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GOLD CATALYSED INTERMOLECULAR ATOM TRANSFER REACTIONS ON HETEROATOM-SUBSTITUTED ALKYNES

by

Alex Cremonesi

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Abstract

In this thesis the development of several novel gold-catalysed transformations are reported. Two intermolecular atom transfer processes have been designed and developed to access gold carbenoid reactivity. The latter reactive species allowed the synthesis of various α,β-unsaturated carboxylic acid derivatives and trisubstituted oxazoles.

Numerous nitrogen- and oxygen substituted alkynes have been prepared and employed in oxygen transfer processes promoted by gold complexes. Using pyridine *N*-oxide, both ynamides and ynol ethers underwent regioselective intermolecular oxidation reactions under mild gold catalysis conditions. During the transformation, an α-oxo gold carbenoid intermediate is accessed which develops through a rapid 1,2-insertion reaction to yield α,β-unsaturated imides and vinylogous carbimates. The strategy has proved to be a valid alternative to the use of hazardous α-oxo diazo compound when carbene reactivity is desired.

Appling a similar strategy, *N*-imido pyridonium ylides have been used as an *O*,*N*-dipole onto gold activated ynamides and ynol ethers. The overall [3+2] cyclisation occurred through a nitrene transfer process followed by a cycloisomerisation step. Under this approach, ynamides and ynol ethers have been converted into highly functionalised trisubstituted oxazoles. The mild gold catalysis conditions allowed the use of a wide range of functionality. Moreover, the α-imido gold carbenoid involved as a reaction intermediate displayed the possibility to utilise such protocol to access α-imido carbene reactivity.

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List of abbreviations

Å	Amstrong
Au(I)	gold in oxidation state +1
Au(III)	gold in oxidation state +3
Ac	acetyl
Ar	aromatic
Bn	benzyl
C	Celsius
δ	chemical shift
d	doublet
DIAD	diisopropyl azodicarboxylate
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppm	1,1-Bis(diphenylphosphino)methane
dr	diastereomeric ratio
DS	delivery system
E	electrophile
EI	electronic impact
eq	equivalent(s)
Eq.	equation(s)
ESI	electronic spray ionisation
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
g	gram(s)
h	hour(s)

HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	hertz(s)
IR	infrared
^{i}Pr	isopropyl
IPr	1,3-bis(2,6- diisopropylphenyl)imidazol-2-ylidene
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
L	litre(s)
LG	leaving group
L_n	ligand(s)
LHMDS	lithium bis(trimethylsilyl)amide
M	metal
m	multiplet
m	meta
m-CPBA	*m*-chloroperbenzoic acid
Me	methyl
Mes	2,4,6-trimethylphenyl
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methansulfonyl
^{n}Bu	normal-butyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Noe	nuclear overhauser effect
^{n}Pr	normal-propyl
Ns	nitrobenzenesulfonyl

Nu	nucleophile
n/z	mass/charge
o	ortho
p	para
Ph	phenyl
Piv	pivaloyl
ppm	part per million
Py	pyridine
q	quartet
RT	room temperature
s	singlet
T	temperature
t	triplet
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogen sulfate
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonate
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
$\text{Tpm}^{*,\text{Br}}$	tris(3,5-dimethyl-4-bromopyrazolyl)methane
TMS	trimethylsilyl
TOF	time of flight
THP	tetrahydropyran
Ts	4-toluenesulfonyl

ν	frequency
z	atomic number

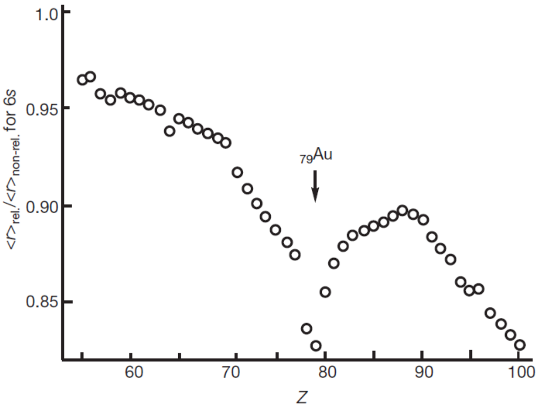
Chapter 1: Introduction

1.1 Gold: a central metal in human history

Gold has played a major role in the history of mankind, society and its development. From the beginning of human civilisation, gold was used by artisans to manufacture coinage, jewellery and other arts long before written history and for millennia it had represented a symbol of purity, value and royalty. From a symbol of health and prestige, it later became the vehicle for monetary exchange, both directly and indirectly. It still maintains a vital role in modern times, in that a nation's reserve of gold protects against economic disruptions.[1] In addition to its symbolic and monetary values, gold has more recently found practical applications in many different fields, including electronics and dentistry.[2] This utility is due to it possessing a numbers of favourable physical characteristics, such as high malleability, ductility, resistance to corrosion and electrical conductivity. Gold can also undergo a diverse range of reactions. Gold compounds have performed a key role in the medical field where they show excellent biocompatibility and biological activity. For example, "gold salts" are gold compounds (mainly gold complexes) used in chrysotherapy and aurotherapy, primarily to slow disease progression in patients with rheumatoid arthritis and to reduce inflammation.[3] More recently, gold nanoparticles have been widely studied as drug delivery systems to target organs in diseases like cancer.[4] The potential use of gold as a transition metal catalyst in organic reactions had on the whole been ignored for a long time while the chemistry community focused on the development of other transition metals (*e.g.* palladium, platinum, rhodium). This lack of interest was due to the assumption of a relative chemical inertness of gold. In the last few decades the dramatic increase in the use of homogeneous catalysis to achieve convenient chemical modifications on organic molecules finally gave gold the attention it deserved, where its specific type of chemoselectivity often proves an advantage and is used to gain higher selectivity and control over chemical transformations. Major advances in the field have led to gold being routinely used in heterogeneous and homogeneous catalysis.[5] In the next sections, only selected examples of the latter will be covered, providing some theoretical and experimental studies which will be helpful in rationalising the reaction manifolds available in this catalysis.

1.2 General reactivity of gold in homogeneous catalysis

Gold (Au) in homogeneous catalysis is found in the ionic forms of the Au(I) and the Au(III) oxidation states. The starting point of this discussion must be the electronic structure of Au which determines its behaviour. Relativistic effects strongly influence the electron distribution of gold and these effects can be used to rationalise the observed reactivity for gold complexes.[6] Relativistic effects are determined by two opposite tendencies: *s*-orbitals tend to contract with increasing atom number, while *d* and *f* orbitals tend to expand because of the shielding effect caused by the contracted core. The relativistic contraction of 6*s* orbitals results in a strengthening of the Au-L bond in comparison to other metals (*e.g.* Pt and Hg).[7] These effects are highest for gold comparing to its atomic neighbours and they are more significant than for any other metal (Figure 1).



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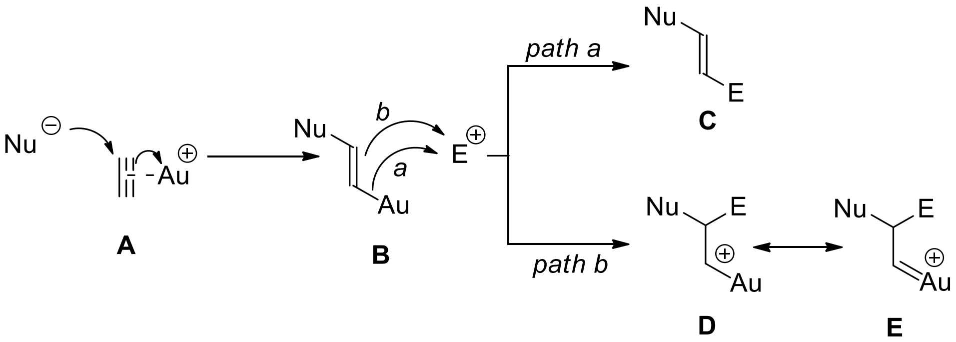
http://www.nature.com/nature/index.html

Figure 1. Calculated relativistic contraction of the 6*s* orbital. The relativistic and non-relativistic 6*s* orbital radii were determine computationally.[8]

The relativistic effects held accountable for the expansion of the *d* orbitals explain the chemically “soft” character of Au, with its cations being involved in orbital rather than charge interactions.[9] For this reason, gold catalysts are preferentially active as π-Lewis acids to “soft” nucleophilic systems like alkynes, alkenes and allenes. Theoretical studies also indicate that due to the diffuse Au 5*d* electrons, electron-electron repulsion is decreased, resulting in a less nucleophilic character of Au species. A direct consequence of this latter point accounts for gold's tendency not to readily undergo oxidative addition,[10] although such reactivity can be accessible under specific conditions.[11]

The propensity of gold to activate π-systems, especially alkynes, towards nucleophilic addition has been extensively studied and reviewed.[12] Kinetic discrimination allows nucleophiles to select between different electrophilic species in favour of the Au-alkyne **A** (Scheme 1), such that gold complexes catalyse transformations of alkynes preferentially over other π-systems. This latter characteristic is commonly referred as gold "alkynophilicity".

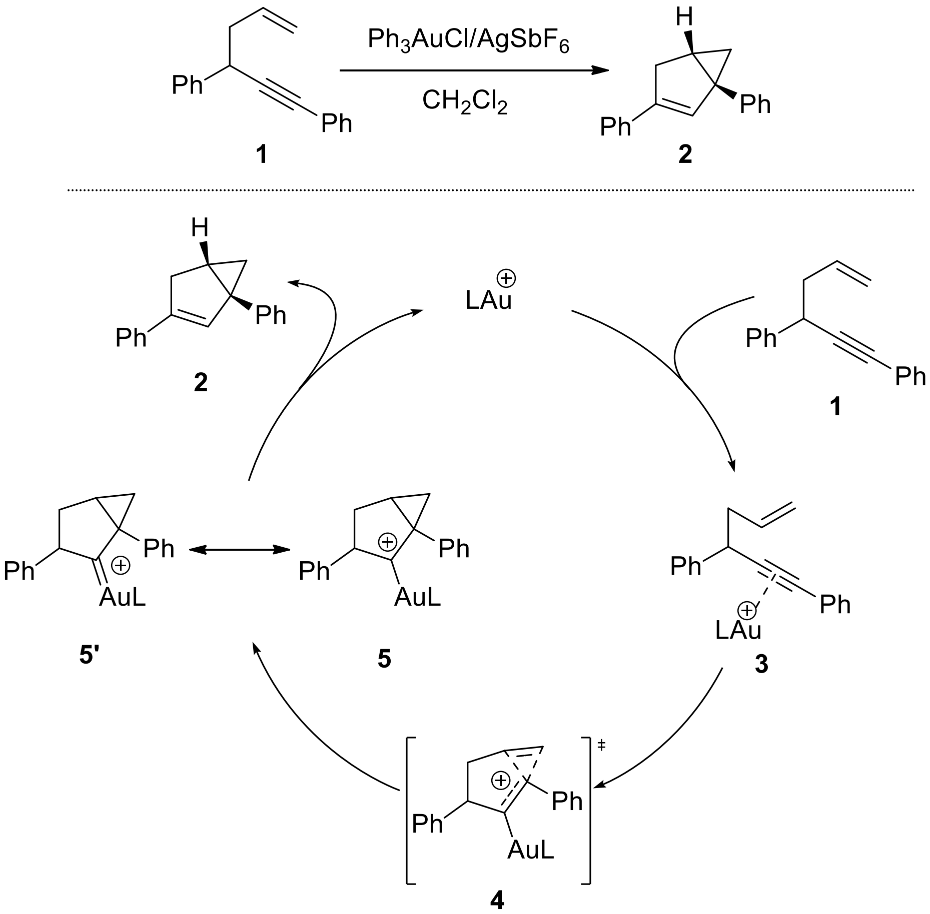
Back bonding is another crucial aspect that needs to be considered when analysing gold catalysis intermediates, especially when the latter is compared to its transition metal neighbours. In the view of the Dewar-Chatt-Duncanson model,[13] *σ*-bonding is formed by the donation of electron-density from the π-system to an empty orbital of the metal catalyst. Electron density is then backdonated from the catalyst *d*-orbitals to the π*-antibonding orbitals of the ligand to create a π-interaction (this aspect will be discussed in more detail in the next section). In the case of Au(I), backbonding cannot meaningfully occur because the π*-antibonding orbitals are too high in energy. The reluctance of the metal centre to back-donate electrons results in a deficiency of electron density in the π-system and this promotes the addition of the nucleophile. The vinyl-Au intermediate **B** formed is subject to proto-demetallalation or trapping by other appropriate electrophiles (path a, Scheme 1). However, based on theoretical studies,[14] another destiny for the vinyl-gold species can be hypothesised. According to the computational data obtained, it was envisaged that backbonding from the relativistically expanded 5*d* orbitals into the non-bonding *p* orbitals occurs. These *p* orbitals are more suitable for overlap because they are lower in energy compared to the π*-antibonding orbitals mentioned above. It can therefore be envisaged that backbonding into the non-bonding *p* orbitals of the developing conjugated carbocation in **B** can facilitate trapping of electrophiles in another fashion (path b, Scheme 1).



Scheme 1. Different electrophile addition pathways onto vinyl-gold complexes.

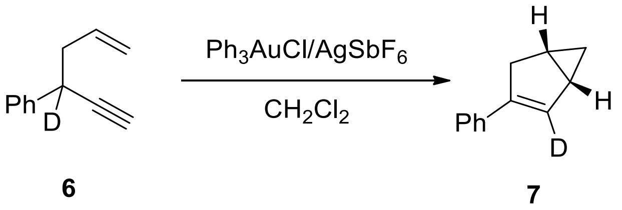
Experimentally, the latter manifold has been proved independently by the Echavarren group,[15] the Fürstner group[16] and the Toste group[17] in the cycloisomerisation of 1,5-enynes promoted by gold(I) catalysts which in some cases proceed through cationic intermediates.

In the cycloisomerisation of 1,5-enynes of type **1**, the olefin acts concertedly as a nucleophile and electrophile onto the gold-alkyne complex **3** to form a cyclopropylcarbinyl cation intermediate **5** (Scheme 2)**.** It was hypothesised that a stabilising delocalisation of the positive charge by backbonding electrons from the gold (resonance form **5'**) could potentially play a role in lowering the energy barrier for the cycloisomerisation to occur and also could confer carbenic character to the gold intermediates.



Scheme 2. Gold catalysed cycloisomerisation of 1,5-enynes.

Although the 1,2-hydride shift on the gold intermediate **5** and **5'** (vide supra) was proved by deuterium labelling experiments (Scheme 3), the extent of carbocation character as opposed to carbene character could not be distinguished. It was not possible to exclude a concerted versus stepwise mode for the cyclisation and therefore some other intermediates might also be suggested.



Scheme 3. Deuterium labelling experiments for the cycloisomerisation of 1,5-enynes.

This ambiguous gold stabilised carbocation *vs.* gold stabilised carbene nature of such organogold species has attracted great interest in the organic chemistry community.

1.3 Gold carbenoid: an ongoing debate

Metal stabilised carbenes, or metal carbenoids, are potent reactive units for carbon-carbon and carbon-heteroatom bond formation and are involved in many reactions of high synthetic interest (Figure 2, M equal *e.g.* Rh, Cu, Pd). Standard methods for the generation of this moiety depend upon the use of sacrificial functionalities such as diazo units **8**. These decompose in the presence of certain transition metal catalysts affording the desired metal stabilised carbene species.[18]

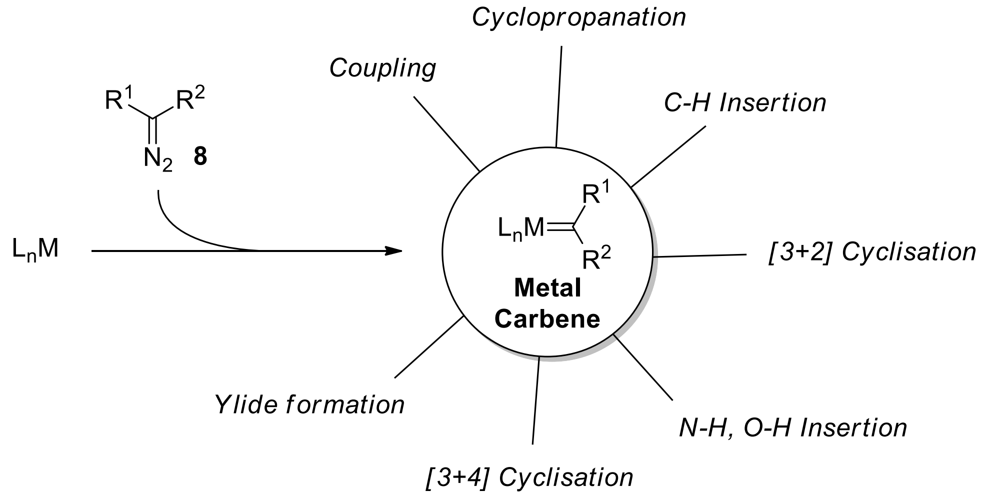


Figure 2. Formation of metal stabilised carbenes from diazo compounds and some generic reactions in which they are involved.

The distinction between gold carbenoids and gold-stabilised carbocations of gold intermediates is more than just a semantic discussion; as it will be shown in this section, it is needed for predicting, modulating and explaining their reactivity. Until recently, the majority of theoretical investigations and experimental observations on organogold species mostly support the cationic resonance forms,[19] but those arguments did not bring the discussion to a conclusion.

The cycloisomerisation mechanism of 1,*n*-enynes, which was briefly mentioned in the previous section, is the perfect example to explain such controversy. After the initial attack of alkene **10** onto the activated gold-alkyne complex **9**, different mesomeric/tautomeric intermediates of non classical carbocations **F-I** can be envisioned (Figure 3). Among the different mesomeric cationic forms, gold stabilised carbocation **G** can be seen in mesomeric relationship with carbonic resonance from **I**.

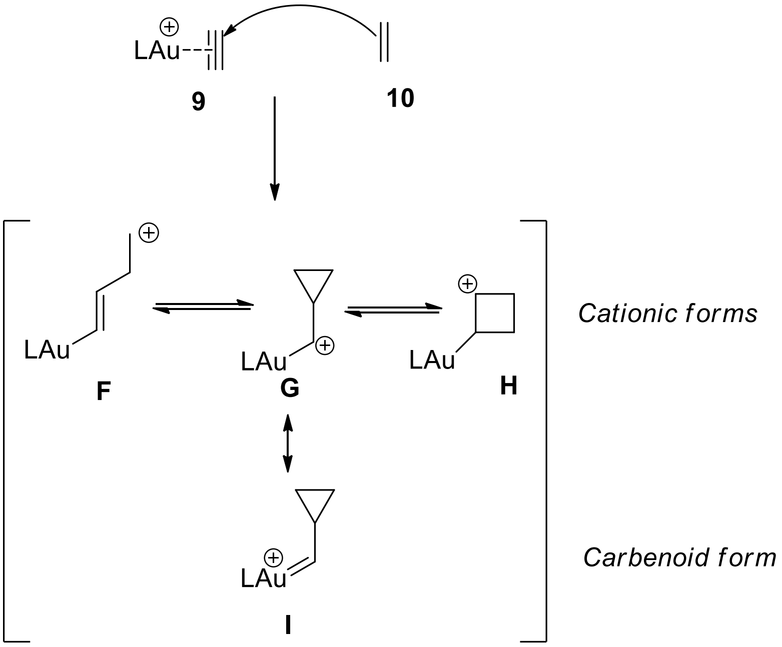
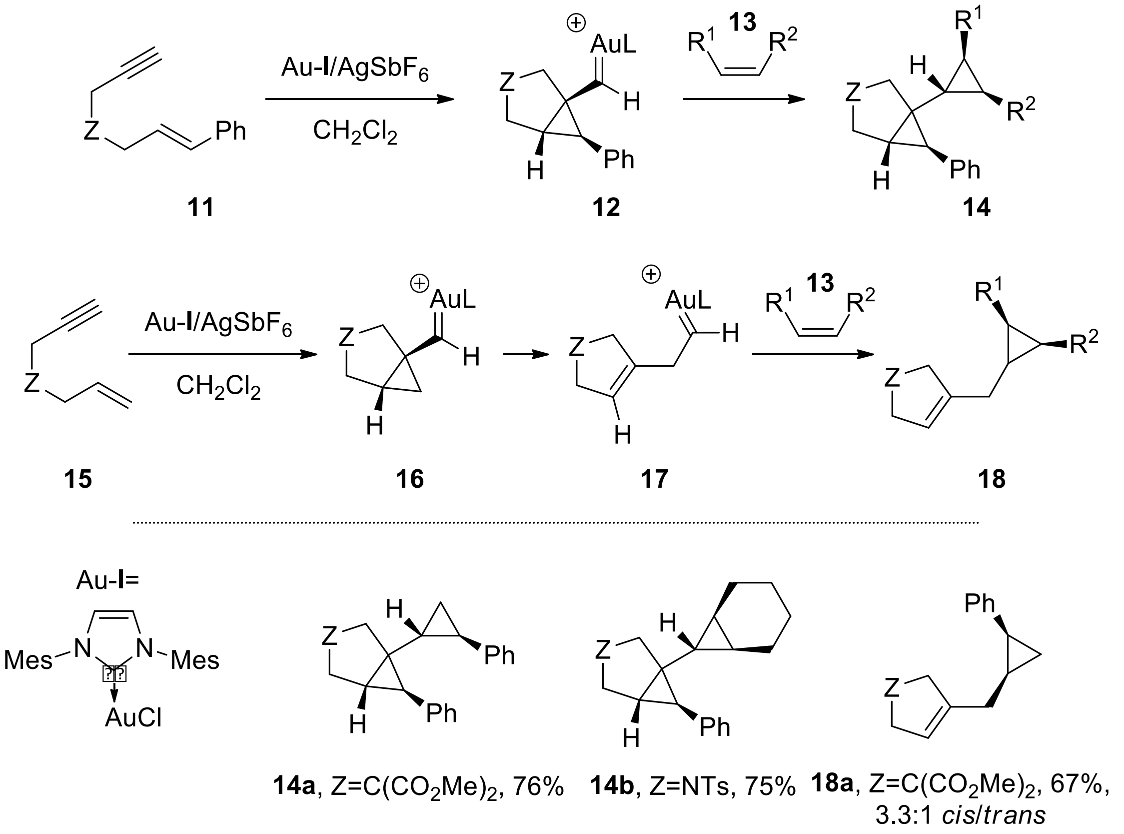


Figure 3. Mesomeric and tautomeric organogold intermediates in reaction between gold-activated alkynes and alkenes.

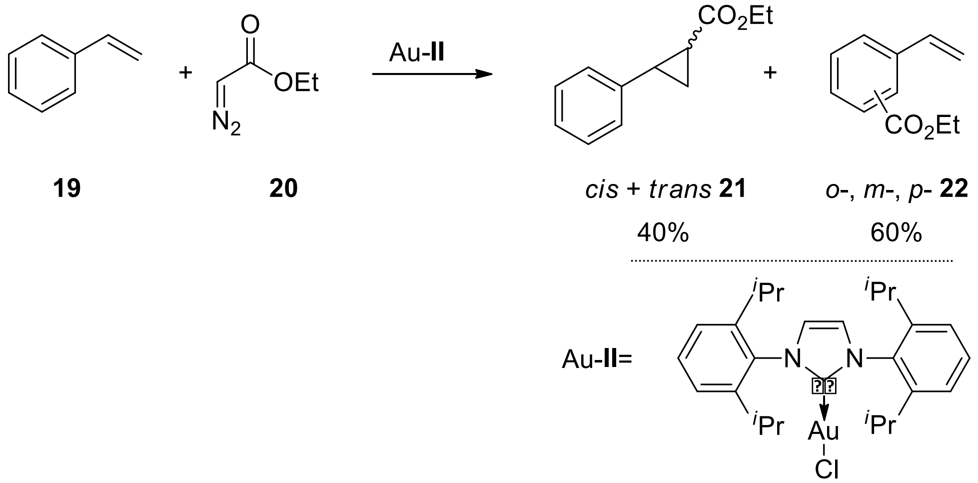
In the gold catalysed intermolecular cyclopropanation of 1,6-enynes and alkenes, Echavarren *et al.* were able to intermoleculary trap different gold carbenoids with alkenes (*e.g.* norbornene and cyclohexene) providing for the first time what they thought to be a compelling evidence for the existence of the carbene nature of the intermediate **12**, **16** and **17** (Scheme 4).[20] The stereospecific formation of cyclopropane frameworks in the product **14** and **18** should endorse the carbene-character of the organogold species based on similar outcomes from the behaviour of traditional carbenes.[21]



Scheme 4. Intermolecular cyclopropanation of enynes and alkenes.

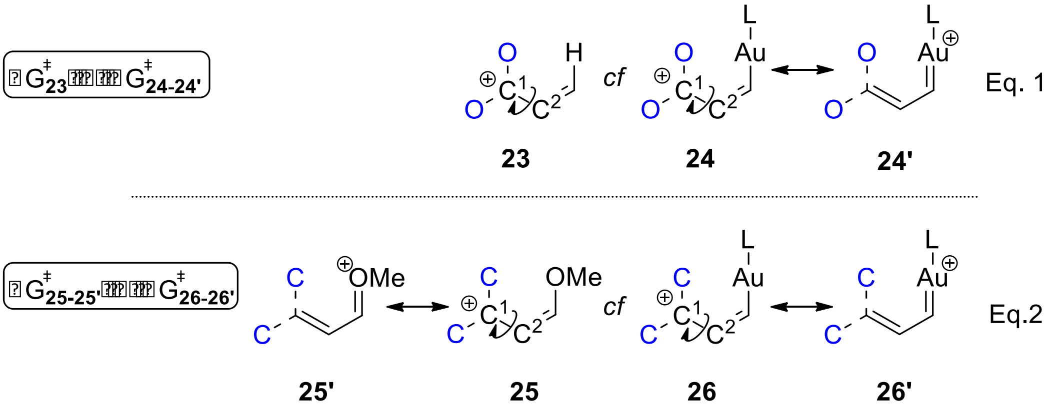
Nolan and co-workers also contributed in supporting carbene-like intermediates and achieved the first gold catalysed decomposition of diazo compounds.[22] As shown at the beginning of this section, this is the traditional strategy to access transition metal stabilised carbene (*vide supra*). *N*-heterocyclic gold catalyst complex [(IPr)AuCl] (Au-**II**) promoted the transfer of a carbene unit from ethyl diazoacetate **20** to styrene **19** (Scheme 5). A mixture of different products was obtained: *cis* and *trans* cyclopropanes **21** and a mixture of monosubstituted styrenes **22**.

This outcome strongly suggests a carbene species transfer being involved in the transformation since cyclopropanes are easily accessible through the reaction between carbenes and alkenes. Moreover, the formation of a mixture of *o*-, *m*- and *p*- aromatic addition products (**22**) suggests a non-regioselective insertion pathway of the gold-carbenoid species into the aromatic *C-H* bonds rather than a more regiospecific electrophilic aromatic substitution reaction of a carbocation species.



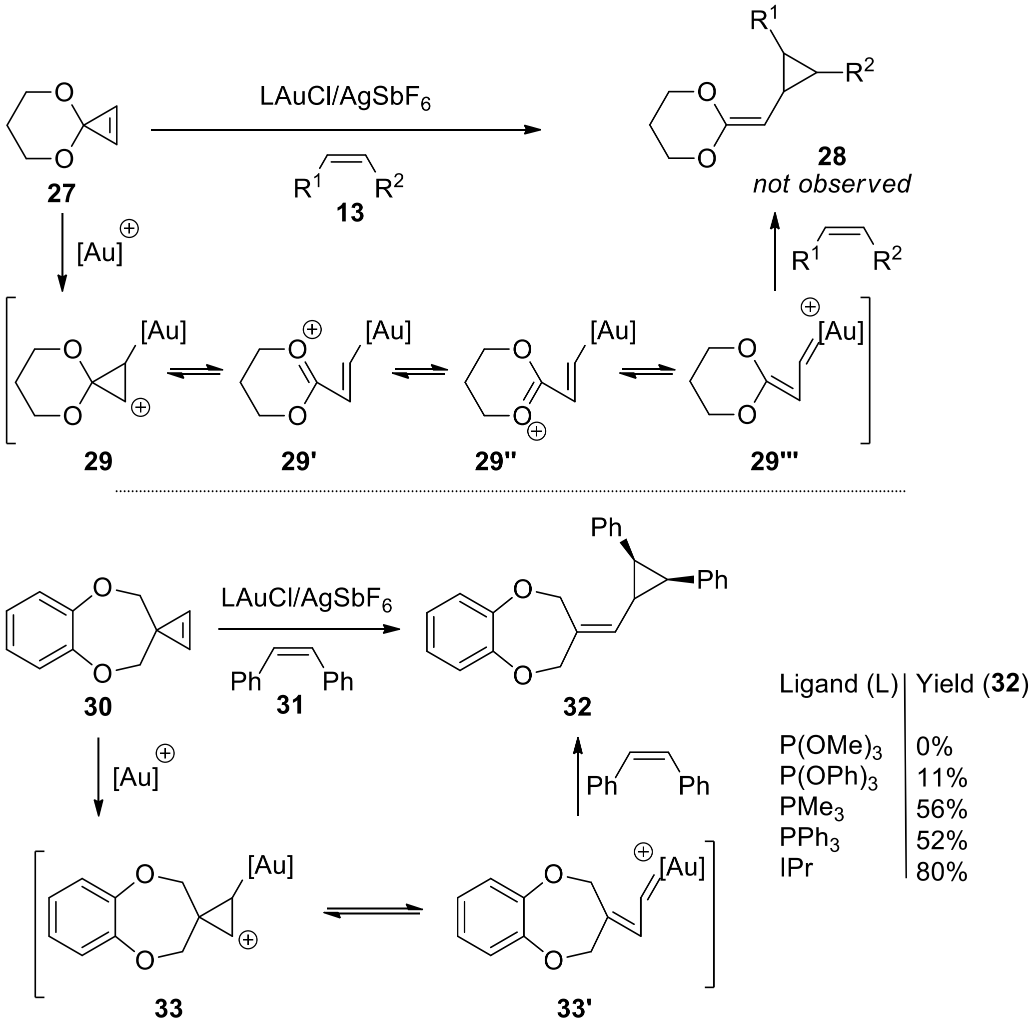
Scheme 5. Carbene unit transfer from diazo compounds onto alkenes promoted by gold.

Decisive work was published by Toste *et al.*, who performed theoretical studies on various gold catalysis key intermediates in order to fulfil the lack of understanding of the Au-C bond nature.[23] The bond rotation energy barriers were considered as a practical indicator of the π character of the bond. Transition metal-free allyl cations **23** and **25** were compared with gold allyl cations **24** and **26** in order to estimate the carbenoid resonance form contribution for these latter two entities (Scheme 6). For example, if we consider the resonance forms **24** and **24'**, a high energy barrier for C^1-C^2 bond rotation implies more C^1-C^2 double bond character, which would in turn indicate a major contribution of resonance form **24'**. It was calculated that when carbocation stabilising atoms were present (*e.g.* oxygen atoms), the C^1-C^2 rotation energy values for organogold species of type **24**-**24'** were close to the ones calculated for **23** rather than **25**-**25'**, indicating a strong predominance of gold-carbocation species **24** over **24'** (Eq. 1, Scheme 6). Therefore, this means that the gold-carbon bond possesses more single bond character. In the absence of carbocation stabilising atoms, the rotation energy values for gold intermediates of type **26**-**26'** were similar to the ones calculated for **25**-**25'** rather than **23**, showing that in this instance the AuL would have an allylic cation stabilisation activity comparable to the methoxy group (Eq. 2, Scheme 6). It can be concluded the resonance form **24** is a better descriptor of cation **24**-**24'**, while it can also be concluded that **26'** represents in a better way the situation of cation **26**-**26'**.



Scheme 6. Comparison of different gold allyl cations.

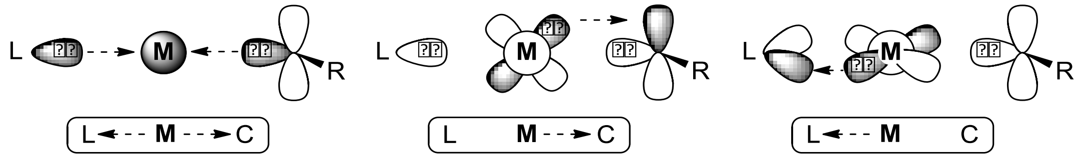
Experimentally this was confirmed by cyclopropanation reactions promoted by gold on two different cyclopropenes **27** and **30** (Scheme 7)**.** In the case of dioxane **27**, no reaction was observed, suggesting a predominance of an oxygen-stabilised cationic gold intermediate of type **29'** and **29''** (strong vinylic stabilisation) *versus* gold-carbenoid species **29'''**. The latter is the active species that would have led to the formation of the cyclopropylic product **28**. Conversely, dioxepane **30** reacted with *cis*-stilbene **31** in a "carbene fashion" (weak vinylic stabilisation) due to the effective formation of gold intermediate **33'**. The latter reaction also showed a great dependence on the nature of the ligand complexed with the gold atom (see Table in Scheme 7). A carbocation-like reactivity is expected with π-acid ligands which decrease the gold to carbon σ-donation as in the case of $P(OMe)_3$. Conversely, *N*-heterocyclic ligand IPr decreases the σ-donation bond favouring a more carbene-like reactivity in virtue of its weak π-acidity and strong σ-donating capability.



Ligand (L)	Yield (**32**)
$P(OMe)_3$	0%
$P(OPh)_3$	11%
PMe_3	56%
PPh_3	52%
IPr	80%

Scheme 7. Cyclopropanation reactions promoted by gold catalysts.

This latter observation was explained by considering the filled gold *d*-orbitals from which electrons can be donated to π-acceptors. The π-backbonding to the spectator ligand and to the substrate is not mutually exclusive but rather a distribution of gold electro-density between these two systems (Figure 4). Therefore, the competing electrophilicity of the ligand is not innocent but participates in determinating the degree of backbonding from gold to the substrate. In fact, weak π-acid *N*-heterocyclic ligands (*e.g.* IPr in Scheme 7 and Scheme 5, IMes in Scheme 4) performed best in comparison to the others tested in the cyclopropanation reaction (Scheme 7). These electron donating ligands increased the π-donation from the gold to the alkylidene and ultimately promoted a more carbene-like reactivity.



3 centre-4 electron □-bond *Metal-alkylidene □-bond* *Metal-ligand □-bond*

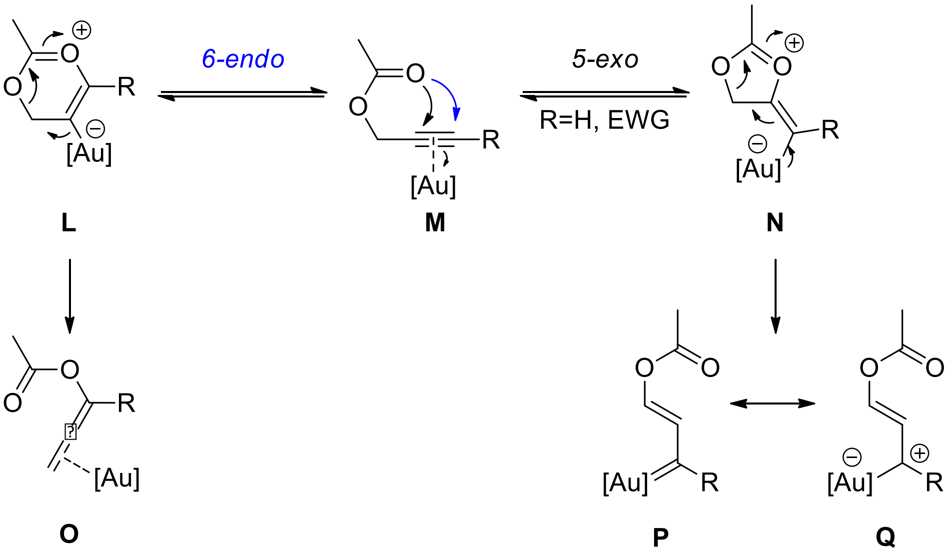
Figure 4. Schematic representation of the ligand-gold-substrate complex electronic distribution.

In conclusion, gold stabilised carbocation/carbene dualistic reactivity is influenced by a series of different factors that always need to be taken in consideration: the ligand electronic properties, the substrate substituents and the electronic effects involved with gold.

1.3.1 Atom-transfer gold catalysed processes

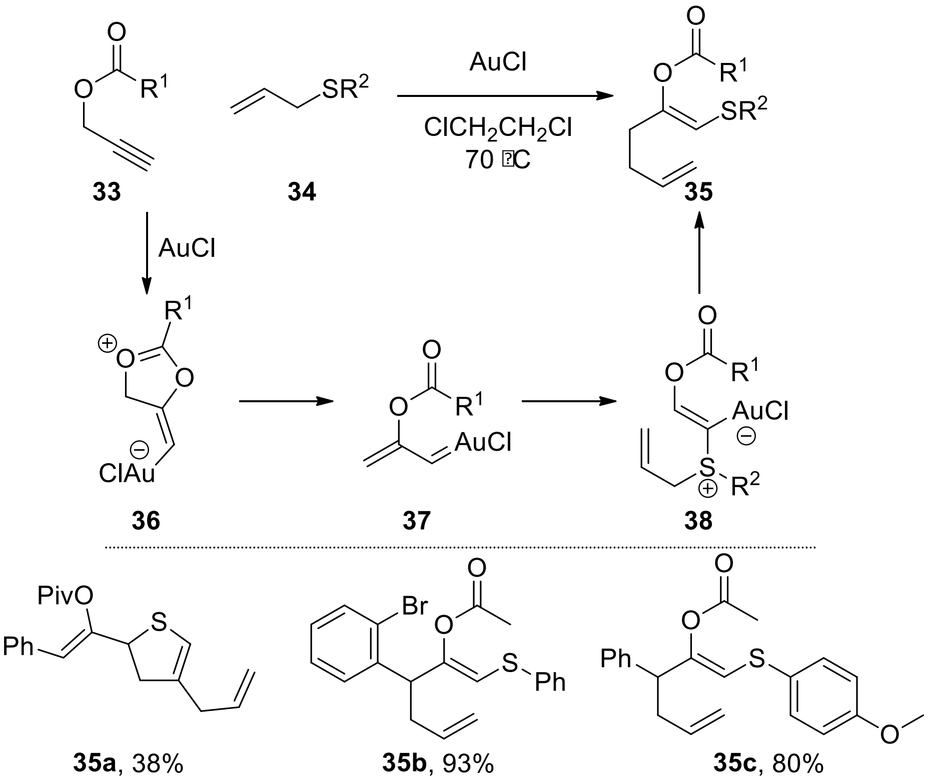
An atom transfer process consists of the relocation of an atom, or a group of atoms, within a molecule; the formal “delivery system” is not bonded anymore to the delivered atom in the final product. Some of these processes have shown to allow the access of gold-carbenoid intermediate. As seen in the previous section, metal carbenoids are extremely useful reactive species which are capable of promoting unique transformations. Moreover, traditional methods require the use of hazardous diazo compounds and expensive catalysts. Therefore, the development of new ways to engage their reactivity has gained great attention. Gold complexes in atom transfer processes have proved in some cases to be a valid alternative. For these reasons, this section will focus on atom transfer processes promoted by gold that form gold carbenoid species and a selection of published examples will be given.

As shown in the previous section, cyclisation of 1,*n*-enynes have, depending on the substrate and the gold catalysis conditions, allowed access to gold-carbenoids (see before). Later, other methods were developed. Among them the use of propargylic carboxylates allowed the formation of gold intermediates of type **L** and **N** (Scheme 8). The cyclisation mode was shown to be dependent on the nature of the substrate; terminal or electro-withdrawing substituted alkynes are capable of forming carbenoid species of type **N** through a 5-*exo* cyclisation to access gold intermediate of type **P** and **Q**.



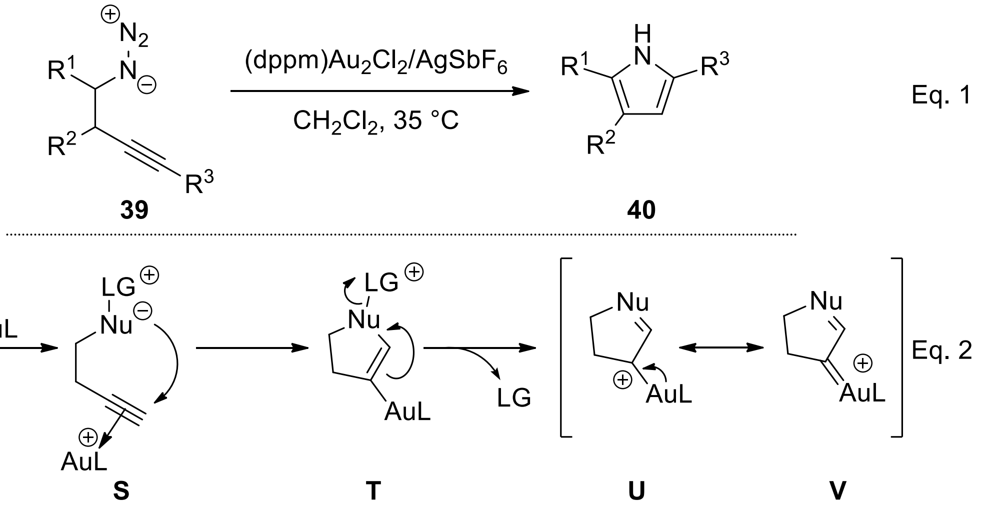
Scheme 8. Intermediates derived from the gold activation of propargylic carboxylates.

From our research group[24] and others,[25] this reactivity has been studied with a series of propargylic acetyl, pivaloyl and benzoyl esters of type **33**, which were reacted with different allylic sulfides **34** under gold catalysis conditions (Scheme 9). As predicted, the nucleophilic oxygen of the carboxylic group attacked the gold activated alkyne unit. It was suggested that the 5-*exo* cyclisation is followed by backbonding of electrons from the catalyst to generate an α-oxo gold carbenoid **37**. These reactive intermediates have recently gained enormous interest in the organic chemistry community due to their comparable reactivity with α-oxo carbenes, which are usually accessed through expensive and limited preparation procedures. Intermolecular reaction between the generated gold carbenoid and the thioester **34** led to the formation of sulfonium ylide **38** which elaborated through a sequential rearrangement of the allyl fragment followed by demetallation to afford substrate **35**.



Scheme 9. Gold catalysed reaction between propargylic esters and allylic sulfides.

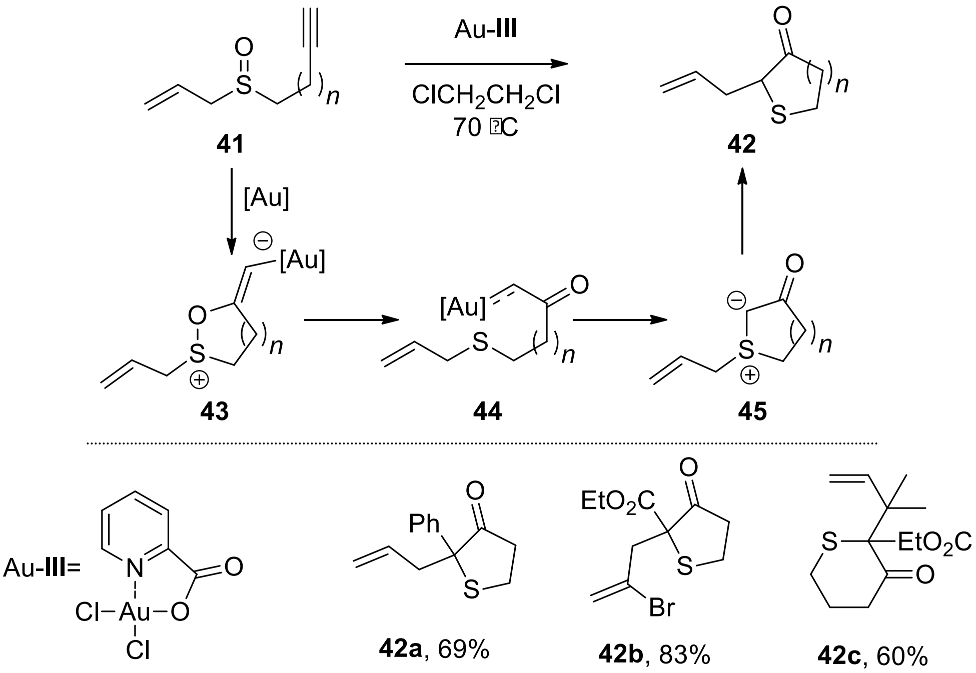
An alternative way to access gold carbenoids was published in 2005 by Toste and co-workers[26] who achieved the first gold-catalysed intramolecular acetylenic Schmidt reaction (Scheme 10, Eq. 1). Different homopropargyl azides **39** were successfully transformed into multiply-substituted pyrroles **40** under mild gold catalysis conditions. This new transformation promoted by gold indicated the possibility of a new reactive strategy to access gold carbenoids of type **V**. In Toste's example, the leaving group (LG) is pendant to the nucleophile and when the "electron-push" occurs, this assists the electrophile release. Overall, under a general strategy overview, the LG-system can be seen as a nucleophile delivering group. The whole mechanism is reminiscent of an intramolecular nitrene transfer process catalysed by a gold catalyst (Scheme 10, Eq. 2).



Scheme 10. Gold-catalysed intramolecular acetylenic Schmidt reaction.

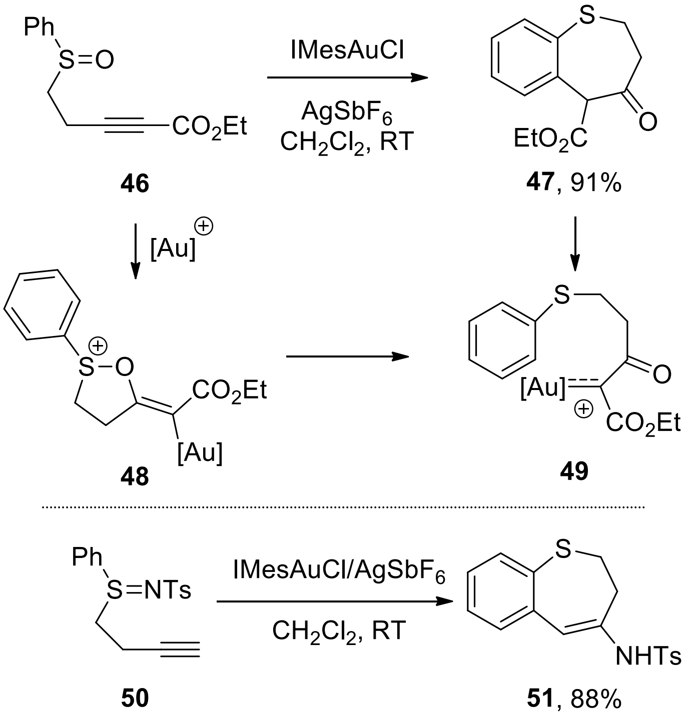
After Toste's example, many transformations in a similar fashion have been developed towards heteroatom transfer to alkyne units π-activated by gold complexes.

For instance, the reactivity of sulfoxides and alkynes to be engaged in internal redox promoted by gold has also been extensively studied in our group.[27] In light of the *S*=*O* bond polarisation which confers nucleophilic character to the oxygen, a series of alkynyl tethered sulfoxides of type **41** underwent intramolecular 5-*exo* cyclisation when treated with gold catalyst of type Au-**III**.[28] This step simultaneously provided both a gold carbenoid and an allyl sulfide functionality which then reacted to form cyclic sulfur ylide **45** (Scheme 11). This zwitterionic species would progress through a 2,3-sigmatropic rearrangement to afford sulfur heterocyclic product **42** as the only product.



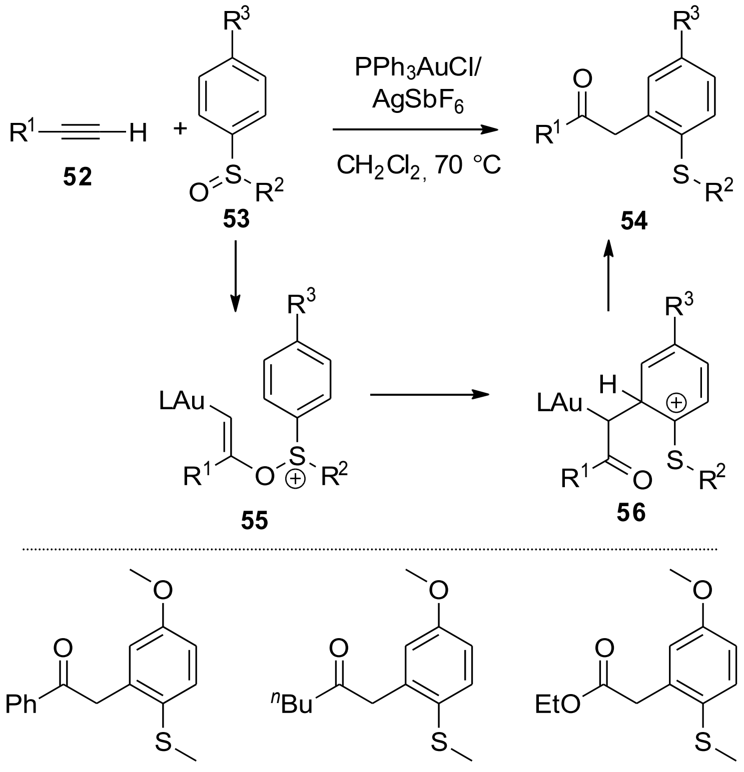
Scheme 11. Internal redox reaction of alkynyl-sulfoxide catalysed by gold complexes.

Toste[29] and Zhang[30] explored independently a gold-catalysed intramolecular oxygen transfer cyclisation with tethered alkynyl sulfoxides of type **46** (Scheme 12). In this case, the gold intermediate **49** evolved through a formal Friedel-Crafts type alkylation forming the 1-benzothiepin-4-one **47** with the release of the gold catalyst. Different benzothiepinones and benzothiopines were obtained depending on the alkyne substituents present, which control the 5-*exo* versus 6-*endo* gold cyclisation mode. Remarkably, very recently Toste proved that the same strategy could also be applied to the rearrangement of sulfimine of type **50**. The transfer of a tosylamino unit was consistent with the previous results and provided *N*-tosyl enamine **51** in 88% yield under the same reaction conditions optimised for sulfoxides.



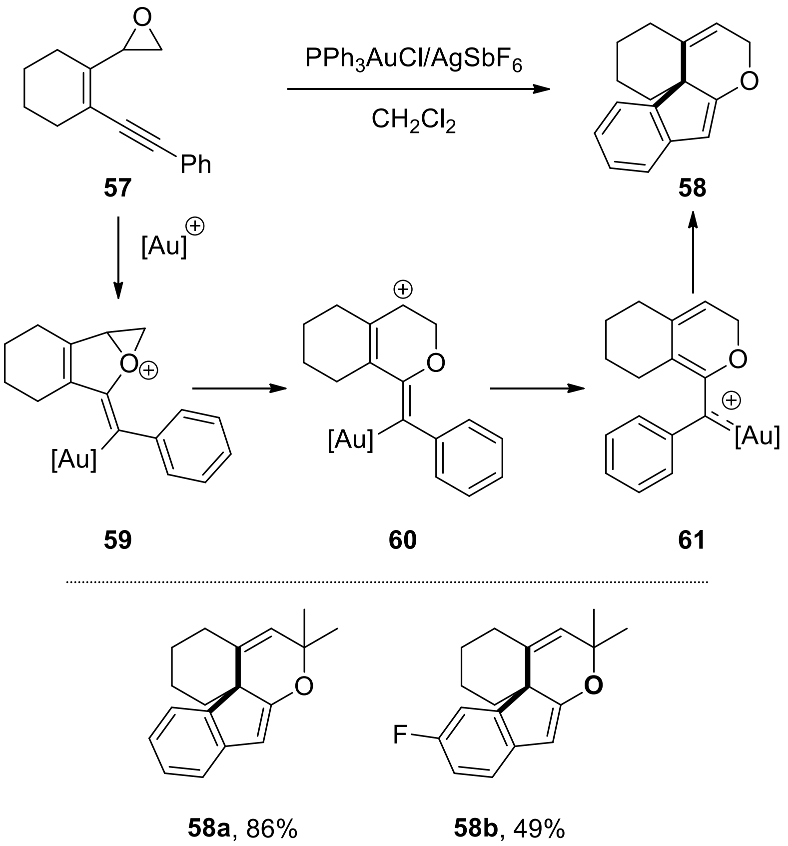
Scheme 12. Synthesis of benzothiepines 47.

Asensio and co-workers explored the intermolecular version of the gold promoted redox reaction between sulfoxides and acetylenes.[31] Different arylsulfides **52** regioselectively functionalised *ortho* to the sulfur position were obtained in good yields (Scheme 8). Surprisingly, in all cases a different regioisomer from the expected Friedel-Crafts regioselectivity was observed as the only product (Scheme 13). DFT studies were carried out to explain the unusual outcome and Asensio's group proposed an alkenyl gold intermediate **56** as the key intermediate. It was suggested that the vinyl-gold species **55** would evolve to intermediate **56** via [3,3']-sigmatropic rearrangement rather than evolving to the carbene that undergoes a Friedel-Crafts electrophilic aromatic substitution.



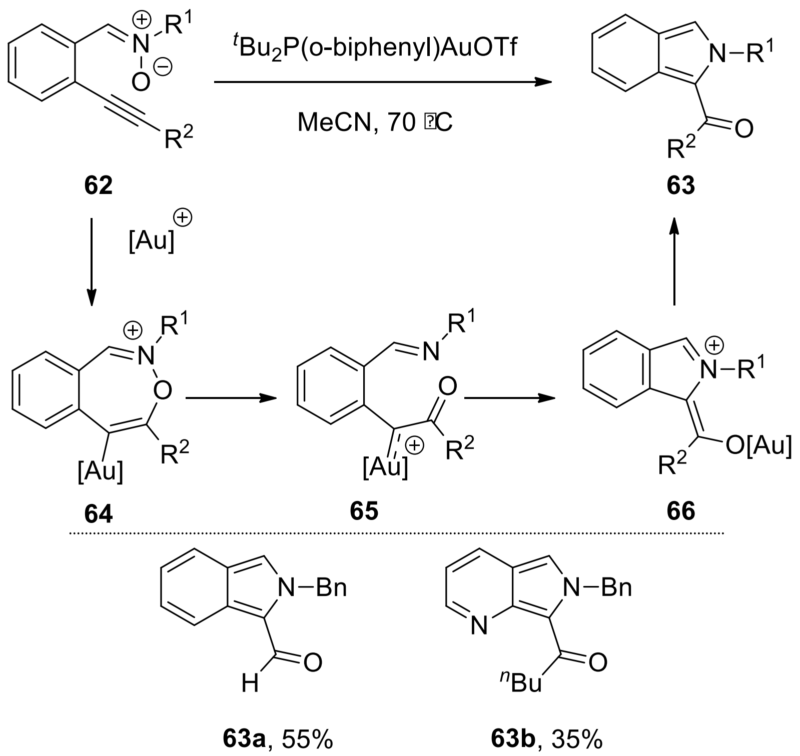
Scheme 13. Intermolecular reaction between alkynes and arylsulfoxide.

Epoxides have also been used as a source of an oxygen atom in intramolecular redox reactions promoted by gold. In a study by Li and co-workers,[32] different epoxy tethered enynes were π-acid activated by gold catalysts and underwent intramolecular nucleophilic attack from the epoxide oxygen onto the acetylenic fragment (Scheme 14). Under optimised conditions, gold catalysis straightforwardly promoted the conversion of alkynyl epoxide of type **57** to tetracyclic 2*H*-pyran derivatives **58** through a consecutive internal redox, Nazarov rearrangement and protodemetallation.



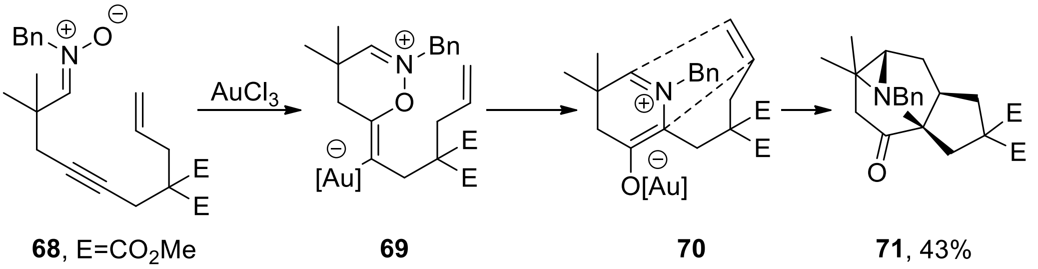
Scheme 14. Cycloisomerisation of epoxy-enynes.

In an effort to access α-oxo gold carbenoid reactivity, Shin[33] employed readily available nitrones as an oxygen delivery system. For example, simple nitrone tethered alkynes of type **62** were transformed into isoindoles **67** under optimised gold catalytic conditions. The proposed mechanism envisaged a fast 7-*endo*-dig cyclisation followed by a redox step, which formed gold intermediate **64** (Scheme 15). The imine group reacted with the proposed carbenoid to form azomethine ylide **66**, from which the catalyst is regenerated to afford the product.



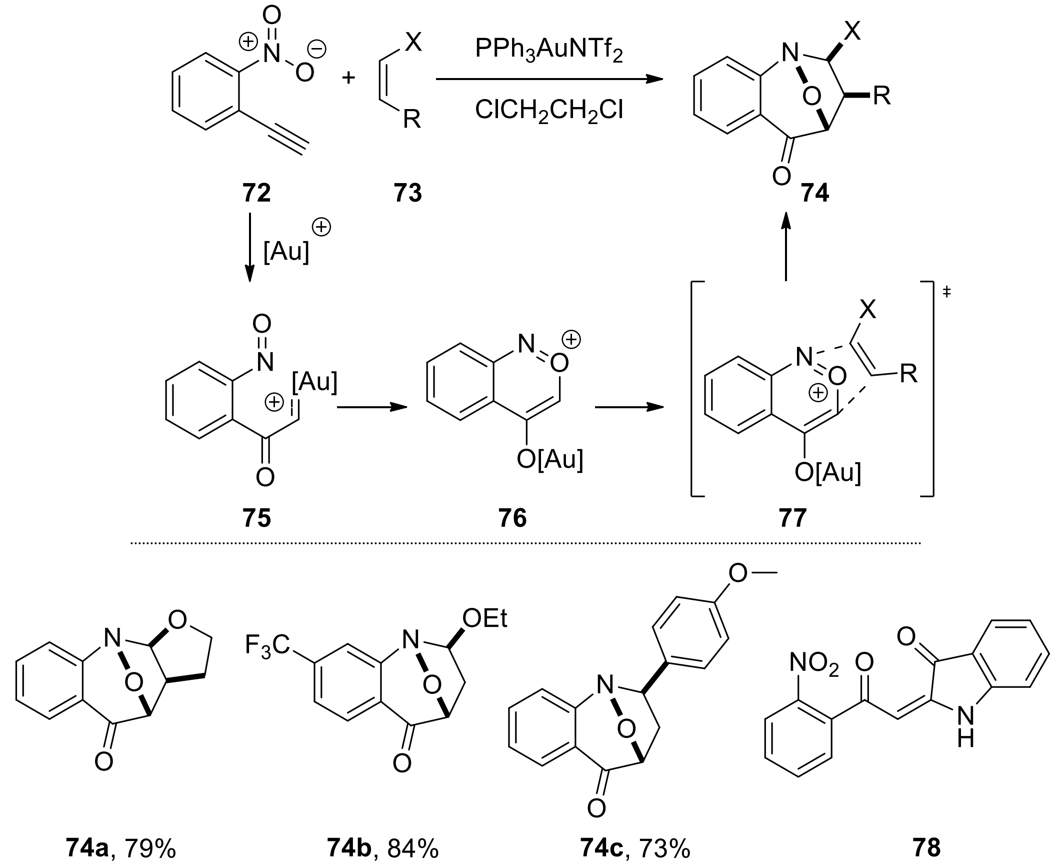
Scheme 15. Nitrones in the synthesis of isoindoles.

The methodology proved to be successful for the preparation of different isoindoles and also related nitrogen-containing heterocycles. Shin elegantly showed the potential of this transformation in an internal redox/dipolar cycloaddition cascade (IR/DC) of tethered nitrone enynes to afford azabicyclo[3.2.1]octanes **71** in a highly diastereoselective manner (Scheme 16).[34]



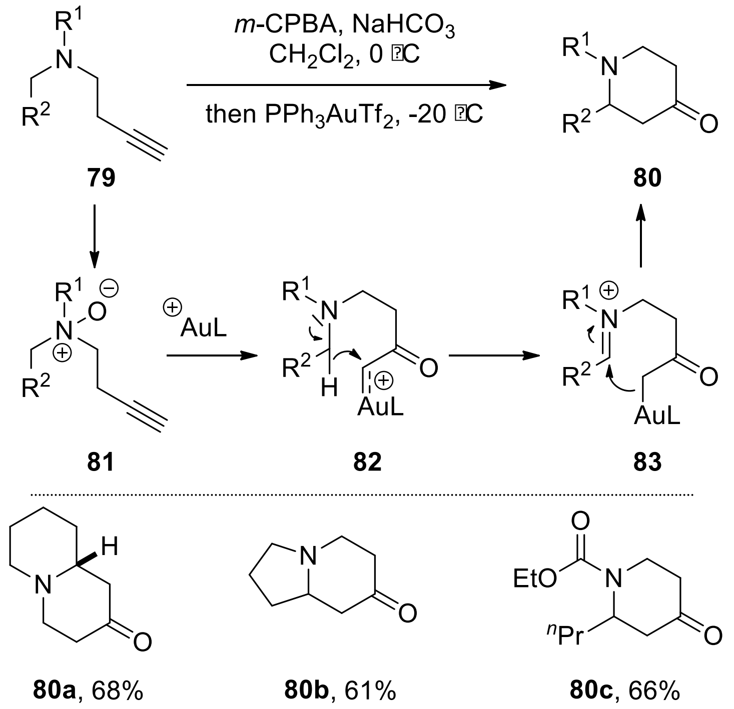
Scheme 16. Synthesis of azabicyclo[3.2.1]octanes 71.

