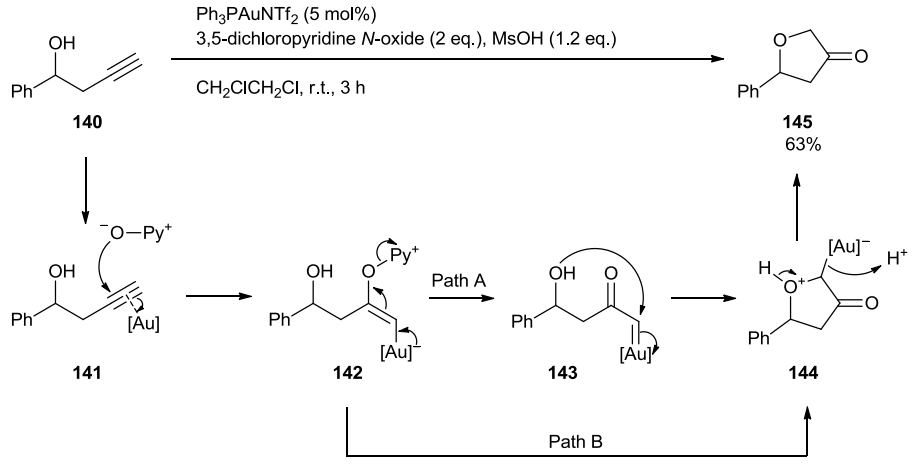
Scheme 28: Liu's oxidant trap and crossover experiments

Liu attempted to observe crossover of the liberated sulfide, by mixing diphenyl sulfoxide and methyl phenyl sulfide, which would suggest carbenoid formation via a stepwise process. However no

crossover product (**139**) was observed, lending further weight to Asensio's assertion that the reaction proceeds via a concerted [3,3] sigmatropic rearrangement. Also important to note is the robust nature of Liu's protocol, despite superstoichiometric presence of sulfide at the beginning of the reaction, catalyst performance is not attenuated. Zhang's and Toste's equivalent intramolecular reactions were subsequently found to follow the same rearrangement pathway as proposed by Asensio and Liu (Scheme 8 and Scheme 9).[31]

Early pyridine *N*-oxide reactions

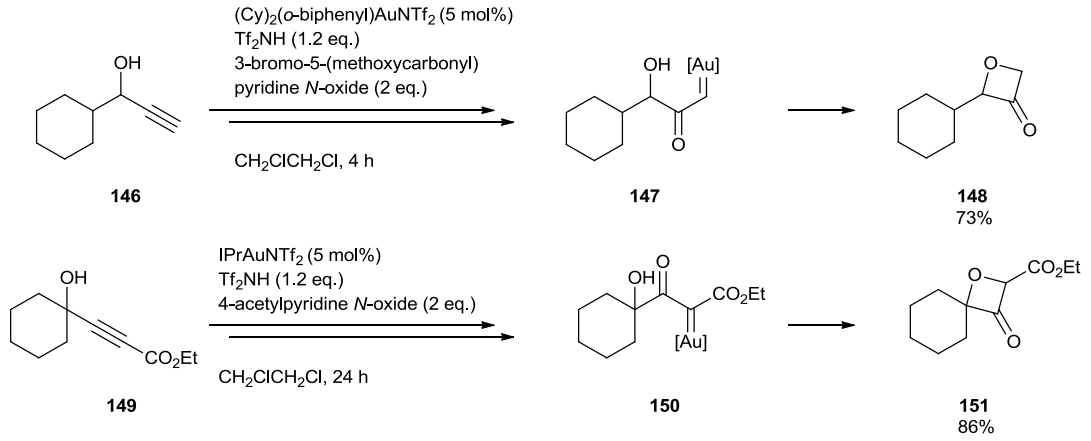
The first successful oxidative intermolecular carbenoid synthesis was reported by L. Zhang's group in 2010. Avoiding the use of sulfoxides, Zhang screened a variety of pyridine *N*-oxides as intermolecular oxidants, 3,5-dichloropyridine *N*-oxide proving optimal (Scheme 29).



Scheme 29: Zhang's intermolecular carbenoid synthesis

Like Asensio's sigmatropic rearrangement, Zhang's reaction may proceed via emission of the leaving group and carbenoid formation (**143**) (path A), or immediate trapping of the vinyl gold complex (**142**) by the adjacent alcohol group as an S_N2' process (Path B). It is important to note that in this instance the vinyl gold species **142** can also be formally considered a carbenoid, as it is electrophilic α to the gold atom and gives the same overall "carbene" reactivity. Whether gold carbenoid reactions of this kind proceed via a π-bonded carbenoid or vinyl gold species, and the implications this has on their reactivity, became a matter of considerable debate in subsequent publications.

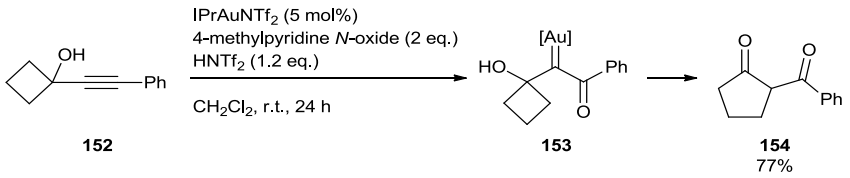
Zhang's protocol successfully demonstrated that alkynes could be used as direct α-keto carbenoid equivalents without having to incorporate the oxidant into the substrate architecture. Observing significantly reduced yields compared to previously reported intramolecular systems (*vide supra*), Zhang suggested that liberated pyridine was attenuating catalyst activity. Accordingly, addition of methanesulfonic acid, to prevent the pyridine by-product from poisoning the gold catalyst, gave a marked increase in yield.[48] Exploring the scope of this protocol, Zhang was able to obtain oxetan-3-ones (**148** & **151**) from easily-constructed propargylic alcohols (Scheme 30).[49]



Scheme 30: Zhang's oxetan-3-one synthesis

Regiocontrol for terminal, secondary propargylic alcohols was good; however, tertiary alcohols required an ester-substituted alkyne to retain the regioselectivity of carbenoid formation. Racemisation of enantioenriched alcohols was not observed, allowing the formation of enantioenriched oxetanones. Again Zhang added an acid, in this case triflimidic acid, preventing the use of substrates with acid-labile groups.

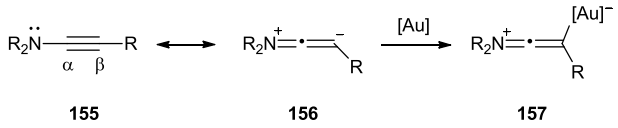
In 2012, Hashmi showed that if the ester substituent is replaced with an aryl group, the opposite regioselectivity may be obtained from internal alkynes with tertiary alcohols (Scheme 31).[50]



Scheme 31: Hashmi's regioselectivity switch

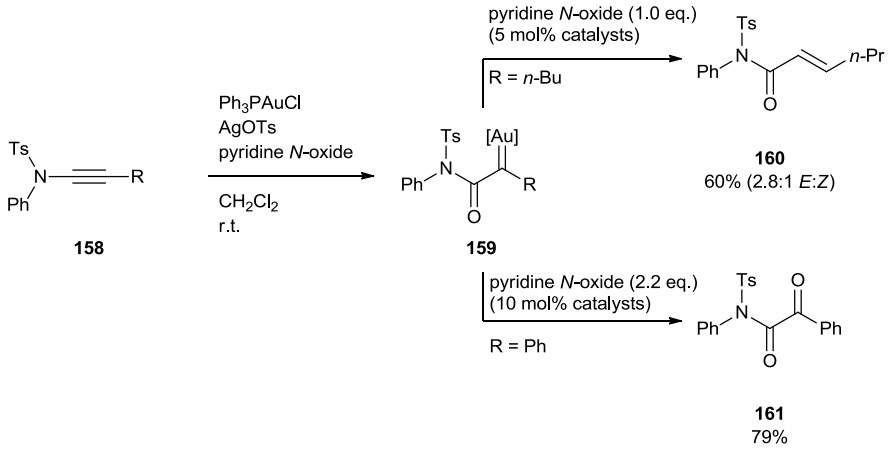
Ring expansion occurred, rather than cyclisation, however this selectivity was only possible with tertiary alcohols and alkynes not bearing strongly electron-withdrawing groups.

In 2011, soon after Zhang, Davies *et al.* also reported the synthesis of gold carbenoids, using pyridine *N*-oxide. Rather than terminal alkynes, Davies employed a range of ynamides. The adjacent nitrogen atom renders the β carbon of the ynamide nucleophilic, which, upon complexation with the catalyst, forms a gold ketene-iminium (**157**) (Scheme 32).[51]



Scheme 32: Ynamide resonance forms

Davies used this electronic bias as a highly effective regiocontrol, ensuring site-specific formation of both the ketone and carbenoid (**159**).

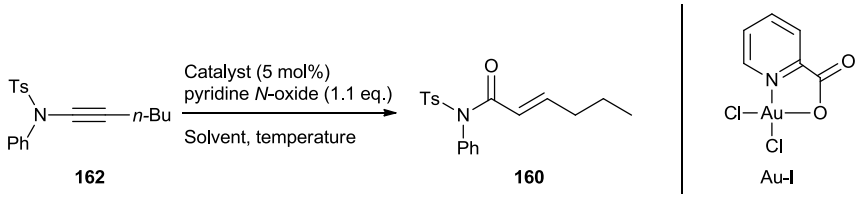


Scheme 33: Enimide *vs.* ketoimide formation

A 1,2-hydride shift followed carbenoid formation (**160**); however, this was in competition with a second pyridine *N*-oxide trapping the gold carbenoid to give an α-keto sulfonimide (**161**) (Scheme 33). Further optimisation of the reaction conditions suppressed formation of the competing oxidation product, by using air-stable Au(III) catalysts at elevated temperature or air-sensitive Au(III) catalysts at room temperature (Table 2).

The catalytic system proved extremely selective, even in substrates containing a second alkyne, only the ynamide was oxidised. No acid additive was necessary; with the catalyst proving sufficiently robust to withstand the pyridine by-product.

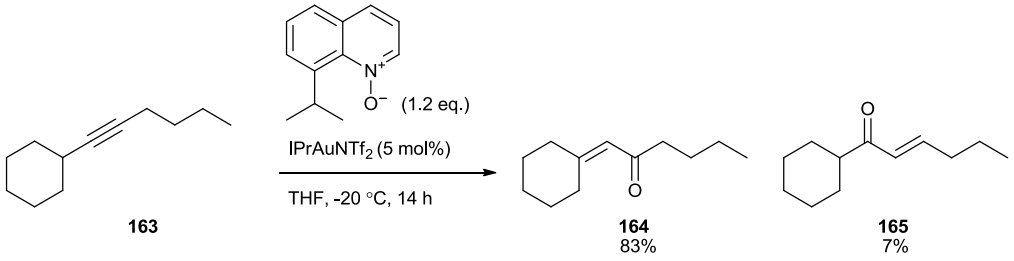
Table 2: Davies' optimised conditions



162 160 Au-**I**

Catalyst	Conditions	Yield (%)	*E*:*Z* ratio
Au-**I**	CH_2ClCH_2Cl, 70 °C	71	2.3:1
$AuBr_3$	THF, r.t.	70	3.7:1

Shortly after Davies' publication, Zhang's group reported a similar 1,2-hydride shift using alkynes instead of ynamides. The lack of a controlling electronic effect meant that Zhang observed regioisomeric products (**164** & **165**) arising from carbenoid formation at both alkyne positions (Scheme 34).[52]



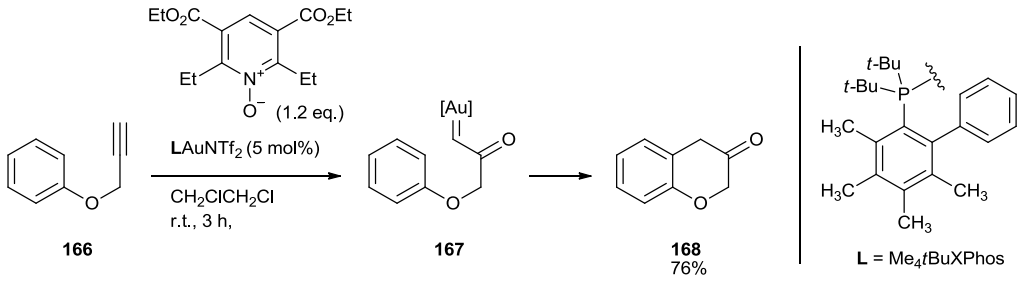
163 → **164** 83% + **165** 7%

Scheme 34: Regioisomers from Zhang's 1,2-shift

Despite the issues with regioselectivity, Zhang did not observe any diketone formation, which Zhang ascribed to the lower nucleophilicity of the bulky 8-isopropylquinoline *N*-oxide, compared to that of pyridine *N*-oxide.

Electrophilic aromatic substitutions

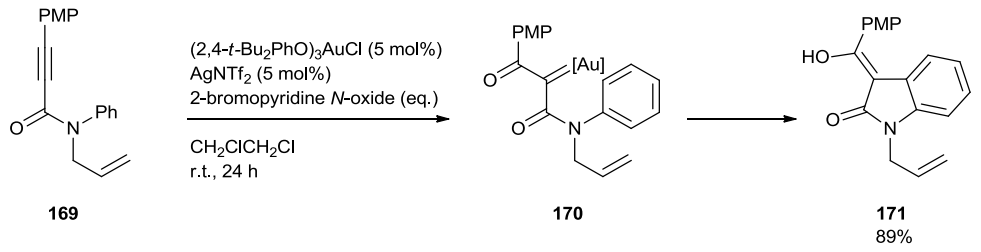
Zhang's group developed increasingly complex oxidants and catalysts, reporting the synthesis of chroman-3-ones from propargyl ethers. This reaction is conceptually an intermolecular equivalent of Zhang's sulfur and nitrogen electrophilic aromatic substitutions, however, competition between the tethered aryl group and the pyridine *N*-oxide led to high yields of the doubly-oxidised product observed by Davies (Scheme 35 and Scheme 33).[53]



Scheme 35: Zhang's chromanone synthesis

Zhang was forced to use an elaborate tetrasubstituted *N*-oxide and an extremely bulky phosphine ligand to sterically disfavour over-oxidation of the alkyne. These chromanones (**168**) are accessed in two steps, compared to the four required for the equivalent diazo route.

Other groups subsequently obtained a range of bicyclic compounds via this route. J. Zhang's group showed that the opposite regioselectivity for carbenoid formation may be obtained for these substitution reactions by utilising an electron-deficient alkyne (**169**), obtaining a range of substituted oxindoles (**171**) in this way (Scheme 36).[54]

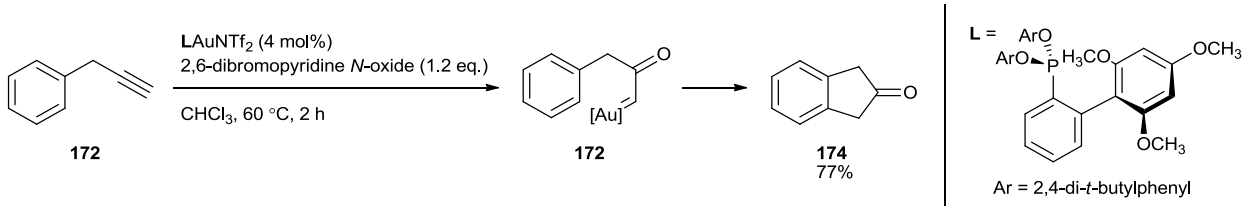


Scheme 36: J. Zhang's oxindole synthesis

Using a phosphite-gold complex, J. Zhang observed complete selectivity for electrophilic aromatic substitution, even in the presence of allyl substituents, which are susceptible to cyclopropanation.

Gagosz's group has also shown that the equivalent process for propargyl arenes is viable, employing a novel biarylphosphonite catalyst in conjugation with 2,6-dibromopyridine *N*-oxide (

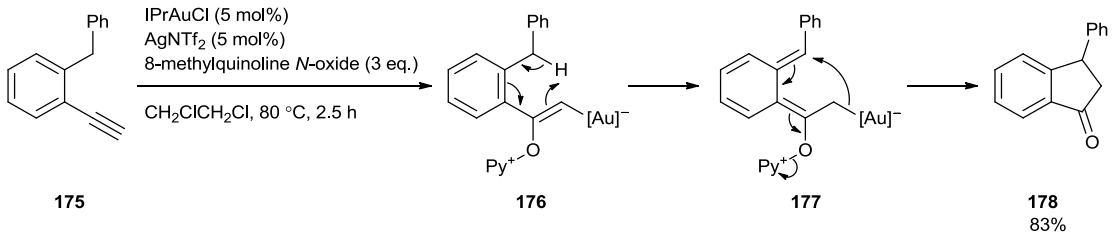
Scheme 37).[55]



Scheme 37: Gagosz's electrophilic aromatic substitution

Ensuring that the gold complex displays sufficient carbenoid character to accomplish a given transformation can be challenging. Gagosz was forced to develop an elaborate catalyst as Zhang's Me_4*t*BuXPhos gave extremely poor yields when applied to Gagosz's substrates, despite the minor variation in structure, highlighting the frequently capricious nature of these catalytic systems (Scheme 35 vs. Scheme 37).

Not all substrates are suitable for electrophilic aromatic substitution in this manner. Liu's group observed that substrates with alkyl substituents can undergo a 1,5-hydride shift instead of carbenoid formation (Scheme 38).[56]

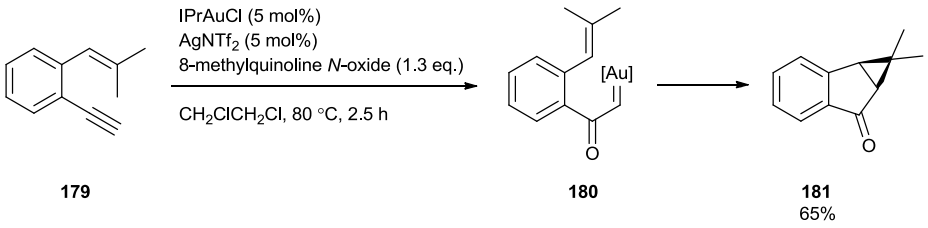


Scheme 38: Liu's 1,5-hydride shift

Liu suggested that this hydride shift occurs much faster than carbenoid formation, preventing electrophilic aromatic substitution. To test this hypothesis Liu synthesised the equivalent diazo compounds which, when reacted with a suitable gold catalyst, formed the corresponding carbenoid without passing through a vinyl gold intermediate. With carbenoid formation electrophilic aromatic substitution of the pendant arene was observed, supporting Liu's proposal that the hydride shift does not proceed via a carbenoid.

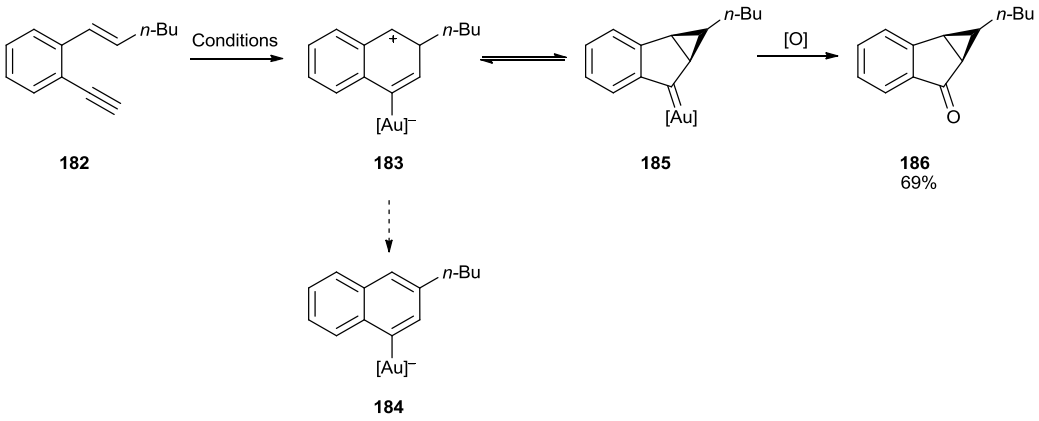
Enyne reactions

Cyclopropanation is also possible for substrates bearing accessible alkenes. In 2011 Liu's group reported the cyclopropanation of 1,5-enynes to give tricyclic indanone derivatives (**181**) (Scheme 39).[57]



Scheme 39: Liu's enyne cyclopropanation

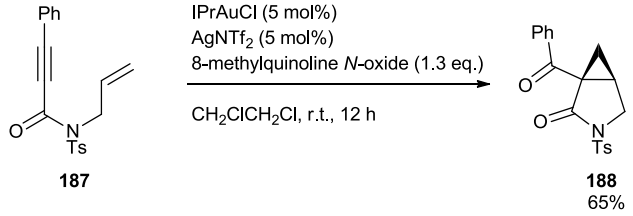
Because a gold carbenoid may also form through the reaction of gold-activated enynes, Liu suggested that the reaction may proceed via an α-keto gold carbenoid (Scheme 39) or enyne cyclopropanation/carbenoid formation, with subsequent quenching of the carbenoid by the intermolecular oxidant (Scheme 40).



Scheme 40: Alternative cyclopropanation pathway

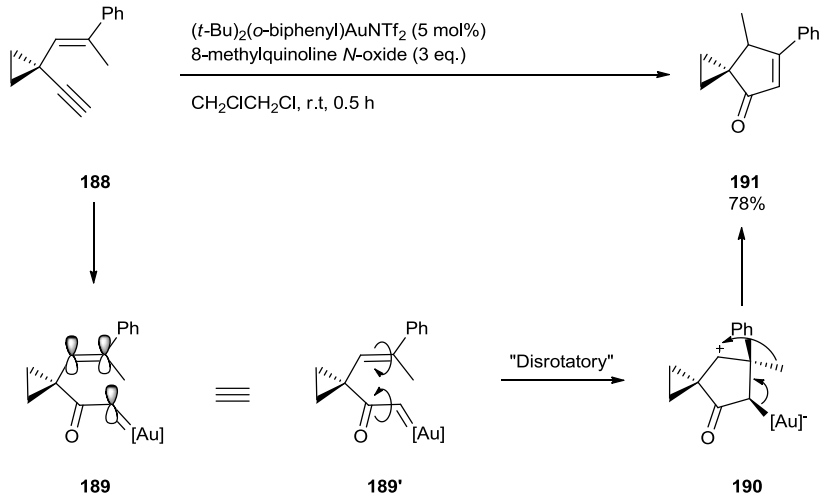
Liu proposed that α-keto gold carbenoid **180** formation was more likely, given that monosubstituted enynes did not give the potentially competing naphthalene (**184**) from elimination of the cationic intermediate **183**.

J. Zhang's group subsequently expanded Liu's work to include electron-deficient alkynes (**187**), giving the opposite regioselectivity (Scheme 41).[58]



Scheme 41: Cyclopropanation of electron-deficient alkynes

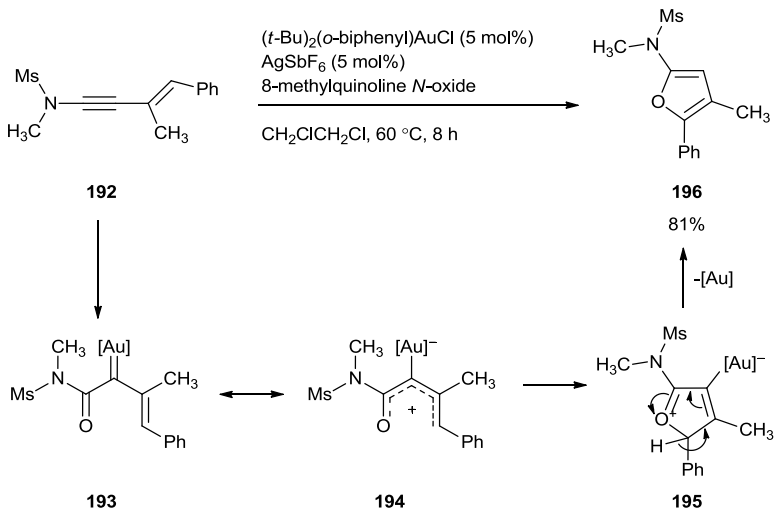
Liu's group observed that 1,4-enynes do not undergo cyclopropanation, due to the ring strain which would develop, instead undergoing a Wagner-Meerwein rearrangement after carbenoid (**189**) formation and initial cyclisation (**190**) (Scheme 42).[59] Initially the redox cascade provides an α-keto gold carbenoid (**189**), however it cannot undergo cyclopropanation, instead cyclising to provide a secondary cation (**190**) which is quenched by a 1,2-migration and simultaneous elimination of the gold catalyst.



Scheme 42: Liu's Wagner-Meerwein rearrangement

Using a combination of experimental and DFT studies, Liu determined that selectivity for the migrating group is not controlled by steric factors. The *Z* substituent of the alkene, in this case a methy group, was always observed to be the migrating group. To explain the selectivity for the migrating group Liu suggested that the orbital arrangement depicted in structure **189** favours "disrotation" to form the core cyclopentane. The gold complex then activates the substituent *anti* to the catalyst for migration.

Liu's group also demonstrated that the use of an intermolecular oxidant can allow a formal [4+1] cycloaddition, with a suitable conjugated enyne (**192**), to access trisubstituted furans (**196**) (Scheme 43).[60]

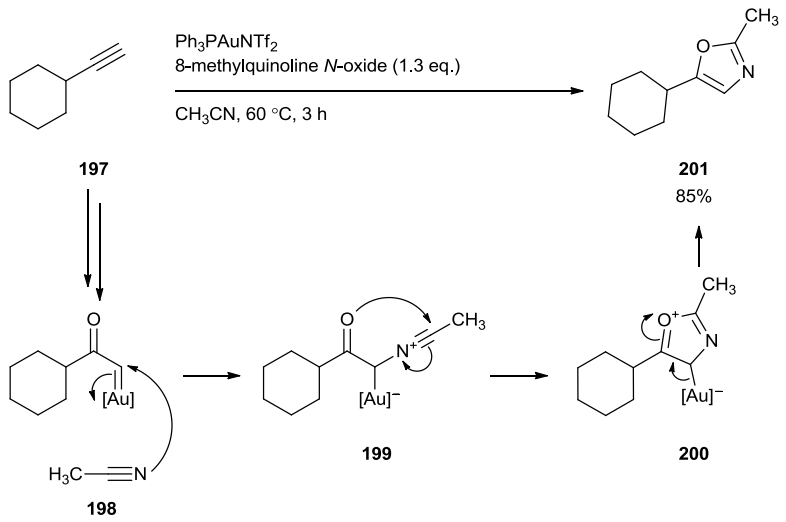


Scheme 43: Liu's electrocyclisation

Liu proposed that the reaction proceeds via an oxa-Nazarov cyclisation. Liu found Buchwald phosphine-ligated gold complexes most efficient, reasoning that these complexes behave as a gold-stabilised cation, in agreement with Toste's model, rather than as a carbene. Use of IPrAuCl gave mostly α-diketone, due to the NHC-ligated complex's greater carbene character.

Intermolecular carbenoid reactions

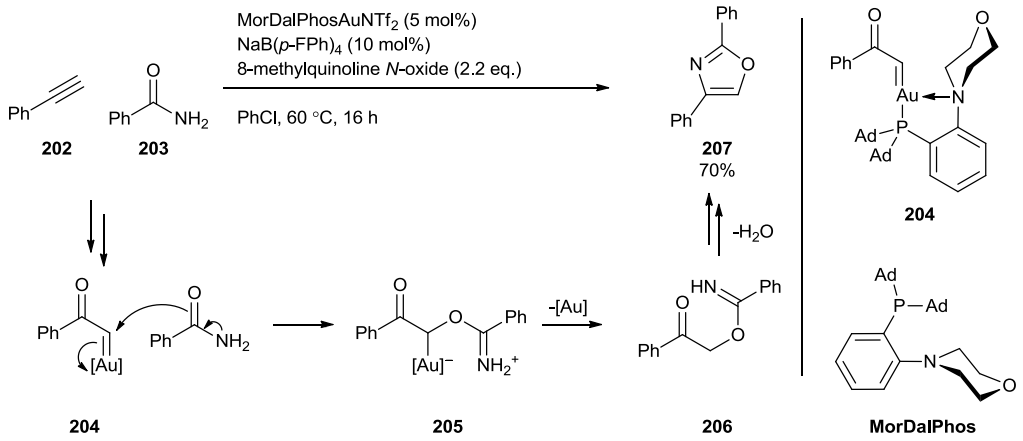
L. Zhang's group have demonstrated that the carbenoid may be intermolecularly trapped by a variety of nucleophiles, the first example being a carbenoid trap by a nitrile solvent, to give disubstituted oxazoles (**201**).[61]



Scheme 44: Zhang's oxazole synthesis

Complete regioselectivity was observed, however the reaction was limited to terminal alkynes. Formation of α-diketones was not observed owing to the high concentration of nitrile compared to *N*-oxide. The use of the nitrile as the solvent, or in large excess, renders the reaction impractical if the nitriles used are difficult to obtain.

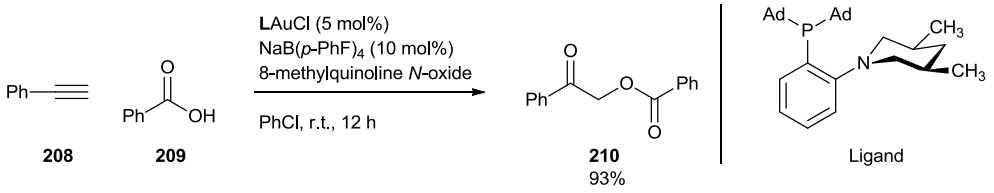
Zhang's group was able to trap the carbenoid with other nucleophiles. Amides proved possible, using Stradiotto's MorDalPhos as ligand for the gold catalyst, to give disubstituted oxazoles (**207**).[62] MorDalPhos was designed as a bidentate ligand and Zhang proposed that in this case the carbenoid was stabilised by chelation from the nitrogen, forming a tricoordinate carbenoid complex (**204**) increasing the longevity of the carbenoid intermediate (Scheme 45).[62, 63]



Scheme 45: Zhang's oxazole synthesis via a tricoordinate carbenoid

Carbenoid formation (**204**), followed nucleophilic attack by the amide, proto-demetallation and condensation gave the desired oxazole (**207**). Zhang rationalised the regiochemistry of the product oxazole by invoking *O*-attack of the amide, rather than the *N*-attack one might expect. Due to the poor nucleophilicity of the amide oxygen, compared to that of the *N*-oxide, Zhang was forced to introduce the oxidant gradually via syringe pump to prevent glyoxal formation.

Continued investigation of these tricoordinate carbenoid complexes led Zhang to report the coupling of α-keto carbenoids with carboxylic acids (Scheme 46).[64]

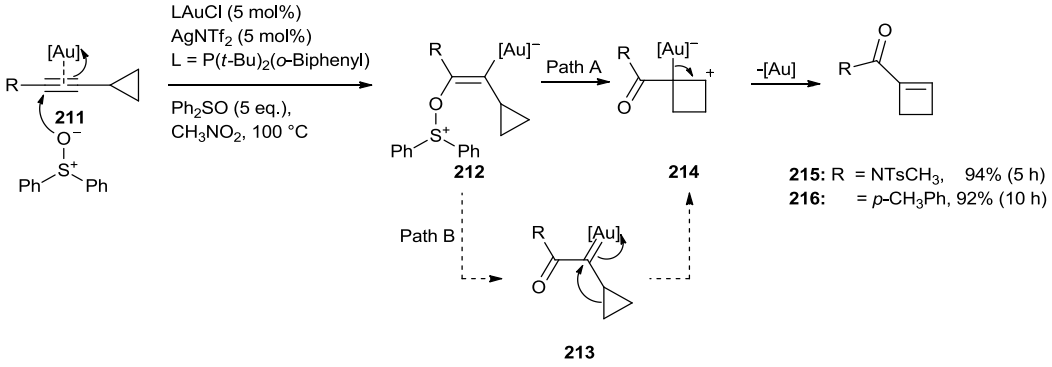


Scheme 46: Carboxylic acid coupling with Zhang's optimised ligand

Zhang designed and screened a range of catalysts derived from MorDalPhos to maximise the stabilisation from the ligand. Optimisation of the ligand structure allowed coupling with carboxylic acids in near quantitative yield, although oxidant delivery still required the use of a syringe pump. Using this catalyst, Zhang was able to exert quite considerable control over the carbenoid, as commercial ligands including PPh_3, IPr and BrettPhos gave less than 7% yield for this transformation.

Sulfoxide oxidants

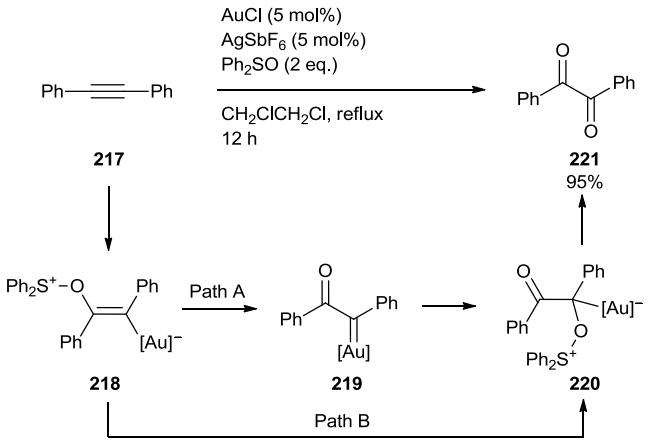
In late 2010, Liu's group reported a successful intermolecular carbenoid synthesis using sulfoxides as oxidants. Liu employed diphenylsulfoxide to access carbenoid reactivity with cyclopropylethyne derivatives (**211**), which readily underwent ring expansion to give valuable α-keto cyclobutenes (**215** & **216**). This protocol was applicable to both alkynes and ynamides and the regioselectivity of oxidation was preserved regardless of whether electron-donating or -withdrawing substituents were present on the alkyne (Scheme 47).[47]



Scheme 47: Liu's gold-catalysed ring expansion

The reaction pathway is believed to proceed via a concerted ring expansion and sulfide elimination (Path A), rather than stepwise "carbene" formation **213**, followed by ring expansion.

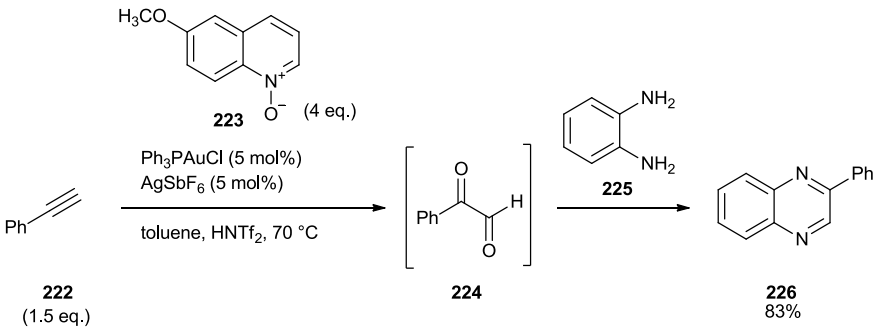
Following Liu's publication, C,-Y. Li's group reported the general synthesis of α-diketones (**221**) from a range of aryl-substituted alkyne and ynamide derivatives. Expanding upon the double oxidation observed by Davies, Li used refluxing conditions combined with diphenyl sulfoxide to ensure complete conversion (Scheme 48).[65] Li suggested that the reaction proceeded via S_N2' addition to the vinyl gold intermediate **218** (Path B), despite not observing the 3,3-sigmatropic rearrangement, reported by both Liu and Asensio, that would compete with this pathway.[45, 47]



Scheme 48: Chuan-Ying Li's double oxidation

As Li did not report the products of alkyl-substituted substrates, a gold "carbene" (**219**) pathway cannot be ruled out (Path A).

Hashmi's group also investigated this type of double oxidation, albeit with 6-methoxyquinoline *N*-oxide (**223**), reasoning that terminal alkynes would allow access to reactive glyoxal moieties (**224**) (Scheme 49).[66]

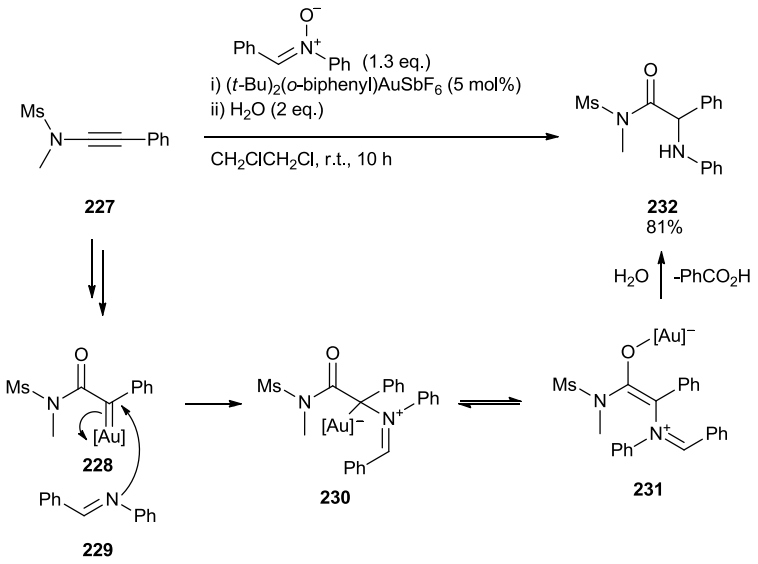


Scheme 49: Hashmi's glyoxal synthesis

Hashmi was unable to isolate the glyoxal (**224**), instead trapping it *in situ* with *o*-phenyldiamine (**225**) to form quinoxalines (**226**).

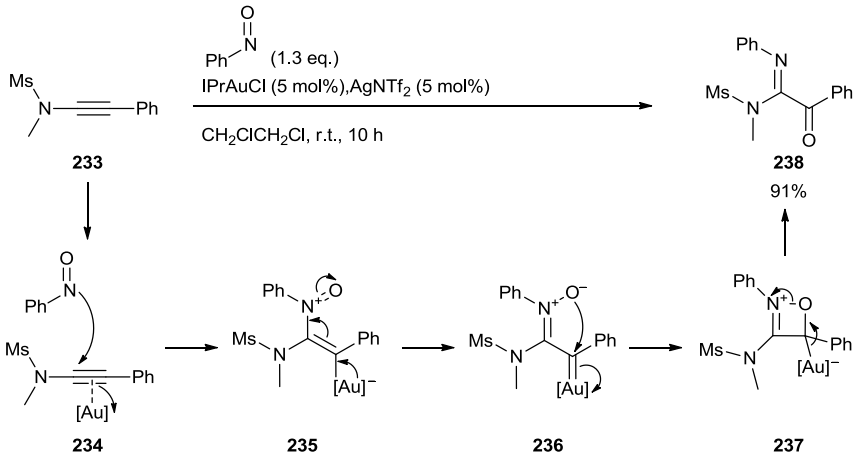
Other *N*-oxides

Carbenoid formation by intermolecular oxidants is not limited to pyridine *N*-oxide or sulfoxide-based oxidants; in 2011, Liu's group reported the generation of gold carbenoids from nitrones and nitrosobenzenes (Scheme 50).



Scheme 50: Liu's intermolecular nitrone oxidation

These oxidants, like their intramolecular equivalents, are able to effect carbenoid formation and the reduced leaving group immediately traps the carbenoid.[67] Liu's first system generated a gold carbenoid (**228**) from the ynamide/nitrone pair and the liberated imine (**229**) immediately trapped the nascent carbenoid. Hydrolysis of the gold iminium enolate (**231**) gave the final structure (**232**). Liu failed to observe crossover of the reduced oxidant in any of the experiments, leading to the suggestion that the reaction proceeds via a carbenoid, which is held in close proximity to the reduced nitrone by the solvent shell, immediately reacting to quench the carbenoid. Liu was also able to use nitrosobenzenes to obtain similar reactivity (Scheme 51).



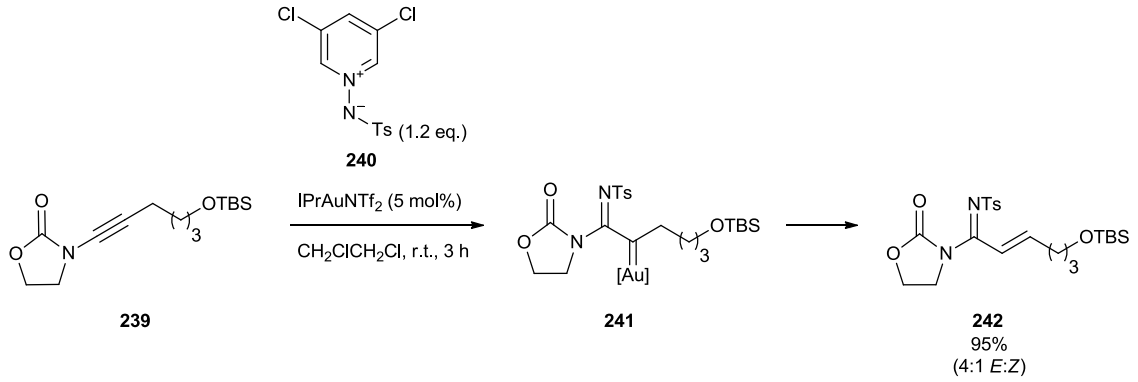
Scheme 51: Liu's intermolecular nitrosobenzene oxidation

Re-optimisation of the reaction conditions allowed oxo-imination (**238**) in almost quantitative yield. Liu conducted a number of reactions to probe the mechanisms of these transformations, observing a 1,2-hydride shift with alkyl-substituted ynamides and electrophilic aromatic substitution of the phenyl substituent of the oxidant, both indicative of carbenoid formation.

Pyridinium ylides

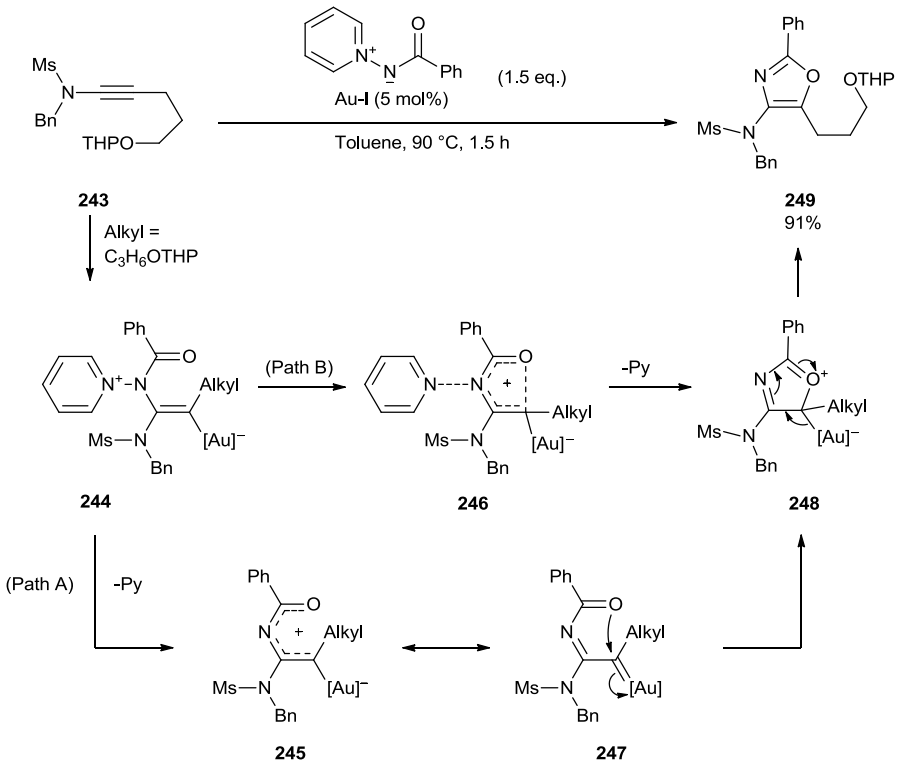
Examples of intermolecular α-imino carbenoids are rare, compared to their intramolecular equivalents. However, while exploring hydride shifts, L. Zhang's group replaced the *N*-oxide component with an aminopyridinium ylide (**240**), allowing the formation of an α-imino carbenoid (**241**) (Scheme 52).[68]

As with Zhang's previous examples, it was necessary to optimise the oxidant in order to ensure that it was sufficiently reactive, while suppressing side reactions. With these pyridinium ylides the formation of an α-diimine side product was not observed.



Scheme 52: Hydride shift from Zhang's α-imino carbenoid

More complex pyridinium ylides have been combined with gold catalysis. In 2011, Davies' group reported the use of aminopyridinium ylides, reasoning that the ylide could be used to generate the required carbenoid (**247**) which could then immediately trap the ylide oxygen, to give a formal 3+2 cycloaddition. Davies obtained trisubstituted oxazoles (**249**) as single regioisomers (Scheme 53).[69]



Scheme 53: Davies' oxazole synthesis

While the reaction was designed envisaging a carbenoid pathway (Path A), Davies suggested that a 4π electrocyclisation, from the vinyl gold pyridinium complex **244**, was more feasible (path B). This was supported by the observation that alkyl-substituted ynamides did not undergo 1,2-hydride shift, suggesting that cyclisation to form the C-O bond is a rapid process, occurring concomitantly with N-N bond cleavage. Were a carbenoid pathway dominating, this hydride shift would be expected to compete with cyclisation.

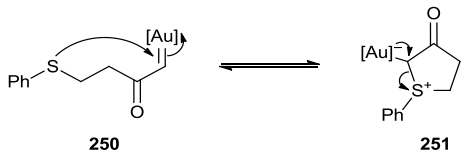
Synthesis of ylides by gold catalysis

Sulfonium ylides are valuable synthetic intermediates, allowing access to a diverse range of reactions that are capable of migrations, ring expansions and contractions, and wide range of cyclisation processes.[70, 71] The classical approaches to ylide syntheses can broadly be divided into two groups: synthesis of ylides via diazo derivatives or via sulfonium salts. While these reactions have seen considerable development since their conception, they still possess significant drawbacks.[72-74] The use of diazo moieties is frequently challenging, their instability and toxicity make them difficult to

handle and their installation adds synthetic complexity.[6-8, 75, 60] Complex sulfonium salts can be difficult to prepare, especially with sterically demanding substituents, frequently requiring strong alkylating agents and super-stoichiometric silver salts.[76] Transformation of a sulfonium salt to the desired ylide may also be problematic, requiring either a strong base or fluoride source. Also, the ylide anion may equilibrate with a more acidic hydrogen before it is quenched, which can lead to complex mixtures of undesirable side-products.[77-79] Alternative routes to sulfonium ylides are therefore extremely attractive and their synthesis by gold catalysis has recently become an emerging field.

Sulfonium ylides

L. Zhang's group's 2007 paper, one of the earlier examples of gold-catalysed oxidative carbenoid synthesis, proposed that the gold carbenoid (**250**) was stabilised by interaction with the pendant sulfide, generating a gold-stabilised sulfonium ylide (**251**).[29]



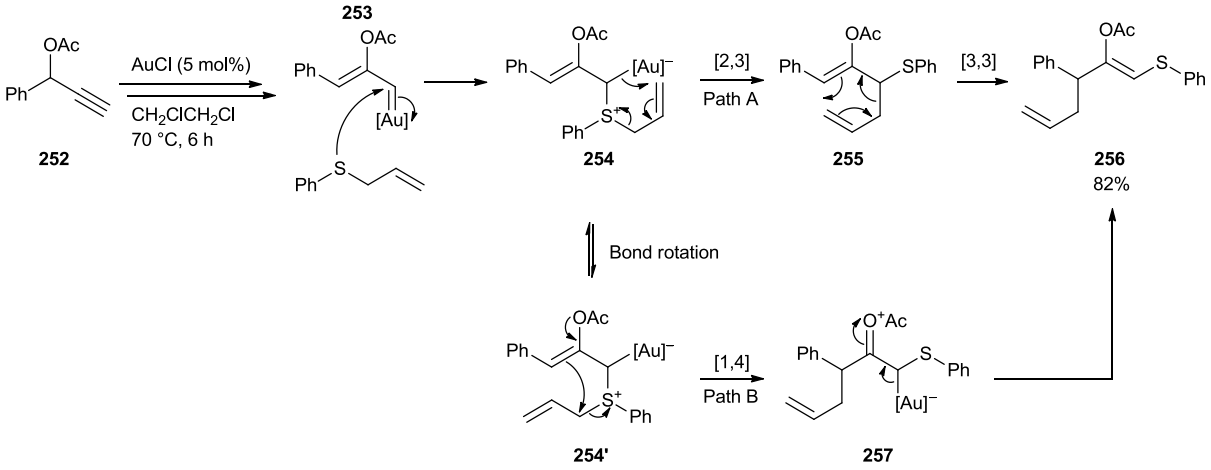
250 **251**

Scheme 54: Ylide stabilisation of gold carbenoids

Liu's group concurred, suggesting that heteroatomic stabilisation of the carbenoid in this manner renders it less electrophilic and is responsible for the difficulty in intermolecularly trapping these carbenoids experienced by many groups.[80] Gold-ylide complexes had been reported; however as these have not been used for typical ylide reactions, it was not known whether the stabilisation provided by the gold would impede their reactivity, or whether coordination to the ylide would poison the gold catalyst.[81-83]

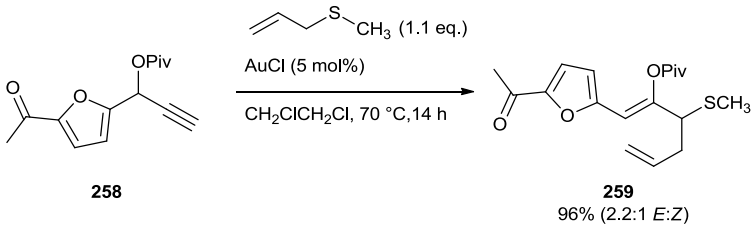
In 2008, Davies's group reported the first synthesis of a sulfonium ylide by gold catalysis. Davies employed a propargylic rearrangement to obtain the necessary carbenoid (**253**), which was

subsequently trapped intermolecularly by an allyl sulfide, providing the ylide moiety **254** (Scheme 55).[84]



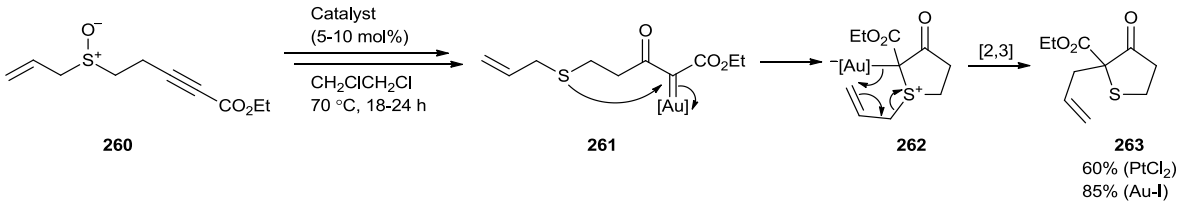
Scheme 55: Davies' sulfonium ylide synthesis

The resulting sulfonium ylide then rearranged to give *Z* alkenyl sulfides, either via a sequential 2,3-sigmatropic rearrangement, then 3,3-Cope rearrangement; or via an oxygen-assisted 1,4-shift and elimination. Competing cyclopropanation was not observed and the simple gold(I) chloride catalyst proved sufficiently robust to withstand catalyst poisoning. For certain examples, the rearrangement could be curtailed after quenching the ylide, by varying the non-migrating sulfur substituent (Scheme 56).[85]



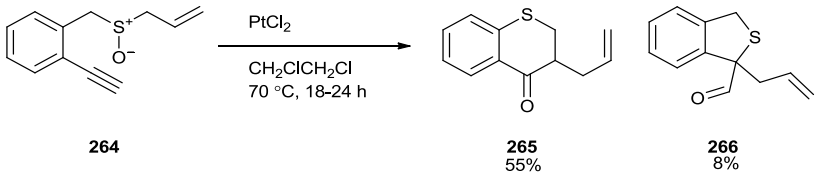
Scheme 56: Halting migration

Davies's group further expanded this methodology, using the recently developed sulfoxide redox cascades of Toste and Zhang (Scheme 8 and Scheme 9). Appending an allyl group onto the sulfide allowed immediate 2,3-sigmatropic rearrangement upon trapping the carbenoid **231**, leading to a range of heterocycles (**233**) previously only accessible via diazo chemistry (Scheme 57).[75]



Scheme 57: Davies' sulfoxide-based ylide synthesis

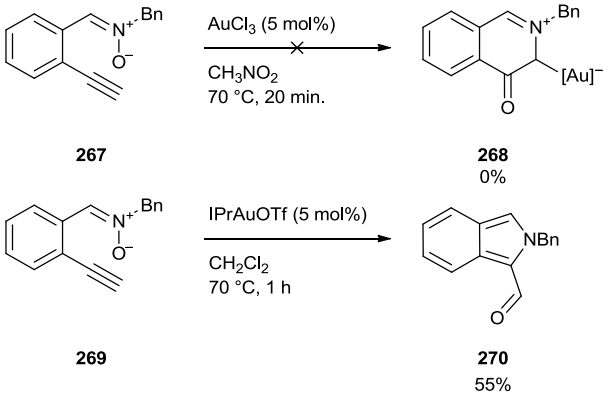
Gold and platinum catalysts were both able to achieve ylide formation, platinum proving more effective for terminal alkynes and gold for internal alkynes. While exploring bicyclic equivalents, Davies observed decreased regioselectivity for attack of the sulfoxide onto the alkyne (Scheme 58).



Scheme 58: Regioselectivity in carbenoid formation

Nitrogen ylides

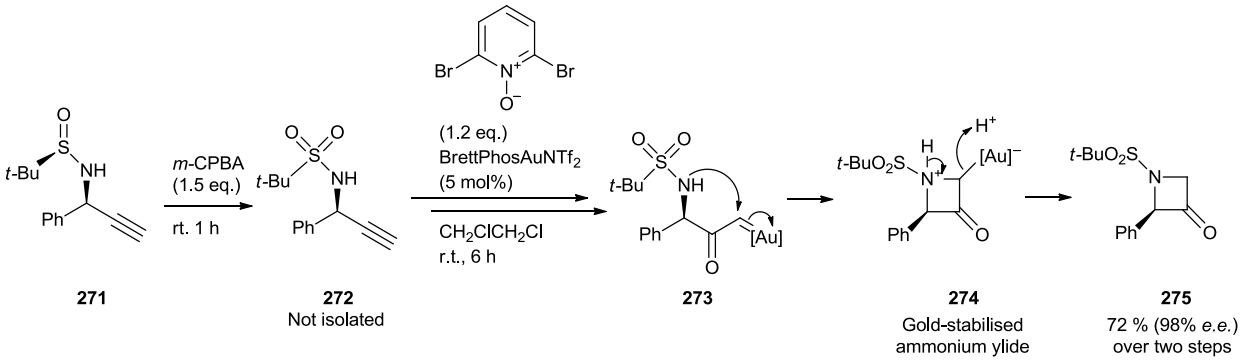
Accessing nitrogen-based ylides is also an attractive target for methodological development. Shin's group has published a [3+2] cycloaddition, proceeding via an azomethine ylide (Scheme 13). Shin attempted to obtain a free ylide (**268**) using a modification of his optimised protocol (Scheme 59).[32]



Scheme 59: Shin's attempts to isolate an azomethine ylide

No consumption of the starting material was observed, despite applying identical reaction conditions to the [3+2] cycloaddition. Modification of the reaction conditions only gave indole **270**; in no case was a free or gold-ligated ylide isolated.

