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Exploring Regiocontrolled Gold-Catalysed Alkyne Activation for Efficient Synthesis of Nitrogen Heterocycles

by

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Abstract

In this thesis the development of regiocontrolled gold-catalysed reactions for the synthesis of complex heterocycles are described.

A new methodology for the formation of all-carbon fully substituted oxazoles was designed and developed, through a novel gold-catalysed intermolecular formal [3+2]-cycloaddition across the π-system of electron-rich internal alkynes by employing conjugated *N*-ylides as *N*-nucleophilic 1,3-*N,O*-dipole equivalents. This intermolecular addition to unsymmetrical internal alkynes represents a considerable regioselectivity and reactivity challenge, as there are no examples of intermolecular atom-transfer nitrene addition.

A new design of substrates incorporating an electron-rich π-system and a tethered oxidant or a nitrene delivery system was investigated. Several strategies towards the formation of these systems were proposed and the exhibiting limitations were identified.

A novel gold-catalysed reaction has been developed for the formation of complex polycyclic systems, which involves a [1,5]-hydride transfer/cyclisation cascade of functionalised aromatic and aliphatic ynamides. Under mild conditions, the process rapidly generates three fused ring systems by the formation of three new $C(sp^3)$-$C(sp^3)$ bonds and up to four contiguous stereogenic centres, in a single manipulation.

Acknowledgments

What doesn't kill you makes you stronger. Looking back four years ago, I wouldn't have imagined myself able to make it until the end and actually submit this thesis. Excitement about the new discoveries, curiosity, hard work, dedication, lots of patience and love about every single experiment were some of the keys that gave me strength to face with a smile, most of the times, the challenges of this PhD. However, nothing would be possible without the help and the invaluable support of several people, especially the select few I am going to mention.

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Of course I could never forget to thank my *Pink Angel Giagia*: she is my main inspiration in every path I follow.

Ποτέ το πλάνο ψήλωμα κισσού μη σε θαμπώσει,

Κι ας μείνεις χαμηλό δεντρί, αυτό καρπούς θα δώσει.

Γ. Φ., Ηράκλειο Κρήτης 2001

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List of Abbreviations

Å	Ångström
Ac	acetyl
Alk	alkyl
Ar	aromatic
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bpy	2,2’-bipyridine
Bn	benzyl
Bs	*p*-bromobenzenesulfonyl
Bu	butyl
C	Celsius
CSA	camphorsulfonic acid
COSY	correlation spectroscopy
Cy	cyclohexyl
d	chemical shift
d	doublet
DNBS	2,4-dinitrobenzene-1-sulfonate
DMS	dimethyl sulfide
DS	Dean Stark
DMEDA	1,2-bis(methylamino)ethane
DBU	2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine

1,2-DCE	1,2-dichloroethane
DIPA	diisopropylamine
DMPU	1,3-dimethyltetrahydropyrimidin-2(1*H*)-one
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EWG	electron withdrawing group
EDG	electron donating group
E	electrophile
ee	enantiomeric excess
EI	electron impact
ERC	electrocyclic ring closure
eq.	equivalent
ESI	electronspray ionisation
Et	ethyl
FT-IR	Fourier transform infrared
g	gram(s)
h	hour(s)
HT	hydride transfer
HSQC	heteronuclear single quantum correlation
HMBC	heteronuclear multiple bond correlation

HRMS	high resolution mass spectrometry
HMDS	hexamethyldisilazane
Hz	Hertz
IR	infrared
IBX	2-iodobenzoic acid
IPr	1,3-bis(2,4,6-diisopropylphenyl)-imidazolium
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
J	coupling constant
L	litre
LG	leaving group
m	multiplet
[M]	metal
M	molar
*m*CPBA	*meta*-chloroperbenzoic acid
min	minute(s)
mol	moles
mp	melting point
MS	molecular sieves
MS	mass spectroscopy
MW	microwave
Ms	methanesulfonyl

m/z	mass/charge
NIS	*N*-iodosuccinimide
n	normal
NBS	*N*-bromosuccinimide
Nu	nucleophile
NMR	nuclear magnetic resonance
nosyl	4-nitrobenzenesulfonyl
n*O*e	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NHC	N-heterocyclic carbene
o	ortho
[O]	oxidation
p	para
Ph	phenyl
ppm	part(s) per million
Ph	phenyl
Pr	propyl
py	pyridine
q	quartet
quint	quintuplet
rac	racemic

rt	room temperature
s	singlet
T	temperature
t	triplet
TES	triethylsilane
Tf	trifluoromethanesulfonyl
TIPS	triisopropylsilyl
TFA	trifluoroacetic acid
TBHP	*tert*-butyl hydroperoxide
TBDMS	*tert*-butyldimethylsilane
THF	tetrahydrofuran
Ts	toluenesulfonyl
UV	ultraviolet
v	frequency

1. Chapter 1:

Gold catalysis in organic synthesis

1.1 Gold activation: Key features

Gold catalysis, an area which has been thriving over the last decade, has efficiently provided access to novel transformations *via* the activation of carbon-carbon multiple bonds (Figure 1). This remarkable applicability is attributed to the excellent chemoselectivity, mild conditions and minimal use of additives that gold-catalysed reactions generally exhibit. Furthermore the use of robust, air stable and easily accessible gold complexes render these strategies practically appealing, while their superb functional group tolerance makes them compatible with the formation of key bonds in a late stage syntheses of complex and fragile natural products.[1]

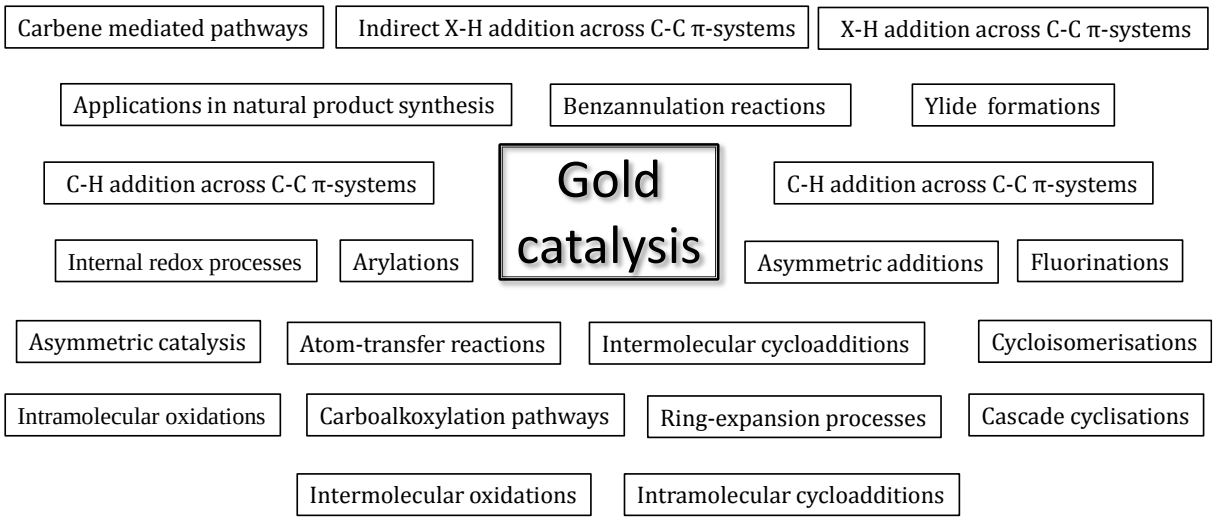


Figure 1: Broad range of transformations accessing by gold catalysis

The reactivity of gold complexes is rationalised by a consideration of the significant contraction of s- and p-orbitals of the metal leading to a short and strong bond between the metal and the ligand, as well as expansion of the 5d and 4f-orbitals.[2]

The diffusion of the d-orbitals allows gold catalysts to act as π-acids able to activate alkenes, allenes and alkynes, generating electrophilic organogold species. The Dewar-Chatt-Duncanson (DCD) model describes synergistic σ- and π-interactions between the metal and the ligand (Figure 2).[3] This model assumes that a σ-bond is formed from the π-system of the ligand (either alkene or alkyne) and an empty orbital of the metal with a suitable geometry. Back-donation of electron density from a filled orbital of the metal into the empty π* orbital of the ligand results in an additional π-interaction. Finally weaker, orthogonal π- and δ-interactions are involved between the π-orbital of an alkyne ligand and the metal (weak interactions are represented by dashed arrows in Figure 2). The combination of these interactions leads to elongation of the π-system (electrons are moved from a filled π-orbital to an empty π* orbital) and distortion of its initial geometry.[4]

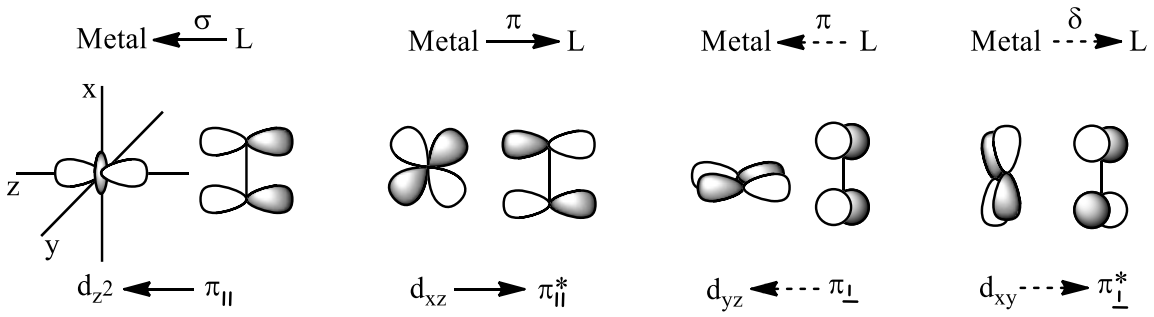
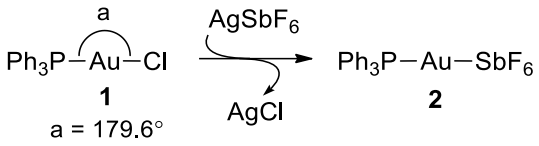


Figure 2: Interactions between gold and alkyne ligand according to DCD model

While two-coordinate gold(I) prefers to adopt a linear geometry, gold(III) forms four coordinate square planar species. In solution, dissociation of one of the ligands in gold(I) species is required to give reactive cationic gold complexes with a vacant coordination site (Scheme 1).[1e] This ligand abstraction (usually a chloride, for example **1**) can be facilitated by the addition of a silver

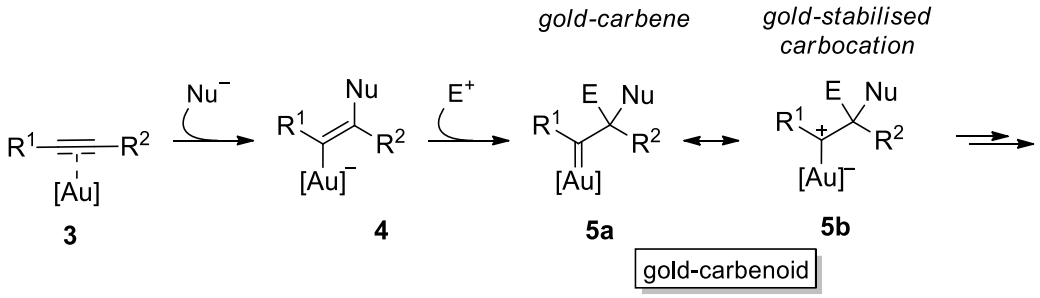
salt, generating AgCl along with a the weakly coordinated cationic gold species (**2**).[5] The 'silver effect' will be discussed in detail in Chapter 2 (section 3.2.2).



Scheme 1: Ligand metathesis between PPh_3AuCl and $AgSbF_6$

1.2 Gold carbenes

The dramatic increase in applications of gold catalysis is largely due to the ability of gold catalysts to form gold carbenoids which can subsequently be trapped either intramolecularly or intermolecularly by various nucleophiles, allowing diverse reaction pathways (Scheme 2). One of the main goals of this PhD research was to explore this reactivity pattern both by enabling alternative synthetic routes towards the formation of these reactive species and by investigating their subsequent development.



Scheme 2: Formation of gold carbenes *via* gold activated alkynes

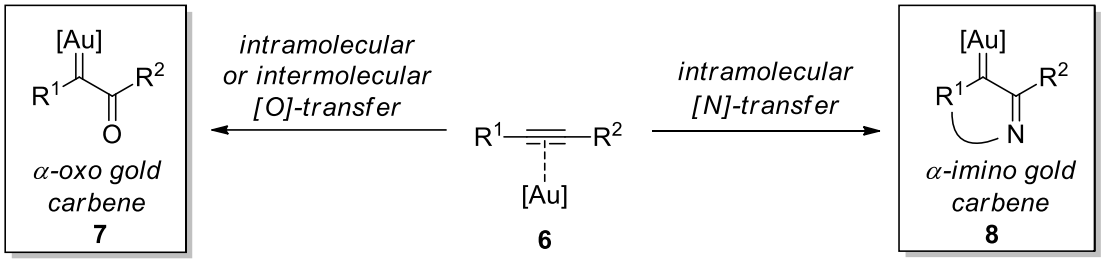
Upon activation of the π-system, the electrophilic gold-alkyne complex **3** is susceptible to nucleophilic attack by a nucleophile giving vinyl gold intermediate **4**. Either an internal or an

external electrophile can be added to the β-carbon of the nucleophilic vinyl species **4** generating gold carbenoid **5**.[6],[7] Attack of the α-carbon is also known and provides competing pathways towards the formation of alternative products.