Liu and co-workers used a similar IR/DC transformation intermolecular approach where 1-ethynyl-2-nitrobenzene derivatives **72** and alkenes **73** reacted under gold catalytic conditions to afford azacyclic compounds **74** (Scheme 17).[35] The key step in the mechanism was the formation of ketonyl oxonium **76** which underwent a [3+2] cycloaddition reaction via transition state **77**. An excess of alkene and a slow addition of the nitro alkyne are required for optimal reaction conditions; this precaution circumvents the gold-catalysed dimerisation of the olefin which forms undesired product **78**.



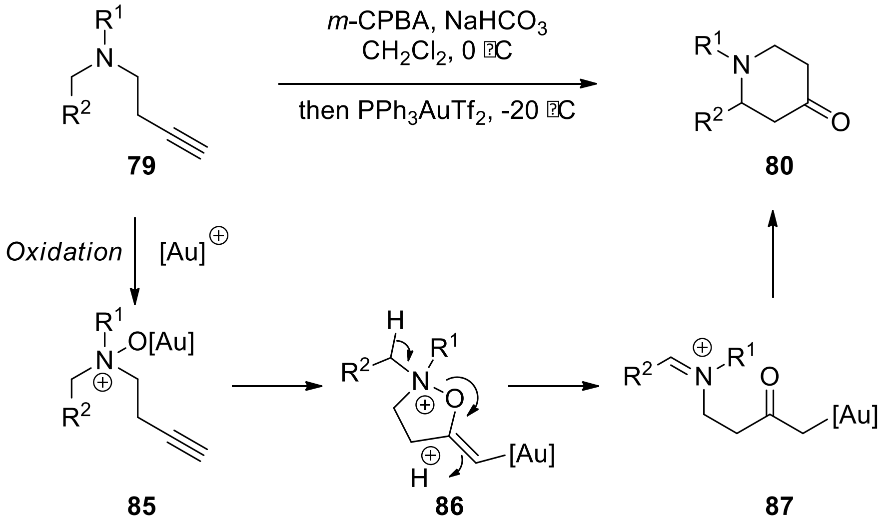
Scheme 17. Redox/dipolar cycloaddition cascade reaction between nitrobenzene derivatives and dienophiles.

In 2009 Zhang *et al.* explored a new intramolecular oxygen atom transfer from amine *N*-oxides to alkynes promoted by a gold complex.[36] A range of different homopropargyl amines **79** were easily oxidised with *m*-chloroperbenzoicacid (*m*-CPBA) and straightforwardly submitted to gold catalysis reaction conditions to give piperidin-4-ones **80** in a one-pot manner (Scheme 18). The proposed mechanism envisaged a subsequent gold-catalysed intramolecular alkyne oxidation and a ring opening step to form organogold **82**. An intramolecular *N*-methylene hydride migration from the pendent amino group provided the imminium intermediate of type **83**, which then underwent a Mannich-type cyclisation with the gold enolate to provide the desired product.



Scheme 18. Synthesis of piperidin-4-ones from the oxidation of homopropargyl amines.

Successively, Zhang's and Houk's groups carried out a computational investigation on the mechanism of gold catalysed rearrangement of acetylenic amine *N*-oxide previously reported.[37] It was calculated that a more energetically favoured mechanism would involved a heteroretroene reaction. In light of this study, intermediate **86** undergoes a 1,6-hydride shift leading to gold species **87** which further rearranges through a cyclisation to release the catalyst and form the product **80** (Scheme 19). The study has also highlighted a *syn* oxygen-gold addition to the alkyne unit rather than the most widely reported *anti* version suggested for similar transformation. This unusual behaviour was explained in virtue of a more favourable gold-coordinated *N*-oxide species **85** rather than a gold-alkyne complex.

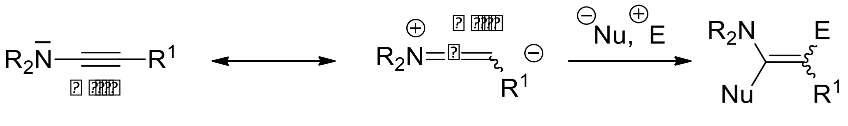


Scheme 19.

The strategies presented in this section show various methodologies for atom transfer processes catalysed by gold catalysts, which allow access to overall carbene-like reactivity. The nature of the gold-intermediate involved in these transformations has been suggested to be represented by a gold carbenoid species, although care must be taken as different mechanism pathways could also be possible.

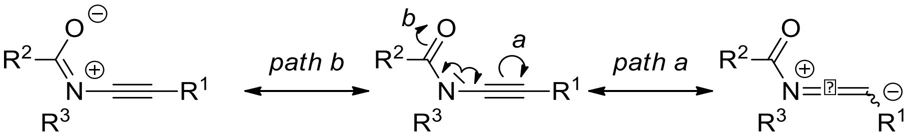
1.4 Ynamides as versatile tools in gold chemistry

Heteroatom-substituted alkynes represent a versatile and interesting class of substituted alkynes. The presence of the heteroatom electron-donating ability strongly polarises the triple bond, which allows access to exceptional differentiation between the two *sp*-carbon atoms in the catalysis. This is reflected in a predictable regioselectivity to the addition of electrophiles or nucleophiles onto the triple bond as in the case of ynamines (Scheme 20).[38]



Scheme 20. Possible resonance forms for ynamines and their reactivity with nucleophiles and electrophiles.

The first synthesis of ynamines, nitrogen-substituted alkynes, was reported by Zaugg *et al.* while studying the unusual reaction between propargyl bromide and phenothiazine.[39] Although the first ynamine had finally been isolated and characterised, a practical synthesis was only achieved five years later by Viehe.[40] Despite the ynamides synthetic potential was immediately recognised by the organic community, their use in organic synthesis remained rather limited compared with, for example, closely related enamines.[41] Difficult preparations and intrinsic instability were accountable for limiting their employment. Adding a *N*-electron-withdrawing substitution to access ynamides enhanced stability in comparison to ynamines whilst maintaining to a good degree the triple bond polarisation (Scheme 21).



Scheme 21. Possible resonance forms for ynamides.

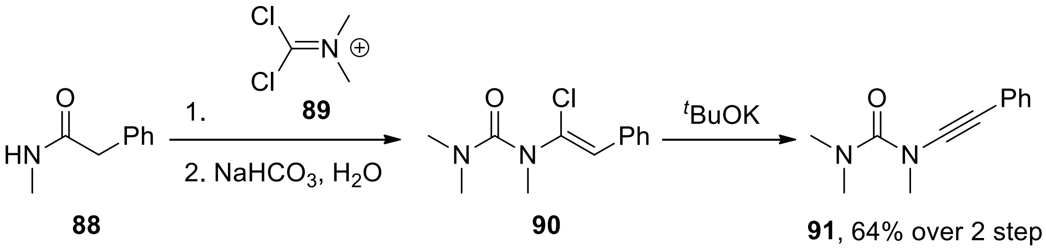
Furthermore, ynamides survive aqueous work-up, silica gel purifications and thermal conditions.

1.4.1 Ynamide synthesis

For ynamides to be efficiently employed as organic chemistry tools, a reliable method for their synthesis was required. Over the years different methods have been optimised which utilised elimination processes, isomerisation reactions and the use of alkynyliodonium salts, but it was only until the discovery of copper-mediated *N*-alkylynation process that more general ynamide syntheses have finally been accomplished.

1.4.1.1 Preliminary ynamide preparations

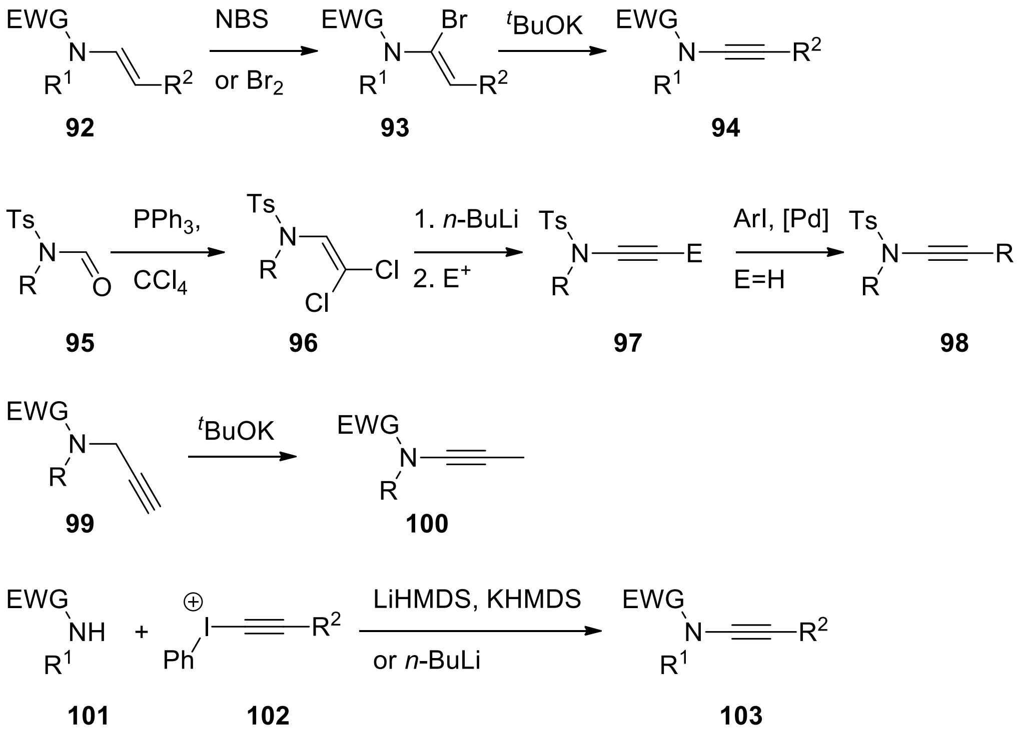
In 1972 Viehe and co-workers published the first synthetic methods to obtain urea-derived ynamides **91** by elimination of HCl from the corresponding α-chloroenamide **90** in the presence of a base (Scheme 22).[42] Although the procedure suffered from several limitations (*e.g.* limited substrate scope, use of harsh reagents), this elimination based synthetic protocol was the first preparation method where ynamides could be obtained in good yield.



Scheme 22. The first ynamide synthesis.

It was almost 30 years later, in 2001, that Hsung *et al.* improved the procedure by employing a more easily available enamide **92** which, on bromination, provided β-bromoenamides **93**. The elimination of HBr from **93** afforded different pyrrolidinine-, oxazolidinone-, and imidazolidinone-derived ynamides **94** in good yield (Scheme 23).[43] Employing the elimination approach, β,β-dicholoroenamides **96** were also found to be suitable starting materials which are smoothly synthesised by treatment of formamides **95** with tetrachloromethane and triphenylphosphine. The use of BuLi as a strong base promoted the elimination of HCl and the Li-exchange, forming the cationic precursor of ynamide **97** which could be trapped with a series of electrophiles similar to a modified Corey-Fuchs protocol. When terminal ynamides are obtained (E=hydrogen atom), different Sonogashira and Negishi functionalisation protocols can be applied as described for the preparation of ynamides of type **98**.

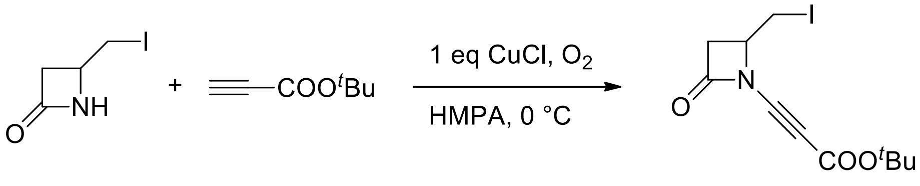
Although these and other methods[44] (Scheme 23) have provided access to a number of ynamides in good yield, all of them suffer important limitations such as low substrate scope, difficult access to the starting materials, harsh reaction conditions or multistep preparation.



Scheme 23. Different preparations of ynamides.

1.4.1.2 Amidative cross-coupling copper mediated for ynamide synthesis

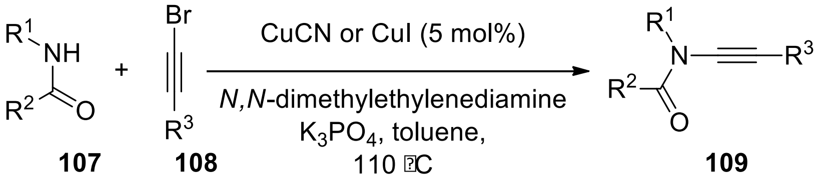
Balsamo and Domiano serendipitously observed the formation of ynamides **106** from the reaction between β-lactam **104** and copper(I)-propiolic ester complex.[45] The latter was formed *in situ* by the treatment of propiolic ester **105** in the presence of equimolar amount of copper(I) chloride (Scheme 24).



104 **105** **106**, 40%

Scheme 24. First copper-mediated preparations of ynamides.

The first copper-catalysed coupling between amides **107** and alkynylbromide **108** was reported by Hsung *et al.* in 2003[46] and represented a major breakthrough over the existing methods. This protocol based on Buchwald's approach[47] copper catalysed *N*-arylation of amides was successful for oxazolidinone and lactam ynamide derivatives but it was found unsatisfactory when imidazolidinones and sulfonamides were employed as the amide compound.

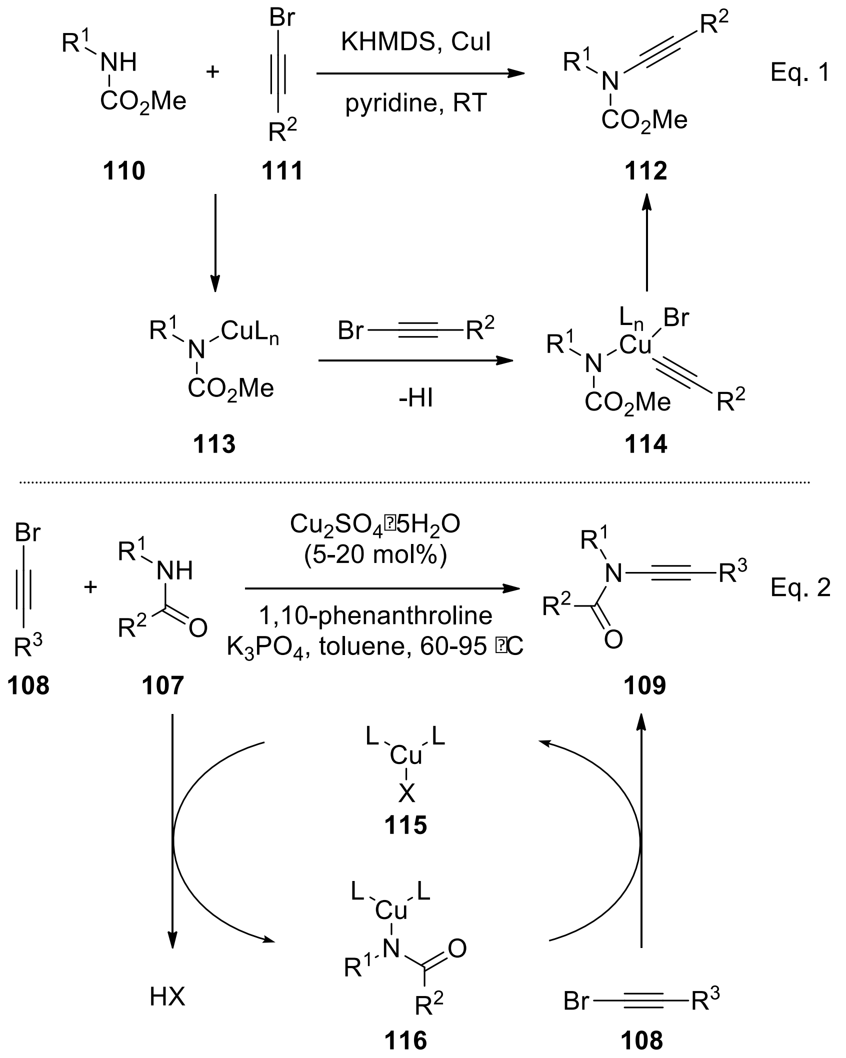


107 **108** **109**

Scheme 25. Hsung's first generation ynamide preparation protocol.

In the same year, the Danheiser group[48] also developed a copper-mediated coupling of amides with alkynyl bromides (Scheme 26, Eq. 1). A wide range of different amides **110** could now be employed under much milder conditions but preformation of the copper amide intermediate with a stoichiometric amount of CuI was required.

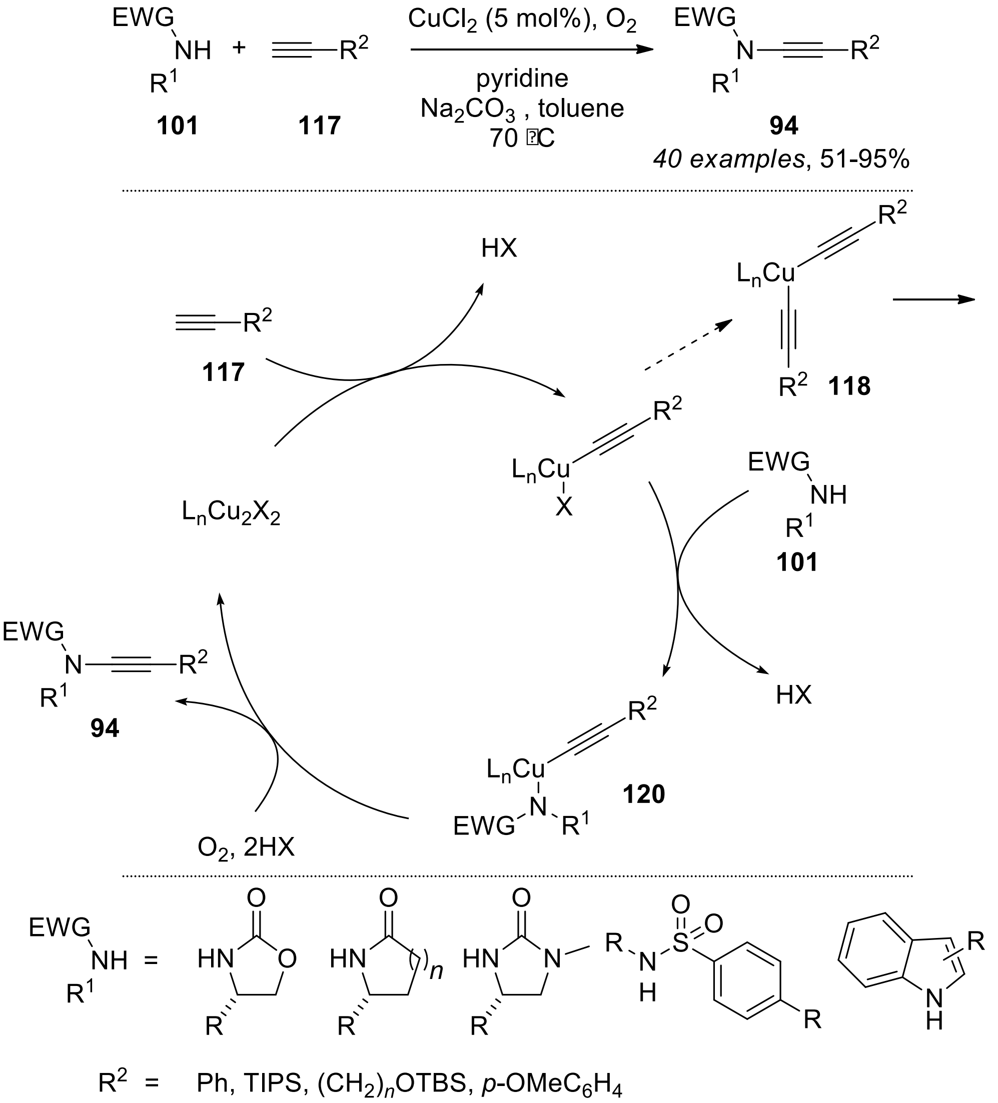
Hsung *et al.*[49] improved their previous reported method by employing a better catalytic system (cheaper and more environmentally friendly copper source), which improved the previous reported reaction conditions, scope of the reaction and overcome some of the limitations previously experienced (Scheme 26, Eq. 2).



Scheme 26. Danheiser's protocol (top) and Hsung's second generation ynamide preparation (bottom).

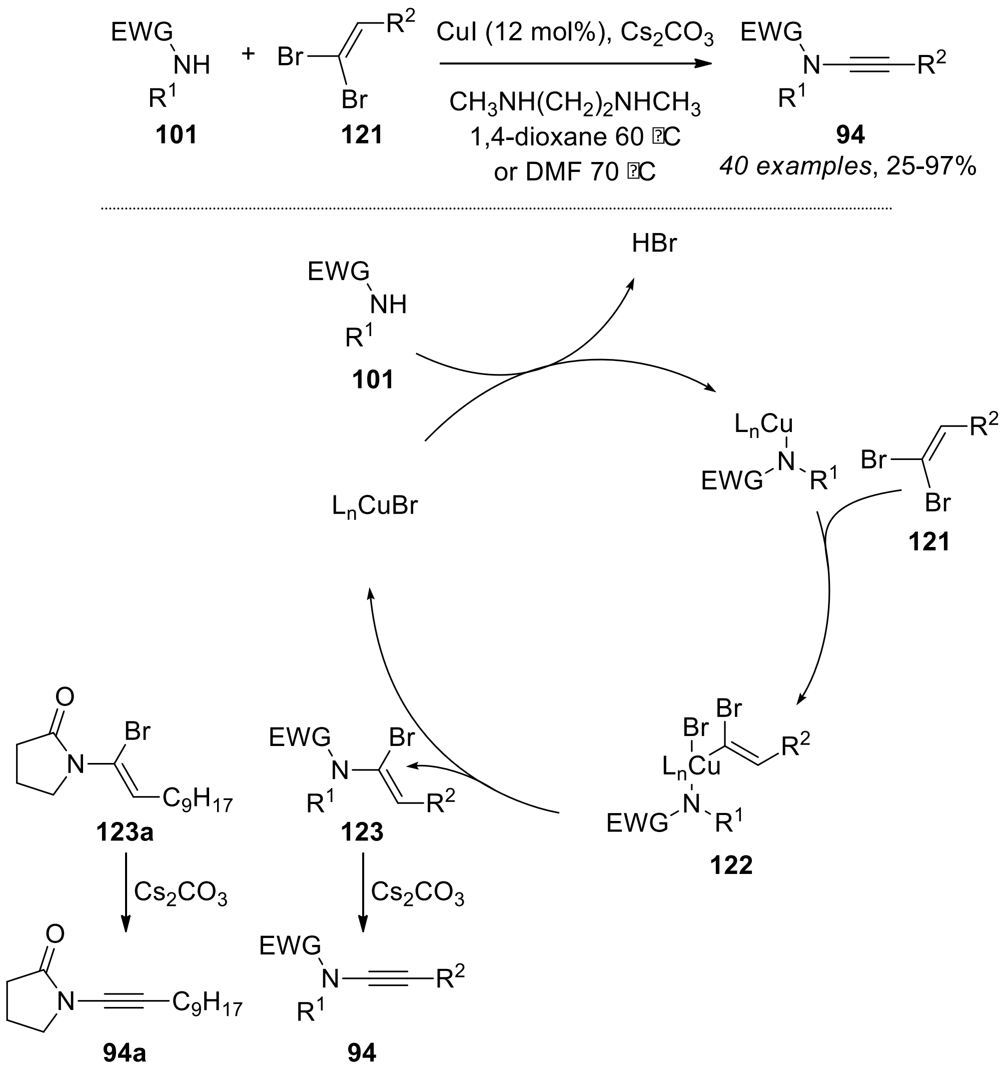
Continuing with the study reported by Balsamo and Domiano (*vide supra*), a new copper catalysed coupling between amides **101** and terminal alkynes **117** has also been proved a very successful and convenient strategy for the synthesis of ynamides. This particularly elegant alkynylation procedure was developed by Stahl and co-workers and employs molecular oxygen as the terminal oxidant (Scheme 27).[50] This new protocol attracted great attention due to the very wide scope of the reaction; different amides and alkynes can be employed with good to excellent yield. Like Hsung's strategy, a catalytic amount of copper was used but the employment of terminal alkynes rather than their brominated derivatives represented a welcome advantage.

To avoid the competing alkyne homodimerisation side processes that lead to the formation of diyne **119**, slow addition of the alkylynating agent and an abundant excess of amide is required.



Scheme 27. Stahl's ynamide preparation.

Evano *et al.* were able to obtain ynamides from the copper-catalysed coupling between amides **101** and vinyl-dibromides **121** (Scheme 28).[51] This efficient alternative method employed vinyl-dibromides as a synthetic equivalent to bromo alkynes. Oxidative addition of **101** with a copper catalyst and reductive elimination-amination affords α-bromoenamide **123**. The ynamide formation is mediated by a HBr elimination step promoted in the presence of the base. This proposed mechanism was confirmed by the isolation of side product **123a** which on treatment with Cs_2CO_3 produced ynamide **94a** as the only product.



Scheme 28. Evano's ynamides preparation.

1.5 Selected example of ynamides under gold catalysis conditions

Although ynamides have only been used intensively in the last decade,[52] some gold catalysed reactions have already been discovered and optimised (Figure 5). Herein, we report a selection of examples which show the similarities between ynamide and alkyne reactivities in reactions promoted by gold catalysis. Moreover, we are going to highlight the advantages that the nitrogen presence confers to the triple bond system.

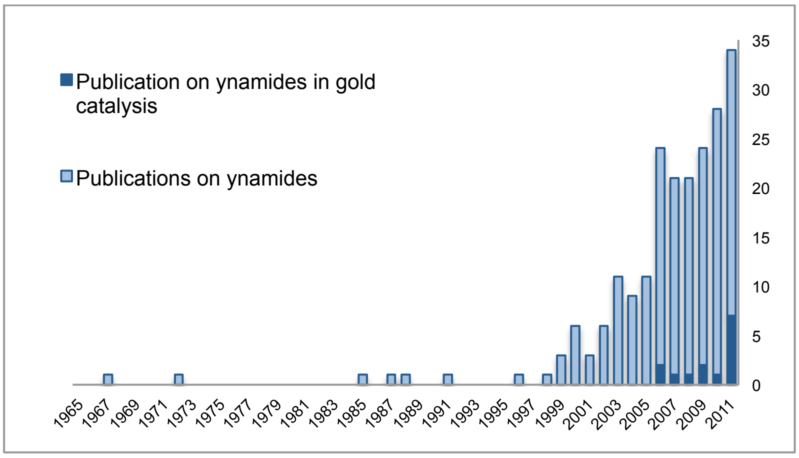
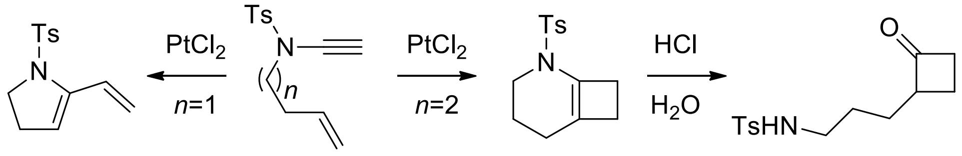


Figure 5. Publications on ynamides and ynamides in gold catalysis in the last decades.[53]

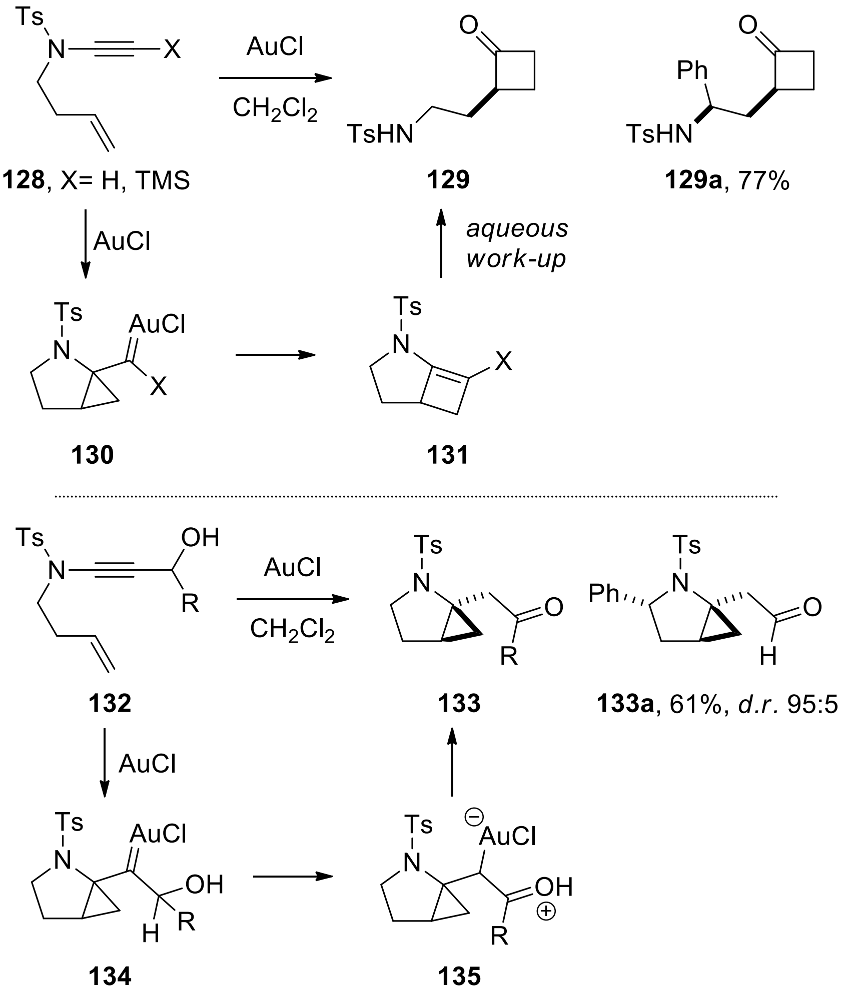
A study focused on the cycloisomerisation of 1,6-ene-ynamides of type **125** (n=1) promoted by platinum led to the formation of a so called “formal metathesis product” **124** in excellent yield while 1,7-ene-ynamides **125** (n=2) produced cyclobutanone **127** as the only product (Scheme 29).[54]



124 **125** **126** **127**

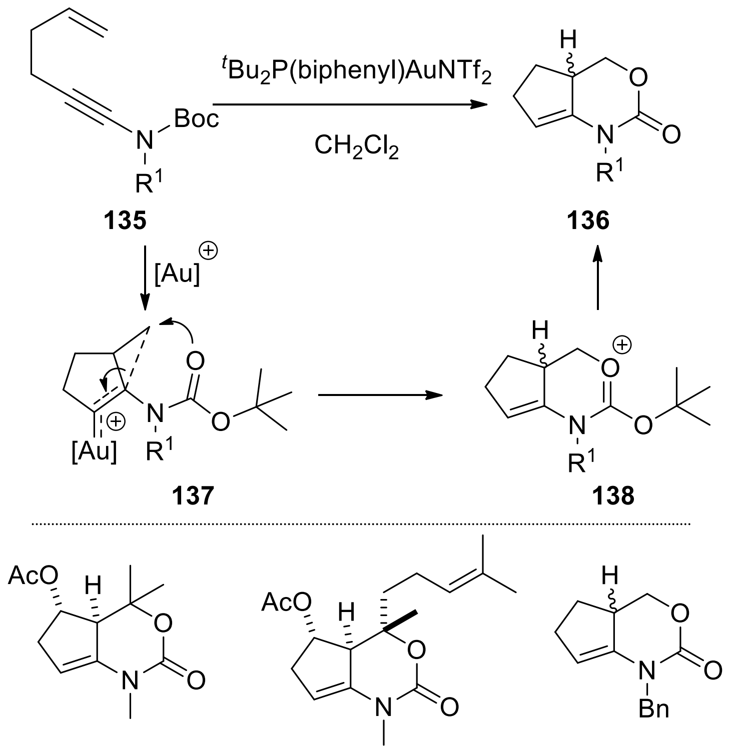
Scheme 29. Cycloisomerisation of 1,6- and 1,7-ene-ynamides promoted by platinum.

The reactivity of platinum catalyst π-acids is established to be closely related to the one observed for gold complexes.[12a] Based on this assumption, Cossy and co-worker published one of the first gold catalysed cycloisomerisation reactions of 1,6-ene-ynamides.[55] They hypothesised that under the milder conditions required by gold catalysis 1,6-ene-ynamides would lead instead to a cyclobutanone product **129**. They envisaged that ynamide of type **128** would undergo a regioselective gold-promoted cycloisomerisation as seen for enynes in Section 1.3 to form gold intermediate **130**, which would rearrange to form the desired product. Optimised conditions allowed the successful synthesis of cyclobutanones **129a** in good yield. More interestingly, 1,6-ene-ynamides bearing a propargylic alcohol such as **132** diverted the course of the reaction to an alternative ketone product of type **133**. This different reaction outcome derived from a 1,2-hydride shift assisted by the hydroxyl group followed by protodeauration (Scheme 30).



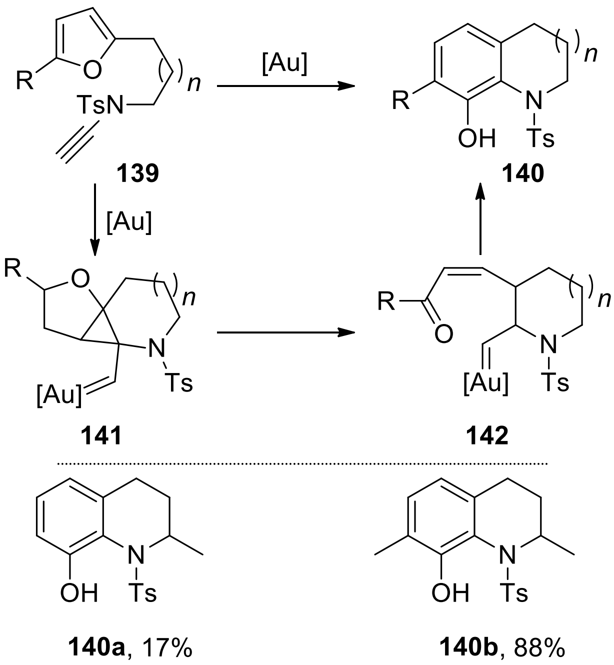
Scheme 30. Cycloisomerisation of 1,6-ene-ynamides promoted by gold.

Later on, Gagosz reported the conversion of *N*-alkylnyl *tert*-butyloxycarbamates **135** in the presence of a gold(I) complex into a range of functionalised bicyclic carbamates **136** (Scheme 31).[56] The formal [4+2] cycloaddition was derived from cycloisomerisation of the enynes and intramolecular attack of the *tert*-butyloxycarbamates to stereoselectively trap the gold intermediate. In absence of the olefinic unit, the ynamide would instead undergo nucleophilic addition from the *tert*-butyloxycarbamate unit.[57]



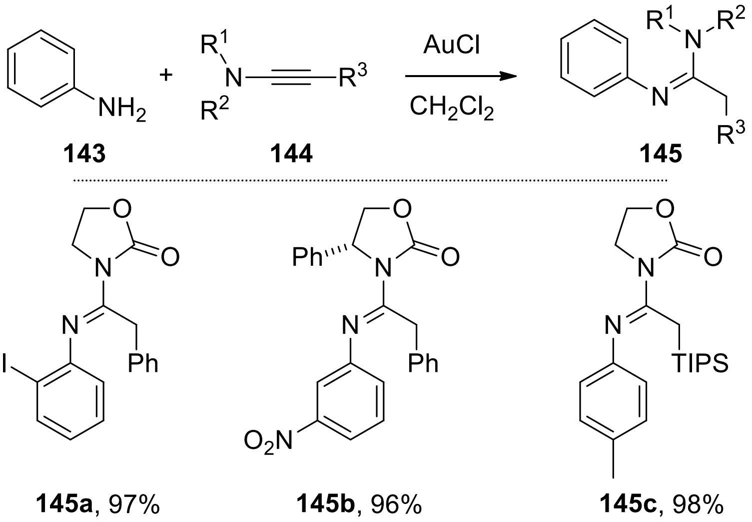
Scheme 31. Intramolecular cyclisation of *N*-alkylnyl *tert*-butyloxycarbamates.

Hashmi's gold-catalysed phenol synthesis has been proven to be a powerful tool for the synthesis of various phenol derivatives.[58] Hashmi *et al.* considered ynamides as a possible alkyne substitutes for their strategy in order to extend the pool of different phenolic structures that can be accessed. Various dihydroindoles (*n*=0) and tetrahydroquinolines (*n*=1) of type **140** were synthesised from pendant furan ynamides **139** using different gold complexes and reaction conditions (Scheme 32).[59]



Scheme 32. Hashmi's gold-catalysed phenol synthesis using ynamides.

The powerful intrinsic regioselective control of ynamides has been further proven by Skrydstrup and co-workers.[60] Ynamides **144** underwent regioselective hydroamination with anilines **143** providing a useful imidoyl precursor **145** for indole synthesis (Scheme 33). The regiocontrol provided by the nitrogen atom overcomes the scope limitations often seen in similar indole preparations using alkynes, which often lack of regioselectivity.



Scheme 33. Regioselective amination of ynamides.

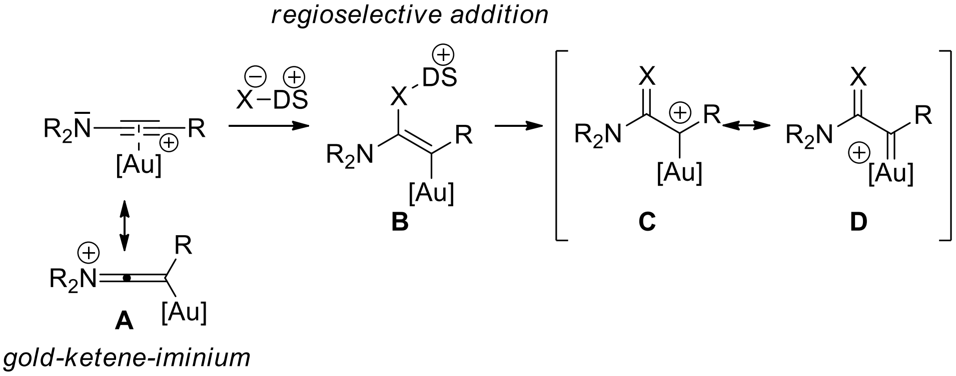
1.6 Conclusion

Homogeneous gold catalysis has proved to be a successful tool in organic chemistry. Mild reaction conditions, high tolerance towards various chemical functionalities and selective activation of *C-C* triple bonds by gold complexes are triggering a wider interest in this noble metal. In the last decade, new methodologies have been discovered and optimised, providing new procedures to form *C-C* and *C*-heteroatom bonds and therefore increase molecular complexity. In this respect, intermolecular atom transfer processes catalysed by gold catalysts have been shown to be a potentially useful approach amongst the different strategies available especially for potentially accessing gold carbenoid reactivity.

Ynamides have recently been discovered as useful substrates in organic chemistry and new reliable procedures for the synthesis of stable ynamides have led to an increased interest in such molecules. Due to the presence of a *C-C* triple bond, ynamides have emerged as suitable functionalities to be efficiently employed in gold catalysis. Over the last few years this hypothesis has been proven, different reactivity pathways have been discovered and more applications of ynamides in gold catalysis should emerge in the near future.

1.7 Aim and objectives

The aim of this study is to develop a novel gold-catalysed atom transfer process. Adapting the synthesis so that it proceeds in an intermolecular fashion will enhance the synthetic flexibility of atom transfer processes, which is usually limited to intramolecular versions. By virtue of their triple bond polarisation, ynamides were chosen as a suitable π-system in order to provide control over the regioselective installation of the heteroatom across the acetylene fragment. Activation of an ynamide by a gold complex would increase its electrophilicity allowing the addition of a nucleophilic heteroatom delivery system (Scheme 34). Based on previous knowledge of related intramolecular processes involving alkynes, we envisaged that the backbonding occurring from the gold species **B** would cause the cleavage of the delivery system (DS) to form the desired gold-carbenoid intermediate **C**/**D**.



Scheme 34. Proposal of intermolecular atom transfer onto ynamides promoted by gold complexes.

A useful gold carbenoid species should be generated and this can react further depending on its carbocation versus carbenoid nature, the functionalities present and the reaction conditions.

To study this proposal, a series of ynamides with suitable substitutions such as allyl, aryl, alkyl and allyloxy were designed and prepared. These installed functionalities should react intramoleculary with the gold carbenoids generated during the atom transfer processes to access typical carbene transformations, such as cyclopropanation, ylide formation and *C-H* insertion reaction.

Chapter 2: Gold-catalysed synthesis of α,β-unsaturated carboxylic acid derivatives from ynamides and ynol ethers

2.1 Introduction

In light of the previously introduced advances in gold-catalysed atom-transfer processes on alkynes, an intermolecular regioselective atom-transfer transformation onto ynamides was proposed. It was envisaged that through the reaction intermediates, gold carbenoid reactivity would be accessible (Figure 6).

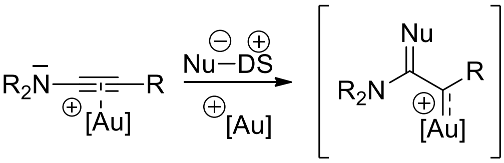


Figure 6. Proposal of gold-carbenoid access from ynamides.

Among the different metal carbenoid species, α-oxo metal stabilised carbenes **F** have been widely studied and employed in organic chemistry but their preparation normally requires the use of potentially hazardous and toxic diazocompounds of type **E** (Figure 7). Employing such undesirable reagents is usually labour intensive and often comes at the expense of the efficiency of the overall process. For these reasons the development of new flexible and reliable methods to generate α-oxo metal stabilised carbenes through alternative routes is highly attractive. Many of the atom-transfer processes onto alkynes catalysed by gold complexes present in the literature have demonstrated an easy and straightforward alternative method to access α-oxo gold carbenoids.[24-36] Although the great utility of these processes is indisputable, they rely on an intramolecular approach that requires the pre-installation of a suitable functionality in the substrate and a favourable tether length between the delivered oxygen atom and the reactive centre (Figure 7, **G**). These major limitations would be overcome by an intermolecular approach, increasing flexibility and synthetic applicability of the transformation.

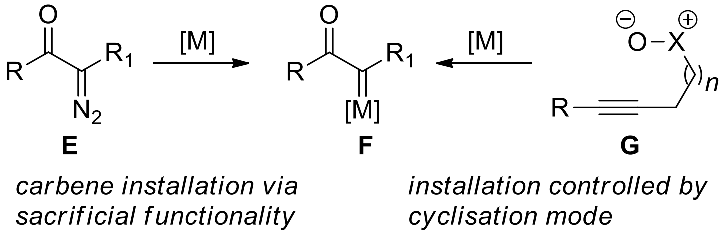
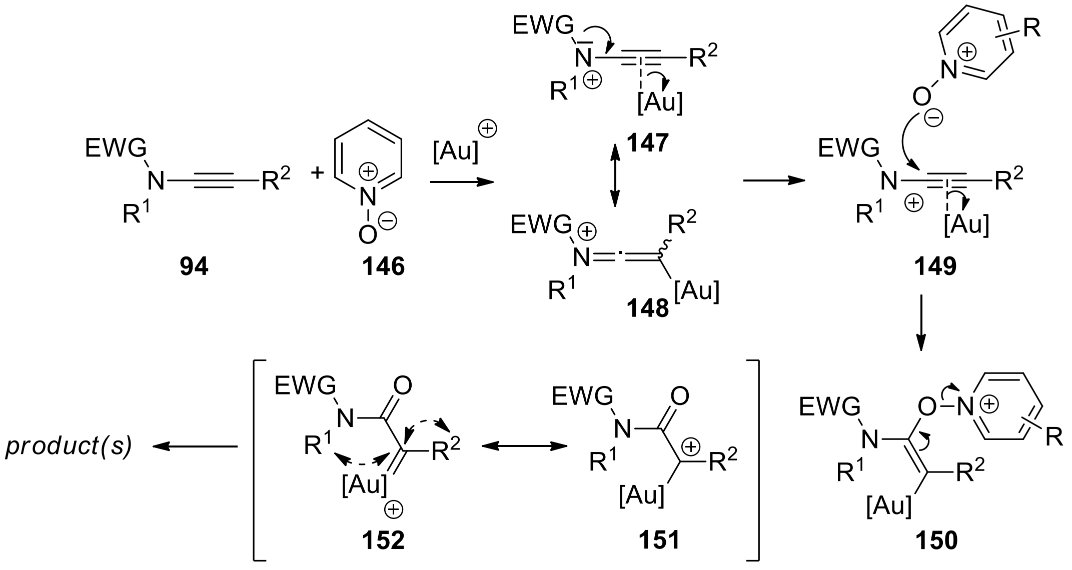


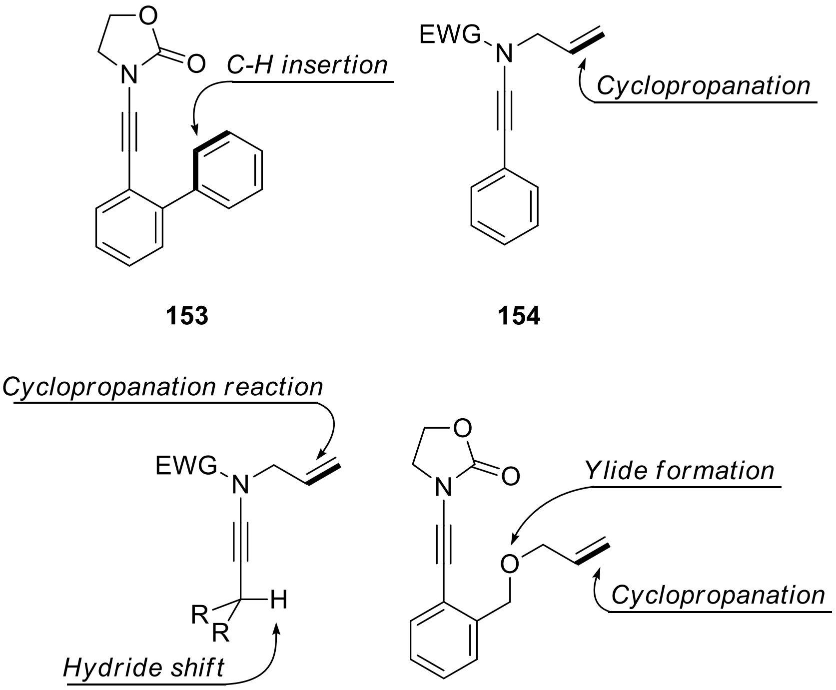
Figure 7

In order to apply our intermolecular concept for the generation of such valuable species, pyridine *N*-oxide derivatives were selected as a suitable commercially available *O*-nucleophilic oxidant. According to this proposal, the employment of a ynamide would ensure regio-control over the oxygen installation. Under suitable conditions, formation of complex **150** should therefore be possible. The electron pull would lead to the cleavage of the *N-O* bond and the formation of gold intermediate **152**, which should be carbenoid in nature (Scheme 35). As shown in the previous chapter, these gold carbenoid species can undergo different reactivity pathways depending on the other functionalities present.



Scheme 35. Proposed gold intermediate reactivity pathways for the selected ynamides to be studied.

To explore different gold-carbenoid outcomes, ynamides **153-156** were prepared as suitable, readily obtainable and simple ynamides bearing appropriate functionalities. These ynamides should allow, after revealing the gold carbenoid reactivity, the reproduction of carbene quenching pathways described in the literature, such as 1,2-hydride shift, ylide formation, *C-H* insertion onto the aryl unit and cyclopropanation (Scheme 36) (see section 1.2 and 1.3).



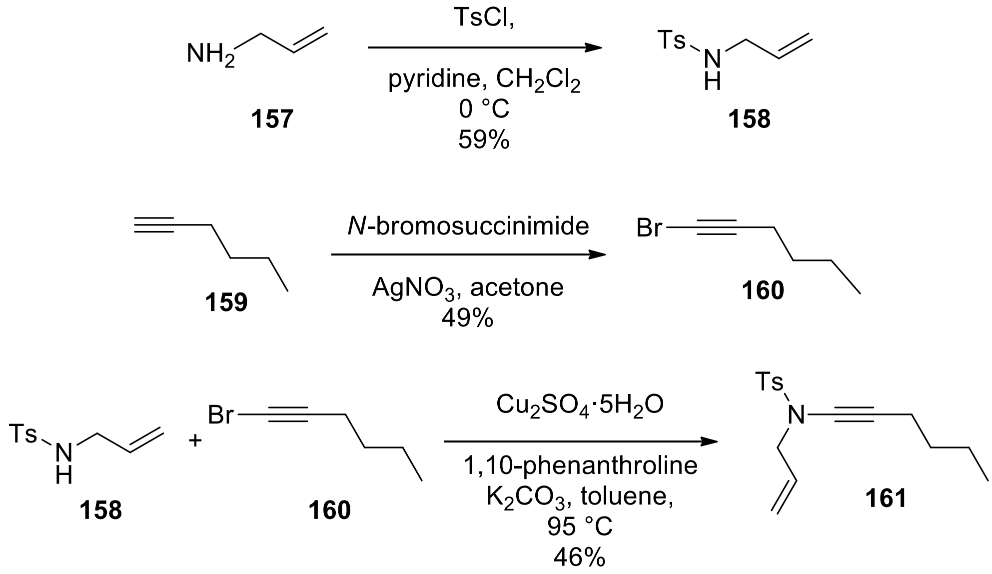
153 **154** **155** **156**

Scheme 36. Functionalised ynamides for reactivity testing.

2.2 Preparation of ynamide substrates

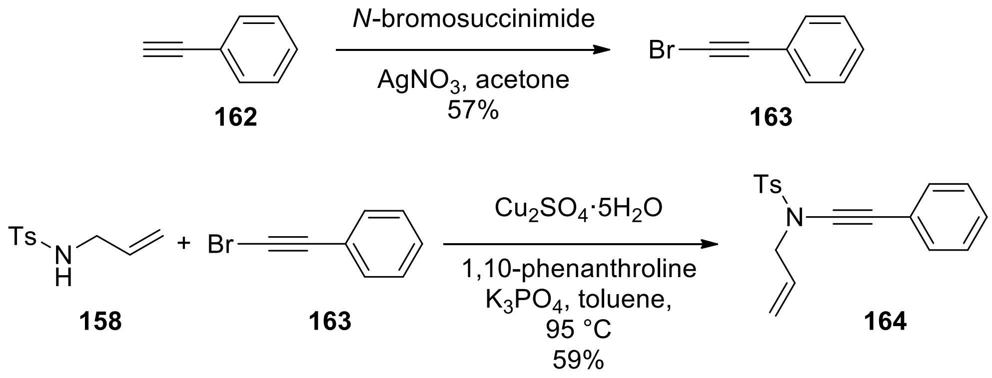
From the different synthetic preparations of ynamides available, we focused our attention on the previously described second-generation copper-catalysed coupling developed by Hsung and co-workers.[49]

For the synthesis of ynamide precursor **161** and **164**, tosyl substituted allyl amine **158** was prepared in good yield by a slow addition of tosyl chloride to a solution of allyl amine and pyridine in CH_2Cl_2 at 0 °C. Bromination of 1-hexyne **159** with *N*-bromo succinimide catalysed by silver nitrate in acetone afforded bromoalkyne **160** in good yield. Under Hsung's reaction conditions, the coupling between **158** and **160** produced ynamide **161** in decent yield (Scheme 37).



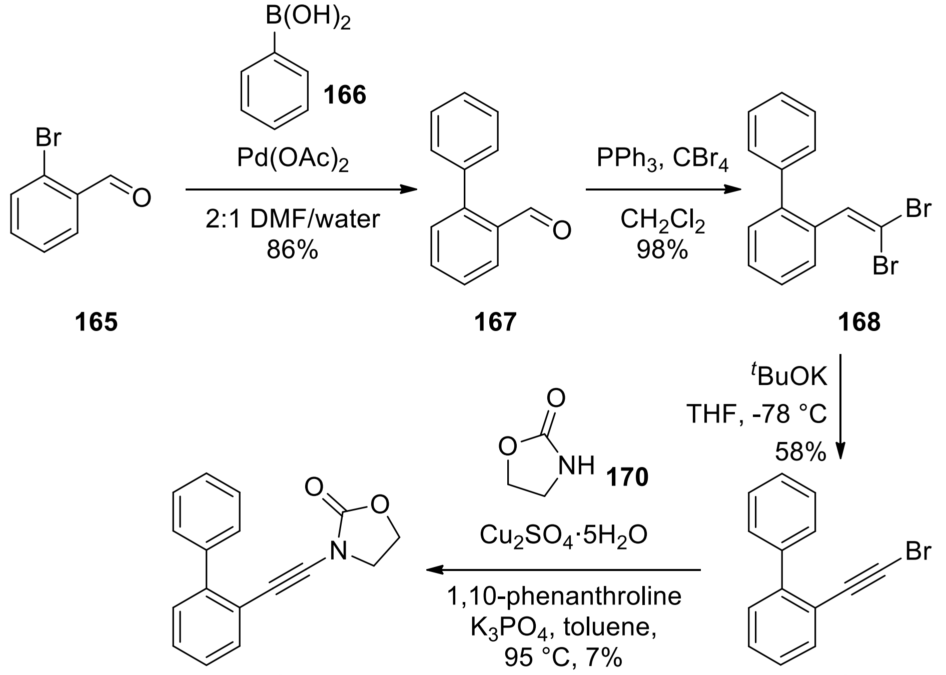
Scheme 37. Preparation of ynamide 161.

The same approach was also employed for the preparation of ynamide precursor **164**. Phenyl acetylene **162** was converted to its brominated derivative **163** and then submitted to copper-catalysed coupling conditions with allyl sulfonamide **158**, affording the desired *N*-alkynyl sulfonamide **164** in good yield (Scheme 38).



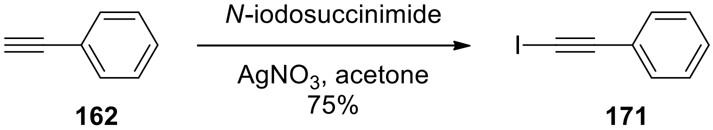
Scheme 38. Preparation of ynamide 164.

For the preparation of ynamide **153**, 2-bromobenzaldehyde was treated with phenylboronic acid in a Pd-catalysed Suzuki coupling reaction to obtain bisarylaldehyde **167**. Treatment of **167** with triphenylphosphine and carbon tetrabromide in dichloromethane provided dibromoalkene **168** in excellent yield. In order to obtain the desired bromoalkyne derivative **169**, an elimination process promoted by *tert*-butoxide was employed and afforded the desired product in good yield. Unfortunately, the copper catalysed ynamide forming reaction with 2-oxazolidinone **170** afforded the product in very low yield (Scheme 39). Hsung's second-generation ynamide synthesis protocol has been reported to be significantly affected by the quality of the reagents used,[61] and this could explain the poor result observed in the synthesis of ynamide **153**.



Scheme 39. Synthesis of ynamide 153 under Hsung's reaction conditions.

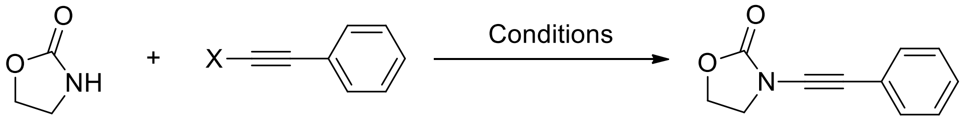
Due to this disappointing result, we decided to execute a comparative study in order to evaluate the efficiency of the different ynamide preparation methodologies available. In order to explore alternative preparations, iodoalkyne **171** was prepared employing *N*-iodosuccinimide, as an electrophilic source of iodine, with phenyl acetylene **162** and silver nitrate in acetone (Scheme 40).



Scheme 40. Preparation of iodoalkyne 171.

Different copper and metal catalysed coupling processes were then tested for the preparation of oxazolidinone ynamide **172**. In the case of Hsung's coupling conditions, both halogenated phenylacetylene **163** and **171** proved to be unsuccessful (Entries 1 and 2, Table 1). Moreover, the iron-based procedure developed by Zhang also did not provide the ynamide **172** formation (Entry 3) even though this product was reported.[62] Instead, the aerobic copper-catalysed protocol developed by Stahl and co-workers[50] was the only successful protocol and yielded the product in 85% of yield (Entry 4).

Table 1. Ynamides preparation methods-comparison study.

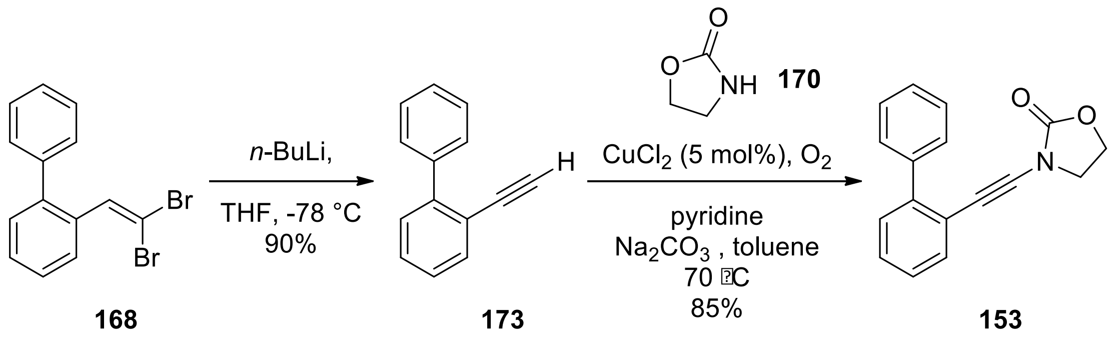


170 **172**

Entry	*Phenylacetylene derivative*	*Conditions*	***172** Yield*[a]
1	**163** (X=Br)	$Cu_2SO_4 \cdot 5H_2O$, 1,10-phenanthroline, K_2CO_3, toluene, 75 °C	-[b]
2	**171** (X=I)	$Cu_2SO_4 \cdot 5H_2O$, 1,10-phenanthroline, K_2CO_3, toluene, 75 °C	-[b]
3	**171** (X=I)	$FeCl_3$, TMEDA, K_2CO_3, toluene, 90 °C	-[b]
4	**162** (X=H)	$CuCl_2$, O_2, pyridine Na_2CO_3, toluene, 70 °C	85%

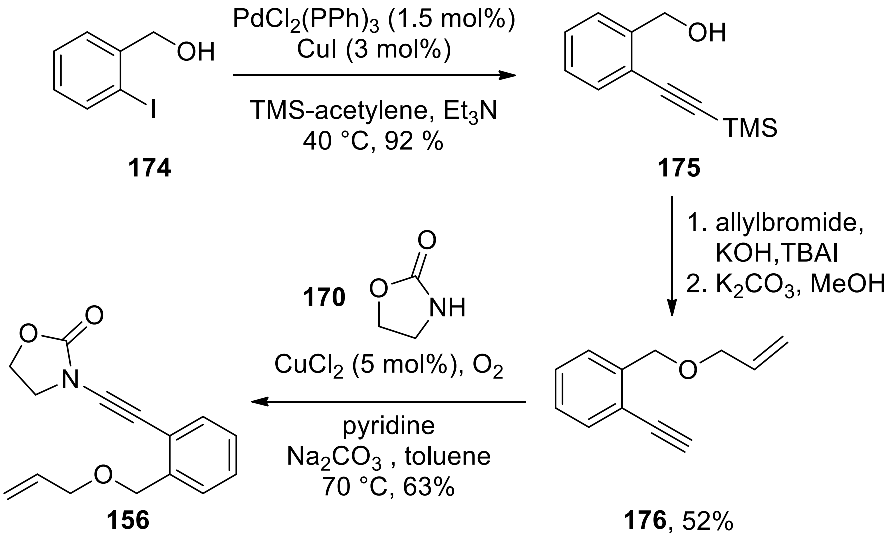
[a]Reactions executed on 1 mmol scale of 2-oxazolidinone 170. [b]No reaction was observed.

Therefore, it was decided that the preparation of ynamide **153** should be performed under Stahl's reaction conditions which employ copper (I) chloride as a catalyst in the presence of pyridine, sodium carbonate and molecular oxygen as oxidant in toluene. Terminal alkyne **173**, prepared using a Corey-Fuchs protocol from the previously prepared dibromo derivative **168**, was then submitted to the aerobic copper-catalysed coupling with 2-oxazolidinone, which finally afforded ynamide **153** in good yield (Scheme 41).