Ammonium intermediates have also been suggested for other catalytic systems. L. Zhang's group reported the synthesis of azetidin-3-ones, which were proposed to form via an ammonium ylide. Zhang's system used chiral sulfinamide derivatives (271) to obtain azetidin-3-ones (275) in high optical purity (Scheme 60).[86]

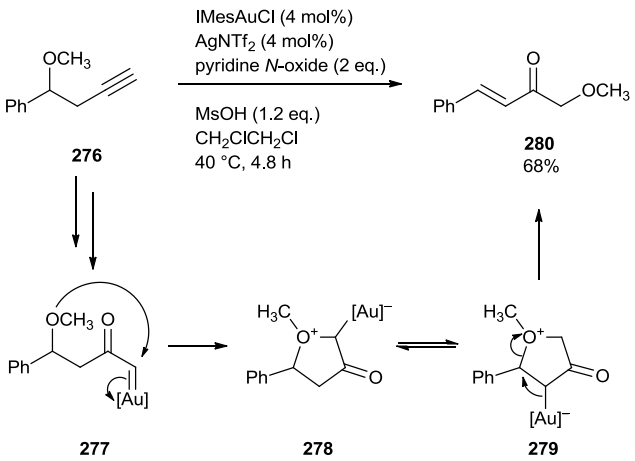


Scheme 60: Zhang's ammonium ylide intermediate

In Zhang's example the ylide decays by proton transfer, simultaneously effecting proto-demetallation of the catalyst. Zhang did not report migrating groups other than a proton, despite allyl and benzyl migrating groups being widely explored for ammonium ylides derived by classical means.[87]

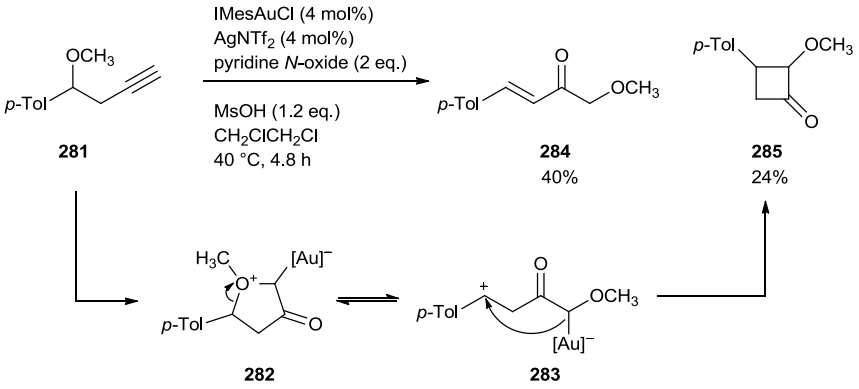
Oxonium ylides

Oxonium ylides have recently been obtained via gold catalysis. Oxonium ylide cascade reactions can be difficult to control, owing to the instability of the oxonium ylide.[88] In late 2012, C.-Y. Li's group published the first gold-catalysed oxonium ylide synthesis. Using pyridine *N*-oxide as an intermolecular oxidant, Li generated a carbenoid (**277**) which was intercepted by a tethered ether appended to the alkyne (**278**). These ylides underwent typical decay processes: β-elimination (**280 & 284**) and ring contraction (**285**) (Scheme 61 and Scheme 62).[89]



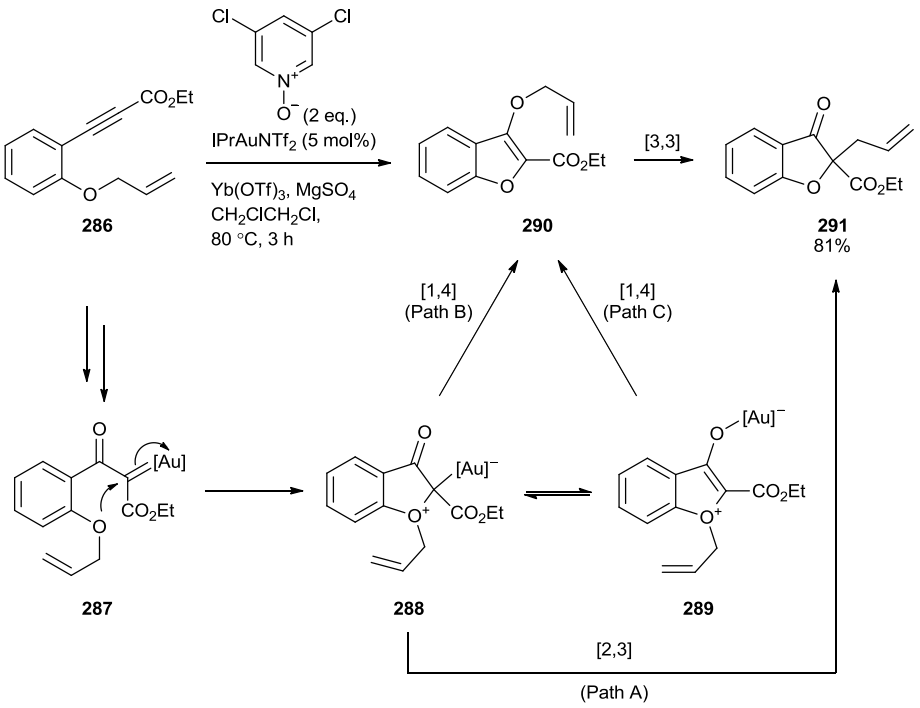
Scheme 61: Li's oxonium ylide synthesis and β-elimination

Selectivity was poor, with Li frequently observing mixtures of products due to competing decay processes, particularly with electron-donating substituents, which are able to stabilise carbocation formation. While Li's reaction lacked synthetic utility, it ably demonstrated that this highly reactive class of ylides could be obtained via diazo-free gold catalysis.



Scheme 62: Ylide decay by ring contraction

Tang's group subsequently combined Li's approach with a more controllable 2,3-sigmatropic rearrangement, to access highly-substituted dihydrofuranones (Scheme 63).[90]



Scheme 63: Tang's oxonium ylide synthesis

The reaction pathway was ambiguous, with Tang proposing a number of possible mechanisms. A direct 2,3-sigmatropic rearrangement of the oxonium ylide **288** may directly give the final product (path A). In some examples Tang observed the formation of benzofuran **290**, suggesting that a formal 1,4-shift occurs from the ylide **288** (path B), or its enolate tautomer **289** (path C), followed by a Cope rearrangement. Tang screened a variety of Lewis and Brønsted acids, which are typically added to gold reactions of this type to inhibit catalyst poisoning by the pyridine by-product, finding $Yb(OTf)_3$ the most efficacious.[91] Rare earth salts are not commonly used for this process and it has been suggested that the increase in yield from ytterbium(III) triflate is also due to participation in other processes in the catalytic cycle.[92]

Conclusion

The synthesis of α-keto and α-imino carbenoids via gold catalysis has seen rapid development over the past six years. From intramolecular sulfoxide redox cascades a wide range of catalytic systems have been developed, utilising *N* and *S*-oxides, ylides, azides and sulfonimines with a broad selection of gold catalysts. These processes allow access to complex, often polycyclic, heterocycles from

comparatively simple starting materials, without the significant drawbacks of classical diazo chemistry.

These redox cascades are not without problems; they are frequently complex, due to their propensity for multiple reaction pathways, resulting from regiochemical issues with initial attack onto alkynes and the presence of multiple electrophilic and nucleophilic sites during the catalytic cycle. The nature of the key gold complexes involved is still ambiguous, which can hinder reaction design. A given reaction may proceed via a gold "carbene" complex, a gold-stabilised cation, a vinyl gold complex or a sigmatropic rearrangement, while still displaying overall carbene-like reactivity.

Project Aims

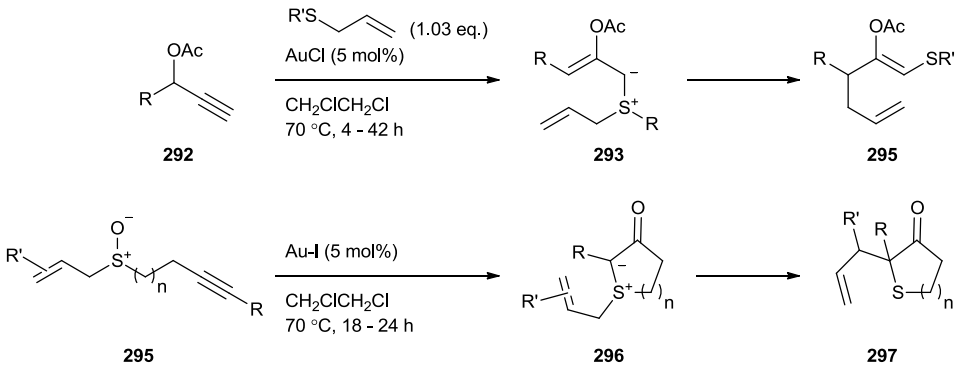
Gold catalysis has been demonstrated to be a viable means of obtaining sulfonium ylides. Thus far these ylides have only been used for intramolecular reactions. This research project aims to explore the following:

- To investigate whether the reactivity of gold-derived sulfonium ylides can be expanded. Specifically, whether these ylides can react with electrophiles in an intermolecular fashion and to investigate the ylide structures that may be obtained via gold catalysis.
- To apply the most recently developed techniques of gold catalysis to the synthesis of these ylides, such as the use of pyridine *N*-oxides, Zhang's chelating Buchwald phosphines, ynamide substrates and cooperative silver catalysis.
- To explore the structural motifs that may be obtained via gold-derived ylides. Specifically, to target motifs which are difficult to access *via* established methods and may be of pharmaceutical value.
- To gain further insights into the catalytic cycle when using gold complexes to generate sulfonium ylides.

Chapter 2: Ketone-stabilised ylides

Introduction

When this project commenced in 2009, there was little literature regarding the synthesis of ylides by gold catalysis. These examples were exclusively intramolecular ylide reactions and the first aim of this research project was to expand this reactivity to include intermolecular ylide reactions. Davies *et al* had reported the synthesis of sulfonium ylides (**293** & **296**) from gold-catalysed carbonyl rearrangements and from a sulfoxide redox cascade (Scheme 64).[75, 84]



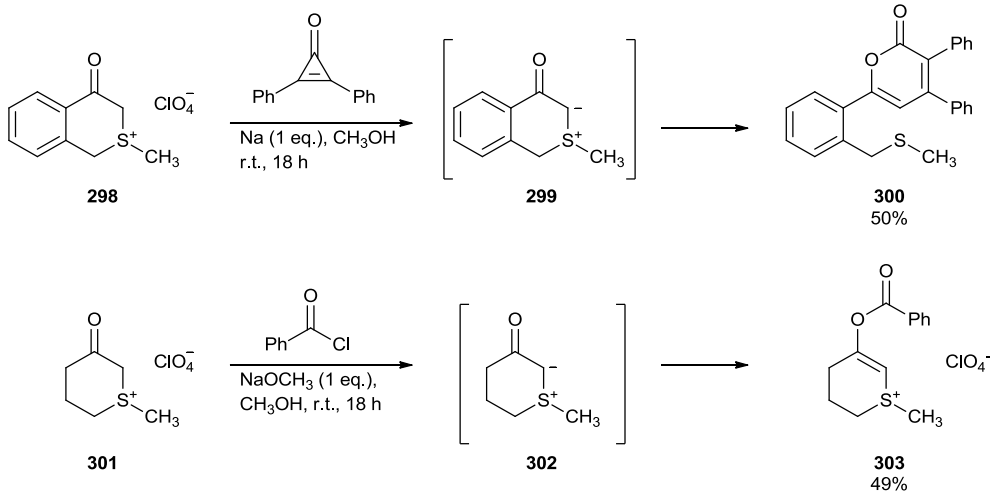
Scheme 64: Davies' gold-catalysed sulfonium ylide reactions

These systems quenched the ylide by sigmatropic rearrangement, therefore the first objective was to synthesise an ylide which could not undergo intramolecular rearrangement but could instead be intercepted with a suitable electrophile.

Davies' sulfoxide protocol was used as the basis for this work, as the sulfoxide carbenoid synthesis is more flexible in terms of the substrate structures that it will tolerate. When combined with an intermolecular electrophile this would give a two-component coupling, rather than the three components necessary for an intermolecular version of Davies' acetate migration. The use of minimal components would reduce overall reaction complexity, limiting potential side reactions and simplifying reaction development. An intermolecular protocol based on Davies' acetate rearrangement would also be of lower impact, as Toste has already reported a direct intermolecular cyclopropanation from the intermediate carbenoid, rendering sulfonium ylide formation unnecessary to access this reactivity.[17]

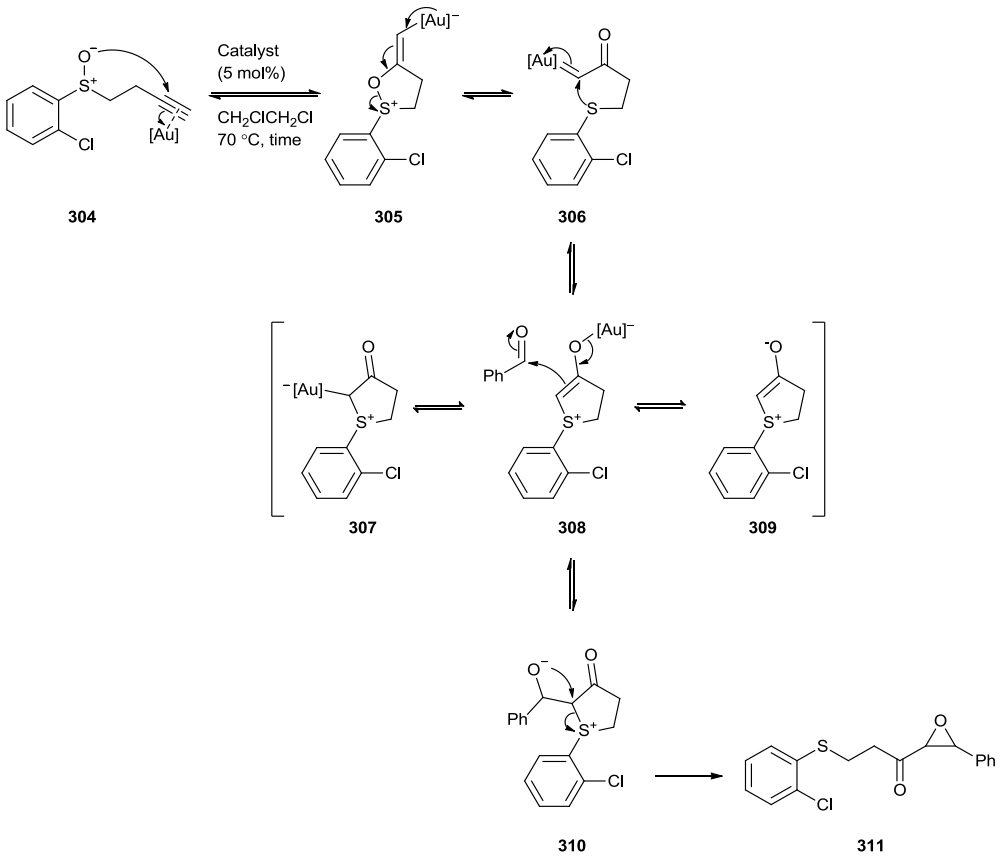
Examples of intermolecular reactions by cyclic ylides, where the ylidic anion and cation are within the same ring, were also rare, but not unheard of.[93-96] Moreover, classical intermolecular ylide reactions, such as epoxidation or cyclopropanation, had not been reported for cyclic ylides. While these cyclic ylides are challenging substrates for intermolecular reactions, and the envisaged epoxidation is not reported, the manifold benefits of developing a non-classical ylide synthesis/intermolecular trap cascade make this a worthwhile target, none the less.

Tanaka's group has reported the intermolecular trapping of cyclic ylides (**299** & **302**) with cyclopropenones and benzoyl chloride (Scheme 65).[93]



Scheme 65: Tanaka's intermolecular cyclic ylide reactions

Tanaka's electrophiles are incompatible with the gold-catalysed cascade. Cyclopropenes have been shown to react with gold catalysts and an acid chloride would bond to the sulfoxide substrate. The use of electrophiles which are unreactive until ylide formation has occurred was therefore imperative. The initial reaction screening was conducted with benzaldehyde as an electrophilic trap which, if successful, would generate keto-epoxide **311** (Scheme 66). Benzaldehyde was selected as the epoxidation of carbonyl compounds is well understood and synthetically useful.[97] A carbonyl compound could also take advantage of gold's capability of functioning as a Lewis acid, potentially increasing the reactivity of the electrophile.[98]

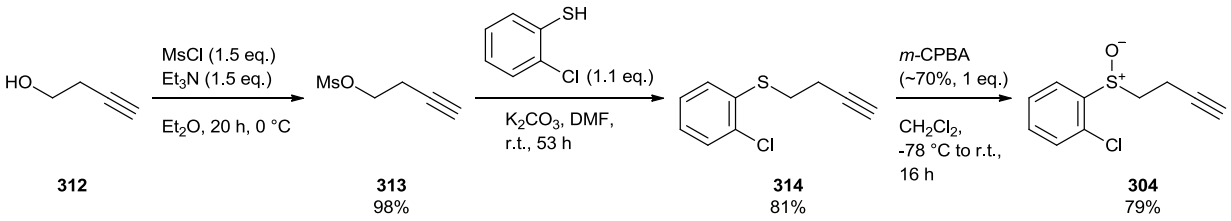


Scheme 66: Envisaged reaction pathway

Initial substrate design was straightforward and based on a combination of Davies' and L. Zhang's sulfoxide conditions (Scheme 66). Zhang's group has shown that appending these substrates with *o*-chlorophenyl substituents can avoid electrophilic aromatic substitution; therefore the allyl substituent of Davies' ylide precursor was replaced with an *o*-chlorophenyl moiety.[29] The designed ylide needed to be sufficiently stable to avoid decay before being intercepted, but nucleophilic enough to react with a range of electrophiles. Whether the ylide reacts as the gold-stabilised ylide, gold enolate or free ylide was uncertain and therefore the degree of stabilisation imparted by coordination to the gold was unknown. Whether the equivalent copper and rhodium ylides react via a metal-bound or free ylide is still a matter of considerable debate.[99] A terminal alkyne was chosen in order to minimise steric demands at the anionic position of the ylide.

Five-membered cyclic ylides

The necessary *o*-chlorophenyl sulfoxide was synthesised in three steps from butynol (Scheme 67).

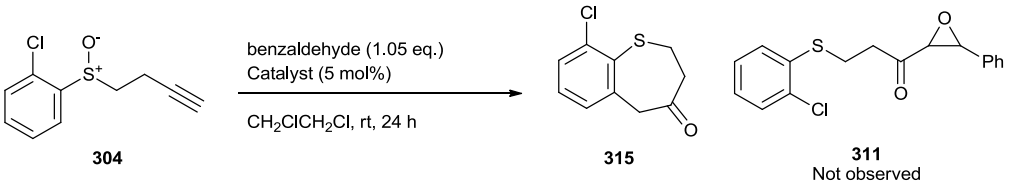


312 | **313** 98% | **314** 81% | **304** 79%

Scheme 67: Synthesis of the *o*-chlorophenylsulfoxide

Mesylation, followed by substitution with *o*-chlorothiophenol and oxidation with *m*-CPBA gave the butynyl sulfoxide. The substrate was subjected to L. Zhang's conditions for ylide formation with a small range of catalysts and in the presence of an excess of benzaldehyde (Table 3).

Table 3: Yields of substitution product

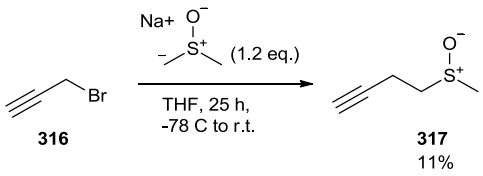


304 | **315** | **311** Not observed

Catalyst	Time (h)	Yield of 315 [a]
AuCl	17	74
Au-**I**	17	89
$PtCl_2$	17	- [b]
$(PPh_3AuNTf_2)_2$.toluene [c]	22	65

[a] Yield determined by NMR spectroscopy calibrated against a known mass of 1,2,4,5-tetramethylbenzene. [b] No reaction. [c] 2.5 mol% of catalyst.

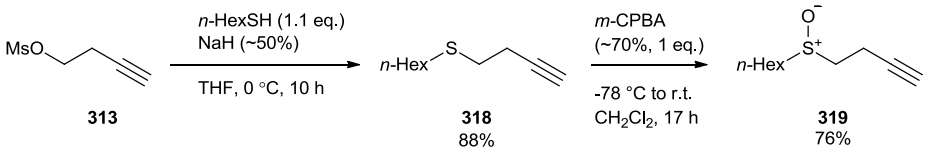
The reaction proved facile at room temperature, however epoxide formation was not observed; instead substitution of the aryl substituent occurred with Au(I) and Au(III).[31] $PtCl_2$ was not active for this transformation. Evidently, the *o*-chloro substituent was not deactivating the aromatic system sufficiently to prevent substitution competing with ylide formation. Rather than continue screening, steps were taken to prevent this competing reactivity The aryl substituent was replaced with an alkyl substituent, which is unable to undergo the observed substitution, either by 3,3-sigmatropic rearrangement or by electrophilic aromatic substitution. A methyl group was envisaged as the ideal replacement for the *o*-chlorophenyl substituent, owing to its minimal steric bulk. Synthesis of the required methyl sulfoxide **317** by the previous reaction sequence (Scheme 67) would necessitate the formation of methybutynylsulfide, the volatility of which would render it difficult to handle. Instead, substitution of propargyl bromide by a dimsyl ion was attempted, as it would bypass the volatile sulfide and also shorten the synthetic sequence (Scheme 68).[100]



Scheme 68: Attempted synthesis of methylbutynylsulfoxide via a dimsyl ion

This approach was unsuccessful; while the desired substrate was obtained, the yield was extremely poor owing to the relative pK_as of the dimsyl ion (35.1 in DMSO) and the alkyne proton (approximately 26.7 in DMSO, based on hexyne).[101, 102] Deprotonation of the alkyne led to significant polymerisation of the starting material and was not a practical substrate synthesis.

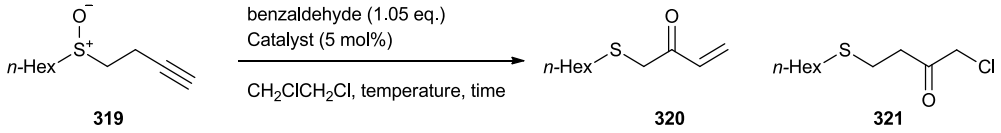
Instead, an analogous synthesis to that of **304** was employed, replacing the *o*-chlorothiophenol with hexanethiol. The hexyl substituent offered a minimal increase in steric bulk over the desired methyl group and the resulting sulfide was sufficiently non-volatile to be isolated, with careful handling (Scheme 69).



Scheme 69: Synthesis of the hexyl sulfoxide

The *n*-hexyl sulfoxide **319** was synthesised in the same manner as **304**, however sodium hydride was used to deprotonate the sulfide, prior to substitution, owing to its reduced acidity compared to thiophenol (approximately 17.0 and 10.3 respectively, in DMSO).[103] This alkyne was also subjected to L. Zhang's conditions, again with benzaldehyde as the electrophile (Table 4).

Table 4: Yield of enone and α-chloro ketone

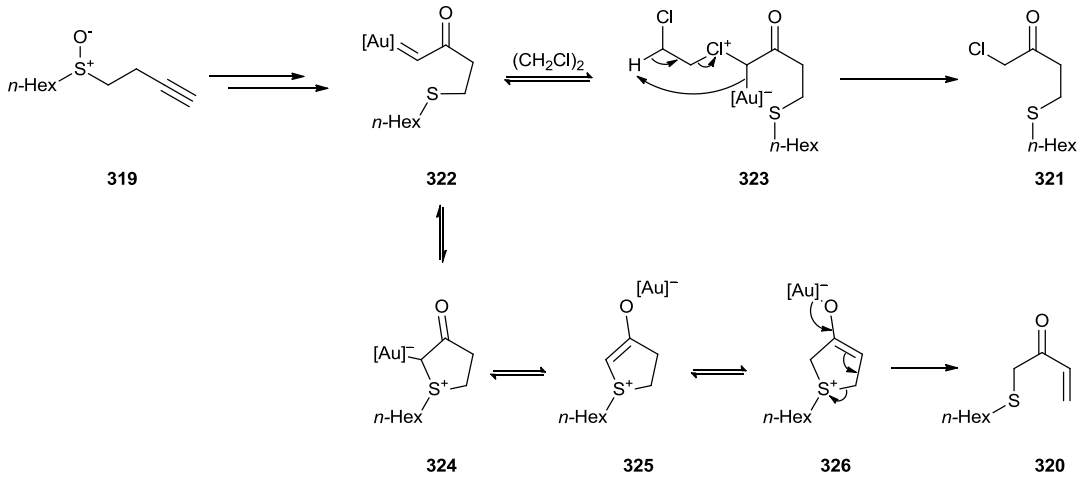


Catalyst	Time (h)	Temperature (°C)	Yield of 320 (%) [a]	Yield of 321 (%) [a]
Au-**I**	24	r.t.	- [b]	- [b]
Au-**I**	18	80	21	Trace
$PtCl_2$	18	80	23	Trace
AuCl	20	80	Trace	Trace
$(PPh_3AuNTf_2)_2$.toluene [c]	18	80	- [b]	- [b]

[a] Yield determined by NMR spectroscopy calibrated against a known quantity of 1,2,4,5-tetramethylbenzene. [b] No reaction. [c] 2.5 mol% of catalyst.

L. Zhang's conditions proved ineffective, even with the temperature elevated in excess of that reported by Davies in an attempt to force an intermolecular reaction. Epoxidation of the ylide was

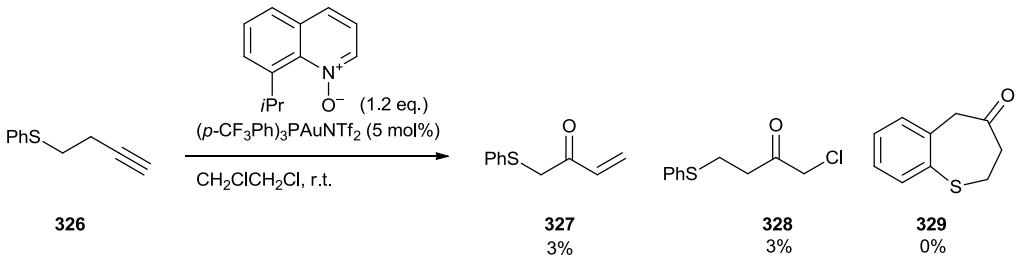
again not observed, despite preventing the competing electrophilic aromatic substitution, instead enone **320** was obtained, accompanied by the formation of traces of α-chloro ketone **321**.



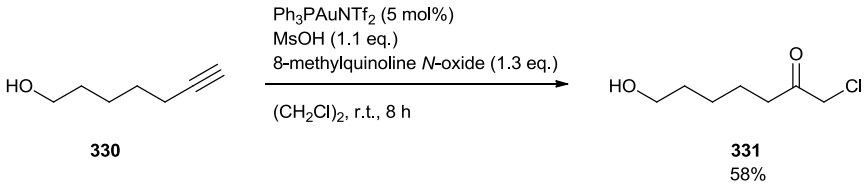
Scheme 70: Proposed mechanism for the formation of catalysis products 320 and 321

The enone arises from elimination of the ylide **324**: a decay process commonly observed for ylides.[89, 104-106] Davies' group had also observed the formation of chlorides during their gold-catalysed, sulfoxide-based ylide protocol.[75] These may arise from abstraction of a chlorine atom from the dichloroethane solvent by the gold carbenoid (**322**), combined with proto-demetallation.[107] Alternatively, decomposition of the catalyst may liberate the necessary chloride. While not successful as an intermolecular trap, these results confirmed that carbenoid and ylide formation were occurring with the modified substrates and that this ylide was sufficiently long-lived to undergo equilibration and elimination.

Zhang's group has very recently observed similar reactivity with ylides obtained via an intermolecular oxidation (Scheme 71) and subsequently optimised the chloride abstraction process (Scheme 72).[31, 107]



Scheme 71: Decay products from Zhang's intermolecular ylide synthesis

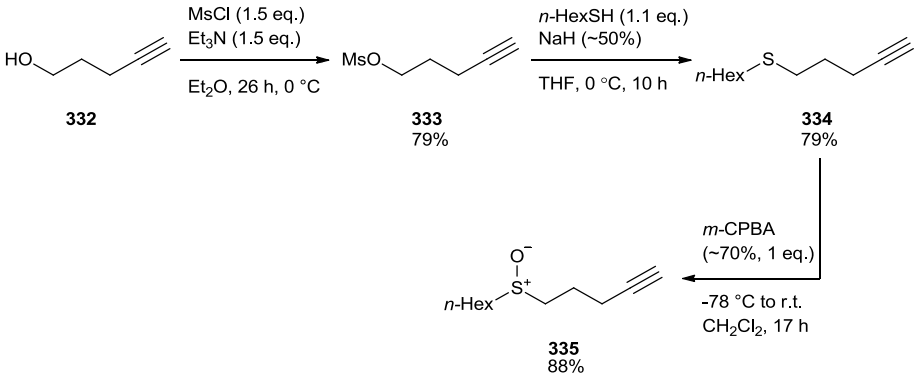


Scheme 72: Zhang's optimised α-chloro ketone synthesis

Zhang did not observe substitution of the aryl sulfide to give **329**, as the 3,3-sigmatropic rearrangement that is believed to be responsible for this product is not possible with an intermolecular oxidant. Electrophilic aromatic substitution of the aryl ring, by the intermediate carbenoid, is also prevented. Zhang suggested that substitution is not competitive with ylide formation, however, the (p-$CF_3Ph)_3P$ ligand is extremely π-acidic, which imparts a significantly cationic character to the carbenoid, which may also prevent this pathway.[23, 108]

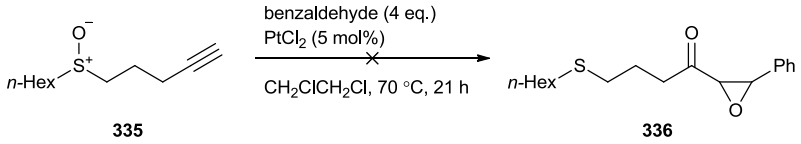
Six-membered cyclic ylides

In order to avoid the undesired formation of an enone by elimination of the ylide, which was observed for five-membered cyclic ylides, the substrate was modified to prevent the formation of a conjugated alkene, by elongation of the alkyl spacer between the sulfoxide and alkyne. The necessary substrate was synthesised in the same manner as **319**, this time beginning with pentynol (Scheme 73).



Scheme 73: Synthesis of the pentynol-based substrate

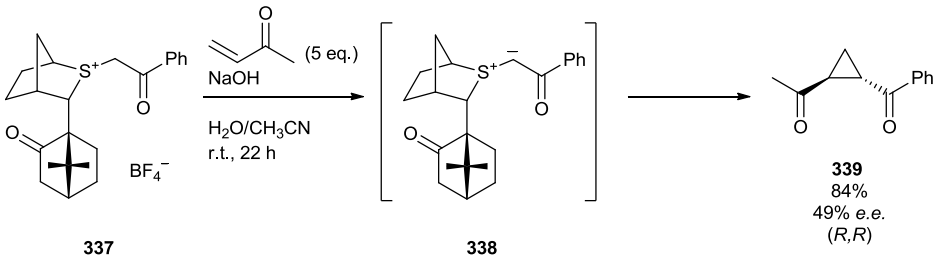
This substrate was then subjected to the ylide-forming conditions with benzaldehyde (Scheme 74).



Scheme 74: Attempted epoxidation with pentynyl sulfoxide

Addition to the ylide was again not observed, however the elimination decay reaction observed for the previous five-membered ylides was suppressed. The starting sulfoxide **335** was returned, as observed by Shin for his ammonium ylide system (Scheme 59).[32] Given the previous success of these reaction conditions, this suggested that although the ylide was forming but was not sufficiently nucleophilic to react with these electrophiles. The presence of the metal catalyst also appeared to stabilise the free ylide, as decay by ring contraction was also not observed.[109]

Attention was turned to electron-deficient alkenes, as Aggarwal's group have shown that these are able to react with acyclic, stabilised ylides (**338**) similar to those obtained in this study (Scheme 75).[110]



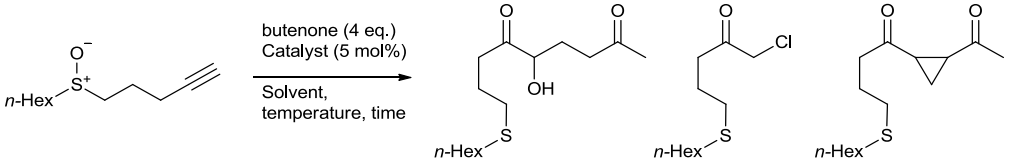
Scheme 75: Cyclopropanation of a ketone-stabilised ylide

The pentynyl sulfoxide **335** was subjected to gold catalysis with butenone, using Davies' conditions as the starting point, as Zhang's had proved ineffective for the butynyl sulfoxide substrate (Table 5). Intermolecular trapping of the ylide was observed, however the expected cyclopropane did not form. Instead, α-hydroxy ketone **340** was obtained, corresponding to incorporation of water in addition to the butenone. This was accompanied by chloride **341**, as observed for previous reactions.

The addition of 4 Å molecular sieves did not prevent the formation of **340**, suggesting that at least a portion of the water involved in the reaction is introduced during work up. The slight decrease in yield may not result from reduced water present in the reaction mixture, as Davies's group observed the addition of molecular sieves was detrimental to the 2,3-sigmatropic rearrangement of ylides derived in this manner.[75]

Varying the solvent proved unproductive; toluene was screened with the aim of destabilising the intermediate betaine to promote cyclisation to **342**, however only a low yield of **340** was achieved. Polar solvents that could promote betaine formation, acetonitrile and nitromethane, were also examined, but these proved incompatible with the gold-catalysed cascade, giving only complex mixtures of degradation products. Introducing water to the reaction mixture in an attempt to allow complete conversion to **340** was unsuccessful, although the cascade reaction proved sufficiently robust to withstand its presence, despite the reaction normally being conducted under strictly anhydrous conditions. By screening alternative catalysts the yield of **340** could be improved, although still in single figures, with the IPrAuCl/AgOTs catalyst pair proving most effective.

Table 5: Survey of reaction conditions

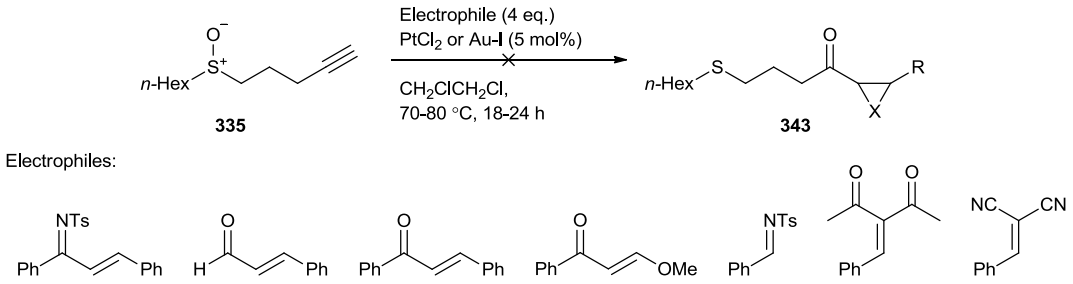


335 **340** **341** **342** Not observed

Catalyst	Additive	Solvent	Temp. (°C)	Time (h)	Yield of 340 (%)[a]	Yield of 341 (%) [a]
$PtCl_2$	-	CH_2ClCH_2Cl	70	20	6[b]	2 [b]
$PtCl_2$	4 Å sieves	CH_2ClCH_2Cl	70	17	4	Trace
$PtCl_2$	4 Å sieves	toluene	70	17	4	Trace
$PtCl_2$	4 Å sieves	CH_3CN	70	17	- [c]	- [c]
$PtCl_2$	4 Å sieves	$MeNO_2$	70	17	- [c]	- [c]
$PtCl_2$	H_2O (1 eq.)	CH_2ClCH_2Cl	70	17	7	Trace
Au-**I**	-	CH_2ClCH_2Cl	70	18	Trace	5
$Ph_3PAuCl/AgSbF_6$	-	CH_2ClCH_2Cl	70	18	- [d]	- [d]
$AuCl_3$	-	CH_2ClCH_2Cl	70	18	-	5
Au-**I**	-	CH_2ClCH_2Cl	80	22	6	-
IPrAuCl/AgOTs	-	CH_2ClCH_2Cl	80	22	9	-

[a] Yield determined by NMR spectroscopy calibrated against a known quantity of 1,2,4,5-tetramethylbenzene. [b] Isolated yield. [c] Complex mixture. [d] No reaction.

Mayr's group had recently published a reactivity scale of ylides and electrophiles which suggested a number of electrophiles should, ignoring steric factors, successfully react with ketone-stabilised ylides similar to those being studied (Scheme 76).[111]

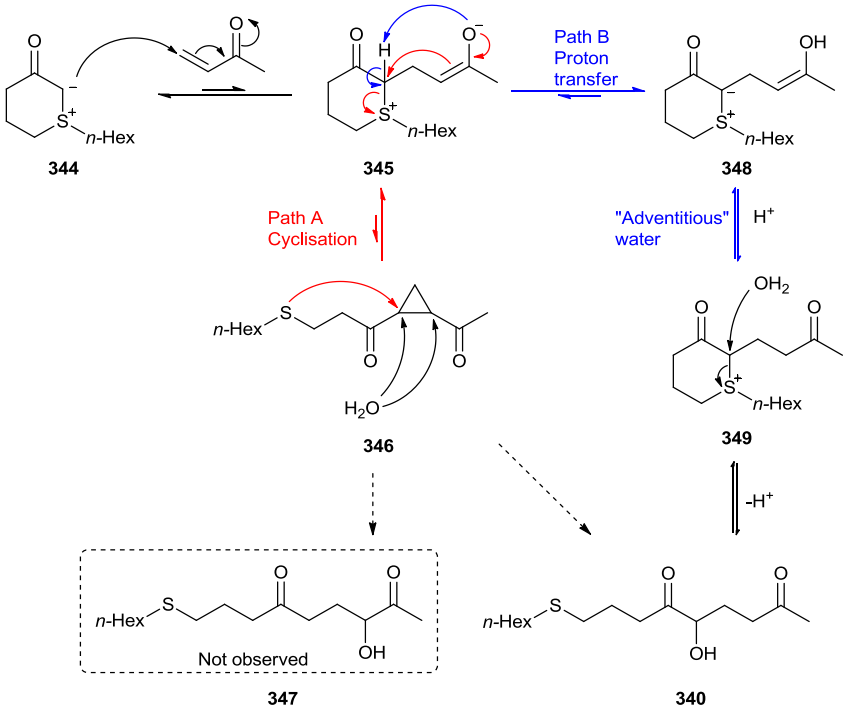


Scheme 76: Electrophiles screened

A range of these electrophiles was screened; however successful trapping of the ylide could not be extended to other electrophiles, these electrophiles proving unreactive, giving only small traces of chlorinated **341** with both platinum and gold catalysts.

Proposed mechanism and rationale

The intermolecular reactivity of the gold-derived six-membered ylide is atypical and, to the author's knowledge, no other three-component ylide couplings of this type have been reported. The observed product may be explained by two plausible reaction mechanisms: ring opening of the desired cyclopropane or equilibration of the ylide (Scheme 77).

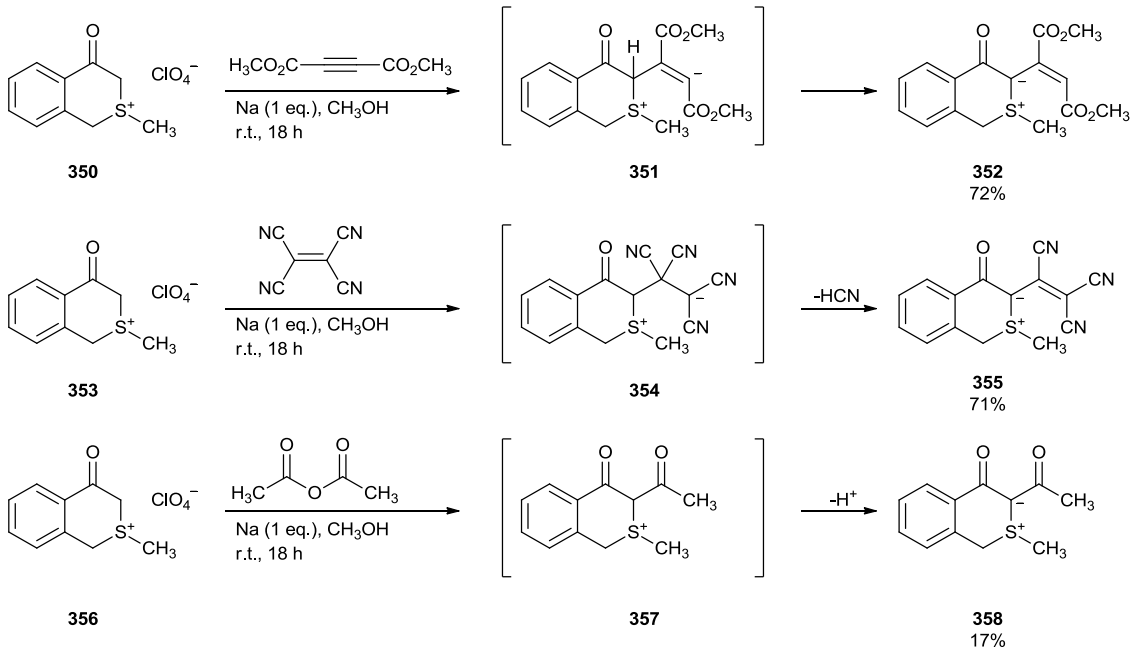


Scheme 77: Proposed mechanism for observed reactivity

The reaction proceeds via nucleophilic attack of ylide **344** (depicted as the ylide resonance form and unligated to the catalyst for simplicity) onto the butenone to form betaine **345**. This has been demonstrated to be a reversible process by Crudden and Aggarwal's groups.[97, 110, 112-114] This addition appears to be the controlling factor for the reaction's tolerance of the screened electrophiles. Unsubstituted butenone undergoes this addition; however the β-substituted enones do not. This is in contrast with acyclic ketone-stabilised ylides which have been demonstrated to react with substituted and unsubstituted enones and alkenes.[115, 116] This may be due to the increased steric demands of the cyclic ylides, as the rigid cyclic structure reduces the conformational freedom of the ylide and betaine, which has been shown to be of significant importance during ylide cyclisations.[110]

Betaine **345** may then cyclise as per acyclic ylide reactivity, with loss of the sulfide, to give the desired cyclopropane (Path A). The observed hydroxy ketone **340** would then arise from ring opening of the cyclopropane **346**, which is known for keto-cyclopropanes in the presence of Lewis acids.[117, 118] This ring opening could conceivably be in competition with ring opening by the tethered sulfide to reform betaine **345**. This pathway is unlikely to be responsible for the observed products as no trace of cyclopropane **346** was detected, including via mass spectrometry of the crude reaction mixtures. More tellingly, regioisomer **347** was also not obtained. This product would arise from ring-opening at the alternative cyclopropane and an approximately 1:1 mixture of regioisomers would be expected from this pathway.

Alternatively, cyclopropanation may be prevented by proton transfer at betaine **345**, regenerating the ylide and forming **348** (Path B). Proton transfer during the reaction of ylides with enones had been studied by Aggarwal *et al* and is particularly prevalent with ketone-stabilised ylides such as these. This is due to the high acidity of the conjugate base and the disparity in acidity between the enolate and ylide (approximately 26.5 and 8.4 respectively, based on acetone and $Bu_2S^+CH_2C(O)Ph$ in DMSO).[119-121] For acyclic ylides, this equilibrium leads to a reduced *e.e.* in the final cyclopropane. This proton transfer has also been observed by Tanaka's group during the reaction of cyclic ylides, albeit derived by classical means (Scheme 78).[93]



Scheme 78: Proton transfer in Tanaka's cyclic ylides

Initial trapping of the ylide by a dipolarophile then leads to proton transfer to reform the ylide (**352**, **355** & **358**), rather than ring closure. In Tanaka's case these ylides were heavily stabilised and no subsequent reactivity was observed, although this did allow them to be successfully isolated.

For the gold-derived cyclic ylide **344**, ring closure to form cyclopropane **346** does not occur, similarly to Tanaka's system. Instead, quenching of the reformed ylide **348** by water, either during the reaction or upon workup, leads to sulfonium **349**. This quenching process has not been previously reported for ylides, however an equivalent process has been postulated by Crudden's group to explain a loss of enantioselectivity in epoxidation reactions.[113, 114] Subsequent nucleophilic attack upon sulfonium ions by water is also a known process and would give the observed keto-alcohol **340** and exclude the formation of regioisomer **347**.[122, 123]

Summary

A gold-catalysed ylide synthesis has been developed, the ylide product of which is able to undergo subsequent intermolecular reaction. This is the first example of ylides derived by gold catalysis reacting in this manner. The reactivity of the ylide is also novel; proton transfer to regenerate the ylide, combined with the incorporation of water has not been reported for cyclic or acyclic ylides.

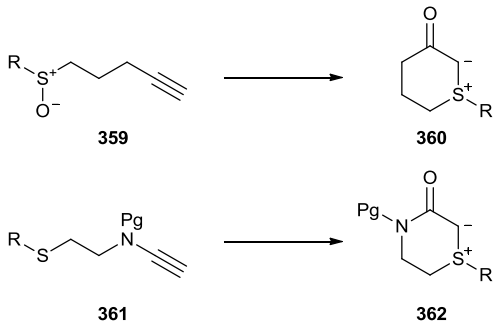
While the objective of trapping the ylide was successfully completed, it was not possible to optimise this procedure to give a viable synthetic reaction.

Chapter 3: Amide-stabilised ylides

Introduction

The previous chapter detailed the development of a gold-catalysed ylide synthesis, which generated an ylide able to undergo an intermolecular reaction. While it was demonstrated that such a reaction was possible, the reactivity of the ketone-stabilised, cyclic ylide was atypical, failing to undergo the desired cyclopropanation. Instead, a three-component coupling incorporating water was observed. The failure of this ylide to undergo cyclopropanation was likely due to the cyclic nature of the ylide and the ketone group which stabilises the ylide anion, lowering its nucleophilicity to the extent that the ylide was unreactive towards β-substituted enones. The ketone stabilisation also resulted in a highly ylidic proton leading to reformation of the ylide, impeding further reactivity.

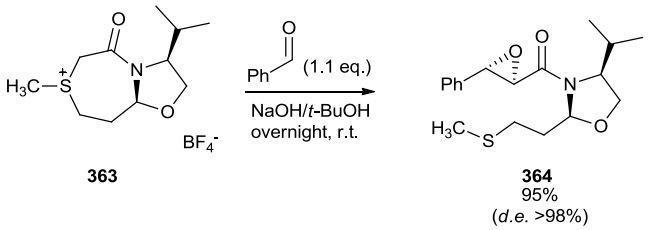
In order to overcome these limitations, the ylide was modified to increase its nucleophilicity and decrease the acidity of the ylidic proton. To accomplish this, the alkyne (**359**) used in the synthesis of the previous substrates was replaced with an ynamide (**361**), in order to obtain an amide-stabilised (**362**) rather than ketone-stabilised ylide (**360**) (Scheme 79).



Scheme 79: Alkyne- vs. ynamide-derived ylide products

Amide-stabilised ylides have been demonstrated to be more nucleophilic than their ketone-stabilised equivalents and the lower acidity of the ylidic proton reduces the likelihood of proton transfer occurring, following betaine formation.[110, 111, 120] Crucially, examples of amide-stabilised, cyclic ylides undergoing classical, intermolecular ylide reactions have been reported. Sarabia's group has demonstrated that cyclic, amide-stabilised ylides derived from Gleason-type chiral auxiliaries can undergo epoxidation reactions with aromatic and aliphatic aldehydes. Epoxidations of this kind are

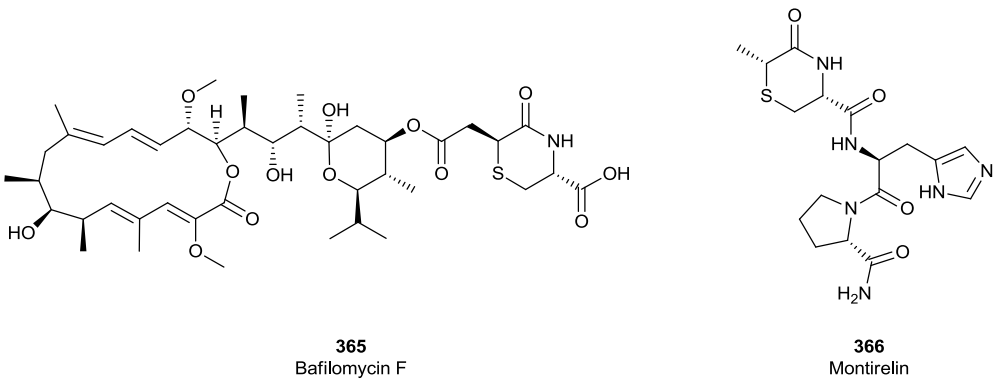
not known for ketone-stabilised, cyclic ylides, therefore Sarabia's results were highly encouraging (Scheme 80).[124]



Scheme 80: Sarabia's epoxidation

Sarabia's protocol used a preformed sulfonium salt (**363**) which was subsequently deprotonated in sodium hydroxide and *t*-butanol. Attack via the convex face of the ylide furnished epoxide **364** in near quantitative yield.

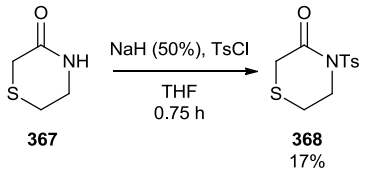
Modifying the targeted ylide also addresses the wider objective of examining the gold-catalysed ylide cascade and exploring its applicability to a wider range of structural motifs. The thiomorpholinone products obtained by employing ynamide triple bonds are also valuable. This moiety is found in the natural product bafilomycin F (**365**), the brain antagonist analogue montirelin (**366**) and has been patented in potential drugs (Scheme 81).[125-127]



Scheme 81: Bafilomycin F (365) and montirelin (366)

Sulfonate-protected thiomorpholinones are particularly useful, having been patented for the treatment of thyroid conditions and multiple sclerosis, but are difficult to access.[128, 129] There are currently no reported syntheses of sulfonate-protected thiomorpholinones. Application of reported

conditions for Boc and alkyl protections gave low yields of the sulfonate-protected thiomorpholinone **368** (Scheme 82).[130]



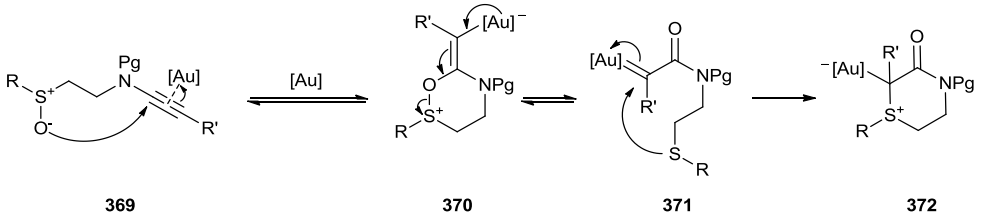
Scheme 82: Tosylation of a simple thiomorpholinone

A successful gold-catalysed approach to protected thiomorpholinones would therefore expand the applicability of gold-catalysed ylide synthesis and allow access to valuable compounds that are not easily available via conventional means.

Sulfoxide oxidants

Intramolecular oxidants

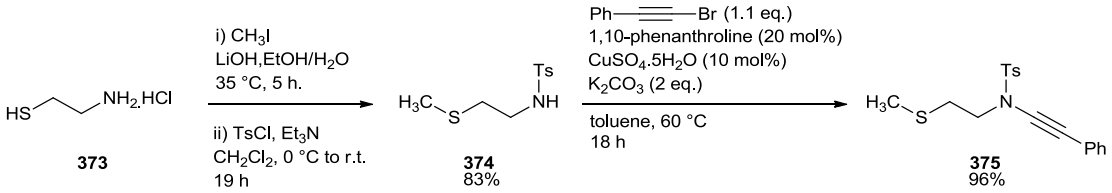
The initial approach to the application of ynamide substrates was to employ the substrate design and reaction conditions which had been successfully applied to the previous alkynyl sulfoxides, with an ynamide moiety replacing the alkyne (Scheme 83).



Scheme 83: Envisaged intramolecular ynamide-based ylide synthesis

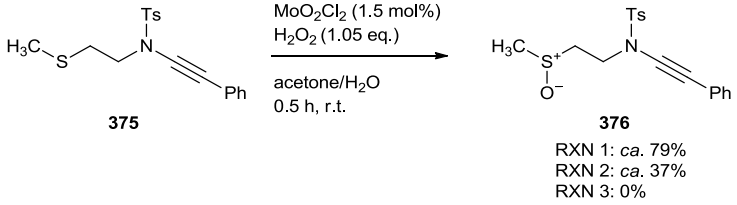
A tosyl group was selected to protect the ynamide as similar structures bearing tethered oxygen atoms had been reported by Hsung's and Y. Zhang's groups.[131, 132] By using cysteamine hydrochloride as the starting material, smaller sulfide substituents were accessible as the sulfide itself was preinstalled, thus making volatile sulfides was unnecessary. This allowed access to the methyl sulfides that had proven difficult to obtain with alkynyl sulfoxide substrates (Scheme 68). A phenyl-substituted ynamide was initially targeted because terminal ynamides have been demonstrated to be

unstable; therefore it was decided to investigate the behaviour of substituted ynamides under gold catalysis before returning to terminal ynamides with a better understanding of their reactivity.[133, 134] The desired ynamide was synthesised in a straightforward manner over three steps (Scheme 84).