The nature, precise structure and the nomenclature of these complexes are a subject of debate amongst the scientific community.[8] The term 'gold carbenoid' is often used to refer to a carbon species bearing a formal positive charge and a gold-carbon bond at the same site. Over the course of the reaction, these intermediates react like carbenes, thus can be interpreted as 'gold carbenes' (represented as **5a**), or as carbon-centered cations where the term 'gold-stabilised carbocation' (represented as **5b**) seems to be more suitable. Based on the DCD-model, computational studies showed that on formation of a gold carbene **5** from a vinyl gold species **4**, the back donation of electrons from the metal is increased while the σ-interaction is decreased resulting in a bond order less than (but close to) one.[9] No structural or spectral evidence exists for gold-carbon double bonds and the precise structure of 'gold carbenoids' is very likely closer to metal-stabilised carbocations.[10] It should be highlighted that the ligands on the metal might have some effect on the extent of the σ- and back donation, whilst the carbene centre can be further stabilised by interactions from neighbouring substituents.[11]

For the sake of simplicity, the term 'gold carbenes' is used throughout the thesis and demonstrates the ability of these highly electrophilic intermediates to act as classical metal carbenes. Extensive discussion about the formation of synthetically appealing α-oxo gold carbene species **7** (α-carbonyl gold carbenes) will follow in Chapter 3 (Scheme 3).[12] Classic synthetic strategies for the formation of these intermediates suffer from a lack of efficiency and

functional group tolerance as they rely on metal-promoted decomposition of preformed highly toxic and potentially explosive diazo-precursors.[13]



Scheme 3: Formation of α-oxo or α-imino gold carbenes *via* activated alkynes

Related α-imino-gold carbenes **8**, generated through intramolecular nitrene transfer onto gold-activated alkynes, will also be examined in Chapter 3. The term 'nitrene' refers to neutral, monovalent nitrogen motifs with six valence electrons; these are useful delivery systems for the selective introduction of nitrogen into molecules (Figure 3).[14] However, such substrates are highly reactive and their use often results in rapid and uncontrollable side reactions.[15] In this context, the employment of stable nitrene precursors or nitrene equivalents in combination with a transition metal catalyst allows more controlled use of such reagents.[16]

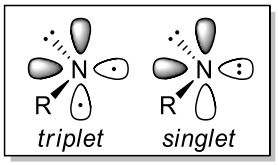
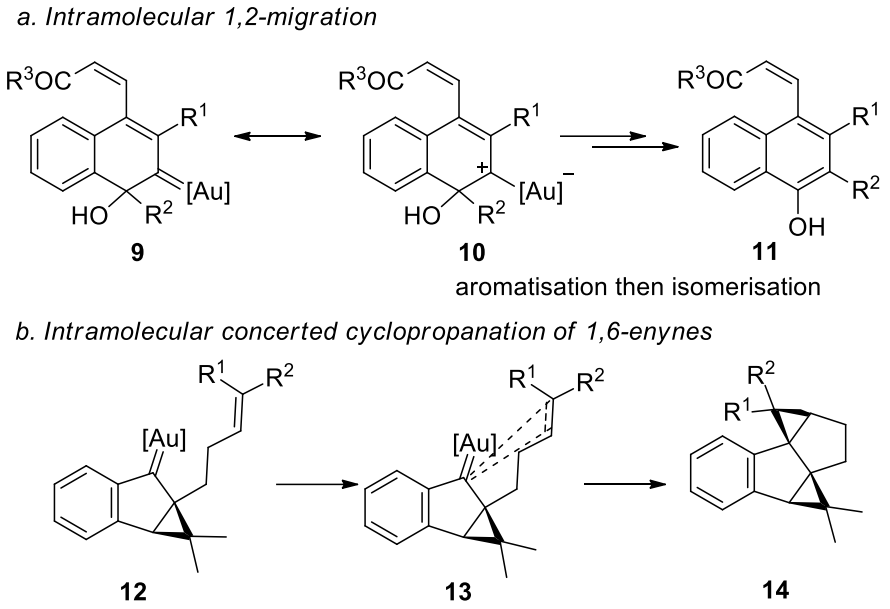


Figure 3: Singlet and triplet nitrenes

Gold carbenes can participate in various reaction pathways leading to the construction of architecturally diverse scaffolds. Some of the key strategies include cycloaddition cascades, electrophilic aromatic substitution reactions, intermolecular or intramolecular cyclisation

pathways when the tethered, usually unsaturated, organic framework reacts with the electrophilic carbene centre, ring expansions and 1,2-hydrogen or 1,2-alkyl or aryl migrations (Scheme 4a).[17]



Scheme 4: 1,2-Migration[18] and cyclopropanation[11] as means to quench gold carbenes

In addition, cyclopropanation is commonly employed when an olefin is available to trap the carbene, leading to the formation of fused ring-systems (Scheme 4b).[19] Chapter 4 demonstrates how this methodology was applied to the gold-catalysed formation of complex tetracycles using a novel C-H insertion to generate the gold carbene.

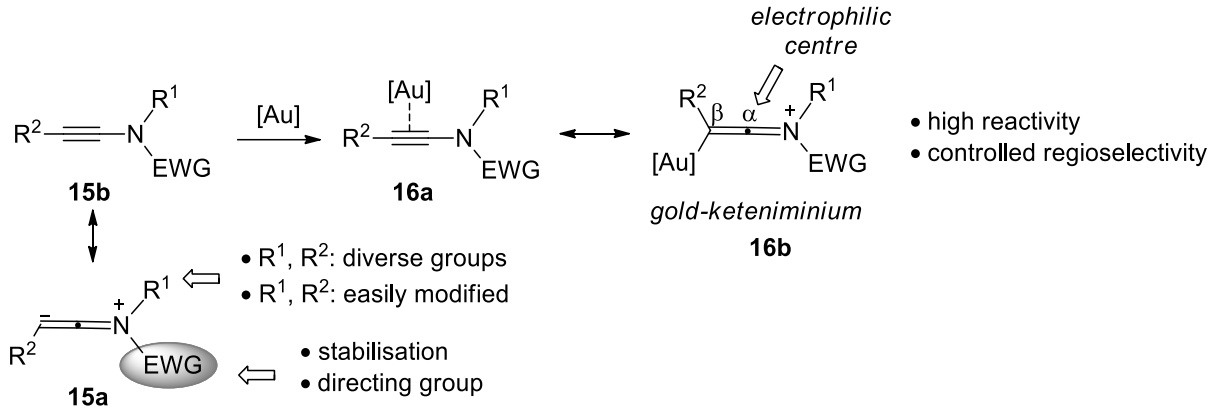
1.3 Ynamides in gold catalysis

Ynamides are electron-rich π-systems with a nitrogen directly attached to the triple bond (Scheme 5). This nitrogen bears an electron-withdrawing group to enhance the stability of the system, however the nitrogen remains an efficient directing group (**15a** and **15b**). These

versatile building blocks can exert both nucleophilic and electrophilic properties depending on the neighbouring substituents. Importantly, the ability of the nitrogen to donate electrons across the π-system allows the strong polarisation of the sp-hybridised carbons; remarkably, this differentiation results in selective reactivity to occur in an elegant fashion.[20]

Although the reactivity of gold-activated alkynes has been broadly investigated whilst gold-activated ynamides have been relatively less widely explored, the interest of the scientific community in their applicability has rapidly increased in the last few years.[12, 21]

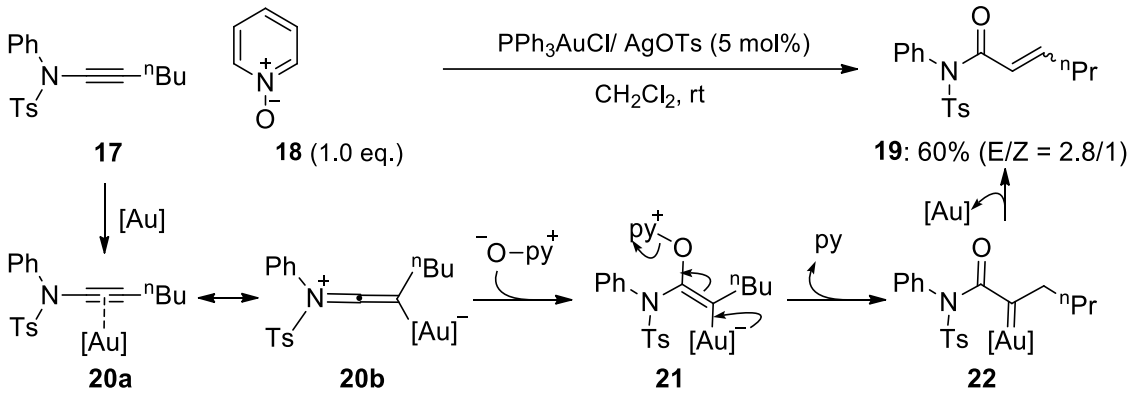
Upon activation of the π-system by gold (**16a** and **16b**), the α-carbon is relatively more electron deficient than the β-carbon, as depicted from the keteniminium resonance form **16b,** enabling a predictable regioselective attack from an internal or external nucleophile.[22]



Scheme 5: Ynamides under gold-catalysis

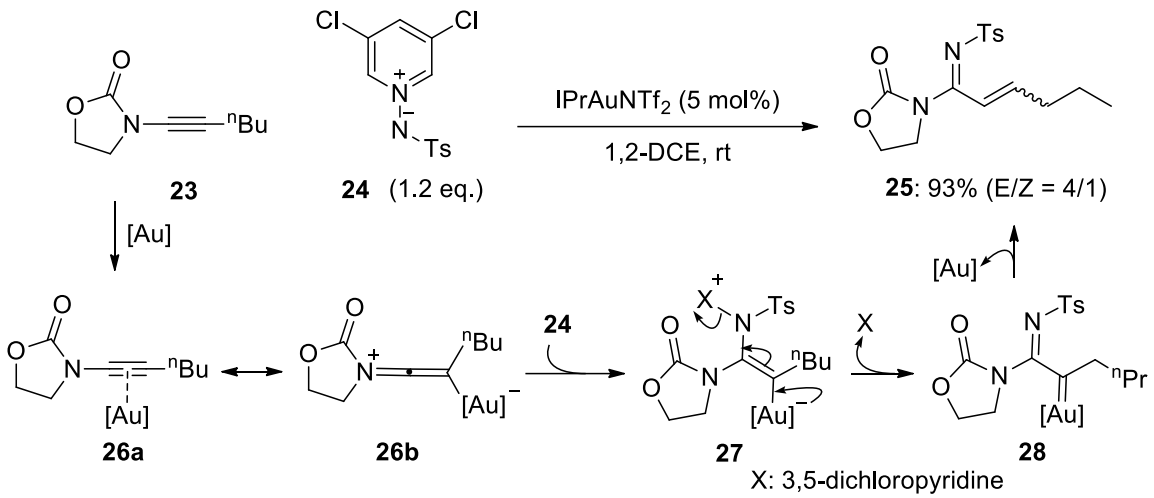
This regioselectivity preference was demonstrated by the Davies group when they reported the first site-specific intermolecular oxidation of ynamides (Scheme 6).[23] In this case, an external nucleophilic oxidant **18** is added selectively to the α-carbon of the gold-activated ynamide **20a**/**20b** forming vinyl gold species **21**. Back donation of electron density from the metal results

in loss of the pyridine moiety as a good leaving group furnishing α-imido gold carbene **22**. Subsequent 1,2-insertion quenches the carbene giving α,β-unsaturated carboxylic acid derivative **19**. In Chapter 3 attempts to further expand this reactivity trend, this time in an intramolecular fashion, are described.



Scheme 6: Site-specific oxidation/1,2-insertion cascade of gold-activated ynamides

In the same context, Zhang and co-workers reported the first intermolecular nitrene transfer onto gold-activated ynamides (Scheme 7).[24] Iminopyridinium ylide **24** functioned as a nitrene delivery system, attacking regioselectively the α-carbon of the ynamide **26a**/**26b** to form vinyl gold intermediate **27**. In analogy to the previous example, **27** evolved through elimination of the pyridine to generate α-imino gold carbene **28**, which was trapped by 1,2-insertion to give α,β-unsaturated amidine **25** in high yield. A part of Chapter 3 will focus on the development of intramolecular nitrene transfer onto gold-activated ynamides.



Scheme 7: Gold-catalysed intermolecular nitrene transfer onto gold-activated ynamides

Further examples which display the applicability of ynamides in gold catalysis along with more recent advances on the reactivity of gold carbenes will be included in the corresponding chapters. Other transition metal mediated processes will also be described and compared to indicate the differences, the advantages and the limitations of each approach.

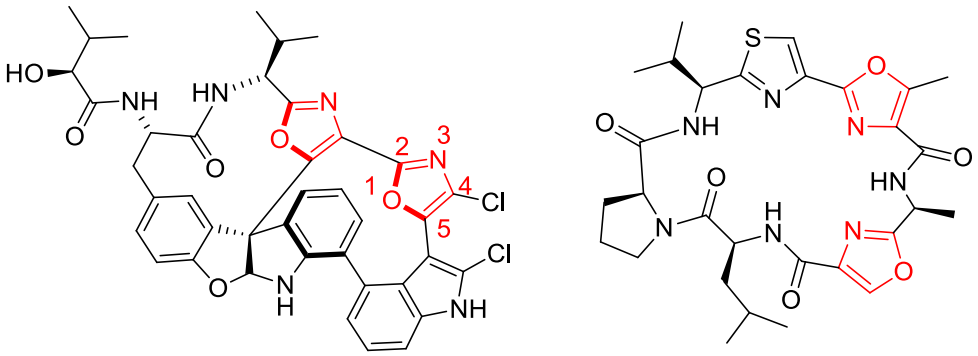
In Chapter 2, a novel oxazole synthesis *via* an intermolecular [3+2]-cycloaddition of alternative pyridine-*N*-amides and gold-activated electron rich internal alkynes is examined in detail. This reaction presents the first example of intermolecular nitrene transfer onto gold-activated internal alkynes. Chapter 3 focuses on gold-catalysed intramolecular oxygen and nitrene-transfer pathways onto ynamides and alkynes. Finally, Chapter 4 describes the development of a cascade reaction which involves the regioselective [1,5]-hydride shift towards gold-keteniminium species followed by cyclisation for the formation of complex polycyclic systems.