Scheme 41. Preparation of ynamide 153 with Stahl's method.

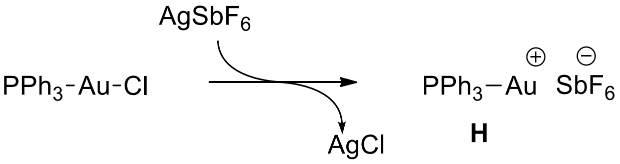
Ynamide **156** was prepared in a similar manner. Commercially available *o*-iodobenzyl alcohol was coupled with trimethylsilylacetylene under Sonogashira conditions using $PdCl_2(PPh_3)_2$ and copper (I) iodide as a catalytic system. The silylphenylacetylene **175** was allylated with allyl bromide in solvent free conditions and the crude reaction mixture was treated with a solution of potassium carbonate in MeOH to afford desilylated alkyne **176** (Scheme 42). Under aerobic copper catalysis, allyl ether with **176** led to the formation of ynamide **156** in good yield.



Scheme 42. Preparation of ynamide 156.

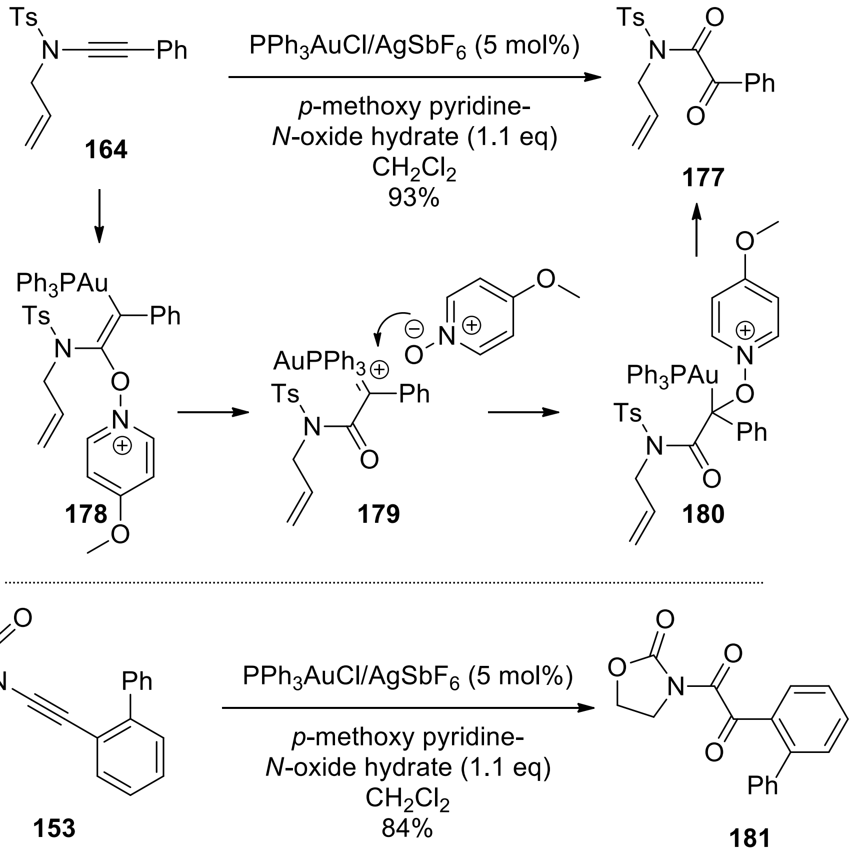
2.3 Preliminary studies of gold-catalysed intermolecular oxygen transfer onto ynamides

To test the gold-catalysed intermolecular oxidation reaction on the selected ynamides, commercially available *p*-methoxy pyridine *N*-oxide hydrate was initially employed as the external oxidant. It was hypothesised that the presence of the electron-donating group would increase the nucleophilic character of the *N*-oxygen atom which is fundamental for the addition onto the electrophilic activated ynamide's triple bond. As standard catalytic conditions, PPh_3AuCl was chosen as a gold catalyst activated by silver salt $AgSbF_6$ through an *in situ* chloride abstraction in CH_2Cl_2 (Scheme 43). The cationic gold species **H**, bearing an empty coordination site, is the active form of the catalyst that would promote the reaction.



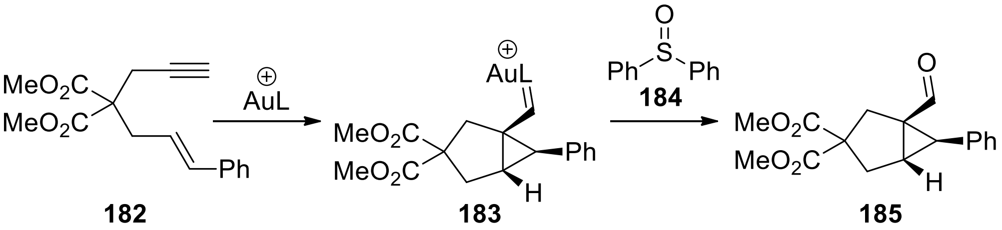
Scheme 43. Metathesis reaction between PPh_3AuCl and $AgSbF_6$.

Under the unoptimised gold catalysis conditions, ynamides **164** and **153** led to the formation of dioxidated oxoacetamide products **177** and **181** respectively (Scheme 44). Access to the dioxidised products was a result of a second oxidation step occurring on the intermediate **179**; surprisingly this intermolecular process was apparently faster than any other intramolecular rearrangement that could have taken place. The reaction did not proceed to completion because an insufficient amount of pyridine *N*-oxide was employed to achieve full conversion to the dioxidised products.



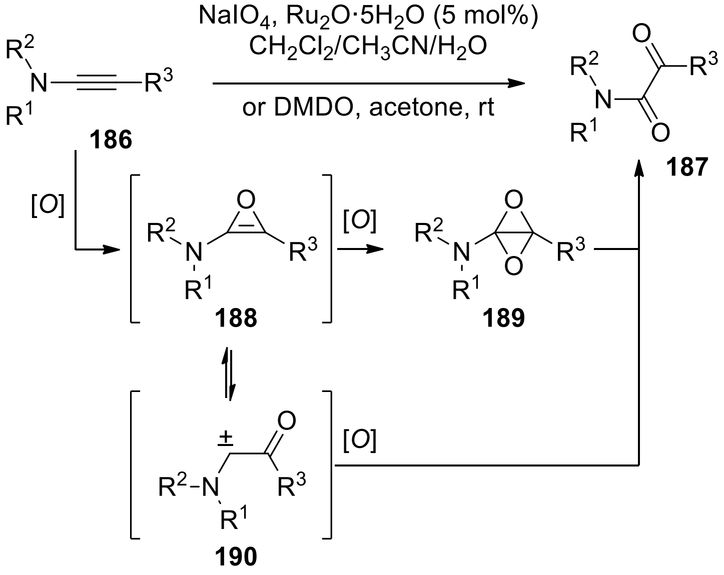
Scheme 44. Dioxidation processes on ynamide 164 and 153 catalysed by gold complexes.

An equivalent oxidation of a gold carbenoid has been reported by Toste *et al.*, who trapped a gold catalysed 1,6-enyne cycloisomerisation carbenoid intermediate **183** with an external sulfoxide **184** as the oxidant (Scheme 45).[63]



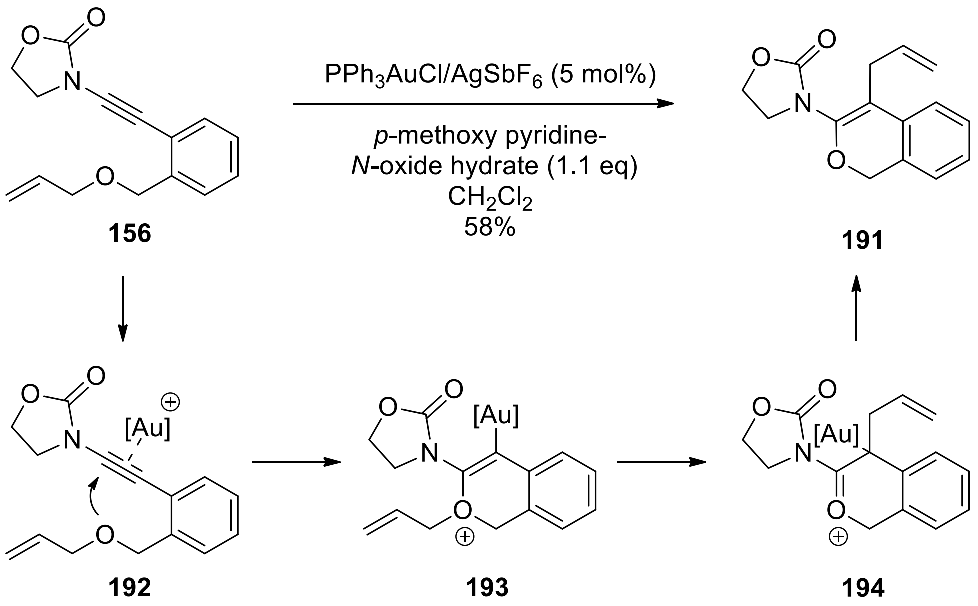
Scheme 45.

Dioxidation processes on ynamides have also been reported by Hsung and co-workers using electrophilic oxidising reagents (*i.e.* RuO_2-$NaIO_4$ and DMDO) (Scheme 45).[64]



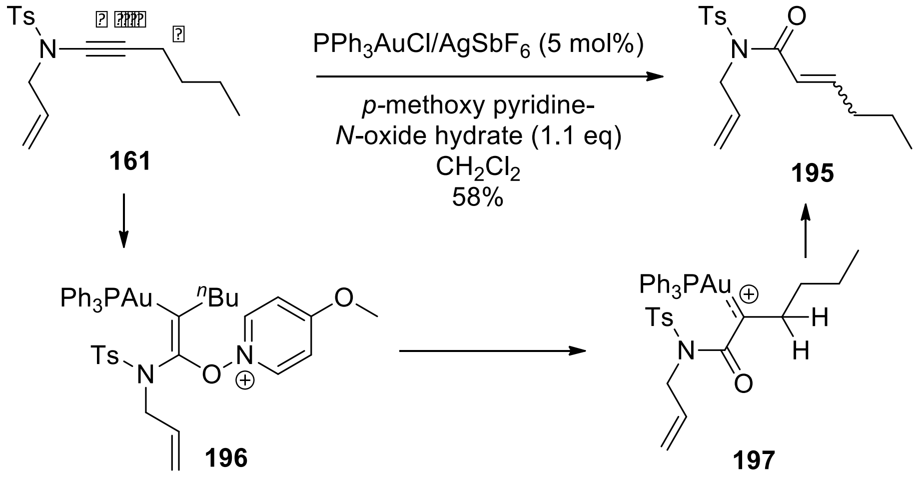
Scheme 46.

Ynamide **156** was also tested under the conditions previously employed. In this instance, the formation of a gold complex promoted a 6-*endo* cyclisation following by an overall ally migration to form product **191** (Scheme 47). This is consistent with the allyl shift observed for a similar reaction catalysed by platinum employed as π-acid,[65] although a Claisen-type rearrangement could not be excluded since it was proved for the cycloisomerisation of ynenyl allyl ethers in the presence of a gold (I) catalyst.[66]



Scheme 47.

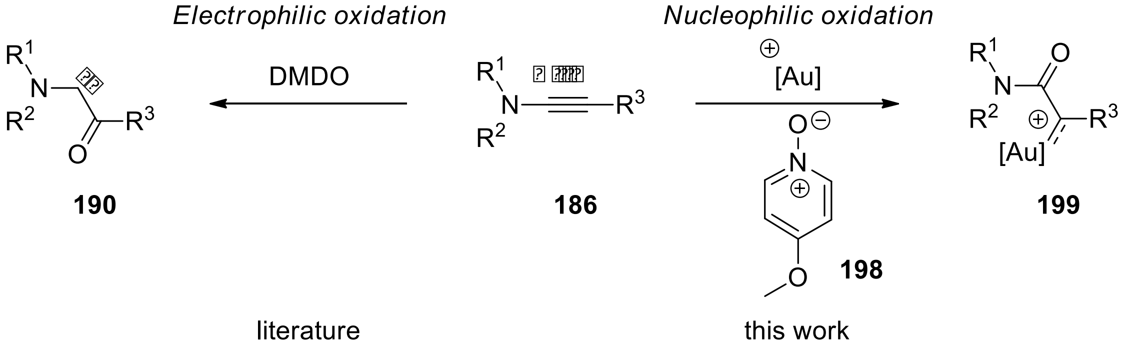
Under gold catalysis, ynamide **161** led to the formation of α,β-unsaturated carboxylic acid derivatives of type **195** (Scheme 48). This latter product was consistent with the hypothesized regioselective intermolecular transfer of an oxygen atom from the pyridinium system to the ynamide triple bond. The cleavage of the *N*-*O* bond led to the formation of an α-oxo gold intermediate of type that could be responsible, either via a gold stabilised carbocation or a gold stabilised carbene, for the observed 1,2-hydride shift. The presence of a hydrogen atom in the γ-position diverts the evolution of the gold intermediate, with the hydride shift process is faster than the previously observed second oxidation step of the gold intermediate.



Scheme 48. Synthesis of 195 under gold-catalysed oxidation conditions.

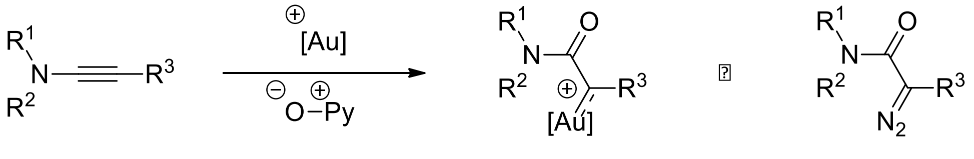
The formation of the vinylogous amide **195** represents a novel alternative method for preparing α,β-unsaturated carboxylic acid derivatives and also an alternative protocol to access α-oxo gold carbenoids as it was proposed.

The α-oxo carbene formation from an ynamide in an oxidation reaction has also been reported in the literature,[67] but interestingly the opposite regioselectivity upon installation of such functionality was observed when DMDO is used as an oxidant (Scheme 49). The opposite outcome of oxygen atom installation-carbene formation is due to the electrophilic nature of the oxidant used.



Scheme 49. Opposite regioselective oxidation outcomes with electrophilic and nucleophilic oxidant on ynamides.

Intrigued by the possibilities to access different α,β-unsaturated imide derivatives via a two-step procedure starting from electron-deficient amides and terminal alkynes,[68, 69] further investigations were carried out. Notably, under this novel protocol, ynamides could be viewed as a direct equivalent of α-oxo gold stabilised carbenoids **199** representing a valid alternative to the use of α-oxo diazo compounds of type **200** (Figure 8).

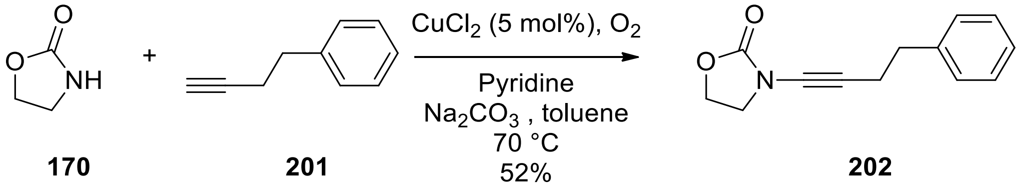


186 **199** **200**

Figure 8.

2.4 Survey of the catalytic conditions for the gold-catalysed oxidation of ynamides

It was decided to conduct a screening study on the different reaction conditions of the gold-catalysed oxidation reported above by using ynamide **202** as a test substrate. This was prepared from commercially available sources (Scheme 50).

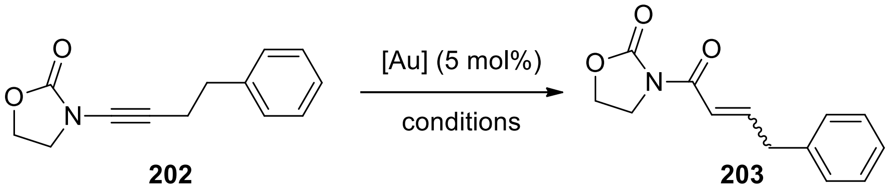


170 **201** **202**

Scheme 50. Preparation of ynamide 202.

^{1}H-NMR analysis of the crude reaction mixture containing a known amount of internal standard (1,2,4,5-tetramethylbenzene) was performed in order to evaluate the catalysis system efficiency (Table 2). Formation of the product **203** as a mixture of *E*:*Z* isomers was observed under mild gold catalysis conditions (Entries 2, 3, 4 and 5) in poor yields, with the exception of $AuBr_3$ (Entry 6). Interestingly, the switch from the *p*-methoxy pyridine *N*-oxide hydrate to anhydrous pyridine *N*-oxide appeared to increase the efficiency of the reaction (Entries 1 and 6 *vs.* Entries 7 and 8 respectively). The presence of the water in the oxidant species might interfere with the reaction and therefore exclusion of water through the use of anhydrous reagents would be preferable. In order to ameliorate the reaction conditions, the temperature was varied. It was noted that at higher temperature, the catalytic system $AuPPh_3Cl$/AgOTs (Entry 12) performed better than $AuPPh_3Cl$ activated by other silver salts (Entries 10 and 11), although additional increase in temperature worsened the catalyst's performance (Entry 13). $AuBr_3$ performed efficiently at room temperature but its activity was reduced by an increase in temperature (Entries 8 and 16). A comparison of different solvents showed THF to be the most suitable when $AuBr_3$ was employed. Au catalyst Au-**III**[28] at moderately high temperature also catalysed the transformation and gave the α,β-unsaturated imide product in good yield (Entry 15).

Table 2. Survey of the reaction conditions.



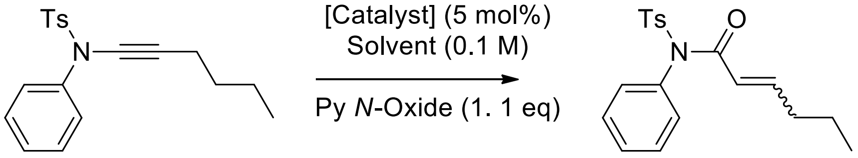
Entry	*Catalyst*	*Oxidant (equivalents)*	*Solvent*	*Temperature (°C)*	*Starting material remaining*	***203** Yield (E:Z ratio)*[a],[b]
1	$AuPPh_3/AgSbF_6$	A (1.1)	CH_2Cl_2	RT	54%	-[c]
2	$AuPPh_3/AgSbF_6$	A (2)	CH_2Cl_2	RT	54%	9% (1:0)
3	Au-**III**	A (1.1)	CH_2Cl_2	RT	68%	14% (1:0)
4	$AuBr_3$	A (1.1)	CH_2Cl_2	RT	22%	12% (1:0)
5	$AuPPh_3/AgOTf$	A (1.1)	CH_2Cl_2	RT	55%	8% (1:0)
6	$AuCl_3$	A (1.1)	CH_2Cl_2	RT	-[c]	65% (5.5:1)
7	$AuPPh_3/AgSbf_6$	B (1.1)	CH_2Cl_2	RT	56%	6% (1:0)
8	$AuBr_3$	B (1.1)	CH_2Cl_2	RT	-[c]	71% (4.6:1)
9	AuCl	B (1.1)	CH_2Cl_2	RT	60%	30% (1:0)
10	$AuPPh_3/AgSbf_6$	B (1.1)	$ClCH_2CH_2Cl$	70	19%	31% (2.9:1)
11	$AuPPh_3/AgOTf$	B (1.1)	$ClCH_2CH_2Cl$	70	17%	23% (4.6:1)
12	$AuPPh_3/AgOTs$	B (1.1)	$ClCH_2CH_2Cl$	70	12%	50% (3.5:1)
13	$AuPPh_3/AgOTs$	B (1.1)	toluene	90	-[c]	47% (2.2:1)
14	Au-**III**	B (1.1)	$ClCH_2CH_2Cl$	50 (7h)	-[c]	58% (5.1:1)
15	Au-**III**	B (1.1)	$ClCH_2CH_2Cl$	70 (3h)	-[c]	69% (5.5:1)
16	$AuBr_3$	B (1.1)	$ClCH_2CH_2Cl$	70	-[c]	71% (7.9:1)
17	$AuBr_3$	B (1.1)	THF	RT	-[c]	61% (12.8:1)
18	$AuBr_3$	B (1.1)	toluene	RT	-[c]	65% (12.0:0)
19	$AuBr_3$	B (1.1)	MeCN	RT	43%	33% (7.2:1)

A= *p*-methoxypyridine *N*-oxide hydrate, B= pyridine *N*-oxide. [a]Reactions were performed employing 0.1 mmol of ynamide 202, A or B (as shown), Catalyst (5 mol%), Solvent (0.1 M), 24 h. [b]NMR yield were calculated against a known amount of internal standard and ratios were determined by ^{1}H-NMR analysis. [c]Not observed in the crude mixture.

Considering all the gold catalytic conditions tested, two promising sets of conditions were identified:

- System A: air-stable dichloro(pyridine-2-carboxylato)gold (III) Au-**III** precatalyst in 1,2-dichloroethane at 70 °C (Table 2, Entry 15) which led to the higher yield.
- System B: $AuBr_3$ in THF at room temperature (Table 2, Entry 17), which led to high (*E*)-selectivity while maintaining good yield. Moreover this system avoids the use of chlorinated solvents.

A parallel study was also performed by Nicolas Martin, a former member of the Davies' group, employing ynamide **204** and comparable results were observed (Scheme 51).[70] Moreover, it was found that platinum(II) salts, Brønsted acids and an electrophilic bromine source gave no reaction and/or degradation.



204 **205**

System A: Au-**III**, $ClCH_2CH_2Cl$, 70 °C 83%, (*E*:*Z*) 2.3:1
System B: $AuBr_3$, THF, RT 86%, (*E*:*Z*) 3.2:1

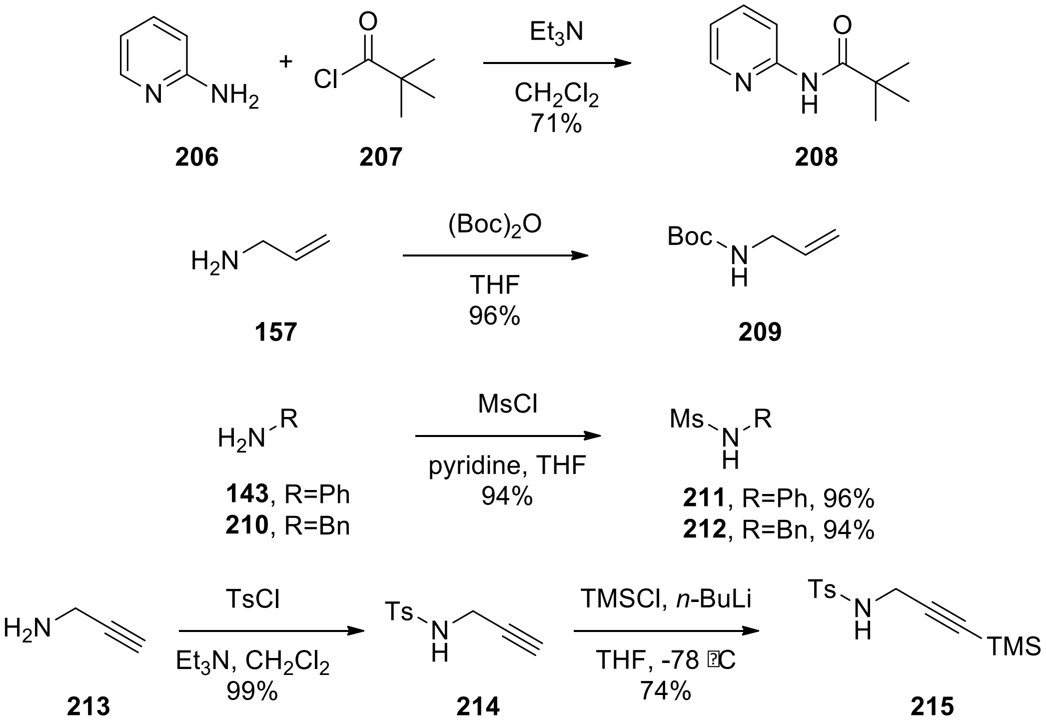
Scheme 51.

Because of the relative advantages to each system it was therefore decided that both systems would be applied to a selection of different ynamides to investigate reaction scope and functional group tolerance.

2.5 Ynamide preparation

In order to explore the scope of this novel intermolecular gold catalysed oxygen transfer reaction, a series of ynamides bearing different functional groups was prepared.

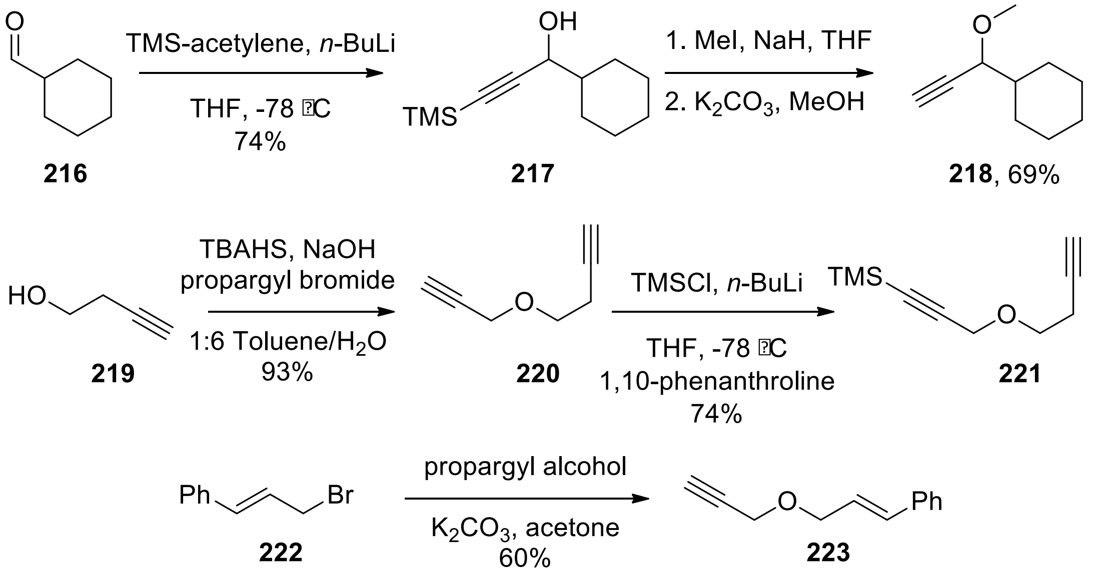
A variety of amides were synthesised following literature procedures (Scheme 52). Amide **208**, Boc-protected **209**, sulfonyl amide **211** and **212** were prepared in good yield by simple addition of the appropriate acid derivatives in the presence of a base when required. Propargyl sulfonamide **214** was obtained using a similar strategy and was further elaborated by silylation at the terminal alkyne position with *n*-BuLi and TMSCl to afford silyl derivative **215** in good yield. This alkyne protection step was necessary to avoid possible competition with the alkynylating reagent employed in the copper-catalysed coupling synthesis of ynamides.



Scheme 52. Preparation of amides.

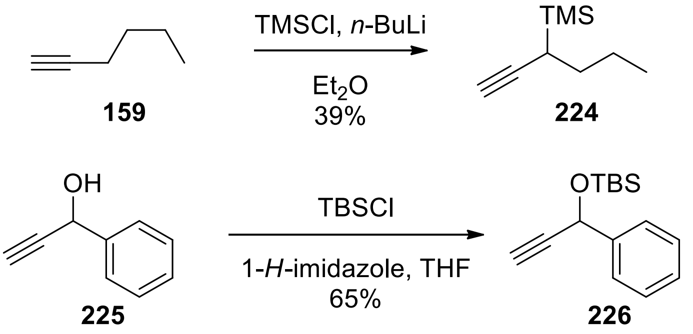
It was decided to prepare a wide range of teminal alkynes, which included different functional groups such as propargylethers, silyl alkynes and different protected alcohols.

Propargylic ether **217** was readily synthesised from cyclohexyl aldehyde and subjected to a methylation-desilylation protocol to afford the propargyl ether **217** in good yield. Unsymmetrical dialkynyl ether **221** was obtained from propargyl bromide and 3-butynyl-1-ol via a phase transfer process in the presence of TBAHS. Regioselective silylation of the propargyl unit over the butynyl framework involved the use of a catalytic amount of 1,10-phenanthroline and yielded the silyl protected alkyne. Propargylic ether **223** was readily obtained by reacting propargyl alcohol and (*E*)-cinnamyl bromide **222** under basic conditions (Scheme 53).



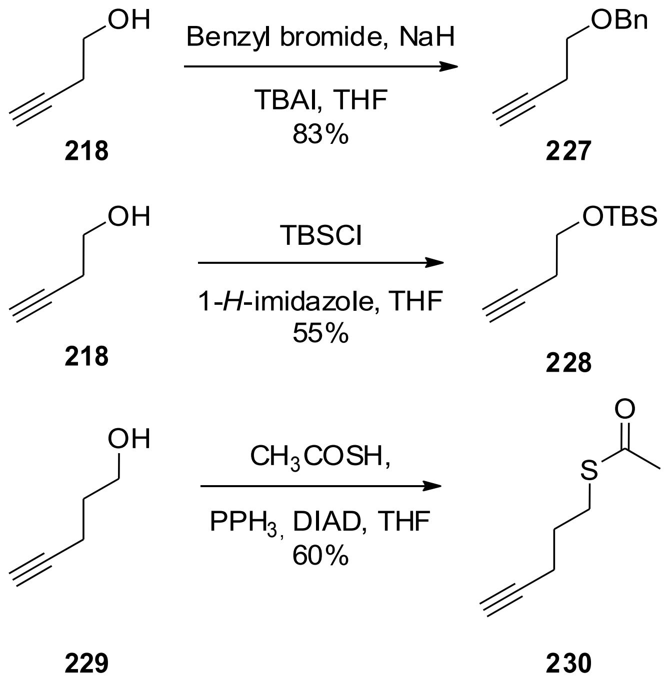
Scheme 53. Preparation of terminal alkynes 218 and 221.

Propargyl silane **224** was synthesised according to a known procedure using 1-hexyne **159** and TMSCl (Scheme 54). Silylation of commercially available 2-phenyl propargyl alcohol with TBSCl in the presence of 1-*H*-imidazole led to the formation of silyl ether **226** in good yield.



Scheme 54. Preparation of alkynes 224 and 226.

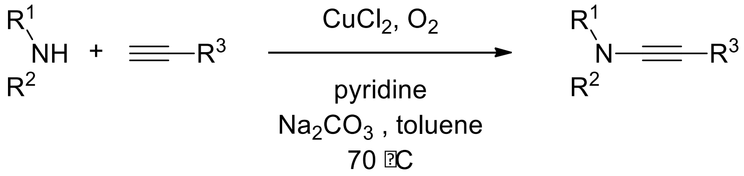
Deprotonation of 4-pentenyl-1-ol **218** with sodium hydride followed by treatment with benzyl bromide produced benzyl ether **227** in excellent yield. 4-pentenyl-1-ol was also silylated with TBSCl in the presence of 1-*H*-imidazole affording silylether **228**. For the synthesis of thioester **230**, a Mitsunobu protocol was applied starting from the commercially available corresponding alcohol **229**, activated with DIAD and thioacetic acid.

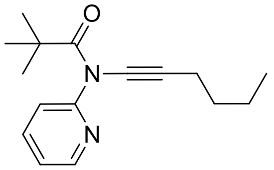
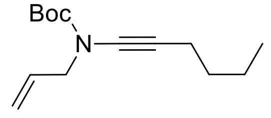
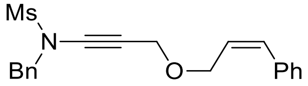
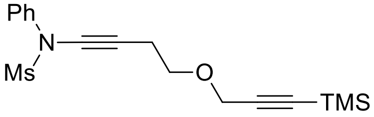
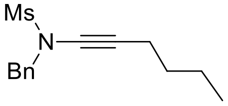
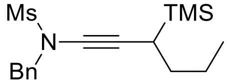
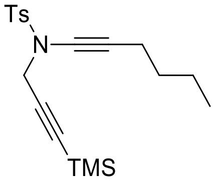


Scheme 55. Preparation of alkynes 227, 228 and 230.

With different amides and terminal alkynes in hand, coupling reactions were performed following Stahl's methodology to synthesise a wide range of *N*-alkynyl amides (Table 3 and Table 4). Amides **208** and **209** (Entries 1 and 2, Table 3) and alkynes **223** did not allow the synthesis of the corresponding ynamides (Entries 3, 4 and 7) and these results were thought to be dependent on the limitations of the method employed; in fact, no amination reaction under Stahl's method have been reported in the literature for such precursors. Good yield were instead obtained in the preparation of ynamides **235**, **236** and **238**.

Table 3. Ynamide synthesis from amides and terminal alkyne.



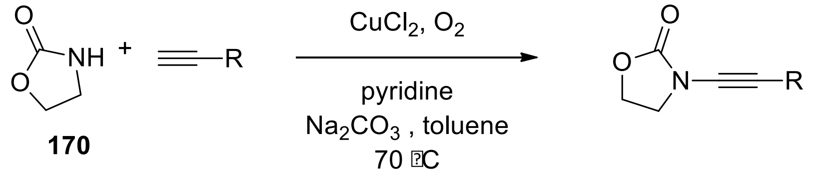
Entry	*Amide*	*Alkyne*	*Product (Yield)*[a],[b]	*Ynamide*
1	**208**	1-hexyne	**232** (-)[c]	
2	**209**	1-hexyne	**233** (-)[c]	
3	**212**	**223**	**234** (-)[c]	
4	**211**	**221**	**235** (59%)	
5	**212**	1-hexyne	**236** (42%)	
6	**212**	**224**	**237** (-)[c]	
7	**215**	1-hexyne	**238** (70%)	

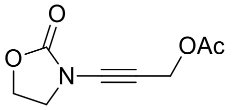
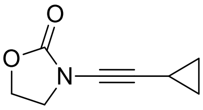
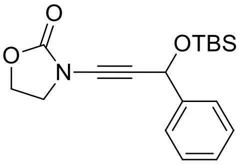
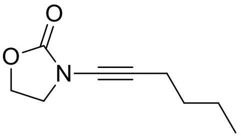
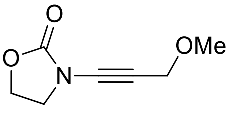
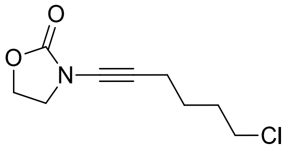
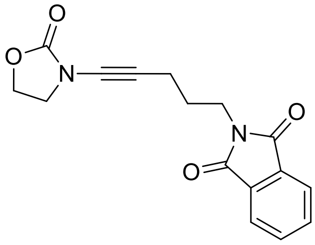
[a] All reactions were executed on a 2 mmol scale related to the alkyne employing amine (10 mmol), $CuCl_2$ (5 mol%), Na_2CO_3 (4 mmol), $CuCl_2$ (0.4 mmol) and toluene (0.1 M). [b] Yields refer to isolated product after column chromatography. [c] No product formation was observed in the crude mixture.

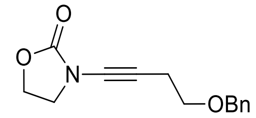
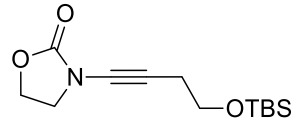
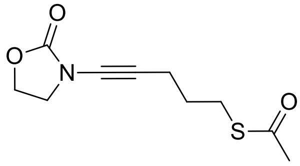
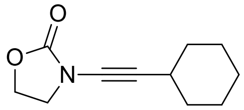
While sulfonyl amides were further investigated by former colleague Nicolas Martin, attention was given in preparing different oxazolidinone derivatised ynamides. As shown in Table 4, 2-oxazolidinone proved to be a suitable commercial available substrate for ynamide preparation

(Entries 1-11). Although ynamide **241** was prepared in good yield and partly characterised, the high instability of the substrate led to its rapid degradation.

Table 4. Ynamide synthesis from 2-oxazolidinone and terminal alkyne.



Entry	*Alkyne*	*Product (Yield)*[a],[b]	*Ynamide*
1	3-acetoxyprop-1-yne	**239** (92%)	
2	cyclopropilacetylene	**240** (59%)	
3	**226**	**241** (70%)[c]	
4	1-hexyne	**242** (43%)	
5	3-methoxyprop-1-yne	**243** (88%)	
6	6-chlorohex-1-yne	**244** (68%)	
7	2-(pent-4-yn-1- yl)- isoindoline-1,3-dione	**245** (74%)	

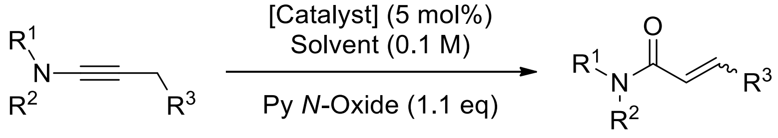
8	**227**	**246** (79%)	
9	**228**	**247** (53%)	
10	**230**	**248** (64%)	
11	ethynylcyclohexane	**249** (54%)	

[a] All reactions were executed on a 2 mmol scale related to the alkyne employing amine (10 mmol), $CuCl_2$ (5 mol%), Na_2CO_3 (4 mmol), $CuCl_2$ (0.4 mmol) and toluene (0.1 M). [b] Yields refer to isolated product after column chromatography. [c]Product quickly degradated after purification.

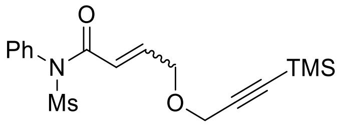
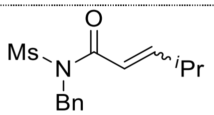
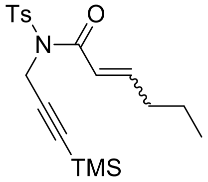
2.6 Synthesis of α,β-unsaturated imides and vinylogous carbimates

The optimised conditions for the formation of α,β-unsaturated imides (System A and B) were applied to the selection of previously prepared ynamides. Good to excellent yields were achieved when sulfonylynamide substrates **235**, **236** and **238** were employed and in all cases the *E*-isomer was formed as the major product (Table 5). Interestingly, excellent chemoselectivity and tolerance were displayed when a pendant silyl-acetylene framework was present in the starting material (Entries 1 and 3).

Table 5. Synthesis of α,β-unsaturated imides.

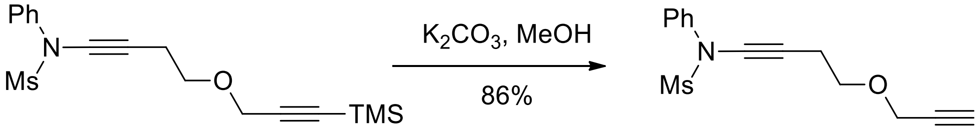


System A: Au-**III**, $ClCH_2CH_2Cl$, 70 °C
System B: $AuBr_3$, THF, RT

Entry	*Ynamide*	*System*	*Product*	*Yield (E:Z ratio)*[a],[b]	*α,β-unsaturated imide*
1	**235**	A B	**250**	66% (2.8:1) 68% (3.2:1)	
2	**236**	A B	**251**	87% (3.6:1)[c] 85% (4.5:1)[c]	
3	**238**	A B	**252**	34% (4.1:1)[c] 31% (6.1:1)[c]	

[a]Reactions were executed on ynamide (0.3 mmol), catalyst (5 mmol%), piridinium *N*-oxide (1.5 eq), solvent (0.1 M). [b]Yields refer to isolated product after column chromatography. *E*:*Z ratio* calculated on isolated products. Reactions were monitored by TLC. [c]Mixture of inseperable isomers.

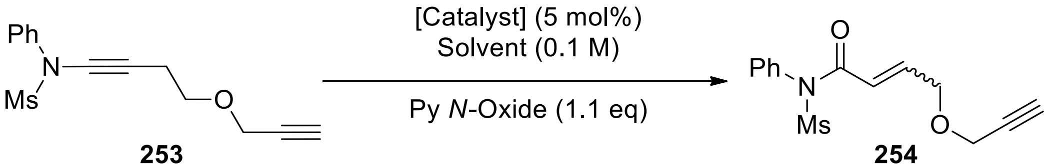
To further stress the chemoselectivity aspect, ynamide **235** was desilylated to reveal its terminal alkyne position (Scheme 56).



235 **253**

Scheme 56. Desilylation of ynamide 253.

Surprisingly, the reaction onto ynamide **253** took place under both sets of conditions, but a lower product yield was observed compared to the one obtained employing the progenitor ynamide (Scheme 57). Formation of unknown by-products and unreacted starting material accounted the for poor transformation efficiency.



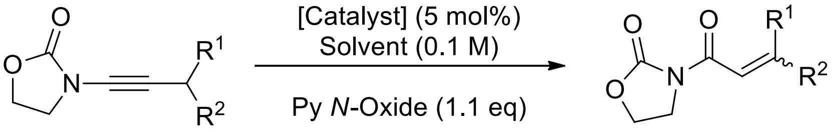
253 **254**

System A: Au-**III**, $ClCH_2CH_2Cl$, 70 °C 53%, (*E*:*Z*) 7.5:1
System B: $AuBr_3$, THF, RT 40%, (*E*:*Z*) 2.8:1

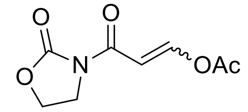
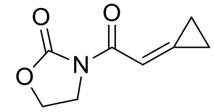
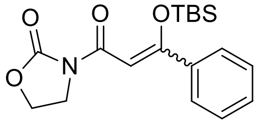
Scheme 57. Gold-catalysed oxidation for ynamide 112.

When ynamide **90**, **91** and **92** were tested, degradation of the starting material was instead observed (Entries 1-3, Table 6). In the case of ynamide **90**, competing reactions could be envisaged as a result of an intramolecular nucleophilic attack by the acyl framework, resulting in complex mixture of unknown products (Entry 1). Also in the case of the cyclopropene substituent the reaction proved unsuccessful, leading to the formation of a mixture of unknown by-product (Entry 2). It was hyphotised that competing processes, as reported in the literature,[71] could explain the poor reaction outcome. As mentioned in the previous section, silyl ynamide **92** displayed high instability and degradation occurred while setting up the reaction. This issue could not be overcome even when such ynamide was employed immediately after purification.

Table 6. Synthesis of α,β-unsaturated imides.



System A: Au-**III**, $ClCH_2CH_2Cl$, 70 °C
System B: $AuBr_3$, THF, RT

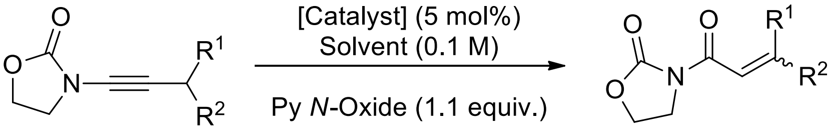
Entry	*Ynamide*	*System*	*Product*	*Yield (E:Z ratio)*[a]	*α,β-unsaturated imide*
1	**239**	A	**255** (-)[b]	-	
		B		-	
2	**240**	A	**256** (-)[b]	-	
		B		-	
3	**241**	A	**257** (-)[b]	-	
		B		-	

[a]Reactions were executed on ynamide (0.3 mmol), catalyst (5 mmol%), piridinium *N*-oxide (1.5 eq), solvent (0.1 M). [b]Complex mixture of product. [c]Ynamide degradation while setting the reaction.

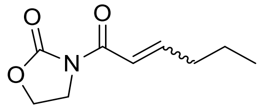
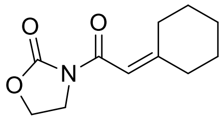
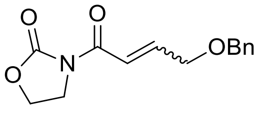
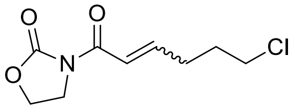
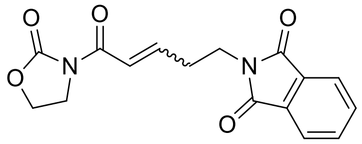
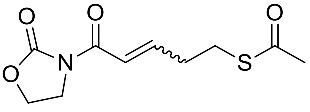
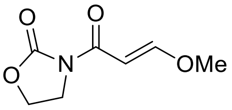
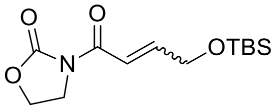
The reaction showed tolerance towards a wide variety of functionalities (Table 7): alkyl (Entries 1 and 2), benzoyl (Entry 3), alkyl chloride (Entry 4), phthalimido (Entry 5) and thioester groups (Entry 6) did not affect the oxidation of the ynamido fragment and survived the reaction conditions. Synthetically valuable vinylogous carbimate **264** can also be prepared by employing substrates with an alkoxy group in the propargylic position (Entry 7). However, for unknown reasons, catalytic System B seemed to be ineffective when such propargylic oxygen atoms bore a methyl group and led to complex mixtures of unknown products (Entry 7b). The same issue was shown also in the case of silyl ether **247** (Entry 8b)**.** Notably, System A proved instead to be efficient in both of these two cases and high yields of the desired products were achieved (Entries 7a and 8a). Moreover, in the case of ynamide **243** (Entry 7), only *E* isomer was observed.

Overall, System A was generally superior in comparison to the conditions of System B with respect to product yield, although the latter usually provided greater *E*:*Z* selectivity.

Table 7. Synthesis of α,β-unsaturated imides.

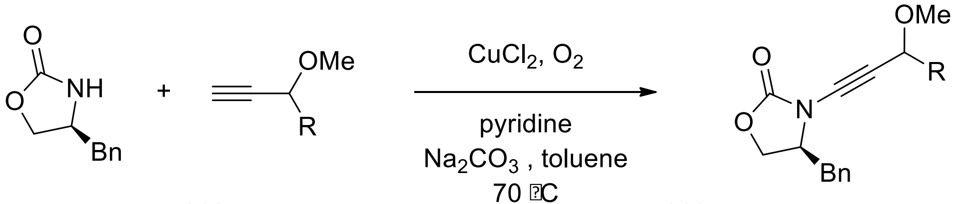


System A: Au-**III**, $ClCH_2CH_2Cl$, 70 °C
System B: $AuBr_3$, THF, RT

Entry	*Ynamide*	*System*	*Product*	*Yield (E:Z ratio)*[a],[b]	*α,β-unsaturated imide*
1	**242**	A B	**258**	63% (3.2:1) 70% (5.0:1)	
2	**249**	A B	**259**	81% 81%	
3	**246**	A B	**260**	73% (2.8:1) 68% (3.1:1)	
4	**244**	A B	**261**	63% (2.9:1) 65% (4.0:1)	
5	**245**	A B	**262**	68% (5.6:1) 75% (6.7:1)	
6	**248**	A B	**263**	75% (2.6:1) 71% (7.7:1)	
7	**243**	A B	**264**	89%[c] -[d]	
8	**247**	A B	**265**	75% (6.7:1) -[d]	

[a]Reactions were executed on ynamide (0.3 mmol), catalyst (5 mmol%), piridinium *N*-oxide (1.5 eq), solvent (0.1 M). [b]Yields refer to isolated product after column chromatography. *E*:*Z ratio* calculated on isolated products. Reactions were monitored by TLC. [c]Only *E*-isomer was observed. [d]Degradation occurred during the reaction.

2-Oxazolidinone derived ynamides proved to be suitable substrates for the gold-catalysed oxidation under investigation and it was intriguing to employ commercially available chiral homologous (*S*)-4-benzyloxazolidin-2-one **267** to prepare optically active vinylogous carbimates. The products of catalysis of these substrates would further enhance their utility as building blocks for organic synthesis providing a source of chirality for stereoselective transformation. Chiral ynamides **269** and **270** were prepared (Scheme 58) and tested under both sets of reaction conditions System A and B.



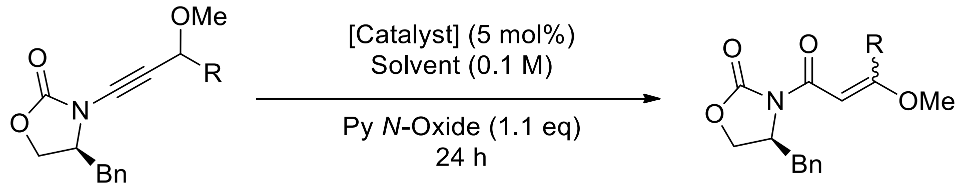
267

268, R=H
218, R=cyclohexyl

269, R=H, 59%
270, R=cyclohexyl, 56%, *dr* 1:1

Scheme 58. Preparation of chiral ynamides.

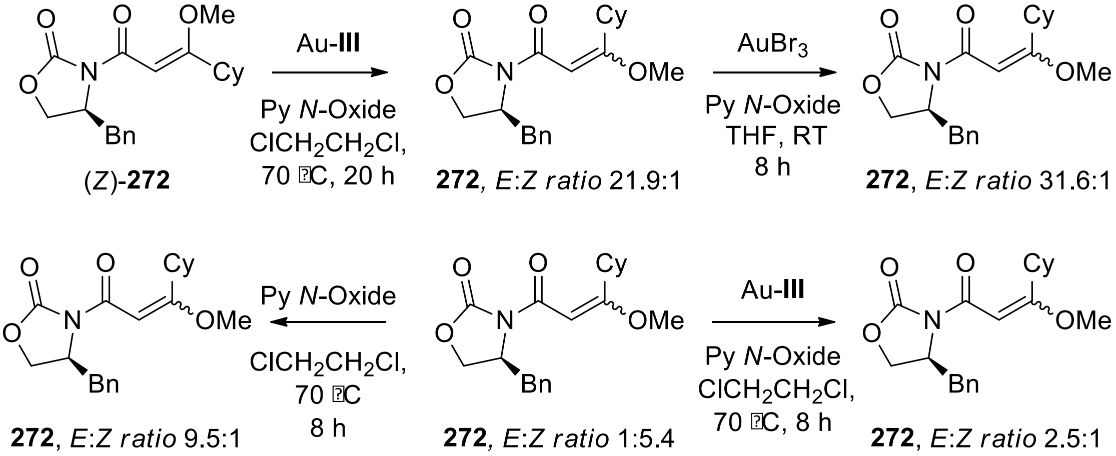
While simple *N*-alkynyl oxazolidinone **243** led to the formation of only the *E*-isomer (Table 7, Entry 7), some *Z*-isomer formation was observed when the chiral analogue **26** was employed (Scheme 59). Unexpectedly, the use of a 1:1 mixture of epimers **270** showed significantly divergent outcomes depending on the catalysis system utilised in terms of *E*:*Z ratio*. Whilst the use of moderately elevated temperature of System A consistently led to the formation of the *E*-isomer **272** as the major product, the milder reaction conditions of System B yielded predominantly the *Z*-isomer **272**. Modulation of the stereochemical outcome by varying the conditions employed could represent a significant utility for the use of these transformations in organic synthesis.[72]



269, R=H	System A: Au-**III**, $ClCH_2CH_2Cl$, 70 ⍰C System B: $AuBr_3$, THF, RT	**271**, 81%, (*E*:*Z)* 1.5:1 81%, (*E*:*Z)* 1.9:1
270, R=Cy	System A: Au-**III**, $ClCH_2CH_2Cl$, 70 ⍰C System B: $AuBr_3$, THF, RT	**272**, 79%, (*E*:*Z)* 10.9:1 88%, (*E*:*Z)* 1:6.1

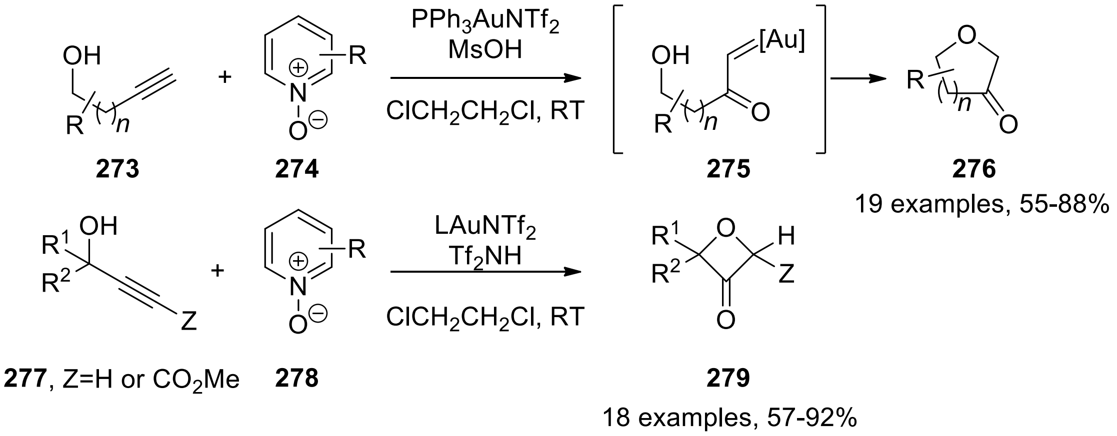
Scheme 59.

A series of tests were conducted in order to understand the unusual behaviour of ynamide **270** under the chosen reaction conditions (Scheme 60). When the major product of System B *Z*-**272** was submitted to the catalysis conditions of System A, an isomerisation to an *E*:*Z ratio* in favour of the *E*-isomer was observed. The olefin geometry conversion was irreversible as shown by the resubmission to the System B reaction conditions (Scheme 60, Eq. 1). Subsequently, an enriched *Z*-isomer mixture of **272** was submitted to both System A and B reaction conditions and the isomerisation conversion switched the *E*:*Z ratio* to a higher *E*-isomer predominance. This effect was more evident with the moderately elevated temperature of the former (System A) (Scheme 60, Eq. 2). It was therefore concluded that *Z*-**272** represents the kinetic product whilst *E*-**272** the thermodynamic one. It was also proven that the isomerisation occurred even in the absence of the catalyst.



Scheme 60. Isomerisation tests on 272.

During the course of our studies, Zhang and co-workers published a similar transformation, where substituted pyridine *N*-oxides were involved in a regio-specific oxidation on terminal alkynes catalysed by gold.[73] The new transformation allowed the synthesis of different dihydrofuran-3-ones **276** and oxetan-3-ones **279** (Scheme 61). Similar to the reaction described on ynamides, the alkyne-gold complex undergoes site-specific nucleophilic addition from the *N*-oxide, and subsequent *O-N* bond cleavage gives a gold carbenoid species of type **275**. Intramolecular trapping by the pendant hydroxyl group of the gold intermediate and subsequent protodeauration led to the products with good to excellent yield.



273 **274** **275** **276**

19 examples, 55-88%

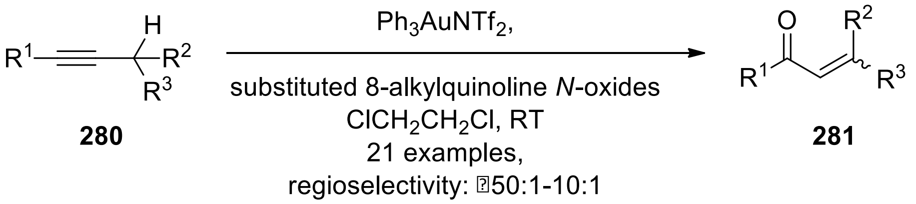
277, Z=H or CO$_2$Me **278** **279**

18 examples, 57-92%

Scheme 61.

A broad range of functionalities were found to be compatible with the reaction conditions (*e.g.* azides, aromatic systems, halogenated alkyl chains). Notably, this method required the synthesis of non-commercially available oxidant and the use of an acid in the reaction mixture which could represent an issue for acid-sensitive substrates. It was suggested that the pyridine formed as by-product would deactivate the gold catalyst and low yields were reported when the acid was absent. On the contrary, such unwelcome effect related to the pyridine formation was not observed in the gold catalysed oxidation of ynamides reported herein.

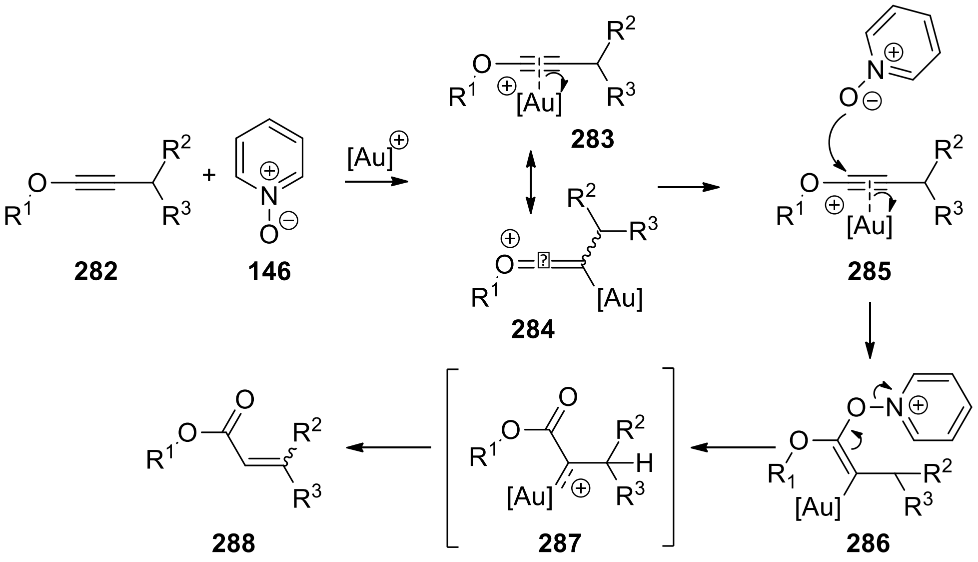
After publication of our results, Zhang and co-workers showed that internal alkynes can undergo regioselective gold catalysed oxidative reactions with pyridine *N*-oxide (Scheme 62).[74] This latter transformation overcomes the problem of restricted employment of terminal or electron-withdrawing group substituted alkynes. Although good to excellent regioselectivity was achieved, often the regiocontrolling factor relied on a different steric hindrance or different capability to favour the proto-elimination between the acetylene substituents. Conversely, the predictable and reliable regioselectivity offered by the nitrogen substitution in ynamides allowed us to regioselectively obtain the oxidation on the carbon next to the nitrogen.



Scheme 62.

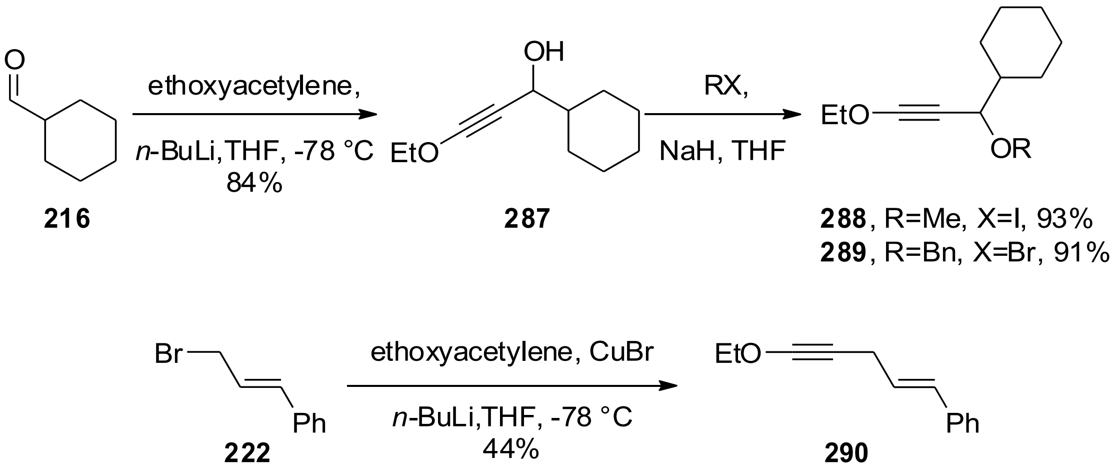
2.6 Synthesis of vinylogous carbonates and $\alpha,\beta,\gamma,\delta$-unsaturated carboxylic esters

Subsequently, the generality of this approach was explored to see if unsaturated carboxylic acid derivatives other than imides could be prepared through the same strategy. In this regard, oxygen substituted alkynes possess some almost superimposable electronic characteristics with ynamides and therefore it was possible to envisage a similar behaviour when engaged in oxidation reactions with pyridinium *N*-oxide catalysed by a gold catalyst (Scheme 63). Although oxygen substituted alkynes have been far less extensively investigated due to the relatively few methods currently available for their synthesis,[75,76] it is worthy of mention that they have already be employed in some gold-catalysed reactions.[77]



Scheme 63.

For these reasons, ynol ethers **288**-**290** were prepared. Commercially available ethoxy acetylene was deprotonated with *n*-BuLi in THF and treated with cyclohexyl aldehyde to form propargyl alcohol **287** in good yield. Alkylation and benzylation with the appropriate bromides in the presence of sodium hydride allowed the isolation of the desired ynol ethers **288** and **289**. Propargylic ynol ether **290** was prepared from (*E*)-cinnamyl bromide under copper-promoted coupling conditions. While ynamides are usually bench-stability due to the presence of their electron-withdrawing substituent, ynol ethers are normally unstable and suffer the tendency to undergo hydrolysis or degradation reactions. Therefore, alkoxyl alkynes thus prepared were engaged in catalysis immediately after purification or stored for a short period of time under appropriate conditions (argon atmosphere, low temperature).