Scheme 84: Synthesis of *S*-methyl ynamide

Cysteamine hydrochloride (**373**) was methylated using a modification of Tochtrop's conditions and after workup the resulting reaction mixture was immediately tosylated.[135] Sulfonamide **374** was then converted to the required ynamide **375** using Hsung's copper-catalysed ynamide formation with bromophenyl acetylene.[131] Installation of the sulfoxide was performed using Chand's molybdenum-catalysed procedure (Scheme 85).[136]



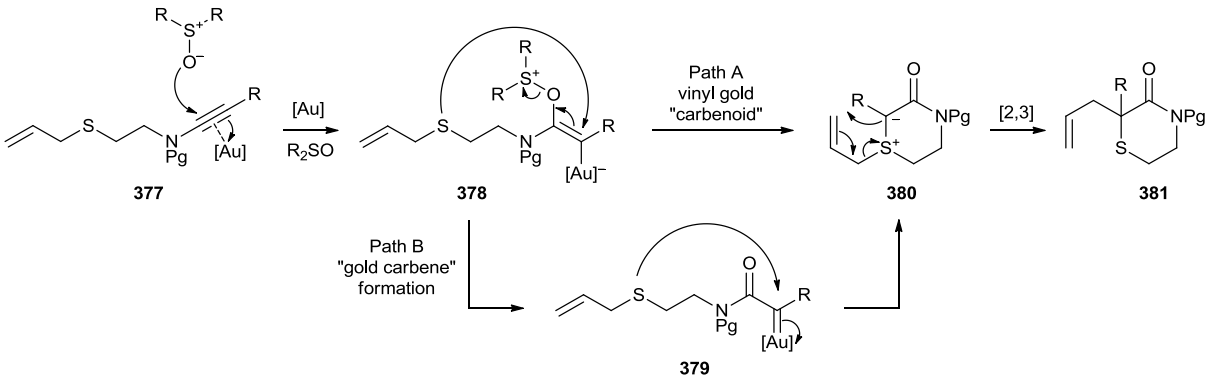
Scheme 85: Molybdenum-catalysed oxidation

Oxidation to the sulfoxide **376** proved capricious, giving varying yields of the desired sulfoxide product. While alternative oxidation conditions may have improved yields of **376**, the sulfoxide was also unstable making it extremely impractical to use. The sulfoxide was not obtained in sufficient purity to test the ylide formation and the decay products were not successfully isolated. It was decided to focus on an intermolecular oxidation strategy, the first examples of which had just been published.[49, 51, 91]

Intermolecular oxidants

Given that the intramolecular sulfoxide oxidant was not feasible, an intermolecular oxidant delivery was envisaged as a suitable replacement. Asensio's and Liu's groups had shown that intermolecular

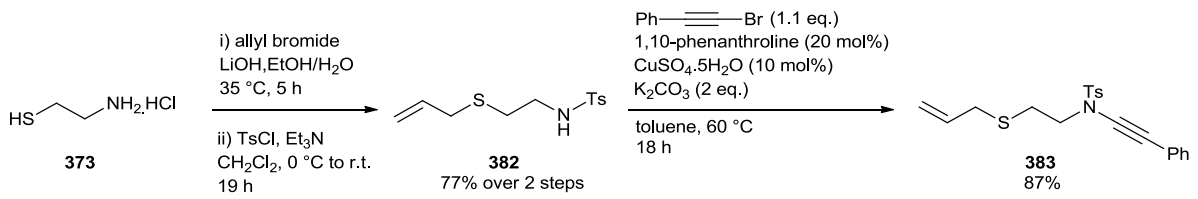
sulfoxides may be used to form vinyl gold species from gold-activated alkynes, which are able to act as carbenoids. C.-Y. Li's group demonstrated that the competing sigmatropic rearrangement, observed by Asensio and Liu, could be avoided.[45, 47, 65] The reaction conditions were expected to vary significantly from the previous intramolecular alkynyl-sulfoxide protocol (Table 5) and controlling the order of reactivity would require careful optimisation to avoid the double oxidation observed previously by Davies and others.[51] With that in mind it was decided to explore the 2,3-sigmatropic rearrangement of these thiomorpholinone ylides first, to obtain viable gold-catalysed cascade reaction conditions before reapplying them to intermolecular ylide reactions. In this way attempting to optimise two unknown processes simultaneously would be avoided. If successful this would also provide access to valuable, functionalised *N*-sulfonyl thiomorpholinone motifs from a readily-obtained starting substrate. Approaching thiomorpholinones in this manner would allow these complex and otherwise inaccessible structures to be obtained (Scheme 86).



Scheme 86: Envisaged intermolecular reaction pathway

Using this intermolecular approach, vinyl gold intermediate **378** would be expected to arise from addition of the gold and sulfoxide to the ynamide **377**. This could then directly cyclise to give the desired ylide **380**, the vinyl gold species **378** in this case acting as a carbenoid (Path A). Alternatively, elimination of the sulfide leaving group would generate a carbene-like, π-bonded gold carbenoid **379** which could also cyclise (Path B). The thiomorpholinone **381** would then form by 2,3-sigmatropic rearrangement of the intermediate ylide **380**. In this manner the readily-available, linear substrate would cyclise, generating a quaternary centre and providing a disubstituted, protected

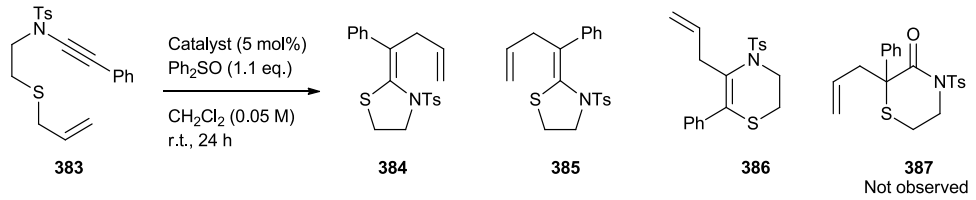
thiomorpholinone in a single synthetic operation. The necessary *S*-allyl ynamide was synthesised in the same manner as **375** (Scheme 87).



Scheme 87: Synthesis of *S*-allyl ynamide

With a substrate capable of undergoing sigmatropic rearrangement in hand, **383** was subjected to gold catalysis with diphenyl sulfoxide as the external oxidant, as employed by Asensio, C.-Y. Li and Liu. Given the significant departure in substrate structure from the alkynyl sulfoxides, re-optimisation was expected to be necessary, therefore initial screening was conducted at room temperature in dichloromethane (Table 6).

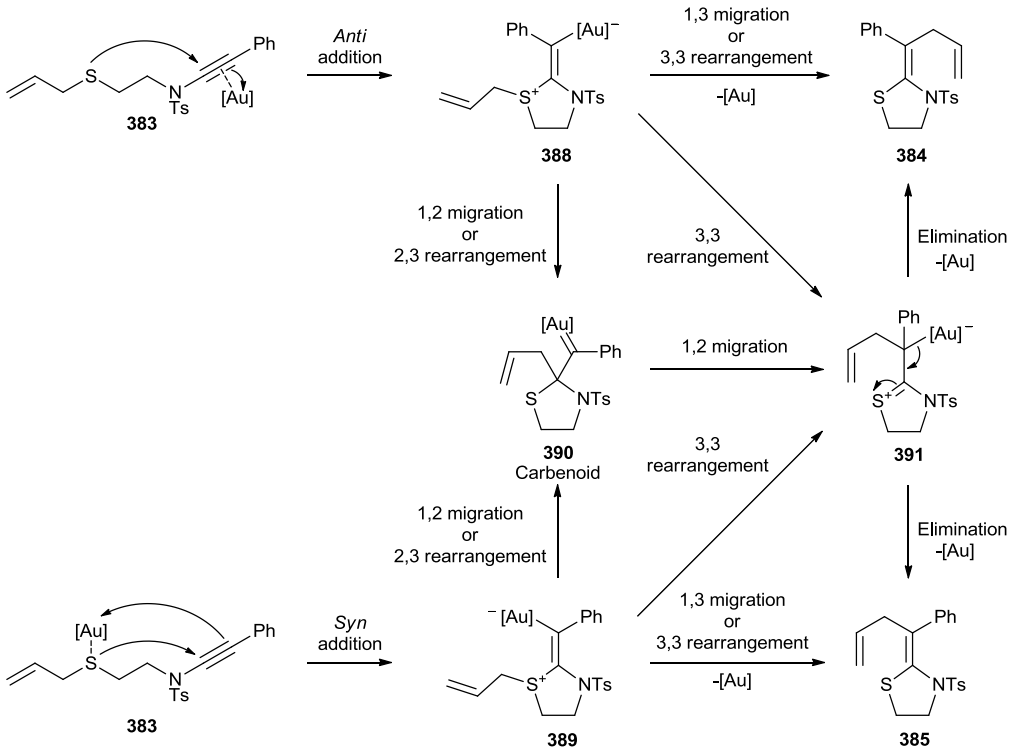
Table 6: Screen of reaction conditions with diphenyl sulfoxide



Entry	Catalyst	Yield of 384 & 385 (%) [a] (Ratio)[b]	Yield 386 (%)[a]	Recovered 383 (%) [a]
1	Au-**I**	8 (1:0) [c]	0 [c]	35 [c]
2	PPh_3AuNTf_2	37 (4:1)	18	0
3	IPrAuCl/AgOTs	45 (3:1)	0	0
4	IPrAuCl/AgOTs [d]	39 (4.5:1)	0	0

[a] Yields and ratios determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene. [b] It was not possible to determine which isomer was the major product. [c] Significant degradation observed, [d] Reaction performed without Ph_2SO.

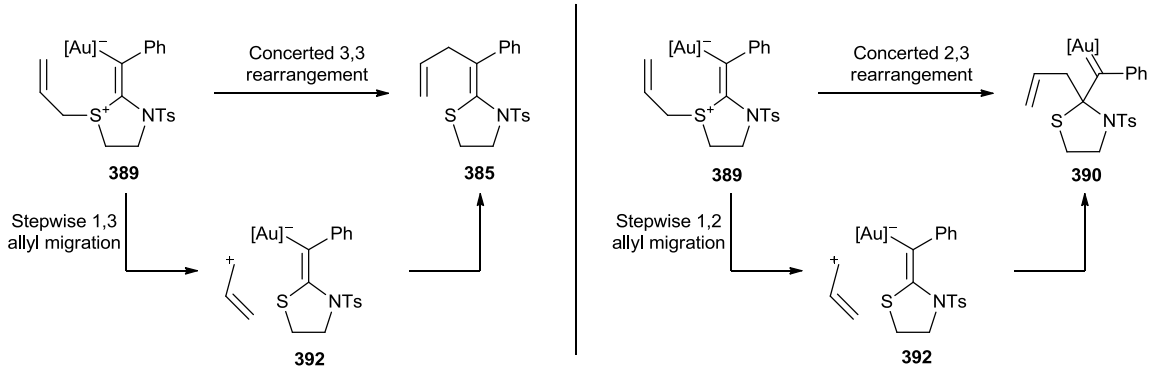
The reaction to form the desired thiomorpholinone **387** was not observed; the oxidant did not attack the ynamide under the reaction conditions and instead the products of a gold-catalysed carbothiolation process were obtained. This was confirmed by conducting the reaction in the absence of an oxidant (Entry 4). A mixture of carbothiolation products were observed for the IPrAuCl and Ph_3PAuCl reactions, however pyridinecarboxylatogold(III) chloride (Entry 1) only gave a poor return of the starting material and very little discernible product. **384** and **385** proved inseparable and it was not possible to determine which stereoisomer was the major product. Mixtures of isomers in gold-catalysed carbothiolations and carboalkoxylations are common.[137-139] Use of Ph_3PAuCl also gave the fascinating, six-membered **386**. Carbothiolation has not previously been reported for ynamides; however the carbothiolation of alkynes under gold catalysis has been extensively explored. **384** and **385** may arise via a number of pathways (Scheme 88).[140]



Scheme 88: Possible pathways to 384 and 385

Initial cyclisation may occur by *anti*-addition of the sulfide to the gold-ligated ynamide to give **388** or by *syn* addition to give **389**.[141, 142] These vinyl gold complexes may then undergo a 1,3 allyl migration or 3,3 sigmatropic rearrangement to give **384** and **385**, respectively. 3,3 Rearrangement may occur

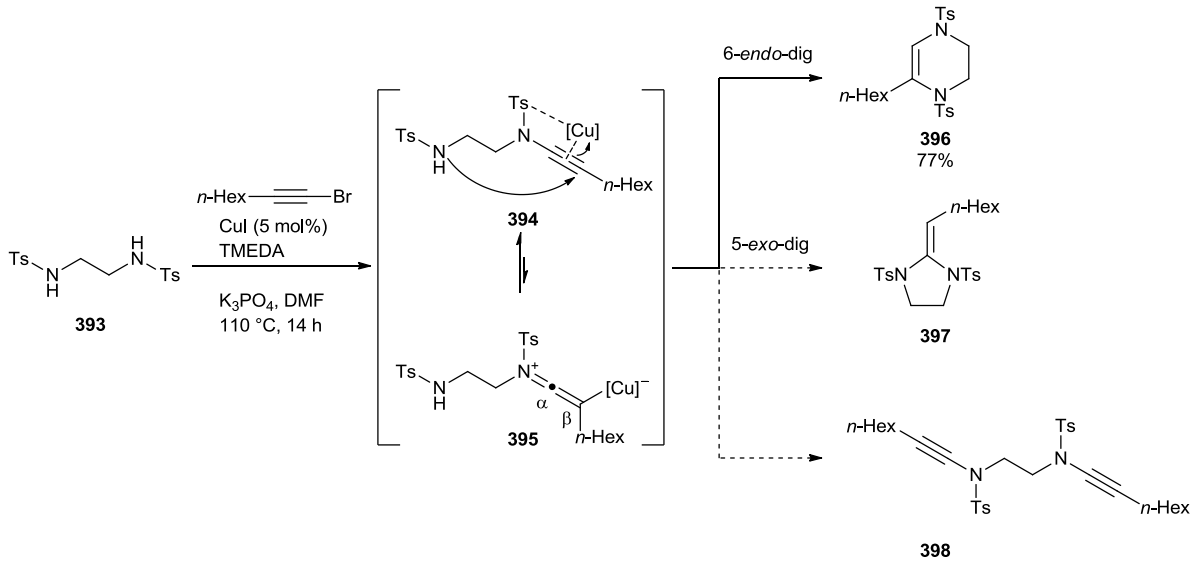
in a single step with concomitant loss of the gold catalyst (e.g. **388** to **384**) or as a two-step process with subsequent elimination of the catalyst (e.g. **388** to **391** to **384**). Alternatively, vinyl complexes **388** and **389** may undergo a 1,2-shift or 2,3-sigmatropic rearrangement to give gold carbenoid **390**. This carbenoid may then undergo a further 1,2-shift, followed by elimination to give a mixture of **384** and **385**, depending upon the conformation during elimination. Carbenoid formation in this manner has been postulated by Nakamura for the rearrangement of benzyl selenonium cations.[143] Each of the rearrangement steps may occur via two mechanisms, as sigmatropic rearrangement pathways compete with stepwise allyl cation formation and migration (**Scheme 89**).



Scheme 89: Stepwise *vs* concerted mechanisms for allyl migration

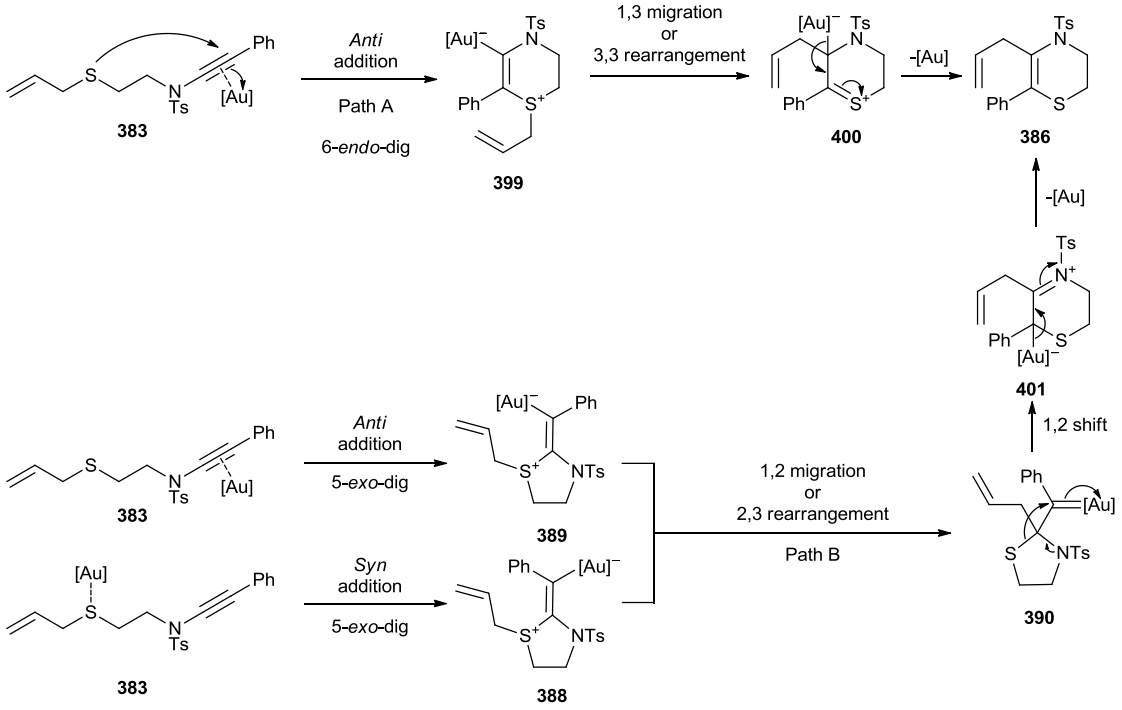
The use of a symmetrical allyl group leads to the same product regardless of the dominating pathway and it is not possible to determine whether allylic inversion, which would indicate a 2,3 rearrangement, is occurring with this migrating group.

The formation of six-membered **386** is especially noteworthy as, upon initial inspection, it appears to form via a 6-*endo*-dig cyclisation, which is unknown for the gold-catalysed cyclisation of ynamides. The only other example of an ynamide reacting in a 6-*endo*-dig fashion under metal catalysis was reported by Urabe's group or a copper-catalysed carboamination. Urabe's group were attempting to form the ynamide **398**, but instead obtained cyclisation product **396** under the ynamide formation conditions (Scheme 90).[144]



Scheme 90: Urabe's copper-catalysed 6-*endo*-dig cyclisation

Ynamides are normally susceptible to nucleophilic addition at the α position, owing to the keteniminium complex **395** that results from ligation to the catalyst.[145, 146] Urabe rationalised the regioselectivity by suggesting that ligation of the copper catalyst to the ynamide is accompanied by ligation to the adjacent tosyl group, forcing the copper to complex at the α position **394**, blocking it from nucleophilic attack and rendering the β position electrophilic.



Scheme 91: Possible pathways to 386

Although nucleophilic addition to the β position has not previously been reported for ynamides under gold catalysis, it could explain the observed product **386** (Scheme 91). 6-*endo*-dig cyclisation of the gold-activated alkyne would give **399**, which could subsequently undergo a 1,3 shift or 3,3 sigmatropic rearrangement to give the observed product **386**. Alternatively, a route via 5-*exo*-dig cyclisation is possible, which does not invoke umpolung ynamide reactivity. After 5-*exo*-dig cyclisation, via a *syn* or *anti* addition, the resulting vinyl gold intermediate may undergo a 1,2-allyl migration or 2,3-sigmatropic rearrangement to generate carbenoid **390**. Ring expansion via a 1,2-shift of the sulfide, followed by elimination, would give the observed product **386**. This route is more plausible, as ring expansion via carbenoids is a known process and it does not require a 6-*endo*-dig cyclisation. [29, 34]

Pyridine *N*-oxide oxidants

The use of sulfoxides as oxidants for the synthesis of thiomorpholinone ylides had proven unsuccessful. Substrates incorporating the sulfoxide were unstable and difficult to obtain reliably. A separate, intermolecular sulfoxide was not sufficiently nucleophilic to oxidise the ynamide substrate and instead competing unoxidised, carbothiolation led to a variety of isomeric products. L. Zhang's and Davies' groups had recently developed methods of obtaining α-keto carbenoids using pyridine *N*-oxides as intermolecular oxidants, therefore it was decided to investigate these oxidants in the place of sulfoxides.[51, 91]

Initial catalyst optimisation

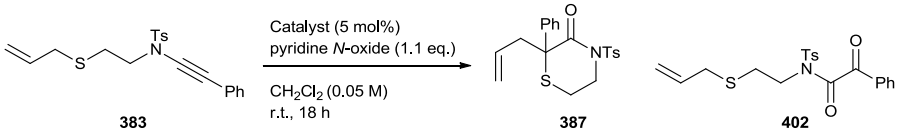
Initial assessment of pyridine *N*-oxides was conducted under the same conditions as the previous diphenyl sulfoxide catalytic screen, in order to provide a direct comparison between the two. Gratifyingly, thiomorpholinone formation was observed using pyridine *N*-oxide, although this was accompanied by an α-diketone, caused by incorporation of a second equivalent of oxidant as observed by Davies and others (Table 7).[2, 65]

Simple gold salts were observed to give similar reactivity (Entries 1 to 4), with consistent yields of **387** and **402** in a 7:4 ratio, regardless of the catalyst oxidation state. Phosphine-ligated gold catalysts

were not suitable (Entries 5 & 6), giving the reverse selectivity and favouring the formation of diketone. The NHC-ligated IPrAuCl proved most effective, providing the highest yield of **387** and the best **387**:**402** ratio of the catalysts screened.

Platinum(II) chloride proved inactive for this transformation, providing only a low yield of **402**. The failure of platinum to catalyse this transformation illustrates the marked difference in reaction conditions between the original alkynyl sulfoxide rearrangements reported by Davies' group, for which platinum was optimal, and the current ynamide/pyridine *N*-oxide pair.[75]

Table 7: Synthesis of thiomorpholinones using pyridine *N*-oxides



383 387 402

Entry	Catalyst	Yield 387 (%) [a]	Yield 402 (%) [a]	Recovered 383 (%) [a]
1	Au-**I**	44	28	14
2	$AuCl_3$	45	29	14
3	AuCl	40	25	22
4	$(CH_3)_2SAuCl$	42	24	13
5	$PPh_3AuCl/AgOTs$	17	39	31
6	PPh_3AuNTf_2	17	37	24
7	IPrAuCl/AgOTs	56	18	13
8	$PtCl_2$	0	10	80

[a] Yields determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene.

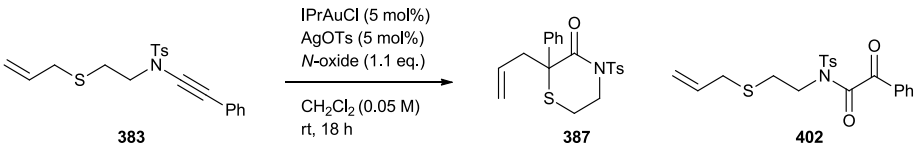
The use of pyridine *N*-oxide had an unexpected benefit: no unoxidised carbothiolation products were observed in any of the above reactions, even for reactions where complete consumption of the oxidant had occurred leaving unreacted starting material. A computational study by L. Zhang's and Houk's groups suggests that pyridine *N*-oxide readily ligates to gold, which may cause activation of the ynamide by the gold catalyst to occur concomitantly with *syn* delivery of the oxidant.[40] This would prevent activation of the ynamide in the absence of oxidant, which would otherwise lead to carbothiolation. The reaction's by-product, pyridine, has been shown to attenuate the catalytic activity of gold. The increasing concentration of pyridine during the reaction may act as a governing

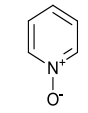
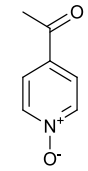
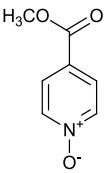
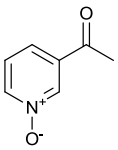
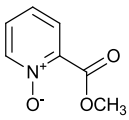
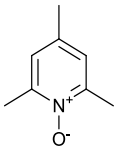
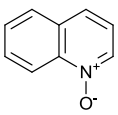
effect; as the oxidant is consumed, the catalytic activity of the gold catalyst is also reduced, preventing undesirable unoxidised carbothiolation from occurring once the *N*-oxide is depleted.

Oxidant optimisation

A wide range of *N*-oxides have been reported as potential oxidants for intermolecular carbenoid formation.[49, 52, 53]

Table 8: Oxidant screen



Entry	Oxidant	Yield 387 (%) [a]	Yield 402 (%) [a]	Recovered 383 (%) [a]
1		56	18	13
2		5	9	0
3		0	18	0
4		19	16	0
5		17	34	0
6		5	7	76
7		22	34	30

[a] Yields determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene.

It was hoped that careful tuning of the oxidant's steric and electronic factors could reduce diketone formation without impacting upon the yield of thiomorpholinone (Table 8). Elaboration of the oxidant structure did not, however, provide any benefit over unsubstituted pyridine *N*-oxide. In all cases except for 3-acetylpyridine *N*-oxide (Entry 4), the yield of thiomorpholinone **387** was significantly reduced and exceeded by the yield of diketone **402**.

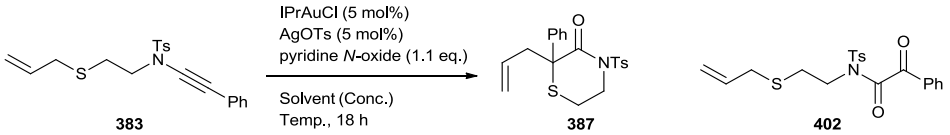
Mesitylene *N*-oxide was curiously unreactive, giving significant return of unreacted starting material but no unoxidised carbothiolation products. It is possible that the *N*-oxide sequesters the available gold catalyst but the additional steric bulk of the *N*-oxide prevents reaction with the ynamide. Alternatively, the bulk of the oxidant may otherwise retard the catalytic cycle, capturing the gold catalyst within the impeded catalytic cycle and preventing it from initiating carbothiolation.

Solvent optimisation

With a suitable oxidant established, attention was focused on improving the overall yield of the reaction by tuning the remaining reaction conditions. A range of aprotic solvents were screened; temperature and concentration were also varied (Table 9). Addition of molecular sieves was not beneficial, a result also observed by Davies' group for ylides derived from alkynyl sulfoxides (Entry 2).[75]

Of the solvents examined, acetonitrile proved the most efficient (Entry 6). This is possibly due to its ability to stabilise the active gold cation, which is generated by precipitation of silver(I) chloride by the reaction of the IPrAuCl and silver(I) tosylate precatalysts.[147] Reducing the reaction concentration by a factor of two had a negligible improvement in overall yield and reduction in doubly oxidised by-product (Entry 7). Reducing the concentration further was not beneficial (Entry 8), nor was elevating the reaction temperature (Entry 9).

Table 9: Screen of further variables



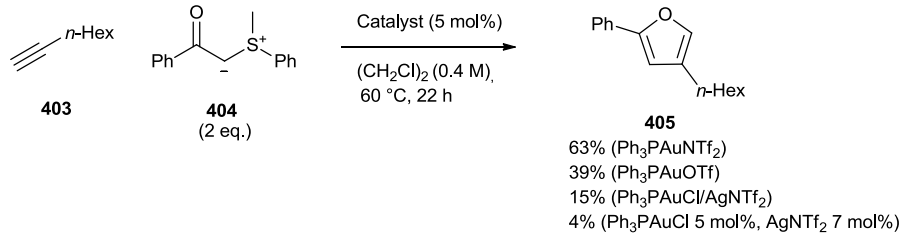
Entry	Solvent	Temperature (°C)	Concentration (M)	Yield 387 (%) [a]	Yield 402 (%) [a]	Recovered 383 (%) [a]
1	CH_2Cl_2	r.t.	0.1	56	18	13
2	CH_2Cl_2 [b]	r.t.	0.1	44	18	15
3	$CHCl_3$	r.t.	0.1	37	26	14
4	toluene	r.t.	0.1	0	0	51
5	THF	r.t.	0.1	- [c]	- [c]	- [c]
6	CH_3CN	r.t.	0.1	73	23	12
7	CH_3CN	r.t.	0.05	74 [d]	17 [d]	7 [d]
8	CH_3CN	r.t.	0.025	59	18	14
9	CH_3CN	40	0.1	65	13	5

[a] Yields determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene. [b] Reaction conducted in the presence of 4 Å mol. sieves. [c] Degradation. [d] Average of two experiments.

Co-catalyst

The neutral NHC and phosphine-ligated gold (I) catalysts were screened in the presence of a silver co-catalyst. The role of the co-catalyst is to provide the gold catalyst with a vacant coordination site by removal of chloride, precipitated as silver(I) chloride, as the gold-chlorine bond is close to covalent in nature and the chloride is otherwise not sufficiently labile to allow efficient catalysis to occur.[148] Depending upon the reaction conditions, some gold-catalysed protocols have been shown to be extremely sensitive to the nature of the silver co-catalyst and the way it is employed. In 2012 Shi's group reported that the presence of silver catalysts in the reaction mixture can change the nature of the gold catalyst, as observed by ^{31}P NMR spectroscopy. Shi showed that IPrAuCl/$AgSbF_6$, IPrAuSbF_6 and IPrAuSbF_6/$AgSbF_6$ precatalyst mixtures can all behave differently and that for some reactions the

presence of excess silver or precipitated silver(I) chloride is necessary, and in other reactions it must be avoided.[149] This is aptly demonstrated by Skrydstrup's gold-catalysed furan synthesis, in which the presence of silver was detrimental to the reaction (Scheme 92).



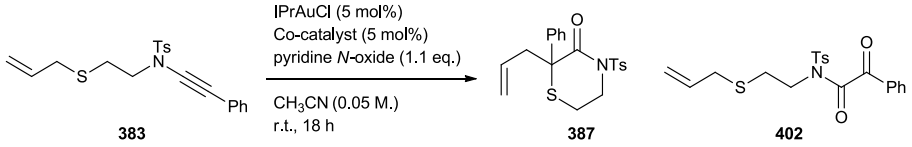
Scheme 92: Skrydstrup's gold-catalysed furan synthesis

Skrydstrup observed the addition of a sulfonium ylide (**404**) to a gold-activated alkyne (**403**) in the presence of Gagosz's pre-complexed gold(I) triflimidate, to give a disubstituted furan (**405**).[150] Catalysts prepared from a mixture of gold and silver salts however proved extremely detrimental and the addition of excess silver(I) triflimidate proved to be even poorer.[76] The source of this silver effect may be attributed to bimetallic gold-silver interactions during the catalytic cycle or co-operative gold and silver catalysis resulting in a more efficient catalytic cycle than for gold alone. Mixtures of gold and silver catalysts have been isolated as gold-silver-gold tri-metallic complexes.[151] Gold-gold organometallic resting states have been isolated and characterised and complexes which are believed to be gold-silver organometallic species have been observed via NMR spectroscopy.[142, 152, 153] Other metal additives have been observed to modify the reactivity of the gold catalysis, gold and ytterbium displaying similar discrepancies in ^{31}P NMR to gold-silver solutions.[38]

The nature of the counterion can also be key; its basicity can influence the longevity of the active catalyst and in extreme cases it may play a part in the catalytic cycle, influencing the final product distribution.[148, 154-156] Based upon these reports, a screen of silver co-catalysts was conducted in order to optimise the transformation and determine whether the reaction was dependent upon the presence of silver. Modifying the silver precatalyst counterion gave very little variation in yield, although tosylate was marginally superior. Silver(I) tosylate was selected as the chosen co-catalyst owing to its air stability and lower cost compared to the triflimidate and hexafluoroantimonate salts.

Silver was omitted from the reaction mixture entirely by preparing an equimolar solution of IPrAuCl and AgOTs in dry acetonitrile and removing the silver(I) chloride precipitate by filtration through Celite, as per Shi's protocol (Entry 4).[149] Removal of the silver significantly reduced the yield of desired thiomorpholinone, with only a small portion of starting material recovered, however double oxidation product **402** was also suppressed.

Table 10: Screen of co-catalysts



Entry	Catalyst	Co-catalyst	Yield 387 (%) [a]	Yield 402 (%) [a]	Recovered 383 (%) [a]
1	IPrAuCl	AgOTs	74 [b]	17 [b]	7 [b]
2	IPrAuCl	$AgSbF_6$	70	26	10
3	IPrAuCl	$AgNTf_2$	74	20	6
4	IPrAuOTS	-	29	- [d]	6
5	-	AgOTs	0	0	>95
6	IPrAuCl [c]	AgOTs [c]	66	14	12
7	$HOTf.H_2O$	-	- [e]	- [e]	- [e]

[a] Yields determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene. [b] Average of two experiments. [c] 2.5 mol% catalyst. [d] Complex mixture. [e] Degradation.

The reactivity of IPrAuCl is in contrast to that of the phosphine-ligated gold catalysts investigated during the initial catalyst screen (Entries 5 & 6). While the NHC-gold complex reaction conditions display a pronounced dependency upon the presence of silver, phosphine-gold-catalysed reactions do not, giving extremely similar results regardless of the presence of silver (Table 7).

Conducting the reaction in the presence of silver(I) tosylate alone did not result in activation of the ynamide, suggesting that the effect upon the NHC-gold-catalysed reaction is the result of bimetallic or cooperative catalysis, rather than solely the silver. The catalyst and co-catalyst loading was reduced to 2.5 mol%, however this was accompanied by a moderate reduction in thiomorpholinone **387** yield (Entry 6).

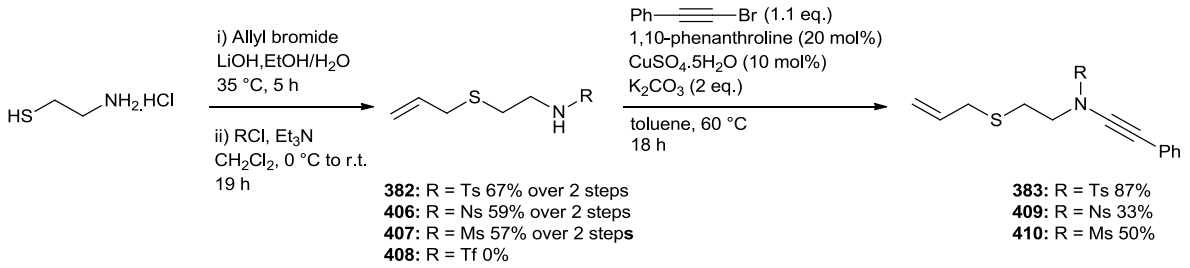
Brønsted acids have been demonstrated to catalyse reactions involving ynamides, as have electrophilic halides, therefore tosic acid was tested as a possible catalyst, unfortunately only a complex mixture of products was observed, none of which was the desired thiomorpholinone **387**.[157]

Substrate elaboration

With optimised conditions for thiomorpholinone formation obtained, employing 5 mol % of IPrAuCl and AgOTs in acetonitrile, attention turned to exploring the substrate scope for this transformation. This accomplished two goals: obtaining a range of valuable thiomorpholinones and simultaneously surveying the ylides accessible through this gold-catalysed cascade.

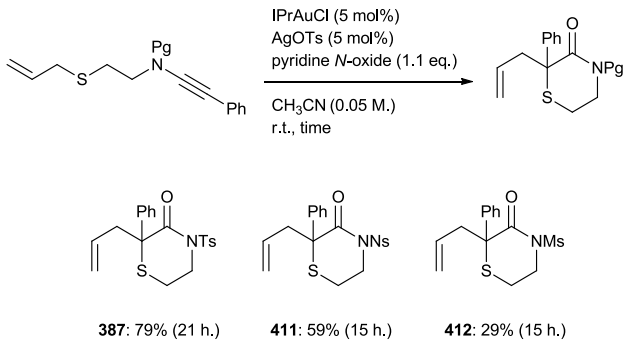
Sulfonamide variation

Initial screening focused on the variation of the sulfonamide protecting group. A range of *N*-sulfonamide-protected ynamides were synthesised, although a triflyl-protected ynamide was not successfully obtained, the reaction mixture underwent severe degradation (Scheme 93).



Scheme 93: Synthesis of various sulfonamide-protected ynamides

The ynamides were duly subjected to the optimised thiomorpholinone-forming conditions until each reaction reached completion (Scheme 94).

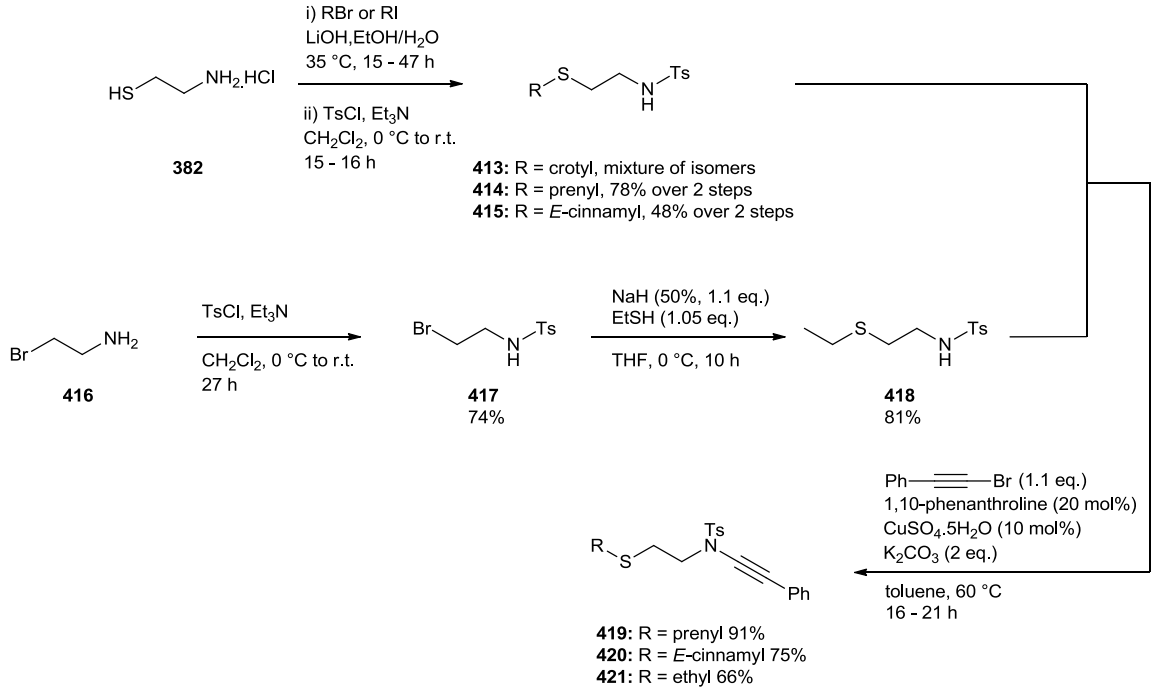


Scheme 94: Synthesis of various sulfonamide N-protected thiomorpholinones

The isolated yield of *N*-tosyl thiomorpholinone **387** was pleasingly higher than observed during the NMR spectroscopy optimisation study, owing to the larger reaction scale. Modifying the electron withdrawing effect of the sulfonamide resulted in decreased yields for the *N*-mesyl and *N*-nosyl thiomorpholinones **411** and **412**.

Migrating group variation

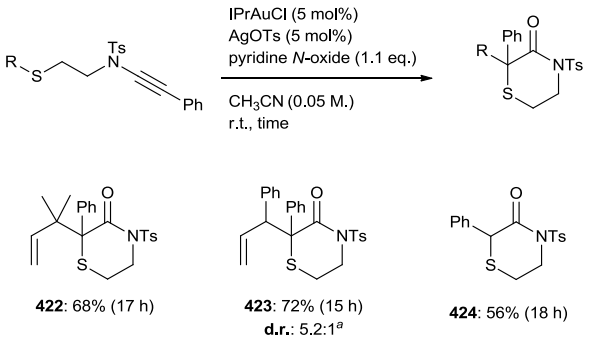
Exploration of a range of migrating groups followed (Scheme 95). The migratory aptitude of substituted allyl moieties was investigated to assess the reactivity of the amide-stabilised ylide.



Scheme 95: Synthesis of a variety of sulfides

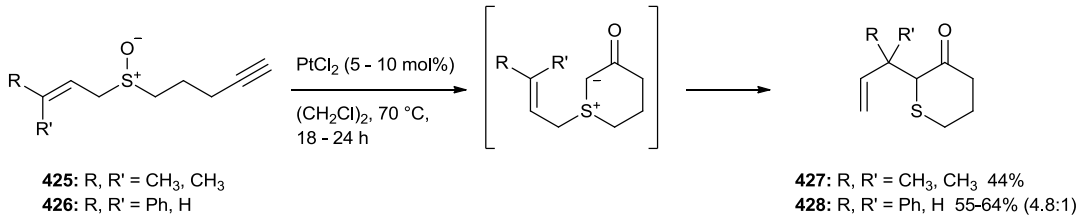
The regiochemistry of the products would also provide insight into the mechanism of the migration. *S*-Prenyl and *S*-cinnamyl ynamides **419** and **420** were readily obtained with the standard ynamide

synthetic sequence. The *S*-crotyl sulfonamide **413** was obtained as an inseparable mixture of regioisomers, caused by allylic inversion (S_N2') during sulfide formation and therefore was not suitable for assessing migrating group aptitude. An *S*-ethyl ynamide **421** was also synthesised, using a modified sequence via tosylation of 2-bromoethanamine **416** and nucleophilic substitution with ethanethiol.



Scheme 96: Migratory aptitude of a variety of ylide substituents

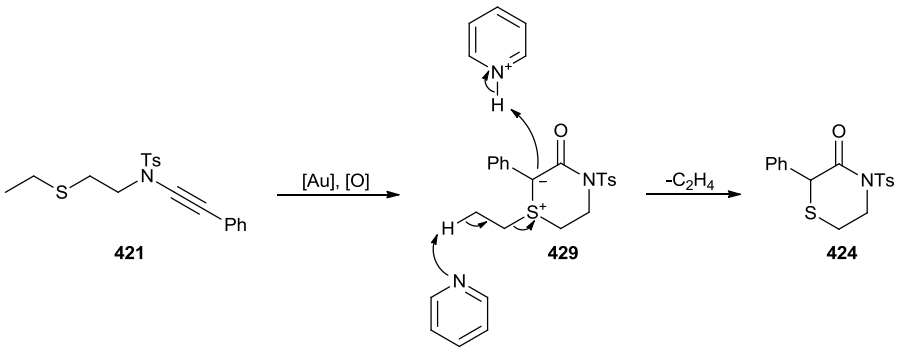
The substituted *S*-allyl ynamides were transformed to the corresponding thiomorpholinones with only a small reduction in yield compared to **387** (79%) (Scheme 96). Complete allylic inversion was obtained, suggesting that the rearrangement is proceeding exclusively via a 2,3-sigmatropic rearrangement pathway and that 1,3 allyl migration is not occurring. The amide-stabilised ylides proved to be more reactive than the ketone-stabilised ylides reported by Davies' group, which were also unsubstituted at the α position (Scheme 97).[75] The heavily substituted thiomorpholinone **422** is of note, as the synthesis of this thiomorpholinone by existing synthetic routes would be extremely challenging but is easily obtained via gold catalysis.



Scheme 97: Davies rearrangement of substituted allyl groups

The yields of thiomorpholinone were extremely promising, as it confirmed that the thiomorpholinone ylides were more reactive than their ketone-stabilised counterparts. This justified

the investigation into thiomorpholinone ylides as their increased reactivity makes them more suitable for intermolecular reactions.

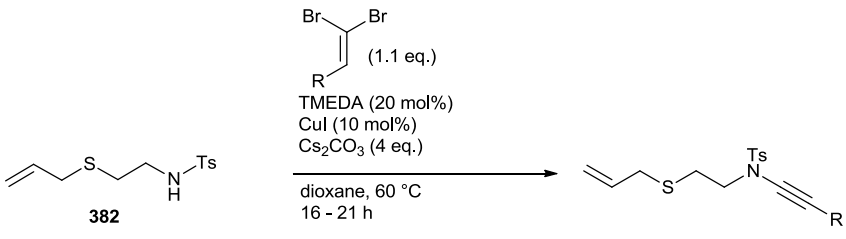


Scheme 98: Elimination of an *S*-ethyl ylide

Use of *S*-ethyl ynamide **421** was also successful, the ethyl moiety eliminating under the basic reaction conditions to quench the ylide **429** and allow access to α-monosubstituted thiomorpholinones such as **424** (Scheme 98).

Ynamide variation

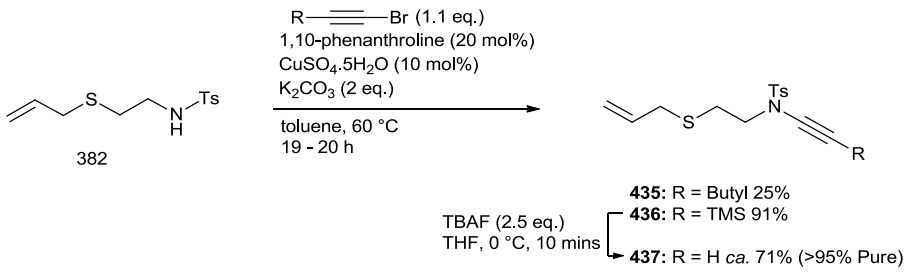
Variation of the ynamide substituent was also examined. The desired ynamides could be easily obtained from dibromo alkenes using Evano's ynamide formation procedure, formed by Wittig olefination of the corresponding aldehyde (Scheme 99).[158, 159]



430: R = 4-MePh 44%
431: R = 4-MeOPh 27%
432: R = 4-$MeCO_2$Ph 56%
433: R = 4-FPh 53%
434: R = 2-furanyl 49%

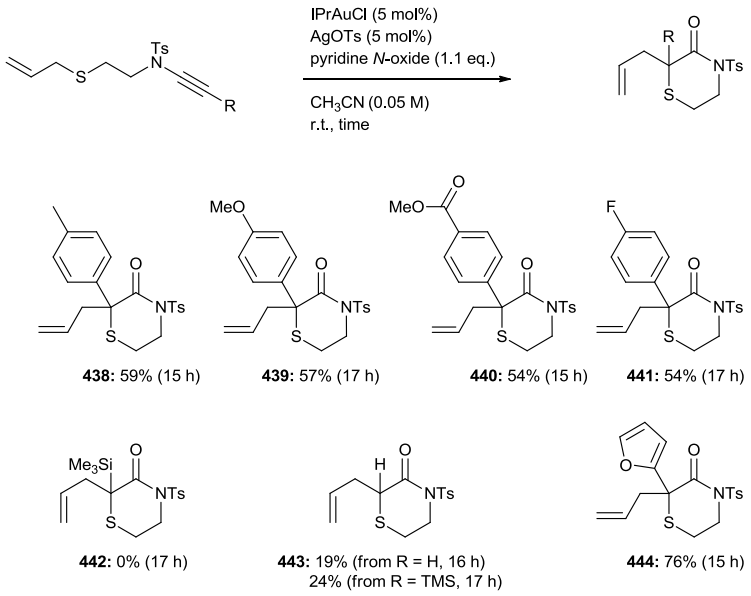
Scheme 99: Synthesis of a variety of substituted ynamides via Evano's protocol

A range of ynamides bearing electron-withdrawing and -donating aromatic groups were successfully synthesised from dibromo olefins, obtained from readily available aldehydes. Alkyl-, terminal- and silane-protected thiomorpholinones were also synthesised, using Hsung's conditions (Scheme 100).[160]



Scheme 100: Synthesis of a variety of substituted ynamides via Hsung's protocol

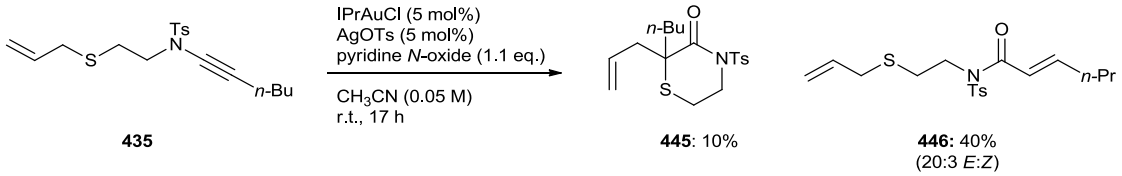
When subjected to the established conditions all of the synthesised ynamides successfully underwent thiomorpholinone formation (Scheme 101).



Scheme 101: Synthesis of various 2-substituted thiomorpholinones

Aromatic substituents were tolerated well, with electron-withdrawing and -donating substituents accepted by the gold-catalysed cascade. The silane-substituted ynamide **436** was desilylated under the reaction conditions, only giving monosubstituted thiomorpholinone **443**. Desilylation of protected triple bonds under gold catalysis is a known side reaction in a number of processes.[161] Terminal ynamide **437** proved extremely unstable, rapidly decaying under high vacuum while drying. It was subjected to the reaction conditions immediately after drying, however the low yield of **443** is likely due to continued degradation under the reaction conditions. Terminal tosyl ynamides have been reported to be unstable by other groups, so the low yield is not surprising.[162] The exact nature of the degradation products was investigated by allowing a portion of the ynamide substrate to

decay, however a complex mixture of products was obtained, rather than a single rearrangement product.



435 **445**: 10% **446:** 40% (20:3 *E*:*Z*)

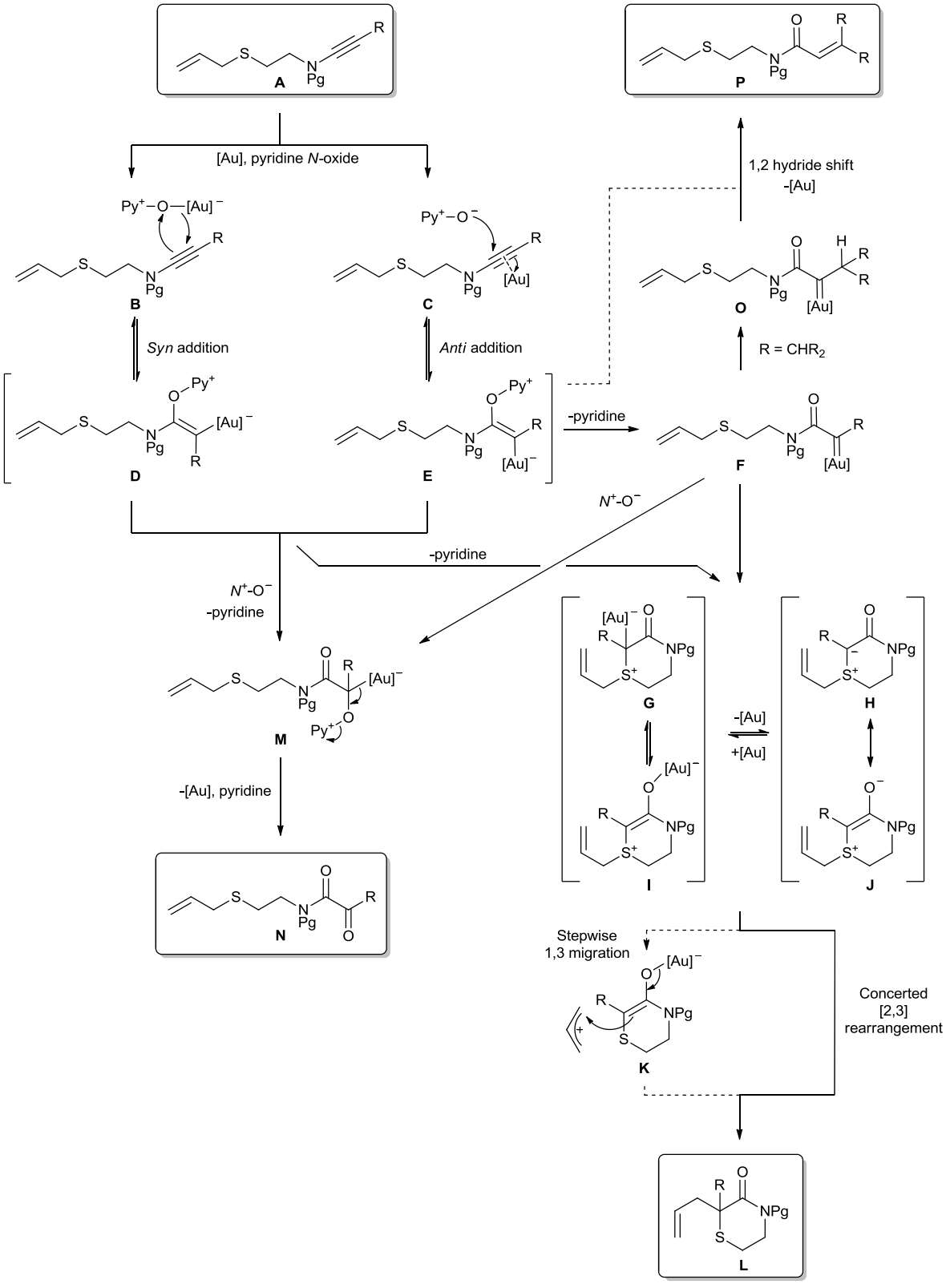
Scheme 102: Competing 1,2-hydride shift and ylide formation

Alkyl-substituted ynamide **435** gave only a low yield of the desired thiomorpholinone **445**, the major product being enamide **446** (Scheme 102). The formation of enamide **446** gives an insight into the catalytic cycle, as it arises from a formal 1,2-hydride shift, implying strong carbene character is present in the intermediate gold-carbenoid complex.[47, 51]

Proposed reaction mechanism

Based on the observed reactivity during optimisation of the catalytic cycle and substrate elaboration, the mechanistic scenario below is proposed (Scheme 103). Activation of the ynamide by the gold catalyst may occur in one of two ways; via a concerted syn addition of the catalyst and oxidant to give D or a stepwise activation of the ynamide followed by *anti*-addition of the oxidant to the gold-activated ynamide, giving E. Isolated and characterised intermediates resulting from both *syn* and *anti* gold-catalysed additions to triple bonds have been reported, although not for pyridine *N*-oxides.[40, 141, 142, 163]

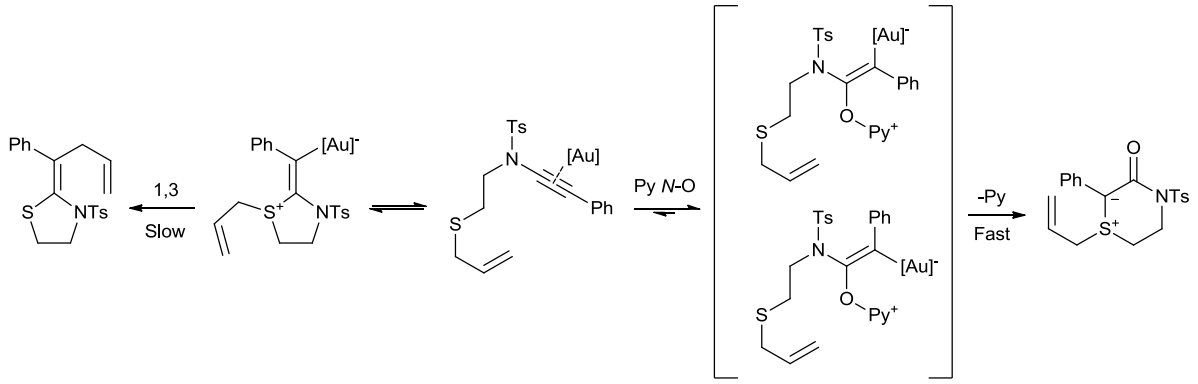
Zhang's group has suggested that the intermolecular addition of pyridine *N*-oxides to triple bonds is more likely to occur in a *syn* than *anti* fashion. Zhang's computational study indicated that strong interaction between the *N*-oxide and gold catalyst is responsible for this *syn* addition and suggested there is no viable transition state for *anti*-addition. *Syn* addition could explain why unoxidised carbothiolation was not observed to compete with oxidised thiomorpholinone formation.