2. Chapter 2:

Gold-catalysed formation of all-carbon trisubstituted oxazoles

2.1 Introduction

As nitrogen- and oxygen-containing heterocycles, oxazoles are of great interest in synthetic chemistry and can be applied to many different fields such as medicine,[25] agriculture,[26] material sciences, organic dyes[27] and polymers.[28] Furthermore, they often exhibit important biological activity as peptidomimetics, amino sugar antibiotics,[29] anti-tumor cytotoxic agents[30] and enzyme inhibitors.[31] Beyond their significant biological role, oxazoles are abundant motifs in complex natural products,[32] for instance diazonamide A **29**[33] and leucamide A **30**[34] (Scheme 8). As such, interest in the synthesis of highly functionalised oxazoles has steadily increased in recent years.



diazonamide A

29

leucamide A

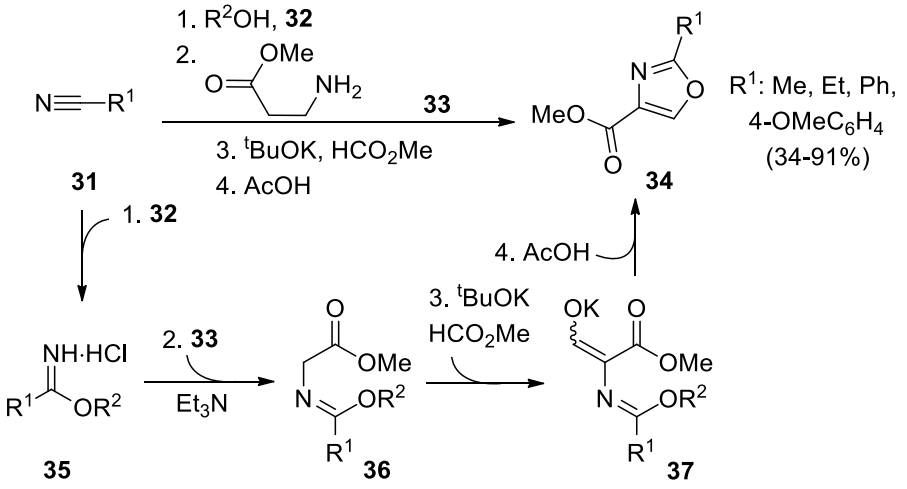
30

Scheme 8: Linked oxazoles in natural products

Classic synthetic methods for the formation of these targets have been widely based on the elaboration of a preformed oxazole ring. However these methods can suffer from several

drawbacks such as multistep syntheses, harsh conditions and the use of difficult-to-access starting materials.[35]

One of the most widely used classic methods was established in 1947 by Cornforth *et al.* In this pioneering work, nitriles and alcohols are involved through a 4-step reaction sequence.[36] Due to the lack of functional group tolerance under these conditions, many synthetic variations were then developed based on this protocol in order to expand the substrate scope (Scheme 9).[35a],[37]



Scheme 9: Cornforth's oxazole synthesis

The development of efficient and flexible syntheses of fully substituted oxazoles in a convergent fashion still remains a challenge in modern synthetic organic chemistry. Protocols which involve metals, however, can provide an alternative to classic methods, accessing new activation modes which often offer high efficiency, mild reaction conditions and low cost.[38]

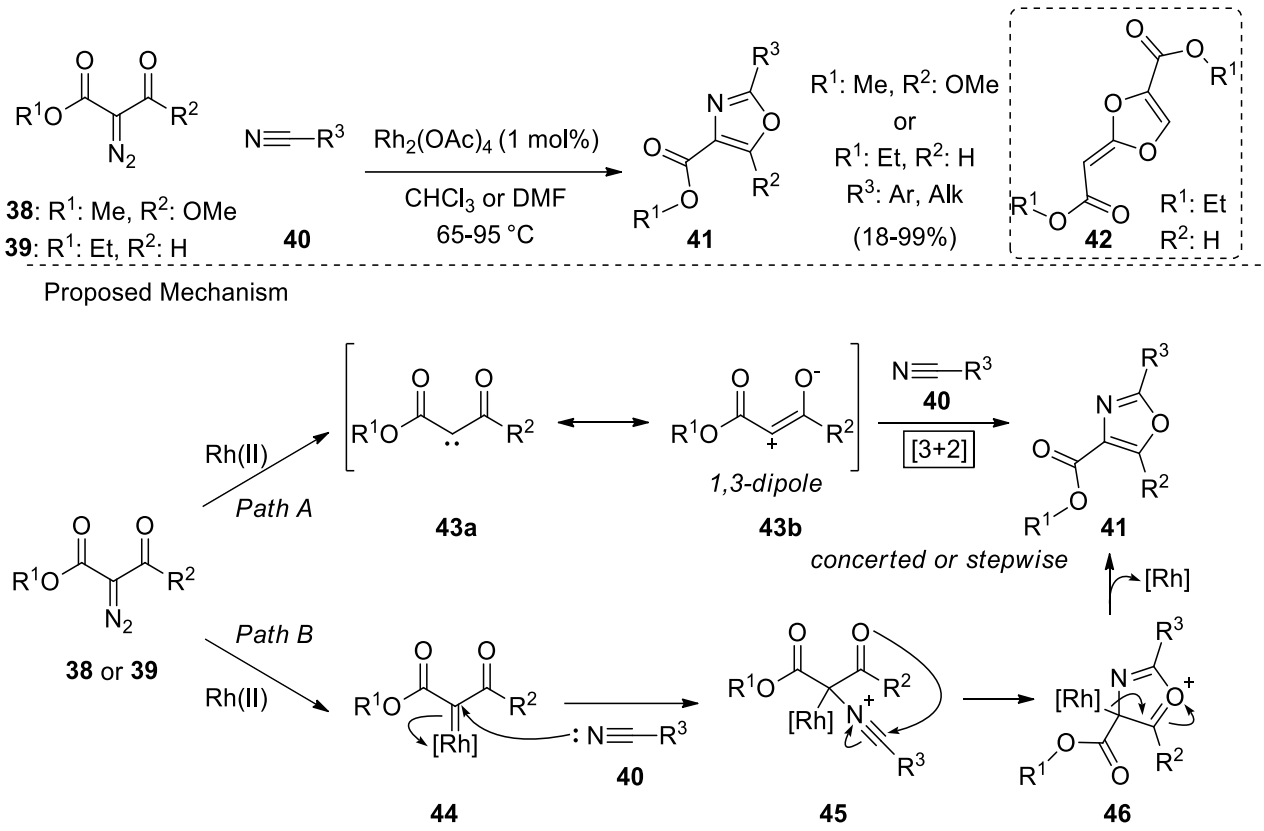
This chapter will focus on selected examples of these metal mediated methods for the formation of di- and tri-substituted oxazoles.

2.2 Metal-catalysed formation of substituted oxazoles

2.2.1 Rhodium-catalysed synthesis of oxazoles

In 1986, Helquist and co-workers developed a Rh(II)-catalysed decomposition of dimethyl diazomalonates **38** or ethyl formyldiazomalonates **39** for the synthesis of tri- or di-substituted oxazoles respectively.[39],[40] *In situ* formation of free acylcarbenes **43a**/**43b** from diazomalonates **38** or **39** at high temperatures can undergo concerted or step-wise formal [3+2]-cycloaddition with nitriles such as **40** (Scheme 10, Path A). An alternative mechanistic approach suggests the more possible formation of a rhodium carbene **44** followed by nucleophilic attack of the nitrile onto the electrophilic carbene centre forming the nitrilium species **45**. Subsequent attack by the more nucleophilic carbonyl and elimination of the metal gives the final oxazole **41** as a single regioisomer (Scheme 10, Path B).

Alkyl and aromatic substituted nitriles were well-tolerated under the reaction conditions, however modifications of the substituents at the 4- and 5-positions of the oxazole were very limited to the methyl-ester and methyl-ether respectively. The main limitation of this method involves the formation of byproduct **42** as a result of carbene dimerisation.

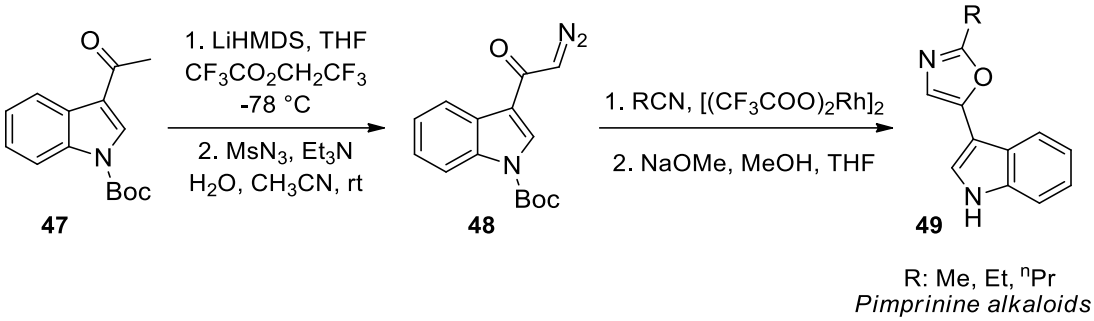


Scheme 10: Rh-catalysed formation of oxazoles employing diazomalonates and nitriles.

This methodology was further explored by several research groups who applied alternative conditions compatible with different substituents at the 4-position such as phosphonates,[41] sulphones,[42] nitriles,[43] oxazoles (formation of bis-oxazoles)[43] and silanes.[44]

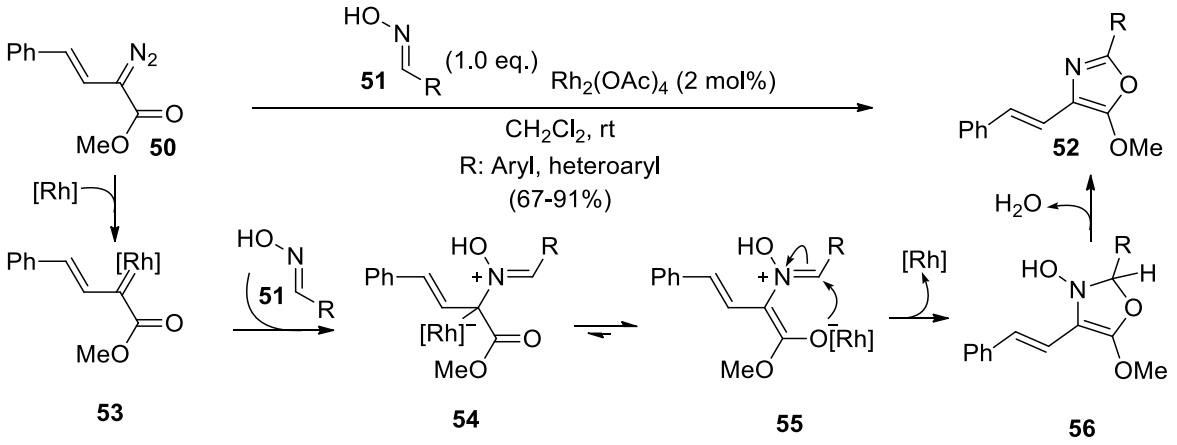
The rhodium-catalysed decomposition of diazocarbonyl compounds in combination with nitriles has also been extended to natural product synthesis. The research groups of Moody and Kozmin have contributed greatly to the field by successfully applying this methodology as a key step for the formation of complex targets such as leucascandrolide A,[45] siphonazole,[46] nocardimicin B[47] and telomestatin.[48] Finally it should be highlighted that the formation of pimprinine alkaloid derivatives **49** can be achieved with the use of protected diazoacetylindole **48** (Scheme

11), a key building block for the construction of diazonamide A (Scheme 8) complex core structure.[49] Biologically interesting pimprinine alkaloids will be discussed later in this chapter.



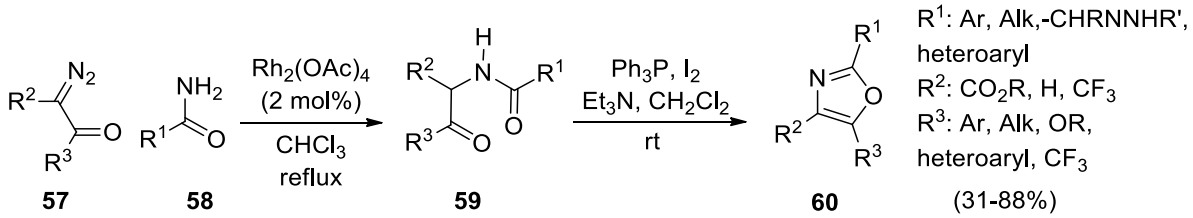
Scheme 11: Rh-catalysed synthesis of pimprinine alkaloids

Doyle and co-workers recently employed aryl oximes **51** as an alternative trap for the *in situ* generated rhodium carbenes **53** from styryl diazoacetates **50** (Scheme 12).[50] As aryl oximes are more reactive than nitriles, the side formation of carbene dimer was reduced, with the oxazole being the sole isolated product. According to the proposed mechanism, azomethine ylide **54** is initially formed which in equilibrium with metal enolate **55** is able to undergo oxo-Mannich addition to form the cyclised intermediate **56**. Dehydrative aromatisation furnishes the desired oxazole **52**. This protocol allows facile access to 4-styryl-5-methoxy oxazoles whilst accommodating a number of aromatic groups on the 2-position.