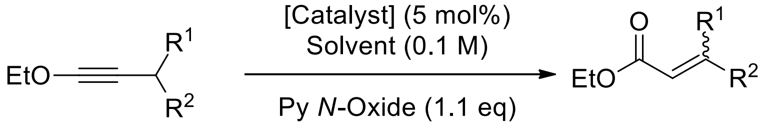


Scheme 64. Preparation of ynol ethers 288, 289 and 290.

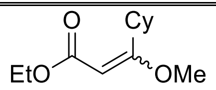
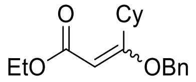
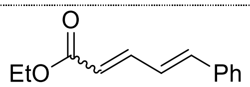
Although ynol ethers are by nature generally more reactive in comparison to ynamides, the same catalytic systems previously optimised for ynamides were employed. Under gold catalysis conditions propargylic ynol ether **288** and **289** successfully underwent the oxidation/1,2-insertion reaction and yielded β-substituted vinylogous carbonates **291** and **292** respectively in good yield (Entries 1 and 2,Table 8).

Extended π-systems can also be prepared by this method as shown in the synthesis of α,β,γ,δ-unsaturated carboxylic ester **293** when 1,4-ynene **290** is oxidised by pyridine *N*-oxide (see table below). In all the cases, catalytic System A afforded the desired product in higher yield while catalytic System B provided a higher *E*:*Z ratio.*

Table 8. Synthesis of α,β-unsaturated carbonates.



System A: Au-**III**, $ClCH_2CH_2Cl$, 70 °C
System B: $AuBr_3$, THF, RT

Entry	*Ynol ether*	*System*	*Product*	*Yield (E:Z ratio)*[a],[b]	*α,β-unsaturated carbonate*
1	**288**	A	**291**	77% (1:0)	
		B		72% (3.9:1)	
2	**289**	A	**292**	89% (2.8:1)[c]	
		B		85% (5.1:1)[c]	
3	**290**	A	**293**	75% (4.3:1)	
		B		88% (6.1:1)	

[a] Reactions were executed on ynamide (0.3 mmol), catalyst (5 mmol%), piridinium *N*-oxide (1.5 eq), solvent (0.1 M). [b]Yields refer to isolated product after column chromatography. *E*:*Z ratio* calculated on isolated products. Reactions were monitored by TLC. [c]Minor product *Z* in a mixture.

2.7 Summary

A new gold catalysed oxidation reaction has been developed employing ynamides and ynol ethers to access a site-specific oxygen transfer process from commercially available pyridine *N*-oxide. This reactivity has been used in the synthesis of a variety of α,β-unsaturated carboxylic acid derivatives such as vinylogous carbonates and carbamates. The mild gold catalysis reaction conditions are tolerant towards a wide range of functional groups including other alkyne moieties. The access to α-oxo gold carbenoid reactivity from ynamides and ynol ethers as direct equivalent to α-oxo diazo compounds has also been shown. Therefore, the gold-catalysed methods described above might lead to further significant developments in organic synthesis when alternative α-oxo carbene reactivity is needed.

Chapter 3: Gold-catalysed synthesis of 2,4,5-trisubstituted oxazoles

3.1 Introduction

The previously reported successful intermolecular transfer reaction of an oxygen atom onto gold activated ynamides and ynol ethers has shown pyridinium *N*-oxides to be an extremely valid oxygen atom delivery system. The organometallic intermediate of this transformation is trapped intramoleculary in the presence of a γ-hydrogen through elimination, leading to the formation of α,β-unsaturated carboxylic acid derivatives (Figure 9, Eq.1). It was also shown that in the absence of hydrogen atoms in the γ-position, a second oxidation step proved to be faster than any of the other intramolecular processes that could have taken place (Figure 9, Eq. 2).

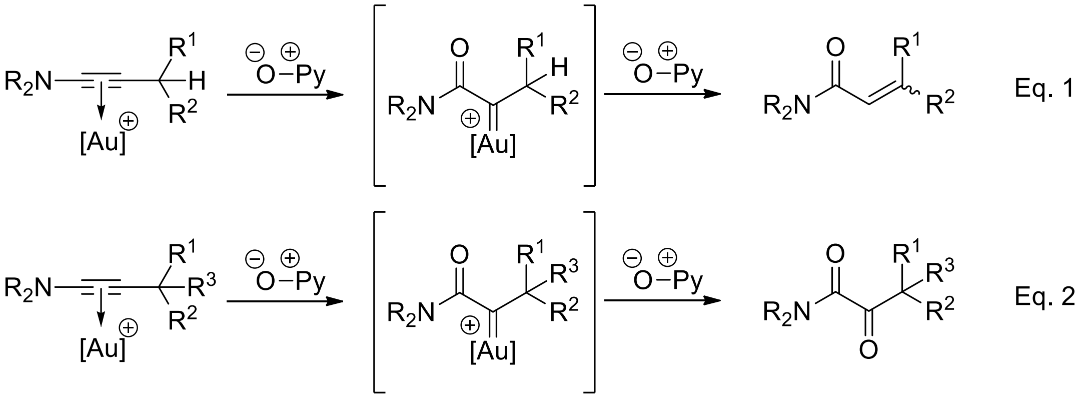


Figure 9. Gold catalysed oxidation of ynamides with pyridine *N*-oxide.

In Chapter 1, it was demonstrated that α-oxo gold carbenoid intermediates can undergo intramolecular nucleophilic attack by a nitrogen, sulfur, carbon or oxygen atom preinstalled in the molecule. In order to divert the reactivity shown in the previous chapter and summarised in the figure above, it was envisaged that while the pyridinium delivering system drives the installation of the nucleophilic heteroatom, it could also introduce a second reactive centre capable of promoting an alternative destiny for the gold carbenoid intermediate (Figure 10). According to this strategy, it should be possible to introduce an additional intramolecular process and, under optimised conditions, the appropriate functionality Z could react with the gold carbenoid intermediate rapidly enough that other possible reactions would be largely suppressed.

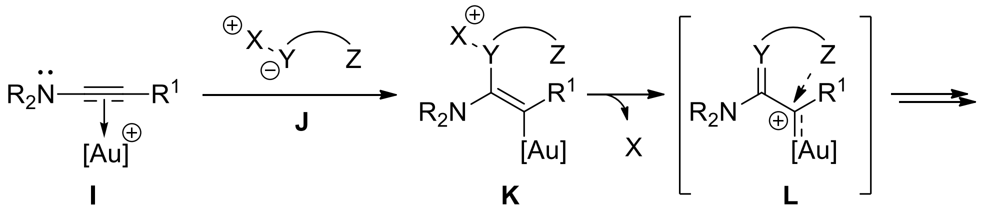


Figure 10.

Maintaining a pyridine system as nucleofuge, *N*-amino pyridonium derivatives of type **J** appeared to be suitable for the concept due to the additional valence allowed by the nitrogen atom (Figure 11). These reagents would allow access to a nitrene transfer rather than oxygen transfer reported in the previous chapter for pyridine *N*-oxides.

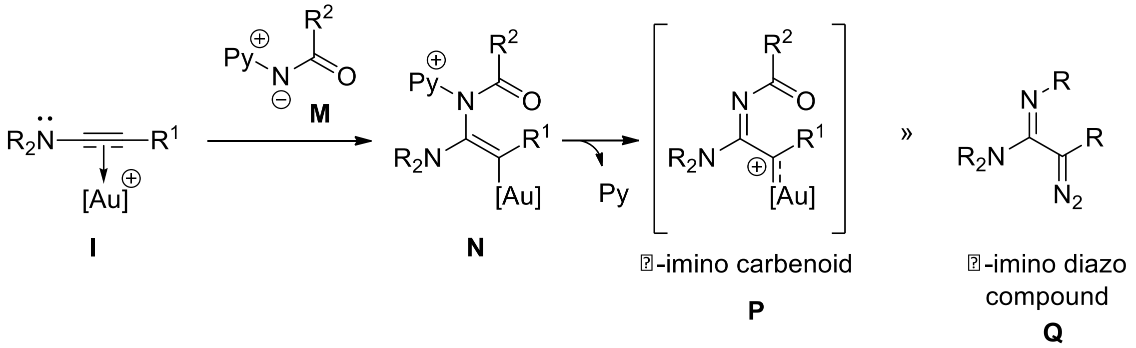
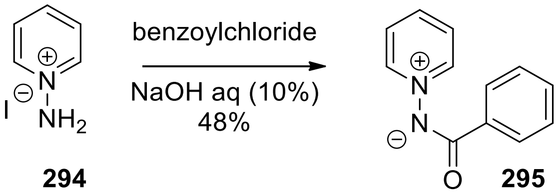


Figure 11.

Nitrene transfer promoted by gold onto alkynes has only been reported intramolecularly by Toste using either a tethered azido alkynes (CHAPTER 1 Scheme 10, Eq. 2,)[26] or a tethered sulfimine alkyne (CHAPTER 1, Scheme 12).[29] Notably, no intermolecular cases have been published and the proposed gold-catalysed nitrene transfer processes would be different from other nitrene transfer modes present in the literature.[78] Such reactivity was of interest considering the possible access to α-imino carbenoid equivalents, which are similarly or more problematic to prepare than their oxygenated homologous.

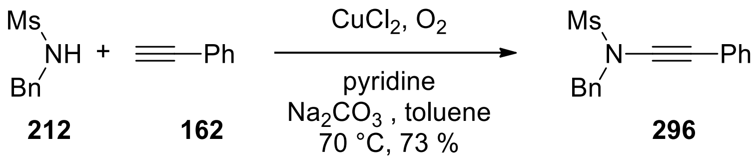
3.2 Preliminary studies

Pyridine *N*-aminides of type **M** were selected as suitable nitrene-delivering oxidants which also bear a second reactive centre represented by the carbonylic oxygen. These robust reagents have been employed as 1,3-*C*,*N* dipoles in cycloadditions that incorporate the pyridine group.[79] Under our catalytic proposal they would instead react as 1,3-*O*,*N*-dipoles. The aminides are readily prepared by acylation of commercially available *N*-amino pyridonium iodide in the presence of a strong base which after acylation promotes the final deprotonation to form the corresponding ylide. Aminide **295** was obtained employing benzoyl chloride in a 10% aqueous solution of sodium hydroxide and was isolated in decent yield as a bench-stable white crystalline solid.



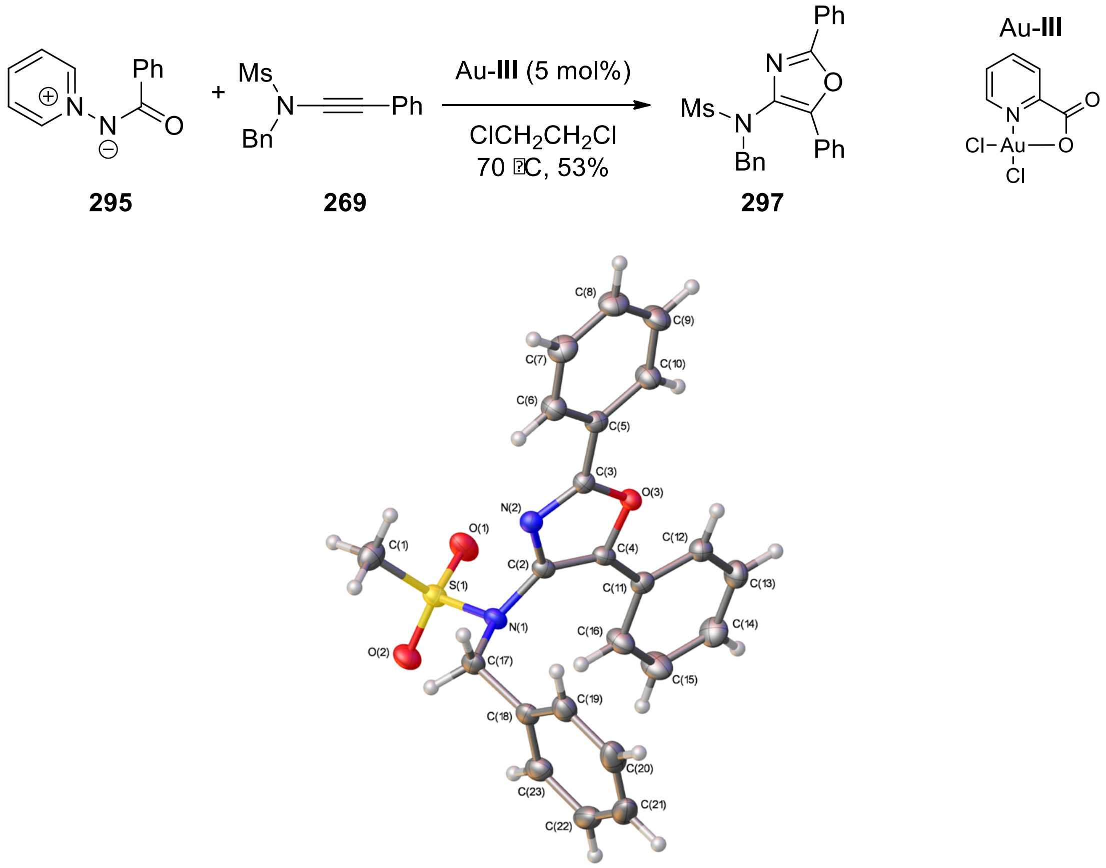
Scheme 65. Preparation of aminide 295.

It was decided to employ nitrogen-substituted alkynes as the acetylenic framework in reaction development in order to ensure a regioselective installation of the nucleophilic heteroatom as previously demonstrated. Previously prepared sulfonyl amide **212** was submitted to a coupling reaction with phenyl acetylene under the optimised Stahl copper-catalysis conditions led to ynamide **296** in 73% yield.



Scheme 66. Preparation of ynamide 296.

The previously optimised catalytic conditions System A, which employ dichloro(pyridine-2-carboxylato)gold(III) precatalyst Au-**III** in $ClCH_2CH_2Cl$ at 70 °C, were chosen as a starting point for the study. Under these unoptimised conditions, the reaction between *N*-ylide **295** and ynamide **296** afforded oxazole **297** as a single regioisomeric product in 53% yield along with recovered unreacted starting material (Scheme 67). The structure of the 4-amino oxazole product was confirmed by single-crystal X-ray diffraction analysis.[80]



Scheme 67. Gold-catalysed formation of oxazole 297.

From the outcome of this preliminary reactivity study, it was concluded that under gold catalysis conditions an aminide can act as an equivalent to an acylnitrene unit, which is regioselectively installed onto π-activated ynamides by the pyridinium carrier.

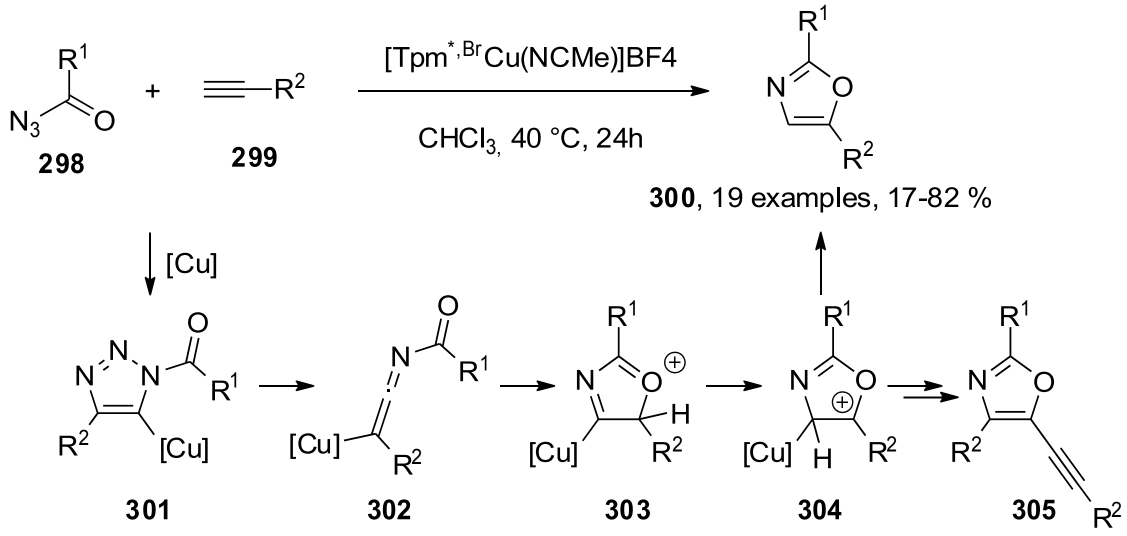
The acyl carbonyl group installed during the ‘nitrene transfer’ promoted the quench of the gold intermediate, in place of other intra- and inter-molecular processes which is consistent with the proposal made at the beginning of this chapter.

Overall, this novel transformation for the oxazole core formation can be seen as a formal [3+2]-cycloaddition between a carbon-carbon triple bond and an acyl-nitrene 1,3-*N*,*O* dipole.

Although [3+2] cycloadditions across π-systems have been widely exploited for the preparation of heterocyclic five membered rings, examples where this strategy has been applied to the synthesis of 1,3-oxazoles are very limited.[81]

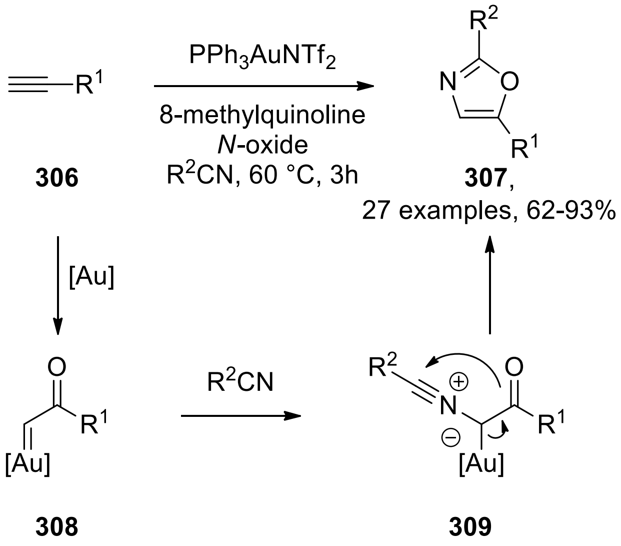
Besides the different manipulations available to functionalise around an intact 1,3-oxazole,[82] classical methods for the *de novo* synthesis of trisubstituted oxazoles usually require multistep reaction processes. Moreover, they often require harsh conditions or highly reactive reagents which can be incompatible with sensitive functional groups.[83] Metal-promoted methodologies (*e.g.* Cu, Ag, and Rh) seem to be more beneficial and can overcome the drawbacks of the classical procedures, although in most cases they display significant substrate-scope limitations and poor overall efficiency. [84]

The synthesis of oxazoles through the cycloaddition of an acylnitrene, obtained from photochemical or thermal decomposition of acyl azides, as a 1,3-*N*,*O*-dipole across an alkyne usually suffer from poor chemoselectivity.[85] Remarkably, it was very recently shown during the course of our studies, 2,5-disubstituted oxazoles have been successfully synthesised through a one-pot regioselective copper (I)-catalysed reaction between acyl azides of type **298** and terminal alkynes **299** (Scheme 68).[86] Rather than the direct formation of an acyl nitrene, the reaction was proposed to proceed through the formation of copper acetylide followed by a [3+2]-cycloaddition with the azide derivatives leading to triazolyl copper-intermediate **301**. This further evolved by extrusion of dinitrogen to copper ketenimid-intermediate **302** which, through subsequent cyclisation and rearrangement, yielded disubstituted oxazole **300** (Scheme 68). The formation of byproduct **305**, incorporating an additional alkyne unit was proposed to derive from a copper-coupling reaction between intermediate **304** and a second copper acetylide unit. Although different acyl azides were explored, only aromatic alkynes were employed while reporting disappointing results were recorded with alkyl alkynes.



Scheme 68.

While this study was in progress, Zhang *et al.* also reported a new synthesis of 2,5-disubstituted oxazoles while working on the formation of α-oxo-gold carbenes from terminal alkynes using *N*-oxides.[87] In their case, the gold carbenoid intermediate derived from the gold-catalysed oxidation reacted intermolecular with different nitriles and underwent a 2+2+1 annulation reaction to yield the 1,3-oxazole of type **307** (Scheme 69). Although this new transformation afforded different oxazoles in good yield under mild conditions, a major limitation of this process is the required use of a large nitrile reagent excess. When the nitrile was not use as the solvent, 3 equivalents were employed giving a reduced yield.



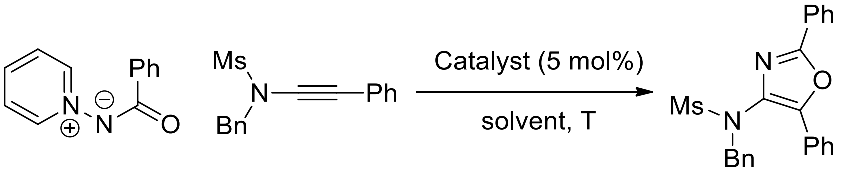
Scheme 69. Intermolecular synthesis of oxazoles *via* gold catalysed alkyne oxidation.

Oxazoles are an important motif found in many natural products, ligand frameworks, materials and biologically active compounds.[88] However, the employment of tri-substituted derivatives in organic synthesis is strongly limited by the lack of mild and widely applicable methods for their preparation. For these reasons, the novel reactivity of the aminide as a potentially controllable *N*-acyl nitrene equivalent to form 2,4,5-trisubstituted oxazoles when reacted with gold activated ynamides were studied in greater detail.

3.3 Optimisation studies

The study of the novel formation of tri-substituted oxazoles from formal acyl-nitrene transfer onto ynamides was started by submitting ynamide **269** to different sets of gold catalysis conditions (Table 9). The analysis of the ^{1}H NMR of the crude reaction mixture containing a known amount of 1,2,4,5-tetramethylbenzene as an internal standard was carried in order to establish the performance of the reaction. No reaction occurred in the absence of a gold-complex (Entry 2) or on its replacement with a Brønsted acid (Entry 3). The use of 1.5 equivalents of aminide **295** improved the efficiency of the transformation (Entry 9) but a further increase of the quantity used was not beneficial (Entry 11). MsOH and *p*-TsOH•H_2O were also employed as acidic additives to exclude the possibility that by-product pyridine formed during the reaction acts to lower the catalyst efficiency as shown in Zhang's work.[73] Their use not only did not provide any improvement in the formation of the 4-amino oxazole, but also led to degradation products in the crude reaction mixture (Entries 12 and 13). The use of toluene as high boiling solvent allowed the reaction to be conducted at 90 °C which resulted in complete consumption of the starting material only when Au-**III** was used (Entry 16). The use of an electrophilic iodide source in replace of the gold catalyst (Entry 17), promoted the degradation of the starting material with no product detected. Silver, copper and ruthenium species also proved to be ineffective at promoting the reaction and no product formation was observed (Entries 18-20).

Table 9. Optimised reaction conditions survey.



295 **296** **297**

Entry	*Catalyst*	*Aminide **295** (eq)*	*Solvent (Temperature, °C)*	***296** (%)[b]*	***297** Yield[a],[b]*
1	Au-**III**	1.1	$ClCH_2CH_2Cl$ (70)	37%	53%[c]
2	-	1.1	$ClCH_2CH_2Cl$ (70)	95%	-[d]
3	*p*-TsOH•H_2O	1.1	$ClCH_2CH_2Cl$ (70)	100%	-[d]
4	$AuPPh_3/AgSbF_6$	1.1	$ClCH_2CH_2Cl$ (70)	47%	53%
5	$AuPPh_3$/AgOTf	1.1	$ClCH_2CH_2Cl$ (70)	27%	70%
6	$AuBr_3$	1.1	$ClCH_2CH_2Cl$ (70)	34%	59%
7	$NaAuCl_4$	1.1	$ClCH_2CH_2Cl$ (70)	57%	40%
8	$AuPPh_3$/AgOTs	1.1	$ClCH_2CH_2Cl$ (70)	72%	25%
9	Au-**III**	1.5	$ClCH_2CH_2Cl$ (70)	6%	79%
10	$AuPPh_3$/AgOTf	1.5	CH_2Cl_2 (40)	37%	55%
11	Au-**III**	2	$ClCH_2CH_2Cl$ (70)	22%	65%
12	Au-**III**	1.5[f]	$ClCH_2CH_2Cl$ (70)	-[d]	-[e]
13	Au-**III**	1.5[g]	$ClCH_2CH_2Cl$ (70)	-[d]	33%[e]
14	$AuPPh_3$/AgOTf	1.5	$ClCH_2CH_2Cl$ (70)	21%	70%
15	PPh_3AuNTf_2	1.5	toluene (90)	-[d]	37%
16	Au-**III**	1.5	toluene (90)	-[d]	95%
17	NIS	1.5	toluene (90)	-[d]	-[e]
18	AgOTf	1.5	toluene (90)	100%	-[d]
19	$Rh_2(OAc)_4$[h]	1.5	toluene (90)	96%	-[d]
20	$Cu(MeCN)_4BF_4$	1.5	toluene (90)	98%	-[d]

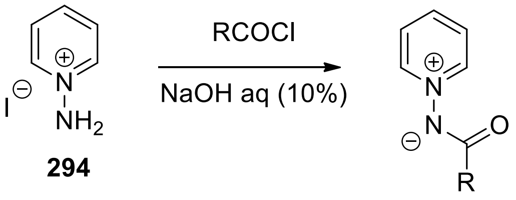
[a]Reactions were performed employing 0.1 mmol of ynamide 296, aminide 295 (as shown), Catalyst (5 mol%), Solvent (0.1 M), 24 h. [b]1H-NMR yields were calculated against a known amount of internal standard.[c]Isolated yield. [d]Not observed in the crude mixture. [e]Complex mixture of unknown products or degradation. [f]MsOH, 1.1 eq. [g]*p*-TsOH•H_2O, 1.1 eq. [h]2.5 mol%.

It was shown by Lidia Dumitrescu of the Davies' group that thermal reactions carried in *o*-xylene at 140 °C in absence of the catalyst saw only trace amounts of oxazole product formed.[89]

The optimised conditions were identified as the air-stable dichloro(pyridine-2-carboxylato)gold (III) Au-**III** precatalyst in toluene at 90 °C with 1.5 equivalents of aminide relative to the ynamide (Table 9, Entry 9).

3.4 Starting material preparation

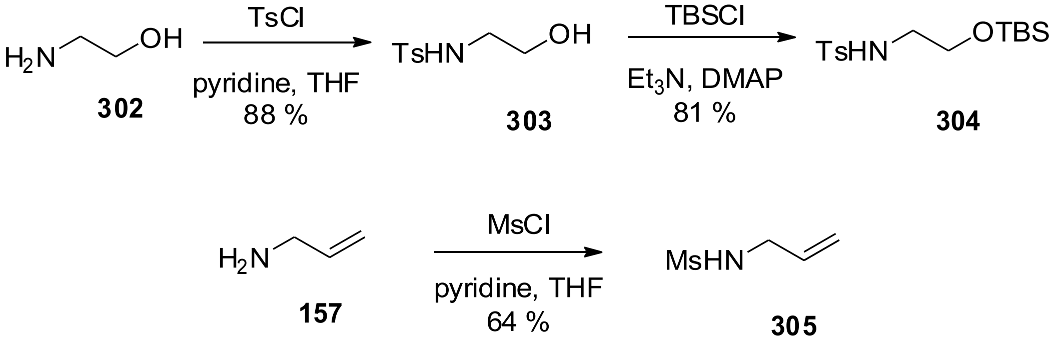
In order to explore the scope of this novel intermolecular gold catalysed nitrene transfer reaction, a series of different aminide **298-301** were prepared in a straightforward manner by the slow addition of the appropriate acyl chloride to a 10% sodium hydroxide water solution of commercially available *N*-amino pyridonium iodide **294** at 0 °C (Scheme 70). The products were then simply extracted from the aqueous solution with CH_2Cl_2 and purified by recrystallisation (Scheme 70).



298, R= *o*-BrC_6H_4, 53%
299, R= 2-furyl, 36%
300, R= methoxy, 84%
301, R= *p*-$NO_2C_6H_4$, 15%

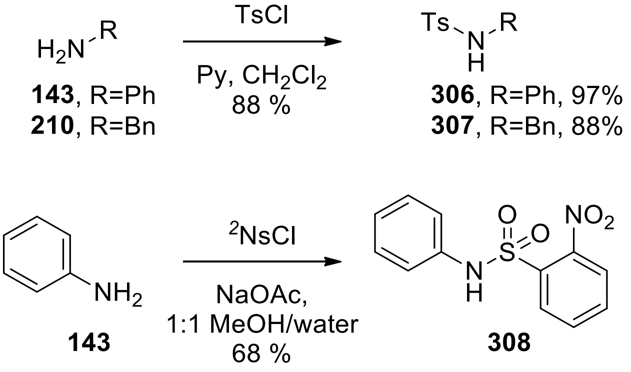
Scheme 70. Preparation of aminides 298-301.

In addition to the amides prepared in the previous chapter, *N*-tosyl amide **304** was prepared following the standard tosylation protocol for the synthesis of sulfonamides (Scheme 71). The hydroxyl group was then protected by treatment with TBSCl in the presence of triethyamine and DMAP affording the desired silylether amide **304** in good yield. Tosyl sulfonyl amide **305** was prepared in good yield following the previous by reported methodology.



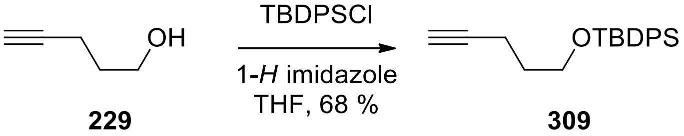
Scheme 71. Sulfonamides 304 and 305 preparation.

Tosyl amides **306** and **307** were also prepared and isolated in excellent yield. It was also decided to explore amides bearing an *o*-nitrophenylsulfonyl protecting group as it is more labile than other sulfonyl groups employed in this study and might therefore be useful for further functionalisations at the 4-amino position.[90]



Scheme 72.

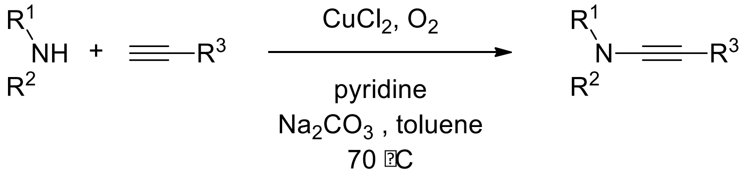
Terminal alkyne **229** was also prepared by treatment of 4-pentynyl-1-ol with TBDPSCl with 1-*H* imidazole in THF (Scheme 73).

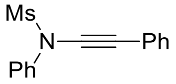
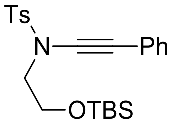
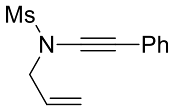
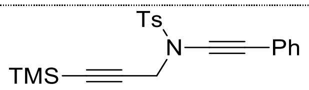
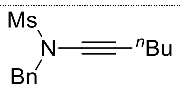
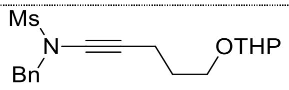
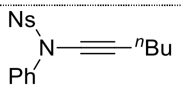
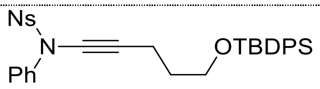
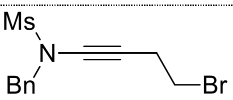
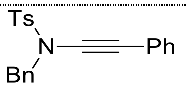
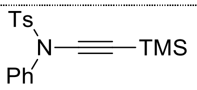


Scheme 73. Preparation of alkyne 161.

Along with silylether **309**, a series of commercially available alkynes were utilised in the coupling with different amides to synthesise various ynamides under Stahl's copper catalysis methodology shown in the previous chapter. Moderate to good yields were obtained in all cases and the pool of functional groups borne by the ynamide framework allowed a wide exploration of reaction tolerance for alkyl, alkyl bromide, alkyl, silyl ether, aryl, ketal and allyl functional groups (Table 10).

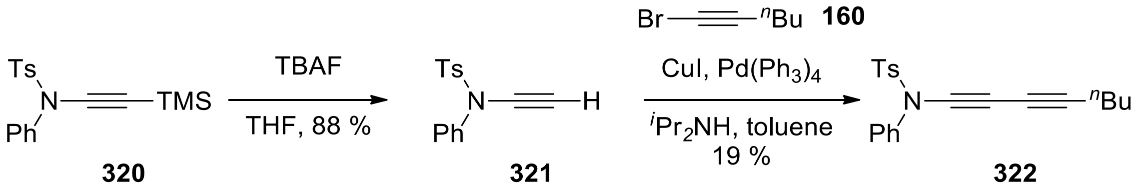
Table 10. Preparation of ynamides



Entry	*Amide*	*Alkyne*	*Product (Yield)*[a],[b]	*Ynamide*
1	**221**	phenylacetylene	**310** (74%)	
2	**304**	phenylacetylene	**311** (58%)	
3	**305**	phenylacetylene	**312** (69%)	
4	**215**	phenylacetylene	**313** (51%)	
5	**221**	1-hexyne	**314** (78%)	
6	**221**	2-(pent-4-yn-1-yloxy)tetrahydro-2H-pyran	**315** (50%)	
7	**308**	1-hexyne	**316** (94%)	
8	**308**	**309**	**317** (74%)	
9	**212**	4-bromo-but-1-yne	**318** (69%)	
10	**306**	phenylacetylene	**319** (44%)	
11	**307**	trimethylsilylacetylene	**320** (82%)	

[a]All reactions were executed on a 2 mmol scale in relation to the alkyne, employing amine (10 mmol), Na_2CO_3 (4 mmol), $CuCl_2$ (0.4 mmol) and toluene (20 mL, 0.1 M). [b]Isolated yield.

Desilylation of silyl ynamide **320** by the action of TBAF in THF led to the formation of ynamide **321** in 88% of yield (Scheme 74). This compound showed thermal instability and so heating processes had to be avoided in its manipulation. Copper coupling with brominated alkyne **160** at room temperature allowed the isolation of dialkyne **322** in modest yield.



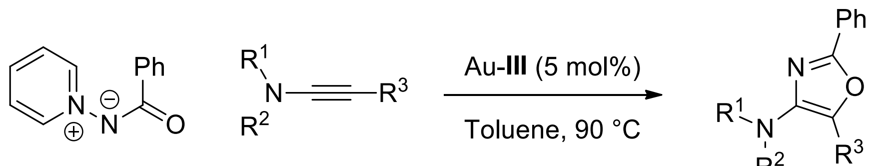
Scheme 74. Preparation of dialkyne 322.

3.5 Synthesis of 4-amino-2,5-disubstituted oxazoles

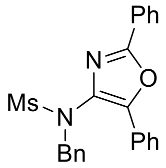
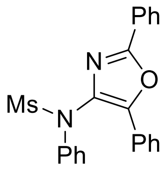
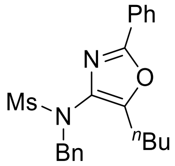
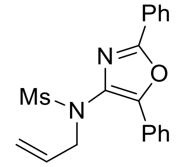
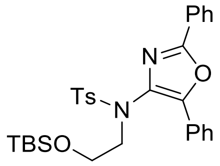
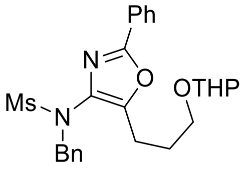
The optimised conditions for the formation of trisubstituted oxazoles were applied to the selection of ynamides previously prepared using aminide **295**.

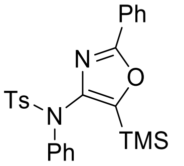
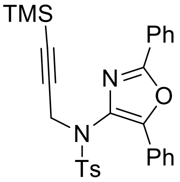
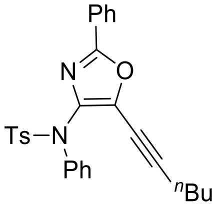
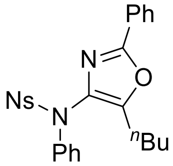
In almost all the tested substrates, when the desired oxazole product was formed, good to almost quantitative yield and no side products in the reaction mixture were observed (Table 11, Entries 1-6 and 8-10). Benzyl, aryl, and alkyl substituents at the nitrogen atom were all well-tolerated Entries 1-3). Remarkably, *N*-allyl ynamide **312** afforded the product in good yield (Entry 4) despite its susceptibility toward Claisen rearrangement.[91] Acid labile silyl ether **311** and tetrahydropyranyl ketal **315** survived the reaction conditions and led to the product in very good yield (Entries 5 and 6). However, in the case of ynamide **320** bearing a labile silyl group at the terminal position of the triple bond, a mixture of unknown products was obtained (Entry 7). *N*-propargyl ynamide **313** showed great chemoselectivity for the oxazole formation distinguishing between the two different acetylenic units present in the substrate (Entry 8). Moreover, when conjugated *N*-substituted dialkyne **322** was employed, remarkable chemo- and regioselectivity was observed and the additional triple bond did not interfere with the outcome of the transformation (Entry 9). Notably, *o*-nitrobenzenesulfonyl ynamide **316** was tested and the geometrically favourable intramolecular redox reaction between the nitro group and the gold-activated π-system did not take place.[92] Instead, under the optimized gold catalysis conditions, the intermolecular nitrene-oxidation afforded desired oxazole **331** in 74% yield (Entry 10).

Table 11. Synthesis of 2-phenyl-4,5-disubstituted oxazoles.



295

Entry	*Ynamide*	*Yield* (time)[a],[b]	*Product*	*Oxazole*
1	**296**	93% (24 h)	**297**	
2	**310**	96% (4 h)	**323**	
3	**314**	82% (2 h)	**324**	
4	**312**	68% (4 h)	**325**	
5	**311**	81% (12 h)	**326**	
6	**315**	91% (1.5 h)	**327**	

7	**320**	-[c](24 h)	**328**	
8	**313**	80% (24 h)	**329**	
9	**322**	83% (18 h)	**330**	
10	**316**	74% (1 h)	**331**	

[a]All reactions were executed on ynamide (0.1 mmol), 295 (0.15 mmol) and Au-III (5 mol%) in toluene (1 mL, 0.1 M) at 90 °C. Reactions were monitored by TLC. [b]Isolated yield. [c]Mixture of unknown products.

As shown, alkyl substituents on the *C*-terminus of the ynamide were well tolerated in this reaction (Table 11, Entries 6-8). This was unexpected, when compared against the results shown in chapter 2 where the incipient gold carbenoid formed by atom transfer underwent facile 1,2-insertion to form an alkene. These results led to re-evaluation of the mechanistic analysis where different pathways can be proposed to explain the reaction outcome. Nucleophilic attack by the ylide occurred on the *sp*-carbon adjacent to the nitrogen of the ynamide to give gold vinyl species **A**. This is consistent with the conceived proposal and the regioselectivity always observed for gold-activated ynamide nucleophile addition (Scheme 69).[89-93] Evolution of **A** by pyridine release prior to cyclisation could be followed by 4π-electrocyclisation of the extensively delocalized gold-stabilized carbocation **B'** to access **C'** or an attack of the acyl oxygen onto the electrophilic gold carbenoid carbon centre in **B** to the cyclised intermediate **C** (Figure 12).[94] However, a more concerted cyclisation alongside fission of the pyridine-*N* bond might also, through transition state **D**, provide gold species **C**. In the absence of competing 1,2-insertion when possible (*vide supra*), which would be associated with the formation of a distinct metal carbenoid, this 'concerted' cyclisation mechanism was considered more likely than the alternatives. Final elimination of the gold-catalyst from **C** yields the oxazole product and closes the catalytic cycle. A mechanism involving the formation of a gold nitrene and an initial chelotropic reaction with the ynamide was excluded since formation of regioisomer 4-amino oxazoles was not observed.[95] Moreover, the absence of product formation in the optimisation study when silver, copper and rhodium catalysts were employed corroborates such assumption.

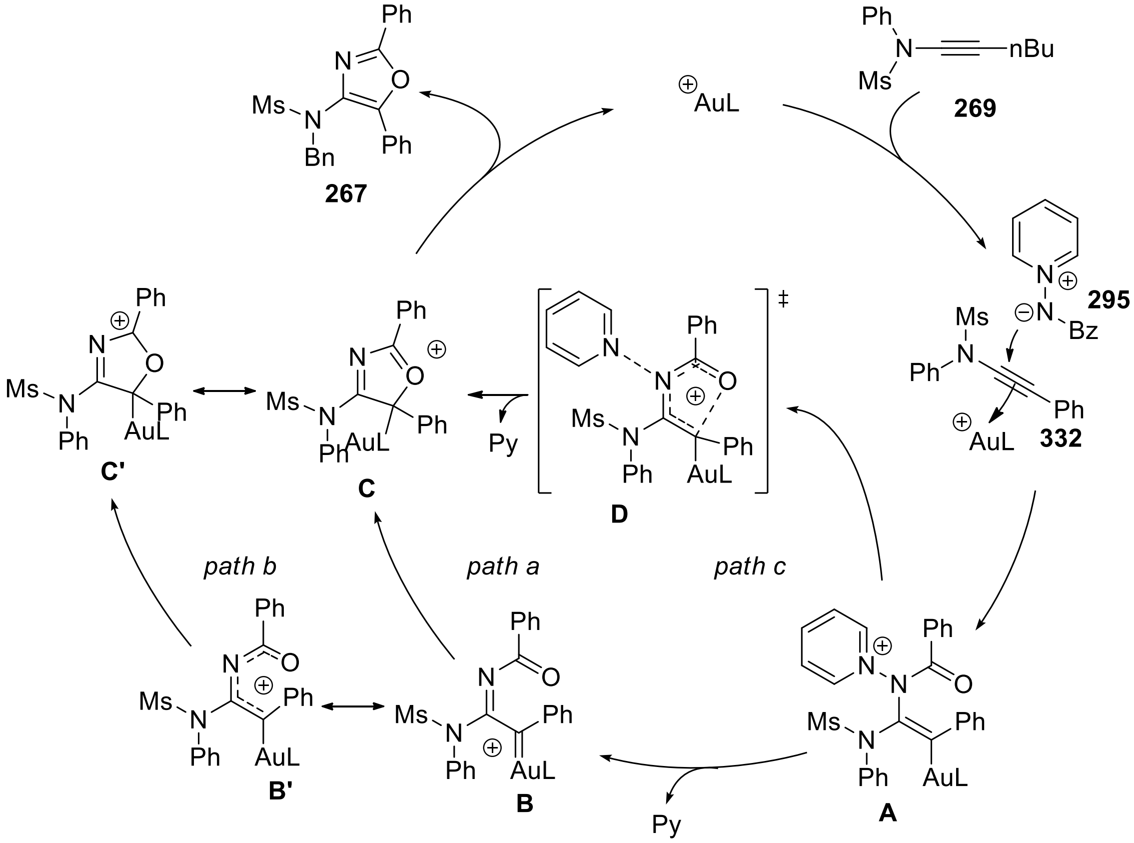
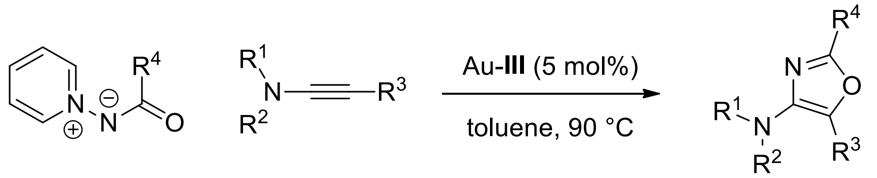


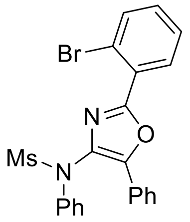
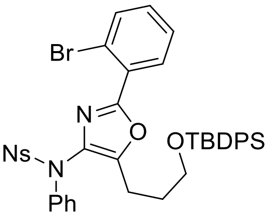
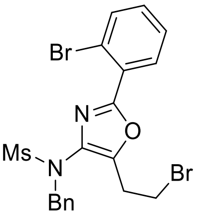
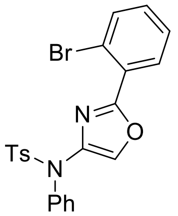
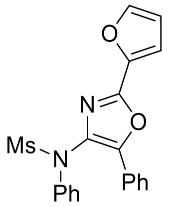
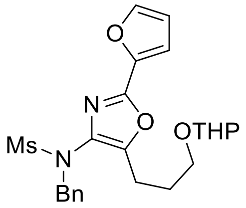
Figure 12. Proposed mechanisms for the formation of 1,3-oxazoles under gold catalysis conditions.

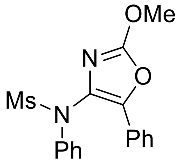
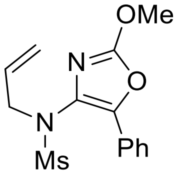
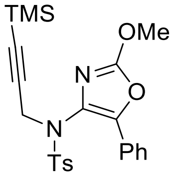
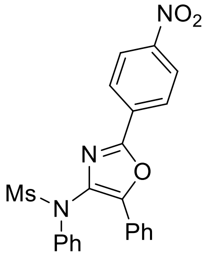
To further explore the reaction scope regarding variation at the 2-position on the oxazole core, different previously prepared aminides **298**-**301** were employed (Table 12). Remarkably, in almost all the cases the transformation led regioselectively and chemioselectively to the formation of the expected trisubstituted oxazoles (Entries 1-3 and 5-9). The acyl *o*-

bromobenzene group substitution on the aminide was tolerated well by the reaction conditions and allowed access to 2-(*o*-bromobenzene) oxazoles in high yield (Entries 1-3). Aryl bromide could be useful if further funtionalisations at the ring system are desired. Disappointingly, ynamide **321** did not provide the corresponding oxazole under optimised reaction conditions (Entry 4). The starting material thermal instability is thought to be accountable of the transformation inefficiency. Heteroaromatic substitution, as in the case of furan aminide **299** was also explored and behaved consistently in regard to other aminides (Entries 5 and 6). Notable, methoxy aminide **300** was also exploited and efficiently allowed access to 2-methoxy-4-amino-5-substituted oxazoles **310**-**313** in near quantitative yield (Entries 7-9). This latter pyridinium *N*-ylide proved to be more reactive in comparison to the other systems used, leading to a faster and higher yield in the reaction. It could be suggested that the cyclisation step, as seen in the proposed mechanism, is assisted by the heteroatom substituent although a smaller steric hindrance of the methoxy group might also provide some beneficial influence. With the use of an electron-withdrawing *p*-nitrobenzene substitution as in the case of substituted aminide **301**, formation of the desired product was not observed (Entry 10). Effect of nitro group on the ylide negative charge decreases the nucleophilic character of the nitrogen atom; this is essential to initiate the nitrogen attack onto the activated *C*-*C* triple bond.

Table 12. Synthesis of 2,4,5-trisubstituted oxazoles.

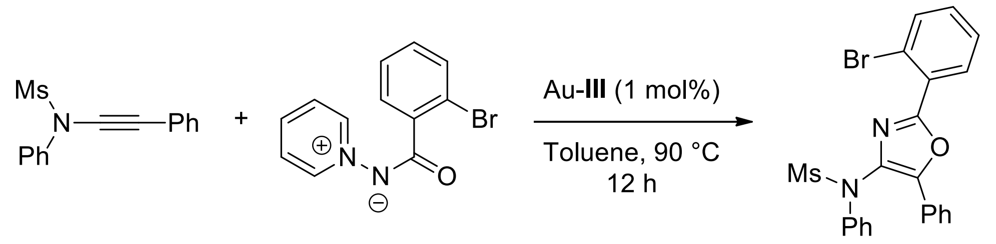


Entry	*Aminide*	*Ynamide*	*Yield* (time)*[a],[b]*	*Product*	*Oxazole*
1	***298***	***310***	90% (3 h)	**333**	
2	***298***	***317***	77% (1 h)	**334**	
3	**298**	**318**	63% (24 h)	**335**	
4	**298**	**321**	-[c] (24 h)	**336**	
5	**299**	**310**	87% (4 h)	**337**	
6	**299**	**315**	97% (1 h)	**338**	

7	**300**	**310**	98% (0.5 h)	**339**	
8	**300**	**312**	87% (0.5 h)	**340**	
9	**300**	**313**	93% (5 min)	**341**	
10	**301**	**311**	-[d] (24 h)	**342**	

[a]Reactions were executed on ynamide (0.1 mmol), aminide (0.15 mmol) and Au-III (5 mol%) in toluene (1 mL, 0.1 M) at 90 °C. Reactions were monitored by TLC. [b]Yields refer to isolated product after column chromatography. [c]Degradation. [d]Unreacted starting material.

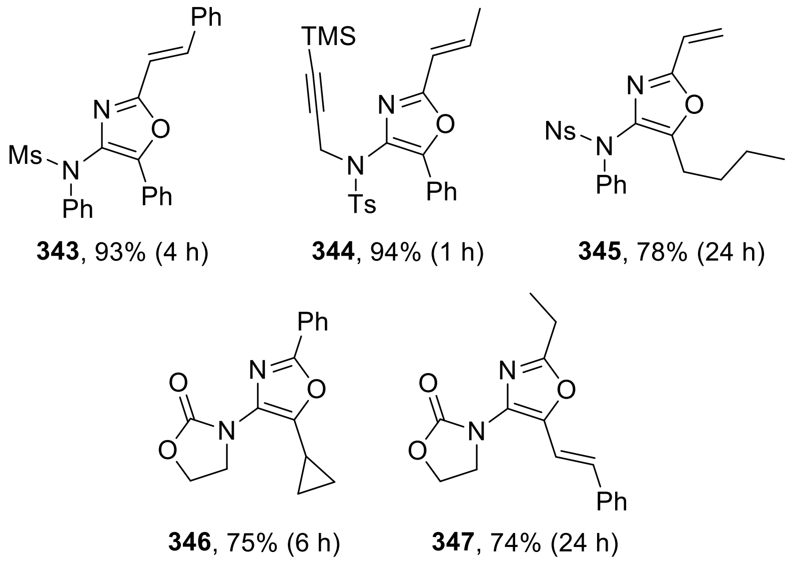
To test the reaction efficiency on a large scale and with a lower catalyst loading, 3.56 mmol of ynamide **310** and 1.5 equivalent of aminide ylide **310** were reacted with only 1 mol% of gold catalyst Au-**III** (in comparison to the 5 mol% previously employed). Remarkably, purification of product by simple filtration through silica followed by recrystallisation from CH_2Cl_2/hexane led to isolated oxazole **333** in high yield (Scheme 75) showing the robust nature of the protocol.



310 3.56 mmol (0.966 g)
310 5.34 mmol (1.476 g)
333 crop 1: 81.4%, crop 2.1: 7.5%
Total: 1.481 g, yield 88.9%

Scheme 75. Large scale test for the preparation of 333.

As demonstrated by Lidia Dumitrescu, a former colleague in the Davies's group, the developed reaction also proved to be efficient for the preparation of 1,3-oxazoles bearing alkynyl, vinyl, crotonyl groups (Scheme 76). Notably, cyclopropyl substitution was also tolerated by the oxazole formation reaction, in contrast with what was observed in the gold-promoted oxygen transfer process onto ynamides reported in the previous chapter.

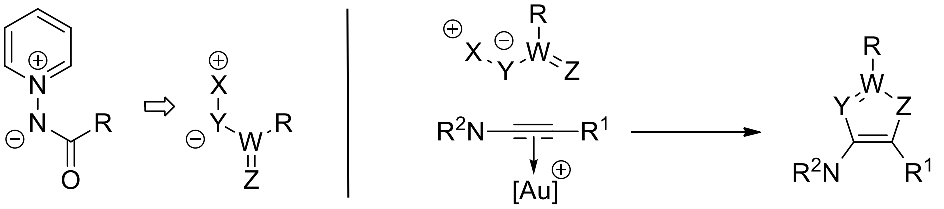


343, 93% (4 h)
344, 94% (1 h)
345, 78% (24 h)
346, 75% (6 h)
347, 74% (24 h)

Scheme 76. Additional oxazoles synthesised.

3.6 Preliminary studies on the synthesis of highly functionalised amino-substituted thiazoles and furans from ynamides

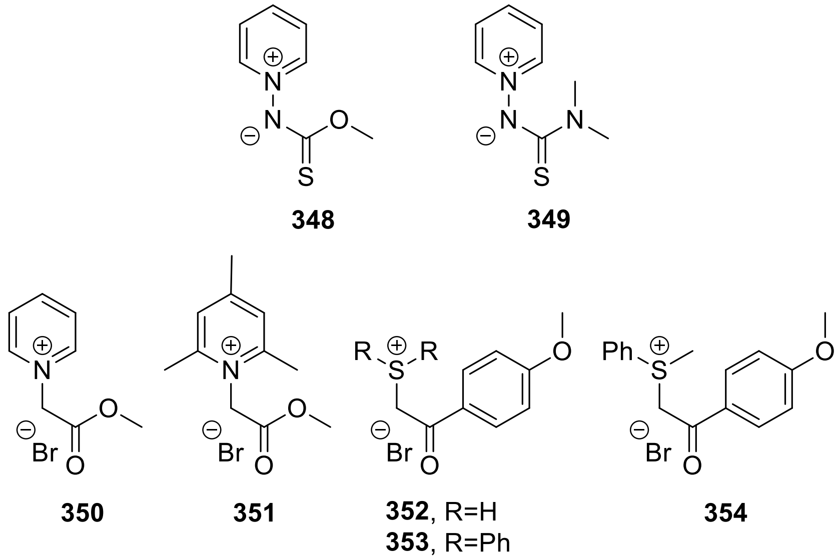
In order to explore the potential of the approach presented in the previous sections for the preparation of heteroaromatic systems in more depth, different *X*-*Y* ylides of type **B** were designed in order to mimic the reactivity of 1,3-*O*,*N* dipoles observed for aminides (Figure 13).



R **S**

Figure 13. General concept for [3+2] cyclisation of 1,3-*Y*-*Z* dipole onto ynamides catalysed by gold complexes.

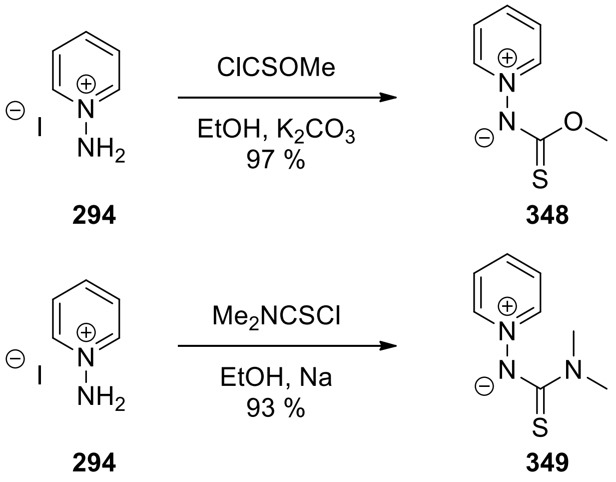
The new *Y*-*Z* dipole should, under appropriate catalysis condition, lead to the formal [3+2] cycloaddition product of type **S** and allow access to different amino-5-membered aromatic derivatives such as aminothiazoles (with ylide **348** and **349**) and furans (with ylide **350**-**354**) (Scheme 77).



Scheme 77. Designed ylides to be used in test gold catalysis reaction with ynamides.

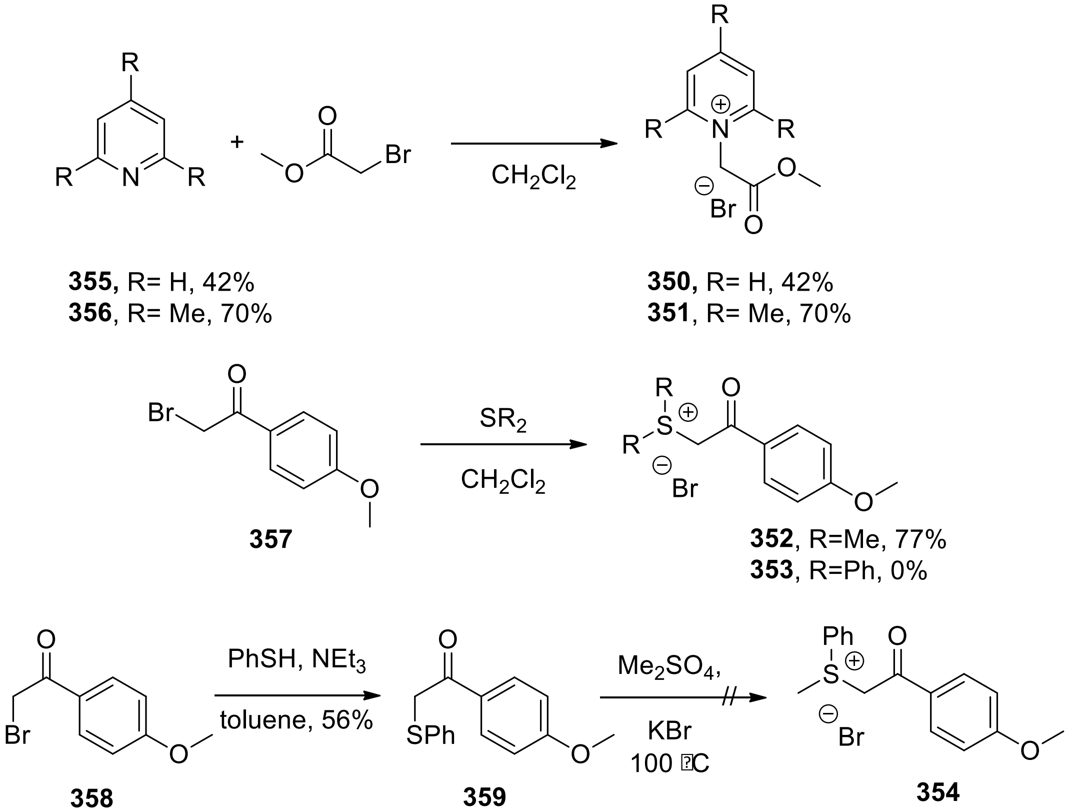
3.6.1 Preparation of ylides

To prepare the required ylides, methylthionochloroformate was freshly prepared and reacted with *N*-amino pyridinium iodide in the presence of potassium carbonate in THF to afford thiourea ylide derivative **348** in 97% yield. Thiourea ylide **349** was prepared employing dimethylthiocarbonyl chloride in a freshly made solution of sodium ethoxide (Scheme 78).



Scheme 78. Preparation of ylides 33, 34 and 35.

Ylide precursors **350** and **351** were prepared by a straightforward substitution reaction between methyl bromoacetate and the corresponding pyridine in CH_2Cl_2 at room temperature. Both ammonium salts were isolated by filtration of the crude mixture in moderate yields (Scheme 79). Pyridinium acetate salts where at least one of the two pyridine *ortho* positions are unsubstituted have already been reported to behave as C_{α}-C^{o} dipoles in a [3+2]-cycloaddition with alkynes to synthesise various nitrogen-containing heterocycles.[96] For this reason, it was reasoned that an *o,o'*-disubstituted derivative also needed to be tested. The same protocol was applied for the preparation of sulfonium salt **352**, starting from bromoacetophenone derivatives **357** and dimethylsulfide in good yield (Scheme 79). Disappointingly, attempts for the preparation of diphenyl sulfur ylide precursor **353** under the same reaction conditions were unsuccessful. In the effort to prepare ylide precursor **354**, thiophenyl acetophenone **359** was prepared by substitution with thiophenol on the bromo ester **358** in the presence of triethylamine. Unfortunately, attempts to obtain the methylated sulfonium salt derivative **354** were unsuccessful.



355, R= H, 42%
356, R= Me, 70%

350, R= H, 42%
351, R= Me, 70%

357

352, R=Me, 77%
353, R=Ph, 0%

358

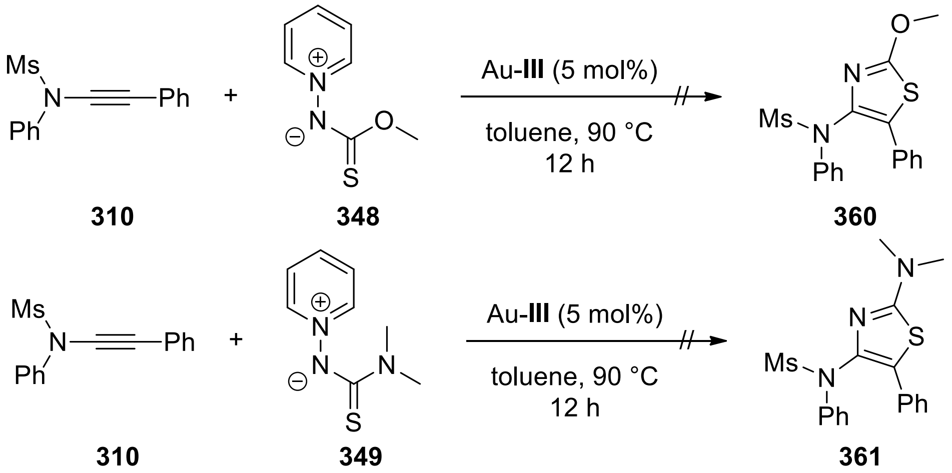
359

354

Scheme 79. Preparation of ylide precursors 352-354.