Scheme 103: Proposed reaction mechanism for gold-catalysed thiomorpholinone formation

Strong gold-*N*-oxide bonding would cause the gold catalyst to be immediately sequestered by the *N*-oxide, preventing the gold catalyst from activating the ynamide without simultaneously delivering the oxidant, as depicted by **B**. The lack of unoxidised carbothiolation (**Table 6**) could also be

explained if the rate of 1,3 migration is significantly slower than the rate of irreversible pyridine loss from **D** or **E**, leading to overall thiomorpholinone ylide formation, assuming the initial carbothiolation step is reversible (Scheme 104).



Scheme 104: Competing carbothiolation and oxidation

After the initial activation and oxidation of the ynamide, **D** and **E** may lose pyridine to generate carbenoid **F**. Alternatively, immediate cyclisation of **D** and **E** may lead directly to thiomorpholinone ylides **G** – **J**. Of these two possibilities, carbenoid **F** formation is more likely, owing to the observation of enamide **P** for alkyl-substituted ynamides. While **D** and **E** may be considered carbenoids due to the electrophilic carbon α to the gold, other reactions that have strong evidence suggesting that they proceed via an equivalent vinyl gold ether do not undergo a 1,2-hydride shift and therefore "carbene" **F** is necessary to explain the formation of **P**.[45, 47]

Doubly oxidised product **N** may arise from the addition of a second molecule of oxidant to **D**, **E** and **F**.[51] Whether the gold-bound ylide exists in the Au-C ylide or Au-O enolate form is unknown, however stabilised ylides do display enolate character, with some ketone-stabilised ylides possessing sufficient enolate character to display *E*/*Z* isomerism.[164] Similarly, it is not known whether the metal-catalysed 2,3-sigmatropic rearrangement of ylides occurs via a metal-bound or free ylide; although Wang has shown that for copper-catalysed ylide formation, and subsequent 2,3 rearrangement, the ylide exists as an equilibrium of the free and metal-bound ylides.[165]

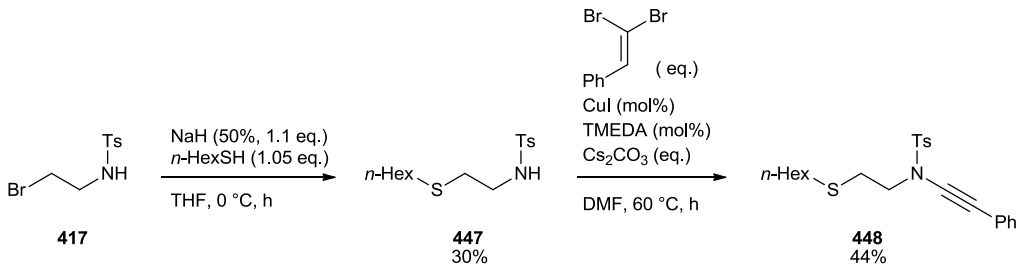
Rearrangement of the ylide to give the final thiomorpholinone **L** may conceivably occur by a direct 2,3-sigmatropic rearrangement or a stepwise 1,3 migration via an allyl cation and gold complex **K**.[140]

Given that complete allylic inversion was observed for all the substituted allyl moieties examined, a 1,3 migration is extremely unlikely.

Application

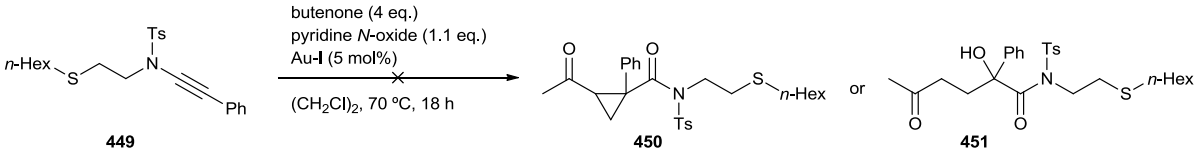
Intermolecular reactions

Having successfully optimised suitable conditions to access and quench thiomorpholinone ylides with a sigmatropic rearrangement, the next objective was the extension of these conditions to intermolecular reactions. These amide-stabilised ylides had proven to be more reactive than their ketone-stabilised equivalents for intramolecular reactions. The application of an amide-stabilised ylide was therefore considered to be a potential means of solving the problems observed when attempting to develop an intermolecular ylide reaction, with ketone-stabilised ylides, as detailed in Chapter 2. During development of the ynamide-based 2,3-sigmatropic rearrangement it became apparent that pyridine *N*-oxides were capable of ylide formation by intermolecular oxidation. An ynamide that could undergo reaction with pyridine *N*-oxide, based upon the previously examined alkynyl sulfoxide system, was therefore synthesised. A substituted ynamide was unfortunately necessary as terminal ynamides had proven highly unstable and low-yielding for thiomorpholinone formation (Scheme 105).



Scheme 105: Synthesis of a *S*-hexyl ynamide

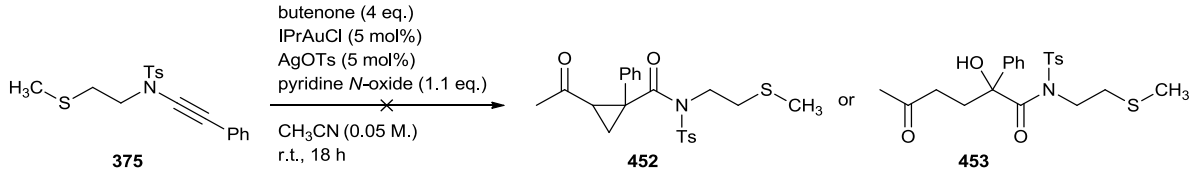
The ylide was subjected to gold catalysis using Davies' original conditions for ylide formation, with pyridine *N*-oxide as the oxidant and butenone as the electrophile (Scheme 106).[75]



449 450 451

Scheme 106: Application of Davies' ylide-forming conditions to intermolecular oxidants

Davies' reaction conditions did not give the desired cyclopropane or the previously observed keto-alcohol. Once fully optimised reaction conditions for 2,3-sigmatropic rearrangement of thiomorpholinone ylides had been obtained these were reapplied to a modified ynamide, bearing an *S*-methyl moiety in place of the *S*-hexyl, to reduce steric bulk at the sulfonamide (Scheme 107).

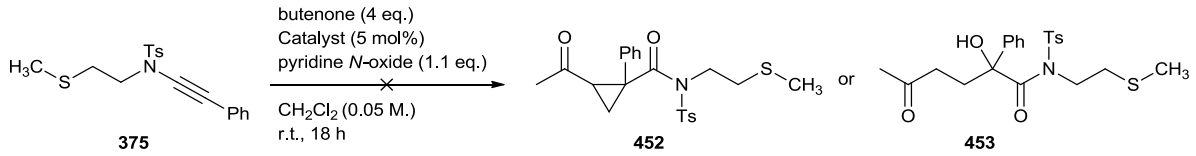


375 452 453

Scheme 107: Attempted intermolecular trapping of a thiomorpholinone ylide

Subjecting ynamide **375** to the optimised thiomorpholinone ylide-forming conditions in the presence of butenone was unsuccessful. The desired cyclopropanation product **452** was not observed nor was replication of the three-component coupling obtained using ketone-stabilised ylides **453**. Small traces of doubly oxidised product were observed, which indicated that activation of the ynamide was proceeding, however this was in such low yield that it could not be isolated. Given the failure of the reaction conditions optimised for sigmatropic rearrangement it was decided to re-optimise with the aim of developing more conducive conditions for intermolecular ylide reaction (Table 11). A number of catalysts that had previously proven successful for the intermolecular reaction of ketone-stabilised ylides were screened. Dichloromethane replaced acetonitrile as the reaction solvent as Aggarwal's group have shown that amide-stabilised ylides can be forced to react with butenone in this solvent.[110] These catalysts were not successful and formation of **452** or **453** was not observed. Moreover, significant decomposition of the ynamide starting material occurred, in contrast to the alkynyl sulfoxide system.

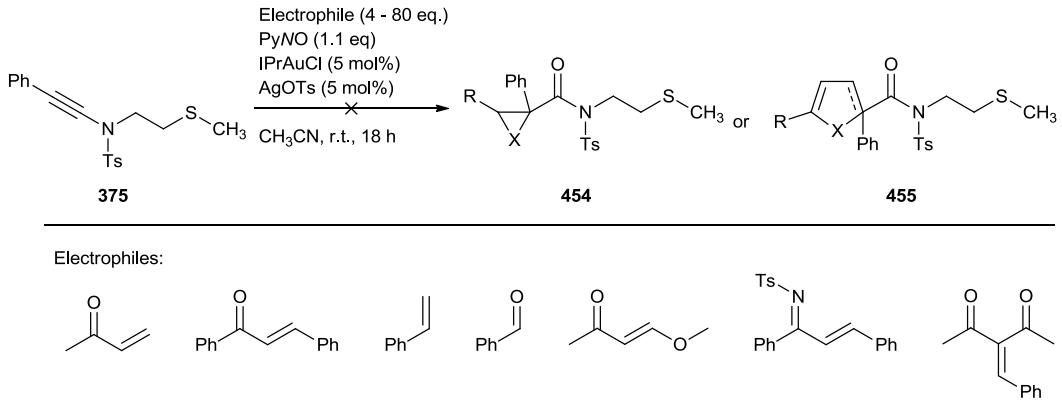
Table 11: Attempted intermolecular trapping of a thiomorpholinone ylide



Entry	Catalyst	Yield 452 (%) [a]	Yield 453 (%) [a]	Recovered 375 (%) [a]
1	IPrAuCl /AgOTs	0	0	12
2	Au-**I**	0	0	18
3	$PtCl_2$	0	0	c.a. 85
4	PPh_3AuNTf_2	0	0	24

[a] Yields determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene.

Attention turned to variation of the electrophilic trap for the ynamide. Given the narrow window of reactivity observed for ketone-stabilised ylides, rescreening of the nucleophile was conducted to ensure that the butenone electrophile was not responsible for the lack of reactivity or degradation (Scheme 108).



Scheme 108: Screen of electrophiles for reaction with thiomorpholinone ylides

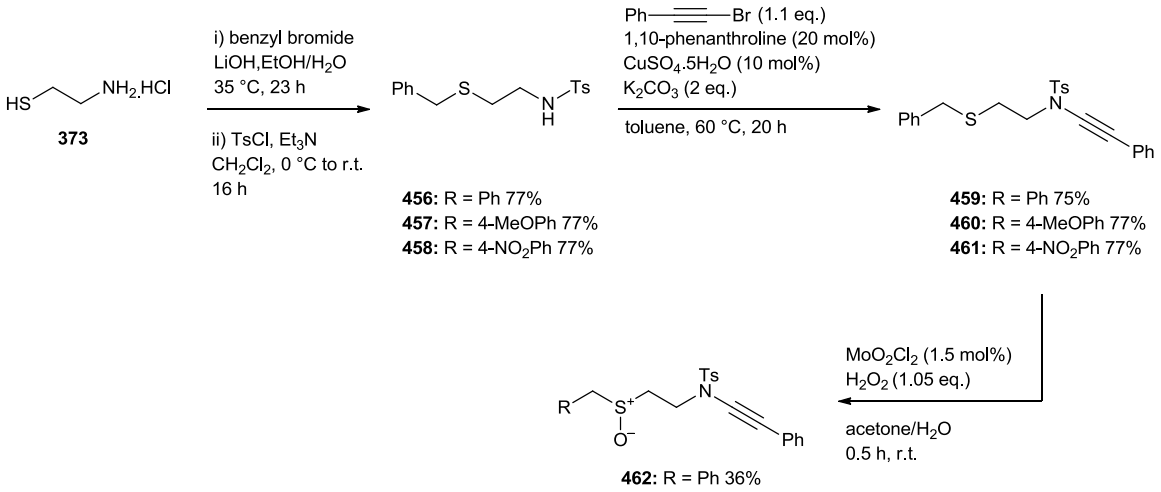
Despite screening a range of electrophiles capable of formal [1+2] and [1+4] cycloadditions to ylides, the only observed products of these reactions were traces of doubly oxidised ynamide and significant degradation of the starting material.[71] Omission of the electrophile did not prevent this degradation.

The attempted intermolecular reaction of these thiomorpholinone ylides revealed two main problems: the inability to replicate the reactivity of the ketone-stabilised ylides, let alone improve upon it and the massive degradation of the ynamide starting material under the reaction conditions.

The failure of the ylides to undergo intermolecular reaction potentially stems from the necessity for the substituted ynamide, as this results in a tertiary ylidic anion. Given that secondary, cyclic ylides have been reported to undergo epoxidation, it might be expected that removal of this substituent would significantly improve the reactivity of the thiomorpholinone ylide. However, during substrate elaboration of the ylide 2,3-sigmatropic shift reaction, it was found that the structural limitations imposed upon the thiomorpholinone ylides by the gold cascade precluded this. The terminal ynamide necessary to obtain a secondary thiomorpholinone ylide is unstable and a very poor substrate for thiomorpholinone formation. Given these limitations the author was forced to conclude that thiomorpholinone ylides are not suitable substrates for intermolecular reaction.

Stevens rearrangement

Thus far the migrating groups studied for the rearrangement of thiomorpholinone ylides have been limited to allyl groups undergoing 2,3-sigmatropic rearrangement. Ylides are also known to undergo 1,2-Stevens rearrangement and 2,3-Sommerlet-Hauser rearrangement of benzyl substituents.[175, 176] These rearrangements are commonly in competition and mixtures of products may arise from ylides undergoing both transformations.[165]



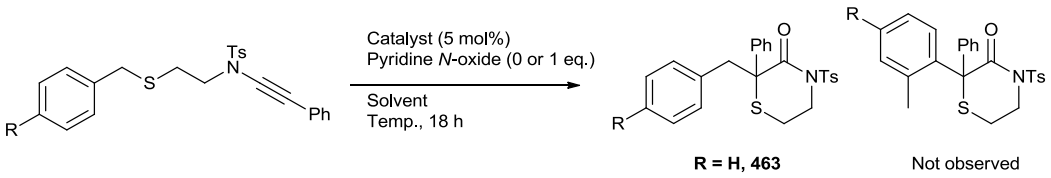
Scheme 109: Synthesis of *S*-benzyl ynamide and *S*-oxide

Stevens and Sommerlet-Hauser rearrangements have not previously been reported for ylides formed by gold catalysis and it was therefore decided to investigate the behaviour of the gold-derived

thiomorpholinone ylides with benzyl migrating groups. A suitable *S*-benzyl ynamide was readily obtained using a modification of the synthetic sequence for allyl ynamides (Scheme 109).

In order to provide a comparison to Davies' ketone-stabilised ylide system, a small portion of the *S*-benzyl substrate was converted to the corresponding sulfoxide **462**. As with previous attempts to make sulfoxide-bearing ynamides, it proved unstable and was used immediately after characterisation.

Table 12: Screen of solvents for the Stevens rearrangement of thiomorpholinone ylides



Entry	Substrate	Catalyst	Solvent	Temperature (°C)	Yield of thiomorpholinone (%) [a]
1	**459** R = H	IPrAuCl/AgOTs	MeCN	r.t.	50
2	**459** R = H	IPrAuCl/AgOTs	CH_2Cl_2	r.t.	65 (54 [b])
3	**459** R = H	IPrAuCl/AgOTs	CH_3Cl	r.t.	24
4	**459** R = H	IPrAuCl/AgOTs	MeOH	r.t.	40
5	**462** R = H [c]	IPrAuCl/AgOTs	CH_2Cl_2	r.t.	0
6	**462** R = H [c]	Au-**I**	$(CH_2Cl)_2$	70	18
7	**460** R = MeO	IPrAuCl/AgOTs	CH_2Cl_2	r.t.	0 [d]
8	**461** R = CF_3	IPrAuCl/AgOTs	CH_2Cl_2	r.t.	0 [d]

[a] Yields determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene. [b] Isolated yield. [c] No pyridine *N*-oxide [d] Degradation.

Gratifyingly, the first attempt at benzyl rearrangement using the previously developed conditions for 2,3-sigmatropic rearrangement was successful, giving thiomorpholinone **463** (Entry 1). Exclusive selectivity for biradical 1,2-Stevens rearrangement was observed and in no entry was the 2,3-sigmatropic Sommerlet-Hauser rearrangement product detected.

Optimisation of the reaction solvent, crucial for Stevens rearrangements as it controls migration of the radical benzyl intermediate, was conducted with solvents that had previously proved compatible with the gold-catalysed cascade (Entries 1 -4).[165] Improvement to the yield of **463** was found by using dichloromethane.

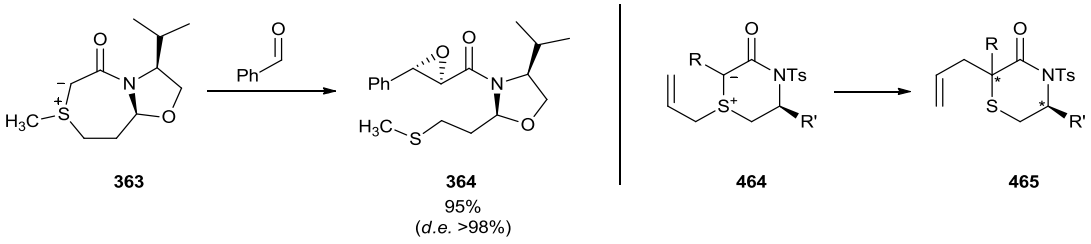
The sulfoxide ynamide **462** was not reactive under the NHC-gold-catalysed conditions (Entry 5), analogous tonearlier attempts to oxidise ynamides with diphenylsulfoxide (

Table 6). Davies' optimised conditions for ketone-stabilised ylide formation were also applied, with successful thiomorpholinone formation occurring, albeit in significantly reduced yield compared to the optimised pyridine *N*-oxide-based conditions (Entry 6).[75]

While simple benzyl migration was successfully achieved, elaboration of the migrating group to include electron-withdrawing and electron-donating aromatic substituents was unsuccessful (Entries 7 & 8). Stabilisation of the benzyl radical led to decomposition of the reaction mixture and only small quantities of the starting materials could be isolated. This effect has been observed by others; small changes to the migrating group frequently have a large impact upon Stevens and Sommerlet-Hauser rearrangements.[77-79, 177]

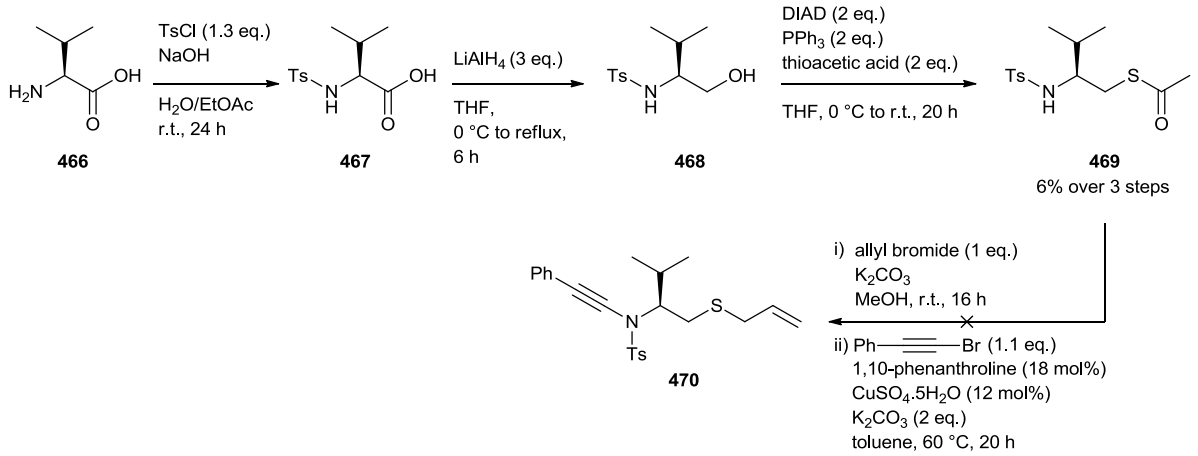
Chiral ynamides

Sarabia's group has reported that cyclic, chiral, amine-stabilised ylides such as **363** may be utilised for stereoselective epoxidation reactions.[124] Construction of ynamides bearing chiral directing groups was envisaged as a means of exerting control over the stereochemistry of the stereogenic centre constructed during thiomorpholinone formation (Scheme 110).



Scheme 110: Potential control of diastereoselectivity

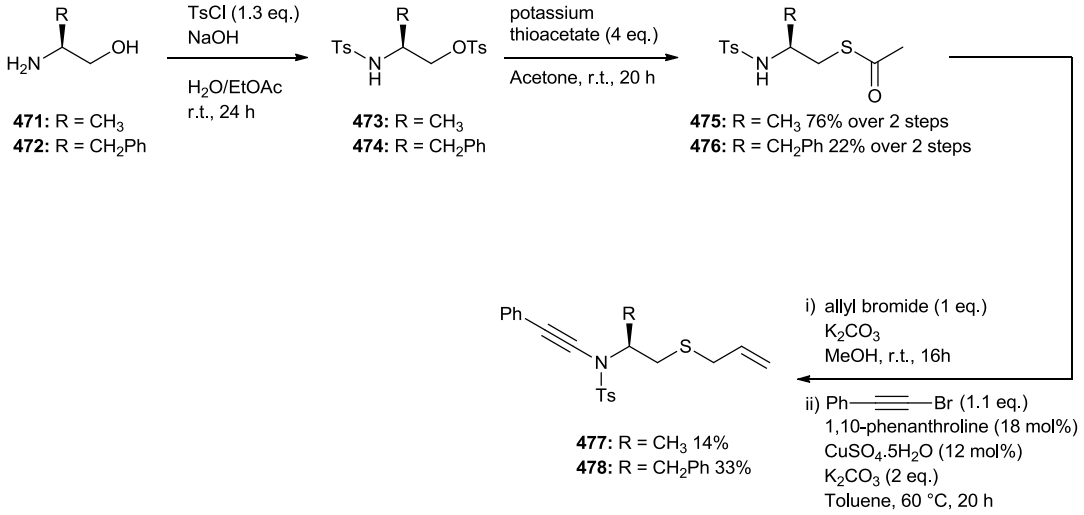
As the thiomorpholinone ylides explored in this project are synthesised from the amino acid derivative cysteamine hydrochloride, the use of modified, enantiopure amino acids allowed construction of the chiral backbone of the substrate (Scheme 111).



Scheme 111: Attempted synthesis of an L-valine-derived ynamide

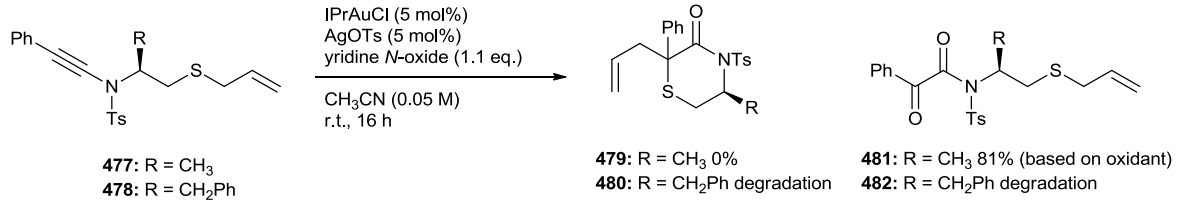
The first chiral ynamide which was targeted derived from L-valine, as the isopropyl group was hoped to be sufficiently bulky to provide the desired directing effect. Tosylation of the amino acid nitrogen, followed by reduction gave *N*-tosyl amino alcohol **468**. A Mitsonobu reaction then installed the necessary sulfur atom, in the form of thioacetate, which was converted to the necessary allyl sulfide by methanolysis in the presence of allyl bromide. Unfortunately, Mitsunobu reactions of the *N*-tosyl amino alcohol were impractical. The thioacetate product co-eluted with the hydrazine dicarboxylate by-product of the Mitsunobu reaction and was extremely difficult to separate, accounting for the low yield of valine-derived thioester **469**.

Having obtained the necessary chiral sulfonamide, formation of the final ynamide substrate **470** was attempted. Ynamide formation using Hsung's copper-catalysed conditions was not successful. The failure of the ynamide formation was believed to be due to the size of the isopropyl group. This promotes chelation of the sulfonamide substrate to the copper catalyst by a reactive rotamer effect, rendering the catalyst inactive. This phenomenon has been observed by the Davies group for similar substrates which possess structures which favour chelation. Replacement of the isopropyl directing group with smaller substituents was therefore attempted (Scheme 112).



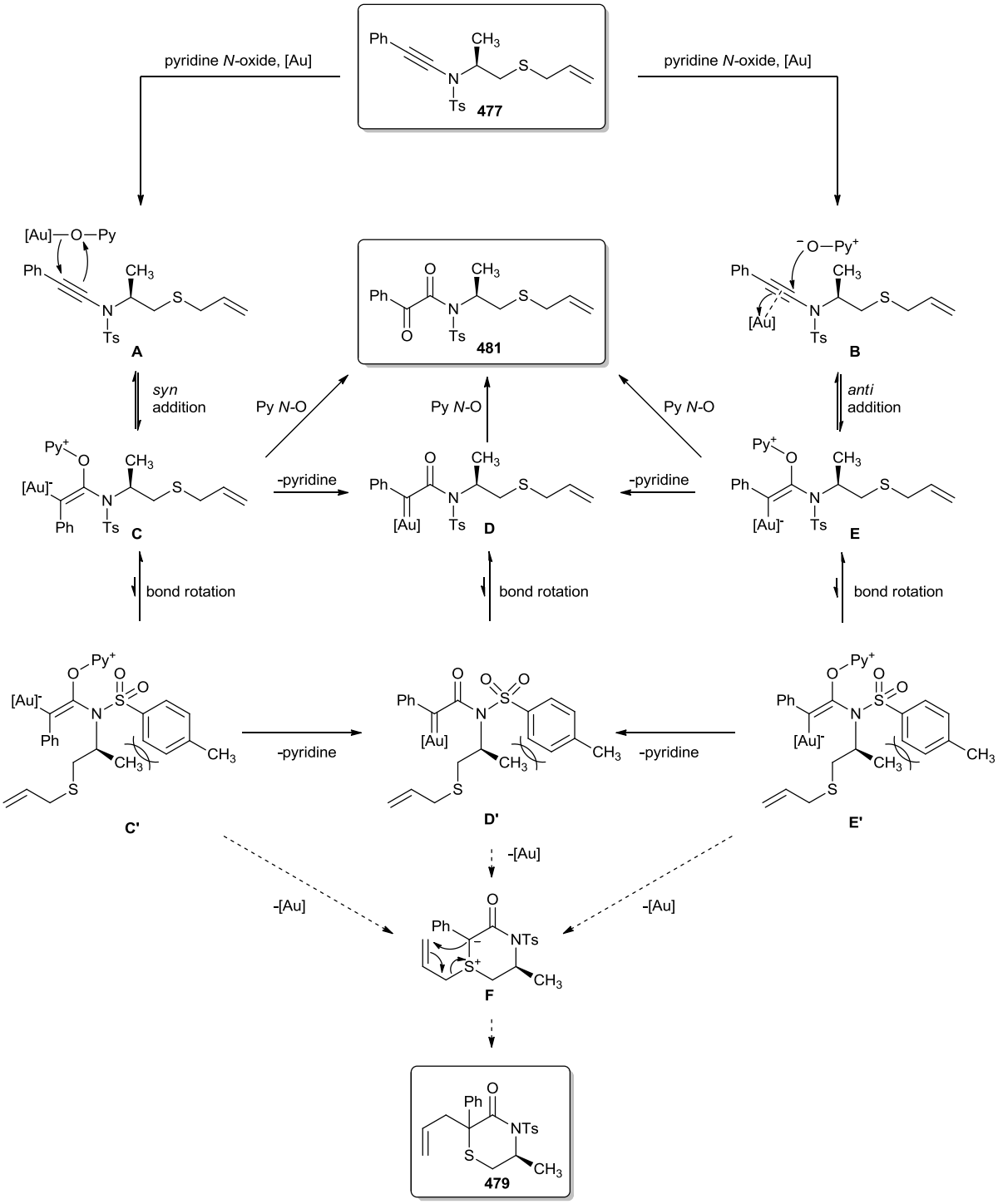
Scheme 112: Synthesis of L-alanine- and L-phenylalanine-derived ynamides

The amino alcohols of L-alanine and L-phenylalanine were examined as viable alternatives. As the synthesis of a chiral thioacetate via a Mitsunobu reaction had proven impractical for the valine-derived substrate, the thioester was installed using a modified strategy. Double tosylation of the amino alcohol, followed by substitution with potassium thioacetate, accessed the desired thioacetates (**475** & **476**). After methanolysis, ynamide formation proceeded smoothly with the smaller directing groups, to give **477** and **478**, albeit in low yield.



Scheme 113: Unsuccessful thiomorpholinone formation with chiral ynamides

The chiral ynamides were then subjected to the optimised ylide formation conditions, but unfortunately no thiomorpholine products were obtained (Scheme 113). The phenylalanine-derived ynamide **478** succumbed to complete degradation under the reaction conditions. Alanine-derived ynamide **477** was converted to the doubly oxidised product **481**, consuming almost all of the available oxidant in the process.



Scheme 114: Proposed mechanistic rationale for the formation of 481

This change in reactivity is believed to be due to steric impedance of the thiomorpholinone ylide formation (Scheme 114). The addition of a substituent to the backbone of the substrate prevents vinyl gold complexes **C** and **E**, and carbene **D** from adopting the conformations **C'**, **E'** and **D'** necessary for cyclisation, by steric clash between the sulfonamide protecting group and the substituent. Instead, the addition of a second molecule of oxidant is uncontested resulting in the exclusive

formation of doubly oxidised **481**. While the tosyl sulfonamide may have been replaced with a smaller mesyl sulfonamide, to reduce the steric interaction between the sulfonamide and the directing group, mesyl-substituted ynamides are poorly tolerated by the gold-catalysed cascade and are therefore unsuitable.

Summary

The gold-catalysed synthesis of thiomorpholinone ylides has been developed. These ylides are derived from novel ynamide substrates, bearing a nucleophile tethered to the ynamide nitrogen, a structural motif that has not previously been investigated for gold catalysis. These thiomorpholinones have been demonstrated to be more reactive than the equivalent ketone-stabilised cyclic ylides.

Reaction conditions are very mild, with reaction occurring at room temperature and in the presence of a weak base. All of the reagents are commercially available and the most expensive component, the gold catalyst, may be reduced to 2.5 mol% loading with only minor reduction in thiomorpholinone yield. The thiomorpholinones obtained are valuable, owing to the difficulty in preparing sulfonamide-protected thiomorpholinones and are readily obtained as complex, polysubstituted motifs from a highly modular synthesis of easily-constructed ynamides. Competition with carbothiolation was successfully controlled, another novel process as ynamides have not thus far been used for gold-catalysed carbothiolation reactions.

The reactivity of these ylides has been explored and is suitable for 2,3-sigmatropic rearrangements and 1,2-Stevens rearrangements, however substitution adjacent to the ynamide nitrogen is not tolerated. The structural constraints introduced by the ynamide moiety render these thiomorpholinone ylides unsuitable for intermolecular reactions, as the necessary ynamide substituent renders the ylidic anion too congested to undergo intermolecular reaction and the substrate degrades under the reaction conditions.

Chapter 4: Thioynol ethers

Introduction

The study of thioynol ethers described here came about through the author's attempted synthesis of glitazones using gold catalysis. Glitazones are a class of drug compounds incorporating the thiazolidinedione motif (Figure 4).

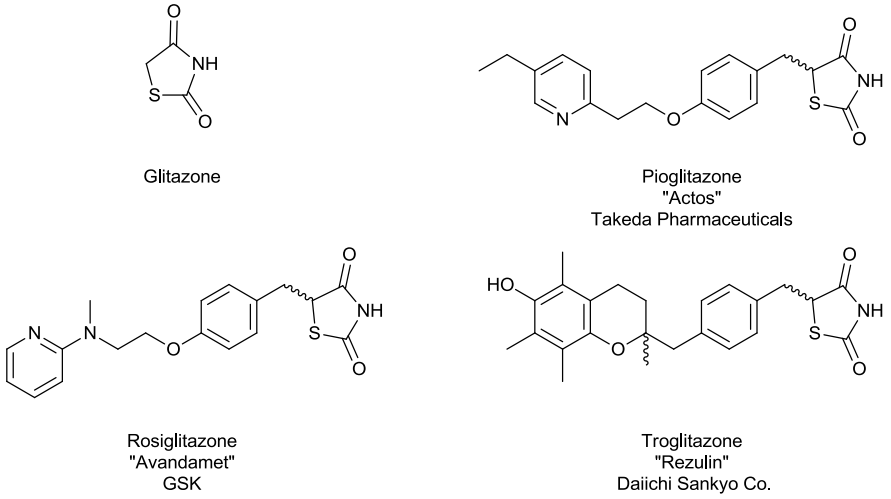
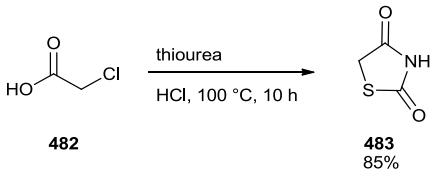


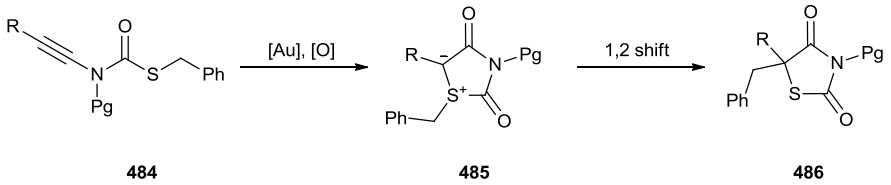
Figure 4: Glitazone and marketed glitazone-based drugs

These compounds are potent peroxisome proliferator-activated receptor (PPAR) activators and have been developed for the treatment of type 2 diabetes. In 2010, Actos was the 11th highest selling drug in the US, with sales in excess of $2.6 billion.[178]



Scheme 115: Synthesis of thiazolidinedione

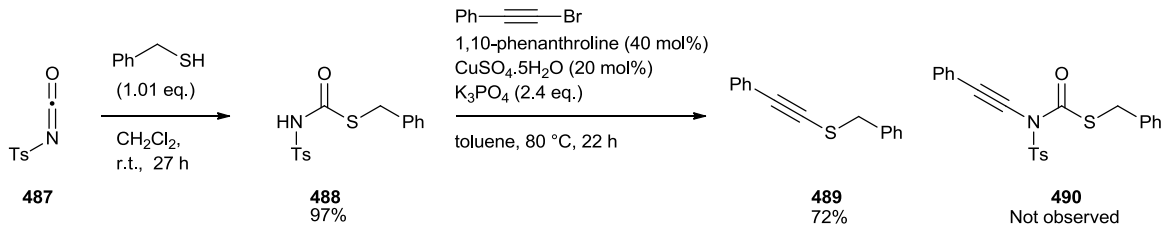
While the thiazolidinedione (**483**) core is simple to construct, such as in the example by Meng *et al.* shown in Scheme 115,[179] application of the gold-catalysed Stevens rearrangement developed in the previous chapter would allow for facile construction of more complex, protected and polysubstituted thiazolidinediones, which would be of interest as potential lead compounds (Scheme 116).



484 **485** **486**

Scheme 116: Proposed gold-catalysed thiazolidinedione synthesis

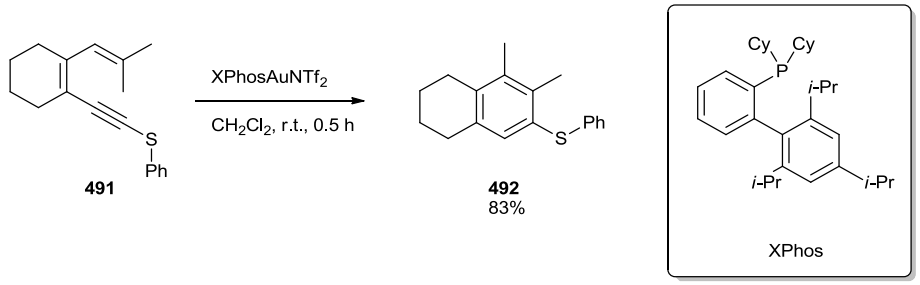
By employing an ynamide with a tethered thioester, oxidative gold-catalysed ylide formation would construct the desired thiazolidinedione core. Migration of the ylide substituent would then quench the ylide and further substitute the thiazolidinedione, leading to a 3,5,5-trisubstituted thiazolidinedione. It was expected that significant re-optimisation of the gold-catalysed ylide formation would be necessary owing to the electronic difference between conjugated ylide **485** and the previously examined thiomorpholinone ylides. A Stevens rearrangement was chosen for the migration to be studied initially, as this would provide thiazolidinedione products similar to the existing glitazone drugs. Synthesis of the necessary ynamide substrate (**489**) began with construction of thiocarbamate **488** from *N*-tosyl isocyanate (Scheme 117).



487
488 97%
489 72%
490 Not observed

Scheme 117: Attempted synthesis of thiazolidinedione precursor ynamide

Installation of the ynamide moiety (**490**) via Gagosz's copper-catalysed conditions was not successful; instead thioynol ether **489** was obtained. This thioynol ether (**489**) likely results from decomposition of thiocarbamate (**488**) due to the presence of the phosphate base. The decomposition of thiocarbamates, by bases, to give isocyanates is well understood.[180] While this made the synthesis of a suitable ynamide precursor impossible, as all ynamide formations are performed under basic conditions,[145, 146] the resulting thioynol ether was intriguing. Thioynol ethers had not been investigated under gold catalysis, with the exception of a single substrate (Scheme 118).[181]

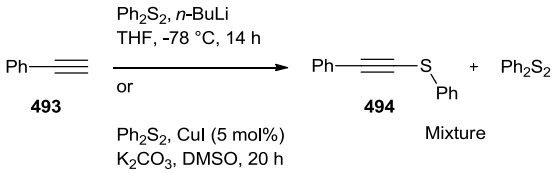


Scheme 118: Sanz's gold-catalysed benzene synthesis

Sanz reported the gold-catalysed cyclisation of sulfide-substituted enyne **491** via a Wagner-Meerwein rearrangement. Given that Sanz had demonstrated that thioynol ethers are suitable for gold catalysis and the electron-rich nature of the triple bond, it was envisaged that these thioynol ethers may undergo similar reactions to ynamides and therefore expand the substrate scope of such reactions.

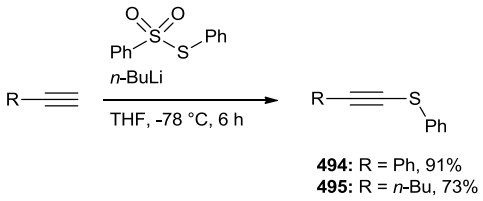
Synthesis of thioynol ethers

Synthesis of suitable substrates for reaction optimisation was attempted with phenyl acetylene and diphenyl disulfide under literature conditions (Scheme 119).[182, 183]



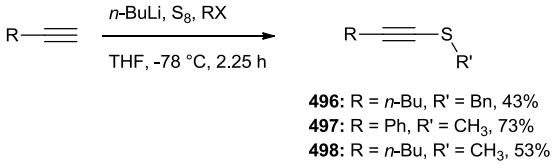
Scheme 119: Attempted synthesis of substrate with diphenyl disulfide

While the desired thioynol ether **494** was formed, it proved inseparable from the diphenyl disulfide starting material, despite following literature conditions. This difficulty stems from the similar and extremely low polarities of both compounds. In one case, careful examination of the supporting information for a supposedly quantitative method of synthesising this class of compounds revealed the same mixture of disulfide and thioynol ether.[184] A more polar sulfide source was therefore employed to aid separation from the reaction product (Scheme 120).[185]



Scheme 120: Synthesis from *S*-phenyl benzenesulfonothioate

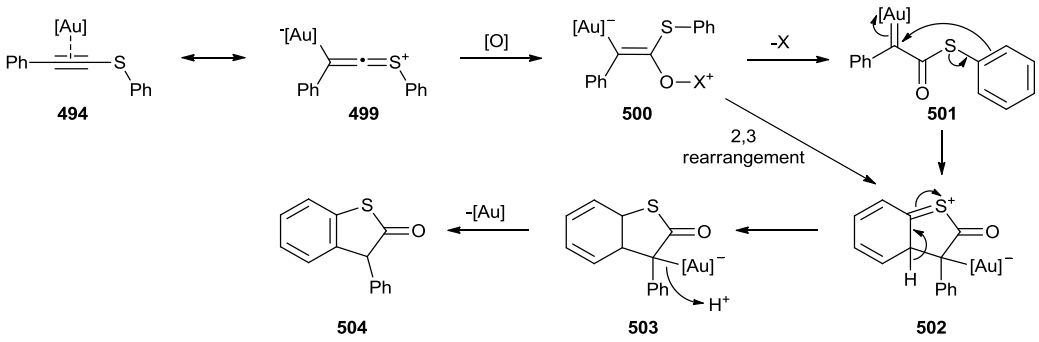
This approach allowed alkyl- and aryl-substituted triple bonds to be synthesised. A variety of sulfur substituents were obtained with Zheng's conditions (Scheme 121).[186]



Scheme 121: Introduction of a variety of sulfide substituents

Electrophilic aromatic substitution

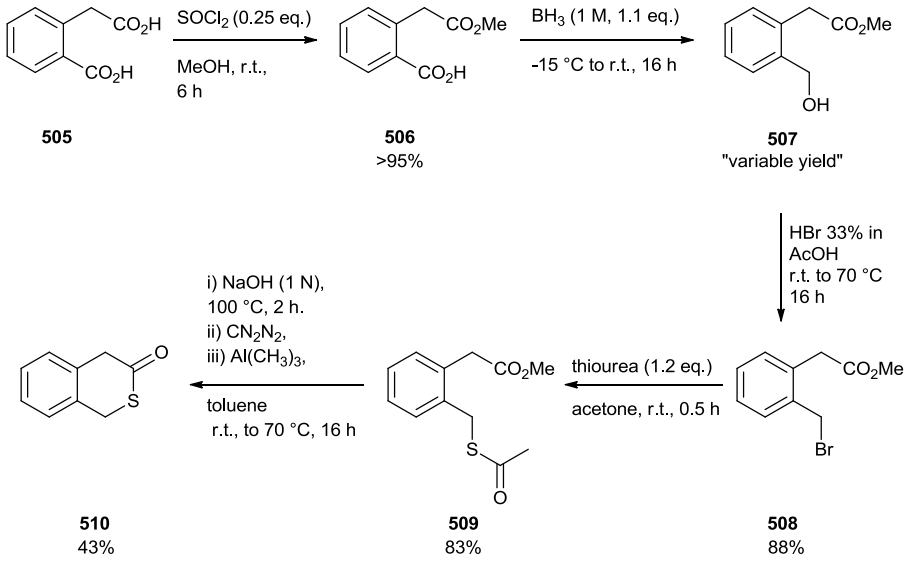
Electrophilic aromatic substitution was targeted as a potential application of these thioynol ethers. Electrophilic substitution would obtain bicyclic thiolactones such as **504** (Scheme 122).



Scheme 122: Proposed gold-catalysed electrophilic aromatic substitution

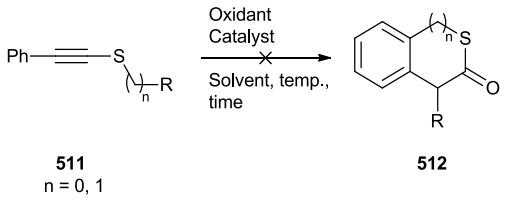
Regioselective activation of the thioynol ether by the gold catalyst would lead to gold thioketene **499**. Nucleophilic attack of a suitable intermolecular oxidant would then generate vinyl gold **500** which could undergo carbenoid formation and subsequent substitution, or a 2,3-sigmatropic rearrangement to give the final thiolactone **504**.[31] This gold-catalysed approach offered significant

improvements over reported means of obtaining bicyclic thiolactones such as **510**. An example synthesis by Haeggström's group requires five steps to reach an unsubstituted isothiochroman-3-one, via a reduction which gave what they describe as "variable yield" (Scheme 123).[187]



Scheme 123: Synthesis of isothiochroman-3-one

The equivalent gold-catalysed synthesis would require two steps to reach a substituted isothiochroman-3-one, a significant improvement in synthetic efficiency and therefore a worthwhile goal.



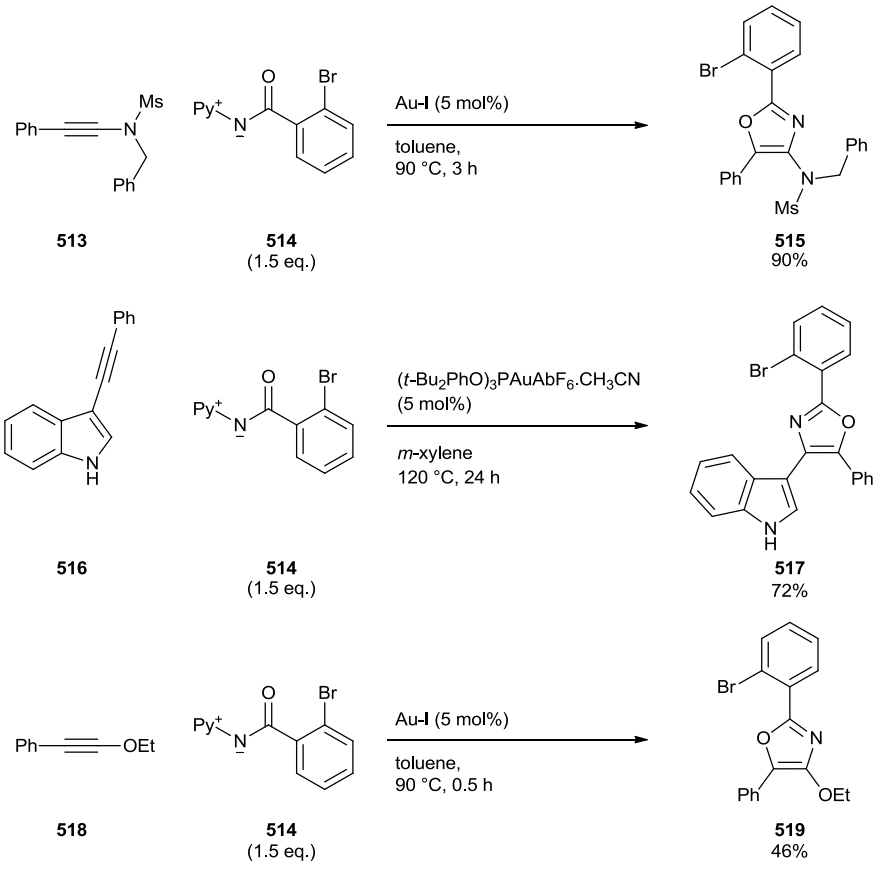
Scheme 124: Attempted synthesis of isothiochroman-3-one derivatives

While a promising target, electrophilic aromatic substitution could not be obtained with either substrate (Scheme 124). A wide range of conditions and catalysts were screened, including NHC, phosphite and Buchwald phosphine complexes. The thioynol ethers proved to be significantly less reactive than the equivalent ynamide or alkyne. In comparison, the first substrate screened in this thesis (**304**) readily underwent electrophilic aromatic substitution, in high yield, with a variety of simple gold catalysts. Despite the electron-rich triple bond, these thioynol ethers appear to

significantly attenuate the catalytic activity, possibly acting as a highly effective ligand for the gold catalyst.

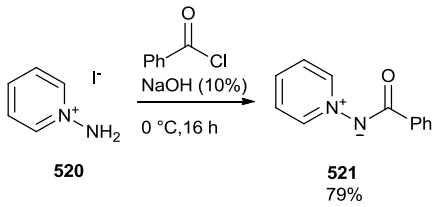
Oxazole synthesis

After the failure of thioynol ethers to undergo electrophilic aromatic substitution, it was decided to focus on another gold-catalysed ynamide reaction. Davies has reported a gold-catalysed oxazole formation from ynamides (**513**) and pyridinium ylides. This transformation can also be performed using alkynyl indoles (**516**) and also ynol ethers (**518**), albeit in reduced yield, suggesting that it may also tolerate the thioynol ethers under investigation in the present work (Scheme 125).[69, 188]



Scheme 125: Davies' oxazole synthesis from ynamides and ynol ethers

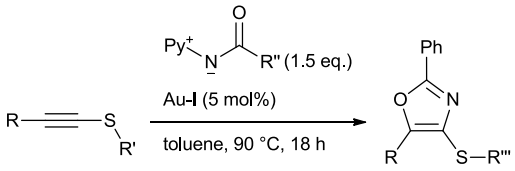
Davies' reaction regioselectively forms oxazoles by a proposed Nazarov 4π electrocyclisation or gold carbenoid (for mechanism and discussion see Scheme 53).[69] The necessary pyridinium ylide was synthesised from aminopyridinium iodide and initial screening was performed with Davies' optimised conditions for ynol ethers (Scheme 126).



Scheme 126: Synthesis of the pyridinium ylide

A range of thioynol ethers were tested, to determine a suitable substrate for more in-depth investigation (Table 13).

Table 13: Screen of thioynol ethers



Ynamide	R	R'	Yield of oxazole (%) [a]
494	Ph	Ph	<5
495	*n*-Bu	Ph	Trace [b]
489	Ph	Bn	Trace [b]
496	*n*-Bu	Bn	Trace [b]
497	Ph	CH_3	13
498	*n*-Bu	CH_3	<5

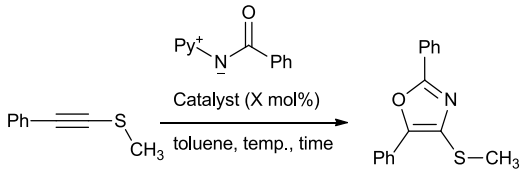
[a] Yields determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene.

[b] Detected by TLC

Thioynol ethers **489**, **494**, **495** and **496** proved largely unreactive, with only traces of the oxazole's characteristic fluorescence detected by TLC. Methyl-substituted thioynol ethers **497** and **498** were slightly more suitable, with successful oxazole formation achieved in 13% yield for the phenylacetylene-based substrate. Thioynol ether **497** was therefore employed in further screening. The successful formation of an oxazole confirmed the hypothesis that thioynol ethers could be used as ynamide equivalents and via an intermolecular process. Further optimisation of the oxazole synthesis was conducted (Table 14).

Applying Davies' conditions for gold-catalysed oxazole formation gave a significantly lower yield than Davies observed for ynol ethers (Scheme 125).[69] Gold(III) chloride gave a slight improvement (Entry 2), however phosphine- and phosphite-ligated gold catalysts were not effective, even with elaborate Buchwald phosphines. (Entries 3 to 6). Elevating the reaction temperature proved beneficial to the yield of oxazole (Entry 7), however increasing it further by using xylene and mesitylene was detrimental to the yield.

Table 14: Optimisation of oxazole synthesis



497 522

Entry	Catalyst (mol %)	Co-catalyst (mol %)	Temperature (°C)	Time (h.)	Yield of **522** (%) [a]
1	Au-**I** (5)	-	90	18	13
2	$AuCl_3$ (5)	-	90	18	15
3	Ph_3PAuCl (5)	$AgNTf_2$ (5)	90	18	10
4	Complex 1 (5)	-	90	18	9
5	Complex 2 (5)	-	90	18	12
6	$(F_3CPh)_3PAuCl$ (5)	$AgSbF_6$ (5)	90	18	<5
7	$AuCl_3$ (5)	-	100	18	27
8	IPrAuCl (10)	$AgNTf_2$ (10)	100	18	24
9	$AuCl_3$ (10)	AgOTs (30)	100	48	37
10	$AuCl_3$ (10)	-	100	48	40
11	Au-**I** (10)	-	100	48	44

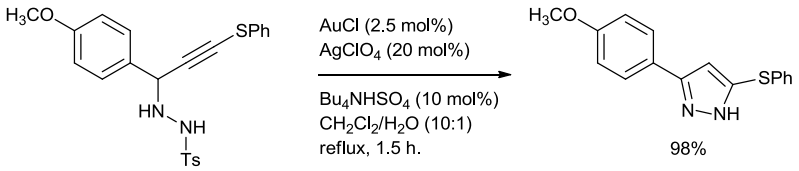
The NHC-ligated IPrAuCl was not as effective as gold (III) chloride, even at double the catalyst stoichiometry. Increasing the reaction time to two days offered significant improvement. This suggests that catalyst activity is being attenuated by the presence of the thioynol ether and requires

a long time period for conversion to occur, rather than the reaction halting due to catalyst degradation. Addition of sufficient silver co-catalyst to create a bare gold (III) cation, to provide maximum coordination sites for reaction to occur was not productive (Entry 9). Ultimately pyridinecarboxylatogold (III) chloride proved most effective (Entry 11).

At the conclusion of laboratory work, the yield of oxazole had successfully been raised to 44%, however further optimisation is continuing within the Davies group. This yield is extremely close to the yields observed by Davies and co-workers for ynol ethers, which are considerably more reactive.[69]

Future work

Thioynol ethers have been confirmed to be able to act as ynamide equivalents under gold catalysis. The optimisation of this process is by no means complete, there remains a large selection of gold catalysts, such as Zhang's recent bidentate Buchwald phosphine derived complexes, and reaction conditions yet to be screened.[64] After sufficient optimisation, these thioynol ethers will allow access to a range of interesting, sulfur-containing oxazoles, from easily obtained ethers.



Scheme 127: Yoshimatsu's pyrazole synthesis

During the preparation of this thesis Yoshimatsu's group published the synthesis of pyrazoles from thioynol ethers, further confirming that these motifs are indeed suitable for gold catalysis.[189]

Chapter 5: Conclusion

Conclusion and Future Work

At the outset, this research project had the following aims:

- To investigate whether the reactivity of gold-derived sulfonium ylides can be expanded. Specifically, whether these ylides can react with electrophiles in an intermolecular fashion and to investigate the ylide structures that may be obtained via this catalysis.
- To apply the most recently developed techniques of gold catalysis to the synthesis of these ylides, such as the use of pyridine *N*-oxides, Zhang's chelating Buchwald phosphines, ynamide substrates and cooperative silver catalysis.
- To explore the structural motifs that may be obtained via gold-derived ylides. Specifically, to target motifs which are difficult to access via established methods and may be of pharmaceutical value.
- To gain further insights into the catalytic cycle when using gold complexes to generate sulfonium ylides.