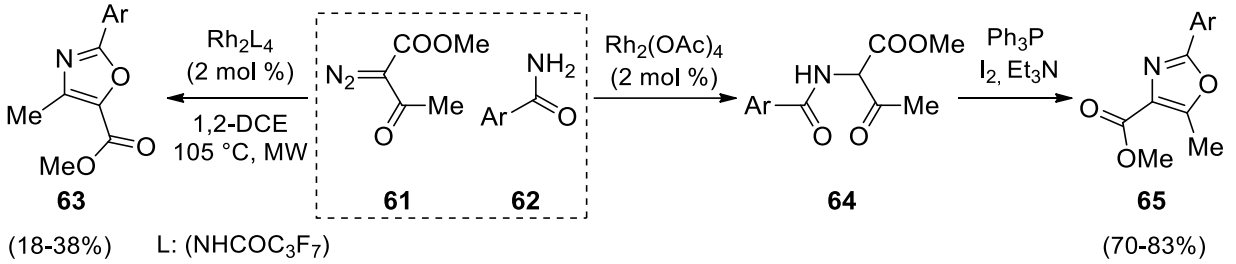
Scheme 12: Use of oximes as intermolecular traps for Rh carbenes

Rhodium carbenes can be also trapped by amides for the formation of fully substituted oxazoles. This robust method, first proposed by Moody,[51],[52] exhibited high functional group tolerance at the 2-position of the oxazole ring, accommodating substituted aryl, heteroaryl and aliphatic groups, as well as amines and ethers in good to high yields (Scheme 13).[51],[53] In addition, the optical purity of chiral amino-acids was not diminished across the transformation, affording optically active oxazoles.[54] Moody suggested that the rhodium carbene inserts into the N-H bond of the amide **58** forming the acyclic isolable intermediate **59**. A Wipf cyclodehydration leads to the desired oxazoles **60**.[55]



Scheme 13: NH- carbene insertion and Wipf cyclisation for the formation of oxazoles

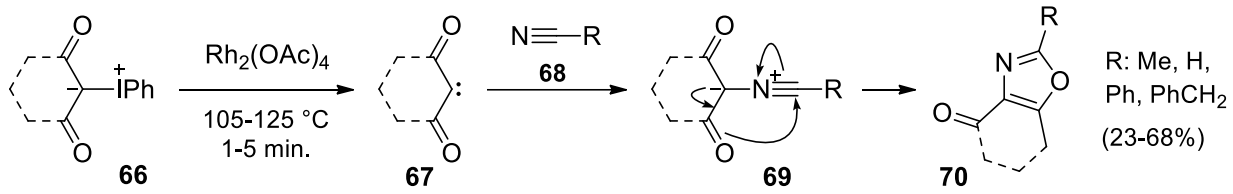
The protocol can be adapted for the formation of isomeric analogues of the oxazoles regioselectively depending on the use of the catalyst (Scheme 14).[56] By tuning the electronic properties of the catalyst and the use of microwave heating, an alternative regioselectivity was achieved, allowing selective access to either 2-aryloxazole-4-carboxylate **65** or 2-aryloxazole-5-carboxylate **63**. Amides **62** reacted with methyl 2-diazo-3-oxobutanoate **61** through the use of $Rh_2(OAc)_4$, giving the corresponding oxazole-4-carboxylates **65** in high yields. However, on treatment with $Rh_2(NHCOC_3F_7)_4$, under microwave irradiation, the same starting precursors (**61** and **62**) gave the isomeric oxazole-5-carboxylate **63** in modest yields (13-38%). The authors vaguely proposed that the change in selectivity arose from electronic factors. The change in ligands in dirhodium (II), the electrophilicity of the intermediate rhodium carbene changed and provided the selective formation of 4- or 5-functionalized oxazoles.



Scheme 14: Regioselective synthesis of oxazole-4- and oxazole-5-carboxylates.

An alternative method based on the use of iodonium ylides **66** instead of diazocarbonyl compounds was reported by Hadjiarapoglou *et al* (Scheme 15).[57] The reaction is proposed to proceed *via* the formation of free carbene **67** which is trapped by nitriles **68** to form substituted oxazoles **70**. Despite the rapid rate of the reaction, the substrate scope was limited to simple

aryl and alkyl groups and the yields were moderate in most cases. Interestingly, the reaction proceeds with the use of copper salt as well, however the substrate scope was not explored further.[58]



Scheme 15: Use of iodonium ylides for the formation of substituted oxazoles

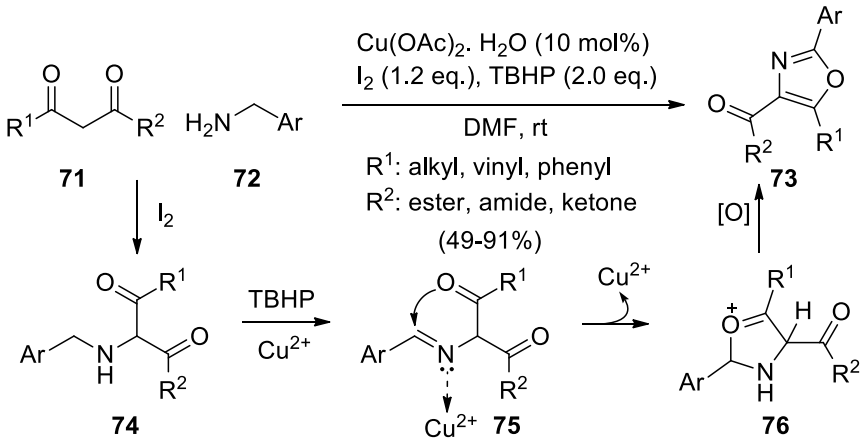
The use of Rh(II) for the preparation of di- and tri-substituted oxazoles has been widely explored allowing access to highly functionalised heterocycles. Although in most cases there is flexibility in the substitution of the 2-position of the ring (as amides or nitriles can be easily modified), these procedures suffer from many limitations regarding the substitution at the 4- and 5-positions. Furthermore, the extra synthetic steps for the preparation of starting materials and the use of potentially explosive diazo-precursors is not desirable especially for large scale reactions.

2.2.2 Copper-catalysed synthesis of oxazoles

Limited success has been achieved in attempts to employ inexpensive copper salts as an alternative to rhodium in diazo chemistry, with the corresponding methods exhibiting limited substrate scope and poor yields.[58-59]

The main advantage for copper-mediated oxazole formation is the possibility of employing diketones instead of diazocarbonyl starting materials. For example, β-diketone derivatives **71**

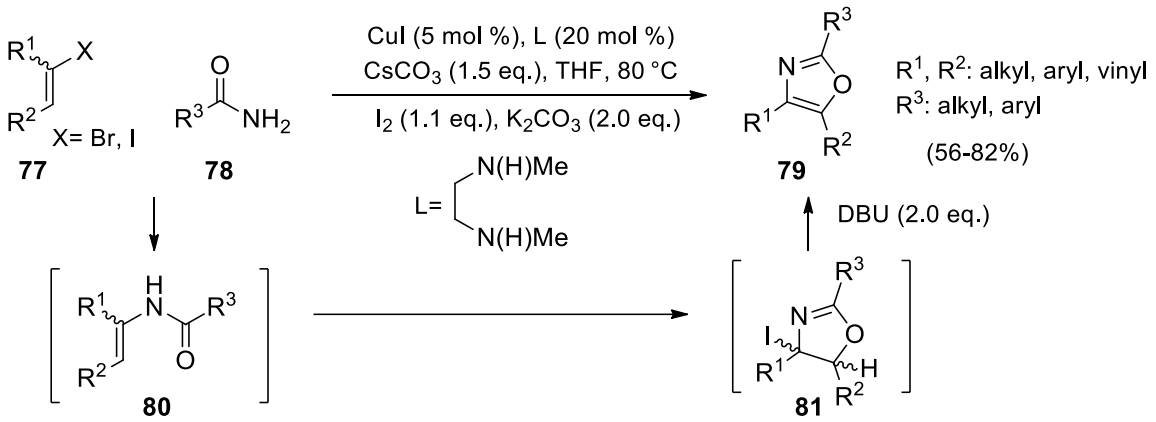
(either β-ketoesters or β-diketones) and benzylamine **72** can be employed in a copper-mediated tandem oxidative cyclization, as reported by Wang (Scheme 16).[60] A plausible mechanism involves the formation of the acyclic intermediate **74** upon treatment with iodine followed by oxidation to form imine **75**. Subsequent copper-promoted intramolecular cyclisation occurs through nucleophilic attack of the carbonyl oxygen onto the electrophilic α-carbon affording intermediate **76** which is further oxidised to give the desired product **73** *(vide infra)*. Several benzylamine derivatives **72** were investigated, revealing that substitution of the aromatic ring with electron donating groups was detrimental, whereas substitution with electron withdrawing groups resulted in better yields. Hindered diketones were not well-tolerated, leading to limited substitution at the 4- and 5-positions.



Scheme 16: Copper-catalysed formation of oxazoles from diketones and amines.

In 2007 Buchwald and co-workers published a novel and flexible regioselective synthesis of highly substituted oxazoles **79** by a sequential copper-catalysed amidation of vinyl halides **77** and iodine-promoted intramolecular cyclisation (Scheme 17).[61] Regardless of the geometry,

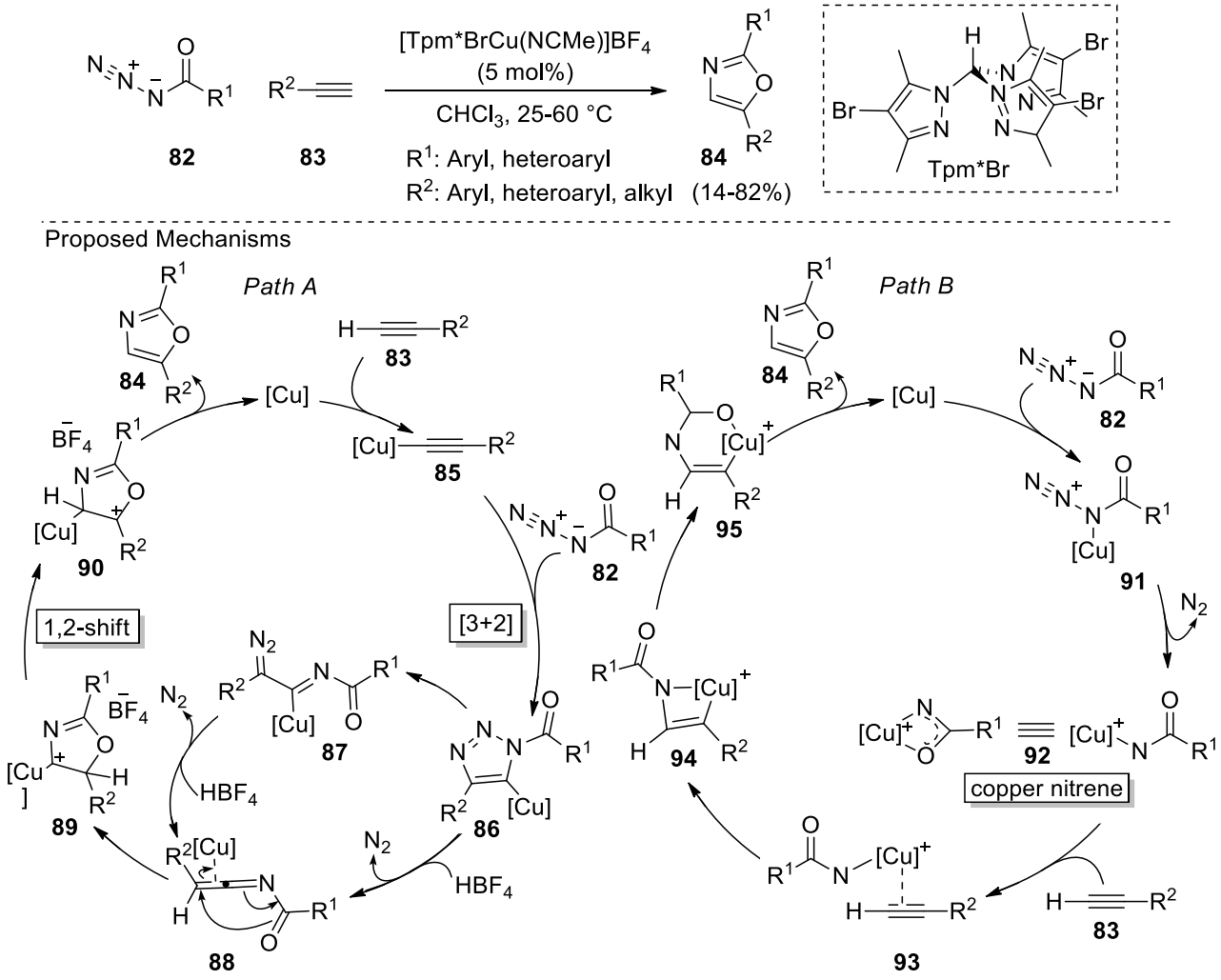
vinyl halides reacted smoothly with aromatic or aliphatic amides. Further, electron-rich or electron-deficient halides presented similar efficiency to yield a wide variety of fully substituted oxazoles **79**.