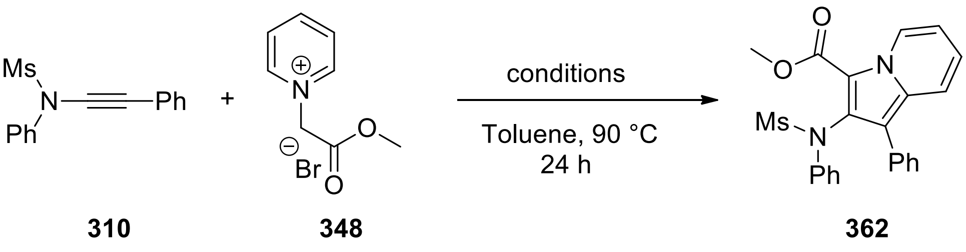
3.6.2 Attempted catalysis to prepare thiazoles

Ynamide **310** was chosen as test substrate for the evaluation of the amino pyridinium ylides **348** and **349**. It was thought that an isosteric relationship between oxygen and sulfur would allow access to thiazoles in a similar fashion to the above reported synthesis of oxazoles. Disappointingly, under the optimised condition for oxazoles, no formation of the desired thiazole was observed with full starting material recovery (Scheme 80).



Scheme 80. Attempts of thiazole formation with ynamides under gold catalysis.

To explore the possibility of using ylides as *C-O* dipoles in gold-catalysis, a series of test reactions were carried out employing ynamide **310**. In the case of pyridinium derivatives **348**, potassium carbonate and sodium hydride were employed to promote the deprotonation and the consequent ylide formation *in situ.* Under gold catalysis conditions, the formation of amino indolizine of type **362** was observed leading to the conclusion that the ylide produced during the reaction behaved as a 1,3-*C,C* dipoles (Scheme 81). This reactivity pathway is consistent to similar reactions observed between pyridinium acetyl ylides and alkynes.

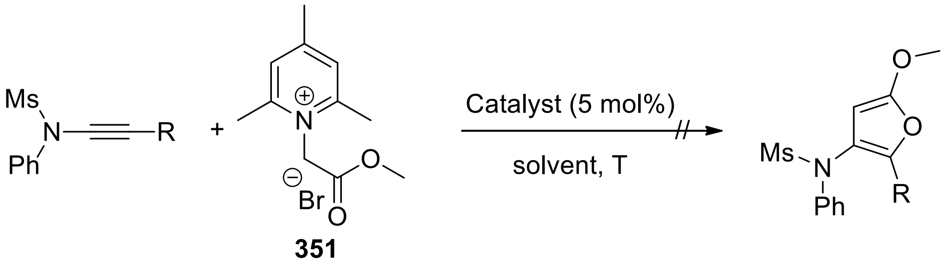


conditions: Au-**III** (5 mol%), NaH (1.6 eq), 45 %
Au-**III** (5 mol%), K_2CO_3 (1.6 eq), 39 %
Au-**III** (5 mol%), 0 %

Scheme 81.

In order to avoid reaction at the pyridine ring, ylide precursor **351** was then assessed. The substitution at both *ortho* positions of the pyridine should prevent the formation of undesired indolizine products. Unfortunately, under the preliminary gold catalysis test conditions, only unreacted starting material was observed in the crude mixture after 24 h (Table 13).

Table 13.



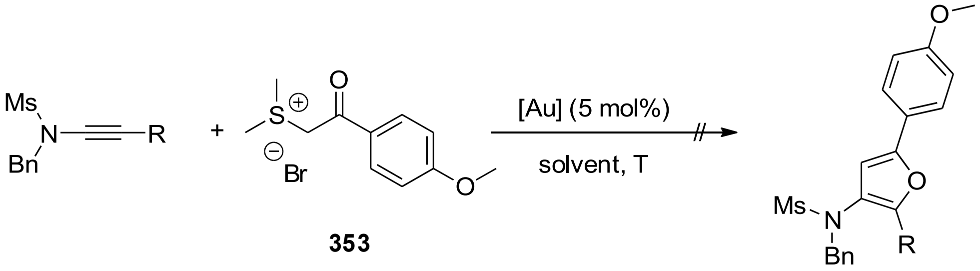
Entry	*Catalyst*	*R*	*Conditions*	*Solvent* (temperature)	*Yield*[a],[b]
1	Au-**III**	Ph (**296**) ^{n}Bu (**314**)	NaH (1.6 eq)	toluene (90 °C)	-[b] -[b]
2	PPh_3AuNTf_2	Ph (**296**) ^{n}Bu (**314**)	K_2CO_3 (1.6 eq)	CH_2Cl_2 (RT)	-[b] -[b]
3	Me_2SAuCl	Ph (**296**) ^{n}Bu (**314**)	K_2CO_3 (1.6 eq)	$ClCH_2CH_2Cl$ (RT)	-[b] -[b]

[a]Reactions were performed employing 0.1 mmol of ynamide, pyridine acetate 351 (0.15 mmol), Catalyst (5 mol%), base (as shown), Solvent (0.1 M), 24 h. [b]Unreacted starting material.

The *ortho* substitution on the pyridine could have prevented ylide formation or more likely inhibited nucleophilic attack onto the gold activated ynamide. A similar study was also performed using *S*-ylide precursor **353** but comparably disappointing results were recorded

(Table 14). Under the tested gold catalysis conditions (Table 14, Entries 1-3) only unreacted starting material was recovered.

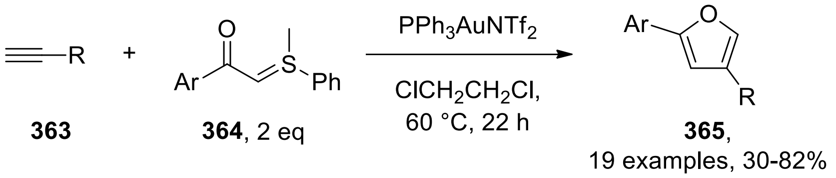
Table 14.



Entry	*Catalyst*	*R*	*Conditions*	*Solvent* (temperature)	*Yield (%)*[a],[b]
1	Au-**III**	Ph (**296**) ^{n}Bu (**314**)	NaH (1.6 eq)	toluene (90 °C)	-[b] -[b]
2	PPh_3AuNTf_2	Ph (**296**) ^{n}Bu (**314**)	K_2CO_3 (1.6 eq)	CH_2Cl_2 (RT)	-[b] -[b]
3	Me_2AuCl	Ph (**296**) ^{n}Bu (**314**)	K_2CO_3 (1.6 eq)	$ClCH_2CH_2Cl$ (RT)	-[b] -[b]

[a]Reactions were performed employing 0.1 mmol of ynamide, 353 (0.15 mmol), Catalyst (5 mol%), base (as shown), Solvent (0.1 M), 24 h. [b]Unreacted starting material.

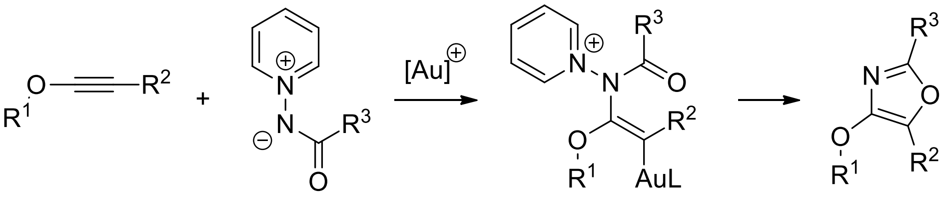
Recently, Skrydstrup *et al.*[97] reported the use of acyl sulfonium ylide **364** as a *C*-*O* dipole to be engaged in a [3+2]-cycloaddition with terminal alkynes to access 2,4-disubstituted furans in an analogous fashion to the oxazole synthesis reported above. According to the study, the substitutions on the sulfur atom proved to be crucial in order to efficiently promote the transformation; in particular, *S*-aryl ylides gave significantly better yields than dimethyl sulfonium derivates. The regioselectivity of the reaction is controlled by the use of terminal alkyne. Although different 2,4-disubstituted furans were obtained in modest to good yield, only aromatic substituents for position 2 and aliphatic substituents for position 4 on the furan ring were explored, representing a major limitation of this methology.



Scheme 82.

3.7 Preliminary studies for the synthesis 4-oxy-2,5-disubstituted oxazoles

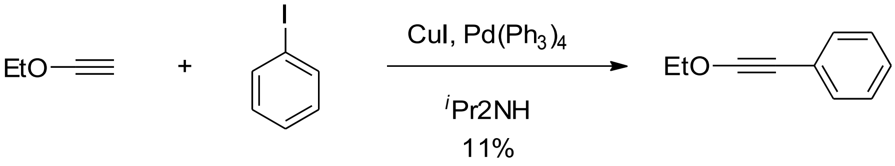
In the previous chapter it was shown that ynol ethers can undergo similar reaction pathways to ynamides due to the structural and electronic similarity between these two heteroatom-substituted alkynes. To further explore the generality of using acyliminopyridinium ylide to obtain 2,4,5-trisubstituted oxazole derivatives, it was decided to employ ynol ethers as the π-system. It was envisaged that under the previously developed protocol, a gold-catalysed acyl-nitrene transfer reaction onto ynol ethers would lead to the formation of 4-oxy-2,5-disubstituted oxazoles (Scheme 83).



366 **367** **368** **369**

Scheme 83.

In this study, the previously prepared ynol ethers **290**, **287**, **288** and commercially available ethoxyacetylene were tested. In addition, ynol ether **371** was prepared by a CuI/$PdCl_2(PPh_3)_2$ coupling procedure with ethoxyacetylene and iodobenzene (Scheme 84).

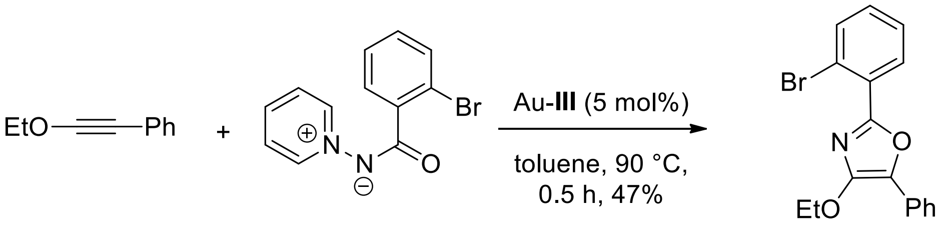


369 **370** **371**

Scheme 84. Preparation of ethoxy phenyl acetylene 371.

Positive results were observed when *O*-substituted alkynes **371** and **298** were tested. In the case of phenylacetylene ether **371**, cycloaddition with aminide **298** afforded 4-ethoxyoxazole

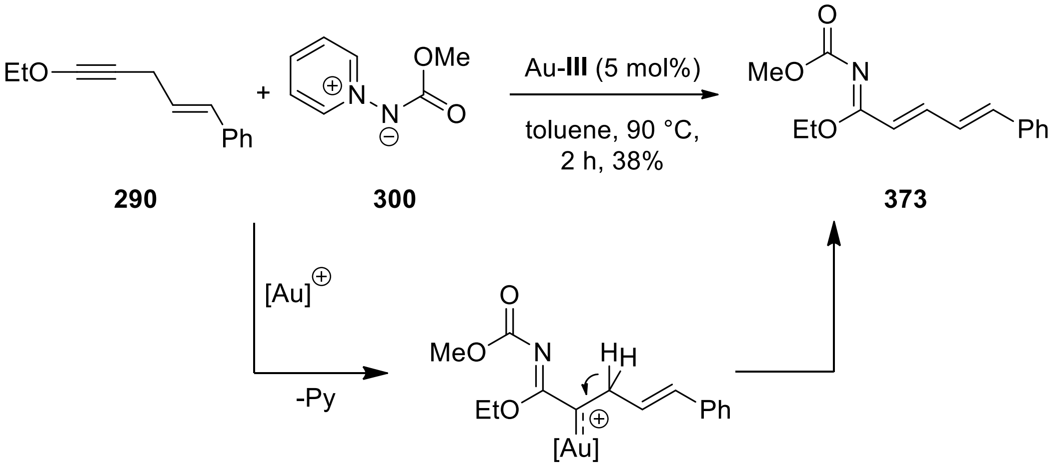
372 in moderate yields proving that the reactivity can be extended beyond ynamides (Scheme 85).



371 **298** **372**

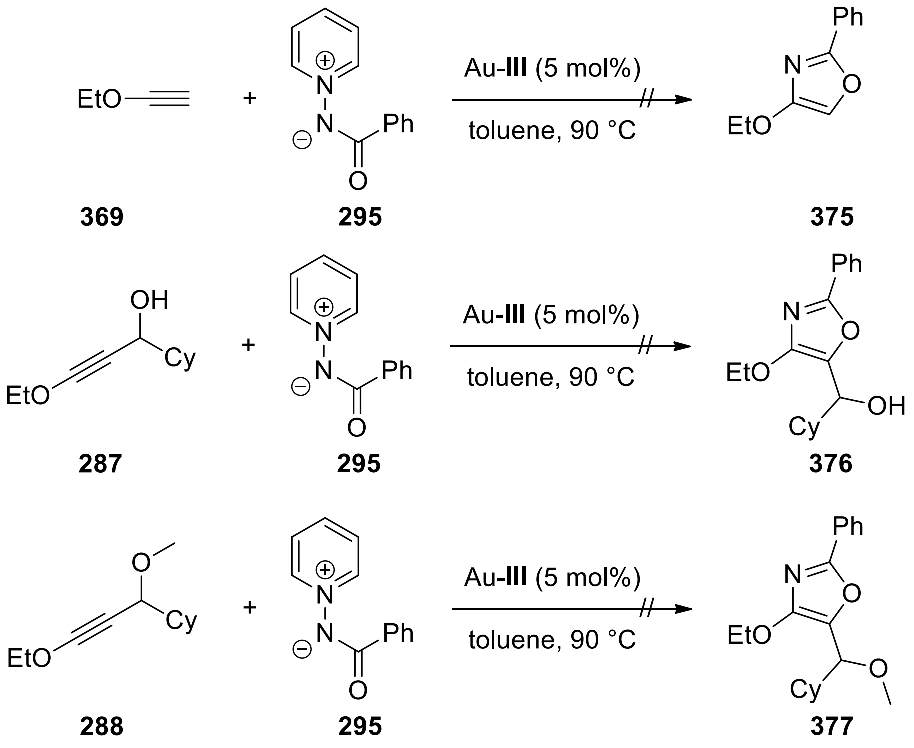
Scheme 85. Gold catalysed acyl-nitrene transfer reaction on ynol ether 371.

Interestingly, skipped enyne **290** reacted with aminide **300** to give the α,β,γ,δ-unsaturated ethylimmidate **373** rather than the expected oxazole product (Scheme 86). Formation of the latter results from a gold-catalysed acyl-nitrene transfer followed by 1,2-insertion, in keeping with the oxidation reactions of alkyl substituted ynamides and ynol ethers presented in the previous chapter. It could be hypothesised that the overall 1,2-hydride shift is rendered favourable over the cyclisation pathway because it leads to a stable extended unsaturated system. Notably, only the *E,E* ethylimmidate stereoisomer **373** was observed.



Scheme 86

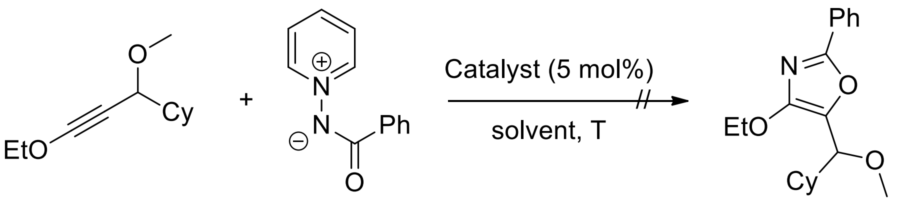
Conversely, under the same conditions employed for the synthesis of **372** and **373**, degradation of the starting material occurred when ethoxyacetylene, **287**, and **288** were tested and no traces of the desired product were recorded by ^{1}H-NMR analysis (Scheme 87).



Scheme 87.

In order to determine whether the moderately high temperature employed in the protocol could be responsible for the failure of the test reactions shown above, it was decided to briefly survey milder conditions (Table 15). Different gold species were employed to promote the transformation at room temperature (Entries 1 and 2) or at 40 °C (Entries 3-5). In all the conditions tested no product formation was detected and only degradation of the propargylic ether was observed. Ynol ethers are known to be highly reactive/unstable and this aspect is thought to be responsible for the lack of success in the acyl-nitrene transfer promoted by gold complexes on such reactive substrates even at milder temperature.

Table 15. Survey of reaction conditions on ynol ether 288.



288 **295** **376**

Entry	*Catalyst*	*Solvent*	*Temperature*	***1*** *Yield%*[a]
1	Au-**III**	$ClCH_2CH_2Cl$	RT	-[b]
2	$AuPPh_3/AgOTf$	$ClCH_2CH_2Cl$	RT	-[b]
3	$AuBr_3$	CH_2Cl_2	40 °C	-[b]
4	PPh_3AgNTf_2	CH_2Cl_2	40 °C	-[b]
5	$AuPPh_3/AgOTs$	CH_2Cl_2	40 °C	-[b]

[a]Reactions were executed on ynol ether 288 (0.1 mmol), aminide 295 (0.15 mmol), Catalyst (as shown, 5 mol%) at solvent (as shown, 1 mL, 0.1 M). Reactions were monitored by TLC. [b]Complex mixture of unknown products or degradation.

3.7 Summary

A new strategy to achieve the [3+2] cycloaddition reaction by addition of a 1,3-*N,O* dipole equivalent across an ynamide triple bond has been achieved. The simultaneous nitrene addition along with the acyl unit installation, that quench the reaction, represents one of the novelty aspects of the reported reaction. Notably, this strategy was unprecedented in the literature for intermolecular gold-catalysed atom-transfer processes.

The optimised catalysis protocol has been used in the synthesis of different trisubstituted oxazoles. The mild gold catalysis reaction conditions proved tolerant towards a wide range of functional groups including other alkyne, alkene and silyl ether moieties.

By this approach, it has also been shown that access to α-imido gold carbenoid intermediate reactivity is possible from ynamides and ynols, which can then be seen as direct equivalents to α-imido diazo compounds. A novel strategy to execute gold-promoted [3+2]-cyclisation was developed and literature examples have already been followed.

Experimental Part

4.1 Instruments

The solvents used were purified using a Pure Solv-MD Solvent Purification System (alumina columns) from Innovative Technology[98] and were transferred under Ar. Asynt DrySyn heating blocks on stirrer hotplates were employed with temperature control via an external probe. Flash chromatography: Fluorochem silica gel 60 (43-63 µm). Thin layer chromatography (TLC): Macherey Nagel silica gel $60F_{254}$ analytical plates (plastic support) which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), phosphomolybdic acid /Δ, and potassium permanganate /Δ. IR: Perkin-Elmer Spectrum 100 FTIR spectrometer, only selected absorbences (ν_{max}) are reported in cm^{-1}. MS and HRMS (EI): VG ProSpec or VG-ZabSpec at 70 eV. High resolution EI spectra were measured using perfluorokerosene (PFK) as an internal calibrant. MS and HRMS (ES): Micromass LCT using a methanol mobile phase. HRMS was obtained using a lock-mass to adjust the calibrated mass scale. MS data are reported as *m/z* (relative intensity). Commercially available compounds were purchased from Aldrich, Fluka, Acros, Strem, Alfa Aesar and used without further purification. NMR: Spectra were recorded on Bruker AVIII300 (^1H = 300 MHz, ^{13}C = 75.5 MHz), Bruker AVIII400 (^1H = 400 MHz, ^{13}C = 101 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 ($CDCl_3$: δ_C = 77.0 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm). Coupling constants (*J*) are reported in Hz. 1D ^{13}C NMR spectra were recorded using the JMOD or PENDANT pulse sequences from the Bruker standard pulse program library. JMOD were combined with DEPT 135 to assign quaternary carbons. Melting points were recorded using open glass capillaries on a Stuart Scientific apparatus and are uncorrected.

4.2 Reactions

Reactions were followed by thin layer chromatography (TLC) using Macherey Nagel silica gel 60F254 analytical plates (plastic support) which were developed using standard visualising agents: UV fluorescence (254 and 366 nm), and potassium permanganate/Δ. Purification by flash chromatography was performed using Fluorochem silica gel 60 (0.043-0.063 nm).

All reactions in non-aqueous solvents were conducted in flame-dried glassware under an argon atmosphere with magnetic stirring. Volumes of less than 0.2 mL were measured and dispensed with gas-tight syringes. Evaporation and concentration under reduced pressure was performed at 10-700 mbar at 40 °C. All pure products of the reactions were dried under high vacuum (1 mbar).

4.3 Chemicals and reagents

All reagents were obtained from commercial sources and used without further preparation. Dichloroethane used were purified by distillation over calcium hydride as a drying agent and transferred under argon. Pyridine was distilled over calcium hydride and used directly. The following cooling baths were used: 0 °C (ice/water) and -78 °C.

4.4 Procedure and Characterisation

General procedures

Formation of ynamides: General procedure 1 (GP1)[49]

Potassium carbonate (2.5 mmol), copper sulphate pentahydrate (0.15 mmol) and 1,10-phenanthroline (0.3 mmol) were added consecutively to a mixture of the corresponding amide (1 mmol) in toluene (1.6 mL). The reaction mixture was added to the bromoacetylene derivate (1.25 mmol) and heated to 65-75 °C and monitored through TLC analysis. Upon completion the reaction mixture was cooled to room temperature before being diluted with EtOAc and filtered through a pad of Celite. The organic solution was concentrated under reduced pressure to provide the crude product. The residue was purified by flash chromatography with the appropriate eluent to afford the desired ynamide.

Formation of ynamides: General procedure 2 (GP2)[50]

$CuCl_2$ (0.2 eq), an appropriate amide (5 eq) and Na_2CO_3 (2 eq) were added to a flame-dried 500 mL three-necked round-bottomed flask. The flask was purged with oxygen for 15 min and a solution of pyridine (2 eq) in dry toluene (0.4 M) was added. A balloon filled with oxygen was connected to the flask and the stirred mixture was heated to 70 °C. After 15 min, a solution of alkyne (1 eq) in dry toluene (0.2 M) was added by syringe pump at a rate of 1.25 mL/h. The mixture was allowed to stir at 70 °C for another 8h and was then cooled to RT. The reaction mixture was then filtered through a pad of silica and concentrated under reduced pressure. The crude mixture was purified by flash chromatography.

Catalytic oxidative reaction: General procedure 3 (GP3)

A solution of PPh_3AuCl (2.5 mg, 0.005 mmol, 5 mol%), $AgSbF_6$ (1.7 mg, 0.005 mmol, 5 mol%) in CH_2Cl_2 (1 mL) was stirred for 5 min before the corresponding ynamide (0.1 mmol, 1 eq) and *p*-methoxy pyridine-*N*-oxide monohydrate (13.7 mg, 1.1 eq) were added to the mixture. The reaction mixture was stirred at room temperature until either the complete consumption of the starting material was observed or a period of 24 h had passed. The reaction mixture was then filtered through a pad of silica. The filtrate was then concentrated under reduced pressure and purification of the residue was performed by flash chromatography.

Optimised gold catalytic oxidative reaction with ynamides and ynol ethers: General procedure 4 (GP4):

System A (GP4A)

A solution of the corresponding ynamide (0.3 mmol, 1 eq) in $ClCH_2CH_2Cl$ (1.5 mL) was added to a mixture of dichloro(2-pyridinecarboxylato)gold (5.9 mg, 0.015 mmol, 5 mol%) and pyridine *N*-oxide (32 mg, 0.34 mmol, 1.1 eq). The reaction mixture was stirred at 70 °C until complete consumption of the starting material was observed before being filtered through a pad of silica.

The filtrate was then concentrated under reduced pressure and purification of the residue was performed by flash chromatography.

System B (GP4B)

A solution of the corresponding ynamide (0.3 mmol, 1 eq) in THF (1.5 mL) was added to a mixture of gold tribromide (6.6 mg, 0.015 mmol, 5 mol%) and pyridine-*N*-oxide (32 mg, 0.34 mmol, 1.1 eq). The reaction mixture was stirred at RT until complete consumption of the starting material was observed before being filtered through a pad of silica. The filtrate was then concentrated under reduced pressure and purification of the residue was performed by flash chromatography.

General alkylation of 1-cyclohexyl-3-ethoxyprop-2-yn-1-ol: General procedure 5 (GP5)

To a solution of propargyl alcohol **287** (182 mg, 1mmol) in dry THF (2 mL, 0.5 M) an appropriate alkylating reagent (1.2 mmol) was added under an Argon atmosphere. The solution was cooled to 0 °C in an ice bath and sodium hydride (57% suspension in oil, 50 mg, 1.2 mmol) was then added. After stirring for 30 min at 0 °C, the mixture was stirred for a further 3 h at room temperature. The reaction was then quenched with a saturated solution of ammonium chloride (10 mL) and the organic phase was extracted with EtOAc (3 x 10 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography.

General procedure for formation of *N*-Substituted Iminopyridinium Ylides (GP6):

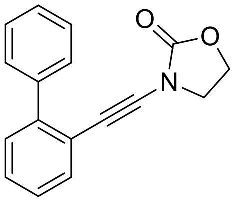
The corresponding acyl chloride (2 eq) was added to a solution of *N*-aminopyridinium iodide (444 mg, 2 mmol) in 20 mL of aqueous NaOH (10%) at 0 °C and stirred overnight. The suspension was then extracted with dichloromethane (3 × 25 mL) and consecutively treated with activated carbon and Na_2SO_4. The organic mixture was filtered through celite and the solvent was removed under reduced pressure. The solid residue was recrystallised to afford the desired ylide.

Optimised gold catalytic reaction for the formation of oxazole from ynamides (GP7)

A solution of the corresponding ynamide or ynol ether (1 eq) in toluene (0.1 M) was added to a mixture of dichloro(2-pyridinecarboxylato)gold (5 mol%) and pyridinium-1-ylamide (1.5 eq). The reaction mixture was stirred at 90 °C until complete consumption of the starting material was observed. The mixture was filtered through a pad of silica and the filtrate concentrated under reduced pressure. If required the residue was purified by flash chromatography.

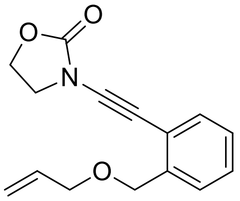
Characterisation for chapter 2

3-([1',1''-Biphenyl]-2-ylethynyl)oxazolidin-2-one (153)



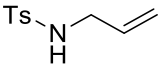
Following GP2 using 2-oxazolidinone **170** (878 mg) and phenylacetylene derivative **173** (356 mg, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (4:1)] ynamide **153** was isolated as a light yellow solid (447 mg, 85%): mp: 91-93 °C; ν_{max} (neat)/cm^{-1}= 3064, 2251 1477, 1403, 1197, 1164, 1029, 745, 702; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.63-7.53 (m, 3H), 7.46-7.27 (m, 6H), 4.40 (t, *J* 8.0, 2H), 3.79 (t, *J* 8.0, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 155.5, 143.5, 140.4, 132.5, 129.4, 129.2 (2C), 128.2, 127.9 (2C), 127.4, 127.0, 120.6, 81.7, 71.2, 62.9, 46.6; HRMS *m/z* (TOF MS ES+): calculated for $C_{17}H_{13}NO_2Na$: 286.0844, found: 286.0842 [*M+Na*].

3-((2'-((Allyloxy)methyl)phenyl)ethynyl)oxazolidin-2-one (156)



Following GP2 using 2-oxazolidinone **170** (878 mg) and phenylacetylene derivative **176** (344 mg, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (5:1)] ynamide **156** was isolated as a light yellow oil (655 mg, 85%): ν_{max} (neat)/cm^{-1}= 3072, 2984, 2915, 2855, 2251, 1764, 1451, 1407, 1195, 1072, 1031, 757, 746; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.46 (dd, *J* 7.3, 1.2, 1H), 7.44 (t, *J* 7.3, 1.2, 1H), 7.32 (td, *J* 7.6, 1.2, 1H), 7.23 (td, *J* 7.6, 1.2, 1H), 5.99 (ddt, *J* 17.2, 10.4, 5.6, 1H), 5.34 (ddt, *J* 17.2, 1.5 and 1.5, 1H), 5.20 (ddt, *J* 10.4, 1.5 and 1.5, 1H), 4.68 (s, 2H), 4.50 (t, 7.4, 2H), 4.10 (dt, *J* 5.6, 1.5, 2H), 4.01 (t, 7.4, 2H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 155.7, 139.9, 134.8, 131.7, 128.3, 127.6, 127.2, 120.9, 117.0, 83.2, 71.6, 70.3, 69.1, 63.0, 47.0; HRMS *m/z* (TOF MS ES+): calculated for $C_{15}H_{15}NO_3Na$: 280.0950, found: 280.0944 [*M+Na*].

N-Allyl-*p*-toluenylsulfonamide (158)

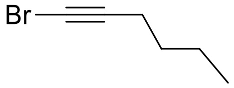


Allyl amine **157** (4.17 mL, 33 mmol) and triethylamine (4.17 mL, 30 mmol) in 140 mL of CH_2Cl_2 was added dropwise to a solution of 4-methylbenzene sulfonyl chloride (5.70 g, 30 mmol) in 10 mL of CH_2Cl_2. After 1 h at reflux and 30 min at room temperature, the crude reaction was added of a saturated aqueous solution of $NaHCO_3$ (150 mL). The organic layer was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. The solution was then concentrated to provide the crude product. After purification by re-crystallisation with CH_2Cl_2/hexane, amide **158** was isolated as a white solid (3.73 g, 59%): mp: 63-65 °C; ν_{max} (neat)/cm^{-1} = 3247, 1595, 1422, 1318, 1156, 1091, 1061, 810, 664; ^{1}H-NMR

(300 MHz; $CDCl_3$): δ_H= 7.84 (d, *J* 8.3, 1H), 7.40-7.24 (m, 4H), 5.79 (ddt, *J* 16.8, 10.1 and 6.3, 1H), 5.29 (dd, *J* 16.8 and 1.2, 1H), 5.24 (dd, *J* 10.1 and 1.2, 1H), 4.05 (d, *J* 6.3, 2H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 143.5, 136.9, 132.9, 129.7 (2C), 127.1 (2C), 117.7, 45.7, 21.5.

Data were in agreement with those reported in the literature.[99]

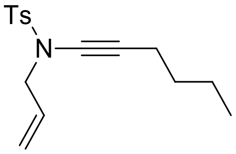
Bromohex-1-yne (160)



A solution of hex-1-yne **159** (1.15 mL, 10 mmol) in acetone (50 mL) was added to *N*-bromosuccinimide (1.30 g, 11 mmol) and silver nitrate (340 mg, 2 mmol). The solution was left under stirring overnight in the dark. The solvent was removed under reduced pressure and the remaining oil was dissolved in *n*-pentane and filtered through a pad of silica. The organic solution was then concentrated under reduced pressure to afford bromoalkyne **160** (789 mg, 49%) as a light yellow oil: ν_{max} (neat)/cm^{-1}= 2930, 2900, 2840, 2180, 1460, 1420, 1370, 1320, 1100, 920, 740; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 2.21 (t, *J* 6.9, 2H), 1.55-1.35 (m, 4H), 0.91 (t, *J* 7.2, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 80.4, 37.4, 30.4, 21.9, 19.4, 13.5.

Data were in agreement with those reported in the literature.[100]

N-Allyl-*N*-(hex-1-yn-1-yl)-4-methylbenzenesulfonamide (161)

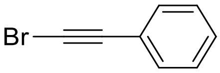


Following GP1 using bromoalkyne **160** (201 mg) and tosylamide **158** (211 mg). Purification by flash chromatography [hexanes:EtOAc (12:1)] gave ynamide **161** (171 mg, 59%) as a light yellow oil: ν_{max} (neat)/cm^{-1}= 3051, 2957, 2931, 2872, 2254, 1706, 1361, 1166, 821, 660; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.78 (d, *J* 8.3, 2H), 7.33 (d, *J* 8.0, 2H), 5.72 (ddt, *J* 16.4, 10.1 and

6.3, 1H), 5.26-5.15 (m, 2H), 3.91 (dt, *J* 6.3 and 1.1, 2H), 2.44 (s, 3H), 2.24 (t, *J* 6.8, 2H), 1.50-1.29 (m, 4H), 0.88 (t, *J* 7.2, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 144.3, 134.7, 131.2, 129.5, 127.7, 119.6, 72.9, 70.4, 54.2, 30.9, 21.7, 21.6, 18.0, 13.5.

Data were in agreement with those reported in the literature.[101]

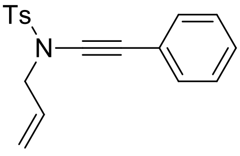
(Bromoethynyl)benzene (163)



A solution of phenylacetylene **162** (0.55 mL, 5 mmol) in acetone (25 mL) was added to *N*-bromosuccinimide (643 mg, 5.5 mmol) and silver nitrate (169 mg, 1 mmol). The solution was left stirring overnight in the dark. The solvent was removed under reduced pressure and the remaining oil was dissolved in hexane and filtered through a pad of silica. The organic solution was then concentrated under reduced pressure affording bromoalkyne **163** (479 mg, 53%) as a light yellow oil: ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.47-7.43 (m, 2H), 7.32 (m, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 132.0 (2C), 128.7, 128.3 (2C), 122.7, 80.0, 49.7.

Data were in agreement with those reported in the literature.[102]

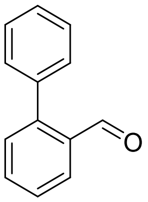
N-Allyl-*N*-(phenylethynyl)-p-toluenylsulfonamide (164)



Following GP1 using bromoalkyne **163** (226 mg) and tosylamide **158** (211 mg). Purification by flash chromatography [hexanes:EtOAc (7:1)] gave ynamide **164** (183 mg, 59%) as a light yellow oil: ν_{max} (neat)/cm^{-1}= 3031, 2923, 1699, 1350, 1164, 1084, 812, 730, 700; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.84 (d, *J* 8.3, 2H), 7.39-7.24 (m, 7H), 5.79 (ddt, *J* 15.5, 10.1 and 6.3, 1H), 5.26 (m, 2H), 4.09-3.99 (m, 2H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 144.7, 134.6, 131.2 (2C), 130.8, 129.7(2C), 128.6, 128.2(2C), 127.7(2C), 122.7, 120.0, 82.2, 70.9, 54.3, 21.6.

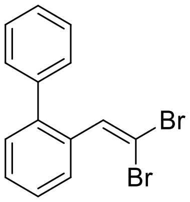
Data were in agreement with those reported in the literature.[49]

[1,1'-Biphenyl]-2-carbaldehyde (167)



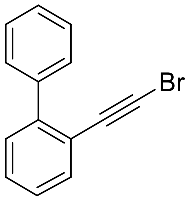
Phenylboronic acid **166** (1.46 g, 12 mmol) was added to a solution containing 2-bromobenzaldehyde **165** (1.39 mL, 12 mmol) and sodium carbonate (1.27 g, 12 mmol) in a 2:1 mixture of DMF/water (25 mL), and stirred for 2 min. $Pd(OAc)_2$ (134 mg, 5 mol%) was then added and the flask was flushed with argon, sealed and the mixture was stirred at room temperature for 12 h. When all the starting material was consumed, the organic phase was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture [hexanes:toluene (5:1)] to afford biphenyl-2-carbaldehyde **167** (1.88 g, 86%) as a colourless liquid: ν_{max} (neat)/cm^{-1}= 3061, 2848, 2753, 1687, 1596, 1473, 1252, 1194, 827, 756, 745, 733, 643; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 10.00 (s, 1H), 8.04 (app dd, *J* 7.7 and 1.4, 1H), 7.64 (dt, *J* 7.5 and 1.5, 1H), 7.52-7.42 (m, 5H), 7.40-7.36 (m, 2H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_H= 192.3, 145.8, 137.6, 133.6, 133.4, 130.6, 130.0 (2C), 128.3 (2C), 128.0, 127.6, 127.4; HRMS *m/z* (TOF MS EI+): calculated for $C_{13}H_{10}O$: 182.0727, found: 182.0732, [*M*].

2-(2,2-Dibromovinyl)-1,1'-biphenyl (168)



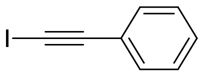
CBr_4 (7.82 g, 23.6 mmol) was added to a solution of PPh_3 (12.4 g, 47.2 mmol) in CH_2Cl_2 (50 mL) and the resulting yellow mixture was stirred for 10 min at 0° C. A solution of biphenyl-2-carbaldehyde **167** (1.72 g, 9.45 mmol) in CH_2Cl_2 (50 mL) was added slowly with continued stirring for 1 h at 0° C. The reaction mixture was then quenched with brine (50 mL) and the organic layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture [hexanes:EtOAc (19:1)], affording dibromoalkene **168** as a yellow liquid (3.10 g, 98%): ν_{max} (neat)/cm^{-1}= 3059, 3018, 2989, 2973, 2901, 1471, 1434, 1073, 1008, 886, 857, 795, 745, 735, 698; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.73-7.63 (m, 1H), 7.48-7.32 (m, 8H), 7.23 (bs, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_H= 141.1, 140.1, 137.5, 133.8, 129.8, 129.5 (2C), 129.2, 128.6, 128.2 (2C), 127.5, 127.1, 90.8; HRMS *m/z* (TOF MS EI+): calculated for $C_{14}H_{10}Br_2$: 337.9129, found: 337.9129 [*M*].

2-(Bromoethynyl)-1,1'-biphenyl (169)



A solution of bromoalkyne **168** (670 mg, 2 mmol) in THF (20 mL) was cooled to -78 °C before adding *tert*-butoxide (2.02 g, 18 mmol). After 5 min the reaction mixture was quenched with brine (20 mL) and allowed to warm to room temperature. The organic layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried over Na_2SO_4. The solution was then concentrated under reduced pressure to provide the crude product, which was purified by flash chromatography [hexane] affording bromoalkyne **169** as a yellow liquid (298 mg, 58%): ν_{max} (neat)/cm^{-1}= 3059, 3023, 2198, 1765, 1472, 1449, 1431, 774, 755, 734, 698; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.66-7.25 (m, 9H); 13C-NMR (101 MHz; CDCl$_3$): δ_C= 144.4, 140.0, 133.6, 129.5, 129.1 (2C), 128.8, 128.0 (2C), 127.5, 126.9, 120.9, 79.6, 52.2; HRMS *m/z* (TOF MS EI+): calculated for $C_{14}H_9Br$: 255.9888, found: 255.9886 [*M*].

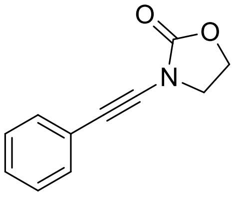
(Iodoethynyl)benzene (171)



A solution of phenylacetylene **162** (0.55 mL, 5 mmol) in acetone (25 mL) was added to *N*-iodosuccinimide (1.26 g, 5.5 mmol) and silver nitrate (169 mg, 1 mmol). The solution was left stirring overnight in the dark. The solvent was removed under reduced pressure and the remaining oil was dissolved in hexane and filtered through a pad of silica. The organic solution was then concentrated under reduced pressure affording iodoalkyne **171** (855 mg, 75%) as a light yellow oil: ν_{max} (neat)/cm^{-1}= 3100, 2170, 1610, 1580, 1490, 1450, 1070, 1025, 915, 755, 685; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.47-7.41 (m, 2H), 7.35-7.29 (m, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 132.3 (2C), 128.8, 128.2 (2C), 123.4, 94.1, 6.1.

Data were in agreement with those reported in the literature.[103]

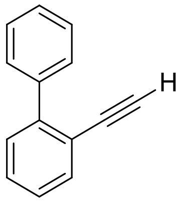
3-(Phenylethynyl)oxazolidin-2-one (172)



Following GP2 using 2-oxazolidinone **170** (878 mg) and phenylacetylene **162** (240 mg, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (4:1)] ynamide **172** was isolated as a white solid (159 mg, 85%): mp: 81-83 °C; ν_{max} (neat)/cm^{-1}= 3052, 3005, 2965, 2910, 2263, 2238, 1752, 1412, 1162, 1211, 1162, 1030, 1021, 744, 688; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.47-7.40 (m, 2H), 7.32-7.27 (m, 3H), 4.48 (t, *J* 8.0, 2H), 4.00 (t, *J* 8.0, 2H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 155.8, 131.5 (2C), 128.3 (2C), 128.2, 122.1, 78.9, 71.2, 63.0, 47.0; HRMS *m/z* (TOF MS EI+): calculated for $C_{11}H_9NO_2$: 187.0633, found: 187.0625 [*M*].

Data were in agreement with those reported in the literature.[50]

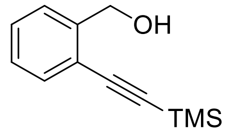
2-Ethynyl-1,1'-biphenyl (173)



n-BuLi (2.5 M in hexane, 3.4 mL, 7.5 mmol) was added drop-wise to a solution of vinylbromide **168** (1.01 g, 3 mmol) in THF (16 mL) at -78 °C under an argon atmosphere. The solution was left stirring for 5 h and the reaction mixture was then quenched with saturated solution of ammonium chloride (20 mL) and allowed to warm to room temperature. The organic layer was extracted with ethyl ether (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4. The solution was then concentrated under reduced pressure to provide the crude product, which was purified by flash chromatography [hexane] affording alkyne **173** as a colourless liquid (481 mg, 90%): ν_{max} (neat)/cm^{-1}= 3284, 3061, 1474, 1432, 757, 737, 698; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.67-7.56 (m, 3H), 7.48-7.36 (m, 5H), 7.31 (ddd, *J* 7.6, 6.6 and 2.2, 1H), 3.04 (s, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 144.4, 140.2, 133.8, 129.5, 129.2 (2C), 128.9, 127.9 (2C), 127.5, 126.97, 120.4, 83.0, 80.1.

Data were in agreement with those reported in the literature.[104]

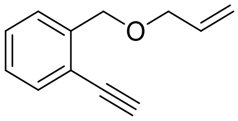
(2-((Trimethylsilyl)ethynyl)phenyl)methanol (175)



A solution of trimethylsilyl acetylene (1.66 mL, 12 mmol) and *o*-iodobenzyl alcohol **174** (1.46 g, 6 mmol) in triethylamine (27 mL) was added of $Pd(PPh_3)_4$ (63 mg, 1.5 mol%) and copper (I) iodide (34 mg, 3 mmol%). The mixture was warmed to 40°C and stirred overnight. The reaction mixture was quenched with a saturated solution of ammonium chloride (30 mL) and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography [hexanes:EtOAc (9:1)] and gave silyl alkyne **175** (1.12g, 92%) as a light yellow oil: ν_{max} (neat)/cm^{-1}= 2921, 2878, 1769, 1682, 1361, 1202, 1102, 1037, 754, 710; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.47 (dd, *J* 7.5 and 1.3, 1H), 7.41 (dd, *J* 7.5 and 1.3, 1H), 7.33 (td, *J* 7.5 and 1.3, 1H), 7.24 (dt, *J* 7.5 and 1.3, 1H), 4.82 (d, *J* 6.6, 2H), 2.24 (t, *J* 6.6, 1H), 0.27 (s, 9H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 143.1, 132.4, 128.9, 127.3, 127.1, 121.1, 102.6, 99.6, 64.1, 0.1.

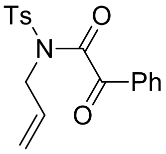
Data were in agreement with those reported in the literature.[105]

1-((Allyloxy)methyl)-2-ethynylbenzene (176)



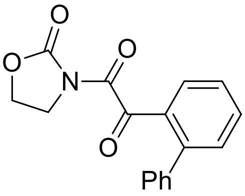
In a round-bottom flask purged with argon, benzyl alcohol **175** (652 mg, 3.2 mmol) was added to potassium hydroxide (85% powder, 422 mg, 6.4 mmol) and tetrabutyl ammonium chloride (59 mg, 5 mmol%) without the addition of any solvent. The reaction was stirred for 24 h at room temperature. The reaction mixture was quenched with a saturated solution of ammonium chloride (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash chromatography [hexanes:toluene (1:1)] and gave alkyne **176** (286 mg, 52%) as a light yellow oil: ν_{max} (neat)/cm^{-1}= 3070, 3018, 2854, 1646, 1448, 1345, 1077, 922, 757, 649; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.50 (m, 2H), 7.37 (td, *J* 7.6 and 1.3, 1H), 7.24 (td, *J* 7.6 and 1.3, 1H), 5.99 (ddt, *J* 17.2, 10.4 and 5.6, 1H), 5.34 (ddt, *J* 17.2, 3.3 and 1.6, 1H), 5.22 (ddt, *J* 10.4, 3.3 and 1.6, 1H), 4.71 (s, 2H), 4.10 (dt, *J* 5.6, 1.6, 2H), 3.30 (s, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 140.8, 134.7, 132.6, 129.0, 127.4, 127.2, 120.5, 117.1, 81.6, 81.2, 71.6, 70.0; HRMS *m/z* (TOF MS ES+): calculated for $C_{12}H_{12}ONa$: 195.0786, found: 195.0783 [*M*+*Na*].

***N*-Allyl-2-oxo-2-phenyl-*N*-(4-methylbenzenesulfonyl)acetamide (177)**



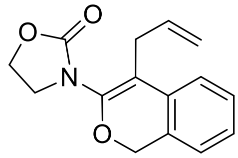
Following GP3 using ynamide **164** (31.1 mg) for 24 h. After purification by flash chromatography [toluene:EtOAc (9:1)], dioxidative **177** was isolated as a cloudy resin (17.5 mg, 93%): ν_{max} (neat)/cm^{-1}= 2924, 2235, 1695, 1596, 1494, 1355, 1166, 1087, 986, 972, 812, 754, 680; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.96-7.87 (m, 4H), 7.65 (tt, *J* 7.6 and 1.3, 1H), 7.57-7.49 (m, 2H), 7.38 (d, *J* 7.6, 2H), 5.76 (ddt, *J* 16.6, 10.2 and 5.9, 1H), 5.25 (dd, *J* 16.6 and 1.1, 1H), 5.16 (dd, *J* 10.2 and 1.1, 1H), 4.35 (dt, *J* 5.9 and 1.1, 2H), 2.46 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 187.7, 166.9, 145.8, 134.4, 132.8, 130.6, 130.0 (2C), 129.7 (2C), 128.8 (2C), 128.6 (2C), 119.4, 47.2, 21.7; HRMS *m/z* (TOF MS EI+): calculated for $C_{18}H_{17}NO_4S$: 366.0776, found: 366.0775 [*M*].

1-([1',1''-biphenyl]-2'-yl)-2-(2'''-oxooxazolidin-3'''-yl)ethane-1,2-dione (181)



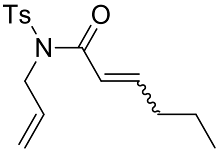
Following GP3 using ynamide **153** (26.3 mg) for 24 h. After purification by flash chromatography [toluene:EtOAc (9:1)] dioxidative **181** was isolated as a light yellow resin (13.6 mg, 84%): ν_{max} (neat)/cm^{-1}= 3065, 2962, 2917, 2849, 2251, 1760, 1477, 1403, 1185, 1028, 735; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.17 (dd, *J* 7.8, 1.4, 1H), 7.64 (td, *J* 7.6 and 1.4, 1H), 7.54 (td, *J* 7.6 and 1.4, 1H), 7.42-7.35 (m, 5H), 7.31 (dd, *J* 7.6 and 1.4, 1H), 4.30 (t, *J* 8.0, 2H), 3.43 (t, *J* 8.0, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 187.5, 165.9, 152.4, 144.1, 139.5, 133.6, 131.6, 131.2, 130.7, 130.4 (2C), 130.0, 127.9, 127.6 (2C), 63.2, 40.8; HRMS *m/z* (TOF MS EI+): calculated for $C_{17}H_{13}NO_4$: 318.0742, found: 318.0735 [*M*].

3-(4'-Allyl-1H-isochromen-3'-yl)oxazolidin-2-one (191)



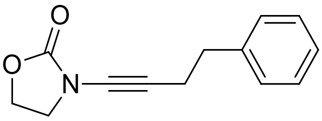
Following GP3 using ynamide **156** (24.3 mg) for 24 h. After purification by flash chromatography [hexene:EtOAc (7:3)] benzopyrane **191** was isolated as a yellow oil (14.9 mg, 58%): ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.31-7.16 (m, 3H), 7.06 (dd, *J* 7.3, 0.6, 1H), 5.90 (ddt, *J* 17.2, 10.1 and 5.9, 1H), 5.14 (ddd, *J* 17.2, 3.5 and 1.7, 1H), 5.09-5.01 (m, 3H), 4.43 (t, *J* 8.0, 2H), 3.90 (t, *J* 8.0, 2H), 3.26 (dt, *J* 5.9, 1.7, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 155.3, 142.4, 136.3, 132.4, 128.8, 128.1, 126.8, 123.7, 122.4, 115.7, 108.2, 69.6, 62.5, 45.5, 30.3; HRMS *m/z* (TOF MS ES+): calculated for $C_{15}H_{15}NNaO_3$: 280.0950, found: 280.0948 [*M+Na*].

(E) and (Z)-N-Allyl-*N*-(4-methylbenzenesulfonyl)hex-2-enamide (195)



Following GP3 using ynamide **161** (29 mg) for 24 h. After purification by flash chromatography [gradient: from hexanes:EtOAc (19:1) to hexanes:EtOAc (9:1)] enimide **195** was afforded in combined yield of 31% [E:Z (3.3:1)]; enimide (*Z*)-**195**, colourless oil: ν_{max} (neat)/cm^{-1}= 2959, 2926, 2855, 1686, 1351, 1164, 1080, 812, 753, 664; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.81 (d, *J* 8.2, 2H), 7.31 (d, *J* 8.2, 2H), 6.31 (dt, *J* 11.6 and 1.6, 1H), 6.10 (dt, *J* 11.6 and 7.5, 1H), 5.92 (ddt, *J* 17.1, 10.3 and 5.5, 1H), 5.34-5.22 (m, 2H), 4.47 (dt, *J* 5.5 and 1.6, 2H), 2.43 (s, 3H), 2.32 (appqd, *J* 7.5 and 1.6, 2H), 1.35 (appsept, *J* 7.5, 2H), 0.84 (t, *J* 7.5, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 165.8, 149.3, 144.6, 137.0, 132.9, 129.5 (2C), 128.0 (2C), 120.9, 118.14, 48.4, 31.5, 22.1, 21.6, 13.7; HRMS *m/z* (TOF MS ES+): calculated for $C_{16}H_{21}NO_3NaS$: 330.1140, found: 330.1153 [*M+Na*].; enimide (*E*)-**195**, colourless oil: ν_{max} (neat)/cm^{-1}= 2961, 2931, 2873, 1682, 1634, 1349, 1163, 1087, 812, 663; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.81 (d, *J* 8.2, 2H), 7.31 (d, *J* 8.2, 2H), 6.95 (dt, *J* 15.1 and 7.2, 1H), 6.49 (dt, *J* 15.1 and 1.5, 1H), 5.91 (ddt, *J* 17.1, 10.5 and 5.4, 1H), 5.28 (m, 2H), 4.49 (dt, *J* 5.4 and 1.5, 2H), 2.42 (s, 3H), 2.14 (dtd, *J* 7.2, 7.2 and 1.5, 2H), 1.42 (tq, *J* 7.2 and 7.2, 2H), 0.88 (t, *J* 7.2, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 165.7, 151.2, 144.6, 136.9, 132.9, 129.5 (2C), 127.9 (2C), 121.1, 118.1, 48.4, 34.6, 21.6, 21.2, 13.6; HRMS *m/z* (TOF MS ES+): calculated for $C_{16}H_{21}NO_3NaS$: 330.1140, found: 330.1138 [*M+Na*].

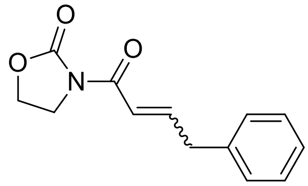
3-(4'-Phenylbut-1'-yn-1'-yl)oxazolidin-2-one (202)



Following GP2 using 2-oxazolidinone **170** (878 mg) and alkyne **201** (390 mg). After purification by flash chromatography [hexanes:EtOAc (4:1)] ynamide **202** was isolated as a light yellow solid (655 mg, 85%): mp: 55-57 °C; ν_{max} (neat)/cm^{-1}= 3027, 2937, 2920, 2854, 2264, 1759, 1413, 1120, 1032, 742, 699; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.34-7.18 (m, 5H), 4.40 (t, *J* 8.0, 2H), 3.83 (t, *J* 8.0, 2H), 2.85 (t, *J* 7.5, 2H), 2.60 (t, *J* 7.5, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 156.5, 140.5, 128.4 (2C), 128.3 (2C), 126.3, 70.8, 70.5, 62.8, 46.9, 35.2, 20.6; HRMS *m/z* (TOF MS ES+): calculated for $C_{13}H_{13}NO_2Na$: 238.0844, found: 238.0848 [*M+Na*].

Data were in agreement with those reported in the literature.[106]

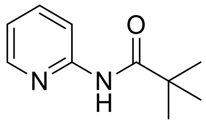
(E) and (Z)-3-(4'-Phenylbut-2'-enoyl)oxazolidin-2-one (203)



Following GP4A using ynamide **202** (64.5 mg) for 3 h. After purification by flash chromatography [gradient: from hexanes:EtOAc (4:1) to hexanes:EtOAc (13:7)] enimide **203** was afforded in combined yield of 69% [E:Z (5.5:1)]. Following GP4B using ynamide **202** (64.5 mg) for 18 h. After purification by flash chromatography [gradient: from hexanes:EtOAc (4:1) to hexanes:EtOAc (13:7)] enimide **203** was afforded in combined yield of 61% [E:Z (12.8:1)]; enimide (*Z*)-**203**, colourless oil: ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.34-7.17 (m, 5H), 7.11 (dt, *J* 11.5 and 1.7, 1H), 6.50 (dt, *J* 11.5 and 7.5, 1H), 4.44 (t, *J* 8.0, 2H), 4.10 (t, *J* 8.0, 2H), 4.00 (dd, *J* 7.5 and 1.7, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 165.8, 149.3, 144.6, 137.0, 132.9, 129.5, 128.0, 120.9, 118.14, 48.4, 31.5, 22.1, 21.6, 13.7; HRMS *m/z* (TOF MS ES+): calculated for $C_{13}H_{13}NNaO_3$: 254.0793, found: 254.0795 [*M+Na*]; enimide (*E*)-**203**, colourless oil: ν_{max}

(neat)/cm^{-1}= 2921, 2852, 1767, 1678, 1632, 1357, 1218, 1111, 1036, 750, 699; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.35-7.16 (m, 7H), 4.38 (t, *J* 8.0, 2H), 4.03 (t, *J* 8.0, 2H), 3.59 (d, *J* 5.6, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 165.0, 153.4, 149.0, 137.6, 128.7 (2C), 128.6 (2C), 126.6, 120.9, 62.0, 42.6, 38.9; HRMS *m/z* (TOF MS ES+): calculated for $C_{13}H_{13}NNaO_3$: 254.0793, found: 254.0785 [*M*+*Na*].

***N*-(Pyridin-2-yl)pivalamide (208)**



A solution of 2-aminopyridine **206** (941 mg, 10 mmol,) and triethylamine (0.17 mL, 12.5 mmol) in CH_2Cl_2 (30 mL) was added drop-wise to a solution of pivaloyl chloride **207** (1.35 mL, 11 mmol) in CH_2Cl_2 (10mL). After 1 h at reflux and 30 min at room temperature, the crude reaction was added to a saturated aqueous solution of $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. The organic solution was then concentrated to provide the crude product. After purification by re-crystallisation with CH_2Cl_2/hexane, amide **208** was isolated as a white solid (1.26 g, 71%): mp: 74-76 °C; ν_{max} (neat)/cm^{-1}= 3304, 3238, 2971, 1674, 1575, 1514, 1429, 1298, 775; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.30-8.20 (m, 2H), 8.02 (bs, 1H), 7.68 (appt, *J* 7.9, 1H), 7.07-6.97 (m, 1H), 1.31 (s, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 177.0, 151.5, 147.6, 138.3, 119.6, 113.9, 39.7, 27.4 (3C).

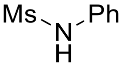
Data were in agreement with those reported in the literature.[107]

***tert*-Butylallylcarbamate (209)**

A solution of allylamine **157** (0.75 mL, 10 mmol,) in THF (7mL) was added to di-*tert*-butyldicarbonate (2.291 g, 10.5 mmol). The reaction mixture was left stirring overnight at room temperature. The reaction solution was concentrated under reduced pressure and the purification by flash chromatography [hexanes:EtOAc (4:1)] gave amide **209** (1.50 g, 96%) as a white solid: mp: 37-39 °C; ν_{max} (neat)/cm^{-1}= 3342, 2977, 2933, 1689, 1513, 1366, 1248, 1165, 736; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 5.84 (m, 1H), 5.14 (m, 2H), 4.57 (br s, 1H), 3.75 (m, 2H), 1.45 (s, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 155.7, 134.9, 115.7, 79.3, 43.1, 28.4 (3C).

Data were in agreement with those reported in the literature.[108]

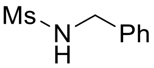
N-Phenylmethanesulfonamide (211)



A solution of the aniline **143** (2.74 mL, 30 mmol,) and pyridine (15 mL, 30 mmol) in CH$_2$Cl$_2$ (50 mL) was added drop-wise to a solution of mesyl chloride (2.8 mL, 36 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C. After stirring overnight at room temperature, the reaction mixture was added to a saturated aqueous solution of NaHCO$_3$ (50 mL). The organic phase was extracted with CH$_2$Cl$_2$ (3 × 40 mL) and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na$_2$SO$_4$. Alter filtration and concentration under reduced pressure, the crude mixture was purified by flash chromatography [hexanes:EtOAc (4:1)] to give mesyl amine **211** (4.92 g, 96%) as a white solid: mp: 100-102 °C; ν_{max} (neat)/cm^{-1}= 3253, 3019, 2933, 1595, 1494, 1471, 1392, 1319, 1300, 1275, 1145, 1075, 1028, 975, 959, 894, 751; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.36 (t, *J* 7.8, 2H), 7.28-7.16 (m, 3H), 7.02-6.67 (m, 1H) 3.02 (s, 3H). ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 136.6, 139.6 (2C), 125.4, 120.8 (2C), 39.2.

Data were in agreement with those reported in the literature.[109]

N-Benzylmethanesulfonamide (212)

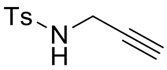


A solution of benzylamine **210** (3.27 mL, 30 mmol) and pyridine (15 mL, 30 mmol) in CH$_2$Cl$_2$ (50 mL) was added drop-wise of a solution of mesyl chloride (2.8 mL, 36 mmol) in CH$_2$Cl$_2$ (10 mL) at

0 °C. After stirring overnight at room temperature, the reaction mixture was added to a saturated aqueous solution of $NaHCO_3$ (50 mL). The organic phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. Alter filtration and concentration under reduced pressure, the crude mixture was purified by flash chromatography [hexanes:EtOAc (3:2)] to give mesyl amine **211** (518 mg, 96%) as a white solid: mp: 63-66 °C; ν_{max} (neat)/cm^{-1}= 3225, 3020, 1455, 1435, 1379, 1294, 1132, 1059, 737, 695; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.43-7.29 (m, 5H), 4.75 (brs, 1H), 4.32 (d, *J* 6.1, 2H), 2.86 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 136.6, 128.9 (2C), 128.1, 127.9 (2C), 47.2, 41.1.

Data were in agreement with those reported in the literature.[109]

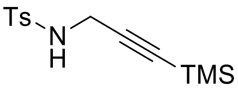
***N*-Propargyl-*N*-(4-methylbenzenesulfonyl)amine (214)**



A solution of the propargyl amine **213** (1.92 mL, 30 mmol) and triethylamine (4.17 mL, 30 mmol) in CH_2Cl_2 (140mL) was added dropwise of a solution of 4-methylbenzene sulfonyl chloride (5.70 g, 30 mmol) in CH_2Cl_2 (10mL). After 1 h at reflux and 30 min at room temperature, the crude reaction was added to a saturated aqueous solution of $NaHCO_3$ (150 mL). The organic phase was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. The solution was then concentrated to provide the crude product. After purification by re-crystallisation with CH_2Cl_2/hexane amide **214** was isolated as a light yellow solid (6.21 g, 99%): mp: 62-64 °C; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.77 (d, *J* 8.3, 1H), 7.31 (d, *J* 8.3, 2H), 4.75 (brs, 1H), 3.82 (dd, *J* 5.8 and 2.5, 2H), 2.43 (s, 3H), 2.10 (t, *J* 2.5, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 144.0, 136.6, 129.8 (2C), 127.5 (2C), 78.0, 73.1, 33.0, 21.7.