Intermolecular reaction of the ylides has proven possible, sulfonium ylides undergoing a novel, three-component coupling. However, development of this proof of concept was not possible, intermolecular reaction of alkynylsulfonium-derived ylides proved too low yielding to be a viable synthetic reaction. During the development of this coupling a range of interesting side reactions were observed, including novel carbothiolations. Thiomorpholinone ylides were developed in an attempt to overcome the limitations of the alkynylsulfonium-derived ylides. These allowed access to more reactive ylides and demonstrated that gold-derived ylides could undergo Stevens rearrangements. Structural limitations unfortunately prevented these ylides from undergoing intermolecular reactions. Many recently developed gold catalysis techniques were successfully applied to the synthesis of sulfonium ylides, although phosphine ligands were not suitable for these transformations. Complex thiomorpholinone structures were obtained, although the ylide concept could not be applied to the synthesis of glitazones. These thiomorpholinones are undergoing biological screening to evaluate their pharmaceutical value (*vida infra*). Evidence for strong

carbenoid character during the catalytic cycle was observed and removal of the silver co-catalyst was detrimental to the reaction.

In addition to the stated aims, the research project also investigated the use of thioynol ethers as ynamide equivalents and successfully demonstrated that these substrates could be used to access the oxazole moiety. Research into these thioynol ethers is continuing, to optimise the oxazole synthesis and explore their reactivity.

Biological Screening

Given the interest in sulfonamide-protected thiomorpholinones for drug applications, [128, 129] the range of thiomorpholinone products obtained during screening was submitted to Eli Lilly's Open Innovation Drug Discovery Program for evaluation as potential lead molecules for drug development.[166] Lilly's program comprised a number of screening modules to assess compounds from academia for their suitability for Lilly's current therapeutic targets. The compounds were initially subjected to *in silico* assessment to determine the thiomorpholinones' suitability for drug applications. The thiomorpholinones were then screened against Lilly's phenotypic, target-based and tuberculosis assays.

Phenotypic screening was conducted *in vitro* against a variety of cell lines to determine whether introduction of these compounds could achieve a desired effect on an entire cellular system. Osteogenic activity was desired, specifically stimulation of GPL-1 secretion for diabetes treatment.[167, 168]

Target-based screening was conducted against a range of receptors in biological assays. These included activation of cells expressing the human GPR119 receptor,[169] for control of glucose homeostasis; inhibition of histone methyl transferase EZH2 to suppress tumour growth and metastasis;[170] inhibition of Calcitonin Gene-Related Peptide for migraine treatment;[171] and antagonism of the mGlu2 receptor for use as a neurological indicator.[172] The

tuberculosis screening module was conducted against a modified, fluorescent strain of *Mycobacterium tuberculosis* (H37Rv), measuring inhibition of bacterial growth.

None of the compounds screened during these assays were sufficiently active to warrant further investigation. They have also been submitted to Lilly's phenotypic drug discovery program to assess their ability to inhibit the production of proprotein convertase subtilisin kexin type 9 (PCSK9), which is currently underway using human hepatoma cell lines (HepG2). Inhibition of PCSK9 synthesis is desired as cholesterol-lowering statins stimulate PCSK9 synthesis which lowers their efficacy.[173, 174]

Appendix 1: Experimental Data

General experimental considerations

Where specified, dry reactions were carried out under argon in flame-dried glassware, using dried solvents; otherwise reactions were carried out under air in oven-dried glassware, using solvents as received, unless otherwise specified. Dry solvents used were purified using a Pure Solv-MD Solvent Purification System (alumina columns) from Innovative Technology and were transferred under argon. Pyridine *N*-oxide was dried as a solution in CH_2Cl_2 over Na_2SO_4, filtered and then concentrated *in vacuo* to give white crystals. Pyridine *N*-oxide was stored under argon in a Schlenk tube or nitrogen in a glove box and was weighed using Schlenk techniques or in the glove box. A Radleys Carousel 12 or Asynt DrySyn heating blocks on stirrer hotplates were employed with temperature control via external digital probe. Carousel and Schlenk tubes were cleaned with aqua regia to ensure they were free from contaminating metals. Extracted reaction mixtures were dried over anhydrous Na_2SO_4 or $MgSO_4$. Solutions used during reaction work up were saturated unless otherwise specified. Flash column chromatography was performed with Merck Geduran® Si 60 silica gel (43-63 μm) following Still's procedure.[190] Thin layer chromatography (TLC) was performed with Merck silica gel 60 F_{254} analytical plates (plastic or aluminium support) which were developed using standard visualising agents: UV fluorescence (254 and 366 nm), ethanolic vanillin /Δ and potassium permanganate /Δ. Melting points were measured using a Stuart Scientific SMP1 instrument, are reported to the nearest degree and are uncorrected. Infra-red spectroscopy was performed using a Perkin-Elmer Spectrum 100 FTIR spectrometer, only selected absorbancies (ν_{max}) are reported in cm^{-1}. Peaks are described as br (broad), s (sharp) and w (weak). Mass spectrometry and high-resolution mass spectrometry (EI) were performed using a VG ProSpec or VG-ZabSpec instrument at 70 eV. High-resolution EI spectra were measured using perfluorokerosene (PFK) as an internal calibrant. Mass spectrometry and HR-MS (ES) were performed using a Micromass LCT instrument using a methanol mobile phase. HR-MS were obtained using a lock-mass to adjust the calibrated mass scale. MS data is reported as *m/z* (relative intensity). Commercially available compounds were purchased from Aldrich, Fisher, Acros, Strem, Alfa Aesar, VWR and used without further purification, unless specified. Pyridine *N*-oxides were kindly donated by Mickael Dos Santos and Holly Adcock. NMR spectra were recorded on

Bruker AVIII300 (300 MHz), Bruker AVIII400 (400 MHz) in the solvents indicated; $CDCl_3$ was purchased from Aldrich (no TMS) and Cambridge Isotope Laboratory (0.05% v/v TMS); Chemical shifts (δ) are given in ppm relative to TMS. In the absence of TMS, solvent signals were used as references and the chemical shifts converted to the TMS scale (residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm, $CDCl_3$: $\delta_C \equiv 77.16$ ppm).[191] Coupling constants (*J*) are reported in Hz. Multiplicity is denoted in ^{1}H NMR spectroscopy by: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), h (hextet), m (multiplet) and br (broad). 1D ^{13}C NMR spectra were recorded using the UDEFT or PENDANT pulse sequences from the Bruker standard pulse program library. UDEFT were combined with DEPT 135 to assign quaternary carbons. 2D NMR spectra were recorded using the COSY, HSQC, HMBC or NOESY pulse sequences from the Bruker standard pulse program library and key couplings are indicated with arrows.

General procedures

GP1: General procedure for gold-catalysed reactions with sulfoxide substrates

The specified electrophile was added under argon to a flame-dried Schlenk flask or Radleys tube containing a stirred solution of sulfoxide substrate (1 eq.) in dry solvent. The specified gold catalyst (0.05 eq.) was then added under argon. If the reaction was conducted at elevated temperature the reaction vessel was then immediately heated to the specified temperature using a preheated block with external temperature probe. After the specified time had elapsed the reaction mixture was cooled to room temperature, filtered through a plug of silica eluting with ethyl acetate, was concentrated *in vacuo* and purified by flash column chromatography to give the catalysis product.

Sulfonamides were synthesised utilising the following general procedures:

GP2: Prepared via a modified literature procedure.[192] An aqueous solution of LiOH (2.1 eq.) was added to a stirred solution of cysteamine hydrochloride (1.0 eq.) and alkyl halide (1.0 eq.) in ethanol and heated to 35 °C. Ethanol was removed *in vacuo* and the resulting oily solution was extracted with CH_2Cl_2 (3 x *ca.* 50 ml), dried over Na_2SO_4 and filtered. The resulting solution was cooled to 0 °C

then sulfonyl chloride (1.01 eq.) and triethylamine (1.75 – 3.33 eq.) were added. The solution was stirred vigorously overnight and a thick, pale yellow precipitate formed. The reaction mixture was added to NH_4Cl solution (*ca.* 100 ml), the organic fraction collected and washed with water (2 x *ca.* 100 ml). The organic phase was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography, to give the sulfonamide.

Ynamides were synthesised utilising the following general procedures:

GP3: Prepared via a literature procedure.[160] Synthesis of bromoalkyne: the necessary bromoalkyne was prepared by the addition of n-butyl lithium (1.05 eq.) to a solution of alkyne in dry THF at -78 °C. After 15 minutes Br_2 (1.10 eq.) was added and the reaction mixture stirred for a further 15 minutes. The reaction was quenched with $Na_2S_2O_3$ solution and extracted three times with CH_2Cl_2. The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude bromoalkyne as a brown oil. The bromoalkynes were not stable and were used immediately, crude, as per Hsung's procedure. Synthesis of ynamide: a portion of freshly synthesised crude bromoalkyne (1.10 eq.) was added under argon to a stirred solution of sulfonamide (1.0 eq.), 1,10-phenanthroline (0.18 – 0.20 eq), $CuSO_4.5H_2O$ (0.10 – 0.12 eq.) and K_2CO_3 (2.0 eq.) in dry toluene. The reaction mixture was immediately heated to 65 °C using a preheated block. After the specified time, the reaction mixture was cooled to room temperature, silica gel was added and then the mixture was concentrated *in vacuo* to give a dry, free-flowing powder that was purified by flash column chromatography to give the ynamide.

GP4: Prepared via a literature procedure.[160] CuI (0.12 eq.) and Cs_2CO_3 (4.0 eq.) were added under argon to a stirred solution of sulfonamide (1.0 eq.), dibromoalkene (1.1 - 1.5 eq.) and dimethylethylenediamine (1.8 eq.) in dry dioxane or DMF. The reaction mixture was immediately heated to 60 °C using a preheated block. After the specified time the reaction mixture was cooled to room temperature. For reactions in dioxane silica gel was added and then the mixture was concentrated *in vacuo* to give a dry, free-flowing powder, the resulting powder was purified by flash column chromatography to give the ynamide.

Optimised conditions for thiomorpholinone formation:

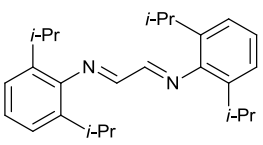
GP5: Catalysis was performed using the following procedure, under Schlenk conditions. Ynamide (1.0 eq.) was added under argon into a flame-dried Schlenk or Radleys tube. Dry CH_3CN (0.2 M based on ynamide) was added under argon, followed by dry pyridine *N*-oxide (1.1 eq.), AgOTs (0.05 eq.) and then IPrAuCl (0.05 eq.). The reaction mixture was stirred for the specified time, filtered through a small plug of silica (*ca.* 500 mg) in a Pasteur pipette, eluting with ethyl acetate, concentrated *in vacuo* and purified by flash column chromatography to give the catalysis product.

Formation of dibromo-olefins:

GP6: PPh_3 (4 eq.) was added to a 0 °C solution of CBr_4 (2 eq.) in dry CH_2Cl_2 (0.1 M based on the aldehyde) with vigorous stirring. After 10 minutes the aldehyde (1 eq.) was added and the reaction mixture was allowed to reach room temperature overnight. Chromatography silica gel was added until the solution decolourised, the reaction mixture was concentrated *in vacuo* to give a dry, free-flowing powder and then purified by flash column chromatography to give the dibromo-olefin.

Synthesis of catalysts

Dimethylsulfidegold(I) chloride Prepared according to literature procedure.[193] $(CH_3)_2S$ (150 µl, 2 mmol, 2.9 eq.) was added to a solution of $NaAuCl_4$ (250 mg, 690 µmol, 1.0 eq.) in dry CH_3OH (10 ml) and the flask was covered in foil. After four hours the white precipitate was collected by suction filtration, washed with CH_3OH (*ca.* 2 ml) and dried *in vacuo* to give dimethylsulfidegold(I) chloride as bright white crystals (138 mg, 68%). Decomposed at approximately 90 °C (Lit.[194] 110 °C). δ_H (300 MHz, $CDCl_3$) 2.75 (6H, s, SCH_3). IR (Neat): ν_{max} = 2994 (CH), 2921 (CH), 1436, 1422, 1412, 1318, 1298, 1032, 994, 954. ^{1}H NMR and IR data in agreement with literature values.[195]



Bis(2,6-diisopropylphenyl)diazabutadiene Prepared according to literature procedure.[196] Glyoxal (40% solution in water, 3.18 ml, 28 mmol, 1 eq.) was added to a solution of 2,6-diisopropylaniline (6.99 ml, 56 mmol, 2 eq.) in

ethanol (10 ml). A drop of formic acid was added and the reaction mixture was stirred for 2 days. The resulting yellow crystals were collected by suction filtration, washed with CH_3OH and dried *in vacuo* to give bis(2,6-diisopropylphenyl)diazabutadiene (5.04 g, 48%). Melting point 100-101 °C from methanol (Lit.[197] 102-103 °C). δ_H (300 MHz, $CDCl_3$) 8.10 (2H, s, CHN), 7.23-7.13 (6H, m, ArH), 3.01-2.84 (2H, m, CH_3CHCH_3), 1.21 (12H, d, *J* 6.9, $CHCH_3$). IR (Neat): ν_{max} = 3065 (CH), 2963 (CH), 2926 (CH), 2865 (CH), 1626 (C=N), 1465, 1436, 1176, 924, 789, 760. Data in agreement with literature values.[196]

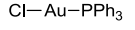
IPr.HCl Prepared according to literature procedure.[196] Paraformaldehyde (402 mg, 13.4 mmol, 1 eq.) was added to a solution of bis(2,6-diisopropylphenyl)diazabutadiene (5.04 g, 13.4 mmol, 1 eq.) in dry toluene (100 ml), the mixture was heated to 100 °C. After 30 minutes the reaction mixture was cooled to 40 °C and a 4 M solution of HCl in dioxane (3.35 ml, 13.4 mmol, 1 eq.) was added; then the reaction mixture was heated to 70 °C for 5 hours. The reaction mixture was cooled to room temperature, the pink precipitate collected by suction filtration and purified by recrystallisation from CH_3OH and diethyl ether to give white crystals. The crystals were dried *in vacuo* at 100 °C for three days to give IPr.HCl (293 mg, 51%). Decomposed at approximately 250 °C (Lit.[198] 250 °C). δ_H (300 MHz, $CDCl_3$) 10.06 (1H, s, NC*H*N), 8.17 (2H, d, *J* 1.6, ArH, NC*HCH*N), 7.70-7.46 (4H, t, *J* 7.8, ArH), 7.35 (2H, d, *J* 7.8, ArH), 2.57-2.33 (4H, m, CH_3CHCH_3), 1.29 (12H, d, *J* 6.8, $CHCH_3$), 1.25 (12H, d, *J* 6.9, $CHCH_3$). IR (Neat): ν_{max} = 3293br (HCl), 3116, (CH), 3069 (CH), 2967 (CH), 2933 (CH), 2871 (CH), 2752 (CH), 1534 (C=C), 1469, 1444, 1332, 1206, 1062, 810. Data in agreement with literature values.[196]

1,3-bis(diisopropylphenyl)imidazol-2-ylidenegold(I) chloride Prepared according to literature procedure.[199] Ag_2O (118 mg, 510 µmol, 1.50 eq.) was added to a solution of bis(2,6-diisopropylphenyl)diazabutadiene (152 mg, 360 µmol, 1.05 eq.) in dry, degassed CH_2Cl (20 ml), stirring in a flame-dried, foil-covered, 50 ml Schlenk flask. After 3.5 hours the reaction mixture was transferred via cannula into a flame-dried Schlenk filter and filtered through a plug of celite, under argon, into a flame-dried, 50 ml Schlenk flask. Freshly prepared $(CH_3)_2SAuCl$ (100 mg, 340 µmol, 1.00 eq.) was added and the reaction mixture

stirred for a further 2.5 hours. Activated charcoal was added and the reaction mixture was transferred via cannula into a flame-dried Schlenk filter and filtered through a plug of celite, under argon, into a fresh, flame-dried, 50 ml Schlenk flask. The Schlenk flask was half immersed in a flask of room temperature water and a pressure-controlled vacuum pump, equipped with a liquid nitrogen trap, was connected directly to the Schlenk flask. The reaction mixture was concentrated *in vacuo* with great care to *ca*. 7 ml and then transferred by syringe to a pre-weighed, flame-dried, 10 ml Schlenk flask, where it was further concentrated *in vacuo* to saturation, ca. 3 ml, at which point small crystals began to appear at the meniscus. *n*-Pentane (*ca*. 3 ml) was carefully layered on top of the CH_2Cl_2 and the resulting precipitated crystals were allowed to settle to the bottom of the flask. The solvent was carefully pipetted off, under a flow of argon, to the level of the crystals. The crystals were washed by decantation with *n*-pentane (3 x 3 ml), each time leaving enough solvent to cover the crystals. The Schlenk flask was reconnected to the vacuum pump and the solution was concentrated *in vacuo* to dryness, to give IPrAuCl as bright white crystals (62.0 mg, 59%). δH (300 MHz, $CDCl_3$) 7.54- 7.46 (2H, t, *J* 7.8, ArH), 7.29 (4H, d, *J* 7.8, ArH), 7.17 (2H, s, NC*HCH*N), 2.62-2.45 (4H, m, CH_3CHCH_3), 1.34 (12H, d, *J* 6.9, $CHCH_3$), 1.22 (12H, d, *J* 6.9, $CHCH_3$). IR (Neat): ν_{max} = 3164 (CH), 3141 (CH), 2967, (CH), 2926 (CH), 2869 (CH), 1583 (C=C), 1550 (C=C), 1470, 1456, 808, 764, 743, 705. Data in agreement with literature values.[5, 200]

Silver(I) triflimidate Prepared according to literature procedure.[201] Ag_2CO_3 (58.8 mg, 213 µmol, 0.6 eq.) was added under argon to $HNTf_2$ (100.0 mg, 356 µmol, 1 eq.), followed by water (1.5 ml). The flask was covered in foil and the reaction mixture heated to 65 °C for 2 hours. The reaction mixture was cooled to room temperature and filtered through a plug of silica. The reaction mixture was concentrated *in vacuo* to give a dirty white solid, which was dissolved in dry diethyl ether (10 ml), stirred for 2 hours and then filtered through a plug of celite. Concentration *in vacuo* gave $AgNTf_2$ as bright white crystals (117 mg, 85%). Decomposed at approximately 200 °C. δ_F (282 MHz, THF) -78.19 (s). IR (Neat): ν_{max} = 1767 vw, 1592, 1332, 1301, 1318, 1193, 1100, 1026, 792, 772, 735. Data in agreement with literature values.[201, 202]

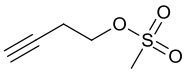
Triphenylphosphine gold(I) chloride 2,2'-Oxydiethanethiol (195 µl, 1.89 mmol, 3.75 eq.) was added



in *ca*. 20 µl portions to a solution of $NaAuCl_4$ (250 mg, 628 µmol, 1.25 eq.) in water (5 ml). The resulting precipitate was allowed to dissolve before the addition of the next portion of thiol. A solution of PPh_3 (132 mg, 502 µl, 1.00 eq.) in ethanol (10 ml) was added dropwise (*ca*. 1 drop per minute) by dropping funnel. After 23 hours the resulting precipitate was collected by vacuum filtration, washed with ethanol and dried *in vacuo* to give Ph_3PAuCl as white crystals (149 mg, 60%). Melting point 240 °C from ethanol (Lit.[203] 239-241 °C). δ_H (300 MHz, $CDCl_3$) 7.61-7.42 (15H, m, ArH). δ_C (101 MHz, $CDCl_3$) 134.4 (CH), 134.3 (CH), 132.2 (CH), 129.5 (CH), 129.3 (CH), 128.6 (C). δ_P (121 MHz, $CDCl_3$) 33.17. IR (Neat): ν_{max} = 3073 (CH), 3060 (CH), 1479, 1433, 1102, 999, 747, 713, 689. Data in agreement with literature values.[204]

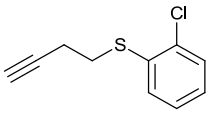
Experimental data

But-3-yn-1-yl methanesulfonate (313) Methanesulfonyl chloride (1.23 ml, 10.7 mmol, 1.5 eq.) was



added to a stirred solution of but-3-yn-1-ol (540 µl, 7.14 mmol, 1.0 eq.) and triethylamine (1.49 ml, 10.7 mmol, 1.5 eq.) in dry diethyl ether (15 ml) under argon. After 20 hours the reaction mixture was added to hexane (20 ml) and washed with brine (3 x 20 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give mesylate **313** as a pale brown oil (1.04 g, 98%) which was used without further purification. δ_H (300 MHz, $CDCl_3$): 4.29 (2H, t, *J* 6.7, CH_2O), 3.02 (3H, s, CH_3), 2.62 (2H, td, *J* 6.7, 2.7, CCH_2CH_2), 2.04 (1H, t, *J* 2.7, CH); δ_C (101 MHz, $CDCl_3$): 78.6 (C), 70.8 (CH), 67.1 (CH_2), 37.4 (CH_2), 19.5 (CH_3). IR (Neat): ν_{max} = 3287 (C≡H), 1350, 1170 (SO_2). Data in accordance with literature values.[205, 206]

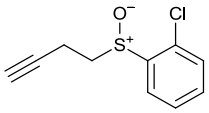
But-3-yn-1-yl(2-chlorophenyl)sulfide (314) A solution of mesylate **313** (1.55 g, 10.4 mmol, 1.0 eq.), in



dry dimethylformamide, (10 ml) was added to a stirred suspension of K_2CO_3 (3.60 g, 26.1 mmol, 2.5 eq.) in dry DMF (50 ml), followed by 2-chlorothiophenol (1.30 ml, 11.5 mmol, 1.1 eq.). After 15 hours the reaction mixture was added to deionised water (30 ml) and the organic phase collected. The aqueous phase was extracted with hexane (2 x 50 ml), the organic fractions were combined, washed with 1 M aqueous HCl (2 x 20 ml), Na_2CO_3 solution (2 x 20

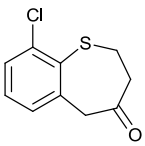
ml) and then brine (2 x 20 ml). The solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give sulfide **314** as a yellow oil (1.67 g, 81 %). δ_H (300 MHz, $CDCl_3$): 7.40-7.31 (2H, m, ArH), 7.25-7.11 (2H, m, ArH), 3.11 (2H, t, *J* 7.5, CH_2S), 2.53 (2H, td, *J* 7.5, 2.7, CCH_2CH_2), 2.07 (1H, t, *J* 2.7, CH); δ_C (101 MHz, $CDCl_3$): 134.6 (C), 134.3 (C), 129.9 (CH), 129.4 (CH), 127.1 (CH), 81.9 (C), 69.9 (CH), 31.5 (CH_2), 18.9 (CH_2); IR (neat): ν_{max} = 3297 (C≡H), 3071 (CH), 2931 (CH), 2116 (C≡C), 1576 (C=C), 1451, 1431, 1252, 1224, 1115, 1035, 742; HR-MS (EI+): *m/z* calcd for $C_{10}H_9ClS$: 196.0110 found 196.0113 [$M^{+\bullet}$].

1-(But-3-yn-1-yl)-1-(2-chlorophenyl)-sulfide (304) 70% *m*-CPBA (1.689 g, 6.90 mmol, 1.0 eq.) was



cautiously added to a stirred solution of sulfide **314** (1.347 g, 6.90 mmol, 1.0 eq.) in CH_2Cl_2 (40 ml) at -78 °C. The reaction was allowed to reach room temperature over a period of 2 hours. The reaction mixture was quenched with $NaHCO_3$ solution (40 ml) and extracted with CH_2Cl_2 (2 x 20 ml). The organic fractions were combined, washed with brine (20 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with 3:1 ethyl acetate:*n*-hexane, gave sulfoxide **304** as colourless crystals (1.250 g, 86%), melting point 62-63 °C from CH_2Cl_2. δ_H (300 MHz, $CDCl_3$): 7.87 (1H, dd, *J* 7.5, 2.0, ArH), 7.54-7.38 (3H, m, ArH), 3.34-3.25 (1H, m, C*H*HS(O)), 3.01-2.92 (1H, m, CH*H*S(O)), 2.84-2.72 (1H, m, CC*H*HCH_2), 2.51-2.39 (1H, m, CCH*H*CH_2), 1.99 (1H, t, *J* 2.7, CH); δ_C (101 MHz, $CDCl_3$) 140.9 (C), 132.3 (CH), 130.2 (C), 130.0 (CH), 128.0 (CH), 126.5 (CH), 80.7 (C), 70.4 (C), 51.8 (CH_2), 11.8 (CH_2); IR (neat): ν_{max} = 3281 (C≡H), 3078 (CH), 2911 (CH), 1572 (C=C), 1446, 1433, 1321, 1271, 1244, 1223, 1098 (SO); MS (EI+): *m/z* (%): 212 (90) [$M^{+\bullet}$], 184 (100), 156 (95); HR-MS (EI+): *m/z* calcd for $C_{10}H_9ClOS$: 212.0063, found 212.0068 [$M^{+\bullet}$].

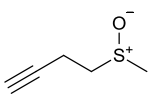
9-chloro-2,3-dihydrobenzo[b]thiepin-4(5*H*)-one (315) Prepared using GP1 with



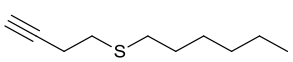
pyridinecarboxylatogold(I) chloride (3.9 mg, 10.0 µmol, 0.0500 eq.), benzaldehyde (21.2 µl 210 µmol, 1.05 eq.) and sulfide **304** (425 mg, 200 µmol, 1.00 eq.) in dry 1,2-dichloroethane (1 ml) for 17 hours. The reaction gave dihydrobenzothiepinone **315** as a pale yellow oil (89% by NMR). The yield was calculated against a known quantity of 1,2,4,5-

tetramethylbenzene. δ_H (300 MHz, $CDCl_3$) 7.36 (1H, d, *J* 2.7, ArH), 7.33 (1H, d, *J* 2.7, ArH), 7.20-7.10 (1 H, m, ArH), 4.00 (2H, s, CCH_2CO), 3.16-3.02 (2H, m, $COCH_2CH_2$), 2.88-2.76 (2H, m, SCH_2CH_2CO). δ_C (101 MHz, $CDCl_3$) 205.4 (CO), 140.4 (C), 137.9 (C), 134.4 (C), 129.1 (CH), 129.1 (CH), 128.8 (CH), 51.8 (CH_2), 44.5 (CH_2), 31.3 (CH_2); IR (neat): ν_{max} = 3053 (CH), 2921 (CH), 1707 (C=O), 1576 (C=C), 1558 (C=C), 1446, 1433, 1321, 1271, 1244, 1223, 1098; MS (EI+): *m/z* (%): 212 (100) [$M^{+\bullet}$], 184 (85), 156 (58); HR-MS (EI+): *m/z* calcd for $C_{10}H_9ClOS$: 212.0063, found 212.0056 [$M^{+\bullet}$].

4-(methylsulfinyl)but-1-yne (317) A freshly prepared and titrated solution of lithium diisopropyl amide in THF (1.55 ml, 4.03 mmol, 1.2 eq.) was added to a solution of dry DMSO (723 µl, 6.72 mmol 2.0 eq.) in dry THF (20 ml) at -78 °C and stirred for 2 hours. A 50% solution of propargyl bromide in toluene (375 µl, 3.36 mmol, 1.0 eq.) was added and after a further hour the reaction was quenched with NH_4Cl solution (50 ml) and allowed to warm to room temperature. The reaction mixture was extracted with ethyl acetate (3 x 50 ml), the organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with ethyl acetate, gave sulfoxide **317** as a yellow oil (21 mg, 11%). δ_H (300 MHz, $CDCl_3$) 3.15-2.83 (2H, m, CH_2S), 2.71 (2H, td, *J* 7.0, 2.6, CHC_2), 2.63 (3H, s, SCH_3), 2.07 (1H, t, *J* 2.6, CH). δ_C (101 MHz, $CDCl_3$) 80.9 (C), 70.7 (CH), 52.9 (CH_2), 38.7 (CH_3), 12.6 (CH_2). IR (neat): ν_{max} = 3228 (C≡CH), 1647, 1426, 1308, 1032, 650: *m/z* (%): 212 (100) [$M^{+\bullet}$], 184 (85), 156 (58); HR-MS (EI+): *m/z* calcd for $C_{10}H_9ClOS$: 212.0063, found 212.0056 [$M^{+\bullet}$].

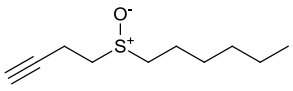


But-3-yn-1-yl(hexyl)sulfide (318) Hexanethiol (2.10 ml, 14.9 mmol, 1.10 eq.) was added to a suspension of 50% NaH (0.682 g, 14.2 mmol, 1.05 eq.) in dry THF (150 ml) under argon at 0 °C. After 1 hour methanesulfonate (**313**) (2.00 g, 13.5 mmol, 1.00 eq.) was added by syringe and the reaction mixture was allowed to reach room temperature. After 24 hours the reaction mixture was quenched with 10% NaOH solution (50 ml) and then extracted with CH_2Cl_2 (2 x 50 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with *n*-hexane, then 9:1 *n*-hexane:CH_2Cl_2, gave sulfate **318** as a colourless oil (2.02 g, 88%). δ_H (300 MHz, $CDCl_3$): 2.67 (2H, t, *J* 7.6, SCH_2), 2.54 (2H, t, *J* 7.6, SCH_2), 2.46 (2H, td, *J*



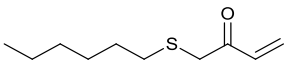
7.6, 2.6, CCH_2), 2.01 (1H, t, *J* 2.6, CH), 1.57 (2H, qn, *J* 7.5 Hz, $SCH_2CH_2CH_2$), 1.41-1.25 (6H, m, $CH_2CH_2CH_2CH_3$), 0.87 (3H, t, *J* 6.8, CH_3); δ_C (100 MHz, $CDCl_3$): δ 82.7 (C), 69.2 (CH), 32.1 (CH_2), 31.3 (CH_2), 30.8 (CH_2), 29.5 (CH_2), 28.4 (CH_2), 22.4 (CH_2), 19.85 (CH_2), 13.9 (CH_3); IR (neat): 3310 (C≡H), 2956 (CH), 2926 (CH), 2856 (CH), 1466, 1434, 1378, 1305, 1223, 1084, 1058; MS (EI+): *m/z* (%): 116 (100) [$M^{+\bullet}$], 64 (66), 53 (79); HR-MS (EI+): *m/z* calcd for C_5H_8OS: 116.0296, found 116.0296 [$M^{+\bullet}$].

But-3-yn-1-yl(hexyl)sulfoxide (319) 70% *m*-CPBA (2.331 g, 10.4 mmol, 1 eq.) was added cautiously



to a stirred solution of sulfide **318** (1.778 g, 10.4 mmol, 1 eq.) in CH_2Cl_2 (200 ml) at -78 °C and allowed to reach room temperature over a period of 17 hours. The reaction mixture was quenched with $NaHCO_3$ (50 ml) and extracted with CH_2Cl_2 (2 x 50 ml). The organic fractions were combined, washed with brine (3 x 50 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with 4:1 ethyl acetate:*n*-hexane, gave sulfoxide **319** as colourless crystals (1.477 g, 76%). Melting point 21-22 °C, from CH_2Cl_2. δ_H (300 MHz, $CDCl_3$): 2.88-2.64 (6H, m, $3CH_2$), 2.07 (1H, t, *J* 2.6, CH), 1.83-1.72 (2H, m, CH_2), 1.54-1.40 (2H, m, CH_2), 1.38-1.29 (4H, m, $2CH_2$) 0.89 (3H, t, *J* 6.9, CH_3); δ_C (100 MHz, $CDCl_3$): 81.0 (C), 70.4 (CH), 52.5 (CH_2), 50.6 (CH_2), 31.3 (CH_2), 28.5 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 13.9 (CH_2), 12.5 (CH_3); IR (neat): ν_{max} = 3217 (CH), 2956 (CH), 2928 (CH), 2859 (CH), 1460, 1408, 1032 (SO), 725; HR-MS (ES+): *m/z* calcd for $C_{10}H_{18}OSNa$: 209.0976 found: 209.0978 [$M+Na^+$].

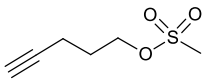
1-(hexylthio)but-3-en-2-one (320) Prepared using GP1 with $PtCl_2$ (2.7 mg, 10.0 µmol, 0.0500 eq.),



benzaldehyde (21.2 µl, 210 µmol, 1.05 eq.) and **319** (37.3 mg, 200 µmol, 1.00 eq.) in dry 1,2-dichloroethane (1 ml) at 80 °C for 18 hours. Purification by flash column chromatography, eluting with 95:5 ethyl acetate:*n*-hexane, gave butenone **320** as a colourless oil (8.2 mg, 23%). δ_H (400 MHz, $CDCl_3$) 6.57 (1H, dd, *J* 17.5, 10.5, $COCHCH_2$), 6.33 (1H, dd, *J* 17.5, 1.2, CHCH*H*), 5.84 (1H, dd, *J* 10.5, 1.2, CHC*H*H), 3.34 (2H, s, SCH_2CO), 2.53-2.43 (2H, t, *J* 7.4, CH_2), 1.56 (2H, qn, *J* 7.4, CH_2), 1.41-1.18 (6H, m, $CH_2CH_2CH_2$), 0.87 (3H, t, *J* 6.9, CH_3). δ_C (101 MHz, $CDCl_3$) 194.5 (C), 134.3 (CH), 129.3 (CH_2), 39.3 (CH_2), 32.2 (CH_2), 31.5 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 22.7 (CH_2), 14.1 (CH_3). IR (neat): 2956 (CH), 2928 (CH), 2857 (CH), 1693 (C=O), 1619 (C=C), 1459, 1401, 1201, 983; MS

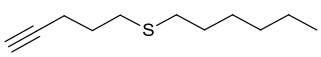
(EI+): *m/z* (%): 186 (100) [$M^{+\bullet}$], 131 (54), 83 (49); HR-MS (EI+): *m/z* calcd for $C_{10}H_{18}OS$: 186.1078, found 186.1084 [$M^{+\bullet}$].

Pent-4-yn-1-yl methanesulfonate (333) Triethylamine (1.24 ml, 8.92 mmol, 1.5 eq.) was added to a



stirred, 0 °C solution of but-3-yn-1-ol (0.55 ml, 5.94 mmol, 1.0 eq.) in dry diethyl ether (10 ml), followed by methanesulfonyl chloride (0.69 ml, 8.92 mmol, 1.5 eq.) and allowed to slowly reach room temperature. After 22 hours the reaction mixture was added to *n*-hexane (10 ml) and washed with brine (3 x 20 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by Kugelrohr distillation gave methanesulfonate **333** as a colourless oil (0.70 g, 79%) δ_H (300 MHz, $CDCl_3$): 4.36 (1H, t, *J* 6.1, CH_2O), 3.03 (3H, s, CH_3), 2.36 (2H, td, *J* 7.0, 2.7, CCH_2), 2.01 (1H, t, *J* 2.7, CH), 1.96 (2H, qn, *J* 6.5, CH_2); δ_C (100 MHz, $CDCl_3$): 82.0 (C), 69.6 (CH), 68.2 (CH_2), 36.9 (CH_2), 27.5 (CH_2), 14.4 (CH_3). MS (EI+): *m/z* (%): 147 (7) [$M^{+\bullet}$], 120 (94), 109 (100); HR-MS (EI+): *m/z* calcd for $C_5H_7O_3S$: 147.0116, found 147.0112 [$M+CH_3^{+\bullet}$].

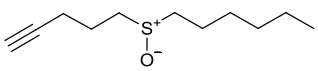
Hexyl(pent-4-yn-1-yl)sulfide (334) Hexanethiol (0.56 ml, 4.00 mmol, 1.2 eq.) was added to a stirred



suspension of 50% NaH (0.18 g, 3.80 mmol, 1.1 eq.) in dry 0 °C THF (30 ml) under argon atmosphere. After 1 hour a solution of methanesulfonate **333** (0.54 g, 3.60 mmol, 1.0 eq.) in dry THF (20 ml) was slowly added by syringe and the reaction mixture was allowed to reach room temperature. After 22 hours the reaction mixture was washed with 10% NaOH solution (2 x 10 ml). CH_2Cl_2 (30 ml) was added and the mixture was washed with brine (3 x 20 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with neat *n*-hexane, then 9:1 *n*-hexane:CH_2Cl_2, then neat CH_2Cl_2, gave sulfide **334** as a colourless oil (0.47 g, 70%). δ_H (300 MHz, $CDCl_3$) 2.62 (2H, t, *J* 7.0, $SCH_2CH_2CH_2C$), 2.51 (2H, t, *J* 7.3, $(CH_2)_3CH_2S$), 2.32 (2H, td, *J* 7.0, 2.7, CCH_2), 1.96 (1H, t, *J* 2.7, CH), 1.80 (2H, qn, *J* 7.0, $SCH_2CH_2CH_2C$), 1.66-1.51 (2H, qn, *J* 7.3, $SCH_2CH_2(CH_2)_3CH_3$), 1.44-1.20 (6H, m, $(CH_2)_3CH_3$), 0.88 (3H, t, *J* 6.8, CH_3); δ_C (100 MHz, $CDCl_3$): δ 83.6 (C), 68.8 (CH), 32.1 (CH_2), 31.4 (CH_2), 30.9 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 22.5 (CH_2), 17.5 (CH_2), 14.0 (CH_3); IR (neat): ν_{max} = 3300 (C≡H), 3240 (C≡H), 2922 (CH), 1449, 1431, 1245,

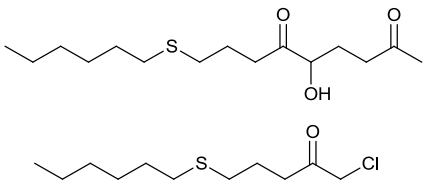
1058, 1025, 756; MS (EI+): *m/z* (%): 183 (10) [$M^{+\bullet}$], 169 (20), 100 (100); HR-MS (EI+): *m/z* calcd for $C_{11}H_{20}S$: 184.1286, found 184.1272 [$M^{+\bullet}$].

Pent-3-yn-1-yl(hexyl)sulfoxide (335) 70% *m*-CPBA (0.136 g, 606 µmol, 1 eq.) was added cautiously to



a -78 °C stirred solution of sulfide **334** (0.112 g, 606 µmol, 1 eq.) in CH_2Cl_2 (30 ml) and allowed to reach room temperature over a period of 16 hours. The reaction mixture was quenched with $NaHCO_3$ (50 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The organic fractions were combined, washed with brine (20 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with 3:1 ethyl acetate:*n*-hexane, gave sulfide **335** as a colourless oil (0.107 g, 88%). δ_H (300 MHz, $CDCl_3$): 2.85-2.57 (4H, m, $2CH_2$), 2.40-2.34 (2H, m, CH_2), 2.04-1.94 (2H, m, CH_2), 2.00 (1H, t, *J* 2.0, CH), 1.74 (2H, m, $CH_2CH_2CH_2$), 1.50-1.36 (2H, m, CH_2), 1.32-1.26 (4H, m, $2CH_2$), 0.86 (3H, t, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$): 82.4 (C), 69.7 (CH), 52.6 (CH_2), 50.9 (CH_2), 31.3 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 21.6 (CH_2), 17.6 (CH_2), 13.9 (CH_3); IR (neat): ν_{max} = 3310 (C≡H), 2959 (CH), 2926 (CH), 2856 (CH), 1455, 1433, 1379, 1281, 1256; MS (EI+): *m/z* (%): 200 (2) [$M^{+\bullet}$], 183 (100), 100 (25); HR-MS (EI+): *m/z* calcd for $C_{11}H_{20}OS$: 200.1235, found 200.1238 [$M^{+\bullet}$].

9-(hexylthio)-5-hydroxynonane-2,6-dione (340) and 1-chloro-5-(hexylthio)pentan-2-one (341)

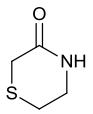


Prepared using GP1 with $PtCl_2$ (6.0 mg, 20 µmol, 0.05 eq.), benzaldehyde (123.8 µl, 1.60 mmol, 4 eq.) and sulfoxide **335** (80.2 mg, 400 µmol, 1 eq.) in dry 1,2-dichloroethane (1 ml) at 70 °C for 17 hours. Purification by flash column chromatography, eluting with 1:19 then 1:9 ethyl acetate:*n*-hexane gave dione **340** as a colourless oil (7.0 mg, 6%) and chloropentanone **341** as a colourless oil (1.7 mg, 2%). 9-(hexylthio)-5-hydroxynonane-2,6-dione (**340**) δ_H (400 MHz, $CDCl_3$) 4.36 (1H, dd, *J* 8.8, 5.0, C*H*OH), 2.84 (1H, dt, *J* 17.9, 7.0, CH*H*COCHOH), 2.75 (1H, dt, *J* 17.9, 7.0, C*H*HCOCHOH), 2.65 (2H, t, *J* 6.8, CH_2COCH_3), 2.53 (2H, t, *J* 7.0, $SCH_2CH_2CH_2CO$), 2.50-2.44 (2H, m, $CH_3(CH_2)_4CH_2S$), 2.34-2.22 (1H, m, C*H*HCHOH), 2.16 (3H, s, $COCH_3$), 2.05 (1H, ddt, *J* 14.9, 8.8, 6.8, CH*H*CHOH), 1.95-1.84 (2H, m, $SCH_2CH_2CH_2CO$), 1.62-1.49 (2H, m, $CH_3(CH_2)_3CH_2CH_2S$), 1.44-1.21 (6H,

m, $CH_3(CH_2)_3$), 0.88 (3H, t, *J* 6.9, CH_3CH_2), O*H* not observed. δ_C (101 MHz, $CDCl_3$) 207.1 (CO), 204.4 (CO), 62.6 (CHOH), 39.4 (CH_2), 37.9 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 31.4 (CH_2), 30.2 (CH_2), 29.7 (CH_3), 28.7 (CH_2), 27.4 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 14.2 (CH_3). IR (neat): ν_{max} = 3320br (OH), 2957 (CH), 2926 (CH), 2858 (CH), 1715 (CO), 1408, 1370, 1225, 1166, 1029, 749. HR-MS (ES-TOF+): *m/z* calcd for $C_{15}H_{28}NO_3SNa$: 311.1657 found: 311.1654 [$M+Na^+$].

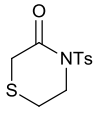
1-chloro-5-(hexylthio)pentan-2-one (**341**) δ_H (400 MHz, $CDCl_3$) 4.10 (2H, s, CH_2Cl), 2.73 (2H, t, *J* 7.0, CH_2CH_2CO), 2.54 (2H, t, *J* 7.0, $SCH_2CH_2CH_2CO$), 2.48 (2H, t, 7.5, $SCH_2(CH_2)_4CH_3$), 1.92 (2H, p, *J* 7.0, CH_2CH_2CO), 1.62-1.50 (2H, m, CH_2), 1.43-1.22 (6H, m, $3CH_2$), 0.89 (3H, t, *J* 7.0, CH_3). δ_C (101 MHz, $CDCl_3$) 202.3 (CO), 48.4 (CH_2Cl), 38.4 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 31.4 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 23.2 (CH_2), 22.7 (CH_2), 14.2 (CH_3). IR (neat): ν_{max} = 2955 (CH), 2927 (CH), 2858 (CH), 1720 (CO), 1459, 1423, 1381, 1292, 1262, 1163, 107; MS (EI+): *m/z* (%): 236 (45) [$M^{+\bullet}$], 201 (50), 144 (53), 115 (100); HR-MS (EI+): *m/z* calcd for $C_{11}H_{21}{}^{35}ClOS$: 236.1002, found 236.1000 [$M^{+\bullet}$].

Thiomorpholin-3-one (367) Prepared via literature procedure.[207] Ethyl bromoacetate (2.23 ml, 20.0



mmol, 1 eq.) was added to a stirred solution of cysteamine hydrochloride (2.27 g, 20.0 mmol, 1 eq.) and K_2CO_3 (5.53 g, 40.0 mmol, 2 eq.) in ethanol (150 ml) and heated to reflux for 3 hours. The reaction mixture was cooled to room temperature, added to water (100 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with ethyl acetate, gave thiomorpholinone **367** as white crystals (1.25 g, 52%), mp 84-85 °C from CH_2Cl_2 (Lit.[208] 84-86 °C). δ_H (300 MHz, $CDCl_3$) 6.75 (1H, brs, NH), 3.77–3.56 (2H, m, CH_2CH_2NH), 3.31 (2H, s, SCH_2CO), 2.88 – 2.71 (2 H, m, SCH_2CH_2). ν_{max} = 3392br (NH), 3186 (NH), 2987 (CH), 2942 (CH), 1662 (CO), 1491. Dat in agreement with literature values.[209]

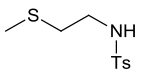
***N*-tosylthiomorpholinone (368)** Prepared via a modified literature procedure.[207] Thiomorpholinone



367 (0.500 g, 42.7 mmol, 1.0 eq.) was added to a stirred suspension of 50% NaH (0.205 g, 42.7 mmol, 1.0 eq.) in dry THF (10 ml) under argon. After 45 minutes tosyl chloride (0.894, 46.9 mmol, 1.1 eq.) was added and the reaction mixture was stirred for 4 hours. Water (20 ml) was

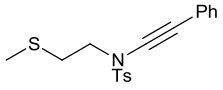
added and the mixture extracted with CH_2Cl_2 (3 x 50 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with 1:5 ethyl acetate:*n*-hexane, gave thiomorpholinone **368** as white crystals (0.202 g, 17%) mp 68-71 °C. δ_H (300 MHz, $CDCl_3$) 7.88 (2H, d, *J* 8.4, ArH), 7.37–7.28 (2H, d, *J* 8.4, ArH), 4.24 (2H, t, *J* 5.8, CH_2CH_2N), 3.24 (2H, s, SCH_2CO), 3.07–2.92 (2H, t, *J* 5.8, SCH_2CH_2), 2.42 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 166.7 (C), 145.2 (C), 135.7 (C), 129.6 (CH), 128.6 (CH), 45.7 (CH_2), 31.3 (CH_2), 27.0 (CH_2), 21.7 (CH_3). IR (Neat): ν_{max} = 3011 (CH), 2931 (CH), 1706 (CO), 1596, 1351, 1321. HR-MS (ES-TOF+): *m/z* calcd for $C_{11}H_{13}NO_3S_2Na$: 294.0235 found: 294.0232 [$M+Na^+$].

***S*-methyl-*N*-tosylcysteamine (374)** Prepared using GP2. Methylation was performed using



cysteamine hydrochloride (5.00 g, 44.0 mmol, 1.00 eq.), CH_3I (2.75 ml, 44.0 mmol, 1.00 eq.) in ethanol (150 ml) and LiOH (2.21, 92.4 mmol, 2.10 eq.) in water (50 ml) for 5 hours. *N*-protection was performed with tosyl chloride (8.47 g, 44.4 mmol, 1.01 eq.) and triethylamine (11 ml, 77.0 mmol, 1.75 eq.) for 19 hours. Purification by flash column chromatography, eluting with 3:7 ethyl acetate:*n*-hexane, gave tosylcysteamine **374** as a colourless oil (8.97 g, 83% over 2 steps). δ_H (300 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.1, ArH), 7.32 (2H, d, *J* 8.1, ArH), 4.92 (1H, t, *J* 6.3, NH), 3.13 (2H, q, *J* 6.3, CH_2NH), 2.57 (2H, t, *J* 6.3, SCH_2CH_2), 2.43 (3H, s, $ArCH_3$), 1.96 (2H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 143.7 (C), 137.0 (C), 129.9 (CH), 127.2 (CH), 41.1 (CH_2), 33.9 (CH_2), 21.7 (CH_3), 14.8 (CH_3). IR (Neat): ν_{max} = 3282br (NH), 2920 (CH), 1598 (C=C), 1426, 1324, 1157s. MS (EI+): *m/z* 245.1 (5) [$M^{+\bullet}$], 14.0 (69), 155.0 (100), 91.1 (15). HR-MS (EI+): *m/z* calcd for $C_{10}H_{15}NO_2S_2$: 245.0546 found: 245.0544 [$M^{+\bullet}$].

***S*-methyl-*N*-phenylethynyl-*N*-tosylcysteamine (375)** Prepared using GP3. Alkynylation was



performed with tosylcysteamine **374** (1.08 g, 4.39 mmol, 1.0 eq.), crude bromophenyl acetylene (0.58 ml, *ca.* 4.83 mmol, 1.1 eq.), 1,10-phenanthroline (158 mg, 878 µmol, 0.20 eq.), $CuSO_4.5H_2O$ (110 mg, 439 µmol, 0.10 eq.) and K_2CO_3 (1.21 g, 8.78 mmol, 2.0 eq.) in toluene (5 ml) for 20 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **375** as a yellow oil (1.45 g, 96%). δ_H (300 MHz, $CDCl_3$)

7.88 (2H, d, *J* 8.3, ArH), 7.43-7.35 (5H, m, ArH), 7.32 (2H, dd, *J* 6.5, 2.7, ArH), 3.72-3.60 (2H, m, CH_2N), 2.87-2.76 (2H, m, SCH_2CH_2), 2.48 (3H, s, CH_3S), 2.16 (3H, s, $ArCH_3$). δ_C (101 MHz, $CDCl_3$) 145.0 (C), 134.7 (C), 131.5 (CH), 123.0 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 122.7 (C), 82.0 (C), 71.2 (C), 51.2 (CH_2), 32.1 (CH_2), 21.8 (CH_3), 15.7 (CH_3). IR (neat): 3062 (CH), 2920 (CH), 2235 (C≡C), 1597w, 1493, 1456, 1363, 1167. HR-MS (ES-TOF+): *m/z* calcd for 368.0755 $C_{18}H_{19}NO_2S_2Na$: 368.0758 found: [$M+Na^+$].

***S*-allyl-*N*-tosylcysteamine (382)** Prepared using GP2. Allylation was performed using cysteamine hydrochloride (1.50 g, 13.2 mmol, 1.00 eq.) and allyl bromide (1.26 ml, 14.5 mmol, 1.10 eq.) in ethanol (45 ml) and LiOH (664 mg, 27.7 mmol, 2.10 eq.) in water (15 ml) for 3 hours. *N*-protection was performed with tosyl chloride (2.54 g, 13.2 mmol, 1.0 eq.) and triethylamine (1.70 ml, 23.1 mmol, 1.75 eq.) for 17 hours. Purification by flash column chromatography, eluting with 1:4 ethyl acetate:*n*-hexane, gave tosylcysteamine **382** as a colourless oil (7.23 g, 67% over 2 steps). δ_H (300 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.2, ArH), 7.30 (2H, d, *J* 8.2, ArH), 5.66 (1H, ddt, *J* 17.0, 9.7, 7.2, CH_2CHCH_2S), 5.08 (1H, br s, NH), 5.03 (1H, dd, *J* 9.7, 1.0, $CHHCHCH_2S$), 5.00 (1H, dd, *J* 17.0, 1.0, $CHHCHCH_2S$), 3.08 (2H, dd, *J* 12.8, 6.5, CH_2NH), 2.98 (2H, d, *J* 7.2, $CHCH_2S$), 2.53 (2H, t, *J* 6.5, SCH_2CH_2), 2.42 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 143.7 (C), 137.0 (C), 133.8 (CH), 129.9 (CH), 127.2 (CH), 117.8 (CH_2), 41.8 (CH_2), 34.3 (CH_2), 30.4 (CH_2), 21.6 (CH_3). IR (neat): ν_{max} = 3286br (NH), 3087 (CH), 2981 (CH), 2918 (CH), 1733w, 1634w, 1598, 1404, 1323, 1154. HR-MS (ES-TOF+): *m/z* calcd for $C_{12}H_{17}NO_2S_2Na$: 294.0598 found: 294.0593 [$M+Na^+$].

***S*-allyl-*N*-phenylethynyl-*N*-tosylcysteamine (383)** Prepared using GP3. Alkynylation was performed with tosylcysteamine **382** (3.00 g, 11.0 mmol, 1.0 eq.), crude bromophenyl acetylene (1.45 ml, *ca.* 12.1 mmol, 1.1 eq.), 1,10-penanthroline (397 mg, 2.20 mmol, 0.1 eq.), $CHSO_4.5H_2O$ (275 mg, 1.10 mmol, 0.2 eq.) and K_2CO_3 (3.04 g, 22.0 mmol, 2 eq.) in toluene (11 ml) for 22 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **383** as a yellow oil (3.55 g, 87%). δ_H (300 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.3, ArH), 7.45–7.31 (4H, m, ArH), 7.3–7.25 (3H, m, ArH), 5.74 (1H, ddt, *J* 17.1, 9.9, 7.2, CH), 5.18–5.06

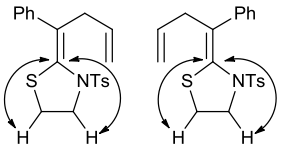
(2H, m, CH_2CHCH$_2$S), 3.64–3.50 (2H, m, CH$_2$N), 3.13 (2H, d, *J* 7.2, CHCH_2S), 2.81–2.66 (2H, m, SCH_2CH$_2$), 2.45 (3H, s, CH$_3$). δ_C (101 MHz, CDCl$_3$) 144.9 (C), 134.8 (C), 133.9 (CH), 131.5 (CH), 123.0 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 122.8 (C), 117.9 (CH$_2$), 82.1 (C), 71.2 (C), 51.4 (CH$_2$), 34.8 (CH$_2$), 28.3 (CH$_2$), 21.8 (CH$_3$). IR (neat): 3066 (CH), 2923 (CH), 2235 (C≡C), 1720w, 1598, 1365, 1168. HR-MS (ES-TOF+): *m/z* calcd for $C_{20}H_{21}NO_2S_2Na$: 394.0911 found: 394.0912 [M+Na$^+$].

2-(1-phenylbut-3-en-1-ylidene)-3-tosylthiazolidine (384 & 385) Prepared using two methods: with and without diphenyl sulfoxide. Ynamide **383** (37.2 mg, 100 µmol, 1.0 eq.) was added under argon into a flame-dried Schlenk tube. Dry CH_2Cl_2 (1 ml) was added under argon, followed by diphenyl sulfoxide (22.2 mg, 110 µmol, 1.1 eq.), AgOTs (1.4 mg, 5.00 µmol, 0.050 eq.) and then IPrAuCl (3.2 mg, 5.00 µmol, 0.050 eq.). The reaction mixture was stirred for 24 hours then filtered through a small plug of silica (*ca.* 500 mg) in a Pasteur pipette, eluting with CH_2Cl_2, and then concentrated *in vacuo*. The yield and ratio of thiazolidines **384** and **385** were determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene (52%, 3.8:1.0). Which structure corresponded to the major isomer could not be determined.