Scheme 17: Synthesis of oxazoles *via* a sequential Cu-catalysed amidation/cyclisation.

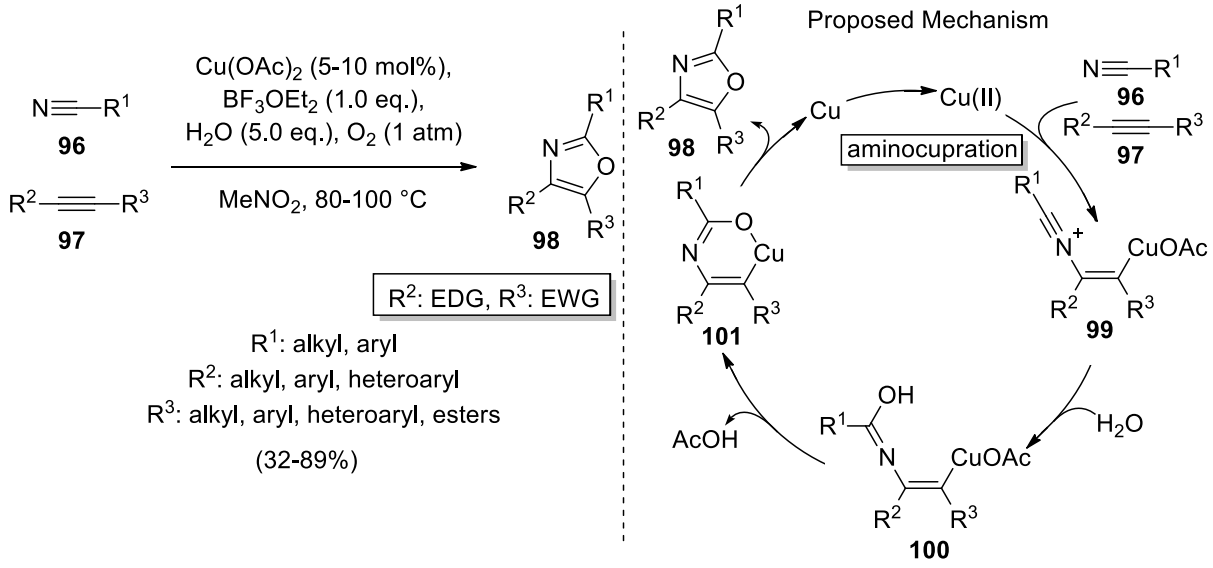
More recently, the Pérez research group reported the regioselective synthesis of 2,5-disubstituted oxazoles through nitrene transfer onto copper-activated terminal alkynes, employing azides **82** and acetylenes **83** (Scheme 18).[62] In the initial research, a plausible mechanism was proposed including the initial formation of copper-acetylide **85** and subsequent [3+2]-intermolecular cycloaddition with the azide to give the triazolium intermediate **86** (Path A). Fragmentation of **86**, *via* **87**, and protonation would lead to copper-ketinimide **88** which can cyclise afterwards to give the cyclic intermediate **89**. Finally, 1,2-hydrogen shift and elimination of the metal would give the di-substituted oxazole **84**. Three years later, mechanistic and computational studies suggested an alternative mechanism involving the formation of copper nitrene **92** following coordination of the metal with the azide (Path B).[63] The metal can then activate the π-system towards regioselective addition of the nitrogen to the terminal carbon the

alkyne (**93** to **94**). Coordination of the metal to the carbonyl oxygen (**95**) and reductive elimination would give the final oxazole **84** as a single regioisomer. Although the scope of the reaction was broad with regards to the incorporation of aromatic and alkyl substituents at the 5-position of the oxazole, alkyl acetylenes and internal alkynes were unreactive. This could potentially be due to the inability to such alkynes to form either the copper-acetylide at the first step (Path A) or the C-N bond (**93** to **94**, Path B).



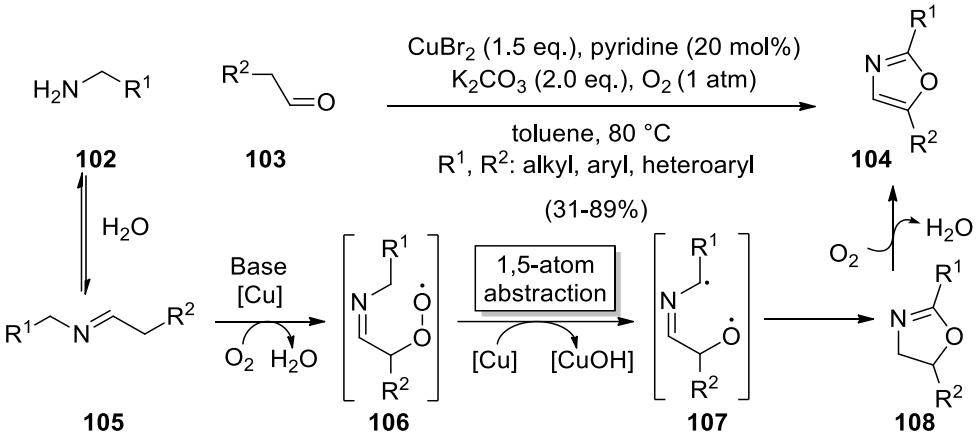
Scheme 18: Copper-catalysed oxazole formation using terminal alkynes and azides

Jiang and co-workers developed a regioselective, three component, copper-catalysed synthesis through a [2+2+1]-cycloaddition of internal alkynes, nitriles and water (Scheme 19).[64] The proposed mechanism is initiated by regioselective nucleophilic attack of the nitrile **96** onto the copper-activated π-system resulting in a *syn*-aminocupration product **99**. The regioselectivity derives from the contrasting electronic properties of the substituents attached to the π-bond. Subsequent nucleophilic attack by water leads to the intermediate **100** which evolves through elimination of AcOH and cyclisation (**101**). Reductive elimination of the metal generates the oxazole **98** and oxidation from molecular oxygen recycles the catalyst and completes the catalytic cycle. Interestingly, the method proved compatible with a wide range of groups and substitution patterns, such as alkyl, aromatic, heteroaromatic, nitriles and esters.



Scheme 19: Cu-catalysed regioselective [2+2+1]-annulation for the formation of oxazoles

Jiang also reported a copper-catalysed, convergent synthesis of 2,5-disubstituted oxazoles **104** employing readily available amines **102** and aldehydes **103** through an overall aerobic oxidative dehydrogenative annulation (Scheme 20).[65] Whilst the mechanism was not fully understood, a radical mediated process was proposed based on mechanistic studies. Initially, dehydration takes place to form imine **105** which can be oxidised by molecular oxygen, under basic conditions, to form radical intermediate **106**. 1,5-Hydrogen atom abstraction (**106** to **107**) is followed by intramolecular radical coupling to give oxazoline **108** which is oxidised in air forming the final oxazole **104**. The scope of the reaction was found to be wide with alkyl, substituted aryl and heteroaryl groups compatible, affording the oxazole in good to excellent yields.

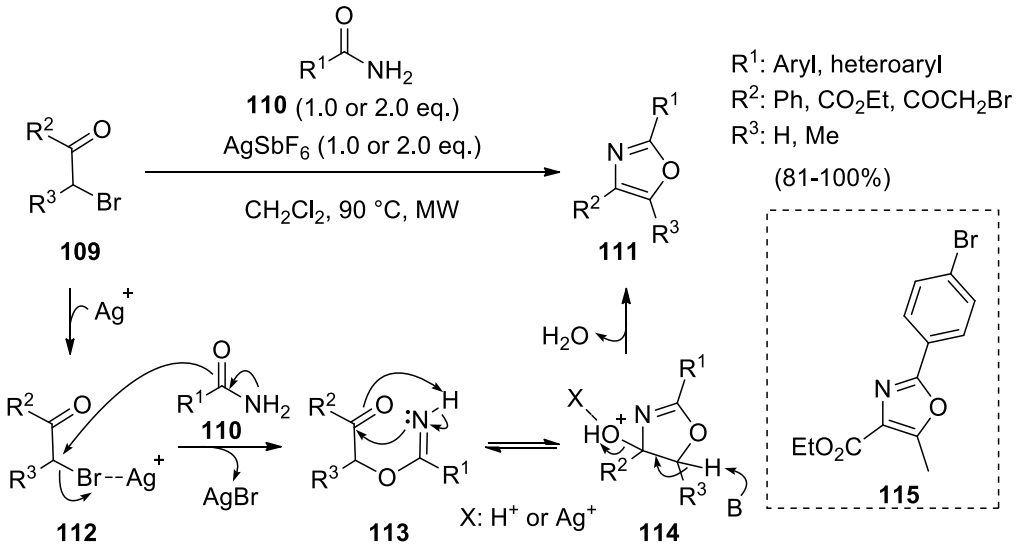


Scheme 20: Copper-catalysed formation of 2,5-disubstituted oxazoles

Although copper catalysis for the synthesis of oxazoles has not been extensively explored in the last decade, novel and elegant transformations have been realised, demonstrating the potential applicability and efficiency of inexpensive copper salts.

2.2.3 Silver-catalysed synthesis of oxazoles

The required elevated temperature for the Blümlein-Lewy oxazole synthesis[66] is not compatible with a range of functional groups. Recently, Moses and co-workers developed an enhancement of this method, employing primary amides **110**, bromopyruvate esters **109** and stoichiometric silver, under microwave conditions (Scheme 21).[67] According to the proposed mechanism, nucleophilic attack of the amide onto the bromopyruvate is driven by the formation of a strong silver halogen bond (intermediate **112**). Dehydration of cyclic intermediate oxazoline **114** may be promoted by either protonation of the tertiary alcohol by the conjugate acid $HSbF_6$ or by coordination to the metal.

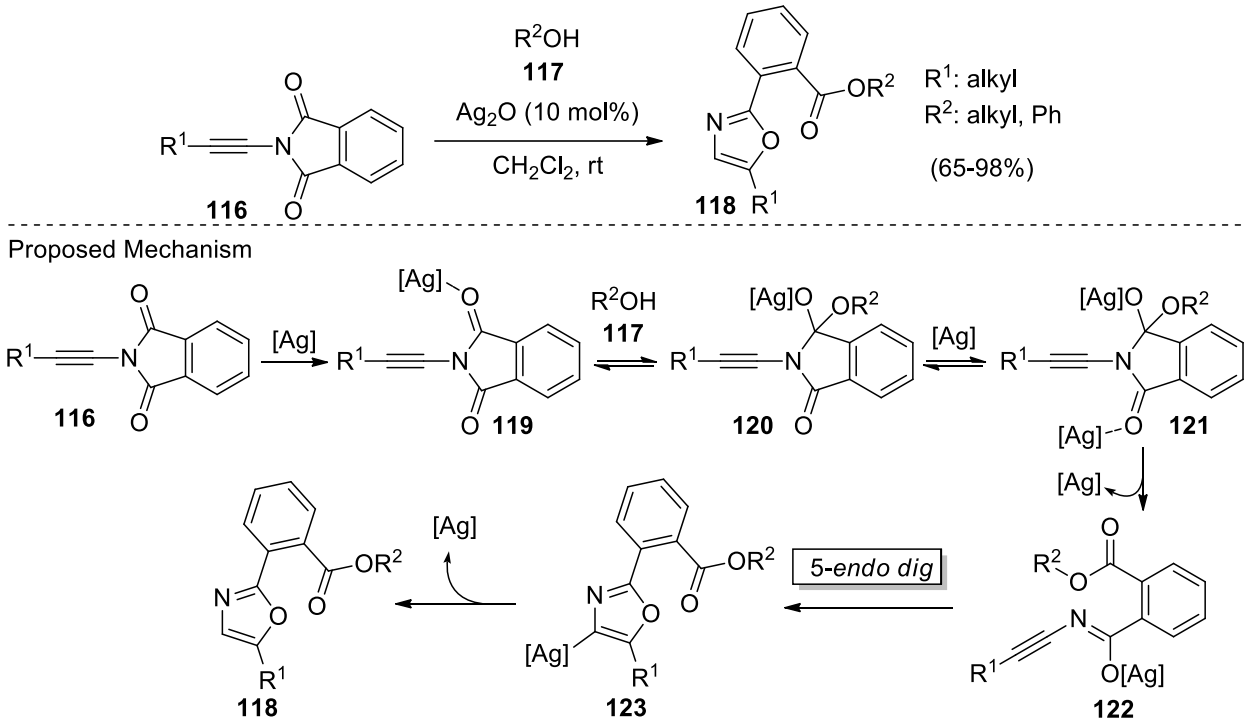


Scheme 21: Silver mediated Blümlein-Lewy synthesis of oxazoles

Whilst some synthetically valuable functionality could be incorporated onto the oxazole ring, this protocol was limited to aromatic amides as alkyl amides were unreactive. Additionally, the bromopyruvate ester cannot be easily modified, resulting in limitations of the substituents at