Data were in agreement with those reported in the literature.[110]

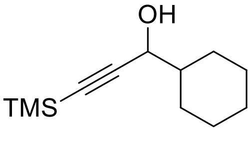
N-(3-(trimethylsilyl)prop-2-yn-1-yl)-*N*-*p*-toluenylsulfonamide (215)



A solution of the propargyl amine **214** (2.09 g, 10 mmol) in THF (20 mL) was added dropwise to a solution of *n*-BuLi (2.5 M in hexane, 7.2 mL, 18mmol) at -78 °C. The solution was warmed to 0 °C and after 45 min, the crude mixture was added of TMSCl (2.54, 20 mmol) and allowed to warm to room temperature and monitored by TLC analysis. Upon completion, 25 mL of water were added. The organic phase was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. Alter filtration and concentration under reduced pressure, the crude mixture was purified by flash chromatography [hexanes:EtOAc (4:1)] to give silyl propargyl amide **215** (2.08 g, 74%) as a white solid: mp: 112-115 °C; ν_{max} (neat)/cm^{-1}= 3266, 2965, 2177, 1432, 1327, 1158, 1083, 838, 810, 666; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.77 (d, *J* 8.3, 2H), 7.31 (d, *J* 8.0, 2H), 4.55 (brs, 1H), 3.86 (d, *J* 6.1, 2H), 2.43 (s, 3H), 0.02 (s, *J* 3.5, 9H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 143.7, 136.8, 129.7 (2C), 127.4 (2C), 99.4, 89.9, 33.9, 21.5, -0.5 (3C).

Data were in agreement with those reported in the literature.[111]

1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-ol (217)

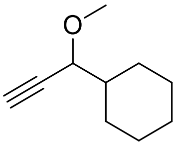


n-BuLi (2.5 M in hexane, 1.6 mL, 4 mmol) was added to a solution of ethynyltrimethylsilane (0.56, 4 mmol) in dry THF (13.3 mL) at -78 °C under argon atmosphere. After stirring for 30 min at -78 °C, the reaction was added to cyclohexyl aldehyde **216** (0.48 mL, 4 mmol) and continued stirring for an additional 30 min. The reaction mixture was allowed to warm to room temperature and was quenched with a saturated solution of ammonium chloride (15 mL). The aqueous phase was extracted with EtOAc (3 x 10 ml) and the combined organic extracts were dried over

Na_2SO_4, filtered and concentrated under reduced pressure. After evaporation of the solvent, the crude mixture was purified by flash chromatography [hexanes:EtOAc (4:1)] to give silyl propargyl amide **217** (621 mg, 74%) as a colourless liquid: ν_{max} (neat)/cm^{-1}= 3353, 2925, 2853, 2171, 1450, 1249, 838, 758; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 4.13 (t, *J* 5.9, 1H), 1.90-1.61 (m, 6H), 1.59-0.96 (m, 5H), 0.90 (t, *J* 7.0, 1H), 0.17 (s, 9H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 105.8, 90.2, 67.6, 44.0, 28.5, 28.1, 26.4, 25.9, 25.8, 0.1 (3C).

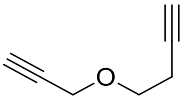
Data were in agreement with those reported in the literature.[112]

(1-methoxyprop-2-yn-1-yl)cyclohexane (218)



Iodomethane (0.22 mL, 3.48 mmol) was added to a solution of **217** (610 mg, 2.90 mmol) in dry THF (8 mL) under an argon atmosphere. The solution was cooled to 0 °C in an ice bath and sodium hydride (57% suspension in oil, 146 mg, 3.48 mmol) was then added. After stirring for 30 min at 0 °C, the mixture was stirred for further 3 h at room temperature. The reaction was quenched with a saturated solution of ammonium chloride (10 mL) and the aqueous phase was extracted with diethyl ether (3 x 10 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes:EtOAc (49:1)] to afford the methylated product as a colourless liquid (565 mg, 87%): ν_{max} (neat)/cm^{-1}= 2927, 2854, 2168, 1450, 1371, 1249, 1111, 1090, 842, 760; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 3.70 (d, J 6.1, 1H), 3.99 (s, 3H) 1.90-1.40 (m, 6H), 1.35-1.95 (m, 5H), 0.18 (s, 9H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 103.8, 91.2, 76.7, 56.6, 42.4, 28.9, 28.3, 26.5, 26.0, 25.9, 0.0 (3C); HRMS *m/z* (TOF MS ES+): calculated for $C_{13}H_{24}NOSi$: 224.1596, found 224.1596 [*M+Na*]. The product (560 mg, 2.5 mmol) was dissolved in methanol (5 mL) and potassium carbonate (862 mg, 6.25 mmol) was added. The reaction mixture was stirred at RT for 2 h before being quenched with aqueous ammonium chloride. The water phase was then extracted with EtOAc (3 x 10 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desilylated product **218** (300.2 mg, 79%) which was employed without further purification to prepare the corresponding ynamide.

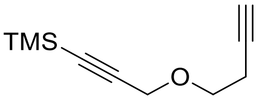
4-(Prop-2-yn-1-yloxy)but-1-yne (220)



Sodium hydroxide (1.60 g, 40 mmol) and tetrabutylammonium hydrogen sulphate (170 mg, 0.5 mmol) were added to a solution of homopropargyl alcohol **219** (0.756 mL, 10 mmol) in water (0.8 mL) and toluene (5 mL). The reaction was cooled to 0 °C and added drop-wise to propargyl bromide (1.225 mL, 11 mmol). The reaction mixture was then allowed to stir for 24 h, gradually warming to room temperature before being quenched with water (10 mL) and diethyl ether (10 mL). The combined organic phase was separated, washed with 10% HCl soln.(10 mL), saturated $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by vacuum distillation (60 °C, 15 mmHg) and afforded the propargyl ether **75** (1.01 g 93%) as a colourless oil: ν_{max} (neat)/cm^{-1}= 2873, 2118, 1358, 1097, 1017, 629; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 4.27 (d, *J* 2.4, 2H), 3.74 (t, *J* 6.9, 2H), 2.58 (td, *J* 6.9 and 2.7, 2H), 2.52 (t, *J* 2.4, 1H), 2.08 (t, *J* 2.7, 1H);^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 80.9, 79.4, 71.6, 69.4, 67.9, 58.2, 19.7.

Data were in agreement with those reported in the literature.[113]

(3-(But-3’-yn-1’-yloxy)prop-1-yn-1-yl)trimethylsilane (221)

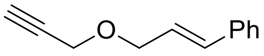


n-BuLi (2.5 M in hexane, 1.44 mL, 3.6 mmol) was added to a solution of propargyl ether **75** (432, 4 mmol) and 1,10-phenanthroline (catalytic quantity, approx. 2 mg) in dry THF (8 mL) at -

78 °C under argon atmosphere. After stirring for 30 min at -78 °C, the reaction was added to TMSCl (0.46 mL, 4 mmol) and allowed to warm to room temperature. The reaction mixture was stirred for a further 3 h before being quenched with a saturated solution of ammonium chloride (15 mL). The organic phase was extracted with diethyl ether (3 x 15 ml) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. After evaporation of the solvent, the crude mixture was purified was purified by vacuum distillation (60 °C, 15 mmHg) and afforded the silylated propargyl ether **76** (480 mg, 74%) as a colourless oil: ν_{max} (neat)/cm^{-1}= 2960, 2175, 1353, 1250, 1100, 991, 838, 759; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 4.17 (s, 2H), 3.62 (t, *J* 6.9, 2H), 2.49 (dt, *J* 6.9 and 2.7, 2H), 1.99 (t, *J* 2.7, 1H), 0.16 (s, 9H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 101.0, 91.6, 81.0, 69.3, 67.6, 58.8, 193.6, -0.3 (3C).

Data were in agreement with those reported in the literature.[113]

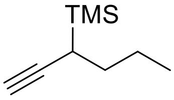
(*E*)-(3-(Prop-2-yn-1-yloxy)prop-1-en-1-yl)benzene (223)



Cinnamyl bromide **222** (985 mg, 5 mmol) was added to a solution of propargyl alcohol (0.36 mL, 6 mmol) and potassium carbonate (828 mg, 6 mmol) in acetone (4 mL) at room temperature and the reaction mixture was refluxed for 12 h. The solution was then cooled to room temperature, added to water (10 mL). The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 15 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes:EtOAc (19:1)] to afford propargyl ether **223** as a colourless oil (568 mg, 66%): ν_{max} (neat)/cm^{-1}= 3290, 3028, 2854, 2116, 1702, 1357, 1072, 966, 691; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.44-7.21 (m, 5H), 6.65 (d, *J* 15.9, 1H), 6.28 (dt, *J* 15.9 and 6.2, 1H), 4.25 (dd, *J* 6.2 and 1.4, 2H), 4.21 (d, *J* 2.4, 2H), 2.46 (t, *J* 2.4, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 136.5, 133.4, 128.5 (2C), 127.8, 126.5 (2C), 125.0, 79.7, 74.5, 70.2, 57.0.

Data were in agreement with those reported in the literature.[114]

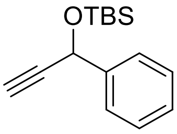
Hex-1-yn-3-yltrimethylsilane (224)



A solution of hex-1-yne **159** (1.15 mL, 10 mmol) in diethyl ether (7 mL) was cooled down at -78 °C and treated with 8 mL of *n*-BuLi (2.5 M in hexane, 20 mmol) and the mixture was then refluxed for 2 h. The reaction mixture was cooled to -20 °C and TMSCl (1.27 mL, 10 mmol) was added over a period of 10 min. The reaction was allowed to warm to 10 °C before being added to ice and water (10 mL). The two phases were separated and the aqueous phases were extracted with diethyl ether (3 x 15 ml) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. After evaporation of the solvent, the crude mixture was purified by vacuum distillation (116 °C, 16 mmHg) and afforded the trimethylsilane **224** (601 mg 39%) as a colourless oil: ν_{max} (neat)/cm^{-1}= 2961, 2857, 1715, 1249, 1177, 840; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 1.96 (d, *J* 2.7, 1H), 1.76-1.57 (m, 2H), 1.48-1.29 (m, 3H), 0.92 (t, *J* 7.0, 3H), 0.09 (s, 9H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 86.9, 68.2, 31.1, 22.6, 19.4, 13.7, -3.3 (3C).

Data were in agreement with those reported in the literature.[115]

tert-Butyldimethyl((1-phenylprop-2-yn-1-yl)oxy)silane (226)

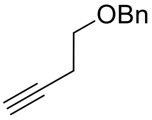


A solution of 1-phenyl-2-propyn-1-ol **225** (0.62 mL, 5 mmol) and 1-*H*-imidazole (340 mg, 5 mmol) in THF (7.5 mL) was added to TBSCl (50% w/w toluene, 2.07 mL, 6 mmol) at room temperature and stirred overnight. The reaction mixture was filtered through a pad of celite and the organic solution was concentrated under reduced pressure. After evaporation of the solvent, the crude mixture was purified by flash chromatography [gradient: from hexane to hexanes: EtOAc (99:1)] to give silyl ether **226** (800 mg, 65%) as a light yellow liquid: ν_{max} (neat)/cm^{-1}=

2955, 2930, 2886, 2857, 1707, 1252, 1090, 1065, 834, 776; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.55-7.46 (m, 2H), 7.40-7.28 (m, 3H), 5.50 (d, *J* 2.1, 1H), 2.56 (d, *J* 2.2, 1H), 0.94 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 141.3, 128.3, 127.8, 126.0, 73.6, 84.7, 64.6, 25.8, 18.3, -4.6 (3C), -5.0 (3C).

Data were in agreement with those reported in the literature.[116]

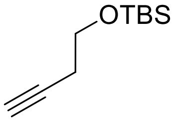
((But-3-yn-1-yloxy)methyl)benzene (227)



A solution of 1-butynyl-1-ol **218** (0.76 mL, 10 mmol) and TBAI (3.70 g, 10 mmol) in THF (7.5 mL) was added to sodium hydride (57% suspension in oil, 440 mg, 11 mmol) and stirred for 30 min at 0 °C. Benzyl bromide (1.25 ml, 10.5 mmol) was added and the reaction mixture was stirred for 8 h at room temperature. The reaction mixture was quenched by addition of ice and water (10 mL). The organic phase was extracted with EtOAc (3 x 15 ml) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. After evaporation of the solvent, the crude mixture was purified by vacuum distillation (120 °C, 17 mmHg) and afforded the benzyl protected alcohol **227** (1.33 g, 83%) as a light yellow oil: ν_{max} (neat)/cm^{-1}= 3294, 3031, 2863, 2121, 1721, 1453, 1362, 1098, 736, 696; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.41-7.28 (m, 5H), 4.58 (s, *J* 6.5, 2H), 3.62 (t, *J* 6.9, 2H), 2.52 (td, *J* 6.9 and 2.7, 1H), 2.02 (t, *J* 2.7, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 137.8, 128.3 (2C), 127.6 (2C), 81.2, 72.9, 69.3, 68.0, 19.8.

Data were in agreement with those reported in the literature.[117]

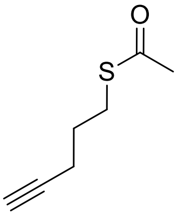
(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (228)



A solution of phenyl 3-butynyl-1-ol **218** (0.76 mL, 10 mmol) and 1-*H*-imidazole (680 mg, 10 mmol) in THF (15 mL) was added to TBSCl (50% w/w toluene, 4.16 mL, 12 mmol) at room temperature and stirred overnight. The reaction mixture was filtered through a pad of celite and the organic solution was concentrated under reduced pressure. After evaporation of the solvent, the crude mixture was purified by flash chromatography [hexanes:diethyl ether (39:1)] to give silyl ether **228** (1.01 g, 55%) as a colourless liquid: ν_{max} (neat)/cm^{-1}= 2955, 2930, 2858, 1472, 1254, 1102, 834, 774; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 3.74 (t, *J* 7.1, 2H), 2.40 (td, *J* 7.1 and 2.7, 2H), 1.96 (t, *J* 2.7, 1H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 81.5, 69.3, 61.7, 25.9, 22.9 (3C), 18.3, -5.3 (2C).

Data were in agreement with those reported in the literature.[118]

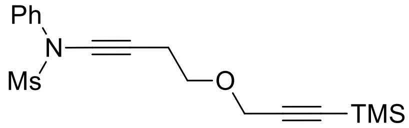
S-Pent-4-yn-1-yl ethanethioate (230)



DIAD (94%, 3.04 g, 15.5 mmol) was slowly added to a solution of triphenyl phosphine (4.01g, 15.5 mmol) in THF (50 mL) at 0 °C. After 30 min, a solution of 3-butynyl-1-ol **229** (0.76 mL, 10 mmol) and thioacetic acid (4.0 mL, 15.5 mL) was added and the reaction was allowed to stir at room temperature for 16 h. The solvent was reduced to 10 mL and hexane was added until no formation of white precipitate was observed. The solution was filtered off and concentrated under reduced pressure to a third of its volume. The solution was filtered through a pad of silica and concentrated under reduced pressure. After evaporation of the solvent, the crude mixture was purified by vacuum distillation (70 °C, 7 mmHg) and afforded the thioester **230** (853 mg, 60%) as a light yellow oil: ν_{max} (neat)/cm^{-1}= 2922, 2852, 1687, 1431, 1104, 951; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 2.97 (t, *J* 7.0, 2H), 2.32 (s, *J* 4.7, 3H), 2.27 (td, *J* 7.0 and 2.6, 2H), 1.97 (t, *J* 2.6, 1H), 1.79 (q, *J* 7.0, 2H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 195.5, 82.9, 69.1, 30.5, 28.2, 27.9, 17.5.

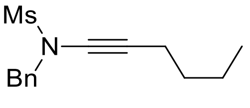
Data were in agreement with those reported in the literature.[119]

***N*-Phenyl-*N*-(4-((3-(trimethylsilyl)prop-2-yn-1-yl)oxy)but-1-yn-1-yl)methanesulfonamide (235)**



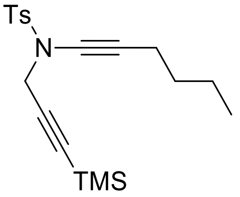
Following GP2 using amide **211** (1.71 g) and alkyne **221** (513 mg, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (4:1)] ynamide **235** was isolated as a colourless oil (617 mg, 59%): ν_{max} (neat)/cm^{-1}= 3021, 2963, 2927, 2842, 2829, 2260, 2174, 1489, 1352, 1247, 1156, 1097, 990, 969, 840, 760, 697; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.54-7.49 (m, 2H), 7.45-7.30 (m, 3H), 4.18 (s, 2H), 3.66 (t, *J* 7.0, 2H), 3.08 (s, 3H), 2.66 (t, *J* 7.0, 2H), 0.18 (s, 9H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 138.9, 129.3 (2C), 128.0, 125.4 (2C), 101.2, 91.6, 74.2, 68.2, 67.8, 58.9, 36.3, 19.8, -0.2 (3C); HRMS *m/z* (TOF MS ES+): calculated for $C_{17}H_{23}NO_3NaSSi$: 372.1066, found 372.1076 [*M*+*Na*].

***N*-benzyl-*N*-(hex-1-yn-1-yl)methanesulfonamide (236)**



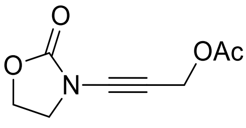
Following GP2 using amide **212** (1.85 g) and hex-1-yne (0.23 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (17:3)] ynamide **236** was isolated as a colourless oil (206 mg, 78%): ν_{max} (neat)/cm^{-1}= 2957, 2932, 2872, 2254, 1684, 1456, 1351, 1159, 1026, 956, 698; ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.48-7.33 (m, 5H), 4.57 (s, 2H), 2.86 (s, 3H), 2.26 (t, *J* 6.9, 2H), 1.52-1.25 (m, 4H), 0.88 (t, *J* 7.2, 3H); ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C = 134.8, 128.9 (2C), 128.6 (2C), 128.5, 72.9, 71.4, 55.6, 38.2, 30.9, 21.8, 18.1, 13.5; HRMS *m/z* (TOF MS ES+): calculated for $C_{14}H_{19}NNaO_2S$: 265.1136, found 265.1137 [*M*+*Na*].

3-(3-((*tert*-Butyldimethylsilyl)oxy)-3-phenylprop-1-yn-1-yl)oxazolidin-2-one (238)



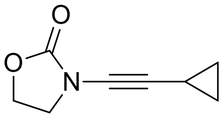
Following GP2 using amide **215** (1.85 g) and hex-1-yne (0.23 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (17:3)] ynamide **238** was isolated as a colourless oil (206 mg, 70%): ν_{max} (neat)/cm^{-1}= 2959, 2927, 2862, 2251, 2183, 1597, 1043, 1165, 845, 703, 666; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.83 (d, *J* 8.2, 2H), 7.32 (d, *J* 8.2, 2H), 4.22 (s, 2H), 2.44 (s, 3H), 2.28 (t, *J* 6.8, 2H), 1.52-1.30 (m, 4H), 0.88 (t, *J* 7.2, 3H), 0.02 (s, *J* 3.6, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 144.3, 134.4, 129.3 (2C), 128.2 (2C), 97.4, 91.35, 72.5, 70.9, 42.6, 30.9, 21.7, 21.6, 18.1, 13.6, -0.5 (3C); HRMS *m/z* (TOF MS ES+): calculated for $C_{19}H_{27}NNaO_2SSi$: 384.1429, found 384.1434 [*M*+*Na*].

3-(2-Oxooxazolidin-3-yl)prop-2-yn-1-yl acetate (239)



Following GP2 using oxazolidin-2-one **170** (878 mg) and 3-acetoxyprop-1-yne (0.20 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (11:9)] ynamide **239** was isolated as a thick oil (206 mg, 92%): ν_{max} (neat)/cm^{-1}= 2989, 2923, 2266, 1763, 1735, 1421, 1192 1112, 1023, 964, 748; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 4.81 (s, 2H), 4.44 (t, *J* 8.0, 2H), 3.93 (t, *J* 8.0, 2H), 2.07 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 170.2, 155.9, 76.5, 66.3, 63.1, 52.3, 46.5, 20.7; HRMS *m/z* (TOF MS ES+): calculated for $C_8H_9NNaO_4$: 206.0429, found 206.0424 [*M+Na*].

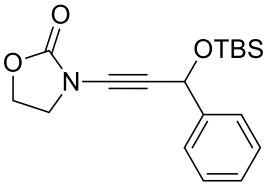
3-(cyclopropylethynyl)oxazolidin-2-one (240)



Following GP2 using oxazolidin-2-one **170** (878 mg) and cyclopropylacetylene (0.26 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (3:2)] ynamide **240** was isolated as a colourless oil (268 mg, 59%): ν_{max} (neat)/cm^{-1}= 3080, 3020, 2982, 2920, 2268, 1742, 1470, 1432, 1293, 1213, 1132, 1029, 932, 813, 746; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 4.39 (t, *J* 8.0, 2H), 3.85 (t, *J* 8.0, 2H), 1.34 (tt, *J* 8.0 and 5.0, 1H), 0.85-0.74 (m, 2H), 0.74-0.67 (m, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 156.7, 75.1, 65.6, 62.7, 47.0, 8.6, -1.0; HRMS *m/z* (TOF MS EI+): calculated for $C_8H_9NO_2$: 151.0633, found 151.0632 [*M*].

Spectroscopic data were identical to those reported in literature.[120]

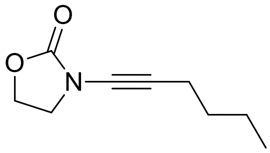
3-(3-((*tert*-Butyldimethylsilyl)oxy)-3-phenylprop-1-yn-1-yl)oxazolidin-2-one (241)



Following GP2 using oxazolidin-2-one **170** (878 mg) and propargyl silyl ether **226** (492 mg, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (7:3)] ynamide **241** was isolated as a light yellow oil (463 mg, 70%): ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.49 (d, *J* 7.3, 2H), 7.39-7.24 (m, 3H), 5.68 (s, 1H), 4.42 (t, *J* 8.1, 2H), 3.88 (t, *J* 8.1, 2H), 0.93 (s, *J* 2.9, 9H), 0.17 (s, 3H), 0.15 (s, 3H).

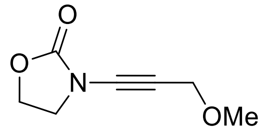
The product was party characterised due to its fast degradation.

3-(Hex-1-yn-1-yl)oxazolidin-2-one (242)



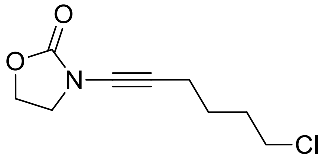
Following GP2 using oxazolidin-2-one **170** (878 mg) and hex-1-yne (0.23 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (7:3)] ynamide **242** was isolated as a colourless oil (143 mg, 43%): ν_{max} (neat)/cm^{-1}= 2959, 2931, 2873, 2273, 1759, 1479, 1413, 1298, 1201, 1113, 1032, 750, 729; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 4.41 (t, *J* 8.2, 2H), 3.87 (t, *J* 8.2, 2H), 2.30 (t, *J* 6.9, 2H), 1.58-1.34 (m, 4H), 0.91 (t, *J* 7.2, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 156.6, 71.1, 70.0, 62.7, 47.0, 30.8, 21.9, 18.0, 13.5; HRMS *m/z* (TOF MS EI+): calculated for $C_9H_{13}NO_2$: 167.0946, found 167.0947 [*M*].

3-(3-Methoxyprop-1-yn-1-yl)oxazolidin-2-one (243)



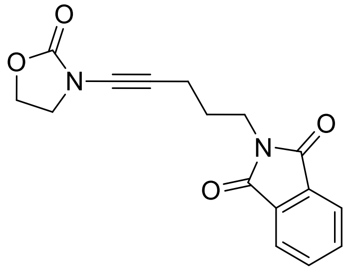
Following GP2 using oxazolidin-2-one **170** (878 mg) and 3-methoxyprop-1-yne (0.17 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (9:11)] ynamide **243** was isolated as a light-yellow oil (272 mg, 88%): ν_{max} (neat)/cm^{-1}= 2989, 2926, 2822, 2261, 1759, 1478, 1415, 1358, 1322, 1187, 1110, 1088, 1030, 931, 893, 748; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 4.44 (t, *J* 7.9, 2H), 4.23 (s, 2H), 3.91 (t, *J* 7.9, 2H), 3.36 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 156.1, 76.3, 67.6, 63.0, 59.8, 57.4, 46.7; HRMS *m/z* (TOF MS EI+): calculated for $C_7H_9NO_3$: 155.0582, found 155.0584 [*M*].

3-(6-Chlorohex-1-yn-1-yl)oxazolidin-2-one (244)



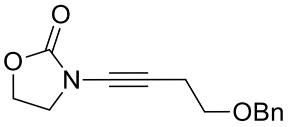
Following GP2 using oxazolidin-2-one **170** (878 mg) and 6-chlorohex-1-yne (0.24 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (6:4)] ynamide **95** was isolated as a light-yellow oil (273 mg, 68%): ν_{max} (neat)/cm^{-1}= 2987, 2949, 2922, 2869, 2268, 1758, 1478, 1413, 1298, 1200, 1111, 1031, 746; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 4.41 (t, *J* 8.0, 2H), 3.86 (t, *J* 8.0, 2H), 3.56 (t, *J* 6.5, 2H), 2.35 (t, *J* 6.9, 2H), 1.95-1.82 (m, 2H), 1.73-1.60 (m, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 156.5, 70.6, 70.2, 62.8, 46.9, 44.5, 31.5, 25.9, 17.7; HRMS *m/z* (TOF MS EI+): calculated for $C_9H_{12}NO_2Cl$: 201.0557, found 201.0552 [*M*].

2-(5-(2-Oxooxazolidin-3-yl)pent-4-yn-1-yl)isoindoline-1,3-dione (245)



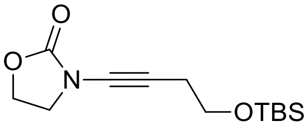
Following GP2 using oxazolidin-2-one **170** (878 mg) and 2-(pent-4-yn-1-yl)isoindoline-1,3-dione (426 mg, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (1:1)] ynamide **245** was isolated as a white solid (441 mg, 74%): mp: 138-139 ºC; ν_{max} (neat)/cm^{-1}= 2988, 2935, 2929, 2265, 1771, 1704, 1466, 1422, 1402, 1375, 1341, 1210, 1402, 1088, 1030, 887, 742, 720; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.88-7.81 (m, 2H), 7.75-7.68 (m, 2H), 4.38 (t, *J* 8.0, 2H), 3.86-3.76 (m, 4H), 2.39 (t, *J* 7.1, 2H), 1.94 (appquint, *J* 7.1, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 168.2 (2C), 156.4, 133.9 (2C), 132.0 (2C), 123.2 (2C), 70.8, 69.6, 62.8, 46.8, 37.1, 27.4, 16.2; HRMS *m/z* (TOF MS ES+): calculated for $C_{16}H_{14}N_2O_4Na$: 321.0851, found 321.0849 [*M+Na*]

3-(4-(Benzyloxy)but-1-yn-1-yl)oxazolidin-2-one (246)



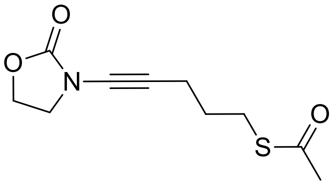
Following GP2 using oxazolidin-2-one **170** (878 mg) and alkyne **227** (292 mg, 2 mmol). After purification by flash chromatography [hexanes:toluene (4:1)] ynamide **246** was isolated as a light-yellow oil (387 mg, 79%): ν_{max} (neat)/cm^{-1}= 3031, 2914, 2864, 2272, 1760, 1718; 1478, 1413, 1270, 1200, 1109, 1030, 738, 698; : ν_{max} (neat)/cm^{-1}= 3051, 2957, 2931, 2872, 2254, 17036, 1361, 1166, 821, 660; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.37-7.27 (m, 5H), 4.55 (s, 2H), 4.41 (t, *J* 7.8, 2H), 3.86 (t, *J* 7.8, 2H), 3.60 (t, *J* 7.0, 2H). 2.63 (t, *J* 7.0, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 156.5, 145.0, 129.6, 128.3 (2C), 127.6 (2C), 72.9, 70.9, 68.3, 67.9, 62.8, 46.8, 19.8; HRMS *m/z* (TOF MS ES+): calculated for $C_{14}H_{15}NO_3Na$: 268.0950, found 268.0956 [*M*+*Na*].

3-(4-((*tert*-Butyldimethylsilyl)oxy)but-1-yn-1-yl)oxazolidin-2-one (247)



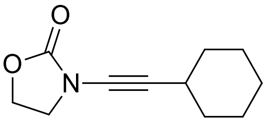
Following GP2 using oxazolidin-2-one (878 mg) and alkyne **228** (368 mg, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (3:1)] ynamide **247** was isolated as a light-yellow oil (428 mg, 53%): ν_{max} (neat)/cm^{-1}= 2954, 2928, 2856, 2268, 1765, 1413, 1252, 1202, 1101, 1035, 834, 775, 749; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 4.41 (t, *J* 8.0, 2H), 3.86 (t, *J* 8.0, 2H), 3.72 (t, *J* 7.1, 2H), 2.52 (t, *J* 7.1, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 156.4, 71.0, 68.2, 62.8, 61.9, 46.9, 25.9 (3C), 22.7, 18.3, -5.3 (2C); HRMS *m/z* (TOF MS EI+): calculated for $C_{13}H_{23}NO_3Si$: 269.1447, found 269.1452 [*M*].

S-(5-(2-Oxooxazolidin-3-yl)pent-4-yn-1-yl) ethanethioate (248)



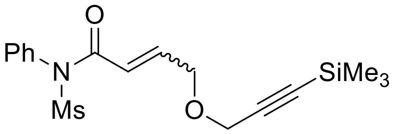
Following GP2 using oxazolidin-2-one **170** (878 mg) and alkyne **230** (284 mg, 2 mmol). After purification by flash chromatography [hexanes:toluene (11:9)] ynamide **248** was isolated as a colourless oil (290 mg, 64%): ν_{max} (neat)/cm^{-1}= 2987, 2928, 2854, 2258, 1734, 1449, 1312, 1247, 1193, 1170, 1135, 1079, 1040, 998, 886, 840; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 4.42 (t, *J* 8.1, 2H), 3.88 (t, *J* 8.1, 2H), 2.97 (t, *J* 7.1, 2H), 2.40 (t, *J* 7.1, 2H), 2.33 (s, 3H), 1.80 (dt, *J* 7.1 and 7.1, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 195.5, 156.5, 70.9, 69.7, 62.8, 46.9, 30.6, 28.6, 28.0, 17.6; HRMS *m/z* (TOF MS ES+): calculated for $C_{10}H_{13}NO_3NaS$: 250.0514, found 250.0511 [*M*+*Na*].

3-(Cyclohexylethynyl)oxazolidin-2-one (249)



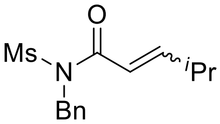
Following GP2 using oxazolidin-2-one **170** (878 mg) and ethynylcyclohexane (0.26 mL, 2 mmol). After purification by flash chromatography [hexanes:toluene (3:2)] ynamide **249** was isolated as a colourless oil (208 mg, 54%): ν_{max} (neat)/cm^{-1}= 2927, 2853, 2268, 1757, 1479, 1448, 1413, 1289, 1202, 1111, 1035, 973, 748; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 4.40 (t, *J* 8.0, 2H), 3.86 (t, *J* 8.0, 2H), 2.47 (tt, *J* 9.3 and 3.6, 1H), 1.87-1.61 (m, 4H), 1.57-1.21 (m, 6H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 156.5, 75.0, 70.2, 62.7, 47.1, 32.7 (2C), 28.8, 25.8, 24.9 (2C); HRMS *m/z* (TOF MS EI+): calculated for $C_{11}H_{15}NO_2$: 193.1103, found 193.1097 [*M*].

(E) and (Z)-N-(methylsulfonyl)-*N*-phenyl-4-((3-(trimethylsilyl)prop-2-yn-1-yl)oxy)but-2-enamide (250)



Following GP4A using ynamide **235** (105 mg) for 1 h. After purification by flash chromatography [hexanes:EtOAc (4:1)] enimide **250** was afforded in combined yield of 66% [*E*:*Z* (2.8:1)]. Following GP4B using ynamide **235** (105 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (4:1)] enimide **250** was afforded in combined yield of 68% [*E*:*Z* (3.2:1)]; enimide (*E*)-**250**, light-yellow oil: ν_{max} (neat)/cm^{-1}= 3041, 2960, 2901, 2850, 1687, 1643, 1351, 1249, 1153, 1119, 961, 840, 761, 694; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.51-7.44 (m, 3H), 7.31-7.24 (m, 2H), 7.10 (dt, *J* 15.3 and 4.2, 1H), 5.77 (dt, *J* 15.3 and 2.1, 1H), 4.11 (dd, *J* 4.2 and 2.1, 2H), 4.02 (s, 2H), 3.47 (s, 3H), 0.14 (s, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 165.8, 145.9, 135.0, 130.0 (2C), 129.9, 129.9 (2C), 120.8, 100.4, 92.3, 67.9, 58.5, 41.9, -0.3 (3C); HRMS *m/z* (TOF MS ES+): calculated for $C_{17}H_{23}NO_4NaSSi$: 388.1015, found 388.1006 [*M*+*Na*]; enimide (*Z*)-**250**, light-yellow oil: ν_{max} (neat)/cm^{-1}= 3061, 2961, 2898, 2849, 1683, 1356, 1250, 1156, 1094, 964, 842, 733, 695; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.51-7.45 (m, 3H), 7.31-7.26 (m, 2H), 6.32 (dt, *J* 11.7 and 4.6, 1H), 5.52 (dt, *J* 11.7 and 2.5, 1H), 4.70 (dd, *J* 4.6 and 2.5, 2H), 4.18 (s, 2H), 3.47 (s, 3H), 0.17 (s, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 166.1, 150.3, 135.3, 130.1, 130.0 (2C), 129.9 (2C), 119.0, 100.9, 91.9, 68.8, 59.0, 41.9, -0.2 (3C); HRMS *m/z* (TOF MS ES+): calculated for $C_{17}H_{23}NO_4NaSSi$: 388.1015, found 388.1027 [*M*+*Na*].

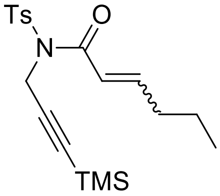
(E) and (Z)-N-benzyl-4-methyl-*N*-(methylsulfonyl)pent-2-enamide (251)



Following GP4A using ynamide **236** (79 mg) for 3 h. After purification by flash chromatography [hexanes:EtOAc (3:1)] enimide **251** was obtained as a mixture in yield of 87% [*E*:*Z* (3.6:1)].

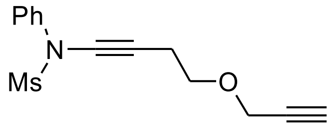
Following GP4B using ynamide **235** (79 mg) for 24 h. After purification by flash chromatography [hexanes:EtOAc (3:1)] enimide **251** was obtained as a mixture in yield of 85% [*E*:*Z* (4.5:1)]; enimide (*E*)-**251**, light-yellow oil: ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.42-7.27 (m, 5H), 7.16 (dt, *J* 14.9 and 7.2, 1H), 6.49 (dt, *J* 14.9 and 1.5, 1H), 5.06 (s, 2H), 3.16 (s, 3H), 2.21 (qd, *J* = 7.2 and 1.5 Hz, 2H), 1.48 (appsext, *J* 7.2, 2H), 0.92 (t, *J* = 7.2, 3H); enimide (*Z*)-**251**, light-yellow oil: ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.38-7.30 (m, 5H), 6.33-6.20 (m, 2H), 5.04 (s, 2H), 3.17 (s, 3H), 2.58-2.48 (m, 2H), 1.49 (qt, *J* 7.4 and 7.4, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

(E) and (Z)-N-(4-methylbenzenesulfonyl)-*N*-(3-(trimethylsilyl)prop-2-yn-1-yl)hex-2-enamide (252)



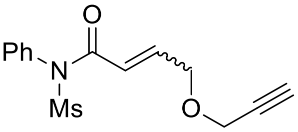
Following GP4A using ynamide **238** (108 mg) for 4 h. After purification by flash chromatography [hexanes:EtOAc (4:1)] enimide **252** was obtained as a mixture in yield of 87% [*E*:*Z* (4.1:1)]. Following GP4B using ynamide **238** (108 mg) for 24 h. After purification by flash chromatography [hexanes:EtOAc (6.1:1)] enimide **252** was obtained as a mixture in yield of 85% [*E*:*Z* (3.2:1)]; enimide (*E*)-**251**, light-yellow oil: ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.94 (d, *J* 8.3, 2H), 7.29 (d, *J* 8.3, 2H), 6.96 (dt, *J* 15.1 and 7.6, 1H), 6.52 (dt, *J* 15.1 and 1.3, 1H), 4.71 (s, 2H), 2.42 (s, 3H), 2.15 (dtd, *J* 7.6, 7.6 and 1.3, 2H), 1.42 (qt, *J* = 7.6 and 7.6, 2H), 0.87 (t, *J* 7.6, 3H), 0.15 (m, 9H); enimide (*Z*)-**251**, light-yellow oil: ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.94 (d, *J* 8.3, 2H), 7.29 (d, *J* 8.3, 2H), 6.32 (dt, *J* 11.6 and 1.5, 1H), 6.11 (dt, *J* 11.6 and 7.4, 1H), 4.68 (s, 2H), 2.42 (s, 3H), 2.31 (qd, *J* 7.4 and 1.5, 2H), 1.33 (appsext, *J* = 7.4, 3H), 0.82 (s, 9H).

(E) and (Z)-N-phenyl-*N*-(4-(prop-2-yn-1-yloxy)but-1-yn-1-yl)methanesulfonamide (253)



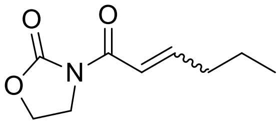
Potassium carbonate was added to a solution of **235** (305 mg, 0.87 mmol) in methanol (1.5 mL) (301 mg, 2.18 mmol). The reaction mixture was stirred at RT for 2 h before being quenched with aqueous ammonium chloride. The two phases were separated and the aqueous layer was extracted with EtOAc (3 x 10 ml).The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes:EtOAc (7:3)] to afford ynamide **253** as a light yellow oil (315 mg, 86%): ν_{max} (neat)/cm^{-1}= 3101, 2987, 2929, 2835, 2258, 1593, 1489, 1360, 1159, 1097, 959, 734, 692; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.54-7.48 (m, 2H), 7.44-7.30 (m, 3H), 4.19 (d, *J* 2.4, 2H), 3.68 (t, *J* 6.9, 2H), 3.08 (s, 3H), 2.66 (t, *J* 6.9, 2H), 2.44 (t, *J* 2.4, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 138.9, 129.3 (2C), 128.1, 125.4 (2C), 79.5, 74.6, 74.2, 68.1, 67.7, 58.1, 36.3, 19.8; HRMS *m/z* (TOF MS EI+): calculated for $C_{15}H_{15}NO_3NaS$: 300.0670, found 300.0674 [*M*+*Na*].

(E) and (Z)-N-(methylsulfonyl)-*N*-phenyl-4-(prop-2-yn-1-yloxy)but-2-enamide (254)



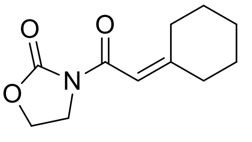
Following GP4A using ynamide **253** (83 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (3:2)] enimide **254** was afforded in combined yield of 53% [*E*:*Z* (7.5:1)]. Following GP4B using ynamide **112** (83 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (3:2)] enimide **113** was afforded in combined yield of 40% [*E*:*Z* (2.8:1)]; enimide (*E*)-**113**, light yellow oil: ν_{max} (neat)/cm^{-1}= 3279, 2937, 2861, 1644, 1686, 1644, 1489, 1348, 1151, 960, 765, 649; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.51-7.44 (m, 3H), 7.31-7.24 (m, 2H), 7.08 (dt, *J* 15.3 and 4.2, 1H), 5.79 (dt, *J* 15.3 and 2.1, 1H), 4.12 (dd, *J* 4.2 and 2.1, 2H), 4.02 (d, *J* 2.4, 2H), 3.46 (s, 3H), 2.39 (t, *J* 2.4, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 165.8, 145.6, 135.0, 130.0 (2C), 130.0 (2C), 129.9, 120.8, 78.7, 75.1, 68.0, 57.8, 41.8; HRMS *m/z* (TOF MS ES+): calculated for $C_{14}H_{15}NO_4NaS$: 316.0619, found 316.0617 [*M*+*Na*]; enimide (*Z*)-**113**, light yellow oil: ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.52 -7.46 (m, 3H), 7.32 -7.27 (m, 2H), 6.31 (dt, *J* 11.7 and 4.6, 1H), 5.53 (dt, *J* 11.7 and 2.5, 1H), 4.72 (dd, *J* 4.6 and 2.5, 2H), 4.18 (d, *J* 2.4, 2H), 3.48 (s, 3H), 2.46 (t, *J* 2.4, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 195.5, 164.7, carbamate CO not observed, 148.2, 120.3, 62.0, 42.5, 30.6, 29.6, 28.1; HRMS *m/z* (TOF MS ES+): calculated for $C_{14}H_{15}NO_4NaS$: 316.0619, found 316.0609 [*M*+*Na*].

(E) and (Z)- **3-(Hex-2-enoyl)oxazolidin-2-one (258)**



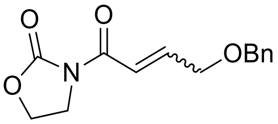
Following GP4A using ynamide **242** (35 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (7:3)] enimide **258** was afforded in combined yield of 63% [*E*:*Z* (3.2:1)]. Following GP4B using ynamide **242** (35 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (7:3)] enimide **258** was afforded in combined yield of 63% [*E*:*Z* (5.0:1)]; enimide (*E*)-**258**, light-yellow oil: ν_{max} (neat)/cm^{-1}= 2961, 2930, 2874, 1769, 1680, 1633, 1384, 1357, 1197, 1101, 1031, 968, 757, 704; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.22-7.09 (m, 2H), 4.41 (t, *J* 8.1, 2H), 4.06 (t, *J* 8.1, 2H), 2.25 (appsext, *J* 7.2 and 7.2, 2H), 1.51 (qt, *J* 7.4 and 7.4, 2H), 0.93 (t, *J* 7.4, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 165.3, 153.5, 151.5, 120.1, 62.0, 42.7, 34.6, 21.3, 13.7; HRMS *m/z* (TOF MS EI+): calculated for $C_9H_{13}NO_3$: 183.0895, found 183.0899 [*M*]; enimide (*Z*)-**258**, light-yellow oil: ν_{max} (neat)/cm^{-1}= 2961, 2928, 2873, 1767, 1679, 1384, 1361, 1284, 1261, 1198, 1122, 1002, 1039, 1023, 952, 796, 758, 717; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.00 (dt, *J* 11.6 and 1.7, 1H), 6.37 (dt, *J* 11.6 and 7.4, 1H), 4.41 (t, *J* 8.4, 2H), 4.06 (t, *J* 8.4, 2H), 2.61 (tdd, *J* 7.4, 7.4 and 1.7, 2H), 1.49 (qt, *J* 7.4 and 7.4, 2H), 0.95 (t, *J* 7.4, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 165.0, 153.3, 152.2, 118.7, 61.9, 42.5, 31.9, 22.2, 13.8; HRMS *m/z* (TOF MS EI+): calculated for $C_9H_{13}NO_3$: 183.0895, found 183.0892 [*M*].

3-(2-Cyclohexylideneacetyl)oxazolidin-2-one (259)



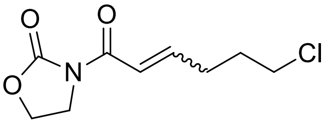
Following GP4A using ynamide **249** (58 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (7:3)] enimide **259** was afforded in yield of 81%. Following GP4B using ynamide **249** (58 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (7:3)] enimide **259** was afforded in yield of 81%; enimide **259**, colourless oil: ν_{max} (neat)/cm^{-1}= 2926, 2852, 1756, 1666, 1621, 1390, 1621, 1390, 1368, 1281, 1258, 1222, 1188, 1111, 1045, 967, 854, 756, 708; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 6.78 (s, 1H), 4.37 (t, *J* 7.7, 2H), 4.01 (t, *J* 7.7, 2H), 2.77 (t, *J* 5.2, 2H), 2.26 (t, *J* 5.2, 2H), 1.71-1.54 (m, 6H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 165.8, 165.3, 153.3, 112.4, 61.7, 42.6, 38.3, 30.7, 28.6, 27.8, 26.1; HRMS *m/z* (TOF MS EI+): calculated for $C_{11}H_{15}NO_3$: 209.1052, found 209.1051 [*M*].

(E) and (Z)-3-(4-(Benzyloxy)but-2-enoyl)oxazolidin-2-one (260)



Following GP4A using ynamide **246** (74 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (1:1)] enimide **260** was afforded in combined yield of 73% [*E*:*Z* (2.8:1)]. Following GP4B using ynamide **246** (74 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (1:1)] enimide **260** was afforded in combined yield of 68% [*E*:*Z* (3.1:1)]; enimide (*E*)-**260**, light-yellow solid: mp: 81-83 ºC; ν_{max} (neat)/cm^{-1}= 3061, 3024, 2924, 2873, 2852, 1762, 1672, 1633, 1424, 1368, 1356, 1275, 1115, 1020, 958, 800, 759, 729, 693; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.51 (dt, *J* 15.5 and 1.9, 1H), 7.40-7.23 (m, 5H), 7.15 (dt, *J* 15.5 and 4.4, 1H), 4.57 (s, 2H), 4.40 (t, *J* 7.5, 2H), 4.23 (dd, *J* 4.4 and 1.9, 2H), 4.05 (t, *J* 7.5, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 164.8, 153.3, 146.1, 137.6, 129.6, 128.4 (2C), 127.7 (2C), 120.0, 72.7, 68.9, 62.0, 42.6; HRMS *m/z* (TOF MS ES+):calculated for $C_{14}H_{15}NO_4Na$: 284.0899, found 284.0895 [*M*+*Na*]; enimide (*Z*)-**260**, waxy white solid: mp: 90-91 ºC; ν_{max} (neat)/cm^{-1}= 3061, 3024, 2921, 2874, 1762, 1672, 1634, 1424, 1387, 1356, 1276, 1213, 1117, 1102, 958, 799, 759, 728, 711, 693; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.38-7.27 (m, 5H), 7.16 (dt, *J* 11.8 and 2.5, 1H), 6.60 (dt, *J* 11.8 and 4.6, 1H), 4.63 (dd, *J* 4.6 and 2.5, 2H), 4.56 (s, 2H), 4.41 (t, *J* 7.9, 2H), 4.03 (t, *J* 7.9, 2H): ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 164.7, 153.2, 150.5, 137.9, 129.7, 128.5 (2C), 127.8 (2C), 117.9, 72.9, 69.4, 61.9, 42.4; HR-MS (ES-TOF): *m/z*: calculated for $C_{14}H_{15}NO_4Na$: 284.0899, found 284.0890 [*M*+*Na*].

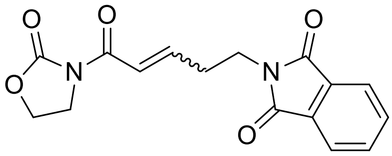
***(E) and (Z)*-3-(6-Chlorohex-2-enoyl)oxazolidin-2-one (261)**



Following GP4A using ynamide **244** (60 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (13:7)] enimide **261** was afforded in combined yield of 63% [*E*:*Z* (2.9:1)]. Following GP4B using ynamide **244** (60 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (13:7)] enimide **261** was afforded in combined yield of 65% [*E*:*Z* (4.0:1)]; enimide (*E*)-**261**, light-yellow oil: ν_{max} (neat)/cm^{-1}= 2960, 2920, 2850, 1767, 1677, 1627, 1423, 1384, 1361, 1284, 1216, 1195, 1111, 1038, 797, 757, 716; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.26 (dt, *J* 15.2 and 1.4, 1H), 7.10 (dt, *J* 15.2 and 6.6, 1H), 4.42 (t, *J* 8.1, 2H), 4.05 (t, *J* 8.1, 2H), 3.55 (t, *J* 6.5, 2H), 2.44 (dtd, *J* 6.6, 6.5 and 1.4, 2H), 1.96 (tt, *J* 6.5 and 6.5, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 164.9, 153.4, 149.0, 121.0, 62.0, 43.9, 42.6, 30.7, 29.7; HRMS *m/z* (TOF MS ES+): calculated for $C_9H_{12}NO_3NaCl$: 240.0403, found 240.0400 [*M*+*Na*]; enimide (*Z*)-**261**, light-yellow oil: ν_{max} (neat)/cm^{-1}= 2991, 2961, 2923, 2871, 1767, 1679, 1634, 1385, 1359, 1277, 1217, 1110, 1037, 977, 757, 705; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.06 (dt, *J* 11.6 and 1.7, 1H), 6.33 (dt, *J* 11.6 and 7.5, 1H), 4.43 (t, *J* 8.1, 2H), 4.06 (t, *J* 8.1, 2H), 3.57 (t, *J* 6.7, 2H), 2.78 (dtd, *J* 7.5, 7.1 and 1.7, 2H), 1.96 (tt, *J* 7.1 and 6.7, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 164.9, Carbamate

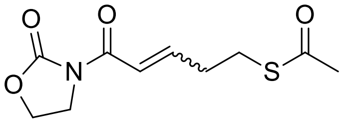
CO not observed, 149.3, 120.0, 62.0, 44.3, 42.5, 31.8, 27.2; HRMS *m/z* (TOF MS ES+): calculated for $C_9H_{12}NO_3NaCl$: 240.0403, found 240.0410 [*M*+*Na*].

(E) and (Z)-2-(5-Oxo-5-(2-oxooxazolidin-3-yl)pent-3-en-1-yl)isoindoline-1,3-dione (262)



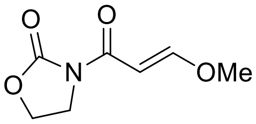
Following GP4A using ynamide **245** (89 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (11:9)] enimide **262** was afforded in combined yield of 68% [*E*:*Z* (5.6:1)]. Following GP4B using ynamide **245** (89 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (7:3)] enimide **262** was afforded in combined yield of 75% [*E*:*Z* (6.7:1)]; enimide (*E*)-**262**, white solid: mp: 146-149 ºC; ν_{max} (neat)/cm^{-1}= 3090, 2923, 2959, 2984, 2852, 1771, 1705, 1680, 1398, 1680, 1357, 1337, 1193, 1147, 957, 761, 721, 705; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.85-7.80 (m, 2H), 7.73-7.68 (m, 2H), 7.26 (dt, *J* 15.4 and 1.5, 1H), 7.07 (dt, *J* 15.4 and 7.0, 1H), 4.39 (t, *J* 8.0, 2H), 4.03 (t, *J* 8.0, 2H), 3.84 (t, *J* 7.0, 2H), 2.66 (tdd, *J* 7.0, 7.0 and 1.5); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 168.0 (2C), 164.6, 153.3, 146.1, 133.9 (2C), 131.9 (2C), 123.3 (2C), 122.1, 62.0, 42.6, 36.3, 31.6; HRMS *m/z* (TOF MS ES+): calculated for $C_{16}H_{14}N_2O_4Na$: 337.0800, found 337.0808 [*M*+*Na*]; enimide (*Z*)-**262**, white solid: mp: 136-138 ºC; ν_{max} (neat)/cm^{-1}= 2991, 2926, 2856, 170, 1706, 1680, 1437, 1392, 1360, 1291, 1210, 1041, 1018, 720; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.86-7.82 (m, 2H), 7.73-7.69 (m, 2H), 7.06 (td, *J* 11.6 and 1.7, 1H), 6.36 (td, *J* 11.6 and 7.5, 1H), 4.37 (t, *J* 8.0, 2H), 3.99 (t, *J* 8.0, 2H), 3.87 (t, *J* 7.5, 2H), 3.02 (tdd, *J* 7.5, 7.5 and 1.7, 2H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 168.3 (2C), 164.6, 153.2, 146.0, 133.9 (2C), 132.1 (2C), 123.2 (2C), 121.4, 61.9, 42.4, 36.8, 29.1; HRMS *m/z* (TOF MS ES+): calculated for $C_{16}H_{14}N_2O_4Na$: 337.0800, found 337.0806 [*M*+*Na*].

(E) and (Z)-S-(5-Oxo-5-(2-oxooxazolidin-3-yl)pent-3-en-1-yl) ethanethioate (263)



Following GP4A using ynamide **248** (68 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (3:2)] enimide **263** was afforded in combined yield of 75% [*E*:*Z* (2.6:1)]. Following GP4B using ynamide **248** (68 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (3:2)] enimide **263** was afforded in combined yield of 71% [*E*:*Z* (7.7:1)]; enimide (*E*)-**263**, colourless oil: ν_{max} (neat)/cm^{-1}= 2982, 2925, 2859, 1768, 1679, 1634, 1385, 1356, 1218, 1133, 1108, 1037, 954, 757, 705; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.25 (dt, *J* 15.4 and 1.4, 1H), 7.05 (dt, *J* 15.4 and 7.0, 1H), 4.41 (t, *J* 7.9, 2H), 4.05 (t, *J* 7.9, 2H), 2.99 (t, *J* 7.0, 2H), 2.54 (tdd, *J* 7.0, 7.0 and 1.4), 2.31 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 195.2, 164.7, 153.4, 147.7, 121.4, 62.0, 42.6, 32.3, 30.5, 27.3; HRMS *m/z* (TOF MS ES+): calculated for $C_{10}H_{13}NO_4NaS$: 266.0463, found 266.0468 [*M*+*Na*]; enimide (*Z*)-**263**, colourless oil: ν_{max} (neat)/cm^{-1}= 2989, 2924, 2854, 1769, 1679, 1627, 1422, 1384, 1360, 1285, 1219, 1196, 1040, 1012, 955, 797, 757, 701; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.09 (dt, *J* 11.6 and 1.7, 1H), 6.32 (dt, *J* 11.6 and 7.1, 1H), 4.42 (t, *J* 8.0, 2H), 4.05 (t, *J* 8.0, 2H), 3.05-3.00 (m, 2H), 2.95-2.88 (m, 2H), 2.33 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 195.5, 164.7, carbamate CO not observed, 148.2, 120.3, 62.0, 42.5, 30.6, 29.6, 28.1; HRMS *m/z* (TOF MS ES+): calculated for $C_{10}H_{13}NO_4NaS$: 266.0463, found 266.0464 [*M*+*Na*].

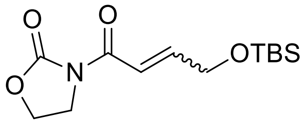
(*E*)-3-(3-Methoxyacryloyl)oxazolidin-2-one (264)



Following GP4A using ynamide **243** (46 mg) for 12 h. After purification by flash chromatography [hexanes:EtOAc (7:3)] enimide (*E*)-**264** was afforded in 89% yield; enimide (*E*)-**264**, colourless oil: ν_{max} (neat)/cm^{-1}= 3124, 2985, 2924, 2850, 1761, 1672, 1594, 1386, 1358, 1197, 1169, 1036, 970, 928, 845, 821, 757, 704; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.81 (d, *J* 12.3, 1H), 6.69 (d, *J* 12.3, 1H), 4.38 (t, *J* 8.7, 2H), 4.04 (t, *J* 8.7, 2H), 3.75 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 165.8, 164.9, 153.7, 95.4, 61.8, 57.6, 42.6; HRMS *m/z* (TOF MS EI+): calculated for $C_7H_9NO_4$: 171.0532, found 171.0526 [*M*].

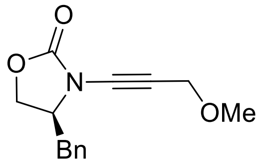
A NOE contact is evident between the vinylic proton at 7.81 ppm and the methyl protons at 3.75 ppm. No NOE contacts were observed between the vinylic protons or between the vinylicprotons at 6.69 and the methyl protons at 3.75 ppm. This confirms the stereochemistry assigned.

(E) and (Z)-3-(4-((*tert*-Butyldimethylsilyl)oxy)but-2-enoyl)oxazolidin-2-one (265)



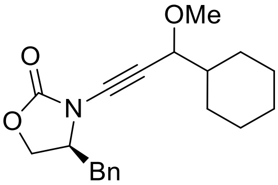
Following GP4A using ynamide **247** (81 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (13:7)] enimide **265** was afforded in combined yield of 75% [*E*:*Z* (6.7:1)]; enimide (*E*)-**265**, light-yellow oil: ν_{max} (neat)/cm^{-1}= 2954, 2927, 2885, 2856, 1767, 1680, 1637, 1359, 1393, 1217, 1107, 1035, 948, 829, 776, 755, 709, 682; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.52 (dt, *J* 15.2 and 2.2, 1H), 7.19 (dt, *J* 15.2 and 3.4, 1H), 4.4 6-4.38 (m, 4H), 4.07 (t, *J* 8.0, 2H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 165.1, 153.3, 149.5, 118.4, 62.9, 61.9, 42.6, 25.8 (3C), 18.2, -5.5 (2C); HRMS *m/z* (TOF MS EI+): calculated for $C_{13}H_{23}NO_4Si$: 285.1396, found 285.1398 [*M*]; enimide (*Z*)-**265**, light-yellow oil: ν_{max} (neat)/cm^{-1}= 2955, 2927, 2888, 2856, 1767, 1681, 1637, 1393, 1330, 1217, 1107, 1035, 948, 829, 776, 756, 708, 682; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.10 (dt, *J* 11.8 and 2.5, 1H), 6.54 (dt, *J* 11.8 and 4.5, 1H), 4.75 (dd, *J* 4.5 and 2.5, 2H), 4.42 (t, *J* 8.0, 2H), 4.05 (t, *J* 8.0, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= Carbamate CO not observed, 164.7, 155.1, 116.3, 62.7, 61.9, 42.4, 25.9 (3C), -5.3 (2C), ^{t}butyl quaternary carbon not observed; HRMS *m/z* (TOF MS EI+): calculated for $C_{13}H_{23}NO_4Si$: 285.1396, found 285.1392 [*M*].

(*S*)-4-benzyl-3-(3-methoxyprop-1-yn-1-yl)oxazolidin-2-one (269)



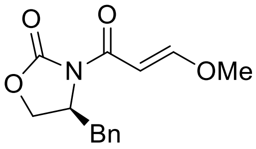
Following GP2 using amide (*S*)-4-benzyloxazolidin-2-one **267** (1.77 g) and 3-methoxyprop-1-yne **268** (0.17 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (11:9 then 2:3)] ynamide **269** was isolated as a light-yellow oil (289 mg, 59%) and unreacted (*S*)-4-benzyloxazolidin-2-one (1.45 g) was recovered; ynamide **269**: ν_{max} (neat)/cm^{-1}= 2930, 2821, 2257, 1765, 1453, 1413, 1352, 1209, 1182, 1110, 1090, 1029, 895, 733, 701; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.38-7.28 (m, 3H), 7.24-7.18 (m, 2H), 4.38-4.22 (m, 4H), 4.16-4.10 (m, 1H), 3.41 (s, 3H), 3.24 (dd, *J* 13.8 and 3.8, 1H), 2.93 (dd, *J* 13.8 and 8.2, 1H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 155.7, 134.1, 129.3 (2C), 129.0 (2C), 127.5, 75.3, 69.8, 67.4, 59.9, 58.1, 57.4, 37.9 HRMS *m/z* (TOF MS ES+): calculated for $C_{14}H_{15}NO_3Na$: 268.0950, found 268.0949 [*M*+*Na*].

(4*S*)-4-Benzyl-3-(3-cyclohexyl-3-methoxyprop-1-yn-1-yl)oxazolidin-2-one (270)



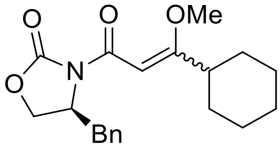
Following GP2 using amide (*S*)-4-benzyloxazolidin-2-one **267** (1.77 g) and (1-methoxyprop-2-yn-1-yl)cyclohexane **218** (304 mg, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (3:2)] unreacted (*S*)-4-benzyloxazolidin-2-one (1.37 g) was recovered along with ynamide **270** was isolated as a white solid (365 mg, 56%, *dr* ~1:1); mp: 73-74 ºC; ν_{max} (neat)/cm^{-1}= 2982, 2924, 2853, 2820, 2253, 1769, 1451, 1410, 1179, 1102, 1083, 750, 737, 701; ^{1}H-NMR (300 MHz; CDCl$_3$): Both diastereoisomers δ_H= 7.39-7.27 (m, 6H), 7.71-7.24 (m, 4H), 4.37-4.21 (m, 4H), 4.17-4.09 (m, 2H), 3.95 (d, *J* 6.2, 1H), 3.94 (d, *J* 6.2, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.23 (dd, *J* 13.7 and 2.7, 2H), 2.95 (dd, *J* 13.7 and 8.1, 2H), 1.92-1.62 (m, 12H), 1.34-1.06 (m, 10H); ^{13}C-NMR (101 MHz; CDCl$_3$): Both diastereoisomers δ_c= 155.6 (2C), 134.1, 134.1, 129.3 (4C), 129.0 (2C), 129.0 (2C), 127.5, 127.4, 76.4, 76.4, 75.4, 75.3, 71.3, 71.2, 67.3, 67.2, 58.2, 58.2, 56.6, 56.6, 42.6, 42.6, 37.8, 37.7, 29.1, 29.0, 28.5 (2C), 26.4 (2C), 25.9 (4C); HRMS *m/z* (TOF MS ES+): calculated for $C_{20}H_{25}NO_3Na$: 350.1732, found 350.1720 [*M*+*Na*].