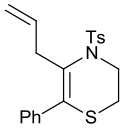
Alternatively, ynmaide **383** (150 mg, 400 µmol, 4 eq.) was added under argon into a flame-dried Schlenk tube. Dry CH_2Cl_2 (4 ml) was added under argon, followed by AgOTs (5.6 mg, 20.0 µmol, 0.2 eq.) and then IPrAuCl (12.8 mg, 20.0 µmol, 0.2 eq.). The reaction mixture was stirred for 18 hours, filtered through a small plug of silica (*ca.* 500 mg) in a Pasteur pipette, eluting with ethyl acetate, and then concentrated *in vacuo*. Purification by flash column chromatography, eluting with 2:3 CH_2Cl_2:*n*-hexane, gave a partially separable mixture of thiazolidines isomers **384** and **385** as a colourless oil (42.3 mg, 29%, 2:1). Which structure corresponded to the major isomer could not be determined. Major isomer: δ_H (300 MHz, CDCl$_3$) 7.36 (2H, d, *J* 8.2, ArH), 7.33 (2H, dd, *J* 8.8, 1.5, ArH), 7.33–7.19 (3H, m, ArH), 7.13 (2H, d, *J* 8.2, ArH), 5.86 (1H, ddt, *J* 16.3, 10.1, 6.2, CH$_2$C*H*CH$_2$C), 5.26 (1H, dd, *J* 16.3, 1.7, C*H*HCHCH$_2$C), 5.11 (1H, dd, *J* 10.1, 1.7, CH*H*CHCH$_2$C), 3.81 (2H, t, *J* 6.3, SCH$_2$CH_2N), 3.21 (2H, dt, *J* 6.2, 1.7, CHCH_2C), 2.86 (2H, t, *J* 6.3, SCH_2CH$_2$N), 2.39 (3H, s, CH$_3$). δ_C (101 MHz, CDCl$_3$) 144.1 (C), 141.0 (C), 135.5 (C), 134.3 (C), 134.2 (CH), 129.7 (C), 129.3 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 126.5

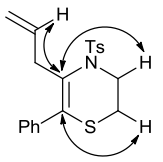
(CH), 116.5 (CH_2), 51.9 (CH_2), 41.7 (CH_2), 31.7 (CH_2), 21.6 (CH_3). Minor isomer: δ_H (400 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.3, ArH), 7.43–7.27 (7H, m, ArH), 5.89 (1H, ddt, *J* 16.8, 10.1, 6.6, CH_2CHCH_2C), 4.98 (1H, dd, *J* 16.8, 1.2, $CHHCHCH_2C$), 4.94 (1H, dd, *J* 10.1, 1.2, $CHHCHCH_2C$), 3.88–3.76 (2H, m, SCH_2CH_2N), 3.67 (2H, dt, *J* 6.6, 1.2, $CHCH_2C$), 2.46 (3H, s, $ArCH_3$), 2.43 (2H, t, *J* 6.8, SCH_2CH_2N). δ_C (101 MHz, $CDCl_3$) 144.9 (C), 140.9 (C), 136.0 (CH), 135.5 (C), 133.7 (C), 133.6 (C), 129.8 (CH), 128.52 (CH), 128.4 (CH), 128.4 (CH), 127.9 (CH), 116.4 (CH_2), 51.7 (CH_2), 39.9 (CH_2), 30.7 (CH_2), 21.9 (CH_3). IR (neat): ν_{max} = 3077 (CH), 2950 (CH), 1638 (C=C), 1597, 1492, 1442, 1356, 1165. HR-MS (ES-TOF+): *m/z* calcd for $C_{20}H_{21}NO_2S_2Na$: 394.0911 found: 394.0899 [$M+Na^+$].

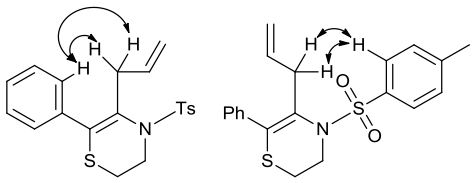
HMBC coupling:



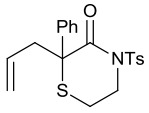
5-allyl-6-phenyl-4-tosyl-3,4-dihydro-2H-1,4-thiazine (386) Ynamide **383** (74.3 mg, 200 µmol, 1.0 eq.) was added under argon into a flame-dried Schlenk tube. Dry CH_2Cl_2 (2 ml) was added under argon, followed by diphenyl sulfoxide (44.4 mg, 220 µmol, 1.1 eq.), and then $(Ph_3PAuNTf_2)_2$.toluene (7.9 mg, 5.00 µmol, 0.025 eq.). The reaction mixture was stirred for 23 hours then filtered through a small plug of silica (*ca.* 500 mg) in a Pasteur pipette, eluting with CH_2Cl_2, and then concentrated *in vacuo*. Yield of thiazine **386** was determined by NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene (20%). Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave thiazine **386** as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.3, ArH), 7.34-7.29 (5H, m, ArH), 7.25-7.19 (2H, m, ArH), 5.69 (1H, ddt, *J* 16.6, 10.1, 6.4, CH_2CHCH_2C), 4.92 (1H, dq, *J* 10.1, 1.4, $CHHCHCH_2C$), 4.86 (1H, dq, *J* 16.6, 1.4, $CHHCHCH_2C$), 3.78 (2H, dd, *J* 7.2, 4.1), 3.22 (2 H, dt, *J* 6.4, 1.4, CH_2N), 2.96-2.86 (2H, m, CH_2S), 2.43 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 143.9 (C), 138.0 (C), 137.8 (C), 135.2 (CH), 129.8 (CH), 129.5 (CH), 128.9 (C), 128.5 (CH), 128.4 (CH), 127.9 (C), 127.4 (CH), 116.2 (CH_2), 45.5 (CH_2), 37.6 (CH_2), 28.2 (CH_2), 21.8 (CH_3). IR (neat): ν_{max} = 2934 (CH), 1638 (C=C), 1598, 1492, 1443, 1343, 1158. HR-MS (ES-TOF+): *m/z* calcd for $C_{12}H_{17}NO_2S_2Na$: 394.0911 found: 394.0910 [$M+Na^+$].



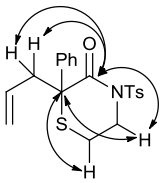
HBMC Coupling: 

NOESY Coupling: 

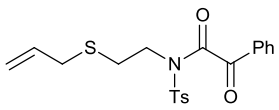
2-allyl-2-phenyl-4-tosylthiomorpholin-3-one (387) Prepared using GP5. Catalysis was performed



using ynamide **383** (87.1 mg, 230 µmol, 1.0 eq.), pyridine *N*-oxide (24.5 mg, 260 µmol, 1.1 eq.), AgOTs (3.3 mg, 12.0 µmol, 0.050 eq.) and IPrAuCl (7.1 mg, 12.0 µmol, 0.050 eq.) in acetonitrile (4 ml) for 21 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **387** as a colourless oil (131 mg, 79%). δ_H (300 MHz, $CDCl_3$) 7.98 (2H, d, *J* 8.2, ArH), 7.56–7.36 (7H, m, ArH), 5.57 (1H, ddt, *J* 14.6, 10.3, 7.4 CH_2CHCH_2C), 5.04 (1H, d, *J* 10.3, $CHHCHCH_2C$), 4.98 (1H, d, *J* 14.6, $CHHCHCH_2C$), 4.74–4.57 (1H, m, CHHN), 3.25–2.99 (2H, m,SCH_2CH_2), 2.98-2.90 (1H, m, CHHN), 2.84 (1H, dd, *J* 14.7, 7.4, CHCHHS), 2.74 (1H, dd, *J* 14.7, 7.4, CHCHHS), 2.61 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 169.6 (CO), 145.0 (C), 139.1 (C), 135.9 (C), 132.2 (CH), 129.5 (CH), 129.0 (CH), 128.6 (CH), 128.0 (CH), 126.1 (CH), 119.0 (CH_2), 58.4 (C), 45.0 (CH_2), 43.4 (CH_2), 26.8 (CH_2), 21.8 (CH_3). IR (neat): ν_{max} = 3073 (CH), 2930 (CH), 1697 (CO), 1598, 1493, 1446, 1354, 1316, 1263. HR-MS (ES-TOF+): *m/z* calcd for $C_{20}H_{21}NO_3S_2Na$: 410.0861 found: 410.0846 [$M+Na^+$].

HBMC Coupling: 

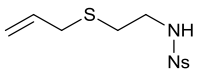
***N*-(2-(allylthio)ethyl)-2-oxo-2-phenyl-N-tosylacetamide (402)** Prepared using GP5. Catalysis was



performed using tosylcysteamine **383** (74.3 mg, 200 µmol, 1.0 eq.), pyridine *N*-oxide (57.1 mg, 600 µmol, 3.0 eq.), $(Ph_3PAuNTf_2)_2$.Toluene (7.9 mg, 5.00 µmol, 0.025 eq.) in acetonitrile (4 ml) for 27 hours. Purification by flash column chromatography, eluting with 20:1:79 diethyl ether:triethylamine:*n*-hexane, gave tosylacetamide **402** as a colourless oil (30.7 mg, 38%). δ_H (300 MHz, $CDCl_3$) 7.96 (2H, dt, *J* 7.4, 1.5, ArH), 7.91 (2H, d, *J* 8.2, ArH), 7.72-7.60 (1H, tt, *J* 7.4, 1.5, ArH), 7.54 (2H, t, *J* 7.4, ArH), 7.40 (2H, d, *J* 8.2, ArH), 5.78 (1H, ddt, *J* 17.1, 9.9, 7.2, CH_2CHCH_2C), 5.20 (1H, d, *J* 17.1, $CHHCHCH_2C$), 5.13 (1H, d, *J* 9.9, $CHHCHCH_2C$), 3.87-3.72 (2H, m,

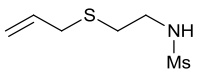
CH_2N), 3.17 (2H, d, *J* 7.2, CHCH_2S), 2.84-2.67 (2 H, m, SCH_2CH_2), 2.48 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 187.9 (CO), 167.4 (CO), 146.2 (C), 134.6 (CH), 134.3 (C), 134.0 (CH), 132.9 (C), 130.3 (CH), 129.9 (CH), 129.0 (CH), 128.6 (CH), 118.0 (CH_2), 45.1 (CH_2), 34.8 (CH_2), 28.5 (CH_2), 21.9 (CH_3). IR (neat): ν_{max} = 3069 (CH), 2922 (CH), 1678 (CO), 1597 (C=C), 1451, 1371, 1207, 1167, 1089, 1053. HR-MS (ES-TOF+): *m/z* calcd for $C_{20}H_{21}NO_4S_2Na$: 426.0810 found: 426.0811 [M+Na^+].

***S*-allyl-*N*-*p*-nosylcysteamine (406)** Prepared using GP2. Allylation was performed using cysteamine



hydrochloride (1.00 g, 8.80 mmol, 1.0 eq.), allyl bromide (1.05 ml, 8.80 mmol, 1.0 eq.) in ethanol (30 ml) and LiOH (443 mg, 18.5 mmol, 2.1 eq.) in water (10 ml) for 3 days. *N*-protection was performed with *p*-nosyl chloride (2.15 g, 9.70 mmol, 1.1 eq.) and triethylamine (1.48 ml, 10.6 mmol, 1.2 eq.) for 23 hours. Purification by flash column chromatography, eluting with 1:3 ethyl acetate:*n*-hexane, gave nosylcysteamine **406** as colourless crystals (1.57 g, 59% over 2 steps), melting point 98-99 °C from CH_2Cl_2. δ_H (300 MHz, $CDCl_3$) 8.38 (2H, d, *J* 9.0, ArH), 8.07 (2H, d, *J* 9.0, ArH), 5.70 (1H, ddt, *J* 17.1, 10.0, 7.2, CH_2CHCH_2S), 5.11-5.07 (1H, br s, NH), 5.09 (1H, dd, *J* 10.0, 1.3, CH*H*CHCH_2S), 5.05 (1H, dd, *J* 16.8, 1.4, C*H*HCHCH_2S), 3.19 (2H, dd, *J* 12.5, 6.3, CH_2NH), 3.04 (2H, d, *J* 7.2, CHCH_2S), 2.59 (2H, t, *J* 6.3, SCH_2CH_2). δ_C (101 MHz, $CDCl_3$) 150.1 (C), 146.2 (C), 133.8 (CH), 128.5 (CH), 124.6 (CH), 118.1 (CH_2), 41.9 (CH_2), 34.5 (CH_2), 30.7 (CH_2). IR (Neat): ν_{max} = 3285br (NH), 3121 (CH), 2922 (CH), 1528s (NO_2), 1404, 1349s, 1162s. MS (EI+): *m/z* 302.0 (28%) [$M^{+\bullet}$], 215.0 (41%), 186.0 (100%), 122.0 (97%), 116.0 (62%), 87.0 (63%). HR-MS (EI+): *m/z* calcd for $C_{11}H_{14}NO_4S_2$: 302.0400 found: 302.0395 [$M^{+\bullet}$].

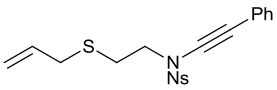
***S*-allyl-*N*-mesylcysteamine (407)** Prepared using GP2. Allylation was performed using cysteamine



hydrochloride (1.00 g, 8.80 mmol, 1.0 eq.) and allyl bromine (77 µl, 8.80 mmol,1.0 eq.) in ethanol (30 ml) and LiOH (443 mg, 18.5 mmol, 2.1 eq.) in water (10 ml) for 3 days. *N*-protection was performed with mesyl chloride (1.11 g, 9.70 mmol, 1.1 eq.) and triethylamine (1.48 ml, 10.6 mmol, 1.2 eq.) for 23 hours. Purified by flash column chromatography, eluting with 2:3 ethyl acetate:*n*-hexane, gave mesylcysteamine **407** as a colourless oil (0.983 g, 57% over 2 steps). δ_H (300 MHz, $CDCl_3$) 5.77 (1H, ddt, *J* 17.0, 9.7, 7.2, CH), 5.13 (1H, dd, *J* 17.0, 1.3,

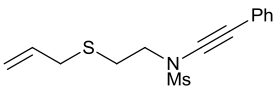
CH*H*CH_2CH_2S), 5.11 (1H, dd, *J* 9.7, 1.3, C*H*HCH_2CH_2S), 4.79 (1H, br s, NH), 3.29 (2H, dd, *J* 12.7, 6.3, CH_2NH), 3.14 (2H, dt, *J* 7.2, 1.0, CHCH_2S), 2.98 (3H, s, CH_3), 2.68 (2H, t, *J* 6.4, SCH_2CH_2). δ_C (101 MHz, $CDCl_3$) 134.0 (CH), 118.0 (CH_2), 42.1 (CH_2), 41.0 (CH_3), 34.6 (CH_2), 31.2 (CH_2). IR (neat): ν_{max} = 3282br (NH), 2925 (CH), 1634 (C=C), 1407, 1315 (SO_2NHR), 1145 (SO_2NHR). MS (EI+): *m/z* 195.0 (85%) [$M^{+\bullet}$], 108.0 (100%), 100.0 (77%), 87.0 (52%). HR-MS (EI+): *m/z* calcd for $C_6H_{13}NO_2S_2$: 195.0392 found: 195.0388 [$M^{+\bullet}$].

***S*-allyl-*N*-phenylethynyl-*N*-nosylcysteamine (409)** Prepared using GP3. Alkynylation was performed



with nosylcysteamine **406** (151 mg, 500 µmol, 1.0 eq.), crude bromophenylacetylene (66.0 µl, *ca.* 550 µmol, 1.1 eq.), 1,10-phenanthroline (16.2 mg, 90.0 µmol, 0.18 eq.), $CuSO_4.5H_2O$ (15.0 mg, 60.0 µmol, 0.12 eq.) and K_2CO_3 (138 mg, 1.00 mmol, 2.0 eq.) in toluene (1 ml) for 20 hours. Purification by flash column chromatography, eluting with 1:4 ethyl acetate:*n*-hexane, gave ynamide **409** as colourless crystals (67.5 mg, 33%) melting point 71-73 °C, from CH_2Cl_2. δ_H (300 MHz, $CDCl_3$) 8.41 (2H, d, *J* 9.0, ArH), 8.15 (2H, d, *J* 9.0, ArH), 7.50–7.27 (5H, m, ArH), 5.75 (1H, ddt, *J* 16.7, 10.2, 7.2, CH), 5.19–5.04 (2H, m, CH_2CHCH_2S), 3.73–3.54 (2H, m, CH_2N), 3.14 (2H, d, *J* 7.3, CHCH_2S), 2.86–2.70 (2H, m, SCH_2CH_2). δ_C (101 MHz, $CDCl_3$) 150.8 (C), 143.0 (C), 133.9 (CH), 131.7 (CH), 129.1 (CH), 128.6 (CH), 128.6 (CH), 124.5 (CH), 121.9 (C), 118.0 (CH_2), 80.7 (C), 71.9 (C), 51.7 (CH_2), 34.8 (CH_2), 28.4 (CH_2). IR (neat): 3105 (CH), 2929 (CH), 2238 (C≡C), 1606w, 1531s (NO_2), 1373, 1349, 1172. HR-MS (ES-TOF+): *m/z* calcd for $C_{19}H_{20}N_2O_5S_2Na$: 443.0711 found: 443.0715 [M+H_2O+Na^+].

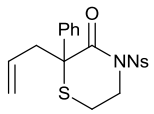
***S*-allyl-*N*-phenylethynyl-*N*-mesylcysteamine (410)** Prepared using GP3. Alkynylation was performed



with mesylcysteamine **407** (97.7 mg, 500 µmol, 1.0 eq.), crude bromophenyl acetylene (66.0 µl, *ca.* 550 µmol, 1.1 eq.), 1,10-phenanthroline (16.2 mg, 90.0 µmol, 0.18 eq.), $CuSO_4.5H_2O$ (15.0 mg, 60.0 µmol, 0.12 eq.) and K_2CO_3 (138.2 mg, 1.00 mmol, 0.20 eq.) in toluene (1 ml) for 20 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **410** as a yellow oil (74.6 mg, 50%). δ_H (300 MHz, $CDCl_3$) 7.5–7.38 (2H, m, ArH), 7.37–7.29 (3H, m, ArH), 5.81 (1H, ddt, *J* 17.1, 9.9,

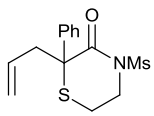
7.2, CH_2CHCH_2C), 5.24–5.12 (2H, m, CH_2CHCH_2S), 3.79–3.69 (2H, m, CH_2N), 3.23 (3H, s, CH_3), 3.19 (2H, d, *J* 7.2, $CHCH_2S$), 2.95–2.79 (2H, m, SCH_2CH_2). δ_C (101 MHz, $CDCl_3$) 133.8 (CH), 131.6 (CH), 128.4 (CH), 128.3 (CH), 122.4 (C), 118.0 (CH_2), 81.1 (C), 71.7 (C), 50.9 (CH_2), 38.9 (CH_2), 34.7 (CH_2), 28.7 (CH_3). IR (neat): 3107 (CH), 2928 (CH), 2236 (C≡C), 1634w, 1357, 1161. HR-MS (ES-TOF+): *m/z* calcd for $C_{14}H_{17}NO_2S_2Na$: 318.0598 found: 318.0610 [$M+Na^+$].

2-allyl-2-phenyl-4-nosylthiomorpholin-3-one (411) Prepared using GP5. Catalysis was performed



using ynamide **409** (105 mg, 260 µmol, 1.0 eq.), pyridine *N*-oxide (27.3 mg, 287 µmol, 1.1 eq.), AgOTs (3.6 mg, 13.0 µmol, 0.050 eq.) and IPrAuCl (8.1 mg, 13.0 µmol, 0.050 eq.) in CH_3CN (3 ml) for 15 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **411** as a colourless oil (64.2 mg, 59%). δ_H (300 MHz, $CDCl_3$) 8.41 (2H, d, *J* 9.0, ArH), 8.22–8.13 (2H, m, ArH), 7.38–7.29 (5H, m, ArH), 5.39 (1H, ddt, *J* 17.3, 10.3, 7.3, CH_2CHCH_2C), 4.92 (1H, d, *J* 10.3, $CHHCHCH_2C$), 4.86 (1H, dd, *J* 17.3, 2.0, $CHHCHCH_2C$), 4.60–4.45 (1H, m, CHHN), 3.18–2.88 (3H, m, CHHN and SCH_2CH_2), 2.67 (1H, dd, *J* 14.3, 7.3, $CHCHHS$), 2.57 (1H, dd, *J* 14.3, 7.3, $CHCHHS$). δ_C (101 MHz, $CDCl_3$) 167.0 (CO), 150.8 (C), 144.4 (C), 138.4 (C), 131.7 (CH), 123.0 (CH), 129.3 (CH), 128.4 (CH), 125.9 (CH), 124.1 (CH), 119.4 (CH_2), 58.5 (C), 44.8 (CH_2), 43.7 (CH_2), 26.7 (CH_2). IR (neat): ν_{max} = 3107 (CH), 2931 (CH), 1698 (CO), 1608, 1530 (NO_2), 1491, 1446, 1349, 1313, 1171. HR-MS (ES-TOF+): *m/z* calcd for $C_{19}H_{18}N_2O_5S_2Na$: 441.0555 found: 441.0546 [$M+Na^+$].

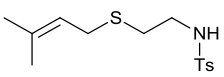
2-allyl-2-phenyl-4-mesylthiomorpholin-3-one (412) Prepared using GP5. Catalysis was performed



using ynamide **410** (80.0 mg, 270 µmol, 1.0 eq.), pyridine *N*-oxide (28.2 mg, 297 µmol, 1.1 eq.), AgOTs (3.8 mg, 14.0 µmol, 0.050 eq.) and IPrAuCl (8.4 mg, 14.0 µmol, 0.050 eq.) in CH_3CN (3 ml) for 15 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **412** as a colourless oil (24.4 mg, 29%). δ_H (300 MHz, $CDCl_3$) 7.60–7.48 (2H, m, ArH), 7.48–7.28 (3H, m, ArH), 5.56 (1H, ddt, *J* 17.1, 10.2, 7.4, CH_2CHCH_2C), 5.00 (1H, d, *J* 10.2, $CHHCHCH_2C$), 4.96 (1H, d, *J* 17.1, $CHHCHCH_2C$), 4.44-4.21 (1H, m, CHHN), 3.44 (3H, s, CH_3), 3.01–2.86 (3H, m, CHHN and SCH_2CH_2), 2.83 (1H, dd, *J* 15.0, 7.4, $CHCHHS$),

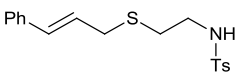
2.78 (1H, dd, *J* 15.0, 7.4, CHCH*H*S). δ_C (101 MHz, $CDCl_3$) 171.4 (CO), 138.9 (C), 132.2 (CH), 129.3 (CH), 128.3 (CH), 126.1 (CH), 119.3 (CH_2), 58.6 (C), 45.2 (CH_2), 42.7 (CH_2), 42.4 (CH_2), 26.8 (CH_3). IR (neat): ν_{max} = 3021 (CH), 2933 (CH), 1692 (CO), 1491, 1446, 1347, 1316, 1163. HR-MS (ES-TOF+): *m/z* calcd for $C_{14}H_{17}NO_3S_2Na$: 334.0548 found: 334.0534 [$M+Na^+$].

***S*-prenyl-*N*-tosylcysteamine (414)** Prepared using GP2. Allylation was performed using cysteamine



hydrochloride (1.00 g, 8.80 mmol, 1.00 eq.) and prenyl bromide (1.02 ml, 8.80 mmol, 1.00 eq.) in ethanol (30 ml) and LiOH (443 mg, 18.5 mmol, 2.10 eq.) in water (10 ml) for 47 hours. *N*-protection was performed with tosyl chloride (1.70 g, 8.90 mmol, 1.01 eq.) and triethylamine (2.15 ml, 29.3 mmol, 3.30 eq.) for 16 hours. Purification by flash column chromatography, eluting with 1:4 ethyl acetate:*n*-hexane, gave tosylcysteamine **414** as a yellow oil (2.05 g, 78% over 2 steps). δ_H (300 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.2, ArH), 7.31 (2H, d, *J* 8.2, ArH), 5.18–5.03 (1H, m, CH), 4.90 (1H, t, *J* 5.9, NH), 3.09 (2H, q, *J* 6.3, CH_2NH), 3.00 (2H, d, *J* 7.8, CHCH_2), 2.54 (2H, t, *J* 6.3, SC$H_2$$CH_2$), 2.43 (3H, s, Ar$CH_3$), 1.70 (3H, s, CH_3), 1.57 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 143.7 (C), 137.1 (C), 136.3 (C), 129.9 (CH), 127.3 (CH), 120.1 (CH), 41.9 (CH_2), 31.0 (CH_2), 29.1 (CH_2), 25.8 (CH_3), 21.7 (CH_3), 17.8 (CH_3). IR (neat): ν_{max} = 3279b (NH), 2972 (CH), 2924 (CH), 2859 (CH), 1599 (C=C), 1440, 1324, 1156. HR-MS (ES-TOF+): *m/z* calcd for $C_{14}H_{21}NO_2S_2Na$: 322.0911 found: 322.0909 [$M+Na^+$].

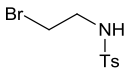
***S*-cinnamyl-*N*-tosylcysteamine (415)** Prepared using GP2. Allylation was performed using



cysteamine hydrochloride (1.00 g, 8.80 mmol, 1.0 eq.) and cinnamyl bromide (1.73 g, 8.80 mmol, 1.0 eq.) in ethanol (30 ml) and LiOH (443 mg, 18.5 mmol, 2.1 eq.) in water (10 ml) for 23 hours. *N*-protection was performed with tosyl chloride (1.70 g, 8.90 mmol, 1.01 eq.) and triethylamine (2.15 ml, 29.3 mmol, 3.3 eq.) for 15 hours. Purified by crystallisation, from CH_2Cl_2 and *n*-hexane, gave tosylcysteamine **415** as white crystals (1.42 g, 48% over 2 steps). δ_H (300 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.3, ArH), 7.32 (4H, m, ArH), 7.30-7.23 (3H, m, ArH), 6.36 (1H, d, *J* 15.7, PhC*H*CH), 6.07 (1H, dt, *J* 15.7, 7.4, CHC*H*CH_2), 4.89 (1H, s, NH), 3.19 (2H, dd, *J* 7.4, 1.1, CHC*H*2S), 3.12 (2H, m, CH_2N), 2.58 (2H, t, *J* 6.5, SC$H_2$$CH_2$), 2.41 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$)

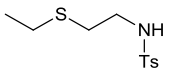
143.7 (C), 137.0 (C), 136.5 (C), 133.0 (CH), 129.9 (CH), 128.8 (CH), 128.0 (CH), 127.2 (CH), 126.5 (CH), 125.3 (CH), 46.0 (CH_2), 34.0 (CH_2), 30.6 (CH_2), 21.7 (CH_3). IR (neat): ν_{max} = 3308b (NH), 3024 (CH), 2977 (CH), 1665 (C=C), 1599 (C=C), 1440, 1417, 1351, 1316, 1148, 1086. HR-MS (ES-TOF+): *m/z* calcd for $C_{18}H_{21}NO_2S_2Na$: 370.911 found: 370.0910 [$M+Na^+$].

***N*-tosyl-2-bromoethanamine (417)** Tosyl chloride (9.40 g, 49.3 mmol, 1.01 eq.) and then



triethylamine (17.0 ml, 122.0 mmol, 2.50 eq.) were added to a stirred solution of bromoethanamine (10.0 g, 48.8 mmol, 1.00 eq.) in dry CH_2Cl_2 (100 ml) under argon at 0 °C. After 27 hours the reaction mixture was washed with NH_4Cl solution (100 ml) and then water (2 x 100 ml). The organic fraction was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography, eluting with 3:7 ethyl acetate:*n*-hexane, to give tosylcysteamine **417** as white crystals (10.1 g, 74%), mp 88-89 °C from CH_2Cl_2 (Lit.[210] 88-90 °C). δ_H (300 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.3, ArH), 7.32 (2H, d, *J* 8.0, ArH), 5.16 (1H, s, *J* 5.8, NH), 3.40-3.33 (4H, m, CH_2CH_2), 2.43 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 144.0 (C), 137.0 (C), 123.0 (CH), 127.2 (CH), 44.65 (CH_2), 31.7 (CH_2), 21.7 (CH_3). IR (neat): ν_{max} = 3269br (NH), 3030 (CH), 2966 (CH), 2923 (CH), 1597, 1449, 1423, 1313, 1150, 1087. Data in agreement with literature values.[210]

***S*-ethyl-*N*-tosylcysteamine (418)** Ethanethiol (0.28 µl, 3.80 mmol, 1.05 eq.) was cautiously added to a



stirred suspension of 50% NaH (192 mg, 4.00 mmol, 1.10 eq.) in dry THF (50 ml) under argon at 0 °C. After 25 minutes sulfonamide **417** was added (1.00 g, 3.60 mmol, 1.00 eq.). The reaction was allowed to warm to room temperature over a period of 10 hours and then added to 10% NaOH solution (50 ml). The organic fraction was collected and the aqueous fraction extracted with CH_2Cl_2 (2 x 50 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography, eluting with 1:3 ethyl acetate:*n*-hexane, to give tosylcysteamine **418** as a yellow oil (0.756 g, 81%). δ_H (300 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.3, ArH), 7.31 (2H, d, *J* 8.0, ArH), 4.69 (1H, br s, NH), 3.11 (2H, t, *J* 6.4, C*H*$_2$NH), 2.60 (2H, t, *J* 6.4, SC*H*$_2$CH$_2$), 2.43 (3H, s, CH_3), 2.40 (2H, q, *J* 7.4, CH_3CH_2), 1.17 (3H, t, *J* 7.4, C*H*$_3$CH$_2$). δ_C (101 MHz, $CDCl_3$) 143.7 (C), 137.1 (C), 129.9 (CH), 127.3 (CH), 41.8 (CH_2), 31.5 (CH_2), 25.5

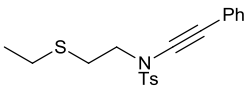
(CH_2), 21.7 (CH_3), 14.8 (CH_3). IR (Neat): ν_{max} = 3279br (NH), 2967 (CH), 2924 (CH), 2859 (CH), 1598, 1450br, 1322, 1156. HR-MS (ES-TOF+): *m/z* calcd for $C_{16}H_{19}NO_2S_2Na$: 282.0593 found: 282.0598 [M+Na^+].

***S*-prenyl-*N*-phenylethynyl-*N*-tosylcysteamine (419)** Prepared using GP3. Alkynylation was performed with tosylcysteamine **414** (300 mg, 1.00 mmol, 1.0 eq.), crude bromophenyl acetylene (181 µl, *ca.* 1.10 mmol, 1.1 eq.), 1,10-phenanthroline (32.4 mg, 180 µmol, 0.18 eq.), $CuSO_4.5H_2O$ (30.0 mg, 120 µmol, 0.12 eq.) and K_2CO_3 (276 mg, 2.00 mmol, 2.0 eq.) in toluene (1 ml) for 21 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **419** as a yellow oil (364 mg, 91%). δ_H (300 MHz, $CDCl_3$) 7.98–7.79 (2H, m, ArH), 7.40–7.32 (4H, m, ArH), 7.32–7.27 (3H, m, ArH), 5.19 (1H, m, C*H*CH_2), 3.67–3.47 (2H, m, CH_2N), 3.16 (2H, d, *J* 7.8, CHC*H*$_2$), 2.81–2.69 (2H, m, SC*H*CH_2), 2.46 (3H, s, ArCH_3), 1.70 (3H, s, CH_3), 1.66 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 144.9 (C), 136.2 (C), 134.8 (C), 131.6 (CH), 130.0 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 122.8 (C), 120.4 (CH), 82.2 (C), 71.2 (C), 51.8 (CH_2), 29.7 (CH_2), 29.1 (CH_2), 25.8 (CH_3), 21.8 (CH_3), 17.9 (CH_3). IR (neat): 3052 (CH), 2923 (CH), 2234 (C≡C), 1602w, 1440, 1367, 1165. HR-MS (ES-TOF+): *m/z* calcd for $C_{22}H_{25}NO_2S_2Na$: 422.1215 found: 422.1224 [M+Na^+].

***S*-cinnamyl-*N*-phenylethynyl-*N*-tosylcysteamine (420)** Prepared using GP3. Alkynylation was performed with tosylcysteamine **415** (348 mg, 1.00 mmol, 1.0 eq.), crude bromophenyl acetylene (181 µl, *ca.* 1.10 mmol, 1.1 eq.), 1,10-phenanthroline (32.4 mg, 180 µmol, 1.8 eq.), $CuSO_4.5H_2O$ (30.0 mg, 120 µmol, 0.12 eq.) and K_2CO_3 (276 mg, 2.00 mmol, 2.0 eq.) in toluene (4 ml) for 16 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **420** as a yellow oil (300 mg, 75%). δ_H (300 MHz, $CDCl_3$) 7.86–7.71 (2H, d, *J* = 8.4, ArH), 7.40 –7.14 (12H, m, ArH), 6.48 (1H, d, *J* 15.7, PhCH), 6.11 (1H, dt, *J* = 15.7, 7.3, CHC*H*CH_2), 3.70–3.51 (2H, m, CH_2CH_2N), 3.33 (2H, dd, *J* 7.3, 1.1, CHC*H*$_2$S), 2.87 – 2.68 (2H, m, SC*H*$_2CH_2$), 2.42 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 144.7 (C), 136.5 (C), 134.7 (C), 132.9 (CH), 131.4 (CH), 129.8 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 127.7 (3 CH), 126.4

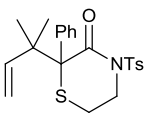
(CH), 125.4 (CH), 122.6 (C), 82.0 (C), 71.1 (C), 51.5 (CH_2), 34.3 (CH_2), 28.3 (CH_2), 21.6 (CH_3). IR (neat): 3028 (CH), 2923 (CH), 2234 (C≡C), 1597w, 1493, 1443, 1395, 1168. HR-MS (ES-TOF+): *m/z* calcd for $C_{26}H_{25}NO_2S_2Na$: 470.1224 found: 470.1223 [$M+Na^+$].

***S*-ethyl-*N*-phenylethynyl-*N*-tosylcysteamine (421)** Prepared using GP3. Alkynylation was performed



with tosylcysteamine **418** (1.08 g, 4.39 mmol, 1.0 eq.), crude bromophenyl acetylene (0.58 ml, *ca.* 4.83 mmol, 1.1 eq.), 1,10-phenanthroline (158 mg, 878 µmol, 0.2 eq.), $CuSO_4.5H_2O$ (110 mg, 439 µmol, 0.10 eq) and K_2CO_3 (1.21 g, 8.78 mmol, 2.0 eq.) in toluene (5 ml) for 20 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **421** as a yellow oil (167 mg, 66%). δ_H (300 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8.4, ArH), 7.42–7.32 (4H, m, ArH), 7.32–7.26 (3H, m, ArH), 3.65–3.53 (2H, m, CH_2N), 2.88–2.74 (2H, m, SCH_2CH_2), 2.56 (2H, q, *J* 7.4, CH_3CH_2S), 2.46 (3H, s, $PhCH_3$), 1.26 (3H, t, *J* 7.4, CH_3CH_2). δ_C (101 MHz, $CDCl_3$) 145.0 (C), 134.8 (C), 131.6 (CH), 123.0 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 122.8 (C), 82.1 (C), 71.2 (C), 51.7 (CH_2), 29.5 (CH_2), 26.2 (CH_2), 21.8 (CH_3), 14.9 (CH_3). IR (neat): 3065 (CH), 2976 (CH), 2926 (CH), 2877 (CH), 2235 (C≡C), 1597w, 1494, 1456, 1365, 1169. HR-MS (ES-TOF+): *m/z* calcd for 382.0911 $C_{19}H_{21}NO_2S_2Na$: 382.0908 found: [$M+Na^+$].

2-prenyl-2-phenyl-4-tosylthiomorpholin-3-one (422) Prepared using GP5. Catalysis was performed



using ynamide **419** (218 mg, 550 µmol, 1.0 eq.), pyridine *N*-oxide (57.2 mg, 600 µmol, 1.1 eq.), AgOTs (7.7 mg, 28.0 µmol, 0.05 eq.) and IPrAuCl (17.1 mg, 28.0 µmol, 0.050 eq.) in CH_3CN (11 ml) for 17 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **422** as a yellow oil (154.5 mg, 68%). δ_H (300 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.3, ArH), 7.38 (2H, d, *J* 8.1, ArH), 7.31 (5H, m, ArH), 6.13 (1H, brs, CH_2CHCH_2C), 4.91 (1H, d, *J* 10.0, $CHHCHCH_2C$), 4.92–4.68 (1H, m, $CHHCHCH_2C$), 4.47 (1H, ddd, *J* 14.2, 6.8, 2.5, $CHHN$), 3.01 (1H, td, *J* 11.4, 6.8, $CHHN$), 2.90–2.60 (2H, m, SCH_2CH_2), 2.51 (3H, s, $ArCH_3$), 1.41–0.72 (6H, m, CH_3CCH_3). δ_C (101 MHz, $CDCl_3$) 169.0 (CO), 144.7 (C), 144.1 (CH), 136.0 (C), 135.9 (C), 129.3 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 113.4 (CH_2), 44.9 (C), 43.1 (C), 26.4 (CH_2), 24.5 (CH_3), 21.8 (CH_3). IR (Neat): ν_{max} = 3067 (CH), 2973 (CH), 2902 (CH), 1698 (CO), 1596, 1491, 1445,

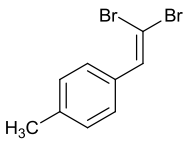
1394, 1311, 1166. HR-MS (ES-TOF+): *m/z* calcd for $C_{22}H_{25}NO_3S_2Na$: 438.1174 found: 438.1177 [M+Na^+].

2-cinnamyl-2-phenyl-4-tosylthiomorpholin-3-one (423) Prepared using GP5. Catalysis was performed using ynamide **420** (38.5 mg, 86.0 µmol, 1.0 eq.), pyridine *N*-oxide (9.0 mg, 95.0 µmol, 1.1 eq.), AgOTs (1.2 mg, 4.30 µmol, 0.050 eq.) and IPrAuCl (2.7 mg, 4.30 µmol, 0.050 eq.) in CH_3CN (2 ml) for 15 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **423** as a colourless oil (28.7 mg, 72%, d.r.: 5.2:1). δ_H (300 MHz, $CDCl_3$) 7.88 (2H, d, *J* 8.3, ArH), 7.38 (2H, d, *J* 8.3, ArH), 7.35–7.30 (1H, m, ArH), 7.23–6.91 (7H, m, ArH), 6.85–6.67 (2H, m, ArH), 6.22 (1H, ddd, *J* 17.0, 10.5, 6.5, CH_2CHCH_2C major), 5.90 (1H, ddd, *J* 17.0, 10.4, 8.4, CH_2CHCH_2C minor), 5.04 (1H, dt, *J* 10.5, 1.5, CHHCHCH_2C major), 4.94 (1H, d, *J* 10.4, CHHCHCH_2C minor), 4.83 (1H, dt, *J* 17.0, 1.4, CHHCHCH_2C), 4.58 – 4.37 (1H, m, CHHN), 4.25 (1H, d, *J* 6.5, CHPh major), 4.18 (1H, d, *J* 8.5, CHPh minor), 3.18–2.95 (2H, m, SCH_2CH_2), 2.95–2.68 (1H, m, CHHN), 2.52 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 168.8 (CO), 144.8 (C), 138.1 (C), 137.5 (C), 137.4 (C), 135.7 (C), 130.5 (CH), 129.3 (CH), 128.6 (CH), 128.4 (CH), 127.7 (CH), 127.3 (CH), 126.7 (CH), 126.6 (CH), 117.7 (CH_2), 63.5 (C), 57.6 (C), 43.5 (CH_2), 26.2 (CH_2), 21.7 (CH_3). IR (neat): ν_{max} = 3029 (CH), 2927 (CH), 1699 (CO), 1596, 1492, 1447, 1356, 1316, 1169. HR-MS (ES-TOF+): *m/z* calcd for $C_{26}H_{25}NO_3S_2Na$: 486.1174 found: 486.1176 [M+Na^+].

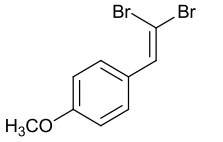
2-phenyl-4-tosylthiomorpholin-3-one (424) Prepared using GP5. Catalysis was performed using ynamide **421** (206 mg, 570 µmol, 1.0 eq.), pyridine *N*-oxide (59.9 mg, 630 µmol, 1.1 eq.), AgOTs (2.8 mg, 10.0 µmol, 0.050 eq.) and IPrAuCl (6.2 mg, 10.0 µmol, 0.05 eq.) in CH_3CN (4 ml) for 18 hours. Purification by flash column chromatography, eluting with 1:4 ethyl acetate:*n*-hexane, gave thiomorpholinone **424** as a yellow oil (111 mg, 56%). δ_H (300 MHz, $CDCl_3$) 7.92 (2H, d, *J* 8.4, ArH), 7.51–7.16 (7H, m, ArH), 4.69 (1H, s, CHPh), 4.33 (1H, dt, *J* 14.6, 5.4, CHHN), 4.20 (1H, ddd, *J* 14.6, 7.3, 5.4, CHHN), 3.20–3.02 (2H, m, SCH_2), 2.47 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 167.8 (CO), 145.2 (C), 135.9 (C), 133.9 (C), 129.7 (CH), 128.92 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 48.3 (CH), 44.9 (CH_2), 27.9 (CH_2), 21.9 (CH_3). IR (Neat): ν_{max} = 3065 (CH), 2923 (CH), 1677 (CO), 1597,

1451, 1367, 1205, 1167. HR-MS (ES-TOF+): *m/z* calcd for $C_{17}H_{17}NO_3S_2Na$: 370.0548 found: 370.0543 [M+Na^+].

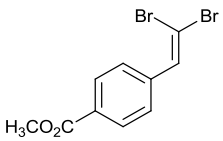
1-(2,2-dibromovinyl)-4-methylbenzene Prepared using GP6, with *para*-methylbenzaldehyde (0.59 ml, 5.00 mmol, 1 eq.), CBr_4 (3.3 g, 10.0 mmol, 2 eq.) and PPh_3 (5.3 g, 20.0 mmol, 4 eq.) in dry CH_2Cl_2 (50 ml). Purification by flash column chromatography, eluting with *n*-hexane, gave the dibromoalkene as a yellow oil (320 mg, 23%). δ_H (300 MHz, $CDCl_3$) 7.45 (1H, s, $CHCBr_2$), 7.44 (2H, d, *J* 8.0, ArH), 7.18 (2H, d, *J* 8.1, ArH), 2.34 (3H, s, CH_3). IR (neat): ν_{max} = 3025 (CH), 2920 (CH), 1510 (C=C), 875. Data in agreement with literature values.[211]



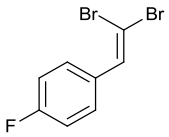
1-(2,2-dibromovinyl)-4-methoxybenzene Prepared using GP6, with *para*-anisaldehyde (0.61 ml, 5.00 mmol, 1 eq.), CBr_4 (3.3 g, 10.0 mmol, 2 eq.) and PPh_3 (5.3 g, 20.0 mmol, 4 eq.) in dry CH_2Cl_2 (50 ml). Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave the dibromoalkene as yellow crystals (1.3 g, 92%), m.p. 31-32 °C from CH_2Cl_2 (Lit.[212] 31 - 33 °C). δ_H (300 MHz, $CDCl_3$) 7.51 (2H, d, *J* 8.8, ArH), 7.41 (1H, s, CH), 6.89 (2H, d, *J* 8.8, ArH), 3.82 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 159.8 (C), 136.5 (CH), 130.0 (CH), 128.0 (C), 114.0 (CH), 87.4 (CBr_2), 55.5 (CH_3). IR (neat): ν_{max} = 3026 (CH), 2931 (CH), 2836 (CH), 1606 (C=C), 1509(C=C), 1249, 1178, 1032, 804. Data in agreement with literature values.[213]



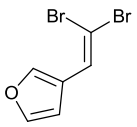
Methyl 4-(2,2-dibromovinyl)benzoate Prepared using GP6, with methyl *para*-formylbenzoate (0.820 g, 5.00 mmol, 1 eq.), CBr_4 (3.32 g, 10.0 mmol, 2 eq.) and PPh_3 (5.25 g, 20.0 mmol, 4 eq.) in dry CH_2Cl_2 (50 ml). Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave the dibromoalkene as a yellow oil (399 mg, 25%). δ_H (300 MHz, $CDCl_3$) 8.03 (2H, d, *J* 8.2, ArH), 7.60 (2H, d, *J* 8.2, ArH), 7.52 (1H, s, $CHCBr_2$), 3.92 (3H, s, CH_3). IR (neat): ν_{max} = 3007 (CH), 2957 (CH), 1727 (C=C), 1286, 1114, 885. Data in agreement with literature values.[214]



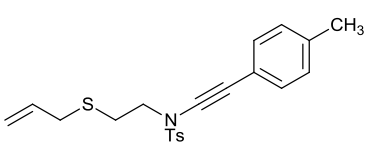
1-(2,2-dibromovinyl)-4-fluorobenzene Prepared using GP6, with *para*-fluorobenzaldehyde (0.54 ml, 5.00 mmol, 1 eq.), CBr_4 (3.32 g, 10.0 mmol, 2 eq.) and PPh_3 (5.25 g, 20.0 mmol, 4 eq.) in dry CH_2Cl_2 (50 ml). Purification by flash column chromatography, eluting with *n*-hexane, gave the dibromoalkene as a yellow oil (1.14 g, 82%). δ_H (300 MHz, $CDCl_3$) 7.52 (2H, dd, *J* 8.6, 5.4, ArH), 7.44 (1H, s, $CHCBr_2$), 7.06 (2H, t, *J* 8.6, ArH). δ_C (101 MHz, $CDCl_3$, CF Coupled) 162.60 (d, *J* 249.5, CF), 135.9 (s, *C*$HCBr_2$), 131.6 (d, *J* 3.4, *C*$CHCBr_2$), 130.4 (d, *J* 8.3, CH), 115.6 (d, *J* 21.7, CH), 89.8 (s, CBr_2). IR (neat): ν_{max} = 3018 (CH), 1603 (C=C), 1506 (C=C), 1230, 1160, 875, 813. Data in agreement with literature values.[215]



3-(2,2-dibromovinyl)furan Prepared using GP6, with furfural (0.41 ml, 5.00 mmol, 1 eq.), CBr_4 (3.32 g, 10.0 mmol, 2 eq.) and PPh_3 (5.25 g, 20.0 mmol, 4 eq.) in dry CH_2Cl_2 (50 ml). Purification by flash column chromatography, eluting with *n*-hexane, gave the dibromoalkene as brown crystals (763 mg, 60%). δ_H (300 MHz, $CDCl_3$) 7.44 (1H, d, *J* 1.8, ArH), 7.41 (1H, s, C*H*CBr_2), 6.94 (1H, t, *J* 3.5, ArH), 6.46 (1H, dd, *J* 3.5, 1.8, ArH). δ_C (101 MHz, $CDCl_3$) 150.2 (C), 142.7 (CH), 126.6 (CH), 111.7 (CH), 111.6 (CH), 87.3 (CBr_2). IR (neat): ν_{max} = 3152 (CH), 3033 (CH), 1805, 1481, 1230, 1142, 1020, 947, 836, 741. Data in agreement with literature values.[216, 217]

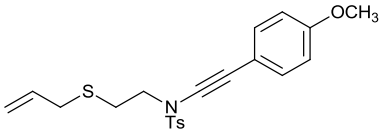


***S*-allyl-*N*-4-methylphenylethynyl-*N*-tosylcysteamine (430)** Prepared using GP4. Alkynylation was performed with tosylcysteamine **382** (280 mg, 1.03 mmol, 1.0 eq.), 1-(2,2-dibromovinyl)-4-methylbenzene (313 mg, 1.13 mmol, 1.1 eq.), *N*,*N*-dimethylethylenediamine (20.0 µl, 185 µmol, 0.18 eq.), CuI (40.3 mg, 124 µmol, 0.12 eq.) and Cs_2CO_3 (785 mg, 4.12 mmol, 4.0 eq.) in dioxane (3 ml) for 17 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **430** as a colourless oil (173 mg, 44%). δ_H (300 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.2, ArH), 7.37 (2H, d, *J* 8.1, ArH), 7.27 (2H, d, *J* 8.0, ArH), 7.12 (2H, d, *J* 8.0, ArH), 5.77 (1H, ddt, *J* 17.1, 9.9, 7.2, C*H*CH_2CH_2C), 5.15 (1H, dd, *J* 17.1, 1.4, C*H*$HCHCH_2C$), 5.13 (1H, d, *J* 9.9, $CHHCHCH_2C$), 3.67–3.52 (2H, m, CH_2N), 3.16 (2H, d, *J* 7.2, $CHCH_2N$), 2.84–2.72 (2H, m, CH_2CH_2S), 2.48 (3H, s, CH_3), 2.36 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 144.9 (C), 138.3 (C), 134.9 (C), 134.0 (CH), 131.6 (CH), 129.9 (CH), 129.2 (CH),

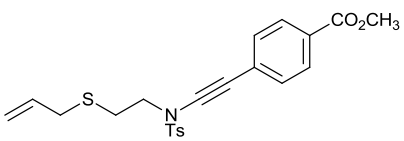


127.9 (CH), 119.6 (C), 117.9 (CH_2), 81.4 (C), 71.2 (C), 51.4 (CH_2), 34.9 (CH_2), 28.4 (CH_2), 21.8 (CH_3), 21.6 (CH_3). IR (neat): ν_{max} = 3035 (CH), 2921 (CH), 2236 (C≡C), 1597w, 1365, 1168. HR-MS (ES-TOF+): *m/z* calcd for $C_{21}H_{23}NO_2S_2Na$: 408.1068 found: 408.1056 [$M+Na^+$].

***S*-allyl-*N*-4-methoxyphenylethynyl-*N*-tosylcysteamine (431)** Prepared using GP4. Alkynylation was performed with tosylcysteamine **382** (207 mg, 760 µmol, 1.0 eq.), 1-(2,2-dibromovinyl)-4-methoxybenzene (248 mg, 840 µmol, 1.1 eq.), *N*,*N*-dimethylethylenediamine (15 µl, 137 µmol, 0.18 eq.), CuI (29.7 mg, 92.0 µmol, 0.12 eq.) and Cs_2CO_3 (580 mg, 3.00 mmol, 4.0 eq.) in dioxane (2 ml) for 17 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **431** as a colourless oil (81.5 mg, 27%). δ_H (300 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.3, ArH), 7.36 (2H, d, *J* 8.0, ArH), 7.30 (2H, d, *J* 8.9, ArH), 6.83 (2H, d, *J* 8.9, ArH), 5.75 (1H, ddt, *J* 17.1, 9.9, 7.2, CH_2CHCH_2S), 5.12 (1H, dd, *J* 17.1, 1.4, $CHHCHCH_2S$), 5.10 (1H, d, *J* 9.9, $CHHCHCH_2S$), 3.81 (3H, s, OCH_3), 3.61–3.48 (2H, m, CH_2N), 3.14 (2H, d, *J* 7.2, $CHCH_2S$), 2.83–2.68 (2H, m, SCH_2CH_2), 2.46 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 159.8 (C), 144.8 (C), 134.9 (C), 134.0 (CH), 133.6 (CH), 129.9 (CH), 127.9 (CH), 117.9 (CH), 114.7 (C), 114.1 (CH_2), 80.7 (C), 70.8 (C), 55.5 (CH_3), 51.5 (CH_2), 34.8 (CH_2), 28.4 (CH_2), 21.8(CH_3). IR (neat): ν_{max} = 3075 (CH), 2922 (CH), 2841 (CH), 2237 (C≡C), 1605w, 1512, 1363, 1167. HR-MS (ES-TOF+): *m/z* calcd for $C_{21}H_{23}NO_3S_2Na$: 424.1017 found: 424.01021 [$M+Na^+$].

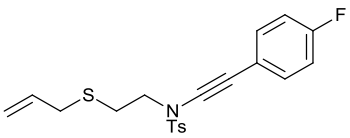


***S*-allyl-*N*-(4-methylcarboxy)-phenylethynyl-*N*-tosylcysteamine (432)** Prepared using GP4. Alkynylation was performed with tosylcysteamine **382** (271 mg, 1.00 mmol, 1.0 eq.), methyl 4-(2,2-dibromovinyl)benzoate (351 mg, 1.10 mmol, 1.1 eq.), *N*,*N*-dimethylethylenediamine (20 µl, 180 µmol, 0.18 eq.), CuI (39.1 mg, 120 µmol, 0.12 eq.) and Cs_2CO_3 (762 mg, 4.00 mmol, 4.0 eq.) in dioxane (3 ml) for 17 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **432** as a colourless oil (240 mg, 56%). δ_H (300 MHz, $CDCl_3$) 7.96 (2H, d, *J* 8.4, ArH), 7.84 (2H, d, *J* 8.4, ArH), 7.44–7.30 (4H, m, ArH), 5.76 (1H, ddt, *J* 17.2, 10.0, 7.2, CH_2CHCH_2S), 5.14 (1H, d, *J* 17.2, $CHHCHCH_2S$), 5.11 (1H, d, *J* 10.0, $CHHCHCH_2S$), 3.91 (3H, s, CO_2CH_3),

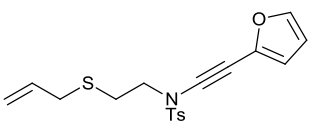


3.65–3.50 (2H, m, CH_2N), 3.15 (2H, d, *J* 7.2, CHC*H*$_2$S), 2.83–2.67 (2H, m, CH_2CH_2S), 2.46 (3H, s, CH3). δ_C (101 MHz, $CDCl_3$) 166.7 (C), 145.2 (C), 134.8 (C), 134.0 (CH), 130.8 (CH), 130.1 (CH), 129.7 (CH), 129.1 (C), 127.9 (CH), 127.8 (CH), 118.0 (CH_2), 85.4 (C), 71.3 (C), 52.3 (CH_3), 51.3 (CH_2), 34.9 (CH_2), 28.5 (CH_2), 21.8 (CH_3). IR (neat): ν_{max} = 3081 (CH), 2951 (CH), 2231 (C≡C), 1719s, 1605w, 1405, 1364, 1274, 1167. HR-MS (ES-TOF+): *m/z* calcd for $C_{22}H_{23}NO_4S_2Na$: 425.0966 found: 425.0991 [M+Na^+].