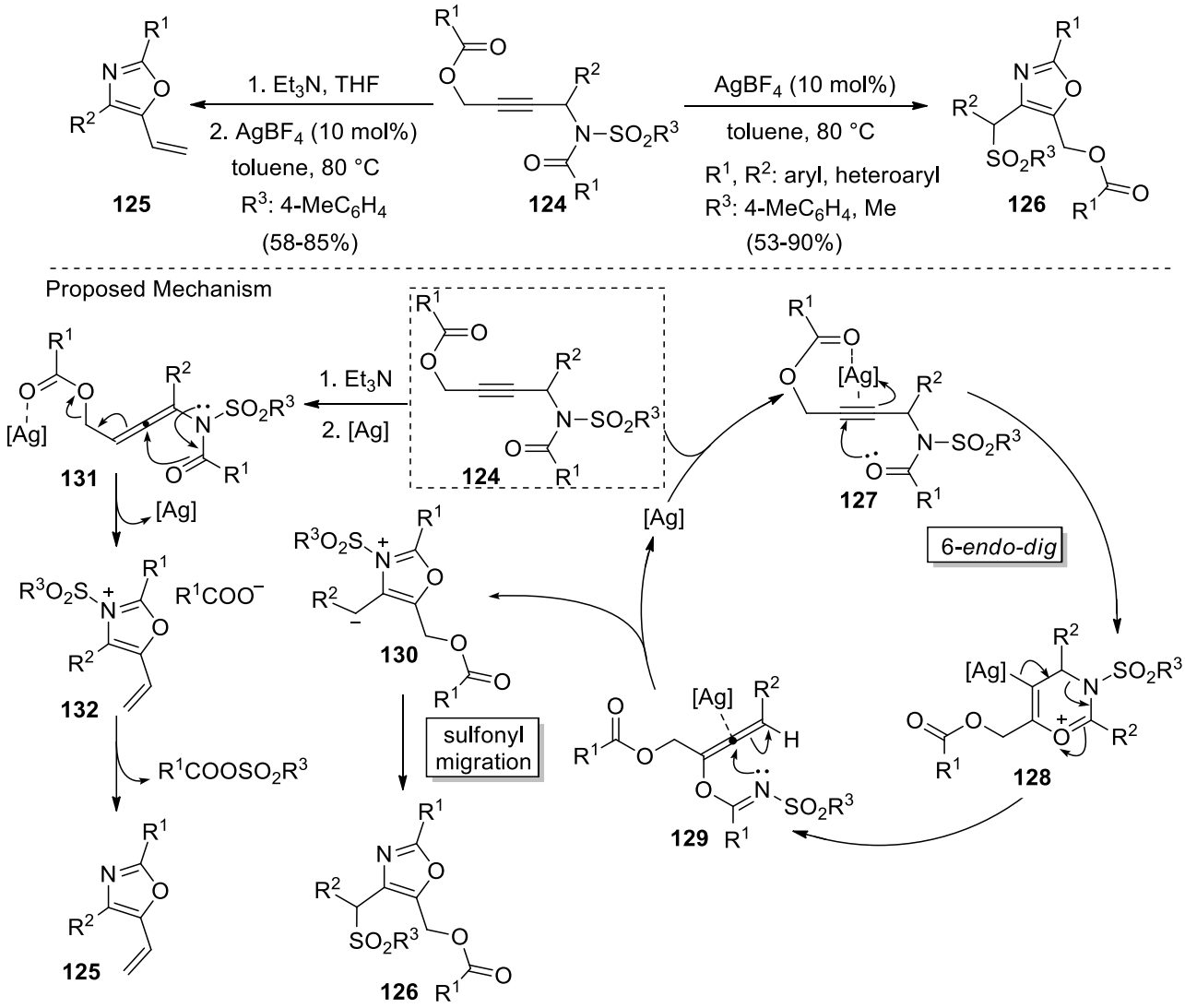
the 4- and 5-positions of the oxazole ring. For this reason trisubstituted oxazoles were not readily accessed by this method, with the only exception shown above (ester **115**).

The Sueda research group reported the silver-catalysed formation of 2,5-disubstituted oxazoles **118**, employing ynimides **116** and alcohols **117** (Scheme 22).[68] The proposed reaction mechanism invokes the carbonyl activation of the ynimide by silver (**119**) followed by nucleophilic attack of the alcohol **117**. Further activation of the metal and ring opening of **121** generates intermediate **122** that undergoes cyclisation in a 5-*endo*-*dig* fashion (**123**) and protodematallation to give the oxazole **118**. The protocol provides an easy way to form highly functionalised oxazoles under mild conditions with alkyl groups on the 2- and 5-positions being well-tolerated. However, bulky aromatic substituents either required harsher conditions or proved totally unreactive.



Scheme 22: Silver-catalysed formation of 2,5-disubstituted oxazoles

Interestingly, Wan and co-workers described the silver-catalysed synthesis of *N*-sulfonyl oxazoles **126** from aryl-substituted *N*-sulfonyl-propargylamides **124** (Scheme 23).[69]



Scheme 23: *N*-sulfonyl-propargylamides for Ag-catalysed oxazole formation

A plausible mechanism involves the complexation of the metal with both the π-system and the acyloxy group of **127** promoting 6-*endo-dig* cyclisation *via* intramolecular nucleophilic attack of the acyloxy moiety. Intermediate **128** then fragments to form allene **129** which undergoes nucleophilic attack by the nitrogen onto the more electron-deficient allenyl carbon to give the cyclised ylide **130**. Finally, highly regioselective migration of the sulfonyl group takes place to

form the final product **126**. The method could also be extended to the formation of 5-vinyl oxazoles **125**. Intriguingly, upon treatment with Et_3N, *N*-sulfonyl-propargylamides **124** were converted to allenylamides **131** that gave alternative 5-vinyl oxazoles following treatment with silver. The reaction is thought to proceed through an intramolecular nucleophilic attack by the oxygen of the amide (**131** to **132**). Elimination of both the alkoxy and sulfonyl groups gives the substituted 5-vinyloxazoles **125**.

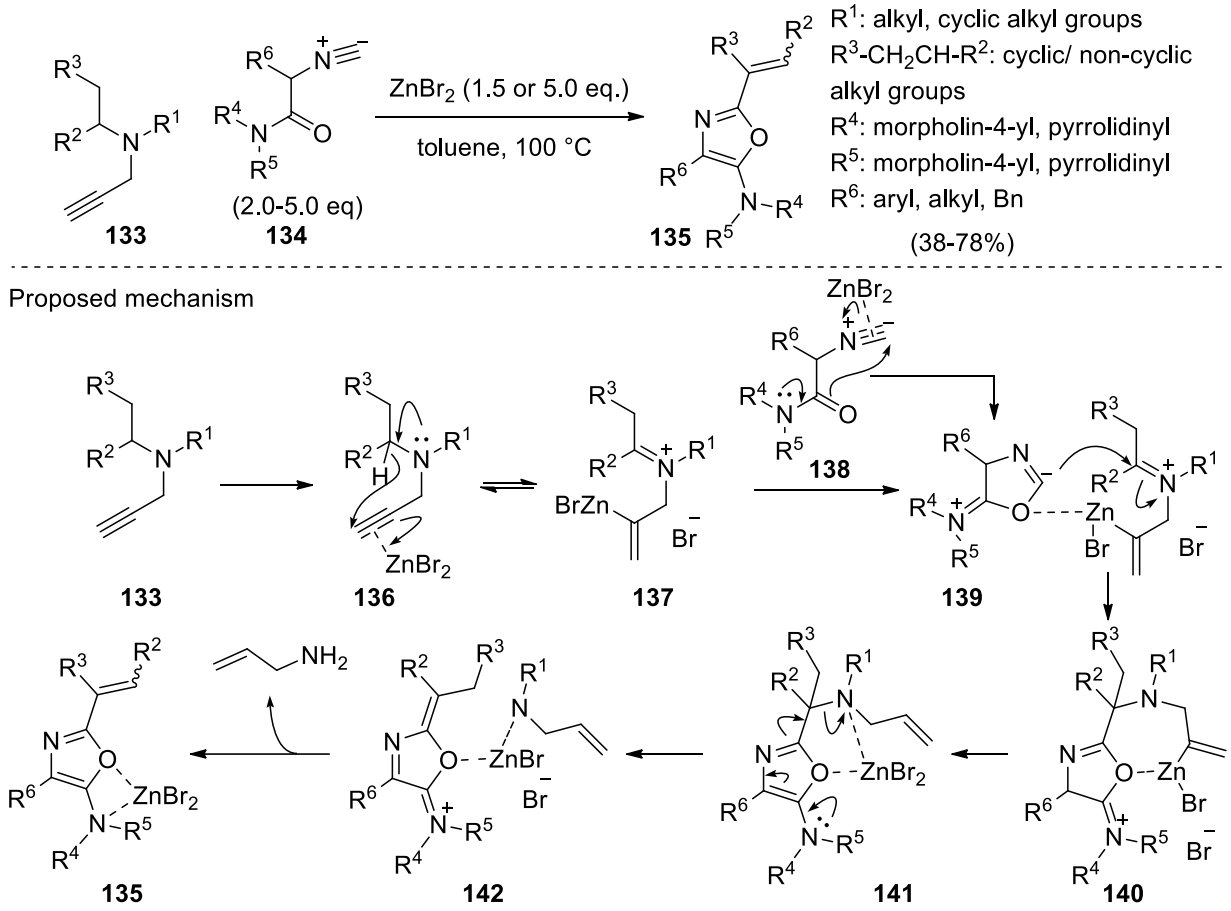
Silver-catalysed methods developed so far for the formation of oxazoles gave access to synthetically valuable scaffolds under mild conditions. The observed lack of functional group tolerance in certain cases is expected to be improved as research in this area is ongoing.

2.2.4 Zinc-mediated formation of oxazoles

It has recently emerged that zinc salts can be employed as effective catalysts for the formation of oxazoles. Although this has not been widely explored, the research group of Zhu has developed a novel method for rapid access to these molecules.

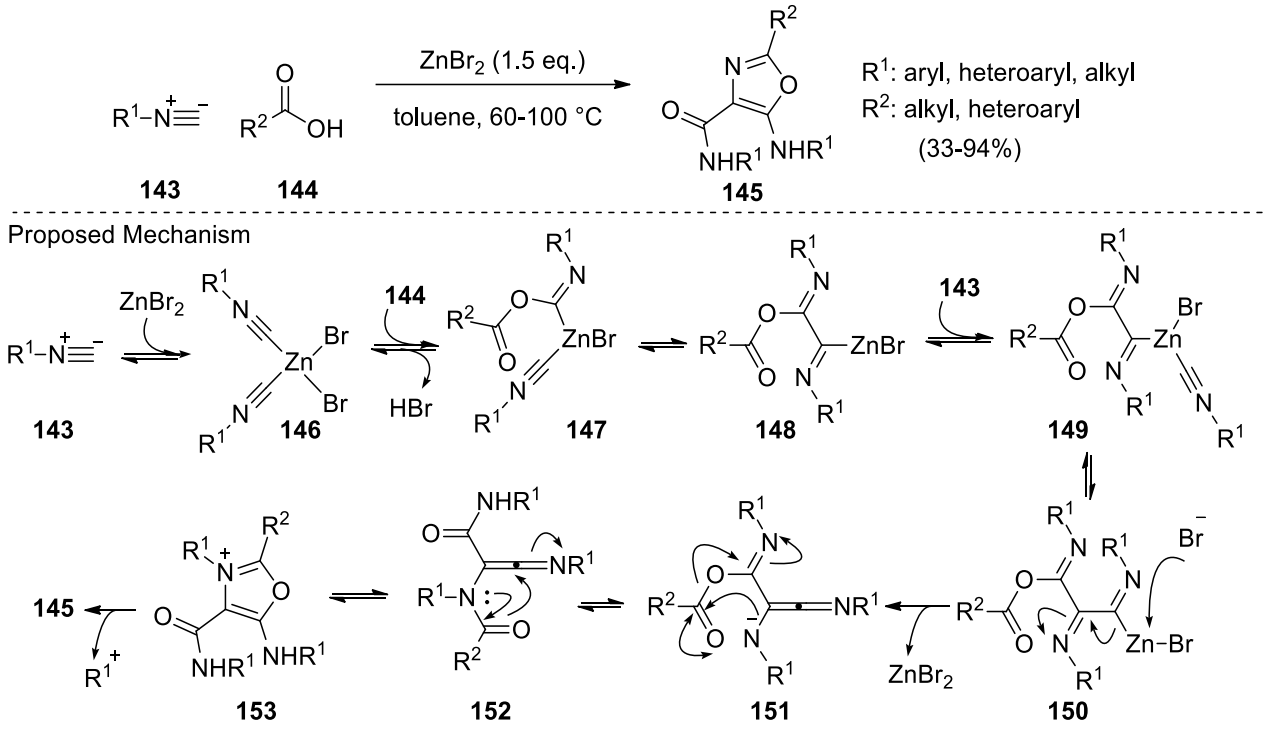
Zhu and co-workers used *N*-propargyl amides **133** as vinyl cation equivalents in combination with α-isocyanoacetamides **134** and an excess of $ZnBr_2$ to form trisubstitued 2-vinyl-5-aminooxazoles **135** through a domino addition/cyclisation/elimination process (Scheme 24).[70] Mechanistic studies indicated that the first step involves zinc-activation of the π-system promoting an unprecedented 1,5-hydride shift to form iminium ion **137**. Zinc coordination to the isocyanoacetamide **138** would trigger its nucleophilic attack onto the iminium, generating nitrilium intermediate which undergoes aromatisation and protodemetalation (**139** to **141**).

Coordination of zinc with the tertiary allylamine **141** facilitates elimination of the allyl amine to give **142**. Finally proton transfer and isomerisation gives the oxazole **135**, potentially coordinated to zinc. The method was compatible with a wide range of benzyl, alkyl and aryl substituted isocyanoacetamides. As well as this, highly functionalised alkyl substituted propargylamines were well tolerated introducing additional complexity on the 2-position of the oxazole ring.