(E) and (Z)-(*S*)-4-Benzyl-3-(3-methoxyacryloyl)oxazolidin-2-one (271)



Following GP4A using ynamide **269** (74 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (1:1)] **271** was afforded in combined yield of 81% [*E*:*Z* (1.5:1)]. Following GP4B using ynamide **269** (74 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (1:1)] **271** was afforded in combined yield of 91% [*E*:*Z* (1.9:1)]; enimide (*E*)-**271**, white solid: mp: 117-119 ºC; ν_{max} (neat)/cm^{-1}= 3066, 3034, 2997, 2939, 2867, 1767, 1669, 1606, 1387, 1347, 1309, 1206, 1171, 1107, 1076, 1019, 978, 798, 753, 702; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.91 (d, *J* 12.4, 1H), 7.40-7.21 (m, 5H), 6.77 (d, *J* 12.4, 1H), 4.81-4.71 (m, 1H), 4.26-4.14 (m, 2H), 3.81 (s, 3H), 3.34 (dd, *J* 13.4 and 3.3, 1H), 2.82 (dd, *J* 13.4 and 9.5, 1H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 162.8, 162.6, 153.4, 135.6, 129.4 (2C), 128.8 (2C), 127.1, 95.1, 65.8, 63.1, 55.2, 38.0; HRMS *m/z* (TOF MS EI+): calculated for $C_{14}H_{15}NO_4$: 261.1001, found 261.1008 [*M*]; (*Z*)-**271**, colourless oil: ν_{max} (neat)/cm^{-1}= 3063, 3029, 2981, 2940, 1769, 1677, 1599, 1388, 1355, 1202, 1171, 1054, 823, 811, 730, 699; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.41-7.24 (m, 5H), 6.69 (d, *J* 7.1, 1H), 6.43 (d, *J* 7.1, 1H), 4.79-4.70 (m, 1H), 4.24-4.14 (m, 2H), 4.02 (s, 3H), 3.42 (dd, *J* 13.2 and 3.0, 1H), 2.79 (dd, *J* 13.2 and 9.8, 1H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 165.6, 165.2, 153.6, 135.5, 129.4 (2C), 128.9 (2C), 127.2, 95.8, 65.9, 57.7, 55.2, 38.0; HRMS *m/z* (TOF MS EI+): calculated for $C_{14}H_{15}NO_4$: 261.1001, found 261.0998 [*M*].

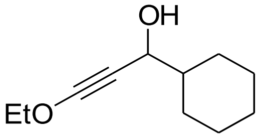
(E) and (Z)-(*S*)-4-Benzyl-3-(3-cyclohexyl-3-methoxyacryloyl)oxazolidin-2-one (272)



Following GP4A using ynamide **270** (98 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (4:1)] **272** was afforded in combined yield of 79% [*E*:*Z* (10.9:1)]. Following GP4B using ynamide **270** (98 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (4:1)] **272** was afforded in combined yield of 88% [*E*:*Z* (1:6.1)]; (*E*)-**272**, colourless oil: ν_{max} (neat)/cm^{-1}= 2926, 2853, 1764, 1673, 1588, 1384, 1347, 1286, 1196, 1170, 1069, 1037, 822, 810, 728, 699; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.32-7.17 (m, 5H), 6.43 (s, 1H), 4.77-4.66 (m, 1H), 4.14-4.02 (m, 2H), 3.74-3.58 (m, 1H), 3.67 (s, 3H) 3.31 (dd, *J* 13.4 and 3.4, 1H), 2.74 (dd, *J* 13.4 and 9.6, 1H), 1.81-1.59 (m, 5H), 1.53-1.06 (m, 5H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 182.8, 164.8, 153.8, 135.7, 129.5 (2C), 128.8 (2C), 127.1, 89.2, 65.5, 55.9, 55.2, 40.6, 38.2, 29.8, 29.5, 26.1, 26.0, 25.9; HRMS *m/z* (TOF MS ES+): calculated for $C_{20}H_{25}NO_4Na$: 366.1681, found 366.1672 [*M+Na*]; (Z)-**272**, colourless oil: ν_{max} (neat)/cm^{-1}= 2930, 2855, 1768, 1668, 1600, 1451, 1385, 1347, 1246, 1194, 1077, 1006, 826, 735, 732, 700; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.32-7.16 (m, 5H), 6.29 (s, 1H), 4.71-4.61 (m, 1H), 4.14-4.00 (m, 2H), 3.89 (s, 3H), 3.32 (dd, *J* 13.3 and 3.2, 1H), 2.70 (dd, *J* 13.3 and 9.8, 1H), 2.30-2.16 (m, 1H), 1.96-1.60 (m, 5H), 1.42-1.09 (m, 5H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 179.7, 163.2, 153.6, 135.7, 129.4 (2C), 128.8 (2C), 127.1, 93.2, 65.6, 58.8, 55.2, 43.1, 38.1, 31.2, 31.2, 26.1 (2C), 25.8; HRMS *m/z* (TOF MS ES+): calculated for $C_{20}H_{25}NO_4Na$: 366.1681, found 366.1688 [*M+Na*].

(*E*)-**272**: a NOE contact is evident between the vinylic proton at 6.43 ppm and the methyl protons at 3.67 ppm. No NOE contacts were observed between the vinylic proton and the proton at 1.82-3.67 ppm, or between the vinylic proton and the methylene protons at 1.81-1.59 ppm or 1.53-1.06 ppm. This confirms the stereochemistry assigned.

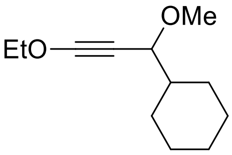
1-Cyclohexyl-3-ethoxyprop-2-yn-1-ol (287)



To a solution of ethoxyacetylene (40% w/w h exanes, 1.05 mL, 4.4 mmol)) in dry THF (15 mL) at -78 °C under argon atmosphere was added *n*-BuLi (2.5 M in hexane, 1.8 mL, 4.4 mmol). After stirring for 30 min at -78 °C, the reaction was added of cyclohexyl aldehyde **216** (0.54 mL, 4.4 mmol) and kept stirring for additional 30 min. The reaction mixture was allowed to warm up to room temperature and quenched with a saturated solution of ammonium chloride (15 mL). The aqueous layer was separated and extracted with EtOAc (3 x 10 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. After evaporation of the solvent, the crude mixture was purified by flash chromatography [hexanes:EtOAc (4:1)] to give alcohol **287** (621 mg, 84%) as a colourless liquid: ν_{max} (neat)/cm^{-1}= 3461, 2926, 2853, 2262, 2225, 1731, 1654, 1226, 1449, 1177, 1093, 994; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 4.18 (t, *J* 5.6, 1H), 4.09 (q, *J* 7.1, 2H), 1.91 -1.41 (m, 6H), 1.37 (t, *J* 7.1, 3H), 1.33 -0.95 (m, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 94.4, 74.6, 67.1, 44.7, 38.4, 28.7, 28.1, 26.5, 25.9 (2C), 14.4; HRMS *m/z* (TOF MS EI+): calculated for $C_{11}H_{18}O_2$: 182.1307, found: 182.1309 [*M*].

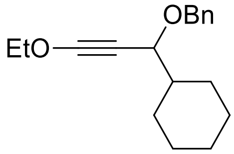
Data were in agreement with those reported in the literature.[121]

(3-Ethoxy-1-methoxyprop-2-yn-1-yl)cyclohexane (288)



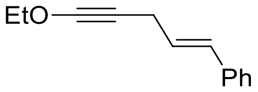
Following GP5 using iodomethane (74 µL). After purification by flash chromatography [hexanes:EtOAc (19:1)] to give ynol ether **288** as a light-yellow oil (182 mg, 93%): ν_{max} (neat)/cm^{-1}= 2928, 2854, 2259, 1734, 1449, 1373, 1274, 1170, 1135, 1108, 1085, 1040, 999, 955, 886, 841, 757 ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 4.10 (q, *J* 7.1, 2H), 3.74 (d, *J* 5.9, 1H), 3.66 (s, 3H), 1.88-1.48 (m, 5H), 1.38 (t, *J* 7.1, 3H), 1.31-1.00 (m, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 95.1, 76.3, 74.5, 56.2, 43.1, 35.7, 29.1, 28.4, 26.5, 26.0, 26.0, 14.4; HRMS *m/z* (TOF MS EI+): calculated for $C_{12}H_{20}O_2$: 196.1463, found 196.1460 [*M*].

(((1-Cyclohexyl-3-ethoxyprop-2-yn-1-yl)oxy)methyl)benzene (289)



Following GP5 using benzyl bromide (0.15 mL,) and a catalytic amount of *n*-tetrabutylammonium iodide (36.9 mg, 0.1 mmol). After purification by flash chromatography [hexanes:EtOAc (19:1)] gave ynol ether **289** as a colourless oil (248 mg, 91%): ν_{max} (neat)/cm^{-1}= 2925, 2852, 2258, 1182, 1164, 1451, 1243, 1101, 1085, 996, 1027, 996, 842, 734, 696; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.39-7.23 (m, 5H), 4.77 (d, *J* 12.0, 1H), 4.47 (d, *J* 12.0, 1H), 4.11 (q, *J* 7.1, 2H), 3.99 (d, *J* 6.2, 1H), 1.92-1.56 (m, 5H), 1.40 (t, *J* 7.1, 3H), 1.34-0.90 (m, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 138.8, 128.2 (2C), 127.8 (2C), 127.3, 95.1, 74.5, 73.6, 70.0, 43.3, 36.1, 29.2, 28.7, 26.6, 26.0 (2C), 14.4; HRMS *m/z* (TOF MS ES+) calculated for $C_{18}H_{24}NO_2Na$: 295.1674, found 295.1670 [*M+Na*];

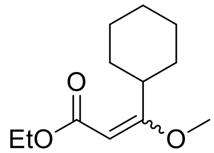
(*E*)-(5-Ethoxypent-1-en-4-yn-1-yl)benzene (290)



To a solution of ethoxyacetilene (40% in hexanes, 0.72 mL, 3 mmol) in dry THF (1.9 mL, 1.6 M) at -78 °C was added *n*-butyl lithium (2.5 M in hexane, 1.26 mL, 3.15 mmol). After stirring for 30 min at -78 °C, cynnamyl bromide (650 mg, 3.3 mmol) and a catalytic amount of copper bromide (24 mg, 0.17 mmol) were added and the mixture was stirred at 50 °C for 5 h. The reaction was quenched with EtOAc (5 mL) and the organic mixture was quickly washed with water (10 mL).

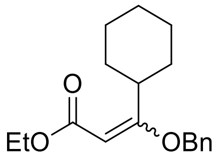
The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes:toluene (9:1)] gave *ynol ether* **8** as a colourless oil (492mg, 44%): ν_{max} (neat)/cm^{-1}= 3038, 3060, 3028, 2982, 2899, 2270, 1495, 1448, 1221, 1011, 963, 868, 844, 750, 729, 691; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.33-7.14 (m, 5H), 6.58 (dt, *J* 15.7 and 1.8, 1H), 6.15 (dt, *J* 15.7 and 5.5, 1H), 4.05 (q, *J* 7.1, 2H), 3.04 (dd, *J* 5.5 and 1.9), 1.35 (t, *J* 7.1, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 137.4, 130.3, 128.5 (2C), 127.1, 126.3, 126.2 (2C), 91.4, 74.1, 34.3, 20.9, 14.4; HRMS *m/z* (TOF MS EI+): calculated for $C_{13}H_{14}NO$: 186.1045, found 186.1053 [*M*].

(*E*)-Ethyl 3-cyclohexyl-3-methoxyacrylate (291)



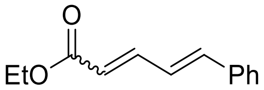
Following GP4A using *ynol ether* **288** (59 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (24:1)] *ester* (*E*)-**291** was afforded in yield of 77%. Following GP4B using *ynol ethers* **288** (59 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (24:1)] *ester* **291** was afforded in yield of 72% [*E*:*Z* (3.9:1)]; *ester* (*E*)-**291**, colourless oil: ν_{max} (neat)/cm^{-1}= 2927, 2853, 1705, 1612, 1449, 1381, 1276, 1231, 1133, 1065, 1042, 821; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 4.99 (s, 1H), 4.12 (q, *J* 7.1, 2H), 3.88 (s, 3H), 2.19-2.06 (m, 1H), 1.89-1.63 (m, 4H), 1.33-1.15 (m, 6H), 1.26 (t, *J* 7.1, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 176.7, 165.8, 94.4, 59.5, 59.4, 43.4, 31.1 (2C), 26.2 (2C), 26.0, 14.3; HRMS *m/z* (TOF MS EI+):calculated for $C_{12}H_{20}O_3$: 212.1412, found 212.1408 [*M*]; *ester* (*Z*)-**291**, colourless oil: ν_{max} (neat)/cm^{-1}= 2927, 2854, 1707, 1611, 1449, 1381, 1277, 1232, 1131, 1065, 1042, 820; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 4.88 (s, 1H), 4.12 (q, *J* 7.1, 2H), 3.72-3.56 (m, 1H), 3.59 (s, 3H), 1.81-1.60 (m, 4H), 1.52-1.04 (m, 6H), 1.27 (t, *J* 7.1, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 180.1, 167.6, 89.0, 59.2, 55.4, 39.5, 29.8 (2C), 26.2 (2C), 26.0, 14.4; HRMS *m/z* (TOF MS EI+): calculated for $C_{12}H_{20}O_3$: 212.1412, found 212.1415 [*M*].

Ethyl 3-(benzyloxy)-3-cyclohexylacrylate (292)



Following GP4A using *ynol ether* **289** (82 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (3:2)] *ester* **292** was afforded in combined yield of 89% [*E*:*Z* (2.8:1)]. Following GP4B using *ynol ether* **289** (82 mg) for 20 h. After purification by flash chromatography [hexanes:EtOAc (3:2)] *ester* **292** was afforded in combined yield of 85% [*E*:*Z* (5.1:1)]; *ester* (*E*)-**292**, colourless oil: ν_{max} (neat)/cm^{-1}= 2980, 2927, 2854, 1706, 1609, 1450, 1377, 1276, 1229, 1130, 1058, 819, 733, 695; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.43-7.28 (m, 5H), 5.01 (s, 1H), 4.81 (s, 2H), 4.12 (q, *J* 7.1, 2H), 3.74 (tt, *J* 11.5 and 3.0, 1H), 1.82-1.13 (m, 13H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 178.9, 167.5, 136.0, 128.5 (2C), 128.0, 127.1 (2C), 90.2, 69.9, 59.2, 39.7, 29.9 (2C), 26.1 (2C), 25.9, 14.4; HRMS *m/z* (TOF MS ES+): calculated for $C_{18}H_{24}O_3Na$: 311.1623, found 311.1634 [*M*+*Na*].

(*E,E*) and (*E,Z*)-ethyl 5-phenylpenta-2,4-dienoate (293)

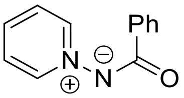


Following GP2A using *ynol ether* **290** (56 mg) for 20 min. After purification by flash chromatography [hexanes:EtOAc (24:1)] *ester* **293** was afforded in combined yield of 75% [*E*:*Z* (4.3:1)]. Following GP2B using *ynol ether* **290** (56 mg) for 1 h. After purification by flash chromatography [hexanes:EtOAc (24:1)] *ester* **293** was afforded in combined yield of 88% [*E*:*Z* (4.1:1)]; *ester* (*E*,*E*)-**293**, colourless oil: ν_{max} (neat)/cm^{-1}= 3059, 3027, 2981, 2935, 2904, 1703, 1625, 1366, 1258, 1235, 1175, 1130, 1035, 996, 754, 713, 689; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.50-7.28 (m, 6H), 6.90 (s, 1H), 6.88 (d, *J* 5.2, 1H), 5.98 (d, *J* 15.3, 1H), 4.23 (q, *J* 7.2, 2H), 1.32 (t, *J* 7.2, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 167.0, 144.5, 140.3, 136.0, 129.0, 128.8 (2C), 127.1 (2C), 126.2, 121.3, 60.3, 14.3; HRMS *m/z* (TOF MS EI+): calculated for $C_{13}H_{14}O_2$:

202.0994, found 202.0986 [*M*]; *ester* (*E*,*Z*)-**293**, colourless oil: ν_{max} (neat)/cm^{-1}= 3063, 3027, 2981, 2932, 2871, 1709, 1622, 1601, 1450, 1419, 1175, 1233, 1030, 999, 960, 755, 698; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.15 (ddd, *J* 15.7, 11.4 and 0.9, 1H), 7.56-7.49 (m, 2H), 7.39-7.27 (m, 3H), 6.82 (d, *J* 15.7, 1H), 6.74 (td, *J* 11.4 and 0.9, 1H), 5.72 (d, *J* 11.4, 1H), 4.23 (q, *J* 7.2, 2H), 1.33 (t, *J* 7.2, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 166.6, 144.7, 141.1, 136.4, 128.9, 128.7 (2C), 127.5 (2C), 125.0, 117.5, 60.0, 14.3; HRMS *m/z* (TOF MS EI+): calculated for $C_{13}H_{14}O_2$: 202.0994, found 202.0988 [*M*].

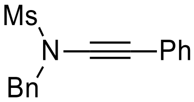
Characterisation for chapter 3

N-Benzoyliminopyridinium ylide (295)



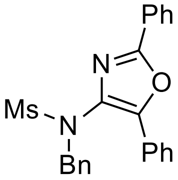
Following GP6 using *N*-aminopyridinium iodide **294** (444 mg, 2 mmol) and benzoyl chloride (0.46 mL, 4 mmol). After recrystallisation from dichloromethane-diethylether ylide **295** was isolated as a white solid (190 mg, 48%): mp:187-189 ºC; ν_{max} (neat)/cm^{-1}= 3098, 3064, 2944, 1618, 1590, 1547, 1464, 1332, 1295, 1180, 904, 710; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.85-8.81 (m, 2H), 8.18-8.13 (m, 2H), 7.97-7.91 (m, 1H), 7.73-7.66 (m, 2H), 7.46-7.38 (m, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 170.7, 143.3 (2C), 137.2, 136.6, 130.1, 128.0 (2C), 127.8 (2C), 125.9 (2C); HRMS *m/z* (TOF MS EI+): calculated for $C_{12}H_{10}N_2O$: 198.0793, found 198.0795 [*M*].

N-Benzyl-*N*-phenylethynyl-methanesulfonamide (296)



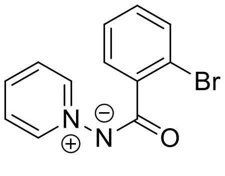
Following GP2 using amide **212** (2.78 g, 15 mmol) and phenylacetylene **162** (0.33 mL, 3 mmol). After purification by flash chromatography [hexanes:toluene (4:1)] ynamide **296** was isolated as a light-yellow solid (624 mg, 73%): mp: 50-52 ºC; ν_{max} (neat)/cm^{-1}= 3056, 3036, 3008, 2926, 2235, 1498, 1457, 1349, 1156, 1121, 966, 944; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.60-7.15 (stach, 10H), 4.68 (s, 2H), 2.90 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 134.5, 131.3 (2C), 129.0 (2C), 128.8 (2C), 128.7, 128.3 (2C), 128.0, 122.4, 82.0, 71.6, 55.9, 38.9; HRMS *m/z* (TOF MS ES+): calculated for $C_{16}H_{15}NO_2NaS$: 308.0721, found 308.0729 [*M*+*Na*]. Spectroscopic data were identical to those reported in literature.[122]

***N*-Benzyl-*N*-(2,5-diphenyl-oxazol-4-yl)-methanesulfonamide (297)**



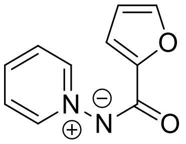
Following GP7 using ynamide **296** (28.5 mg, 0.1 mmol) and ylide **295** (29.7 mg, 0.15 mmol) for 24 h. After purification by flash chromatography [hexanes:EtOAc (4:1)] oxazole **297** was isolated as a white solid (37.7 mg, 93%): mp: 156-158 ºC; ν_{max} (neat)/cm^{-1}= 3064, 3027, 3005, 2929, 1620 1448, 1345, 1221, 1155, 1053, 1024, 958, 854, 757, 699, 686, 683; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.13-8.04 (m, 2H), 7.81-7.74 (m, 2H), 7.55-7.49 (m, 3H), 7.39-7.24 (m, 5H), 7.17-7.12 (m, 3H), 4.84 (s, 2H), 3.23 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 158.3, 147.2, 134.6, 132.7, 130.7, 129.4 (2C), 128.8 (2C), 128.8 (2C), 128.3 (2C), 128.2 (2C), 128.0, 127.0, 126.5, 126.3 (2C), 125.5, 54.8, 38.5; HRMS *m/z* (TOF MS ES+):calculated for $C_{23}H_{20}N_2O_3NaS$: 427.1092, found 427.1101 [*M*+*Na*].

***N*-2-Bromobenzoyliminopyridinium ylide (298)**



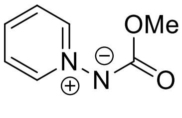
Following GP6 using *N*-aminopyridinium iodide **294** (444 mg, 2 mmol) and 2-bromobenzoyl chloride (0.55 mL, 4 mmol). After recrystallisation from dichloromethane-diethylether ylide **298** was isolated as a white solid (290 mg, 53%): mp: 102-103 ºC; ν_{max} (neat)/cm^{-1}= 3107, 3056, 3027, 1582, 1558, 1464, 1344, 1251, 1168, 1020, 774, 748, 677; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 8.92-8.86 (m, 2H), 8.03-7.92 (m, 1H), 7.98-7.90 (m, 2H), 7.65-7.57 (m, 2H), 7.37-7.29 (m, 1H), 7.24-7.16 (m, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 172.5, 143.1 (2C), 140.4, 137.4, 133.0, 129.5, 129.2, 127.1, 126.2 (2C), 120.7; HRMS *m/z* (TOF MS ES+): calculated for $C_{12}H_9N_2O_2NaBr$: 298.9796, found 298.9783 [*M+Na*].

***N*-2-Furoyliminopyridinium ylide (299)**



Following GP6 using *N*-aminopyridinium iodide **294** (444 mg, 2 mmol) and 2-furoyl chloride (0.39 mL, 2 mmol). After recrystallisation from dichloromethane-diethylether ylide **299** was isolated as a white solid (135 mg, 36%): mp: 184-186 ºC; ν_{max} (neat)/cm^{-1}= 3105, 3057, 3029, 2930, 2857, 1556, 1530, 1466, 1327, 1172, 1194, 1107, 1005, 754, 683, 622; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 8.84 (d, *J* 6.7, 2H), 7.98-7.88 (m, 1H), 7.68 (t, *J* 7.0, 2H), 7.49 (br s, 1H), 7.07 (d, *J* 3.3, 1H), 6.51-6.40 (m, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 163.6, 151.2, 143.4 (2C), 143.2, 136.9, 126.0 (2C), 112.8, 111.1; HRMS *m/z* (TOF MS ES+): calculated for $C_{10}H_8N_2O_2Na$: 211.0483, found 211.0484 [*M+Na*].

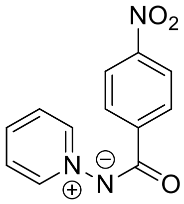
***N*-Methoxycarbonyliminopyridinium ylide (300)**



Following GP1 using *N*-aminopyridinium iodide **294** (444 mg, 2 mmol) and methyl chloroformate (0.31 mL, 4 mmol). After recrystallisation from dichloromethane-diethylether ylide **300** was isolated as a white solid (255 mg, 84%): mp: 92-94 ºC; ν_{max} (neat)/cm^{-1}= 3044, 3075, 3010, 2941, 2912, 2822, 1629, 1597, 1480, 1464, 1434, 1285, 1191, 1065, 772, 682; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 8.65-8.60 (m, 2H), 7.70-7.63 (m, 1H), 7.45 (t, *J* 7.2, 2H), 3.52 (s, 3H); ^{13}C-

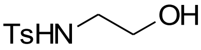
NMR (101 MHz; $CDCl_3$): δ_c= 163.6, 142.0 (2C), 135.1, 125.6 (2C), 51.3; HRMS *m/z* (TOF MS EI+): calculated for $C_7H_8N_2O_2$: 152.0586, found 152.0580 [*M*].

N-4-nitrobenzoyliminopyridinium ylide (301)



Following GP1 using *N*-aminopyridinium iodide **294** (444 mg, 2 mmol) and methyl chloroformate (0.31 mL, 4 mmol). After recrystallisation from dichloromethane-diethylether ylide **301** was isolated as a white solid (255 mg, 84%): mp: 92-94 ºC; ν_{max} (neat)/cm^{-1}= 3112, 3075, 3048, 2923, 2853, 1554, 1506, 1460, 1308, 870, 852, 772, 712, 674, ; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 8.65-8.60 (m, 2H), 7.70-7.63 (m, 1H), 7.45 (t, *J* 7.2, 2H), 3.52 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 163.6, 142.0 (2C), 135.1, 125.6 (2C), 51.3; HRMS *m/z* (TOF MS ES+): calculated for $C_{12}H_9N_3O_3Na$: 266.0542, found: 266.0549 [*M+Na*].

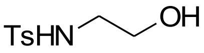
N-(4-methylbenzenesulfonyl)hydroxyethyl amide (303)



A solution of the ethanolamine **302** (4.06 mL, 67.5 mmol) and thiethylamine (10.6 mL, 76.5 mmol) in CH_2Cl_2 (100 mL) was added to a solution of 4-methylbenzene sulfonyl chloride (8.59 g, 45 mmol) in 10 mL of CH_2Cl_2. After 1 h at reflux and 30 min at room temperature, the crude reaction was added to a saturated aqueous solution of $NaHCO_3$ (150 mL). The organic phase was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated to provide the crude product. After purification by re-crystallisation with CH_2Cl_2/Hexane amide **303** was isolated as a white solid (8.47 g, 88%): mp: 53-55 °C; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.75 (d, *J* 8.3, 2H), 7.31 (d, *J* 8.3, 2H), 5.25 (brs, 1H), 3.69 (q, *J* 5.4, 2H), 3.08 (q, *J* 10.4, 2H), 2.42 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 143.6, 136.6, 129.8 (2C), 127.1 (2C), 61.3, 45.2, 21.5.

Data were in agreement with those reported in the literature.[123]

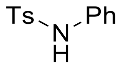
N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-methylbenzenesulfonamide (304)



TBSCl (50% sol. in toluene, 13.4 mL, 38.5 mmol) was added to a solution of the ethanolsulfonylamine **303** (7.52 g, 35 mmol), triethylamine (15 mL, 115 mmol) and dimethylamino pyridine (213 mg, 5 mol%) in CH_2Cl_2 (170 mL) at 0 ºC. After 1 h at reflux and 30 min at room temperature, the crude reaction was added to a saturated aqueous solution of ammonium chloride (150 mL). The organic phase was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated to provide the crude product. After purification by flash chromatography [hexanes:EtOAc (17:3)] silyl ether **304** was isolated as a light yellow liquid (9.29 g, 81%): ν_{max} (neat)/cm^{-1}= 3560, 3262, 2882, 2935, 1597, 1427, 1308, 1150, 1065, 950, 812, 660; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.74 (d, *J* 8.0, 2H), 7.30 (d, *J* 8.0, 2H), 4.79 (brs, 1H), 3.60 (t, *J* 5.6, 2H), 3.02 (q, *J* 5.6, 2H), 2.42 (s, 3H), 0.83 (s, 9H), -0.02 (s, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 143.3, 136.9, 129.6 (2C), 127.0 (2C), 61.2, 45.1, 25.7 (3C), 21.4, 18.1, -5.5 (2C).

Data were in agreement with those reported in the literature.[124]

4-methyl-*N*-phenylbenzenesulfonamide (306)

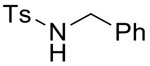


$$\mathrm{Ts}\diagdown\underset{\mathrm{H}}{\mathrm{N}}\diagup\mathrm{Ph}$$

A solution of aniline **143** (2.70 mL, 30 mmol,) and pyridine (15 mL, 30 mmol) in CH_2Cl_2 (50 mL) was added drop-wise to a solution of tosyl chloride (6.86 g, 36 mmol) in CH_2Cl_2 (10 mL) at reflux. After 2 h, the solution is left stirring overnight at room temperature. The reaction mixture was added to a saturated aqueous solution of $NaHCO_3$ (50 mL). The organic phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. After purification of the solid by re-crystallisation with CH_2Cl_2/hexanes, sulfonylamide **306** was isolated as a white solid (7.20 g, 97%): mp: 102-104 °C; ν_{max} (neat)/cm^{-1}= 3237, 3061, 2980, 2899, 1597, 1481, 1414, 1336, 1319, 1291, 1223, 1186, 1031, 810, 753; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.67 (d, *J* 8.3, 2H), 7.26-7.20 (m, 4H), 7.12-7.06 (m, 3H), 6.94 (s, 1H), 2.37 (s, 3H), ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 143.9, 136.5, 136.1, 129.7 (2C), 129.3 (2C), 127.3 (2C), 125.3, 121.6 (2C).

Data were in agreement with those reported in the literature.[125]

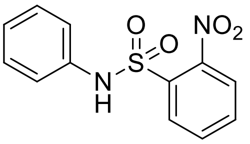
***N*-benzyl-4-methylbenzenesulfonamide (307)**



A solution of benzylamine **210** (2.74 mL, 30 mmol,) and pyridine (15 mL, 30 mmol) in CH_2Cl_2 (50 mL) was added drop-wise to a solution of tosyl chloride (6.86, 36 mmol) in CH_2Cl_2 (10 mL) at reflux. After 2 h, the solution is left stirring overnight at room temperature. The reaction mixture was added to a saturated aqueous solution of $NaHCO_3$ (50 mL). The organic phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. After purification of the solid by re-crystallisation with CH_2Cl_2/hexanes, sulfonylamide **307** was isolated as a white solid (6.89 g, 88%): mp: 113-115 °C; ν_{max} (neat)/cm^{-1}= 3361, 3284, 3033, 2925, 2872, 1599, 1456, 1330, 1162; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.76 (d, *J* 8.4, 2H), 7.31-7.25 (m, 5H), 7.24-7.17 (m, 2H), 4.57 (t, *J* 5.7, 1H), 4.13 (d, *J* 6.0, 2H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_C= 143.6, 137.0, 136.4, 129.9 (2C), 128.8 (2C), 128.0 (2C), 128.0, 127.3 (2C), 47.4, 21.7.

Data were in agreement with those reported in the literature.[126]

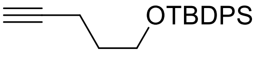
2-Nitro-*N*-phenylbenzenesulfonamide (308)



2-nitrobenzenesulfonyl chloride (3.32 g, 15 mmol) was added to a solution of aniline **143** (1.06 mL, 18 mmol) and sodium acetate (1.72 g, 21) in 15 mL of 1:1 MeOH/water over 30 min. The mixture was heated at 60 °C for 1 h. The solution was cooled to room temperature and diluted with water (60 mL). The water solution was treated with HCl conc. (36% w/w) until pH = 2 was reached and filtered off. After purification of the solid by re-crystallisation with EtOAc/Hexane sulfonylamide **308** was isolated as a yellow solid (3.43 g, 68%): mp: 111-113 °C; ν_{max} (neat)/cm^{-1}= 3319, 3100, 2892, 1538, 1496, 1403, 1358, 1168, 1126, 921, 854, 782, 741, 695, 656.; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.85 (dd, *J* 8.1 and 1.4, 1H), 7.82 (dd, *J* 7.9 and 1.1, 1H), 7.69 (td, *J* 8.1 and 1.4, 1H), 7.57 (td, *J* 7.9 and 1.1 Hz, 1H), 7.31-7.23 (m, 3H), 7.22-7.13 (m, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 148.2, 135.5, 133.9, 132.5, 132.2, 131.8, 129.4 (2C), 126.6, 125.3 (2C), 123.3; HRMS *m/z* (TOF MS EI+): calculated for $C_{14}H_{10}Br_2$: 337.9129, found: 337.9129, [*M*].

Data were in agreement with those reported in the literature.[127]

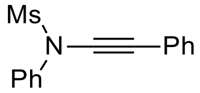
tert-Butyl(pent-4-yn-1-yloxy)diphenylsilane (309)



TBDPSCl (3.12 mL, 12 mmol) was added to a solution of 4-Pentyn-1-ol **229** (0.96 mL, 10 mmol) and 1-*H*-imidazole (680 mg, 10 mmol) in THF (15 mL) at room temperature and stirred overnight. The reaction mixture was filtered through a pad of celite and the organic solution was concentrated under reduced pressure. After evaporation of the solvent, the crude mixture was purified. The residue was purified by vacuum distillation (200 °C, 16 mmHg) and afforded the silyl ether **309** (2.19 g, 68%) as a colourless oil: ν_{max} (neat)/cm^{-1}= 3307, 3017, 2931, 2857, 1589, 1472, 1361, 1104, 981, 822, 739, 699; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.70 -7.64 (m, 4H), 7.45 -7.35 (m, 6H), 3.75 (t, *J* 6.0, 2H), 2.35 (td, *J* 7.2, 2.7, 2H), 1.92 (t, *J* 2.7, 1H), 1.84 - 1.70 (m, 2H), 1.05 (s, 9 H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 135.5 (2C), 133.8, 129.5, 127.6 (2C), 84.2, 68.2, 62.2, 31.4, 26.8, 19.2, 14.9.

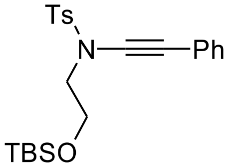
Data were in agreement with those reported in the literature.[128]

***N*-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-*N*-phenylethynyl-methanesulfonamide (310)**



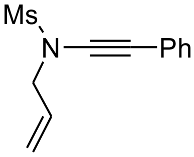
Following GP2 using amide **221** (2.57 g, 15 mmol) and phenylacetylene (0.33 mL, 3 mmol). After purification by flash chromatography [hexanes:EtOAc (4:1)] ynamide **310** was isolated as a white solid (601 mg, 74%): mp: 75-77 ºC; ν_{max} (neat)/cm^{-1}= 3078, 3009, 2928, 2243, 1588, 1482, 1365, 1324, 1164, 1156, 962, 893, 744, 689; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.64-7.55 (m, 2H), 7.51-7.28 (m, 8H), 3.17 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 138.7, 131.6 (2C), 129.5 (2C), 128.3 (3C), 128.2, 125.6 (2C), 122.3, 82.0, 71.0, 36.8; HRMS *m/z* (TOF MS EI+): calculated for $C_{15}H_{13}NO_2S$: 271.0667, found 271.0668 [*M*].

***N*-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-*N*-phenylethynyl-methanesulfonamide (311)**



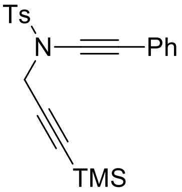
Following GP2 using amide **304** (4.93 g, 15 mmol) and phenylacetylene (0.33 mL, 3 mmol). After purification by flash chromatography [hexanes:EtOAc (23:4)] ynamide **311** was isolated as a light-yellow oil (749 mg, 58%): ν_{max} (neat)/cm^{-1}= 2953, 2928, 2856, 2235, 1597, 1365, 1254, 1169, 1089, 1002, 915, 811, 775; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.89-7.82 (m, 2H), 7.42-7.27 (m, 7H), 3.87 (t, *J* 6.1, 2H), 3.54 (t, *J* 6.1, 2H), 2.45 (s, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 144.5, 134.9, 131.3 (2C), 129.7 (2C), 128.2 (2C), 127.7 (3C), 122.9, 82.7, 70.3, 60.6, 53.6, 25.8 (3C), 21.6, 18.3, -5.4 (2C); HRMS *m/z* (TOF MS ES+): calculated for $C_{23}H_{31}NO_3NaSiS$: 452.1692, found 452.1687 [*M*+*Na*].

***N*-Allyl-*N*-phenylethynyl-methanesulfonamide (313)**



Following GP2 using amide **305** (1.35 g, 10 mmol) and phenylacetylene (0.22 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (4:1)] ynamide **312** was isolated as a yellow solid (324 mg, 69%): mp: 50-52 ºC; ν_{max} (neat)/cm^{-1}= 3081, 3052, 3029, 3008, 2933, 2278, 2241, 1596, 1440, 1344, 1330, 1158, 1105, 1023, 932, 915, 754, 691; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.43-7.38 (m, 2H), 7.33-7.27 (m, 3H), 6.00 (ddt, *J* 16.8, 10.1, 6.4, 1H), 5.44 (ddt, *J* 16.8, 1.2 and 1.2, 1H), 5.38 (ddt, *J* 10.1, 1.2 and 1.2, 1H), 4.17 (dt, *J* 6.4 and 1.2, 2H), 3.14 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 131.5 (2C), 130.9, 128.3 (2C), 128.0, 122.5, 120.5, 81.6, 71.2, 54.4, 39.0; HRMS *m/z* (TOF MS ES+): calculated for $C_{12}H_{13}NO_2NaS$: 258.0565, found 258.0567 [*M*+*Na*].

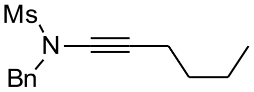
4-Methyl-*N*-phenylethynyl-*N*-(3-trimethylsilanyl-prop-2-ynyl)-benzenesulfonamide (312)



Following GP2 using amide **215** (4.22 g, 15 mmol) and phenylacetylene (0.33 mL, 3 mmol). After purification by flash chromatography [hexanes:EtOAc (19:1)] ynamide **312** was isolated as a white solid (582 mg, 51%): mp: 97-99 ºC; ν_{max} (neat)/cm^{-1}= 3084, 3030, 2960, 2899, 2235, 2185, 1595, 1493, 1421, 1362, 1246, 1171, 1040, 998, 842, 755, 662; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.91-7.87 (m, 2H), 7.42-7.28 (m, 7H), 4.35 (s, 2H), 2.46 (s, 3H), 0.04 (s, 9H); ^{13}C-

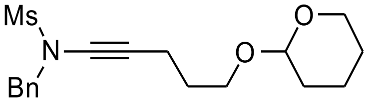
NMR (101 MHz; $CDCl_3$): δ_c= 144.8, 134.3, 131.6 (2C), 129.6 (2C), 128.3 (2C), 128.2 (2C), 127.9, 122.7, 97.0, 91.9, 81.8, 71.2, 42.7, 21.7, -0.5 (3C); HRMS *m/z* (TOF MS ES+): calculated for $C_{21}H_{23}NO_2NaSiS$: 404.1116, found 404.1120 [*M*+*Na*].

N-Benzyl-*N*-hex-1-ynyl-methanesulfonamide (314)



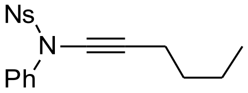
Following GP2 using amide **211** (925 mg, 5 mmol) and hex-1-yne (0.12 mL, 1 mmol). After purification by flash chromatography [hexanes:EtOAc (17:3)] ynamide **314** was isolated as a colorless oil (206 mg, 78%): ν_{max} (neat)/cm^{-1}= 2957, 2932, 2872, 2254, 1684, 1456, 1351, 1159, 1026, 956, 698; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.48-7.33 (m, 5H), 4.57 (s, 2H), 2.86 (s, 3H), 2.26 (t, *J* 6.9, 2H), 1.52-1.25 (m, 4H), 0.88 (t, *J* 7.2, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 134.8, 128.9 (2C), 128.6 (2C), 128.5, 72.9, 71.4, 55.6, 38.2, 30.9, 21.8, 18.1, 13.5; HRMS *m/z* (TOF MS ES+): calculated for $C_{14}H_{19}NO_2NaS$: 288.1034, found 288.1024 [*M*+*Na*].

N-Benzyl-*N*-[5-(tetrahydro-pyran-2-yloxy)-pent-1-ynyl]-methanesulfonamide (315)



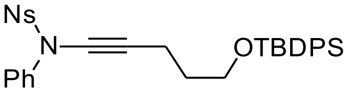
Following GP2 using amide **221** (2.78 g, 15 mmol) and 2-pent-4-ynyloxy-tetrahydro-pyran (0.52 mL, 3 mmol). After purification by flash chromatography [hexanes:EtOAc (7:3)] ynamide **315** was isolated as a yellow oil (526 mg, 50%): ν_{max} (neat)/cm^{-1}= 2939, 2869, 2259, 2042, 1680, 1454, 1352, 1305, 1133, 1074, 1030, 954, 758, 699; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.46-7.32 (m, 5H), 4.57 (s, 2H), 4.54 (t, *J* 3.5, 1H), 3.88-3.80 (m, 1H), 3.76 (dt, *J* 9.8 and 6.2, 1H), 3.52-3.43 (m, 1H), 3.39 (dt, *J* 9.8, 6.2, 1H), 2.85 (s, 3H), 2.39 (t, *J* 7.1, 2H), 1.90-1.44 (m, 8H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 134.8, 128.8 (2C), 128.7 (2C), 128.5, 98.8, 73.2, 70.7, 65.8, 62.3, 55.6, 38.3, 30.7, 29.1, 25.4, 19.6, 15.4; HRMS *m/z* (TOF MS ES+): calculated for $C_{18}H_{25}NO_4NaS$: 374.1402, found 374.1403 [*M*+*Na*].

N-Hex-1-ynyl-*N*-phenyl-2-nitro benzenesulfonamide (316)



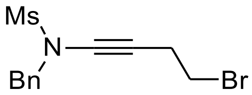
Following GP2 using amide **308** (1.39 g, 5 mmol) and hex-1-yne (0.12 mL, 1 mmol). After purification by flash chromatography [hexanes:EtOAc (9:1)] ynamide **316** was isolated as a light-yellow solid (336 mg, 94%): mp: 77-79 °C; ν_{max} (neat)/cm^{-1}= 3106, 2961, 2930, 2862, 2256, 1606, 1588, 1526, 1487, 1376, 1345, 1180, 1157, 1087, 934, 854, 737; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.37-8.29 (m, 2H), 7.88-7.79 (m, 2H), 7.41-7.30 (m, 3H), 7.28-7.17 (m, 2H), 2.31 (t, *J* 7.1, 2H), 1.58-1.31 (m, 4H), 0.91 (t, *J* 7.1, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 150.7, 141.1, 138.6, 129.4 (2C), 129.3 (2C), 128.5, 125.9 (2C), 123.9 (2C), 72.9, 71.3, 30.8, 21.9, 18.1, 13.5; HRMS *m/z* (TOF MS ES+): calculated for $C_{18}H_{18}N_2O_4NaS$: 381.0885, found 381.0892 [*M*+*Na*].

N-[5-(*tert*-Butyl-diphenyl-silanyloxy)-pent-1-ynyl]-*N*-phenyl-2-nitro benzenesulfonamide (317)



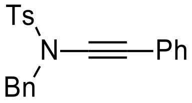
Following GP2 using amide **308** (1.39 g, 5 mmol) and *tert*-butyl-pent-4-ynyloxy-diphenyl-silane **309** (0.32 g, 1 mmol). After purification by flash chromatography [hexanes:toluene (9:1)] ynamide **317** was isolated as a light-yellow oil (442 mg, 74%): ν_{max} (neat)/cm^{-1}= 3108, 3070, 2694, 2934, 2852, 2255, 1525, 1426, 1374, 1348, 1174, 1089, 972, 733, 697, 604; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.25 (d, *J* 8.7, 2H), 7.83-7.75 (m, 2H), 7.68-7.59 (m, 4H), 7.47-7.27 (m, 9H), 7.24-7.16 (m, 2H), 3.72 (t, *J* 6.6, 2H), 2.48 (t, *J* 6.6, 2H), 1.76 (tt, *J* 6.6, 6.6, 2H), 1.03 (s, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 150.6, 141.1, 138.6, 135.5 (4C), 134.8, 133.7, 129.6 (2C), 129.3 (2C), 129.3 (2C), 128.5, 127.7 (4C), 125.9 (2C), 123.9 (2C), 73.0, 70.8, 62.3, 31.7, 26.8 (3C), 19.2, 15.0; HRMS *m/z* (TOF MS ES+): calculated for $C_{33}H_{34}N_2O_5NaSiS$: 621.1855, found 621.1859 [*M*+*Na*].

N-Benzyl-*N*-(4-bromo-but-1-ynyl)-methanesulfonamide (318)



Following GP2 using amide **212** (1.85 g, 10 mmol) and 4-bromo-but-1-yne (0.19 mL, 2 mmol). After purification by flash chromatography [hexanes:EtOAc (4:1)] ynamide **318** was isolated as a light yellow oil (432 mg, 69%): ν_{max} (neat)/cm^{-1}= 3067, 3031, 2972, 2930, 2255, 2048, 1738, 1210, 1351, 1269, 1210, 1158, 956, 979, 756, 699, 581; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.51-7.36 (m, 5H), 4.61 (s, 2H), 3.42 (t, *J* 7.0, 2H), 2.90 (s, 3H), 2.87 (t, *J* 7.0, 2H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 134.5, 128.9 (2C), 128.7 (2C), 128.6, 75.1, 68.5, 55.6, 38.6, 30.2, 23.0; HRMS *m/z* (TOF MS ES+): calculated for $C_{12}H_{14}NO_2NaBrS$: 337.9826, found 337.9820 [*M*+*Na*].

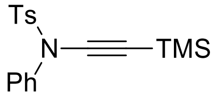
N-Benzyl-4-methyl-*N*-phenylethynyl-benzenesulfonamide (319)



Following GP2 using amide **306** (3.1 g, 12 mmol) and phenylacetylene (0.25 mL, 2.4 mmol). After purification by flash chromatography [hexanes:EtOAc (17:3)] ynamide **319** was isolated as a white solid (381 mg, 44%): ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.80 (d, *J* 8.2, 2H), 7.33-7.31 (m, 6H), 7.26-7.21 (m, 6H), 4.58 (s, 2H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 144.6, 134.9, 134.6, 131.3 (2C), 129.9 (2C), 129.0 (2C), 128.7 (2C), 128.5, 128.3 (2C), 127.9 (2C), 127.8, 123.0, 82.8, 71.6, 55.9, 21.8; HRMS *m/z* (TOF MS ES+): calculated for $C_{22}H_{19}NO_2NaS$: 384.1034, found 384.1022 [*M*+*Na*].

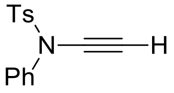
Spectroscopic data were identical to those reported in literature.[129]

4-methyl-*N*-phenyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (320)



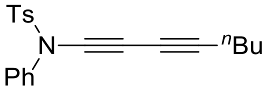
Following GP2 using amide **307** (3.71 g, 15 mmol) and ethynyltrimethylsilane (0.42 mL, 3 mmol). After purification by flash chromatography [hexanes:EtOAc (19:1)] 4-methyl-*N*-phenyl-*N*-trimethylsilanylethynyl-benzenesulfonamide **320** was isolated as a white solid (843 mg, 82%): mp: 88-91 °C; ν_{max} (neat)/cm^{-1}= 3069, 3034, 2961, 2904, 2165, 1592, 1490, 1365, 1248, 1160, 1085, 842, 812, 691, 660; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.58 (d, *J* 8.3, 2H), 7.38-7.21 (m, 7H), 2.46 (s, 3H), 0.19 (s, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 144.9, 138.6, 132.8, 129.3 (2C), 129.0 (2C), 128.4 (2C), 128.2, 126.1 (2C), 95.3, 73.2, 21.7, 0.0 (3C); HRMS *m/z* (TOF MS ES+): calculated for $C_{18}H_{21}NO_2NaSiS$: 366.0960, found 366.0959 [*M*+*Na*].

N-ethynyl-4-methyl-*N*-phenylbenzenesulfonamide (321)



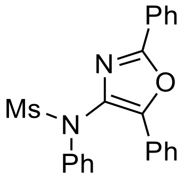
A solution of tetra-*n*-butylammonium fluoride (1 M in THF, 2.5 eq) was added to a solution of ynamide **320** (832 mg, 2.43 mmol) in THF (18 mL) at 0°C and stirred for 5 min. Saturated ammonium chloride solution (20 mL) was added and the aqueous phase was extracted with EtOAc (3 × 25 mL). The organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography [hexanes:EtOAc (9:1)] to give *N*-ethynyl-4-methyl-*N*-phenyl-benzenesulfonamide **321** as a light yellow solid (580 mg, 88%): mp: 76-78 °C; ν_{max} (neat)/cm^{-1}= 3275, 3060, 3041, 2962, 2923, 2125, 1595, 1489, 1361, 1164, 1097, 1086, 806, 683, 657; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.61-7.56 (m, 2H), 7.35-7.23 (m, 7H), 2.83 (s, 1H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 145.0, 138.3, 133.0, 129.5 (2C), 129.1 (2C), 128.4, 128.3 (2C), 126.3 (2C), 58.9, 21.7; HRMS *m/z* (TOF MS ES+): calculated for $C_{15}H_{13}NO_2NaS$: 294.0565, found 294.0555 [*M*+*Na*].

4-methyl-*N*-(octa-1,3-diyn-1-yl)-*N*-phenylbenzenesulfonamide (322)



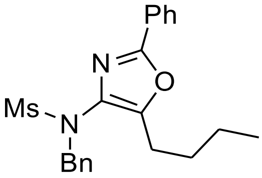
Ynamide **321** (580 mg, 2.13 mmol) was added to 1-bromo-hex-1-yne **160** (443 mg, 2.77 mmol), copper iodide (48 mg, 0.15 mmol) and $Pd(Ph_3)_4$ (123 mg, 0.11 mmol) in a 2:1 solution of diisopropylamine-toluene (50 mL). The reaction was then allowed to stir overnight at room temperature. The mixture was then diluted with dichloromethane (40 mL) and filtered through celite. The solution was concentrated under reduced pressure and purified by flash chromatography [hexanes:EtOAc (9:1)] to give ynamide **322** as a light brown solid (138 mg, 19%): mp: 59-61 ºC; ν_{max} (neat)/cm^{-1}= 2965, 2933, 2872, 2860, 2258, 2169, 1593, 1486, 1375, 1169, 1086, 1040, 888, 778, 692, 665, 572; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.58 (d, *J* 8.3, 2H), 7.38-7.17 (m, 7H), 2.44 (s, 3H), 2.31 (t, *J* 6.9, 2H), 1.58-1.33 (m, 4H), 0.91 (t, *J* 7.2, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 145.1, 138.3, 133.1, 129.6 (2C), 129.2 (2C), 128.5, 128.2 (2C), 126.3 (2C), 84.5, 67.6, 64.3, 58.1, 30.3, 21.9, 21.7, 19.3, 13.5; HRMS *m/z* (TOF MS ES+): calculated for $C_{21}H_{21}NO_2NaS$: 374.1191, found 374.1182 [*M*+*Na*].

N-(2,5-Diphenyl-oxazol-4-yl)-*N*-phenyl-methanesulfonamide (323)



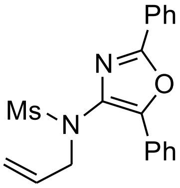
Following GP7 using ynamide **310** (27.1 mg, 0.1 mmol) and ylide **295** (29.7 mg, 0.15 mmol) for 4 h, oxazole **323** was isolated as a white solid (37.4 mg, 96%): mp: 233-235 ºC; ν_{max} (neat)/cm^{-1}= 3056, 3021, 2926, 1619, 1595, 1484, 1446, 1348, 1161, 1141, 961, 756, 694, 684; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 8.15-8.12 (m, 2H), 8.02-7.97 (m, 2H), 7.75-7.71 (m, 2H), 7.54-7.49 (m, 3H), 7.48-7.42 (m, 2H), 7.41-7.33 (m, 3H), 7.32-7.26 (m, 1H), 3.34 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 158.3, 146.0, 140.1, 134.2, 130.9, 129.3 (2C), 129.0, 128.9 (2C), 128.8 (2C), 127.7, 127.0, 126.9 (2C), 126.7, 126.4 (2C), 125.4 (2C), 38.7; HRMS *m/z* (TOF MS ES+): calculated for $C_{22}H_{18}N_2O_3NaS$: 413.0936, found 413.0930 [*M*+*Na*].

***N*-Benzyl-*N*-(5-butyl-2-phenyl-oxazol-4-yl)-methanesulfonamide (324)**



Following GP7 using ynamide **314** (26.5 mg, 0.1 mmol) and ylide **295** (29.7 mg, 0.15 mmol) for 2 h. After purification by flash chromatography [hexanes:EtOAc (4:1)] oxazole **324** was isolated as a white solid (31.6 mg, 82%); mp: 90-92 ºC; ν_{max} (neat)/cm^{-1}= 2953, 2927, 2869, 1644, 1487, 1448, 1342, 1150, 1049, 957, 785, 695; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.91-7.86 (m, 2H), 7.41-7.35 (m, 3H), 7.27-7.16 (m, 5H), 4.67 (s, 2H), 3.06 (s, 3H), 2.32 (t, *J* 7.5, 2H), 1.19-0.96 (m, 4H), 0.71 (t, *J* 7.0, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 158.3, 151.6, 135.8, 132.1, 130.0, 129.3 (2C), 128.7 (2C), 128.4 (2C), 127.9, 127.4, 126.0 (2C), 53.9, 38.0, 29.3, 23.7, 22.3, 13.6; HRMS *m/z* (TOF MS ES+): calculated for $C_{21}H_{24}N_2O_3NaS$: 407.1405, found 407.1397 [*M*+*Na*].

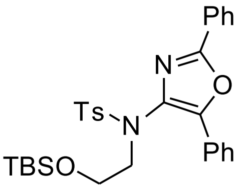
***N*-Allyl-*N*-(2,5-diphenyl-oxazol-4-yl)-methanesulfonamide (325)**



Following GP7 using ynamide **312** (23.5 mg, 0.1 mmol) and ylide **295** (29.7 mg, 0.15 mmol) for 4 h. After purification by flash chromatography [toluene:EtOAc (19:1)] oxazole **325** was isolated as a white solid (23.6 mg, 67%): mp: 88-90 ºC; ν_{max} (neat)/cm^{-1}= 3062, 3021, 2928, 1614, 1487, 1449, 1345, 1151, 1069, 959, 764, 701, 688; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.05 (m, 4H), 7.53-7.41 (m, 5H), 7.41-7.34 (m, 1H), 5.87 (ddt, *J* 16.9, 10.1 and 6.7, 1H), 5.20 (ddd, *J* 16.9, 2.5 and 1.1, 1H), 5.08 (dd, *J* 10.1 and 1.1, 1H), 4.31 (d, *J* 6.7, 2H), 3.22 (s, 3H); ^{13}C-NMR (101

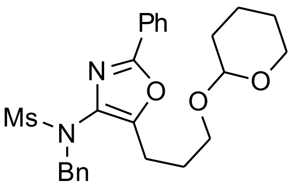
MHz; $CDCl_3$): δ_c= 158.3, 146.8, 133.0, 131.7, 130.8, 129.0, 128.8 (2C), 128.7 (2C), 127.0, 126.8, 126.3 (2C), 125.4 (2C), 120.0, 53.8, 38.8; HRMS *m/z* (TOF MS ES+): calculated for $C_{19}H_{18}N_2O_3NaS$: 377.0936, found 377.0938 [*M*+*Na*].

***N*-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-*N*-(2,5-diphenyl-oxazol-4-yl)-4-methyl-benzenesulfonamide (326)**



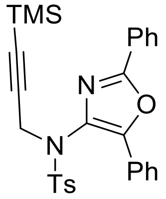
Following GP7 using ynamide **311** (42.9 mg, 0.1 mmol) and ylide **295** (29.7 mg, 0.15 mmol) for 12 h. After purification by flash chromatography [hexanes:EtOAc (9:1)] oxazole **326** was isolated as a white solid (44.2 mg, 81%): mp: 90-92 ºC; ν_{max} (neat)/cm^{-1}= 3061, 2955, 2928, 2856, 1598, 1488, 1448, 1357, 1256, 1165, 1088, 1006, 835, 775, 704, 689, 665; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 8.15-8.07 (m, 2H), 8.02-7.94 (m, 2H), 7.79 (d, *J* 8.3, 2H), 7.52-7.42 (m, 5H), 7.40-7.28 (m, 3H), 3.67 (m, 4H), 2.46 (s, 3H), 0.75 (s, 9H), -0.12 (s, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 157.8, 146.9, 143.8, 135.6, 133.5, 130.5, 129.3 (2C), 128.8 (3C), 128.6 (2C), 128.6 (2C), 127.2 (2C), 126.2 (2C), 125.6 (2C), 60.9, 52.1, 25.7 (3C), 21.6, 18.1, -5.6 (2C); HRMS *m/z* (TOF MS ES+): calculated for $C_{30}H_{36}N_2O_3NaSiS$: 571.2063, found 571.2057 [*M*+*Na*].

***N*-Benzyl-*N*-{2-phenyl-5-[3-(tetrahydro-pyran-2-yloxy)-propyl]-oxazol-4-yl}-methanesulfonamide (327)**



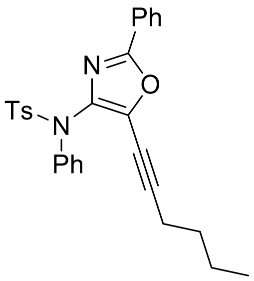
Following GP7 using ynamide **315** (35.2 mg, 0.1 mmol) and ylide **295** (29.7 mg, 0.15 mmol) for 1.5 h. After purification by flash chromatography [hexanes:EtOAc (3:1)] oxazole **327** was isolated as a yellow oil (42.8 mg, 91%): ν_{max} (neat)/cm^{-1}= 2939, 2868, 1640, 1449, 1343, 1155, 1118, 1028, 959, 867, 776, 758, 692; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.03-7.93 (m, 2H), 7.52-7.42 (m, 3H), 7.38-7.24 (m, 5H), 4.76 (s, 2H), 4.54 (t, *J* 3.5, 1H), 3.85 (m, 1H), 3.61 (dt, *J* 9.8 and 6.4, 1H), 3.56-3.47 (m, 1H), 3.23 (dt, *J* 9.8 and 6.4, 1H), 3.15 (s, 3H), 2.52 (td, *J* 7.4 and 2.6, 2H), 1.92-1.46 (m, 8H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 158.5, 151.0, 135.7, 132.3, 130.3, 129.2 (2C), 128.7 (2C), 128.4 (2C), 128.0, 127.3, 126.0 (2C), 98.6, 66.4, 62.1, 53.9, 38.0, 30.6, 27.4, 25.5, 21.0, 19.5; HRMS *m/z* (TOF MS ES+): calculated for $C_{25}H_{30}N_2O_5NaS$: 493.1773, found 493.1750 [*M*+*Na*].

***N*-(2,5-Diphenyl-oxazol-4-yl)-4-methyl-*N*-(3-trimethylsilanyl-prop-2-ynyl)-benzenesulfonamide (329)**



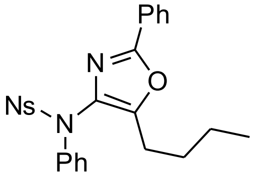
Following GP7 using ynamide **313** (38.1 mg, 0.1 mmol) and ylide **295** (29.7 mg, 0.15 mmol) for 24 h. After purification by flash chromatography [hexanes:EtOAc (9:1)] oxazole **329** was isolated as a white solid (40.2 mg, 80%): mp: 141-143 ºC; ν_{max} (neat)/cm^{-1}= 3060, 3028, 2962, 2181 1596, 1488, 1359, 1252, 1074, 836, 806, 706, 679, 674; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.15-8.09 (m, 2H), 8.01-7.95 (m, 2H), 7.86-7.79 (m, 2H), 7.47 (m, 5H), 7.41-7.29 (m, 3H), 4.34 (s, 2H), 2.47 (s, 3H), -0.12 (s, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 157.9, 147.7, 144.0, 135.3, 132.6, 130.5, 129.3 (2C), 128.9, 128.8 (2C), 128.8 (2C), 128.6 (2C), 127.2, 127.0, 126.2 (2C), 125.6 (2C), 98.3, 91.1, 41.2, 21.6, -0.7 (3C); HRMS *m/z* (TOF MS ES+): calculated for $C_{28}H_{28}N_2O_3NaSiS$: 532.1488, found 523.1482 [*M*+*Na*].

N-(5-(hex-1-yn-1-yl)-2-phenyloxazol-4-yl)-4-methyl-N-phenylbenzenesulfonamide (330)



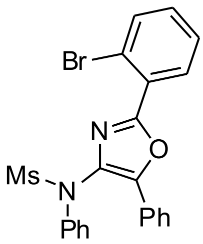
Following GP7 using ynamide **322** (35.1 mg, 0.1 mmol) and ylide **295** (29.7 mg, 0.15 mmol) for 18 h. After purification by flash chromatography [hexanes:EtOAc (4:1)] oxazole **330** was isolated as a light yellow oil (39.1 mg, 83%): ν_{max} (neat)/cm^{-1}= 3064, 2957, 2931, 2872, 2234, 1595, 1485, 1449, 1361, 1166, 1133, 1090, 704, 691, 667; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.31 (m, 2H), 7.75 (d, *J* 8.3, 2H), 7.48-7.35 (m, 5H), 7.32-7.24 (m, 5H), 2.47 (t, *J* 6.9, 2H), 2.44 (s, 3H), 1.67-1.39 (m, 4H), 0.96 (t, *J* 7.2, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 158.4, 143.7, 141.5, 139.6, 136.2, 131.5, 130.8, 129.1 (2C), 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.0, 126.9, 126.5 (2C), 103.1, 66.7, 30.1, 21.9, 21.6, 19.5, 13.6; HRMS *m/z* (TOF MS ES+): calculated for $C_{28}H_{26}N_2O_3NaS$: 493.1562, found 493.1557 [*M*+*Na*].