***S*-allyl-*N*-4-fluorophenylethynyl-*N*-tosylcysteamine (433)** Prepared using GP4. Alkynylation was performed with tosylcysteamine **382** (92.8 mg, 342 µmol, 1.0 eq.), 1-(2,2-dibromovinyl)-4-fluorobenzene (105mg, 380 µmol, 1.1 eq.), *N*,*N*-dimethylethylenediamine (6.6 µl, 62.0 µmol, 0.18 eq.), CuI (13.4 mg, 41.0 µmol, 0.12 eq.) and Cs_2CO_3 (261mg, 1.37 mmol, 4.0 eq.) in dioxane (1 ml) for 17 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **433** as a colourless oil (70.3 mg, 53%). δ_H (300 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.3, ArH), 7.42-7.29 (4H, m, ArH), 6.99 (2H, app. t, *J* 8.7, ArH), 5.75 (1H, ddt, *J* 17.2, 9.9, 7.2, CH_2CHCH_2S), 5.12 (1H, d, *J* 17.2, C*H*HCHCH$_2$S), 5.11 (1H, d, *J* 9.9, CH*H*CHCH$_2$S), 3.65-3.47 (2H, m, CH_2N), 3.14 (2H, d, *J* 7.2, CHC*H*$_2$S), 2.82-2.67 (2H, m, SC*H*$_2$CH$_2$), 2.46 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$, CF coupled) 162.5 (d, *J* 249.3, CF), 145.0 (C), 134.8 (C), 134.0 (CH), 133.6 (s, *J* 8.6, CH), 129.0 (CH), 127.8 (CH), 118.8 (C), 117.9 (CH), 115.8 (CH), 115.6 (CH_2), 81.7 (C), 70.1 (C), 51.4 (CH_2), 34.8 (CH_2), 28.4 (CH_2), 21.8 (CH_3). IR (neat): ν_{max} = 3082 (CH), 2923 (CH), 2238 (C≡C), 1599w, 1509, 1365, 1168. HR-MS (ES-TOF+): *m/z* calcd for 412.0817 $C_{20}H_{20}NO_2S_2FNa$: 412.0815 found: [M+Na^+].

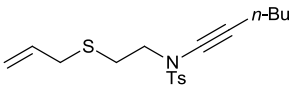


***S*-allyl-*N*-(2-furanyl)-ethynyl-*N*-tosylcysteamine (434)** Prepared using GP4. Alkynylation was performed with cysteamine **382** (250 mg, 920 µmol, 1.0 eq.), 2-(2,2-dibromovinyl)furan (252 mg, 1.00 mmol, 1.1 eq.), *N*,*N*-dimethylethylenediamine (18 µl, 166 µmol, 0.18 eq.), CuI (35.8 mg, 110 µmol, 0.12 eq.) and Cs_2CO_3(701 mg, 36.8 mmol, 4.0 eq.) in dioxane (5 ml) for 17 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **434** as colourless crystals (163 mg, 49%) melting point 32-33 °C. δ_H (300 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.3, ArH), 7.38 (1H, dd, *J* 1.9,



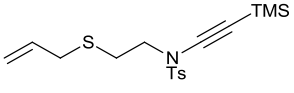
0.7, ArH), 7.35 (2H, d, *J* 8.3, ArH), 6.60 (1H, dd, *J* 3.4, 0.7, ArH), 6.38 (1 H, dd, *J* 3.4, 1.9, ArH), 5.72 (1 H, ddt, *J* 17.1, 9.9, 7.2, CH_2CHCH_2S), 5.10 (1H, dd, *J* 17.1, 1.3, $CHHCHCH_2S$), 5.08 (1H, d, *J* 9.9, $CHHCHCH_2S$), 3.65–3.45 (2H, m, CH_2N), 3.10 (2H, d, *J* 7.2, $CHCH_2S$), 2.81–2.61 (2H, m, CH_2CH_2S), 2.44 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 145.07 (C), 144.18 (CH), 136.60 (C), 134.68 (C), 133.77 (CH), 129.97 (CH), 127.68 (CH), 117.87 (CH2), 117.40 (CH_2), 111.18 (CH), 86.12 (C), 62.00 (C), 51.36 (CH_2), 34.69 (CH_2), 28.19 (CH_2), 21.71 (CH_3). IR (neat): ν_{max} = 3122 (CH), 3072 (CH), 2922 (CH), 2225 (C≡C), 1597w, 1491, 1364, 1167. HR-MS (ES-TOF+): *m/z* calcd for $C_{18}H_{19}NO_3S_2Na$: 384.0704 found: 384.0698 [$M+Na^+$].

***S*-allyl-*N*-hexynyl-*N*-tosylcysteamine (435)** Prepared using GP3. Alkynylation was performed with



tosylcysteamine **382** (1.0 g, 3.70 mmol, 1.0 eq.), crude bromohexyne (0.71 ml, *ca.* 5.55 mmol, 1.5 eq.), 1,10-phenanthroline (120 mg, 666 µmol, 0.18 eq.), $CuSO_4.5H_2O$ (110 mg, 444 µmol, 0.12 eq.) and K_2CO_3 (1.0 g, 7.40 mmol, 2.0 eq.) in toluene (10 ml) for 19 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave ynamide **435** as a colourless oil (324.8 mg, 25%). δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.2, ArH), 7.33 (2H, d, *J* 8.2, ArH), 5.75 (1H, ddt, *J* 16.7, 9.4, 7.2, CH_2CHCH_2S), 5.12 (1H, d, *J* 16.7, $CHHCHCH_2S$), 5.11 (1H, d, *J* 9.4, $CHHCHCH_2S$), 3.52–3.33 (2H, m, CH_2N), 3.12 (2H, d, *J* 7.3, $CHCH_2SH$), 2.75–2.58 (2H, m, SCH_2CH_2), 2.45 (3H, s, CH_3), 2.25 (2H, t, *J* 6.9, $C{\equiv}CCH_2$), 1.51–1.21 (4H, m, $CH_2CH_2CH_3$), 0.89 (3H, t, *J* 7.2, CH_2CH_3). δ_C (101 MHz, $CDCl_3$) 144.5 (C), 134.9 (C), 134.0 (CH), 129.8 (CH), 127.8 (CH), 117.8 (CH_2), 72.9 (C), 70.8 (C), 51.3 (CH_2), 34.8 (CH_2), 31.1 (CH_2), 28.3 (CH_2), 22.0 (CH_2), 21.8 (CH_3), 18.3 (CH_2), 13.7 (CH_3). IR (Neat): ν_{max} = 2957 (CH), 2930 (CH), 2871 (CH), 2253 (C≡C), 1597w, 1444, 1362, 1166. HR-MS (ES-TOF+): *m/z* calcd for 374.1224 $C_{18}H_{25}NO_2S_2Na$: 374.1236 found: [$M+Na^+$].

***S*-allyl-*N*-trimethylsilylethynyl-*N*-tosylcysteamine (436)** Prepared using GP3. Alkynylation was



performed *S*-allyl-*N*-tosylcysteamine **382** (98 mg, 500 µmol, 1.0 eq.), crude bromotrimethylsilyl acetylene (83 µl, *ca.* 550 µmol, 1.1 eq.), 1,10-phenanthroline (16 mg, 90.0 µmol, 0.18 eq.), $CuSO_4.5H_2O$ (15 mg, 60.0 µmol, 0.12 eq.) and K_2CO_3

(140 mg, 1.00 mmol, 2.0 eq.) in toluene (1 ml) for 20 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **436** as a yellow oil (75 mg, 50%). δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.2, ArH), 7.34 (2H, d, *J* 8.2, ArH), 5.73 (1H, ddt, *J* = 16.6, 10.2, 7.2, CH_2CHCH_2S), 5.14 (1H, d, *J* 16.6, $CHHCHCH_2S$), 5.11 (1H, d, *J* 10.2, $CHHCHCH_2S$), 3.57–3.33 (1H, m CH_2N), 3.11 (1H, d, *J* 7.2, $CHCH_2S$), 2.76–2.58 (1H, m, CH_2CH_2S), 2.45 (3H, s, CH_3), 0.15 (9H, s, $Si(CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 144.9 (C), 134.7 (C), 133.9 (CH), 129.8 (CH), 127.9 (CH), 117.9 (CH_2), 94.8 (C), 73.8 (C), 51.04 (CH_2), 34.74 (CH_2), 28.14 (CH_2), 21.77 (CH_3), 0.19 (3 CH_3). IR (Neat): ν_{max} = 2958 (CH), 2166 (C≡C), 1597w, 1370, 1170. HR-MS (ES-TOF+): *m/z* calcd for $C_{17}H_{25}NO_2S_2SiNa$: 390.0994 found: 390.0999 [$M+Na^+$].

***S*-allyl-*N*-ethynyl-*N*-tosylcysteamine (437)** A 1 M solution of TBAF (3.93 ml, 3.93 mmol, 2.5 eq.) was added under argon to a 0 °C solution of ynamide **436** (577 mg, 1.57 mmol, 1.0 eq.) in dry THF (12 ml). After 10 minutes the reaction mixture was quenched with NH_4Cl solution (20 ml) and extracted with ethyl acetate (3 x 25 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **437** as a yellow oil which proved unstable while drying under high vacuum and was therefore used immediately (350 mg, >95% purity). δ_H (300 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.3, ArH), 7.36 (2H, d, *J* 8.3, ArH), 5.74 (1H, ddt, *J* 16.8, 9.6, 7.2, $CHCH_2CH_2S$), 5.13 (1H, d, *J* 16.8, $CHHCHCH_2S$), 5.12 (1H, d, *J* 9.6, $CHHCHCH_2S$), 3.56–3.41 (2H, m, CH_2N), 3.12 (2H, d, *J* 7.2, $CHCH_2S$), 2.76 (1H, s, CH), 2.74–2.62 (2H, m, CH_2CH_2S), 2.45 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 145.1 (C), 134.8 (C), 133.9 (CH), 130.0 (CH), 127.8 (CH), 118.0 (CH_2), 75.9 (C), 59.7 (CH), 51.0 (CH_2), 34.8 (CH_2), 28.2 (CH_2), 21.8 (CH_3). IR (neat): ν_{max} = 3298 (CH), 3088 (CH), 2923 (CH), 2166 (C≡C), 1597w, 1367, 1168. HR-MS (ES-TOF+): *m/z* calcd for $C_{14}H_{17}NO_2S_2Na$: 318.0596 found: 318.0593 [$M+Na^+$].

2-allyl-2-(4-tolyl)-4-tosylthiomorpholin-3-one (438) Prepared using GP5. Catalysis was performed using ynamide **430** (77.1 mg, 200 µmol, 1.0 eq.), pyridine *N*-oxide (20.9 mg, 220 µmol, 1.1 eq.), AgOTs (2.8 mg, 10.0 µmol, 0.050 eq.) and IPrAuCl (6.2 mg, 10.0 µmol, 0.050 eq.) in CH_3CN (4 ml) for 15 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **438** as a colourless oil (47.4 mg, 59%). δ_H (300 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8.4, ArH), 7.36 (2H, d, *J* 8.1, ArH), 7.20 (2H, d, *J* 8.4, ArH), 7.09 (2H, d, *J* 8.1, ArH), 5.43 (1H, ddt, *J* 17.1, 10.3, 7.2, CH_2CHCH_2C), 4.91 (1H, d, *J* 10.3, $CHHCHCH_2C$), 4.87 (1 H, d, *J* 17.1, $CHHCHCH_2C$), 4.63–4.43 (1H, m, CHHN), 3.15–2.98 (2H, m, SCH_2CH_2), 2.98–2.84 (1H, m, CHHN), 2.69 (1H, dd, *J* 14.5, 7.2, CHCHHC), 2.59 (1H, dd, *J* 14.5, 7.2, CHCHHC), 2.48 (3H, s, CH_3), 2.33 (3, s CH_3). δ_C (101 MHz, $CDCl_3$) 169.9 (CO), 145.0 (C), 137.9 (C), 136.2 (C), 136.0 (C), 132.4 (CH), 129.8 (CH), 129.5 (CH), 128.6 (CH), 126.0 (CH), 118.9 (CH_2), 58.2 (C), 45.1 (CH_2), 43.5 (CH_2), 26.9 (CH_2), 21.9 (CH_3), 21.1 (CH_3). IR (neat): ν_{max} = 3074 (CH), 2979 (CH), 2924 (CH), 1698 (CO), 1597, 1509, 1432, 1406, 1353, 1317, 1168. HR-MS (ES-TOF+): *m/z* calcd for $C_{21}H_{23}NO_3S_2Na$: 424.1017 found: 424.1009 [$M+Na^+$].

2-allyl-2-(4-methoxyphenyl)-4-tosylthiomorpholin-3-one (439) and *N*-(2-(allylthio)ethyl)-2-(4-methoxyphenyl)-2-oxo-*N*-tosylacetamide Prepared using GP5. Catalysis was performed using ynamide **431** (81.5 mg, 200 µmol, 1.0 eq.), pyridine *N*-oxide (20.9 mg, 220 µmol, 1.1 eq.), AgOTs (2.8 mg, 10.0 µmol, 0.050 eq.) and IPrAuCl (6.2 mg, 10.0 µmol, 0.050 eq.) in CH_3CN (4 ml) for 15 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave an inseparable 2:1 mixture of thiomorpholinone **439** and tosylacetamide as a colourless oil (60.1 mg, 72%).

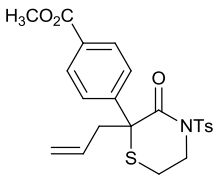
2-allyl-2-(4-methoxyphenyl)-4-tosylthiomorpholin-3-one δ_H (400 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.3, ArH), 7.37 (2H, d, *J* 8.3, ArH), 7.25 (2H, d, *J* 8.9, ArH), 6.83 (2H, d, *J* 8.9, ArH), 5.46 (1H, ddt, *J* 17.1, 10.2, 7.2, CH_2CHCH_2C), 4.93 (1H, dd, *J* 10.2, 1.9, $CHHCHCH_2C$), 4.88 (1H, dd, *J* 17.1, 1.8, $CHHCHCH_2C$), 4.55 (1H, ddd, *J* 13.8, 5.6, 2.9, CHHN), 3.81 (3H, s, OCH_3), 3.15-3.07 (1H, m, CHHN), 3.02 (1H, td, *J* 11.6, 5.6,

SCH*H*CH_2N), 2.91 (1H, ddd, *J* 11.6, 4.3, 2.9, SC*H*HCH_2N), 2.69 (1H, dd, *J* 14.5, 7.2, CHCH*H*C), 2.62 (1H, dd, *J* 14.5, 7.2, CHC*H*HC), 2.49 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 169.8 (CO), 159.2 (C), 144.8 (C), 135.9 (C), 132.3 (CH), 130.9 (C), 129.4 (CH), 128.5 (CH), 127.3 (CH), 118.8 (CH_2), 114.2 (CH), 57.8 (C), 55.3 (CH_3), 45.1 (CH_2), 43.3 (CH_2), 26.8 (CH_2), 21.2 (CH_3).

N-(2-(allylthio)ethyl)-2-(4-methoxyphenyl)-2-oxo-*N*-tosylacetamide δ_H (400 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8.3, ArH), 7.93 (2H, d, *J* 8.9, ArH), 7.41 (2H, d, *J* 8.3, ArH), 7.02 (2H, d, *J* 8.9, ArH), 5.80 (2H, ddt, *J* 17.1, 10.0, 7.2, CH_2CHCH_2S), 5.21 (1H, dd, *J* 17.1, 1.3, C*H*HCHCH_2S), 5.14 (1H, dd, *J* 10.0, 1.3, CH*H*CHCH_2S), 3.91 (3H, s, CH_3), 3.87–3.77 (2H, m, SCH_2CH_2N), 3.18 (2H, d, *J* 7.2, CHCH_2S), 2.82-2.75 (2H, m, SCH_2CH_2N), 2.48 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 186.5 (CO), 167.4 (CO), 164.7 (C), 145.9 (C), 134.3 (C), 133.9 (CH), 132.1 (CH), 130.1 (CH), 127.3 (CH), 125.8 (C), 117.9 (CH_2), 114.4 (CH), 55.7 (CH_3),45.0 (CH_2) 35.6 (CH_2), 28.4 (CH_2), 21.2 (CH_3).

IR (neat): ν_{max} = 3076 (CH), 2928 (CH), 2840 (CH), 1696 (CO), 1599 (C=C), 1509 (C=C), 1357, 1251, 1167. HR-MS (ES-TOF+): *m/z* calcd for $C_{21}H_{23}NO_4S_2Na$: 440.0966 found: 440.0952 [$M+Na^+$].

2-allyl-2-(4-methylcarboxy)-4-tosylthiomorpholin-3-one (440) Prepared using GP5. Catalysis was performed using ynamide **432** (85.9 mg, 200 µmol, 1.0 eq.), pyridine *N*-oxide (20.9 mg, 220 µmol, 1.1 eq.), AgOTs (2.8 mg, 10.0 µmol, 0.050 eq.) and IPrAuCl (6.2 mg, 10.0 µmol, 0.050 eq.) in CH_3CN (4 ml) for 15 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **440** as a colourless oil (48.1 mg, 54%). δ_H (300 MHz, $CDCl_3$) 7.95 (2H, d, *J* 8.5, ArH), 7.84 (4H, d, *J* 8.5, ArH), 7.39 (2H, d, *J* 8.4, ArH), 7.36 (2H, d, *J* 8.4), 5.41 (1H, ddt, *J* 17.2, 10.2, 7.2, CH_2CHCH_2C), 4.91 (1H, dd, *J* 10.2, 1.7 Hz, C*H*HCHCH_2C), 4.82 (1H, dd, *J* 17.2, 1.7, CH*H*CHCH_2C), 4.62–4.48 (1H, m, C*H*HN), 3.91 (3H, s, CH_3), 3.09–2.98 (2H, m, SCH_2CH_2), 2.98–2.83 (1H, m, CH*H*N), 2.70 (1H, dd, *J* 14.4, 7.2, CHCH*H*S), 2.60 (1H, dd, *J* 14.4, 7.2, CHC*H*HS), 2.48 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 169.0 (CO), 166.4 (CO), 145.1 (C), 144.3 (C), 135.6 (C), 131.5 (CH), 130.2 (CH), 129.9 (C), 129.5 (CH), 128.5 (CH), 126.2 (CH), 119.4 (CH_2), 58.3 (C), 52.2 (CH_2), 44.8 (CH_2), 43.5 (CH_2), 26.8 (CH_3), 21.7 (CH_3). IR (neat): ν_{max} = 3081 (CH), 2953 (CH), 1721 (CO), 1698 (CO), 1640, 1607, 1435, 1407, 1355,



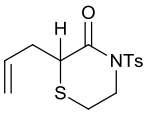
1315, 1278, 1167. HR-MS (ES-TOF+): *m/z* calcd for $C_{24}H_{22}NO_5S_2Na$: 468.0939 found: 468.0933 [M+Na^+].

2-allyl-2-(4-fluorophenyl)-4-tosylthiomorpholin-3-one (441) Prepared using GP5. Catalysis was performed using ynamide **433** (70.3 mg, 180 µmol, 1.0 eq.), pyridine *N*-oxide (18.9 mg, 199 µmol, 1.1 eq.), AgOTs (2.6 mg, 9.40 µmol, 0.050 eq.) and IPrAuCl (5.80 mg, 9.4 µmol, 0.050 eq.) in CH_3CN (4 ml) for 15 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **441** as a colourless oil (39.3 mg, 54%). δ_H (300 MHz, $CDCl_3$) 7.88 (2H, d, *J* 8.3, ArH), 7.39 (2H, d, *J* 8.3, ArH), 7.36–7.22 (2 H, m, ArH), 7.00 (2H, t, *J* 8.6, ArH), 5.44 (1H, ddt, *J* 17.2, 10.1, 7.2, CH_2CHCH_2C), 4.95 (1H, dd, *J* 10.1, 1.7, C*H*HCHCH_2C), 4.87 (1H, dd, *J* 17.2, 1.6, CH*H*CHCH_2C), 4.66–4.49 (1H, m, CH*H*N), 3.18–2.99 (2H, m, SCH_2CH_2), 2.99-2.88 (1H, m, C*H*HN), 2.71 (1H, dd, *J* 14.4, 7.2, CHCH*H*S), 2.61 (1H, dd, *J* 14.4, 7.2, CHC*H*HS), 2.51 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$, CF coupled) 169.5 (CO), 162.4 (d, *J* 245, CF), 145.1 (C), 135.8 (C), 135.1 (C, d, *J* 2.5, CF), 131.9 (CH), 129.5 (CH), 128.6 (CH), 128.1 (d, *J* 8.1, CH), 119.35 (CH_2), 116.0 (d, *J* 22.0, CH), 57.78 (C), 45.18 (CH_2), 43.70 (CH_2), 26.84 (CH_2), 21.83 (CH_3). IR (neat): ν_{max} = 3083 (CH), 2927 (CH), 1698 (CO), 1599, 1505, 1355, 1316, 1168. HR-MS (ES-TOF+): *m/z* calcd for $C_{20}H_{20}NO_3S_2FNa$: 428.0766 found: 428.0773 [M+Na^+].

2-allyl-2-(2-furanyl)-4-tosylthiomorpholin-3-one (**442**) Prepared using GP5. Catalysis was performed using ynamide **434** (40.0 mg, 110 µmol, 1.0 eq.), pyridine *N*-oxide (11.4 mg, 120 µmol, 1.1 eq.), AgOTs (1.5 mg, 5.50 µmol, 0.050 eq.) and IPrAuCl (3.4 mg, 5.50 µmol, 0.050 eq.) in CH_3CN (2 ml) for 15 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **442** as a colourless oil (31.5 mg, 76%). δ_H (300 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.4, ArH), 7.39–7.28 (3H, m, ArH), 6.33 (1H, dd, *J* 3.3, 0.9, ArH), 6.31 (1H, dd, *J* 3.3, 1.8, ArH), 5.52 (1H, ddt, *J* 17.3, 10.6, 7.2, CH_2CHCH_2C), 4.96 (2H, d, *J* 17.3, C*H*HCHCH_2C), 4.92 (2H, d, *J* 10.6, CH*H*CHCH_2C), 4.54 (1H, dt, *J* 14.1, 5.0, C*H*HN), 3.62 (1H, dt, *J* 14.1, 6.9 Hz, CH*H*N), 3.00 (2H, dd, *J* 6.9, 5.0, CHCH_2S), 2.85 (1H, dd, *J* 14.3, 7.2, CHC*H*HS), 2.69 (1H, dd, *J* 14.3, 7.2, CHCH*H*S), 2.45 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 167.5 (CO),

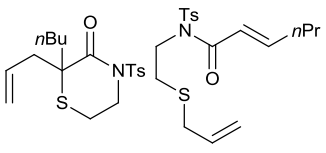
152.4 (C), 145.1 (C), 143.0 (CH), 135.9 (C), 132.0 (CH), 129.5 (CH), 128.7 (CH), 119.3 (CH_2), 110.7 (CH), 109.1 (CH), 52.8 (C), 45.2 (CH_2), 42.2 (CH_2), 26.8 (CH_2), 21.8 (CH_3). IR (Neat): ν_{max} = 3074 (CH), 2925 (CH), 1701 (CO), 1596, 1495, 1463, 1353, 1315, 1168. HR-MS (ES-TOF+): *m/z* calcd for $C_{18}H_{19}NO_4S_2Na$: 400.0653 found: 400.0656 [$M+Na^+$].

2-allyl-4-tosylthiomorpholin-3-one (433) Prepared using GP5 from two starting materials. From



ynamide **436** (50.1 mg, 140 µmol, 1.0 eq.) catalysis was performed using pyridine *N*-oxide (14.3 mg, 15.0 µmol, 1.1 eq.), AgOTs (2.0 mg, 7.00 µmol, 0.050 eq.) and IPrAuCl (4.3 mg, 7.00 µmol, 0.050 eq.) in CH_3CN (3 ml) for 16 hours. Purification by flash column chromatography, eluting with 20:1:89 ethyl acetate:triethylamine:*n*-hexane, gave thiomorpholinone **433** as a colourless oil (15.4 mg, 29%). From ynamide **437** (88.6 mg, 300 µmol, 1.0 eq.) catalysis was performed using pyridine *N*-oxide (31.4 mg, 33 µmol, 1.1 eq.), AgOTs (4.1 mg, 15 µmol, 0.050 eq.) and IPrAuCl (9.3 mg, 15 µmol, 0.050 eq.) in CH_3CN (6 ml) for 17 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **433** as a colourless oil (17.4 mg, 19%). δ_H (400 MHz, $CDCl_3$) 7.90 (2H, d, *J* 8.3, ArH), 7.33 (2H, d, *J* 8.3, ArH), 5.87–5.63 (1H, m, CH_2CHCH_2CH), 5.09 (1H, d, *J* 17.4, $CHHCHCH_2CH$), 5.06 (1H, d, *J* 9.3, $CHHCHCH_2CH$), 4.84 (1H, ddd, *J* 14.8, 4.7, 3.4, CHHN), 3.84–3.68 (1H, ddd, *J* 14.8, 11.9, 3.4, CHHN), 3.58 (1H, dd, *J* 8.0, 5.5, SCHCO), 3.07 (1H, dt, *J* 11.9, 3.4, $SCHHCH_2$), 2.96 (1H, td, *J* 11.9, 4.8, $SCHHCH_2$), 2.71 (1H, dt, *J* 15.5, 8.0, CHCHHSCH), 2.44 (3H, s, CH_3), 2.24 (1 H, dt, *J* 15.5, 8.0, CHCHHCH). δ_C (101 MHz, $CDCl_3$) 169.0 (CO), 145.19(C), 136.0 (C), 133.9 (CH), 129.7 (CH), 128.6 (CH), 118.2 (CH_2), 44.9 (CH_2), 42.3 (CH), 33.2 (CH_2), 27.7 (CH_2), 21.8 (CH_3). IR (Neat): ν_{max} = 3076 (CH), 2924 (CH), 2853 (CH), 1703 (CO), 1596, 1494, 1464, 1353, 1314, 1166. HR-MS (ES-TOF+): *m/z* calcd for $C_{14}H_{17}NO_3S_2Na$: 334.0548 found: 334.0561 [M+Na].

2-allyl-2-(butyl)-4-tosylthiomorpholin-3-one (445) and *N*-(2-(allylthio)ethyl)-*N*-tosylhex-2-enamide



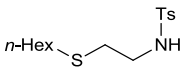
(446) Prepared using GP5. Catalysis was performed using ynamide **435** (106 mg, 300 µmol, 1.0 eq.), pyridine *N*-oxide (31.5 mg, 330 µmol, 1.1 eq.), AgOTs (4.20 mg, 15 µmol, 0.050 eq.) and IPrAuCl (9.30 mg, 15

μmol, 0.05 eq.) in acetonitrile (6 ml) for 17 hours. Purification by flash column chromatography, eluting with 15:1:84 diethyl ether:triethylamine:*n*-hexane, gave 2-allyl-2-(butyl)-4-tosylthiomorpholin-3-one as a colourless oil (11.0 mg, 10%) and an inseparable 20:3 mixture of *E* and *Z* *N*-(2-(allylthio)ethyl)-*N*-tosylhex-2-enamide (40.6 mg, 40%).

2-allyl-2-(butyl)-4-tosylthiomorpholin-3-one (**445**): δ_H (300 MHz, $CDCl_3$) 7.88 (2H, d, *J* 8.3, ArH), 7.32 (2H, d, *J* 8.3, ArH), 5.63 (1H, ddd, *J* 17.3, 10.5, 7.3, CH_2CHCH_2C), 5.02 (2H, d, *J* 17.3, $CHHCHCH_2C$), 4.97 (1H, d, *J* 10.5, $CHHCHCH_2C$), 4.41–4.17 (2H, m, CH_2N), 3.04–2.82 (2H, m, SCH_2CH_2N), 2.61 (1H, dd, *J* 14.1, 7.2, CHCHHS), 2.43 (3H, s, $ArCH_3$), 2.38 (1H, dd, *J* 14.1, 7.2, CHCHHS), 1.84 (1H, ddd, *J* 13.8, 11.9, 4.4, $CCHHCH_2CH_2$), 1.75–1.51 (1H, m, $CCHHCH_2CH_2$), 1.36–0.85 (4H, m, $(CH_2)_2CH_3$), 0.79 (3H, t, *J* 7.1, CH_2CH_3). δ_C (101 MHz, $CDCl_3$) 171.5 (CO), 145.0 (C), 136.0 (C), 132.4 (CH), 129.4 (CH), 128.9 (CH), 119.5, (CH_2), 50.3 (CH_2), 44.2 (CH_2), 39.7 (CH_2), 29.8 (C), 26.5 (CH_2), 25.2 (CH_2), 22.9 (CH_2), 21.8 (CH_3), 14.0 (CH_3). IR (neat): ν_{max} = 2957 (CH), 2928 (CH), 2860 (CH), 1679 (CO), 1639, 1597, 1465, 1406, 1356, 1167. HR-MS (ES-TOF+): *m/z* calcd for $C_{18}H_{25}NO_3S_2Na$: 390.1174 found: 390.1177 [$M+Na^+$]. (*E*)-*N*-(2-(allylthio)ethyl)-*N*-tosylhex-2-enamide (**446**): δ_H (300 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.2, ArH), 7.32 (2H, d, *J* 8.2, ArH), 6.95 (1H, dt, *J* 15.1, 6.9, $CHCHCH_2$), 6.65 (1H, dt, *J* 15.1, 1.5, COCHCH), 5.80 (1H, ddt, *J* 17.0, 9.9, 7.2, CH_2CHCH_2S), 5.21 (1H, dd, *J* 17.0, 1.4, $CHHCHCH_2S$), 5.13 (1H, dd, *J* 9.9, 1.4, $CHHCHCH_2S$), 4.02–3.86 (2H, m, CH_2N), 3.19 (2H, d, *J* 7.2, $CHCH_2S$), 2.82–2.70 (2H, m, SCH_2CH_2), 2.43 (3H, s, $ArCH_3$), 2.16 (2H, dtd, *J* 7.3, 6.9, 1.4, $CHCH_2CH_2$), 1.44 (4H, m, CH_2), 0.88 (3H, t, *J* 7.4, CH_2CH_3). δ_C (101 MHz, $CDCl_3$) 165.7 (CO), 151.2 (CH), 144.8 (C), 136.9 (C), 134.0 (CH), 129.9 (CH), 127.4 (CH), 121.4 (CH), 117.7 (CH_2), 46.1 (CH_2), 34.6 (CH_2), 29.6 (CH_2), 21.6 (CH_3), 21.2 (CH_2), 13.6 (CH_3). (*Z*)-*N*-(2-(allylthio)ethyl)-*N*-tosylhex-2-enamide (**446**): δ_H (300 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.4, ArH), 7.26 (2H, d, *J* 8.0, ArH), 6.42 (1H, dt, *J* 11.6, 1.7, COCHCH), 6.10 (1H, dt, *J* 11.6, 7.4, $CHCHCH_2$), 5.80 (1H, ddt, *J* 17.0, 9.9, 7.2, CH_2CHCH_2S), 5.21 (1H, dd, *J* 17.0, 1.4, $CHHCHCH_2S$), 5.13 (1H, dd, *J* 9.9, 1.4, $CHHCHCH_2S$), 3.61 (2H, t, *J* 7.3, CH_2N), 3.32 (2H, d, *J* 7.0, $CHCH_2S$), 2.79 (2H, t, *J* 7.3, SCH_2CH_2), 2.43 (3H, s, $ArCH_3$), 2.30 (2H, dtd, *J* 7.4, 7.3, 1.7), 1.37–1.23 (4H, m, CH_2), 0.84 (1H, t, *J* 7.4 CH_2CH_2). δ_C (101 MHz, $CDCl_3$) 165.7 (CO), 149.2 (CH), 144.8 (C), 136.9 (C), 134.0 (CH), 129.6 (CH), 127.4 (CH), 121.0 (CH), 115.8 (CH_2), 45.9 (CH_2), 34.6 (CH_2), 29.6 (CH_2), 21.6 (CH_3), 21.2 (CH_2), 13.6 (CH_3). IR (neat): ν_{max}

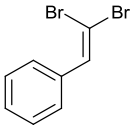
= 2960 (CH), 2925 (CH), 2872 (CH), 1681 (CO), 1634 (C=C), 1597, 1507, 1404, 1352, 1158. HR-MS (ES-TOF+): *m/z* calcd for $C_{18}H_{25}NO_3S_2Na$: 390.1174 found: 390.1177 [M+Na^+].

***S*-hexyl-*N*-tosylcysteamine (447)** Hexanethiol (0.56 µl, 3.95 mmol, 1.1 eq.) was cautiously added to a



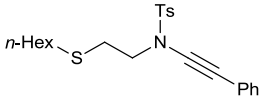
stirred suspension of 50% NaH (207 mg, 4.30 mmol, 1.1 eq.) in dry THF (25 ml) under argon at 0 °C. After 35 minutes bromoethanamine **417** was added (1.00 g, 3.60 mmol, 1.0 eq.). The reaction was allowed to warm to room temperature over a period of 10 hours and then added to 10% NaOH solution (50 ml). The organic fraction was collected and the aqueous fraction extracted with CH_2Cl_2 (2 x 50 ml). All the organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography, eluting with 1:3 ethyl acetate:*n*-hexane, to tosylcysteamine **447** as a colourless oil (0.348 g, 30%). δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.1, ArH), 7.33 (2H, d, *J* 8.1, ArH), 4.93 (1H, t, *J* 6.3, NH), 3.13 (2H, q, 6.3, CH_2N), 2.60 (2H, t, *J* 6.3, SCH_2CH_2N), 2.45 (3H, s, $ArCH_3$), 2.36 (2H, t, *J* 7.4, $SCH_2CH_2CH_2$), 1.55-1.39 (2H, qn, *J* 7.4, $SCH_2CH_2CH_2$), 1.39-1.15 (6H, m, $(CH_2)_3CH_3$), 0.90 (3H, t, *J* 6.9, CH_3). δ_C (101 MHz, $CDCl_3$) 143.7 (C), 137.1 (C), 129.9 (CH), 127.3 (CH), 41.8 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 22.7 (CH_2), 21.7 (CH_3), 14.14 (CH_3). IR (neat): ν_{max} = 3285 (NH), 2958 (CH), 2924 (CH), 2855 (CH), 1599, 1495, 1408, 1326, 1157. HR-MS (ES-TOF+): *m/z* calcd for $C_{15}H_{25}NO_2S_2Na$: 338.1224 found: 390.1212 [M+Na^+].

2,2-dibromovinylbenzene Prepared using GP6, with benzaldehyde (0.54 ml, 5.00 mmol, 1 eq.), CBr_4



(3.316 g, 10.0 mmol, 2 eq.) and PPh_3 (5.246 g, 20.0 mmol, 4 eq.) in dry CH_2Cl_2 (50 ml). Purification by flash column chromatography, eluting with *n*-hexane, gave the bromoalkene as a yellow oil (1.144 g, 82%). δ_H (300 MHz, $CDCl_3$) 7.57–7.50 (2H, m, ArH), 7.49 (1H, s, $CHCBr_2$), 7.42-7.32 (2H, m, ArH). MS (EI+): *m/z* 259.9 (100) [$M^{+\bullet}$], 181 (18), 102.0 (47). Data in agreement with literature values.[218]

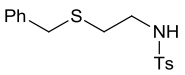
***S*-hexyl-*N*-phenylethynyl-*N*-tosylcysteamine (448)** Prepared using GP4. Alkynylation was performed



with tosylcysteamine **447** (348 mg, 1.10 mmol, 1.0 eq.), 2,2-

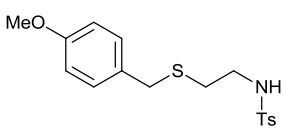
dibromovinylbenzene (0.32 ml, 2.20 mmol, 2.0 eq.), *N*,*N*-dimethylethylenediamine (43 µl, 400 µmol, 0.36 eq.), CuI (84.7 mg, 260 µmol, 0.24 eq.) and Cs_2CO_3 (838 mg, 4.40 mmol, 4.0 eq.) in DMF (8 ml) for 17 hours. The DMF was removed by diluting the reaction mixture with diethyl ether (20 ml) and washing with water (5 x 15 ml). Purification by flash column chromatography, eluting with 1:19 ethyl acetate:*n*-hexane, gave ynamide **448** as a colourless oil (0.202 mg, 44%). δ_H (300 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8.3, ArH), 7.41-7.32 (4H, m, ArH), 7.32- 7.27 (3H, m, ArH), 3.64-3.52 (2H, m, CH_2N), 2.85-2.75 (2H, m, SCH_2CH_2N), 2.58-2.49 (2H, t, *J* 7.3, $SCH_2CH_2CH_2$), 2.46 (3H, s, $PhCH_3$), 1.64-1.49 (2H, qn, *J* 7.3, $SCH_2CH_2CH_2$), 1.42-1.17 (6H, m, $CH_2CH_2CH_2$), 0.88 (3H, t, *J* 6.8, CH_2CH_3). δ_C (101 MHz, $CDCl_3$) 144.9 (C), 134.8 (C), 131.6 (CH), 123.0 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 122.8 (C), 82.1 (C), 71.2 (C), 51.8 (CH_2), 32.4 (CH_2), 31.6 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 22.7 (CH_2), 21.8 (CH_3), 14.2 (CH_3). IR (Neat): ν_{max} = 3062 (CH), 2958 (CH), 2928 (CH), 2862 (CH), 2236 (C≡C), 1686 (CO), 1598 (C=C), 1443, 1367, 1169. HR-MS (ES-TOF+): *m/z* calcd for $C_{23}H_{29}NO_2S_2Na$: 438.1537 found: 438.1545 [$M+Na^+$].

***S*-benzyl-*N*-tosylcysteamine (456)** Prepared using GP2. Benzylation was performed using cysteamine



hydrochloride (1.00 g, 8.80 mmol, 1.00 eq.) and benzyl bromide (1.05 ml, 8.90 mmol, 1.05 eq.) in ethanol (30 ml) and LiOH (443 mg, 18.5 mmol, 2.10) in water (10 ml) for 23 hours. *N*-protection was performed with tosyl chloride (1.70 g, 8.90 mmol, 1.05 eq.) and triethylamine (2.15 ml, 29.3 mmol, 3.30 eq.) for 16 hours. Purification by flash column chromatography, eluting with 1:4 ethyl acetate:*n*-hexane, gave tosylcysteamine **456** as a colourless oil (2.16 g, 77% over 2 steps). δ_H (300 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.5, ArH), 7.33 (2H, d, *J* 8.5, ArH), 7.30–7.18 (5H, m, ArH), 4.80 (1H, t, *J* 6.2, NH), 3.59 (2H, s, CCH_2S), 3.06 (2H, q, *J* 6.2, CH_2NH), 2.51 (2H, t, *J* 6.2, SCH_2CH_2), 2.45 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 143.7 (C), 137.8 (C), 137.1 (C), 129.9 (CH), 128.9 (CH), 128.8 (CH), 127.5 (CH), 127.3 (CH), 41.7 (CH_2), 35.8 (CH_2), 31.2 (CH_2), 21.7 (CH_3). IR (neat): ν_{max} = 3280br (NH), 3067 (CH), 3030 (CH), 2924 (CH), 1599 (C=C), 1495, 1453, 1324, 1157. HR-MS (ES-TOF+): *m/z* calcd for $C_{16}H_{19}NO_2S_2Na$: 344.0757 found: 344.0755 [$M+Na^+$].

***S*-*p*-methoxybenzyl-*N*-tosylcysteamine (457)** Prepared using GP2. Benzylation was performed using cysteamine hydrochloride (0.500 g, 4.40 mmol, 1.00 eq.), *para*-



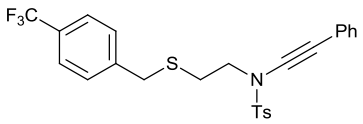
methoxybenzyl bromide (0.61 ml, 4.40 mmol, 1.00 eq.), LiOH (221 mg, 9.40 mmol, 2.10 eq.) in ethanol (15 ml) and water (9 ml) for 2 hours. *N*-protection was performed with tosyl chloride (847 mg, 4.40 mmol, 1.00 eq.) and triethylamine (1.07 ml, 7.70 mmol, 1.75 eq.) for 21 hours. Purification by flash column chromatography, eluting with 1:4 ethyl acetate:*n*-hexane, gave tosylcysteamine **457** as a yellow oil (0.160 g, 10% over 2 steps). δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.2, ArH), 7.31 (2H, d, *J* 8.2, ArH), 7.13 (2H, d, *J* 8.7, ArH), 6.81 (2H, d, *J* 8.7, ArH), 4.79 (2H, t, *J* 6.3, NH), 3.79 (3H, s, CH_3O), 3.53 (3H, s, $PhCH_2S$), 3.03 (2H, q, *J* 6.3, CH_2N), 2.48 (2H, t, *J* 6.3, SCH_2CH_2), 2.43 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 159.0 (C), 143.7 (C), 137.1 (C), 123.0 (CH), 129.9 (CH), 129.6 (C), 127.2 (CH), 114.2 (CH), 55.4 (CH_2), 41.7 (CH_2), 35.2 (CH_2), 31.1 (CH_3), 21.7 (CH_3). IR (neat): ν_{max} = 3288br (NH), 2922 (CH), 2951 (CH), 1610 (C=C), 1584 (C=C), 1511, 1441, 1324, 1157, 1093. HR-MS (ES-TOF+): *m/z* calcd for $C_{17}H_{21}NO_3S_2Na$: 374.0861 found: 374.0865 [$M+Na^+$].

***S*-*p*-trifluoromethylbenzyl-*N*-tosylcysteamine (458)** Prepared using GP2. Benzylation was performed using cysteamine hydrochloride (0.500 g, 4.40 mmol, 1.00 eq.), *para*-trifluoromethylbenzyl bromide (1.052 g, 4.40 mmol, 1.00 eq.) and LiOH (221 mg, 9.40 mmol, 2.10 eq.), in ethanol (15 ml) and water (9 ml) for 2 hours. *N*-protection was performed with tosyl chloride (847 mg, 4.4 mmol, 1.00 eq.) and triethylamine (1.07 ml, 7.7 mmol, 1.75 eq.) for 21 hours. Purification by flash column chromatography, eluting with 1:4 ethyl acetate:*n*-hexane, gave tosylcysteamine **458** as colourless crystals (1.162 g, 68% over 2 steps), m.p 87-88 °C from CH_2Cl_2. δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.3, ArH), 7.55 (2H, d, *J* 8.3, ArH), 7.35 (2H, d, *J* 8.1, ArH), 7.31 (2H, d, *J* 8.1, ArH), 4.80 (1H, t, *J* 6.5, NH), 3.64 (2H, s, $PhCH_2S$), 3.06 (2H, q, *J* 6.5, CH_2N), 2.50 (2H, t, *J* 6.5, SCH_2CH_2), 2.43 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$, CF coupled) 143.8 (C), 142.0 (C), 137.1 (C), 129.9 (CH), 192.3 (C), 129.2 (CH), 127.2 (CH), 125.8 (CH), 125.7 (CH), 124.0 (1C, q, *J* 242, CF_3) 41.8 (CH_2), 35.5 (CH_2), 31.4 (CH_2), 21.7 (CH_3). IR (Neat): ν_{max} = 3280br (NH), 3067 (CH), 3030 (CH), 2924 (CH), 1599 (C=C), 1495, 1453, 1324 (SO_2NHR), 1157 (SO_2NHR). HR-MS (ES-TOF+): *m/z* calcd for $C_{16}H_{19}NO_2S_2Na$: 344.0757 found: 344.0755 [$M+Na^+$].

***S*-benzyl-*N*-phenylethynyl-*N*-tosylcysteamine (459)** Prepared using GP3. Alkynylation was performed with tosylcysteamine **456** (500.0 mg, 1.56 mmol, 1.0 eq.), crude bromophenyl acetylene (0.20 ml, *ca.* 1.70 mmol, 1.1 eq.), 1,10-phenanthroline (50.4 mg, 280 µmol, 0.18 eq.), $CuSO_4.5H_2O$ (46.7 mg, 187 µmol, 0.12 eq.) and K_2CO_3 (431.2 mg, 3.12 mmol, 2.0 eq.) in toluene (3 ml) for 20 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **459** as a yellow oil (492.9 mg, 75%). δ_H (300 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.3 Hz, ArH), 7.41–7.29 (12H, m, ArH), 3.74 (2H, s, $PhCH_2S$), 3.64–3.44 (2H, m, CH_2N), 2.82–2.63 (2H, m, SCH_2CH_2), 2.47 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 144.9 (C), 138.2 (C), 134.8 (C), 131.6 (CH), 129.9 (CH), 129.1 (CH), 128.8 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 127.3 (CH), 122.8 (C), 82.1 (C), 71.2 (C), 51.4 (CH_2), 36.3 (CH_2), 29.0 (CH_2), 21.8 (CH_3). IR (Neat): 3062 (CH), 2923 (CH), 2237 (C≡C), 1598w, 1496, 1456, 1366, 1171. HR-MS (ES-TOF+): *m/z* calcd for 441.1068 $C_{24}H_{23}NO_2S_2Na$: 441.1078 found: $[M+Na^+]$.

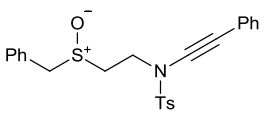
***S*-*p*-methoxybenzyl-*N*-phenylethynyl-*N*-tosylcysteamine (460)** Prepared using GP3. Alkynylation was performed with tosylcysteamine **457** (102 mg, 290 µmol, 1.0 eq.), crude bromophenyl acetylene (38.4 µl, *ca.* 320 µmol, 1.1 eq.), 1,10-phenanthroline (9.4 mg, 52.0 µmol, 0.18 eq.), $CuSO_4.5H_2O$ (8.7 mg, 35.0 µmol, 0.12 eq.) and K_2CO_3 (80.2 mg, 580 µmol, 2.0 eq.) in toluene (2 ml) for 16 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate to *n*-hexane, gave ynamide **460** as a colourless oil (57.4 mg, 77%). δ_H (300 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.3, ArH), 7.44-7.31 (7H, m, ArH), 7.26 (2H, d, *J* 8.6, ArH), 6.84 (2H, d, *J* 8.6, ArH), 3.79 (3H, s, CH_3O), 3.71 (2H, s, $PhCH_2S$), 3.61-3.46 (2H, m, CH_2N), 2.77-2.64 (2H, m, SCH_2CH_2), 2.48 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 158.9 (C), 144.9 (C), 134.7 (C), 131.6 (CH), 130.1 (CH), 129.9 (CH), 129.9 (C), 128.4 (CH), 128.1 (CH), 127.8 (CH), 122.7 (C), 114.1 (CH), 82.1 (C), 71.1 (C), 55.3 (CH_2), 51.4 (CH_2), 35.6 (CH_2), 28.8 (CH_3), 21.8 (CH_3). IR (neat): 3059 (CH), 2925 (CH), 2235 (C≡C), 1617w (C=C), 1598w (C=C), 1494, 1443, 1366, 1324, 1168, 1121. HR-MS (ES-TOF+): *m/z* calcd for 474.1174 $C_{25}H_{25}NO_3S_2Na$: 474.1181 found: 474.1174 $[M+Na^+]$.

***S*-*p*-trifluoromethylbenzyl-*N*-phenylethynyl-*N*-tosylcysteamine (461)** Prepared using GP3.

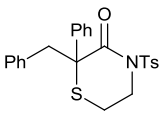


Alkynylation was performed with tosylcysteamine **458** (200 mg, 510 µmol, 1.0 eq.), crude bromophenyl acetylene (68.4 µl, *ca.* 570 µmol, 1.1 eq.), 1,10-penanthroline (16.6 mg, 92.0 µmol, 0.18 eq.), $CuSO_4.5H_2O$ (15.2 mg, 61.0 µmol, 0.12 eq.) and K_2CO_3 (141 mg, 1.0 mmol, 2.0 eq.) in toluene (2 ml) for 16 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **461** as a colourless oil (20. mg, 81%). δ_H (300 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.3, ArH), 7.55 (2H, d, *J* 8.3, ArH), 7.46 (2H, d, *J* 8.1, ArH), 7.40-7.31 (7H, m, ArH), 3.79 (2H, s, $PhCH_2S$), 3.63-3.46 (2H, m, CH_2N), 2.80-2.61 (2H, m, SCH_2CH_2), 2.47 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$, CF coupled) 145.0 (C), 142.3 (C), 134.7 (C), 131.6 (CH), 123.0 (CH), 129.7 (C), 129.4 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 125.7 (CH), 125.7 (CH), 124.0 (q, *J* 275, CF_3), 122.6 (C), 82.0 (C), 71.3 (C), 51.4 (CH_2), 35.8 (CH_2), 29.2 (CH_2), 21.8 (CH_3). IR (Neat): 3069 (CH), 2925 (CH), 2235 (C≡C), 1617w (C=C), 1598w (C=C), 1494, 1443, 1366, 1324, 1167, 1119. HR-MS (ES-TOF+): *m/z* calcd for $C_{25}H_{22}NO_2S_2F_3Na$: 512.0942 found: 512.0943[M+Na^+].

***S*-benzyl-*N*-phenylethynyl-*N*-tosylcysteamine *S*-oxide (462)** MoO_2Cl_2 (1.8 mg, 8.90 µg, 0.0150 eq.) was added to a solution of tosylcysteamine **459** (250 mg, 590 µmol, 1.00 eq.) in a water (7.5 ml) and acetone (11.5 ml) mixture. This was immediately followed by 33% H_2O_2 solution (58 µl, 620 µmol, 1.05 eq.) and the reaction was stirred for 0.5 hours. The reaction was quenched with $NaHCO_3$ carbonate solution (10 ml) and extracted with CH_2Cl_2 (4 x 20 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with 3:1 ethyl acetate:*n*-hexane, gave ynamide **462** as a colourless oil (92.2 mg, 36%). δ_H (300 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.3, ArH), 7.61 (2H, d, *J* 8.3, ArH), 7.43 (2H, d, *J* 8.1, ArH), 7.37 (2H, d, *J* 8.1, ArH), 7.30 (6H, d, *J* 7.3, ArH), 4.14 (1H, d, *J* 13.0, PhC*H*HS), 4.04 (1H, d, *J* 13.0, PhCH*H*S), 3.97-3.71 (2H, m, CH_2N), 3.08 (1H, dt, *J* 13.4, 7.5, SC*H*HCH_2), 2.99-2.83 (1H, m, SCH*H*CH_2), 2.46 (3H, s, CH_3). IR (neat): 3059 (CH), 2926 (CH), 2236 (C≡C), 1619w (C=C), 1598w (C=C), 1494, 1444, 1365, 1324, 1168, 1122, 1067. HR-MS (ES-TOF+): *m/z* calcd for $C_{25}H_{22}NO_2S_2F_3Na$: 460.1017 found: 460.1008 [M+Na^+].

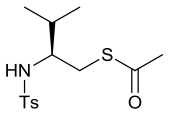


2-benzyl-2-phenyl-4-tosylthiomorpholin-3-one (463) Prepared using GP5. Catalysis was performed



using ynamide **459** (200.0 mg, 474 µmol, 1.0 eq.), pyridine *N*-oxide (496 mg, 522 µmol, 1.1 eq.), AgOTs (6.6 mg, 24.0 µmol, 0.050 eq.) and IPrAuCl (14.7 mg, 24.0 µmol, 0.050 eq.) in CH_2Cl_2 (8 ml) for 21 hours. Purification by flash column chromatography, eluting with 10:1:89 diethyl ether:triethylamine:*n*-hexane, gave thiomorpholinone **463** as a colourless oil (112.4 mg, 54%). δ_H (300 MHz, $CDCl_3$) 7.89 (2H, d, *J* 8.4, ArH), 7.40 (2H, d, *J* 8.0, ArH), 7.350–7.19 (4H, m, ArH), 7.14 (2H, dd, *J* 8.0, 1.5, ArH), 7.05 (2H, t, *J* 7.3, ArH), 6.58 (2H, d, *J* 7.0, ArH), 4.66–4.45 (1H, m, C*H*HN), 3.32 (1H, d, *J* 14.0, PhCH*H*), 3.25 (1H, d, *J* 14.0, PhC*H*H), 3.09 – 2.92 (2H, m, SC$H_2$$CH_2$N), 2.93–2.78 (1 H, m, CH*H*N), 2.53 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 167.0 (CO), 145.0 (C), 138.4 (C), 136.0 (C), 135.0 (C), 131.1 (CH), 129.6 (CH), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 126.9 (CH), 126.7 (CH), 59.6 (C), 46.2 (CH_2), 43.4 (CH_2), 26.9 (CH_2), 21.9 (CH_3). IR (neat): ν_{max} = 3031 (CH), 2930 (CH), 1698 (CO), 1596, 1495, 1454, 1356, 1317, 1168. HR-MS (ES-TOF+): *m/z* calcd for $C_{24}H_{23}NO_3S_2Na$: 460.1017 found: 460.1032 [$M+Na^+$].

(*S*)-*S*-(3-methyl-2-(4-methylphenylsulfonamido)butyl) ethanethioate (469) Prepared via a modified



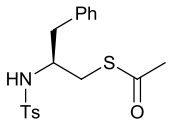
literature procedure.[219] A solution of NaH (2M, 57.5 ml, 115 mmol, 2.70 eq.) was added over 3 hours via dropping funnel to a stirred solution of tosyl chloride (10.58 g, 55.5 mmol, 1.30 eq.) and L-valine (5.00 g, 42.6 mmol, 1.00 eq.) in an ethyl acetate (92 ml) and water (16 ml) mix. After another hour the aqueous phase was separated and 1M HCl solution was added to it. The resulting white precipitate was collected by suction filtration and dried *in vacuo* to give the crude *N*-tosyl valine **467**. The crude tosylate (7.015 g, ca. 25.9 mmol, 0.600 eq.) was dissolved in dry THF (150 ml), the resulting solution was cooled to 0 °C and $LiAlH_4$ (2.944 g, 77.6 mmol, 1.80 eq.) was cautiously added. The reaction was allowed to reach room temperature over 0.5 hours and then heated to reflux for 15 hours. The reaction mixture was then quenched with ethyl acetate (150 ml) and sodium potassium tartrate solution (250 ml) was added. The resulting mixture was extracted with ethyl acetate (3 x 100 ml); the organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude amino alcohol **468**. Diisopropyl azodicarboxylate (9.280 g, 45.9 mmol, 1.06 eq.) was added to a 0 °C solution of PPh_3 (12.039 g, 45.9

mmol, 1.06 eq.) in dry THF (100 ml) and stirred for 0.5 hours. The crude amino alcohol (5.905, ca. 22.9 mmol, 0.530 eq.) was then added, followed immediately by thioacetic acid (3.23 ml, 45.9 mmol, 1.06 eq.) and allowed to reach room temperature over 16 hours. The reaction mixture was concentrated *in vacuo*, *n*-hexane was added and the precipitated phosphine and phosphate removed by suction filtration. Purification by flash column chromatography, eluting with 1:4 ethyl acetate:*n*-hexane, gave ethanethioate **469** as a colourless solid (0.777 g, 6% over 3 steps. Melting point 94-95 °C from CH_2Cl_2 (Lit.[220] 99-101 °C). $[\alpha]_D^{21}$ –10.45 (*c* 0.011 in $CHCl_3$). δ_H (300 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.2, ArH), 7.29 (2H, d, *J* 8.2, ArH), 4.60 (1H, d, *J* 8.2, NH), 3.27 (1 H, tt, *J* 8.2, 5.0, NC*H*CH_2), 2.93 (1H, dd, *J* 14.2, 8.2, CHC*H*H), 2.82 (1H, dd, *J* 14.2, 5.0, CHCH*H*), 2.43 (3H, s, CH_3), 2.20 (3H, s, CH_3), 1.87 (1H, qnd, *J* 6.8, 5.0, CH_3CHCH_3), 0.88 (3H, d, *J* 6.8, CHCH_3), 0.86 (3H, d, *J* 6.8, CHCH_3). IR (neat): ν_{max} = 3307 (CH), 2973 (CH), 2933 (CH), 2878 (CH), 1665 (CO), 1500 (C=C), 1430, 1399, 1161, 1051. Data in agreement with literature values.[220]

(S)-*S*-(2-(4-methylphenylsulfonamido)propyl) ethanethioate (475) Prepared via a modified literature procedure.[221] L-alaninol (1.000 g, 13.3 mmol, 1.0 eq.) was added to a stirred 0 °C solution of tosyl chloride (5.586 g, 29.3 mmol, 2.2 eq.) and pyridine (7.5 ml, 93.0 mmol, 7 eq.) in dry CH_2Cl_2 (10 ml) under argon. The reaction mixture was allowed to reach room temperature over 18 hours, added to 1 M HCl solution (20 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The organic fractions were combined, washed with $CuSO_4$ solution (20 ml) and then brine (20 ml). The organic fraction was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil was dissolved in acetone (150 ml) and potassium thioacetate (6.076 g, 53.2 mmol, 4.0 eq.) was added with stirring. After 20 hours ethyl acetate was added (100 ml), followed by silica gel, then the mixture was concentrated *in vacuo* to give a dry, free-flowing powder. Purification by flash column chromatography, eluting with 1:3 ethyl acetate:*n*-hexane, gave ethanethioate **475** as blood red crystals (2.913 g, 76% over two steps). Melting point 58-60 °C from CH_2Cl_2. $[\alpha]_D^{21}$ -19.33 (*c* 0.015 in $CHCl_3$). δ_H (300 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.2, ArH), 7.32 (2H, d, *J* 8.0, ArH), 4.63 (1H, brd, *J* 7.2, NH), 3.55 (1H, m, CH), 2.93 (2H, qd, *J* 14.1, 5.9), 2.45 (3H, s, $ArCH_3$), 2.29 (3H, s, $COCH_3$), 1.16 (3H, d, *J* 6.6, CHCH_3). δ_C (101 MHz, $CDCl_3$) 195.9 (C), 143.5 (C), 138.1 (C), 129.8 (CH), 127.3 (CH), 50.1 (CH), 35.5

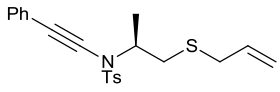
(CH_2), 30.6 (CH_3), 21.7 (CH_3), 21.4 (CH_3). IR (neat): 3273 (NH), 2975 (CH), 2931 (CH), 2874 (CH), 1682 (CO), 1599, 1439, 1420, 1325, 1152, 1140. HR-MS (ES-TOF+): *m/z* calcd for $C_{12}H_{17}NO_3S_2Na$: 310.0548 found: 310.0534 [M+Na^+].