Scheme 24: Zinc-mediated formation of oxazoles with isonitriles and *N*-propargyl amides

The use of isonitriles **143** for zinc-mediated oxazole formation was further explored by the same group by combining them with carboxylic acids **144** (Scheme 25).[71]



Scheme 25: Zinc-mediated formation of oxazoles with isonitriles and carboxylic acids

Coordination of the Lewis acid to the isonitrile generates complex **146** which undergoes nucleophilic attack by the carboxylic acid to give **147**. Migratory insertion then takes place (**147** to **148**), allowing another isonitrile to coordinate to the metal. A second migratory insertion generates intermediate **150** which forms ketenimine **151** on elimination of zinc. Rearrangement of **151** and subsequent intramolecular nucleophilic attack onto the α-carbon of the ketinimine **152** furnishes **153** which evolves through dealkylation to give the final product **145**. This catalytic process requires stoichiometric quantity of $ZnBr_2$, potentially due to strong chelation of the metal to the oxazole. The substrate scope for this transformation was broad with aromatic, heteroaromatic and aliphatic isonitriles and carboxylic acids reacting smoothly in the desired transformation to give good yields in most of cases.

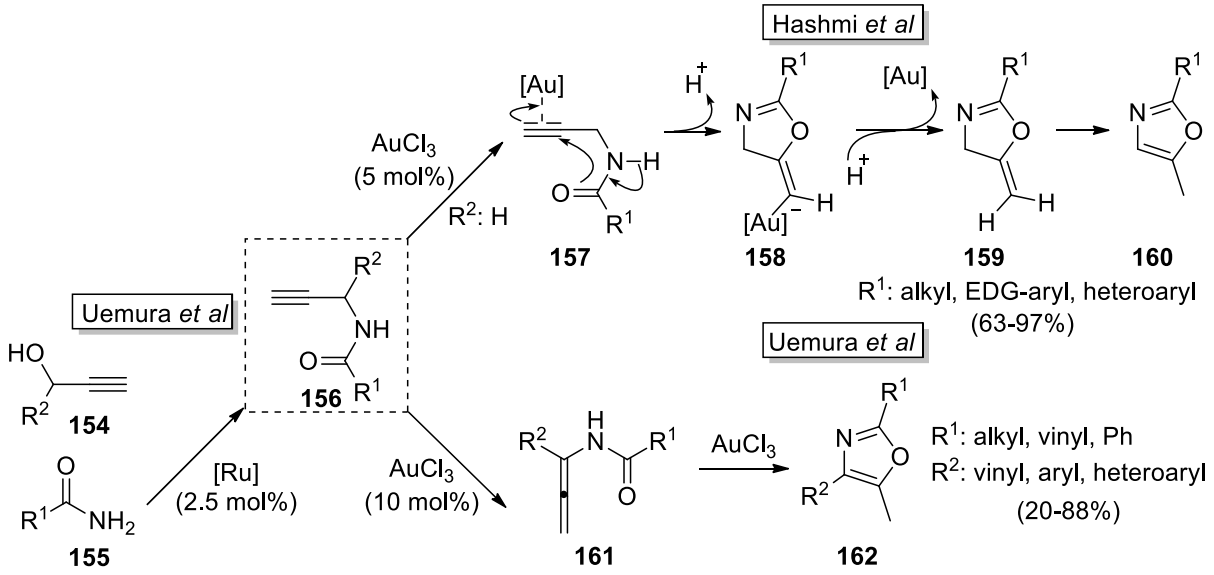
These recently developed methods are representative examples of zinc promoted formation of substituted oxazoles. The necessity of using stoichiometric quantities of the relatively expensive $ZnBr_2$ consists a major disadvantage of these protocols; however this can be counterbalanced by the impressive functional group tolerance they exhibit.

2.2.5 Gold-catalysed formation of oxazoles

Efficient and convergent methods for the synthesis of substituted oxazoles have been developed in the last five years which employ gold as a catalyst. These procedures tend to involve readily available starting materials and mild conditions, while exhibiting great functional group tolerance. As discussed in the previous chapter, a key feature of gold catalysis is the potential ability to generate *in situ* gold carbenes without the need of hazardous and potentially explosive diazocarbonyl precursors.

In 2004 Hashmi and co-workers reported the gold-catalysed, regioselective synthesis of 2,5-di-substituted oxazoles **160** (Scheme 26).[72],[73] On activation of the triple bond, terminal *N*-propargyl amides **156** underwent 5-*exo*-*dig* cyclisation (**157**) and isomerisation of the intermediate oxazoline **159**. The same year, Uemura and co-workers reported a variation of the same method by using propargyl alcohols **154** and amides **155** to generate the reactive *N*-propargyl amides **156** *in situ* under ruthenium catalysis and subsequent treatment with $AuCl_3$ to give the corresponding tri-substituted oxazoles **162**.[74] Although both research groups conducted NMR studies to elucidate the reaction mechanism, their results proved contradictory. Hashmi and co-workers reported that the reaction of *N*-propargyl amides

proceeds through a regioselective *anti*-addition across the gold-activated π-system to form **158**, followed by regioselective protodeauration to generate oxazoline **159**. On the other hand, the Uemura research group reported that the gold-activated *N*-propargyl amides undergo initial isomerisation to form the allenamide **161** which subsequently cyclises to form the oxazole **162**. Five years later, Hashmi and co-workers published further experimental evidence for the intermediacy of oxazoline,[75] while Ahn and co-workers were able to isolate and fully characterise for the first time the vinyl gold species **158** (when R^1: Ph).[76]

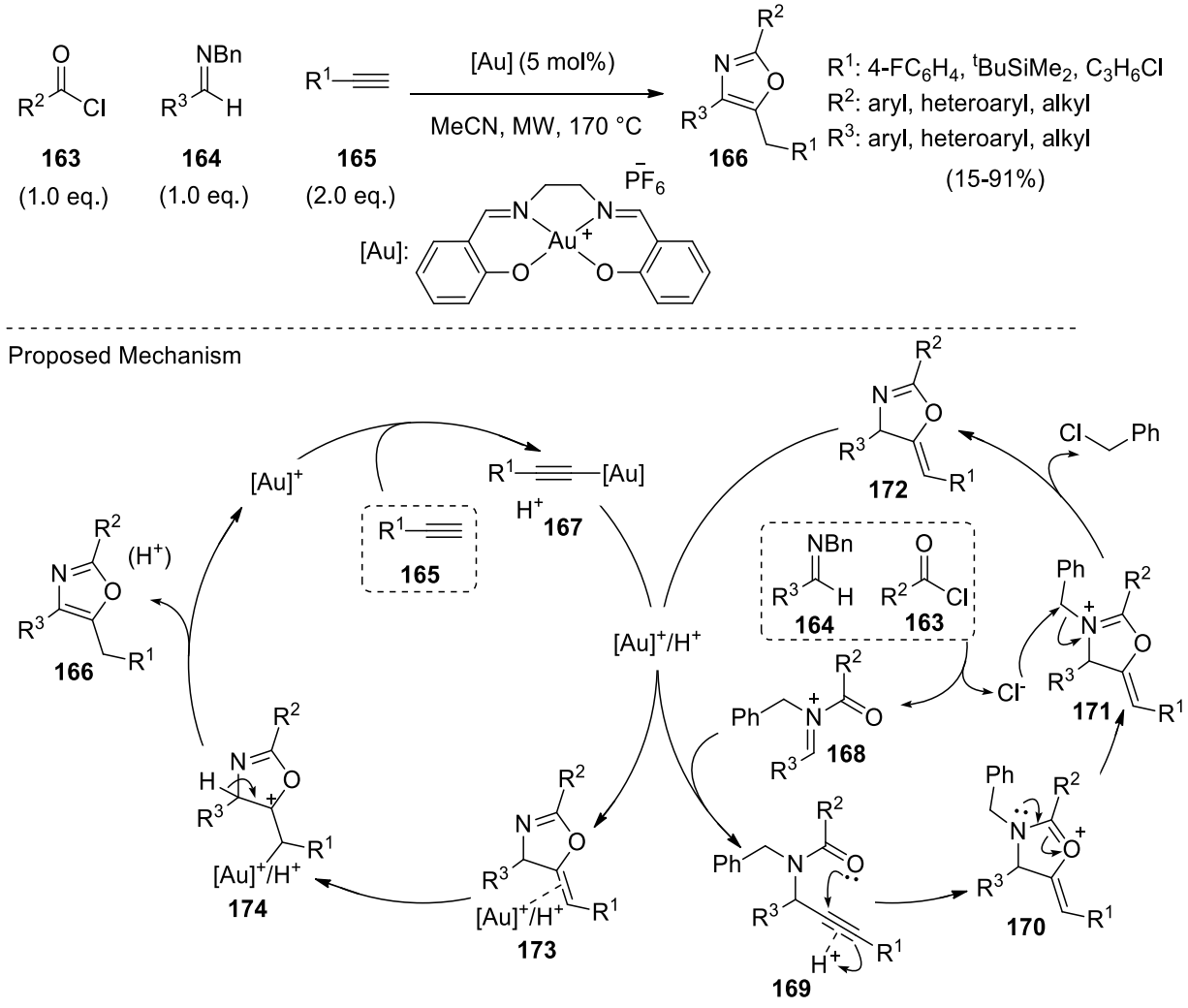


Scheme 26: Gold-catalysed formation of 5-methyl oxazoles from *N*-propargyl amides

Regarding the substrate scope, Hashmi's method was compatible with alkyl and electron-rich aryl and heteroaryl groups in the 2-position, whereas electron-deficient aryl groups proved ineffective, potentially due to the decreased nucleophilicity of oxygen. Similarly, Uemura's method was limited to phenyl, alkyl and vinyl groups at the 2-position and aryl or heteroaryl groups at the 4-position of the oxazole. It should be noted that internal *N*-propargyl amides do

not undergo cycloisomerisation. The methodology was extended further by other research groups, providing access to more complex substitution around the oxazole ring.[77],[78]

Recently, Strand's research group published the three-component domino reaction for the synthesis of oxazoles (Scheme 27).[79]

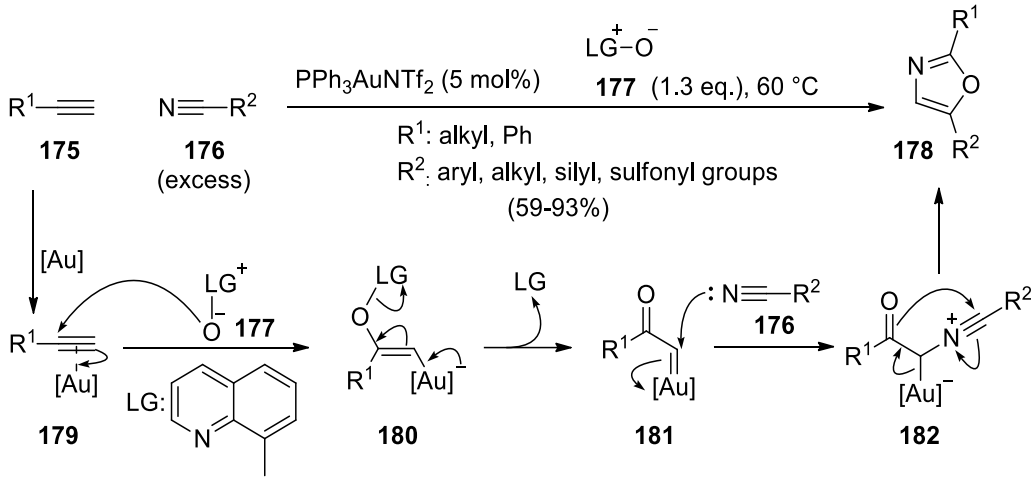


Scheme 27: Three component domino reaction for the formation of oxazoles

The method involved readily available benzyl imines **164**, acyl chlorides **163** and terminal alkynes **165** under microwave conditions. Mechanistic and kinetic investigations suggest either

activation of the triple bond by a protic acid or the formation of the metal acetylide **167** and its subsequent coupling with the *N*-acyl intermediate **168** to form the *N*-propargyl amide **169** *in situ*. Protic activation of the π-system promotes cyclisation to give the iminium **171** (through **170**) which evolves through the release of benzyl chloride forming the oxazoline **172**. Finally, gold and Brønsted acid promoted isomerisation (**173** to **174**) and demetallation generate the trisubstituted oxazole **166**. The substrate scope was generally wide including alkyl, aryl and heteroaryl groups in moderate to excellent yields.

In 2011, Zhang and co-workers reported the formation of 2,5-disubstituted oxazoles **178** through the intermolecular reaction of various nitriles **176** with gold carbenes generated *via* alkyne oxidation (Scheme 28).[80]



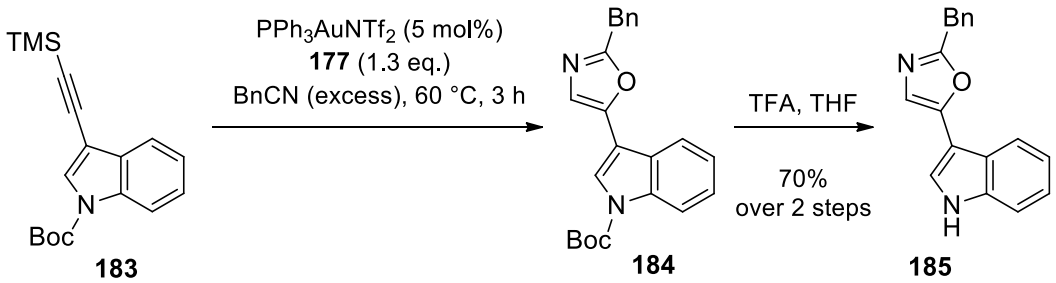
Scheme 28: Gold-catalysed formation of 2,5-disubstituted oxazoles

Initially, nucleophilic attack of the oxidant **177** on the gold-activated π-system **179** generates an α-oxo gold carbene **181**. Intermolecular trapping of the carbene by a nitrile and subsequent cyclisation led to the desired 2,5-substituted oxazoles **178** in a formal convergent [2+2+1]

annulation. A range of nitriles **176** proved reactive: aryl, alkyl and cycloalkyl groups could substitute the 5-position of the oxazole. Substituents at the 2-position of the oxazole ring were however limited to alkyl and unsubstituted phenyl groups. This is potentially due to larger groups blocking the nucleophilic attack by oxygen (**179** to **180**).