N-(5-Butyl-2-phenyl-oxazol-4-yl-*N*-phenyl-2-nitrobenzenesulfonamide (331)



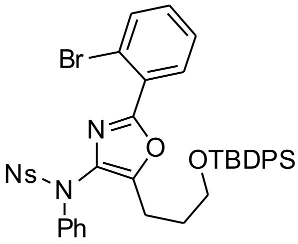
Following GP7 using ynamide **316** (71.6 mg, 0.2 mmol) and ylide **295** (59.4 mg, 0.3 mmol) for 1 h. After purification by flash chromatography [hexanes:EtOAc (9:1)] oxazole **331** was isolated as a light yellow solid (70.8 mg, 74%): mp: 144-146 ºC; ν_{max} (neat)/cm^{-1}= 3114, 3040, 2961, 2932, 2873, 1638, 1523, 1488, 1447, 1361, 1347, 1089, 853, 736, 698, 607; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.31 (dt, *J* 4.5 and 2.3, 2H), 7.96 (m, 2H), 7.93-7.88 (m, 2H), 7.49-7.38 (m, 5H), 7.33-7.27 (m, 3H), 2.81 (t, *J* 7.4, 2H), 1.69 (tt, *J* 7.4 and 7.4, 2H), 1.35 (tq, *J* 7.4 and 7.4, 2H), 0.91 (t, *J* 7.4, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 158.2, 150.6, 144.2, 139.7, 134.4, 130.5, 130.2 (2C), 129.2 (2C), 128.8 (2C), 128.2, 127.8 (2C), 127.3, 127.3, 126.0 (2C), 123.5 (2C), 29.5, 24.1, 22.3, 13.7; HRMS *m/z* (TOF MS ES+): calculated for $C_{25}H_{23}N_3O_5NaS$: 500.1256, found 500.1252 [*M*+*Na*].

***N*-[2-(2-Bromo-phenyl)-5-phenyl-oxazol-4-yl]-*N*-phenyl-methanesulfonamide (333)**



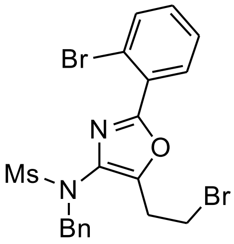
Following GP7 using ynamide **310** (54.2 mg, 0.2 mmol) and ylide **228** (82.8 mg, 0.3 mmol) for 3 h. After purification by flash chromatography [hexanes:EtOAc (4:1)] oxazole **333** was isolated as a white solid (84.3 mg, 90%): mp: 171-173 ºC; ν_{max} (neat)/cm^{-1}= 3086, 3021, 3004, 2925, 1592, 1488, 1447, 1353, 1154, 1025, 971, 757, 724, 685; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.10 (dd, *J* 7.8 and 1.6, 1H), 8.06-8.00 (m, 2H), 7.81-7.73 (m, 3H), 7.51-7.27 (m, 8H), 3.36 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 156.3, 146.3, 140.1, 134.9, 133.9, 131.5, 130.8, 129.4 (2C), 129.2, 128.8 (2C), 127.9, 127.5, 127.3, 127.1 (2C), 126.5, 125.5 (2C), 121.0, 38.4; HRMS *m/z* (TOF MS ES+): calculated for $C_{22}H_{17}N_2O_3NaBrS$: 491.0041, found 491.0039 [*M*+*Na*].

***N*-{2-(2-Bromo-phenyl)-5-[3-(*tert*-butyl-diphenyl-silanyloxy)-propyl]-oxazol-4-yl}-*N*-phenyl-2-nitrobenzenesulfonamide (334)**



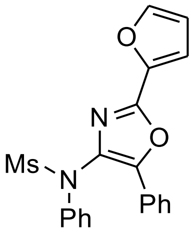
Following GP7 using ynamide **298** (119.6 mg, 0.2 mmol) and ylide **317** (82.8 mg, 0.3 mmol) for 1 h. After purification by flash chromatography [hexanes:EtOAc (9:1)] oxazole **334** was isolated as a light yellow oil (122.2 mg, 77%): ν_{max} (neat)/cm^{-1}= 3069, 2954, 2929, 2856, 1530, 1471, 1427, 1370, 1347, 1171, 1088, 956, 853, 734, 694, 608; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.27 (m, 2H), 8.00 (m, 2H), 7.81 (dd, *J* 7.9 and 1.7, 1H), 7.71 (dd, *J* 7.9 and 1.1, 1H), 7.68-7.62 (m, 4H), 7.45-7.22 (m, 13H), 3.72 (t, *J* 6.1, 2H), 2.99 (d, *J* 7.7, 2H), 2.02-1.90 (m, 2H), 1.07 (s, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 156.3, 150.6, 150.2, 144.0, 139.4, 135.5 (4C), 135.5, 134.8, 134.1, 133.7, 131.2, 130.5, 130.2 (2C), 129.6 (2C), 126.9, 129.3 (2C), 128.3, 127.9 (2C), 127.6 (4C), 127.4, 123.6 (2C), 120.8, 62.9, 30.3, 29.6 (3C), 21.1, 19.2; HRMS *m/z* (TOF MS ES+): calculated for $C_{40}H_{38}N_3O_6NaBrSiS$: 818.1332, found 818.1337 [*M*+*Na*].

***N*-[5-(2-Bromo-ethyl)-2-(2-bromo-phenyl)-oxazol-4-yl]-*N*-phenyl-methanesulfonamide (335)**



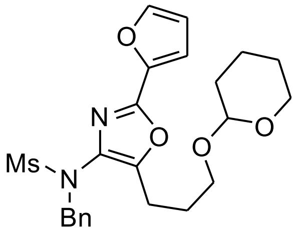
Following GP7 using ynamide **318** (63.0 mg, 0.2 mmol) and ylide **298** (82.8 mg, 0.3 mmol) for 24 h. After purification by flash chromatography [hexanes:EtOAc (17:3)] oxazole **335** was isolated as a light-yellow oil (64.7 mg, 63%): ν_{max} (neat)/cm^{-1}= 3.088, 3030, 2927, 1641, 1456, 1343, 1155, 1025, 959, 853, 766, 726, 698, 612, 580; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.85 (dd, *J* 7.8 and 1.7, 1H), 7.73 (dd, *J* 8.0 and 1.2, 1H), 7.42 (m, 1H), 7.36-7.28 (m, 6H), 4.77 (s, 2H), 3.13 (s, 3H), 3.11-2.96 (m, 4H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 157.4, 148.3, 135.4, 134.7, 133.5, 131.5, 130.8, 129.3 (2C), 128.6 (2C), 128.3, 127.7, 127.4, 121.1, 54.0, 37.9, 27.8, 27.4; HRMS *m/z* (TOF MS ES+): calculated for $C_{19}H_{18}N_2O_3NaBr_2S$: 534.9303, found 534.9307 [*M*+*Na*].

N-(2-Furan-2-yl-5-phenyl-oxazol-4-yl)-*N*-phenyl-methanesulfonamide (337)



Following GP7 using ynamide **310** (54.2 mg, 0.2 mmol) and ylide **299** (56.4 mg, 0.3 mmol) for 4 h, oxazole **337** was isolated as a white solid (73.7 mg, 97%): mp: 178-180 ºC; ν_{max} (neat)/cm^{-1}= 3126, 3064, 3007, 2931, 1633, 1594, 1520, 1490, 1349, 1155, 1128, 962, 899, 743, 687; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 8.00-7.95 (m, 2H), 7.74-7.69 (m, 2H), 7.63 (dd, *J* 1.8 and 0.8, 1H), 7.49-7.27 (m, 6H), 7.13 (dd, *J* 3.5 and 0.8, 1H), 6.60 (dd, *J* 3.5 and 1.8, 1H), 3.31 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 151.1, 145.6, 144.9, 142.5, 139.9, 133.9, 129.4 (2C), 129.2, 128.8 (2C), 127.8, 126.8 (2C), 126.3, 125.5 (2C), 112.4, 112.1, 38.8; HRMS *m/z* (TOF MS ES+): calculated for $C_{20}H_{16}N_2O_4NaS$: 403.0728, found 403.0724 [*M*+*Na*].

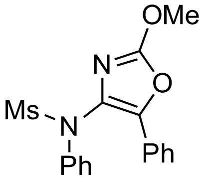
N-Benzyl-*N*-{2-furan-2-yl-5-[3-(tetrahydro-pyran-2-yloxy)-propyl]-oxazol-4-yl}-methanesulfonamide (338)



Following GP7 using ynamide **315** (70.2 mg, 0.2 mmol) and ylide **299** (56.4 mg, 0.3 mmol) for 1 h. After purification by flash chromatography [hexanes:EtOAc (7:3)] oxazole **338** was isolated yellow oil (77.6 mg, 84%): ν_{max} (neat)/cm^{-1}= 2941, 2869, 1635, 1544, 1344, 1156, 1029, 959, 756, 732, 699, 592; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.55 (dd, *J* 1.7 and 0.6, 1H), 7.33-7.22 (m, 5H), 6.93 (dd, *J* 3.5 and 0.6, 1H), 6.53 (dd, *J* 3.5 and 1.7, 1H), 4.74 (s, 2H), 4.50 (t, *J* 3.4, 1H), 3.87-3.76 (m, 1H), 3.56 (dt, *J* 10.0 and 6.4, 1H), 3.52-3.44 (m, 1H), 3.18 (dt, *J* 10.0 and 6.4, 1H), 3.12 (s, 3H), 2.47 (td, *J* 7.4 and 2.6, 2H), 1.86-1.43 (m, 8H); ^{13}C-NMR (101 MHz; CDCl$_3$):

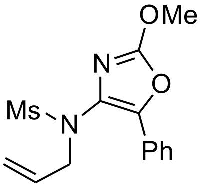
δ_c= 151.5, 150.8, 144.4, 142.6, 135.6, 131.9, 129.1 (2C), 128.5 (2C), 128.0, 111.8, 111.4, 98.6, 66.3, 62.1, 53.7, 38.2, 30.6, 27.4, 25.5, 21.0, 19.5; HRMS *m/z* (TOF MS ES+): calculated for $C_{23}H_{28}N_2O_6NaS$: 483.1566, found 483.1558 [*M+Na*].

***N*-(2-Methoxy-5-phenyl-oxazol-4-yl)-*N*-phenyl-methanesulfonamide (339)**



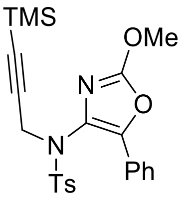
Following GP7 using ynamide **31** (54.2 mg, 0.2 mmol) and ylide **300** (45.6 mg, 0.3 mmol) for 30 min. After purification by flash chromatography [hexanes:EtOAc (4:1)] oxazole **339** was isolated as a white solid (67.5 mg, 98%): mp: 90-92 ºC; ν_{max} (neat)/cm^{-1}= 3063, 3020, 2951, 2853, 1637, 1614, 1593, 1489, 1346, 1333, 1245, 1160, 1008, 970, 765, 687, 676; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.87-7.77 (m, 2H), 7.75-7.65 (m, 2H), 7.39 (m, 4H), 7.34-7.24 (m, 2H), 4.17 (s, 3H), 3.25 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 159.3, 141.8, 140.1, 131.3, 129.7, 129.3 (2C), 128.7 (2C), 128.3, 127.3, 126.6 (2C), 124.7 (2C), 58.2, 38.7; HRMS *m/z* (TOF MS ES+): calculated for $C_{17}H_{16}N_2O_4NaS$: 367.0728, found 367.0721 [*M+Na*].

***N*-Allyl-*N*-(2-methoxy-5-phenyl-oxazol-4-yl)-methanesulfonamide (340)**



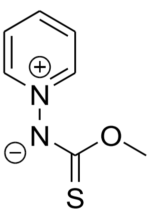
Following GP7 using ynamide **312** (47.0 mg, 0.2 mmol) and ylide **300** (45.6 mg, 0.3 mmol) for 30 min. After purification by flash chromatography [hexanes:EtOAc (7:3)] oxazole **340** was isolated as a white solid (53.6 mg, 87%): mp: 86-88 ºC; ν_{max} (neat)/cm^{-1}= 3091, 3091, 2946, 1638, 1613, 1596, 1493, 1352, 1228, 1161, 1006, 943, 766, 689, 576; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.86-7.78 (m, 2H), 7.42-7.35 (m, 2H), 7.33-7.25 (m, 1H), 5.83 (ddt, *J* 16.9 and 10.1, 6.6, 1H), 5.20 (ddd, *J* 16.9, 2.6 and 1.1, 1H), 5.09 (app dd, *J* 10.1 and 1.1, 1H), 4.20 (dt, *J* 6.6 and 1.1, 2H), 4.08 (s, 3H), 3.14 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 159.2, 142.6, 131.8, 130.1, 128.6 (2C), 128.3, 126.8, 124.7 (2C), 119.8, 58.1, 53.5, 38.9; HRMS *m/z* (TOF MS ES+): calculated for $C_{14}H_{16}N_2O_4NaS$: 331.0726, found 331.0728 [*M*+*Na*].

***N*-(2-Methoxy-5-phenyl-oxazol-4-yl)-4-methyl-*N*-(3-trimethylsilanyl-prop-2-ynyl)-benzenesulfonamide (341)**



Following GP7 using ynamide **313** (76.2 mg, 0.2 mmol) and ylide **300** (45.6 mg, 0.3 mmol) for 5 min. After purification by flash chromatography [hexanes:EtOAc (17:3)] oxazole **341** was isolated as a white solid (84.4 mg, 93%): mp: 146-148 ºC; ν_{max} (neat)/cm^{-1}= 2953, 2922, 2902, 2853, 2180, 1613, 1598, 1380, 1354, 1248, 1167, 1012, 839, 679, 568; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.86 (m, 2H), 7.79 (app d, *J* 8.3, 2H), 7.40-7.32 (m, 2H), 7.31-7.23 (m, 3H), 4.26 (s, 2H), 3.98 (s, 3H), 2.42 (s, 3H), -0.10 (m, 9H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 159.0, 144.0, 143.4, 135.5, 129.7, 129.3 (2C), 128.6 (2C), 128.4 (2C), 128.1, 126.9, 124.9 (2C), 98.4, 90.9, 58.0, 40.8, 21.5, -0.7 (3C); HRMS *m/z* (TOF MS ES+): calculated for $C_{23}H_{26}N_2O_4NaSiS$: 477.1280, found 477.1285 [*M*+*Na*].

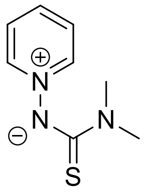
(methoxycarbonothioyl)(pyridin-1-ium-1-yl)amide (348)



A solution of MeOH (0.40 mL, 10 mmol) in diethyl ether (40 mL) at 0 °C of sodium hydride (57% suspension in oil, 421 mg, 10 mmol) was stirred for 15 minute. The reaction mixture was then cooled down to -78 °C and thiophosgene (0.76 mL, 10 mmol) was added. The reaction was kept stirring at -78 °C for an additional 1 h before being warmed to room temperature and then poured into ice-water (40 mL). The organic layer is separated and washed with brine (40 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide thiono chloroformate which was employed as a crude mixture: ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 4.17 (s, 3H). Potassium carbonate (1.6 g) was added to a solution of *N*-amino pyridinium iodide **294** (444 mg, 2 mmol) and methyl chlorothioformate (370 mg) in ethanol (20 mL) at room temperature. The reaction mixture was stirred for 1 day and then filtered through a pad of celite. The solution was concentrated under reduced pressure and the solid was recrystalised with CH_2Cl_2/hexanes to provide the thiourea ylide **348** as a light yellow solid (325 mg, 97%): mp: 128-130 °C; ν_{max} (neat)/cm^{-1}= 3103, 3063, 3047, 2937, 2161, 1613, 1469, 1398, 1373, 1213, 1122, 1041, 1007, 830, 695; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 8.49 (dd, *J* 6.9, 1.3, 2H), 8.11 (tt, *J* 8.1, 1.3, 1H), 7.84-7.73 (m, 2H), 4.02 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 195.4, 143.8 (2C), 139.4, 126.6 (2C), 56.25.

Data were in agreement with those reported in the literature.[130]

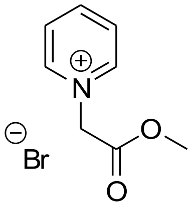
(dimethylcarbamothioyl)(pyridin-1-ium-1-yl)amide (349)



Sodium ethoxyde (136 mg 2 mmol) in ethanol (10 mL) was added to a solution of *N*-amino pyridinium iodide **294** (444 mg, 2 mmol) and *N,N*-dimethylthiocarbonyl chloride (270 mg, 2.2 mmol) in ethanol (10 mL) at room temperature. The reaction mixture was stirred for 1 day and then filtered through a pad of celite. The solution is concentrated under reduced pressure to provide the thiourea ylide **349** as a light yellow solid (337 mg, 93%): mp: 140-134 °C; ν_{max} (neat)/cm^{-1}= 3095, 3071, 3044, 2925, 2212, 1611, 1465, 1369, 1336, 1251, 1121, 943, 828, 692; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 8.43 (dd, *J* 4.2 and 2.5, 2H), 7.96 (ddd, *J* 9.0, 2.5 and 1.3, 1H), 7.69-7.62 (m, 2H), 3.31 (s, 6H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 185.3, 144.8 (2 C), 138.0, 125.7 (2C), 40.0 (2C); HRMS *m/z* (TOF MS ES+): calculated for $C_8H_{11}N_3NaS$: 204.0571, found: 204.0572 [*M+Na*].

Data were in agreement with those reported in the literature.[131]

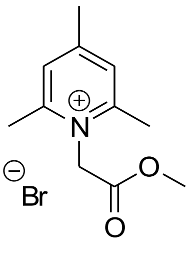
***N*-(methoxycarbonyl)pyridinium bromide (350)**



Pyridine (0.40 mL, 5 mmol) was added to a solution of methylbromoacetate (0.47 mL, 5 mmol) in CH_2Cl_2 (10 mL) and stirred overnight at room temperature. The reaction mixture was filtered and the collected solid was washed 3 times with diethy ether. Pyridinium ylide **350** was isolated as a white solid (487 mg, 42%): mp: 169-172 °C; ν_{max} (neat)/cm^{-1}= 3017, 2998, 2952, 2863, 1746, 1634, 1491, 1360, 1221, 994, 794, 712; ^{1}H-NMR (300 MHz; DMSO): δ_H= 9.11 (dd, *J* 6.8, 1.3, 2H), 8.74 (tt, *J* 8.0, 1.3, 1H), 8.27 (dd, *J* 7.7, 6.8, 2H), 5.76 (s, 2H), 3.77 (s, 3H); ^{13}C-NMR (101 MHz; DMSO): δ_c= 166.8, 146.8, 146.2 (2C), 127.8 (2C), 60.2, 53.1; HRMS *m/z* (TOF MS EI+): calculated for $C_8H_{10}NO_2$: 152.0712, found: 152.0709 [*M*].

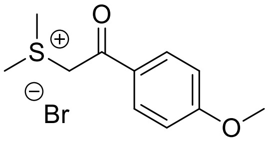
Data were in agreement with those reported in the literature.[132]

2,4,6-trimethyl-*N*-(methoxycarbonyl)pyridinium bromide (351)



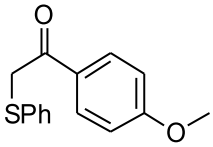
Pyridine (0.66 mL, 5 mmol) was added to a solution of methylbromo acetate (0.47 mL, 5 mmol) in CH_2Cl_2 (10 mL) and stirred overnight at room temperature. The reaction mixture was filtered and the collected solid was washed 3 times with diethy ether. Pyridinium ylide **351** was isolated as a white solid (950 mg, 70%): mp: 183-185 °C; ν_{max} (neat)/cm^{-1}= 3457, 3404, 3026, 2960, 2906, 1743, 1637, 1570, 1436, 1361, 1261, 979, 802; ^{1}H-NMR (300 MHz; DMSO): δ_H= 7.85 (s, 2H), 5.56 (s, 2H), 3.80 (s, 3H), 2.72 (s, 6H), 2.53 (s, 3H); ^{13}C-NMR (101 MHz; DMSO): δ_C= 166.7, 159.5, 155.6 (2C), 128.4 (2C), 53.9, 53.4, 21.6, 21.1 (2C); HRMS *m/z* (TOF MS EI+): calculated for $C_{11}H_{16}NO_2$: 194.1181, found: 194.1182 [*M*].

(2-(4-methoxyphenyl)-2-oxoethyl)(methyl)(phenyl)sulfonium bromide (352)



Dimethylsulphide (0.88 mL, 12 mmol) was added to a solution of 2-bromo-4'-methoxyphenylacetophenone (2.29 mL, 10 mmol) in CH_2Cl_2 (10 mL) and stirred overnight at room temperature. The reaction mixture was filtered and the collected solid was recrystallised with EtOH/AcOEt. Bromonium salt **352** was isolated as a light yellow solid (2.22 g, 77%): ν_{max} (neat)/cm^{-1}= 3010, 2947, 2896, 2839, 1660, 1596, 1571, 4550, 1022, 987, 828, 601; ^{1}H-NMR (300 MHz; DMSO): δ_H= 8.01 (d, *J* 9.0, 2H), 7.15 (d, *J* 9.0, 2H), 5.47 (s, 2H), 3.89 (s, 3H), 2.97 (s, 6H); ^{13}C-NMR (101 MHz; DMSO): δ_C= 189.4, 164.6, 131.2 (2C), 126.7, 114.4 (2C), 55.8, 52.7, 24.6 (2C); HRMS *m/z* (TOF MS EI+): calculated for $C_{11}H_{15}O_2S$: 211.0793, found: 211.0788 [*M*].

1-(4-methoxyphenyl)-2-(phenylthio)ethanone (359)

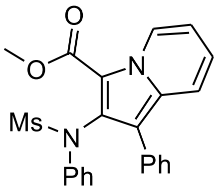


Triethylamine (0.84 mL, 6 mmol) was added to a solution of 2-bromo-4'-methoxyphenylacetophenone (1.15 mg, 5 mmol) and thiophenol (1.54 mL, 15 mmol) in toluene

(7 mL) and stirred overnight at room temperature. The reaction mixture was added to hexane (2 mL) and EtOAc (2 mL), filtered and the collected solid was washed 4 times with EtOAc to give **359** as light yellow solid (722 mg, 56%): mp: 87-88 °C; ν_{max} (neat)/cm^{-1}= 3054, 3017, 2980, 2939, 2906, 1658, 1600, 1571, 1261, 1173, 1023, 817, 734, 689; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.94 (d, *J* 9.0, 2H), 7.43-7.36 (m, 2H), 7.32-7.15 (m, 3H), 6.93 (d, *J* 9.0, 2H), 4.24 (s, 2H), 3.88 (s, 3H);^{13}C-NMR (101 MHz; CDCl$_3$): δ_C= 192.6, 163.7, 135.0, 131.0 (2C), 130.3 (2C), 129.0 (2C), 128.4, 126.9, 113.8 (2C), 55.5, 41.0. HRMS *m/z* (TOF MS ES+): calculated for $C_{15}H_{14}O_2NaS$: 281.0612, found: 281.0614 [*M+Na*].

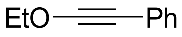
Data were in agreement with those reported in the literature.[133]

Methyl 1-phenyl-2-(*N*-phenylmethylsulfonamido)indolizine-3-carboxylate (362)



A solution of ynamide **310** (54.2 mg, 0.2 mmol) and ylide **350** (45.6 mg, 0.3 mmol) toluene (2 ml, 0.1 M) was added sodium hydride (57% suspension in oil, 13 mg, 0.32 mmol) of and dichloro(2-pyridinecarboxylato)gold (5 mol%) subsequently. The reaction mixture was stirred at 90 °C for 8 h. The mixture was filtered through a pad of silica and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography [hexanes:EtOAc (17:3)] to afford **341** as a white solid (37.7 mg, 45%): ν_{max} (neat)/cm^{-1}= 3063, 2951, 1684, 1454, 1383, 1354, 1197, 1157, 967, 730, 697; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 9.51 (dt, *J* 7.2 and 0.9, 1H), 7.52 (dt, *J* 9.0 and 1.2, 1H), 7.43-7.32 (m, 5H), 7.28-7.21 (m, 5H), 7.15-7.01 (m, 2H), 6.92 (td, *J* 7.0, 1.4, 1H), 3.85 (s, 3H), 2.84 (s, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 200.89, 193.89, 161.01, 142.3, 134.1, 132.0, 130.3 (2C), 129.0 (2C), 128.6 (2C), 127.6 (2C), 124.5, 122.8, 122.0 (2C), 118.0, 117.0, 114.2, 51.0, 40.6; HRMS *m/z* (TOF MS ES+): calculated for $C_{23}H_{20}N_2O_4NaS$: 443.1041, found: 443.1055 [*M+Na*].

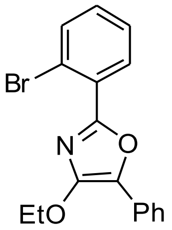
Ethoxyethynyl-benzene (371)



Ethoxyacetylene (40% in Hexene) (0.780 mL, 3.2 mmol) in THF (8.6 mL) was added to iodobenzene (0.335 mL, 3 mmol), copper iodide (12 mg, 0.64 mmol), $PdCl_2(Ph3)_2$ (449 mg, 0.64 mmol) and diisopropylamine (0.63 mL, 4.5 mmol). The reaction was allowed to stir overnight at room temperature. The mixture was then diluted with *n*-hexane (10 mL) and filtered through celite. The solution was carefully concentrated under reduced pressure and purified by flash chromatography [hexane] to give ynol ether **371** as a colourless liquid (48 mg, 11%): ν_{max} (neat)/cm^{-1}= 3059, 2982, 2901, 2253, 1599, 1441 1315, 1058, 1023, 828, 751, 690; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H= 7.37-7.31 (m, 2H), 7.29-7.19 (m, 3H), 4.22 (q, *J* 7.1, 2H), 1.45 (t, *J* 7.1, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 131.5 (2C), 128.1 (2C), 126.5, 124.1, 98.6, 74.9, 39.9, 14.5; HRMS *m/z* (TOF MS EI+): calculated for $C_{10}H_{10}O$: 146.0732, found 146.0731 [*M*].

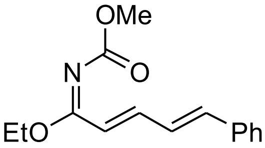
Spectroscopic data were identical to those reported in literature.[134]

2-(2-bromophenyl)-4-ethoxy-5-phenyloxazole (372)



Following GP7 using ynol ether **371** (14.6 mg, 0.1 mmol) and ylide **298** (41.4 mg, 0.15 mmol) for 30 min. After purification by flash chromatography [hexanes:EtOAc (19:1)] oxazole **372** was isolated as a colorless liquid (16.2 mg, 47%): ν_{max} (neat)/cm^{-1}= 3062, 2979, 2929, 2899, 1616, 1601, 1496, 1407, 1383, 1353, 1335, 1150, 1027, 906, 759, 726, 690; ^{1}H-NMR (300 MHz; $CDCl_3$): δ_H=8.04 (dd, *J* 7.9, 1.7, 1H), 7.85-7.80 (m, 2H), 7.72 (dd, *J* 7.9, 1.1, 1H), 7.46-7.37 (m, 3H), 7.30-7.18 (m, 2H), 4.50 (q, *J* 7.1, 2H), 1.49 (t, *J* 7.1, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ_c= 154.3, 150.9, 134.8, 131.1, 130.9, 130.8, 128.7 (2C), 128.6, 128.1, 127.3, 126.4, 123.2 (2C), 120.4, 66.1, 15.2; HRMS *m/z* (TOF MS ES+): calculated for $C_{17}H_{14}NO_2NaBr$: 366.0106, found 366.0103 [*M*+*Na*].

Ethyl *N*-methoxycarbonyl-5-phenylpenta-2,4-dienimidate (373)



Following GP7 using ynol ether **290** (18.6 mg, 0.1 mmol) and ylide **300** (22.8 mg, 0.15 mmol) for 2 h. After purification by flash chromatography [hexanes:EtOAc (19:1)] dienimidate **373** (geometry across C=N is not assigned) was isolated as a colorless liquid (9.9 mg, 38%): ν_{max} (neat)/cm^{-1}= 3026, 2982, 2951, 2904, 1708, 1641, 1623, 1587, 1435, 1370, 1315, 1232, 1056, 993, 752, 691; ^{1}H-NMR (300 MHz; CDCl$_3$): δ_H= 7.48-7.42 (m, 2H), 7.40-7.24 (m, 4H), 6.90-6.86 (m, 1H), 6.24 (d, *J* 15.0, 2H), 4.26 (q, *J* 7.1, 2H), 3.82 (s, 3H), 1.37 (t, *J* 7.1, 3H); ^{13}C-NMR (101 MHz; CDCl$_3$): δ_c= 163.3, 162.0, 142.2, 140.2, 136.1, 129.0, 128.8 (2C), 127.1 (2C), 126.7, 118.3, 63.1, 53.4, 14.0; HRMS *m/z* (TOF MS ES+): calculated for $C_{15}H_{17}NO_3Na$: 282.1106, found 282.1110 [*M*+*Na*].

Crystal structure of 3aa

$C_{23}H_{20}N_2O_3S$, M_r = 404.47, colourless crystal, crystal dimensions: 0.24 x 0.17 x 0.09 mm, monoclinic, space group: $P2_1/c$, a = 12.3313(4), b = 10.8475(3), c = 16.0957(5) Å, β = 110.431(2)°, V = 2017.58(11) Å^3, Z = 4, $\rho_{calculated}$ = 1.332 Mg/m^3, μ = 1.647 mm^{-1}, $\lambda_{Mo\text{-}K\alpha}$ = 1.54178 Å, T = 120(2) K, $2\theta_{max}$ = 140.08°, 19943 reflections measured, 3533 observed reflections, R_1 = 0.0327 (observed reflections), wR = 0.0908 (all data), GOF = 1.060, largest diff. peak and hole: 0.300 and -0.374 e.Å^{-3}. The dataset was measured on a Bruker SMART 6000 diffractometer. The data collection was driven by SMART[135] and processed by SAINTPLUS.[136] An absorption correction was applied using SADABS.[137] The structure was solved using ShelXS-97[138] and refined by a full-matrix least-squares procedure on F^2 in ShelXL-97.[138] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom. Figures were produced using OLEX2.[139] The CIF has been deposited with the CCDC and has been given the deposition number 819432.

Selected bond lengths (Å) and angles (°): C(2) – N(2) = 1.382(2), N(2) – C(3) = 1.293(2), C(3) – O(3) = 1.361(1), O(3) – C(4) = 1.378(1), C(4) – C(2) = 1.354(2), C(2) – N(1) = 1.409(2), C(3) – C(5) = 1.456(2), C(4) – C(11) = 1.453(2), C(2) – N(2) – C(3) = 104.2(1), N(2) – C(3) – O(3) = 113.8(1), C(3) – O(3) – C(4) = 105.36(9), O(3) – C(4) – C(2) = 106.0(1), C(4) – C(2) – N(2) = 110.7(1), N(1) – C(2) – N(2) = 121.4(1), N(2) – C(3) – C(5) = 128.2(1), O(3) – C(4) – C(11) = 117.1(1).

References

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[1] A. Shishmanian, 2012, "A new relevance for gold", http://www.gold.org/download/pub_archive/pdf/G20_Advertorial.pdf [accessed March 2012].

[2] a) World Gold Council’s web site: http://www.gold.org/technology/uses/medicine/ [accessed March 2012].

[3] a) D. T. Felson, J. J. Anderson, R. F. Meenan, *Arthitis Rheum.* 1990, **33**, 1449-1461; b) L. Messori, G. Marcon, *Metal ions and their complexes in medication* 2004, A. Sigel, Sigel Ed, CRC Press, 280-301.

[4] a) A. Casini, C. Hartinger, C. Gabbiani, E. Mini, P. J. Dyson, K. Keppler, L. Messori, *J. Inorg. Biochem.* 2008, **102**, 564-575; b) R. V. Parish, B. P. Howe, J. P. Wright, J. Mark, R. G. Pritchrad, R. G. Buckley, A. M. Elsome, S. P. Fricker, *Inorg. Chem.* 1996, **35**, 1659-1666; c) M. J. McKeage, L. Maharaj, S. J. Bernes-Price, *Coord. Chem. Rev.* 2002, **232**, 127-135.

[5] A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed*. 2006, **45**, 7896-7936.

[6] a) P. Pyykköö, J. P. Desclaux, *Acc. Chem. Res.* 1979, **12**, 276-281; b) P. Pyykköö, *Inorg. Chim. Acta*. 2005, **358**, 4113-4130; c) D. J. Gorin, F. D. Toste, *Nature* 2007, **446**, 395-403; d) P. Pyykköö, *Angew. Chem. Int. Ed,* 2004, **43**, 4412-4456.

[7] a) P. Schwerdfeger, H. L. Hermann, H. Schimidbaur, *Inorg. Chem.* 2003, **42**, 1334-1342; b) G. A. Bowmaker, H. Schmidbaur, S. Kruger, N. Rosch, *Inorg. Chem.* 1997, **36**, 1754-1757.

[8] Reproduced from reference 6c.

[9] N. D. Shapiro, F. D. Toste, *Proc. Natl. Acad. Sci. U.S.A,* 2008, **46**, 3410-3449.

[10] A. Tamaki, J. K. Kochi, *J. Organometall. Chem*. 1974, **64**, 411-425.

[11] W. Nakanishi, M. Yamanaka, E. Nakamura, *J. Am. Chem. Soc*. 2005, **127**, 1446-1453.

[12] For selected general reviews of gold reactivity: a) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* 2007, **46**, 3410-3449; b) D. J. Gorin, F. D. Toste, *Nature* 2007, **446**, 395-403; c) J. Li, C. Brouwer, C. He, *Chem. Rev*. 2008, **108**, 3239-3265; d) A. S. K. Hashmi, *Angew. Chem. Int. Ed*. 2010, **49**, 5232-5241.

---

[13] a) M. J. S. Dewar, *Bull. Soc. Chim. Fr.* 1951, **18,** C71-C79; b) J. Chatt, L. A. Duncanson, *J. Chem. Soc*. 1953, 2939-2947.

[14] a) C. Heinemann, R. H. Hertwig, R. Wesendrup, W. Koch, H.Schwarz, *J. Am. Chem. Soc*. 1995, **117**, 495-500; b) M. Barysz, P, *Chem. Phys. Lett*. 1998, **285**, 398-403; c) F. Aguirre, J. Husband, C.J. Thompson, R.B. Metz, *Chem. Phys. Lett*. 2000, **318**, 466-470.

[15] a) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed,* 2004, **43**, 2402-2406; b) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J*. 2006, **12**, 1677-1693.

[16] V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc*. 2004, **126**, 8654-8655.

[17] M. R. Luzung, J. P. Markham, F. D. Toste*, J. Am. Chem. Soc*. 2004, **126**, 10858-10859.

[18] a) Carbene Chemistry (Ed G. Bertrand), Fontis Media: Lausanne, Switzerland, 2002; b) M. P. Doyle, *Chem. Rev,* 1986, **86**, 919-939; c) J. Barluenga, F. Rodríguez, F. J. Fanãnás, J. Flórez, *Metal Carbenes in Organic Synthesis*, Dötz, K. H, Ed, Topics in Organic Chemistry, Vol. 13, Springer: Berlin, 2004; pp 59-122; d) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998**.**

[19] a) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* 2008, **47**, 6754-6756; b) A. Fürstner, L. Morency, *Angew. Chem. Int. Ed.* 2008, **47**, 5030-5033; c) A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. P. Nolan, L. Cavallo, *Angew. Chem. Int. Ed.* 2008, **47**, 718-721; d) G. Seidel, R. Mynott, A. Fürstner, *Angew. Chem. Int. Ed*. 2009, **48**, 2510-2513.

[20] S. López, E. Herrero-Gómez, P. Pérez-Galán, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* 2006, **45**, 6029-6032.

[21] E. Jiménez-Núñez, Antonio M. Echavarren, *Chem. Rev.* 2008, **108**, 3326-3350.

[22] M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. Mar Díaz-Requejo, P. J. Pérez, *Angew. Chem. Int. Ed.* 2005, **44**, 5284-5288.

---

[23] D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard, F. D. Toste, *Nat. Chem.* 2009, **1**, 482-486.

[24] a) P. W. Davies, S. J.-C. Albrecht, *Chem. Commun.* 2008, 238-240; b) A. S. K. Hashmi*,* G. J. Hutchings*, Angew. Chem. Int. Ed.* 2006*,* **45***,* 7896-7936; c) J. Li, C. Brouwer, C. He, *Chem. Rev.* 2008, **108**, 3239-3265; d) A. S. K. Hashmi, *Angew. Chem. Int. Ed*. 2010, **49**, 5232-5241.

[25] a) For selected examples: N. Marion, S. P. Nolan, *Angew. Chem. Int. Ed.* 2007, **46**, 2750-2752; b) D. Garayalde, E. Gómez-Bengoa, X. Huang, A. Goeke, C. Nevado, *J. Am. Chem. Soc.* 2010, **132**, 4720-4730; c) A. S. Dudnik, T. Schwier, V. Gevorgyan, *J. Orgmet. Chem.* 2009, **694**, 482-485.

[26] D. J. Gorin, N. R. Davis, F. D. Toste*, J. Am. Chem. Soc*. 2005*,* **127***,* 11260-11261*.*

[27] P. W. Davies, S. J.-C. Albrecht, *Ang. Chem. Int. Ed.* 2009, **48**, 8372-8375.

[28] A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph, E. Kurpejovic, *Angew. Chem.Int. Ed.* 2004, **43**, 6545-6547.

[29] N. D. Shapiro, F. Dean Toste, *J. Am. Chem. Soc.* 2007, **129**, 4160-4161.

[30] G. Li, L. Zhang*, J. Am. Chem. Soc*. 2007, **46**, 5156-5159.

[31] A. B. Cuenca, S. Montserrat, K. M. Hossain, G. Mancha, A. Lledós, M. Medio-Simón, G. Ujaque, G. Asensio, *Org. Lett.* 2009, **11**, 4906-4909.

[32] G.-Y. Lin, C.-W. Li, S.-H Hung, R.-S. Liu, *Org. Lett.* 2008, **10**, 5059-5062.

[33] H.-S. Yeom, Y. Lee, J.-E. Leeb, S. Shin, *Org. Biomol. Chem*. 2009, **7,** 4744-4752.

[34] H.-S. Yeom, Y. Lee, J.-E. Leeb, S. Shin, *Angew. Chem. Int. Ed*. 2008, **47**, 7040-7043.

[35] A. M. Jadhav, S. Bhunia, H. Y. Liao, R. S. Liu, *J. Am. Chem. Soc*. 2011, **133**, 1769-1771.

[36] L. Cui, Y. Peng, L. Zhang*, J. Am. Chem. Soc*. 2009, **131**, 8394-8395.

[37] E. L. Noey, Y. Luo, L. Zhang, K. N. Houk, *J. Am. Chem. Soc.* 2012, **134**, 1078-1084.

[38] S. Kramer, Y. Odabachian, J. Overgaard, M. Rottländer, F. Gagosz, T. Skrydstrup, *Angew. Chem. Int. Ed.* 2011, **50,** 5090-5094.

[39] H. E. Zaugg, L. R. Swett, G. R. Stone, *J. Org. Chem*. 1958, **23**, 1389-1390.

---

[40] H. G. Viehe, *Ang. Chem.* 1963, **75**, 638.

[41] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* 2007, **107**, 5471-5569.

[42] Z. Janousek, J. Collard, H. G. Viehe, *Angew. Chem. Int. Ed.* 1972, **11**, 917-918.

[43] L.-L. Wei, J. A. Mulder, H. Xiong, C. A. Zificsak, C. J. Douglas, R. P. Hsung, *Tetrahedron* 2001, **57**, 459-466.

[44] a) D. Brückner, *Tetrahedron* 2006, **62**, 3809-3814; b) D. Rodríguez, M. F. Martínez-Esperón, L. Castedo, C. Saá, *Synlett.* 2007, 1963-1965; c) M. R. Tracey, Y. Zhang, M. O. Frederick, J. A. Mulder, R. P. Hsung, *Org. Lett.* 2004, **6**, 2209-2212; d) M. F. Martínez-Esperón, D. Rodríguez, L. Castedo, C. Saá, *Tetrahedron* 2006, **62**, 3843-3855; e) J. Huang, H. Xiong, R.P. Hsung, C. Rameshkumar, J. A. Mulder, T.P. Grebe, *Org. Lett.* 2002, **4**, 2417-2420; f) K. S. Feldman, M. M. Bruendl, K. Schildknegt, A. C. Bohnstedt, *J. Org. Chem.* 1996, **61**, 5440-5452; g) B. Witulski, B.Stengel, *Angew. Chem. Int. Ed.* 1999, **38**, 2426-2430; h) J. D. Rainier, J. E. Imbriglio, *Org. Lett.* 1999, **1**, 2037-2039.

[45] A. Balsamo, B. Macchia, F. Macchia, A. Rossello, *Tetrahedron Lett.* 1985, **26**, 4141-4144.

[46] M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen, C. J. Douglas, *J. Am. Chem. Soc.* 2003, **125**, 2368-2369.

[47] A. Klapper, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc*. 2002, **124**, 7421-7428.

[48] J. R. Dunetz, R. L. Danheiser, *Org. Lett.* 2003, **5**, 4011-4014.

[49] Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* 2004, **6**, 1151-1154.

[50] T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc.* 2008, **130**, 833-835.

[51] A. Coste, G. Karthikeyan, F. Couty, G. Evano, *Angew. Chem. Int. Ed.* 2009, **48**, 4381-4385.

[52] Recent reviews of ynamide reactivity: a) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev*. 2010, **110**, 5064-5106; b) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed*. 2010, **49**, 2840-2859.

---

[53] Publications on ynamides were calculated from CAS-database (Scifinder) on a structure query: “O=A=N-C≡C”, which was cleaned of mistaken results.

[54] M. Mori, H. Wakamatsu, N. Saito, Y. Sato, R. Narita, Y. Sato, R. Fujita, *Tetrahedron* 2006, **62**, 3872-3881.

[55] S. County, C. Meyer, J. Cossy, *Angew. Chem. Int. Ed.* 2006, **45**, 6726-6730.

[56] A. Buzas, F. Istrate, X. F. Le Goff, Y. Odabachian, F. Gagosz, *J. Orgmet. Chem.* 2009, **694**, 515-519.

[57] a) A. S. K. Hashmi, R. Salathé, W. Frey, *Synlett*. 2007, 1763-1766; b) F. Istrate, A. Buzas, I. Dias Jurberg, Y. Odabachian, F. Gagosz, *Org. Lett*. 2008, **10**, 925-928.

[58] M. Rudolph, M. Q. McCreery, W. Frey, A. S. K. Hashmi*, J. Org. Chem*. 2011, **7**, 794-801 and references therein.

[59] A. S. K. Hashmi, M. Rudolph, J. W. Bats, W. Frey, F. Rominger, T. Oeser, *Chem. Eur. J.* 2008, **14**, 6672-6678.

[60] S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottländer, T. Skrydstrup, *Org. Lett*. 2009, **11**, 4208-4211.

[61] K. Dooleweerdt, H. Birkedal, T. Ruhland, T. Skrydstrup, *J. Org. Chem*. 2008, **73**, 9447-9450.

[62] B. Yao, Z. Liang, T. Niu, Y. Zhang, *J. Org. Chem*. 2009, **74**, 4630-4633.

[63] a) C. A. Whitham, P. Mauleon, N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* 2007, **129**, 5838-5839; b) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* 2008, **130**, 9244-9245.

[64] Z. F. Al-Rashid, W. L. Johnson, R. P. Hsung, Y. Wei, P.-Y. Yao, R. Liu, K. Zhao, *J. Org. Chem.* 2008, **73**, 8780-8784.

[65] a) A. Furstner, P. W. Davies, *J. Am. Chem. Soc.* 2005, **127**, 15024-15025; b) T. Shimada, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* 2004, **126**, 10546-10547; c) I. Nakamura, T. Sato, Y Yamamoto, *Angew. Chem. Int. Ed.* 2006, **45**, 4473-4475.

[66] F. M. Istrate, F. Gagosz, *Beilstein J. Org. Chem*. 2011, **7**, 878-885.

---

[67] a) S. Couty, C. Meyer, J. Cossy, *Synlett.* 2007, 2819-2822; b) Z. F. Al-Rashid, R. P. Hsung, *Org. Lett.* 2008, **10**, 661-663.

[68] J. M. Concellón, H. Rodríguez-Solla, P. Díaz, *J. Org. Chem.* 2007, **72**, 7974-7979 and references therein.

[69] [2+2] cycloaddition/reversion with ynamides and carbonyl moieties to prepare α,β-unsaturated carboxylic imides: a) R. P. Hsung, C. A. Zificsak, L.-L. Wei, C. J. Douglas, H. Xiong, J. A. Mulder, *Org. Lett.* 1999, **1**, 1237-1249; b) K. C. M. Kurtz, R. P. Hsung, Y. Zhang, *Org. Lett*. 2006, **8**, 231-234; c) L. You, Z. F. Al-Rashid, R. Figueroa, S. K. Ghosh, G. Li, T. Lu and R. P. Hsung, *Synlett*, 2007, 1656-1662; d) N. Shindoh, Y. Takemoto and K. Takasu, *Chem. Eur. J*. 2009, **15**, 7026-7030.

[70] N. Martin, 2010. Gold-Catalysed reactions of nitrogen containg molecules. Thesis, (PhD) University of Birmingham.

[71] B.-L. Lu, L. Dai, M. Shi, *Chem. Soc. Rev.* 2012, **41**, 3318-3339.

[72] J. Chen, P.-Q. Huang, Y. Queneau, *J. Org. Chem*. 2009, **74**, 7457-7463.

[73] a) L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* 2010, **132**, 3258-3259; b) L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.* 2010, **132**, 8550-8551.

[74] B. Lu, C. Li, L. Zhang, *J. Am. Chem. Soc.* 2010, **132**, 14070-14072.

[75] For reviews of the chemistry of ynol ethers and the methods for the synthesis of ynol ethers, see: Brandsma, L.; Bos, H. J.; Arens, J. F. In *The Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, **1969**; pp 751-860.Stang, P. J.; Zhdankin, V. V. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons: New York, **1994**; Chapter 19.

[76] a) D. Bruckner, *Synlett,* 2000, **10**, 1402- 1404; b) A, Moyano, F. Charbonnier, A. E. Greene, *J. Org. Chem.* 1987, **52**, 2919-2922; c) M. A. Pericas, F. Serratosa, E. Valenti, *Tetrahedron,* 1987, **10**, 2311-2316; d) R. H. Smithers, *Synthesis,* 1985, 556-558; e) G. Himbert, A. Loffler, *Synthesis,* 1992, 495-498; f) J. R. Sosa, A. A. Tudjarian, T. G. Minehan, *Org. Lett.* 2008, **10**,

---

5091- 5094; g) A. Christopher, D. Brandes, S. Kelly, T. Minehan, *Org. Lett*. 2006, **8**, 451-454; h) A. A. Tudjarian, T. G. Minehan, *J. Org. Chem*. 2011, **76**, 3576-3581; i) V. Tran, T. G. Minehan, *Org. Lett*. 2011, **13**, 6588-6591.

[77] Examples of ynol ethers in gold catalysis: a) L. Zhang, S. A. Kozmin, J*. Am. Chem. Soc*. 2004, **126**, 11806-11807; b) D. A. Engel, G. B. Dudley, *Org. Lett*. 2006, **8**, 4027-4029; c) A. S. K. Hashmi, M. Rudolph, J. Huck, W. Frey, J. W. Bats, M. Hamzić, *Angew. Chem. Int. Ed*. 2009, **48**, 5848-5852.

[78] a) S. Fantauzzi, A. Caselli, E. Gallo, *Dalton Trans*. 2009, 5434-5443; b) M. M. Diaz-Requejo, P. J. Perez, *Chem. Rev*. 2008, **108**, 3379-3394; c) P. Mueller, C. Fruit, *Chem. Rev.* 2003, **103**, 2905-2919.

[79] a) J. Valenciano, E. Sµnchez-Pavón, A. M. Cuadro, J. Alvarez- Builla, J. J. Vaquero, *Eur. J. Org. Chem.* 2007, **15**, 2423-2429; b) J. J. Mousseau, A. Fortier, A. B. Charette, *Org. Lett*. 2010, **12**, 516-519 and references therein.

[80] X-Ray crystal structure was determinate by Dr Louise Male, X-ray Diffraction Facility Officer, School of Chemistry-University of Birmingham.

[81] a) V. V. Fokin in Handbook of Cyclization Reactions, Vol 2 (Ed: S. Ma), Wiley-VCH, Weinheim, 2009, pp. 917-950; b) T. Hashimoto, K. Maruoka in Handbook of Cyclization Reactions, Vol. 2 (Ed: S. Ma) Wiley-VCH, Weinheim, 2009, pp. 87-168.

[82] For selected recent examples: a) N. Chatani, T. Fukuyama, H. Tatamidani, F. Kakiuchi, S. Murai, *J. Org. Chem.* 2000, **65**, 4039-4047; b) B. Clapham, A. J. Sutherland, *J. Org. Chem.* **2001**, 66, 9033-9037; c) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* 2007, **129**, 12404-12405; d) E. F. Flegeau, M. E. Popkin, M. F. Greaney, *Org. Lett.* 2008, **10**, 2717-2720; e) K. Lee, C. M. Counceller, J. P. Stambuli, *Org. Lett*. 2009, **11**, 1457-1459; f) F. Besselièvre, S. Piguel, *Angew. Chem.* 2009, **121**, 9717-9720; g) F. Besseliévre, S. Piguel, *Angew. Chem. Int. Ed.* 2009, **48**, 9553-9556; h) D. R. Williams, L. Fu, *Org. Lett.* 2010, **12**, 808-811.

---

[83] For selected examples: a) J. Wu, W. Chen, M. Hu, H. Zou, Y. Yu, *Org. Lett.* 2010, **12**, 616-618; b) C. Lalli, J. M. Bouma, D. Bonne, G. Masson, J. Zhu, *Chem. Eur. J.* 2011, **17**, 880-889; c) H. Jiang, H. Huang, H. Cao, C. Qi, *Org. Lett*. 2010, **12**, 5561-5563; d) Y. M. Pan, F. J. Zheng, H. X. Lin, Z. P. Zhan, *J. Org. Chem*. 2009, **74**, 3148-3151; e) D. Bonne, M. Dekhane, J. Zhu, *Angew. Chem. Int. Ed*. 2007, **46**, 2485-2488; f) T. Lechel, D. Lentz, H.-U. Reissig, *Chem. Eur. J.* 2009, **15**, 5432-5435; g) C. Wan, L. Gao, Q. Wang, J. Zhang, Z. Wang, *Org. Lett*. 2010, **12**, 3902-3905.

[84] For selected examples: a) B. Shi, A. J. Blake, W. Lewis, I. B. Campbell, B. D. Judkins, C. J. Moody, *J. Org. Chem.* 2010, **75**, 152-161; b) C. Wan, J. Zhang, S. Wang, J. Fan, Z. Wang, *Org. Lett.* 2010, **12**, 2338-2341; c) M. P. Kumar, R.-S. Liu, *J. Org. Chem.* 2006, **71**, 4951-4955; d) M. D. Milton, Y. Inada, Y. Nishibayashi, S. Uemura, *Chem. Commun.* 2004, 2712-2173; d) R. Martín, A. Cuenca, S. L. Buchwald, *Org. Lett.* 2007, **9**, 5521-5524; e) A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus, W. Frey, *Eur. J. Org. Chem.* 2006, 4905-4909; f) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic´, J. Visus, F. Rominger, W. Frey, J. W. Bats, *Chem. Eur. J.* 2010, **16**, 956-963; g) M. Austeri, D. Rix, W. Zeghida, J. Lacour, *Org. Lett.* 2011, **13**, 1394-1397.

[85] a) R. Huisgen, H. Blaschke, *Chem. Ber*. 1965, **98**, 2985-2997; b) M. Mçrtl, D. Knausz, Z. Bçcskei, Z. Kolos, K. Újszμszy, L. Szakμcs, P. Sohμr, *J. Organomet. Chem.* 1995, **492**, 115-119. c) K. U. Clauss, K. Buck, W. Abraham, *Tetrahedron* 1995, **51**, 7181-7192; d) K. Buck, D. Jacobi, Y. Plçgert, W. Abraham, *J. Prakt. Chem*. 1994, **336**, 678-685.

[86] I. Cano, E. Álvarez, M. C. Nicasio, P. J. Pérez, *J. Am. Chem. Soc.* 2011, **133**, 191-193.

[87] W. He, C. Li, L. Zhang, *J. Am. Chem. Soc*. 2011, **133**, 8482-8485.

[88] P. Wipf, *Chem. Rev.* 1995, **95**, 2115-2134; b) V. S.C. Yeh, *Tetrahedron* 2004, **60**, 11995-12042; c) J. Zhong, *Nat. Prod. Rep.* 2009, **26**, 382-445.

[89] P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem. Int. Ed*. 2011, **50**, 8931-8935.

[90] T. Kan, T. Fukuyama, *Chem. Comm.* 2004, 353-359.

---

[91] K. A. DeKorver, R. P. Hsung, A. G. Lohse, Y. Zhang, *Org. Lett.* 2010, **12**, 1840-1843.

[92] a) A. M. Jadhav, S. Bhunia, H. Y. Liao, R. S. Liu, *J. Am. Chem. Soc.* 2011, **133**, 1769-1771; b) N. Asao, K. Sato, Y. Yamamoto, *Tetrahedron Lett.* 2003, **44**, 5675-5677.

[93] C. Li, L. Zhang, *Org. Lett*. 2011, **13**, 1738-1741.

[94] For examples of acyl quench of a metal carbene, see: a) M. Hamaguchi, T. Ibata, *Chem. Lett.* **1976**, 287-288; b) A. Padwa, *J. Organomet. Chem*. 2001, **617**, 3-16; c) A. Escribano-Cuesta, V. López-Carrillo, D. Janssen, A. M. Echavarren, *Chem. Eur. J.* 2009, **15**, 5646-5650 ; d) A. S. K. Hashmi, M. Rudolph, H.-U. Siehl, M. Tanaka, J. W. Bats, W. Frey, *Chem. Eur. J.* 2008, **14**, 3703-3708.

[95] H. Li, R. P. Hsung, *Org. Lett.* 2009, **11**, 4462-4465.

[96] For selected examples: a) M. T. Gandasegui, J. Alvarez-Builla, *J. Chem. Res.,* Synop . 1986, **2**, 74-75; b) K. Matsumoto, N. Hayashi, Y. Ikemi, M. Toda,T, Uchida, K. Aoyama, Y. Miyakoshi, *J. Heterocycl. Chem.* 2001, **38**, 371-377; c) E. Ronald, S. N. Khaffaff, *J. Fluorine Chem.* 1991, **51**, 407-418; d) Y. Miki, N. Nakamura, R. Yamakawa, H. Hachiken, K-I Matsushita, *Heterocycles* 2000, **53**, 2143-2149; d) G. Kaupp, D. Hunkler, I. Zimmermann, *Ber.* 1982, **115**, 2467-2477.

[97] S. Kramer, T. Skrydstrup, *Angew. Chem. Int. Ed.* 2012, **51**, 4681-4684.

[98] Expected Titration Results: http://istcgroup.com/pdf/Pure%20-%20Solv%20Catalog.pdf [accessed March 2012].

[99] M. Niggemann, A. Jelonek, N. Biber, M. Wuchrer, B. Plietker, *J. Org. Chem.* 2008, **73**, 7028-7036.

[100] A. Trofimov, N. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* 2008, **130**, 13538-13539.

[101] K. Jouvin, F.Couty, G. Evano, *Org. Lett.* 2010, **12**, 3272-3275.

[102] M.-L. Yao, M. S. Reddy, L. Yong, I. Walfish, D. W. Blevins, G. W. Kabalka, *Org. Lett.* 2010, **12**, 700-703.

[103] M. Juríček, K. Stout, P. H. J. Kouwer, A. E. Rowan, *Org. Lett.* 2011, **13**, 3494-3497.

---

[104] J. A John, J. M Tour, *Tetrahedron* 1997, **53**, 15515-15534.

[105] N. Asao, T. Asano, T. Ohishi, Y.Yamamoto, *J. Am. Chem. Soc.* 2000, **122**, 4817-4818.

[106] B. Gourdet, H. W. Lam, *J. Am. Chem. Soc.* 2009, **131**, 3802-3803.

[107] N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* 2011, **133**, 8070-8073.

[108] J. D. Kima, G. Hanb, L. Jeongc, H.-J. Parka, O. P. Zeea, Y. H. Jung, *Tetrahedron* 2002, **58**, 4395-4402.

[109] R. Sridhar, B. Srinivas, V. Pavan Kumar, M. Narender, K. Rama Rao, *Adv. Syn. & Cat*. 2007, **349**, 1873-1876.

[110] K. T. Sylvester, P. J. Chirik, *J. Am. Chem. Soc.* 2009, **131**, 8772-8774.

[111] B. M. Trost, M. R. Machacek, B. D. Faulk, *J. Am. Chem. Soc*. 2006, **128**, 6745-6754.

[112] Z.-Y. Li, M. Wang, Q.-H. Bian, B. Zheng, J.-Y. Mao, S.-N. Li, S.-Z. Liu, M.-A. Wang, J.-C. Zhong, H.-C. Guo, *Chem. Eur. J.* 2011, **17**, 5782-5786.

[113] G. B. Jones, J. M. Wright, G. Hynd, J. K. Wyatt, P. M. Warner, R. S. Huber, A. Li, M. W. Kilgore, R. P. Sticca, R. S. Pollenz, *J. Org. Chem.* 2002, **67**, 5727-5732.

[114] H. Kim, C. Lee, *Org. Lett.* 2002, **4**, 4369-4371.

[115] J. W. Herndon, P. P. Patel, *J. Org. Chem.* 1996, **61**, 4500-4501.

[116] A. Bartoszewicz, M. Kalek, J. Stawinski, *Tetrahedron* 2008, **64**, 8843-8850.

[117] I. N. Michaelides, B. Darses, D. J. Dixon, *Org. Lett.* 2011, **13**, 664-667.

[118] K. Ravindar, M. S. Reddy, P. Deslongchamps, *Org. Lett.* 2011, **13**, 3178-3181.

[119] G. Bencivenni, T. Lanza, R. Leardini, M. Minozzi,D. Nanni, P. Spagnolo, G. Zanardi, *Org. Lett*. 2008, **10**, 1127-1130.

[120] K. Jouvin, F Couty, G. Evano, *Org. Lett.* 2010, **12**, 3272-3275.

[121] D. A. Engel, S. S. Lopez, G. B. Dudley, *Tetrahedron* 2008, **64**, 6988-6996.

[122] B. Yao, Z. Liang, T. Niu, Y. Zhang, *J. Org. Chem.* **2009**, *74*, 4630-4633.

[123] T. Miura, T Biyajima, T. Fujii, M. Murakami, *J. Am. Chem. Soc.* 2012, **134**, 194-196.

---

[124] L. A. Gandon, A. G. Russell, T. Güveli, A. E. Brodwolf, B. M. Kariuki, N. Spencer, J. S. Snaith, *J. Org. Chem.* 2006, **71**, 5198-5207.

[125] E. Vellemaee, O. Lebedev, U. Maeeorg, *Tetrahedron Lett.* 2008, **49**, 1373-1375.

[126] B. A. Gellert, N. Kahlcke, M. Feurer, S. Roth, *Chem. Eur. J.* 2011, **17**, 12203-12209.

[127] T. Kubo, C. Katoh, K. Yamada, K. Okano, H. Tokuyama, T. Fukuyama, Tetrehedron 2008, 64, 11230-11236.

[128] Z. Zhang, V. Baubet, C. Ventocilla, C. Xiang, N. Dahmane, J. D. Winkler, *Org. Lett.* 2011, **13**, 4786-4789.

[129] Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M Kurtz, E. L. Vera, *Org. Lett.* 2004, **6,** 1151-1154.

[130] H. Yoshida, K. Urushibata, T. Ogata, *Bull. Chem. Soc. Jap.* 1983, **56**, 1561-1562.

[131] A. Kakehi, S. Ito, K. Nagata, N. Kinoshita, N. Kakinuma, *Chem. Pharm. Bull*. 1987, **35**, 156-169.

[132] P. N. P. Rao, M. Amini, H. Li, A. G. Habeeb, E. E. Knaus, *J. Med. Chem.* 2003, **46**, 4872-4882.

[133] M. Arisawa, K. Suwa, M. Yamaguchi, *Org. Lett.* 2009, **11**, 625-627.

[134] C. H. Weidner, D. H. Wadsworth, C. S. Knop, A. I Oyefesso, B. L. Hafer, R. J. Hartman, R. C. Mehlenbacher, S. C. Hogan, *J. Org. Chem.* **1994**, *59*, 4319-4322.

[135] SMART, program for instrument control and data acquisition. Bruker AXS Inc., Madison, Wisconsin (USA) **1997**.

[136] SAINTPLUS, program suite for data processing. Bruker AXS Inc., Madison, Wisconsin (USA) **1997**.

[137] G. M. Sheldrick, SADABS. Bruker AXS Inc., Madison, Wisconsin (USA) **2007**.

[138] G. M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112-122.

[139] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Crystallogr.* **2009**, *42*, 339-341.