(*S*)-*S*-(2-(4-methylphenylsulfonamido)-3-phenylpropyl) ethanethioate (476)



Prepared via a modified literature procedure.[221] L-phenylalaninol (2.000 g, 13.2 mmol, 1.0 eq.) was added to a stirred 0 °C solution of tosyl chloride (5.537 g, 29.0 mmol, 2.2 eq.) and pyridine (7.5 ml, 92.0 mmol, 7.0 eq.) in dry CH_2Cl_2 (15 ml) under argon. The reaction mixture was allowed to reach room temperature over 18 hours, added to 1 M HCl solution (20 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The organic fractions were combined, washed with $CuSO_4$ solution (20 ml) and then brine (20 ml). The organic fraction was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil was dissolved in acetone (150 ml) and potassium thioacetate (6.030 g, 52.8 mmol, 4.0 eq.) was added with stirring. After 20 hours ethyl acetate was added (100 ml), followed by silica gel, then the mixture was concentrated *in vacuo* to give a dry, free-flowing powder. Purification by flash column chromatography, eluting with 1:3 ethyl acetate:*n*-hexane, gave ethanethioate **476** as blood red crystals (1.043 g, 22% over two steps). Melting point 84-87 °C from CH_2Cl_2. $[\alpha]_D^{21}$ –9.19 (*c* 0.011 in $CHCl_3$). δ_H (300 MHz, $CDCl_3$) 7.61 (2H, d, *J* 8.3, ArH), 7.22 (5H, m, ArH), 7.04 (2H, dd, *J* 7.0, 2.4, ArH), 4.69 (1H, d, *J* 7.1, NH), 3.59 (1H, m, C*H*), 2.95 (1H, dd, *J* 14.2, 6.6, CHCH*H*), 2.89 (1H, dd, *J* 14.3, 5.5, CHC*H*H), 2.86 (1H, dd, *J* 14.1, 6.4, CHC*H*H), 2.79 (1H, dd, *J* 14.1, 7.4, CHCH*H*), 2.31 (3H, s, CH_3), 2.26 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 196.1 (CO), 143.4 (C), 137.5 (C), 136.5 (C), 129.7 (CH), 129.5 (CH), 128.9 (CH), 127.2 (CH), 127.1 (CH), 55.3 (CH), 41.2 (CH_2), 33.2 (CH_2), 30.6 (CH_3), 21.7 (CH_3). IR (neat): 3307 (NH), 3030 (CH), 2926 (CH), 1660 (CO), 1598 (C=C), 1496, 1434, 1399, 1152, 1320, 1157. HR-MS (ES-TOF+): *m/z* calcd for $C_{18}H_{21}NO_3S_2Na$: 386.0861 found: 386.0846 [M+Na^+].

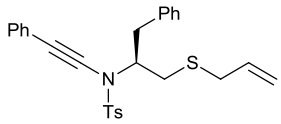
(*S*)-*N*-(1-(allylthio)propan-2-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide (477)



K_2CO_3 (480.9 mg, 3.48 mmol, 2.0 eq.) was added to a stirred solution of

ethanethioate **475** (500.0 mg, 1.74 mmol, 1.0 eq.) in CH_3OH (10 ml), followed by allyl bromide (150 µl, 1.74 mmol, 1.0 eq.). After 17 hours the reaction mixture was added to NH_4Cl solution (20 ml) and then extracted with CH_2Cl_2 (3 x 30 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. A portion of the resulting white crystals (407.1 mg, 1.06 mmol, 0.60 eq) was dissolved in dry toluene (1 ml) and alkynylated with crude bromophenyl acetylene (0.25 ml, *ca.* 2.11 mmol, 1.2 eq.), 1,10-penanthroline (34.2 mg, 190 µmol, 0.11 eq.), $CuSO_4.5H_2O$ (32.5 mg, 130 µmol, 0.075 eq.) and K_2CO_3 (291.6 mg, 2.11 mmol, 1.2 eq.) for 20 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **477** as a yellow oil (58.0 mg, 14%). $[\alpha]_D^{21}$ +85.31 (*c* 0.011 in $CHCl_3$). δ_H (300 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.3, ArH), 7.51–7.16 (7H, m, ArH), 5.74 (1H, ddt, *J* 17.1, 10.0, 7.2, CH_2CHCH_2S), 5.12 (2H, d, *J* 17.1, $CHHCHCH_2S$), 5.11 (1H, d, *J* 10.0, $CHHCHCH_2S$), 4.29–4.07 (1H, m, $CHCH_3$), 3.11 (2H, d, *J* 7.2, $CHCH_2S$), 2.69 (1H, dd, *J* 13.9, 7.0, $SCHHCH$), 2.55 (1H, dd, *J* 13.9, 7.4, $SCHHCH$), 2.45 (3H, s, $ArCH_3$), 1.24 (3H, d, *J* 6.6, $CHCH_3$). δ_C (101 MHz, $CDCl_3$) 144.7 (C), 135.9 (C), 134.1 (CH), 131.4 (CH), 129.8 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 123.1 (C), 117.7 (CH_2), 79.2 (C), 73.5 (C), 56.2 (CH), 35.4 (CH_2), 35.1 (CH_2), 21.8 (CH_3), 18.3 (CH_3). IR (neat): 3065 (CH), 2979 (CH), 2923 (CH), 2237 (C≡C), 1598w, 1363, 1171. HR-MS (ES-TOF+): *m/z* calcd for 408.1068 $C_{21}H_{23}NO_2S_2Na$: 408.1072 found: $[M+Na^+]$.

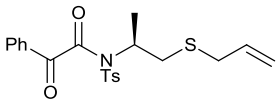
(*S*)-*N*-(1-(allylthio)-3-phenylpropan-2-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide (478)



K_2CO_3 (380 mg, 2.75 mmol, 2.0 eq.) was added to a stirred solution of ethanethioate **476** (500.0 mg, 1.38 mmol, 1.0 eq.) in methanol (10 ml), followed by allyl bromide (120 µl, 1.74 mmol, 1.0 eq.). After 17 hours the reaction mixture was added to NH_4Cl solution (20 ml) and then extracted with CH_2Cl_2 (3 x 30 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. A portion of the resulting white crystals (392.2 mg, 850 µmol, 0.61 eq.) was dissolved in dry toluene (1 ml) and alkynylated with crude bromophenyl acetylene (0.20 ml, *ca.* 1.70 mmol, 1.2 eq.), 1,10-phenanthroline (27.0 mg, 150 µmol, 0.10 eq.), $CuSO_4.5H_2O$ (25.5 mg, 102 µmol, 0.074 eq.) and K_2CO_3 (235.0 mg, 1.70 mmol, 1.2 eq.) for 20 hours. Purification by flash column chromatography, eluting with 1:9 ethyl acetate:*n*-hexane, gave ynamide **478** as a yellow oil (58.0 mg, 14%). $[\alpha]_D^{20}$ -9.10 (*c* 0.022 in $CHCl_3$). δ_H (300

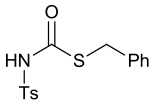
MHz, $CDCl_3$) 7.53 (2H, d, *J* 8.3, ArH), 7.45-7.42 (1H, m, ArH), 7.40 (1H, dd, *J* 5.1, 2.3, ArH), 7.35-7.33 (2H, m, ArH), 7.33-7.30 (1H, m, ArH), 7.24-7.11 (7H, m, ArH), 5.75 (1 H, ddt, *J* 17.2, 9.0, 6.8, CH_2CHCH_2S), 5.07 (1 H, d, *J* 9.0, $CHHCHCH_2S$), 5.06 (2 H, d, *J* 17.2, $CHHCHCH_2S$), 4.43-4.29 (1H, m, $NCHCH_2$), 3.16 (2H, d, *J* 6.8, SCH_2CHCH_2), 3.09 (1H, dd, *J* 13.9, 5.5, CHCHH), 2.91 (1H, dd, *J* 13.9, 8.8, CHCHH), 2.82 (1H, dd, *J* 14.1, 7.4, CHCHH), 2.74 (1H, dd, *J* 14.2, 6.6, CHCHH), 2.41 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 144.2 (C), 137.5 (C), 135.3 (C), 134.0 (C), 131.4 (CH), 129.5 (CH), 129.4 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 126.7 (CH), 123.0 (CH), 117.7 (CH_2), 79.4 (C), 74.3 (C), 62.5 (CH), 38.7 (CH_2), 35.1 (CH_2), 33.9 (CH_2), 21.7 (CH_3). IR (neat): 3035 (CH), 2919 (CH), 2230 (C≡C), 1598w, 1496, 1363, 1168. HR-MS (ES-TOF+): *m/z* calcd for 484.1381 $C_{27}H_{27}NO_2S_2Na$: 484.1386 found: $[M+Na^+]$.

(*S*)-*N*-(1-(allylthio)propan-2-yl)-2-oxo-2-phenyl-*N*-tosylacetamide (481) Prepared using GP5.



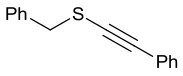
Catalysis was performed using ynamide **477** (42.4 mg, 110 µmol, 1.0 eq.), pyridine *N*-oxide (11.4 mg, 120 µmol, 1.1 eq.), AgOTs (1.4 mg, 5 µmol, 0.050 eq.) and IPrAuCl (3.1 mg, 5. µmol, 0.050 eq.) in CH_3CN (2 ml) for 16 hours. Purification by flash column chromatography, eluting with 20:1:79 diethyl ether:triethylamine:*n*-hexane, gave tosylacetamide **481** as a colourless oil (20.3 mg, 81%). $[\alpha]_D^{21}$ +5.50 (*c* 0.011 in $CHCl_3$).δ_H (300 MHz, $CDCl_3$) 8.00 (2H, d, *J* 7.4, ArH), 7.95 (2H, d, *J* 8.3, ArH), 7.64 (1H, t, *J* 7.4, ArH), 7.53 (2H, t, *J* 7.4, ArH), 7.41 (2H, d, *J* 8.3, ArH), 5.73 (1H, ddd, *J* 17.0, 10.1, 7.2 CH_2CHCH_2), 5.09 (1H, d, *J* 17.0, $CHHCHCH_2S$), 5.06 (1H, d, *J* 10.1, $CHHCHCH_2S$), 4.18–3.99 (1H, m, CH_2CHCH_3), 3.03 (2H, t, *J* 6.8, $CHCH_2S$), 2.48 (3H, s, *J* 7.2, $ArCH_3$), 1.42 (3H, d, *J* 6.3, $CHCH_3$). δ_C (101 MHz, $CDCl_3$) 187.2 (CO), 168.5 (CO), 146.3 (C), 134.9 (C), 134.7 (CH), 134.4 (CH), 133.3 (C), 130.6 (CH), 130.4 (CH), 129.3 (CH), 129.1 (CH), 118.0 (CH_2), 35.3 (CH_2), 34.5 (CH_2), 30.2 (CH), 22.2 (CH_3), 17.3 (CH_3). IR (neat): ν_{max} = 3065 (CH), 2923 (CH), 1677 (CO), 1597 (C=C), 1451, 1367, 1205, 1167. HR-MS (ES-TOF+): *m/z* calcd for $C_{21}H_{23}NO_4S_2Na$: 440.966 found: 440.0970 $[M+Na^+]$.

***S*-benzyl tosylthiocarbamate (488)** Benzyl thiol (0.60 ml, 5.12 mmol, 1.01 eq.) was added to a solution of *N*-tosyl isocyanate (0.77 ml, 5.07 mmol, 1.00 eq.) in dry CH_2Cl_2 (20 ml) and



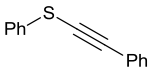
stirred for 26 hours. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography, eluting with 3:2 ethyl acetate:petroleum ether (boiling range 40-60 °C), to give an opaque, viscous oil, which crystallised upon standing to give thiocarbamate **488** as white crystals (0.130 g, 33%), melting point 91-95 °C from CH_2Cl_2. δ_H (300 MHz, $CDCl_3$) 7.96 (2H, d, *J* 8.4, ArH), 7.38 (2H, d, *J* 8.4, ArH), 7.33-7.14 (5H, m, ArH), 4.13 (2H, s, SCH_2), 2.48 (3H, s, $ArCH_3$). δ_C (101 MHz, $CDCl_3$) 165.4 (CO), 145.4 (C), 136.0 (C), 135.5 (C), 129.7 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 127.7 (CH), 34.6 (CH_2), 21.71 (CH_3). IR (neat): ν_{max} = 3218 (NH), 3069 (CH), 2925 (CH), 1700 (CO), 1597, 1432, 1345, 1172, 1079. HR-MS (ES-TOF+): *m/z* calcd for $C_{15}H_{15}NO_3S_2Na$: 344.0391 found: 344.0398 [M+Na].

Benzyl(phenylethynyl)sulfide (489) Prepared using GP3. Alkynylation was performed with



tosylthiocarbamate **488** (500 mg, 1.56 mmol, 1.0 eq.), crude bromophenyl acetylene (220 µl, *ca.* 1.87 mmol, 1.2 eq.), 1,10-phenanthroline (11.3 mg, 624 µmol, 0.40 eq.), $CuSO_4.5H_2O$ (77.9 mg, 31.2 µmol, 0.20 eq.) and K_3PO_4 (79.5 mg, 3.74 mmol, 2.4 eq.) in toluene (5 ml) for 22 hours. Purification by flash column chromatography, eluting with 3:97 ethyl acetate:*n*-hexane, gave sulfide **489** as a yellow oil (250 mg, 71%). δ_H (300 MHz, $CDCl_3$) 7.49- 7.18 (10H, m, ArH), 4.04 (2H, s, CH_2). δ_C (101 MHz, $CDCl_3$) 136.6 (C), 131.3 (CH), 129.1 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 123.4 (C), 94.6 (C), 79.2 (C), 40.5 (CH_2). IR (neat): ν_{max} = 3061 (CH), 3029 (CH), 2927 (CH), 2165 (C≡C), 1595 (C=C), 1486, 752. In agreement with literature data.[186]

Phenyl(phenylethynyl)sulfide (494) Prepared as per literature procedure.[185] A solution of *n*-butyl



lithium (2.5 M, 4.3 ml, 10.8 mmol, 1.1 eq.) in dry THF was added to a -78 °C solution of phenyl acetylene (1.08 ml, 9.80 mmol, 1.0 eq.) in dry THF (100 ml). After 1 hour a solution of *S*-phenyl benzenesulfonothioate (2.929 g, 1.11 mmol, 1.2 eq.) in dry THF (50 ml) was added. After a further 5 hours the reaction mixture was added to NH_4Cl solution (100 ml) and extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with *n*-hexanes, gave sulfide **494** as a colourless oil (1.87 g, 91%). δ_H (300 MHz, $CDCl_3$) 7.58-7.47 (5H, m,

ArH), 7.41-7.32 (5H, m, ArH). δ_C (101 MHz, $CDCl_3$) 133.0 (C), 131.7 (CH), 129.3 (CH), 128.6 (CH), 128.4 (CH), 126.5 (CH), 126.2 (CH), 122.9 (C), 97.9 (C), 75.5 (C). IR (neat): ν_{max} = 3059 (CH), 2168 (C≡C), 1583 (C=C), 1477, 1440, 1023, 752. Data in agreement with literature values.[185]

Phenyl(butylethynyl)sulfide (495) Prepared as per literature procedure.[185] A solution of *n*-butyl lithium (2.5 M, 2.4 ml, 6.10 mmol, 1.0 eq.) in dry THF was added to a -78 °C solution of 1-hexyne (700 µl, 6.10 mmol, 1.0 eq.) in dry THF (50 ml). After 1 hour *S*-phenyl benzenesulfonothioate (1.680 g, 6.71 mmol, 1.1 eq.) was added. After a further 2 hours the reaction mixture was added to NH_4Cl solution (50 ml) and extracted with ethyl acetate (3 x 40 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with *n*-hexane, gave sulfide **495** as a colourless oil (0.85 g, 73%). δ_H (300 MHz, $CDCl_3$) 7.42 (2H, dd, *J* 8.0, 1.2, ArH), 7.33 (2H, t, *J* 8.0, ArH), 7.20 (1H, tt, *J* 7.2, 1.2, ArH), 2.47 (2H, t, *J* 7.0, CCH_2), 1.66-1.54 (2H, m, $CH_2CH_2CH_2$), 1.47 (2H, h, *J* 7.1, CH_2CH_3), 0.95 (3H, t, *J* 7.1, CH_3). δ_C (101 MHz, $CDCl_3$) 134.0 (C), 129.2 (CH), 126.2 (CH), 125.9 (CH), 100.2 (C), 64.7 (C), 30.9 (CH_2), 22.1 (CH_2), 20.1 (CH_2), 13.7 (CH_3). IR (neat): ν_{max} = 3062 (CH), 2958 (CH), 2930 (CH), 2872 (CH), 2167 (C≡C), 1584 (C=C), 1479, 1441, 1024, 736. Data in agreement with literature values.[185]

Benzyl(butylethynyl)sulfide (496) Prepared as per literature procedure.[186] A solution of *n*-butyl lithium (4.3 ml, 10.8 mmol, 1.1 eq.) in dry THF was added to a stirred, -78 °C solution of 1-hexyne (1.12 ml, 9.79 ml, 1.0 eq.) in dry THF. Sulfur (313 mg, 9.79 mmol, 1.0 eq.) was added after 15 minutes and the reaction mixture was allowed to reach 0 °C over a period of an hour. Benzyl bromide (1.16 ml, 9.79 mmol, 1.0 eq.) was added and the reaction mixture stirred for a further hour. The reaction was added to NH_4Cl solution (50 ml) and extracted with diethyl ether (3 x 40 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with *n*-hexane, gave sulfide **496** as a colourless oil (0.863, 43%). δ_H (300 MHz, $CDCl_3$) 7.40-7.27 (5H, m, ArH), 3.89 (3H, s, CH_3), 2.27 (1H, t, *J* 6.9, SCH_2), 1.60-1.22 (4H, m, CH_2CH_2), 0.88 (3H, t, *J* 7.2, CH_3). δ_C (101 MHz, $CDCl_3$) 137.2 (C), 129.2 (CH), 128.6 (CH), 127.7 (CH), 96.2 (C), 68.1 (C), 40.3 (CH_2), 30.9 (CH_2), 22.0 (CH_2), 19.9

(CH_2), 13.7 (CH_3). IR (neat): ν_{max} = 3030 (CH), 2958 (CH), 2927 (CH), 2855 (CH), 2167 (C≡C), 1495, 1455, 1070, 697. Data in agreement with literature values.[186]

Methyl(phenylethynyl)sulfide (497) Prepared as per literature procedure.[186] A solution of *n*-butyl lithium (4.3 ml, 10.8 mmol, 1.1 eq.) in dry THF was added to a stirred, -78 °C solution of phenyl acetylene (1.08 ml, 9.79 ml, 1.0 eq.) in dry THF. Sulfur (313 mg, 9.79 mmol, 1.0 eq.) was added after 15 minutes and the reaction mixture was allowed to reach 0 °C over a period of an hour. CH_3I (610 µl, 9.79 mmol, 1.0 eq.) was added and the reaction mixture stirred for a further hour. The reaction was added to NH_4Cl solution (50 ml) and extracted with diethyl ether (3 x 40 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with *n*-hexane, gave sulfide **497** as a colourless oil (1.1, 73%). δ_H (300 MHz, $CDCl_3$) 7.49-7.35 (2H, m, ArH), 7.35-7.09 (3H, m, ArH), 2.50 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 131.6 (CH), 128.4 (CH), 128.2 (CH), 123.6 (C), 92.0 (C), 81.0 (C), 19.6 (CH_3). IR (Neat): ν_{max} = 3061 (CH), 2926 (CH), 2852 (CH), 2168 (C≡C), 1596, 1487, 1442, 1070, 754. In agreement with literature data.[186]

Methyl(butylethynyl)sulfide (498) Prepared as per literature procedure.[186] A solution of *n*-butyl lithium (4.3 ml, 10.8 mmol, 1.1 eq.) in dry THF was added to a stirred, -78 °C solution of 1-hexyne (1.12 ml, 9.79 ml, 1.0 eq.) in dry THF. Sulfur (313 mg, 9.79 mmol, 1.0 eq.) was added after 15 minutes and the reaction mixture was allowed to reach 0 °C over a period of an hour. CH_3I (610 µl, 9.79 mmol, 1.0 eq.) was added and the reaction mixture stirred for a further hour. The reaction was added to NH_4Cl solution (50 ml) and extracted with diethyl ether (3 x 40 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with *n*-hexane, gave sulfide **498** as a colourless oil (730 mg, 53%). δ_H (300 MHz, $CDCl_3$) 2.35 (3H, s, SCH_3), 2.29 (2H, t, *J* 6.9, CCH_2), 1.59-1.30 (4H, m, $CH_2(CH_2)_2CH_3$), 0.90 (3H, t, *J* 7.2, CH_2CH_3). δ_C (101 MHz, $CDCl_3$) 93.4 (C), 69.9 (C), 31.0 (CH_2), 22.1 (CH_2), 19.9 (CH_2), 19.5 (CH_3), 13.7 (CH_3). IR (Neat): ν_{max} = 2658 (CH), 2927 (CH), 2857 (CH), 1465, 1378, 1314, 1106, 744. Data in agreement with literature values.[186]

Benzoyl(pyridinium)amide (521) Prepared as per literature procedure.[69] Benzoyl chloride (0.52 ml, 9.0 mmol, 2 eq.) was added to a 0 °C stirred solution of aminopyridinium iodide (1.000 g, 4.5 mmol, 1 eq.) in 10% NaOH solution (50 ml). The reaction mixture was allowed to reach room temperature and stirred for 16 hours, then extracted with CH_2Cl_2 (3 x 50 ml). The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Recrystallisation from CH_2Cl_2 and diethyl ether gave pyridinium **521** as light brown needles (0.71 g, 79%), melting point 180-181 °C (Lit.[222] 179-180 °C). δ_H (300 MHz, $CDCl_3$) 8.93-8.79 (2H, dd, *J* 7.0, 1.3, ArH), 8.25-8.16 (2H, m, ArH), 7.96 (2H, t, *J* 7.7, ArH), 7.79-7.65 (2H, m, ArH), 7.51-7.38 (2H, m, ArH). IR (neat): ν_{max} = 3099 (CH), 3065 (CH), 2946 (CH), 2827 (CH), 1591, 1548, 1465, 1331, 1296, 1181. Data in agreement with literature values.[69]

2,5-diphenyl-4-(phenylthio)oxazole (522) AuCl was added to a solution of methyl(phenylethynyl)sulfide and pyridinium **521** in dry toluene in a flame-dried Schlenk flask and then the reaction mixture was immediately heated to 90 °C, using a preheated block. After 18 hours the reaction mixture was cooled to room temperature and filtered through a plug of silica, eluting with ethyl acetate. The filtrate was concentrated *in vacuo* and analysed by NMR spectroscopy. The yield was calculated against a known quantity of 1,2,4,5-tetramethylbenzene (9% by NMR). To acquire sufficient material for characterisation the individual screening reactions were combined and purified by flash column chromatography, eluting with 3:7 toluene:*n*-hexane, to give oxazole **522** as a colourless oil. δ_H (300 MHz, $CDCl_3$) 8.36-7.91 (4H, m, ArH), 7.55-7.42 (5H, m, ArH), 7.41-7.32 (1H, m, ArH), 2.52 (3H, s, SCH_3). δ_C (101 MHz, $CDCl_3$) 162.5 (C), 142.6 (C), 140.3 (C), 131.3 (CH), 130.8 (C), 128.9 (CH), 128.6 (CH), 128.3 (CH), 127.3 (C), 127.3 (CH), 126.7 (CH), 18.8 (CH_3). IR (neat): ν_{max} = 3061 (CH), 2926 (CH), 1554, 1489, 1447, 1341, 1072, 979. MS (EI+): *m/z* (%): 267.1 (40) [$M^{+\bullet}$], 239 (31), 219 (100), 131 (46), 121 (72); HR-MS (EI+): *m/z* calcd for $C_{16}H_{13}NOS$: 267.0718, found 267.0711 [$M^{+\bullet}$].

Appendix 2: References

1. N. Marion and S. P. Nolan, *Chem. Soc. Rev.*, 2008, **37**, 1776-1782.
2. A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem., Int. Ed.*, 2006, **45**, 7896-7936.
3. F. Bonati and Minghett.G, *Gazz. Chim. Ital.*, 1973, **103**, 373-386.
4. Minghett.G and F. Bonati, *J. Organomet. Chem.*, 1973, **54**, C62-C63.
5. M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo and P. J. Pérez, *Angew. Chem., Int. Ed.*, 2005, **44**, 5284-5288.
6. C. Gutsche, *Org. Reactions*, 1954, **8**, 391–394.
7. E. B. E. LeWinn, *Am. J. Med. Sci.*, 1949, **218**, 556-562.
8. J. A. Moore and D. E. Reed, *Org. Syn. Coll. Vol 5*, 1973, 351–355.
9. N. Chatani, K. Kataoka, S. Murai, N. Furukawa and Y. Seki, *J. Am. Chem. Soc.*, 1998, **120**, 9104-9105.
10. A. S. K. Hashmi and M. Rudolph, *Chem. Soc. Rev.*, 2008, **37**, 1766-1775.
11. Z. Liu, A. S. Wasmuth and S. G. Nelson, *J. Am. Chem. Soc.*, 2006, **128**, 10352-10353.
12. A. Furstner and P. Hannen, *Chem. Commun.*, 2004, 2546-2547.
13. C. Aubert, O. Buisine and M. Malacria, *Chem. Rev.*, 2002, **102**, 813-834.
14. A. M. Echavarren and C. Nevado, *Chem. Soc. Rev.*, 2004, **33**, 431-436.
15. C. Bruneau, *Angew. Chem., Int. Ed.*, 2005, **44**, 2328-2334.
16. S. Ma, S. Yu and Z. Gu, *Angew. Chem., Int. Ed.*, 2006, **45**, 200-203.
17. M. J. Johansson, D. J. Gorin, S. T. Staben and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 18002-18003.
18. G. Seidel, R. Mynott and A. Fürstner, *Angew. Chem., Int. Ed.*, 2009, **48**, 2510-2513.
19. A. M. Echavarren, *Nature Chem.*, 2009, **1**, 431-433.
20. A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410-3449.
21. A. Fedorov, M.-E. Moret and P. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 8880-8881.
22. A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2008, **47**, 6754-6756.
23. D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard, 3rd and F. D. Toste, *Nature Chem.*, 2009, **1**, 482-486.
24. N. Ibrahim, M. H. Vilhelmsen, M. Pernpointner, F. Rominger and A. S. K. Hashmi, *Organometallics*, 2013, **32**, 2576–2583.
25. M. Alcarazo, T. Stork, A. Anoop, W. Thiel and A. Fürstner, *Angew. Chem., Int. Ed.*, 2010, **49**, 2542-2546.
26. D. J. Gorin, N. R. Davis and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 11260.
27. K. Hiroya, S. Matsumoto, M. Ashikawa, K. Ogiwara and T. Sakamoto, *Org. Lett.*, 2006, **8**, 5349.
28. N. D. Shapiro and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 4160-4161.
29. G. Li and L. Zhang, *Angew. Chem., Int. Ed.*, 2007, **46**, 5156-5159.
30. X. Huang, S. Klimczyk and N. Maulide, *Synthesis*, 2012, 175-183.
31. B. Lu, Y. Li, Y. Wang, D. H. Aue, Y. Luo and L. Zhang, *J. Am. Chem. Soc.*, 2013, **135**, 8512–8524.
32. H.-S. Yeom, J.-E. Lee and S. Shin, *Angew. Chem.*, 2008, **120**, 7148-7151.
33. A. M. Jadhav, S. Bhunia, H.-Y. Liao and R.-S. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 1769-1771.
34. H.-S. Yeom, Y. Lee, J. Jeong, E. So, S. Hwang, J.-E. Lee, S. S. Lee and S. Shin, *Angew. Chem., Int. Ed.*, 2010, **49**, 1611-1614.
35. H.-S. Yeom, Y. Lee, J.-E. Lee and S. Shin, *Org. Biomol. Chem.*, 2009, **7**, 4744-4752.
36. D. Chen, G. Song, A. Jia and X. Li, *J. Org. Chem.*, 2011, **76**, 8488-8494.
37. H.-S. Yeom, E. So and S. Shin, *Chem. Eur. J.*, 2011, **17**, 1764-1767.
38. L. Cui, G. Zhang, Y. Peng and L. Zhang, *Org. Lett.*, 2009, **11**, 1225-1228.
39. L. Cui, Y. Peng and L. Zhang, *J. Am. Chem. Soc.*, 2009, **131**, 8394-8395.
40. E. L. Noey, Y. Luo, L. Zhang and K. N. Houk, *J. Am. Chem. Soc.*, 2011, **134**, 1078-1084.
41. A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354–7358.
42. B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang and L. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8358-8362.
43. Z.-Y. Yan, Y. Xiao and L. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8624-8627.
44. Y. Xiao and L. Zhang, *Org. Lett.*, 2012, **14**, 4662-4665.
45. A. B. Cuenca, S. Montserrat, K. M. Hossain, G. Mancha, A. Lledós, M. Medio-Simón, G. Ujaque and G. Asensio, *Org. Lett.*, 2009, **11**, 4906-4909.

46. J. Xiao and X. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 7226-7236.
47. C.-W. Li, K. Pati, G.-Y. Lin, S. M. A. Sohel, H.-H. Hung and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2010, **49**, 9891-9894.
48. P. de Frémont, N. Marion and S. P. Nolan, *J. Organomet. Chem.*, 2009, **694**, 551-560.
49. L. Ye, W. He and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 8550-8551.
50. A. S. K. Hashmi, T. Wang, S. Shi and M. Rudolph, *J. Org. Chem.*, 2012, **77**, 7761-7767.
51. P. W. Davies, A. Cremonesi and N. Martin, *Chem. Commun.*, 2011, **47**, 379-381.
52. B. Lu, C. Li and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 14070-14072.
53. Y. Wang, K. Ji, S. Lan and L. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 1915-1918.
54. D. Qian and J. Zhang, *Chem. Commun.*, 2012, **48**, 7082-7084.
55. G. Henrion, T. E. J. Chavas, X. Le Goff and F. Gagosz, *Angew. Chem., Int. Ed.*, 2013, **52**, 6277-6282.
56. S. Bhunia, S. Ghorpade, D. B. Huple and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 2939-2942.
57. D. Vasu, H.-H. Hung, S. Bhunia, S. A. Gawade, A. Das and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 6911-6914.
58. D. Qian and J. Zhang, *Chem. Commun.*, 2011, **47**, 11152-11154.
59. S. Ghorpade, M.-D. Su and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 4229-4234.
60. R. B. Dateer, K. Pati and R.-S. Liu, *Chem. Commun.*, 2012, **48**, 7200-7202.
61. W. He, C. Li and L. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 8482-8485.
62. M. Stradiotto and K. D. Hesp, *J. Am. Chem. Soc.*, 2010, **132**, 18026-18029.
63. Y. Luo, K. Ji, Y. Li and L. Zhang, *J. Am. Chem. Soc.*, 2012, **134**, 17412-17415.
64. K. Ji, Y. Zhao and L. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 6508-6512.
65. C.-F. Xu, M. Xu, Y.-X. Jia and C.-Y. Li, *Org. Lett.*, 2011, **13**, 1556-1559.
66. S. Shi, T. Wang, W. Yang, M. Rudolph and A. S. K. Hashmi, *Chem. Eur. J.*, 2013, **19**, 6576-6580.
67. A. Mukherjee, R. B. Dateer, R. Chaudhuri, S. Bhunia, S. N. Karad and R.-S. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 15372-15375.
68. C. Li and L. Zhang, *Org. Lett.*, 2011, **13**, 1738-1741.
69. P. W. Davies, A. Cremonesi and L. Dumitrescu, *Angew. Chem., Int. Ed.*, 2011, **50**, 8931-8935.
70. A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341-2372.
71. X.-L. Sun and Y. Tang, *Acc. Chem. Res.*, 2008, **41**, 937-948.
72. V. K. Aggarwal, *Synlett*, 1998, **4**, 329-336.
73. J. R. Fulton, V. K. Aggarwal and J. de Vicente, *Eur. J. Org. Chem.*, 2005, **2005**, 1479-1492.
74. A. W. Johnson and R. B. LaCount, *J. Am. Chem. Soc.*, 1961, **83**, 417-423.
75. P. W. Davies and S. J. Albrecht, *Angew. Chem., Int. Ed.*, 2009, **48**, 8372-8375.
76. S. Kramer and T. Skrydstrup, *Angew. Chem., Int. Ed.*, 2012, **51**, 4681-4684.
77. T. Nishimura, C. Zhang, Y. Maeda, N. Shirai, S.-i. Ikeda and Y. Sato, *Chem. Pharm. Bull.*, 1999, **47**, 267-272.
78. T. Tanaka, N. Shirai and Y. Sato, *Chem. Pharm. Bull.*, 1992, **40**, 518-520.
79. T. Tanzawa, M. Ichioka, N. Shirai and Y. Sato, *J. Chem. Soc., Perkin Trans. 1*, 1995, 431-435.
80. C.-W. Li, G.-Y. Lin and R.-S. Liu, *Chem. Eur. J.*, 2010, **16**, 5803-5811.
81. J. Vicente, M. T. Chicote, I. Saura-Llamas, P. G. Jones, K. Meyer-Baese and C. F. Erdbruegger, *Organometallics*, 1988, **7**, 997-1006.
82. J. Stein, J. P. Fackler, C. Paparizos and H. W. Chen, *J. Am. Chem. Soc.*, 1981, **103**, 2192-2198.
83. J. Vicente, M. T. Chicote, R. Guerrero and P. G. Jones, *J. Am. Chem. Soc.*, 1996, **118**, 699-700.
84. P. W. Davies and S. J. C. Albrecht, *Chem. Commun.*, 2008, 238-240.
85. P. W. Davies and S. J. C. Albrecht, *Synlett*, 2012, 70-73.
86. L. Ye, W. He and L. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 3236-3239.
87. J. S. Clark, *Nitrogen, Oxygen and Sulfur Ylide Chemistry*, Oxford University Press, Oxford, 2002.
88. V. K. Aggarwal, J. N. Harvey and R. Robiette, *Angew. Chem., Int. Ed.*, 2005, **44**, 5468-5471.
89. M. Xu, T.-T. Ren and C.-Y. Li, *Org. Lett.*, 2012, **14**, 4902-4905.

90. J. Fu, H. Shang, Z. Wang, L. Chang, W. Shao, Z. Yang and Y. Tang, *Angew. Chem., Int. Ed.*, 2013, **52**, 4198-4202.
91. L. Ye, L. Cui, G. Zhang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 3258-3259.
92. L.-Z. Dai and M. Shi, *Chem. Eur. J.*, 2010, **16**, 2496-2502.
93. K. Tanaka, J.-I. Hayashi and A. Kaji, *Phosphorous and Sulfur and the Relat. Elem.*, 1983, **16**, 201-209.
94. H. M. L. Davies and L. V. T. Crisco, *Tetrahedron Lett.*, 1987, **28**, 371-374.
95. C. J. Moody and R. J. Taylor, *Tetrahedron Lett.*, 1988, **29**, 6005-6008.
96. C. J. Moody and R. J. Taylor, *Tetrahedron*, 1990, **46**, 6501-6524.
97. V. K. Aggarwal, J. N. Harvey and J. Richardson, *J. Am. Chem. Soc.*, 2002, **124**, 5747-5756.
98. V. Terrasson, S. Marque, M. Georgy, J.-M. Campagne and D. Prim, *Adv. Synth. Catal.*, 2006, **348**, 2063-2067.
99. Y. Zhang and J. Wang, *Coord. Chem. Rev.*, 2010, **254**, 941-953.
100. N. P. Botting, A. A. B. Robertson and J. J. Morrison, *J. Labelled, Compd. Rad.*, 2007, **50**, 260-263.
101. W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum and N. R. Vanier, *J. Am. Chem. Soc.*, 1975, **97**, 7006-7014.
102. J. Chrisment, D. Nicole and J.-J. Delpuech, *C. R. Acad. Sc. Paris - Série C*, 1978, **286**, 541.
103. F. G. Bordwell and D. L. Hughes, *J. Org. Chem.*, 1982, **47**, 3224-3232.
104. L. Breau and T. Durst, *Tetrahedron: Asymmetry*, 1991, **2**, 367-370.
105. K. Julienne, P. Metzner and V. Henryon, *J. Chem. Soc., Perkin Trans. 1*, 1999, 731-736.
106. M. Enßle, S. Buck, R. Werz and G. Maas, *Beilstein J. Org. Chem.*, 2012, **8**, 433-440.
107. W. He, L. Xie, J. Xiang and L. Zhang, *Org. Biomol. Chem.*, 2012, **10**, 3168-3171.
108. G. Pacchioni and P. S. Bagus, *Inorg. Chem.*, 1992, **31**, 4391-4398.
109. W. T. Flowers, G. Holt and P. P. McCleery, *J. Chem. Soc., Perkin Trans. 1*, 1978, 446-451.
110. S. L. Riches, C. Saha, N. F. Filgueira, E. Grange, E. M. McGarrigle and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2010, **132**, 7626-7630.
111. R. Appel, N. Hartmann and H. Mayr, *J. Am. Chem. Soc.*, 2010, **132**, 17894-17900.
112. V. K. Aggarwal, J. N. Harvey and R. Robiette, *Angew. Chem.*, 2005, **117**, 5604-5607.
113. D. R. Edwards, P. Montoya-Peleaz and C. M. Crudden, *Org. Lett.*, 2007, **9**, 5481-5484.
114. D. R. Edwards, J. Du and C. M. Crudden, *Org. Lett.*, 2007, **9**, 2397-2400.
115. F. H. Greenberg and E. M. Schulman, *J. Org. Chem.*, 1993, **58**, 5853-5854.
116. Y. Cheng, J. An, L.-Q. Lu, L. Luo, Z.-Y. Wang, J.-R. Chen and W.-J. Xiao, *J. Org. Chem.*, 2010, **76**, 281-284.
117. R. K. Dieter and S. Pounds, *J. Org. Chem.*, 1982, **47**, 3174-3177.
118. Q. Tian, L. Dong, X. Ma, L. Xu, C. Hu, W. Zou and H. Shao, *J. Org. Chem.*, 2011, **76**, 1045-1053.
119. F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456-463.
120. Y. Fu, H.-J. Wang, S.-S. Chong, Q.-X. Guo and L. Liu, *J. Org. Chem.*, 2008, **74**, 810-819.
121. J.-P. Cheng, B. Liu, Y. Zhao, Y. Sun, X.-M. Zhang and Y. Lu, *J. Org. Chem.*, 1999, **64**, 604-610.
122. J. L. Gleave, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 1935, 236-244.
123. P. H. Boyle, A. P. Davis, K. J. Dempsey and G. D. Hosken, *Tetrahedron: Asymmetry*, 1995, **6**, 2819-2828.
124. F. Sarabia, C. Vivar-García, M. García-Castro and J. Martín-Ortiz, *J. Org. Chem.*, 2011, **76**, 3139-3150.
125. G. Carr, D. E. Williams, A. R. Díaz-Marrero, B. O. Patrick, H. Bottriell, A. D. Balgi, E. Donohue, M. Roberge and R. J. Andersen, *J. Nat. Prod.*, 2009, **73**, 422-427.
126. *US Pat.*, 2004/0229817 A1, 2004.
127. R. J. Naftalin, P. Cunningham and I. Afzal-Ahmed, *Br. J. Pharmacol.*, 2004, **142**, 594-608.
128. *US Pat.*, US20010018437 A1, 1999.
129. *US Pat.*, US2002/45751, 2002.
130. M. L. Phillips and J. A. Panetta, *Tetrahedron: Asymmetry*, 1997, **8**, 2109-2114.

131. X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. Shen and M. R. Tracey, *J. Org. Chem.*, 2006, **71**, 4170-4177.
132. B. Yao, Z. Liang, T. Niu and Y. Zhang, *J. Org. Chem.*, 2009, **74**, 4630-4633.
133. A. Sato, H. Yorimitsu and K. Oshima, *Bull. Korean Chem. Soc.*, 2010, **31**, 570-576.
134. N. Martin, University of Birmingham, 2010.
135. S. Ghosh and G. P. Tochtrop, *Tetrahedron Lett.*, 2009, **50**, 1723-1726.
136. K. Jeyakumar and D. K. Chand, *Tetrahedron Lett.*, 2006, **47**, 4573-4576.
137. I. Nakamura, C. S. Chan, T. Araki, M. Terada and Y. Yamamoto, *Org. Lett.*, 2007, **10**, 309-312.
138. I. Nakamura, C. S. Chan, T. Araki, M. Terada and Y. Yamamoto, *Adv. Synth. Catal.*, 2009, **351**, 1089-1100.
139. A. Fürstner, H. Szillat and F. Stelzer, *J. Am. Chem. Soc.*, 2000, **122**, 6785-6786.
140. H. V. Adcock and P. W. Davies, *Synthesis*, 2012, **44**, 3401-3420.
141. D. Vasu, H. H. Hung, S. Bhunia, S. A. Gawade, A. Das and R. S. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 6911-6914.
142. A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2010, **49**, 5232-5241.
143. I. Nakamura, T. Sato, M. Terada and Y. Yamamoto, *Org. Lett.*, 2008, **10**, 2649-2651.
144. Y. Fukudome, H. Naito, T. Hata and H. Urabe, *J. Am. Chem. Soc.*, 2008, **130**, 1820-1821.
145. G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840-2859.
146. K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064-5106.
147. M. Raducan, C. Rodriguez-Escrich, X. C. Cambeiro, E. C. Escudero-Adan, M. A. Pericas and A. M. Echavarren, *Chem. Commun.*, 2011, **47**, 4893-4895.
148. H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov and X. Shi, *J. Am. Chem. Soc.*, 2009, **131**, 12100-12102.
149. D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen and X. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 9012-9019.
150. N. Mézailles, L. Ricard and F. Gagosz, *Org. Lett.*, 2005, **7**, 4133-4136.
151. Y. Zhu, C. S. Day, L. Zhang, K. J. Hauser and A. C. Jones, *Chem. Eur. J.*, 2013, **19**, 12264-12271.
152. D. Weber and M. R. Gagné, *Org. Lett.*, 2009, **11**, 4962-4965.
153. D. Weber, M. A. Tarselli and M. R. Gagné, *Angew. Chem., Int. Ed.*, 2009, **48**, 5733-5736.
154. P. W. Davies, N. Martin and N. Spencer, *Beilstein J. Org. Chem.*, 2011, **7**, 839-846.
155. P. W. Davies and N. Martin, *Org. Lett.*, 2009, **11**, 2293-2296.
156. P. W. Davies and N. Martin, *J. Organomet. Chem.*, 2011, **696**, 159-164.
157. Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer and A. Davis, *Org. Lett.*, 2005, **7**, 1047-1050.
158. A. Coste, G. Karthikeyan, F. Couty and G. Evano, *Angew. Chem., Int. Ed.*, 2009, **48**, 4381-4385.
159. A. Coste, F. Couty and G. Evano, *Org. Synth.*, 2010, **87**, 231-244.
160. X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. Shen and M. R. Tracey, *J. Org. Chem.*, 2006, **71**, 4170-4177.
161. N. Ghosh, S. Nayak and A. K. Sahoo, *J. Org. Chem.*, 2010, **76**, 500-511.
162. M. Bendikov, H. M. Duong, E. Bolanos and F. Wudl, *Org. Lett.*, 2005, **7**, 783-786.
163. M. Joost, P. Gualco, S. Mallet-Ladeira, A. Amgoune and D. Bourissou, *Angew. Chem., Int. Ed.*, 2013, **52**, 7160-7163.
164. B. M. Trost, *J. Am. Chem. Soc.*, 1967, **89**, 138-142.
165. G. Ghigo, S. Cagnina, A. Maranzana and G. Tonachini, *J. Org. Chem.*, 2010, **75**, 3608-3617.
166. J. A. Lee, S. Chu, F. S. Willard, K. L. Cox, R. J. Sells Galvin, R. B. Peery, S. E. Oliver, J. Oler, T. D. Meredith, S. A. Heidler, W. H. Gough, S. Husain, A. D. Palkowitz and C. M. Moxham, *J. Biomol. Screen.*, 2011, **16**, 588-602.
167. Y. Chen and B. A. Alman, *J. Cell. Biochem.*, 2009, **106**, 353-362.
168. L. Shen, S. Zhou and J. Glowacki, *J. Cell. Biochem.*, 2009, **106**, 337-343.
169. Z.-L. Chu, R. M. Jones, H. He, C. Carroll, V. Gutierrez, A. Lucman, M. Moloney, H. Gao, H. Mondala, D. Bagnol, D. Unett, Y. Liang, K. Demarest, G. Semple, D. P. Behan and J. Leonard, *Endocrinology*, 2007, **148**, 2601-2609.

170. A. Chase and N. C. P. Cross, *Clin. Cancer Res.*, 2011, **17**, 2613-2618.
171. E. ter Haar, C. M. Koth, N. Abdul-Manan, L. Swenson, J. T. Coll, J. A. Lippke, C. A. Lepre, M. Garcia-Guzman and J. M. Moore, *Structure*, 2010, **18**, 1083-1093.
172. J. M. Witkin and W. J. A. Eiler Ii, *Drug Dev. Res.*, 2006, **67**, 757-769.
173. A. Mullard, *Nat. Rev. Drug Discov.*, 2012, **11**, 817-819.
174. R. A. Vogel, *J. Am. Coll. Cardiol.*, 2012, **59**, 2354-2355.
175. T. S. Stevens, E. M. Creighton, A. B. Gordon and M. MacNicol, *J. Chem. Soc.*, 1928, 3193-3197.
176. S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, 1951, **73**, 4122-4131.
177. Y. Maeda and Y. Sato, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1491-1494.
178. N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.*, 2010, **87**, 1348-1349.
179. G. Meng, Z.-Y. Li and M.-L. Zheng, *Org. Prep. Proced. Int.*, 2008, **40**, 572-574.
180. N. Bourne, A. Williams, K. T. Douglas and T. R. Penkava, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1827-1832.
181. P. García-García, A. Martínez, A. M. Sanjuán, M. A. Fernández-Rodríguez and R. Sanz, *Org. Lett.*, 2011, **13**, 4970-4973.
182. R. S. Glass, Q. Guo and Y. Liu, *Tetrahedron*, 1997, **53**, 12273-12286.
183. L. W. Bieber, M. F. da Silva and P. H. Menezes, *Tetrahedron Lett.*, 2004, **45**, 2735-2737.
184. D. S. Rampon, R. Giovenardi, T. L. Silva, R. S. Rambo, A. A. Merlo and P. H. Schneider, *Eur. J. Org. Chem.*, 2011, **2011**, 7066-7070.
185. C.-Y. Cheng and M. Isobe, *Tetrahedron*, 2011, **67**, 9957-9965.
186. W. Zheng, F. Zheng, Y. Hong and L. Hu, *Heteroatom Chem.*, 2012, **23**, 105-110.
187. S. Albrecht, A. Defoin, E. Salomon, C. Tarnus, A. Wetterholm and J. Z. Haeggström, *Bioorg. Med. Chem.*, 2006, **14**, 7241-7257.
188. P. W. Davies and Chatzopoulou, *Chem. Commun.*, 2013, **49**, 8617-8619.
189. M. Yoshimatsu, K. Ohta and N. Takahashi, *Chem. Eur. J.*, 2012, **18**, 15602-15606.
190. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923-2925.
191. H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512-7515.
192. S. Fustero, D. Jiménez, J. Moscardó, S. Catalán and C. del Pozo, *Org. Lett.*, 2007, **9**, 5283-5286.
193. F. Medina, C. Michon and F. Agbossou-Niedercorn, *Eur. J. Org. Chem.*, 2012, 6218-6227.
194. R. Heathcote, J. A. S. Howell, N. Jennings, D. Cartlidge, L. Cobden, S. Coles and M. Hursthouse, *Dalton Trans.*, 2007, 1309-1315.
195. T. E. Müller, J. C. Green, D. M. P. Mingos, C. M. McPartlin, C. Whittingham, D. J. Williams and T. M. Woodroffe, *J. Organomet. Chem.*, 1998, **551**, 313-330.
196. L. Jafarpour, E. D. Stevens and S. P. Nolan, *J. Organomet. Chem.*, 2000, **606**, 49-54.
197. J. He, H. Xin, H. Yan, X. Song and R. Zhong, *Helv. Chim. Acta*, 2011, **94**, 159-162.
198. E. M. Higgins, J. A. Sherwood, A. G. Lindsay, J. Armstrong, R. S. Massey, R. W. Alder and A. C. O'Donoghue, *Chem. Commun.*, 2011, **47**, 1559-1561.
199. M. Pažický, A. Loos, M. J. o. Ferreira, D. Serra, N. Vinokurov, F. Rominger, C. Jäkel, A. S. K. Hashmi and M. Limbach, *Organometallics*, 2010, **29**, 4448-4458.
200. S.-T. Liu, C.-I. Lee, C.-F. Fu, C.-H. Chen, Y.-H. Liu, C. J. Elsevier, S.-M. Peng and J.-T. Chen, *Organometallics*, 2009, **28**, 6957-6962.
201. A. Vij, Y. Y. Zheng, R. L. Kirchmeier and J. n. M. Shreeve, *Inorg. Chem.*, 1994, **33**, 3281-3288.
202. M. Stricker, B. Oelkers, C. P. Rosenau and J. Sundermeyer, *Chem. Eur. J.*, 2013, **19**, 1042-1057.
203. N. C. Baenziger, W. E. Bennett, D. M. Soboroff, P. S. O'Donnell and J. R. Doyle, *Polyhedron*, 1998, **17**, 2379-2410.
204. G. Schmid, R. Pfeil, R. Boese, F. Bandermann, S. Meyer, G. H. M. Calis and J. W. A. van der Velden, *Chem. Ber.*, 1981, **114**, 3634-3642.
205. W. Hess and J. W. Burton, *Chem. Eur. J.*, 2010, **16**, 12303-12306.
206. F. K. Cheung, A. M. Hayes, D. J. Morris and M. Wills, *Org. Biomol. Chem.*, 2007, **5**, 1093-1103.
207. K. Khumtaveeporn and H. Alper, *J. Am. Chem. Soc.*, 1994, **116**, 5662-5666.

208. V. P. Arya and et al., *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1977, **15**, 720 - 726.
209. H. Ishibashi, M. Uegaki, M. Sakai and Y. Takeda, *Tetrahedron*, 2001, **57**, 2115-2120.
210. J. Barluenga, C. Jimenez, C. Najera and M. Yus, *J. Chem. Soc., Perkin Trans. 1*, 1984, 721-725.
211. Y. Li, K. Dong, Z. Wang and K. Ding, *Angew. Chem., Int. Ed.*, 2013, **52**, 6748-6752.
212. H. J. Bestmann and H. Frey, *Liebigs Ann. Chem.*, 1980, **1980**, 2061-2071.
213. Y. Araki, K. Kobayashi, M. Yonemoto and Y. Kondo, *Org. Biomol. Chem.*, 2011, **9**, 78-80.
214. D. H. Huh, J. S. Jeong, H. B. Lee, H. Ryu and Y. G. Kim, *Tetrahedron*, 2002, **58**, 9925-9932.
215. A. V. Shastin, V. N. Korotchenko, V. G. Nenajdenko and E. S. Balenkova, *Synthesis*, 2001, 2081-2084.
216. Y. R. Bhorge, C.-T. Chang, S.-H. Chang and T.-H. Yan, *Eur. J. Org. Chem.*, 2012, **2012**, 4805-4810.
217. A. Carpita, R. Rossi and C. A. Veracini, *Tetrahedron*, 1985, **41**, 1919-1929.
218. Q. Wu, J. Hu, X. Ren and J. Zhou, *Chem. Eur. J.*, 2011, **17**, 11553-11558.
219. D. Craig, C. J. T. Hyland and S. E. Ward, *Chem. Commun.*, 2005, 3439-3441.
220. J. C. Anderson, R. Cubbon, M. Harding and D. S. James, *Tetrahedron: Asymmetry*, 1998, **9**, 3461-3490.
221. C. A. M. Cariou, B. M. Kariuki and J. S. Snaith, *Org. Biomol. Chem.*, 2008, **6**, 3337-3348.
222. J. Epsztajn, E. Lunt and A. R. Katritzky, *Tetrahedron*, 1970, **26**, 1665-1673.