The conditions of the reaction were mild, tolerating sensitive functional groups such as silanes, sulfonyl and alkyl groups. However, in order to avoid the large excess of precious nitriles, a more complex and expensive BrettPhos ligand was required. Thus, further investigation of the substrate scope was performed with the use of much less expensive PPh_3AuNTf_2 and nitriles as a solvent.

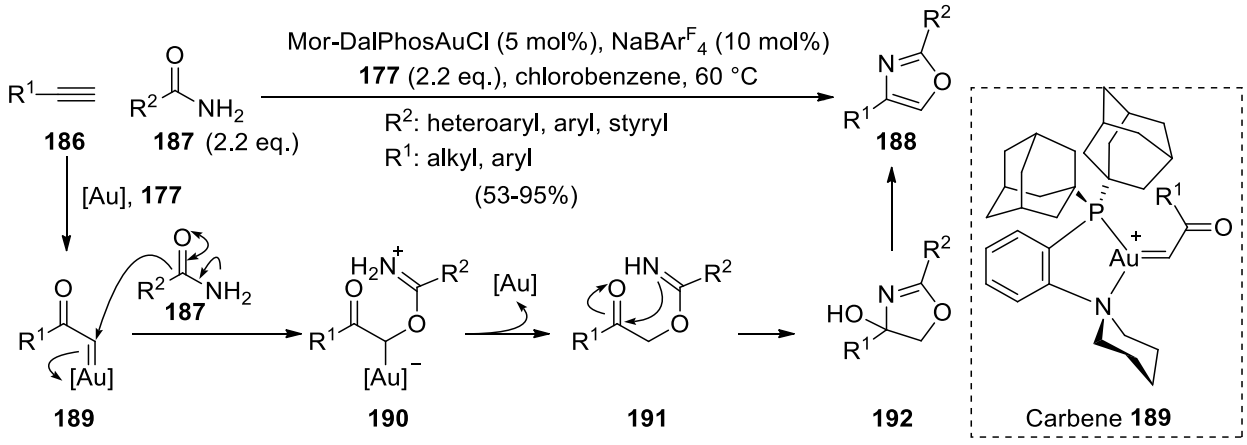
The applicability of this method was demonstrated by the ability to construct a pimprinine derivative, pimprinaphine **185**, in two steps from alkyne **183** (Scheme 29). The gold-catalysed oxazole formation was followed by *N*-deprotection of the indole and the desired natural product was isolated in good yield. Interestingly, complex, low yielding reactions were observed when an *N*-unprotected indole was employed, potentially due to further coordination of the metal with the indole nitrogen that leads to side reactions.



Scheme 29: Gold-catalysed formation of pimprinaphine

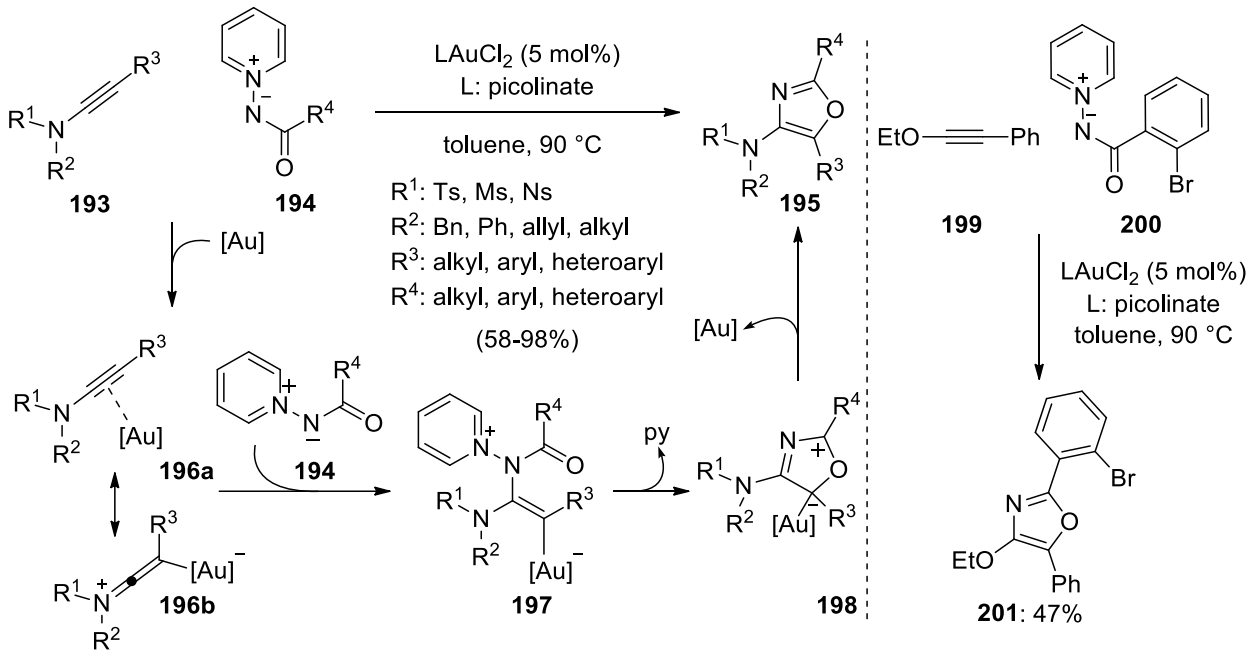
Isomeric analogues of such di-substituted oxazoles could be accessed through a similar approach by trapping the α-oxo gold carbene with amides (Scheme 30).[81] Terminal alkynes **186** and amides **187** reacted smoothly under gold catalysis in an overall [3+2]-annulation to give 2,4-disubstituted oxazoles **188**. In this case, the gold carbene **189**, generated as described above with the use of the same oxidant, is trapped by nucleophilic attack of the amide to form imidate **190**. Protodeauration is followed by cyclisation (**190** to **192**) and dehydration to give the 2,4-substituted products **188**. It is noteworthy that the bidentate MorDalPhos ligand stabilises the carbene by generating a tricoordinate Au(I) complex **189**. The electrophilicity of the carbene centre is reduced this way and allows the intermolecular trapping by the amides to proceed smoothly. The choice of the supporting ligand allowed the efficient trapping of the very reactive α-oxo gold carbene without using an intramolecular trap or solvent as nucleophile, as in the case of the nitriles. Notably, the reaction under the optimised conditions of the [2+2+1] annulation (*vide supra*) gave complicated mixtures.

The substrate scope of the reaction included aryl, heteroaryl and styryl groups at the 2-position of the oxazole and alkyl and aromatic groups could be accommodated on the 4-position.



Scheme 30: Gold-catalysed formation of 2,5-disubstituted oxazoles

Although the methods for the formation of fully substituted oxazoles are based usually on intramolecular cyclisation of a preformed, functionalised precursor, Davies *et al* made a contribution to the field with an alternative, intermolecular approach.[82] In 2011 the research group developed a gold-catalysed synthesis of fully substituted oxazoles **195**, employing ynamides **193** and pyridine *N*-aminides **194** (Scheme 31). The reaction proceeds through a regioselective, formal [3+2]-cycloaddition of the *N*-aminide onto the gold-activated π-system (**196** to **197**). Based on the discussion in the previous chapter concerning the advantageous properties of ynamides, this regioselectivity derives from the fact that, on coordination to gold, the free electron-pair of the nitrogen can be delocalised onto the triple bond, rendering the α-carbon more electrophilic. Cyclisation, followed by elimination of the pyridine (**197** to **198**) and deauration generates the final heterocycle **195**. The mechanism of this reaction will be discussed in detail in the following section.



Scheme 31: Regioselective synthesis of oxazoles with ynamides and pyridine-*N*-aminides

The reaction exhibited wide functional group tolerance with aromatic and alkyl substituents accommodated on the 2- and 5-position of the main ring. Finally, initial studies revealed that the reaction is not only bound to ynamides as aromatic ynol ethers showed the same reactivity forming the corresponding oxazole in moderate yield.

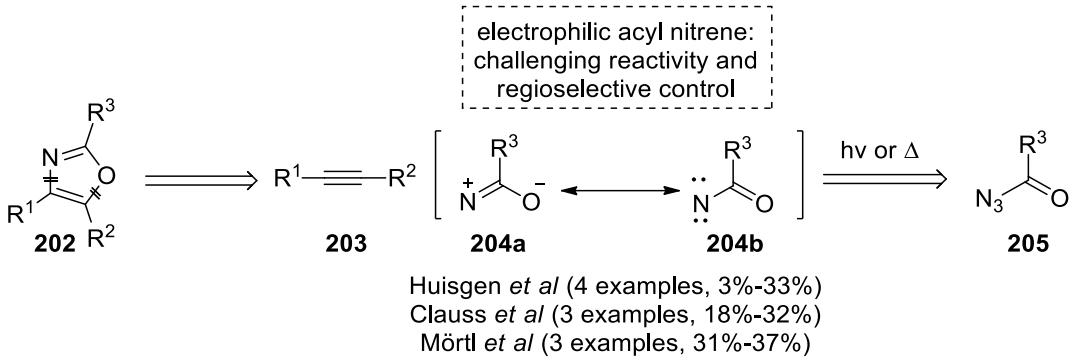
This convergent and powerful method for the synthesis of fully substituted oxazoles was further investigated and the next section of this chapter will be focused on a detailed discussion about the substrate scope development, the plausible mechanistic aspects and additional applications of the products.

2.3 Results and Discussion

2.3.1 Synthesis Design

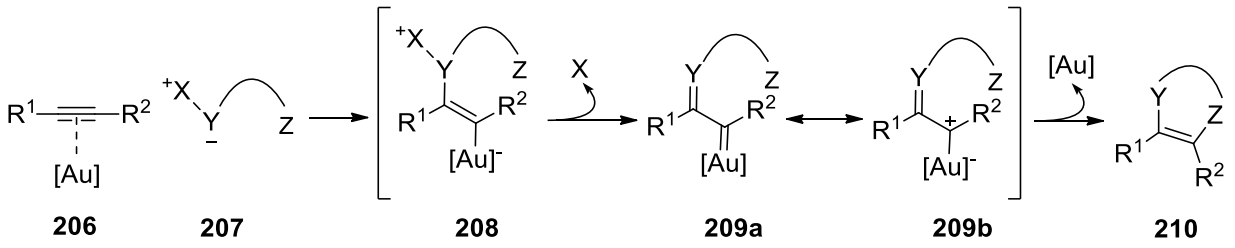
Intrigued by the limited examples of intermolecular approaches for the formation of fully substituted oxazoles in combination with their wide utility and synthetic interest, the design of a two-component method for easily delivering these functionalised heterocycles in a convergent fashion was developed.

A possible disconnection of the main ring that involves the simultaneous cleavage of the C-N and the C-O bond would lead to the use of alkynes **203** and acyl nitrenes **204a**/**204b** as 1,3-*N,O*-dipoles (Scheme 32). However, this approach is not feasible as acyl nitrenes notoriously undergo rapid rearrangement and insertion chemistry,[15] while their challenging preparation through thermal or photochemical fragmentation of acyl azides **205** is not synthetically attractive.[15c] Previously reported methods for the formation of oxazoles with the use of acyl nitrenes are not flexible as their uncontrollable reactivity did not allow the selective formation of the heterocycle in high yields.[15] Additionally, side reactions the acyl nitrenes are involved in the reaction media result in the inability of these methods to exhibit functional group tolerance (*vide infra*).



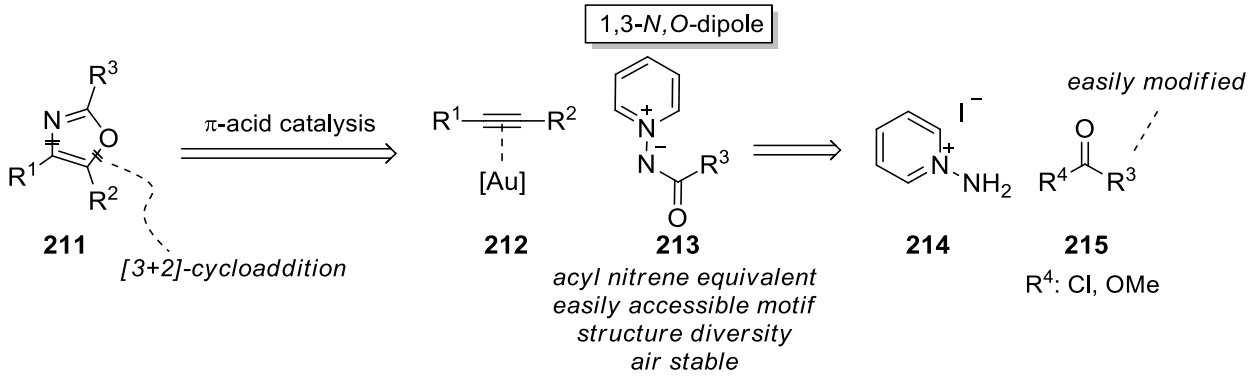
Scheme 32: Alkynes and acyl nitrenes for the oxazole synthesis

Inevitably, an alternative route without the use of acyl nitrenes should be developed. In this context and as discussed in the previous chapter, alkynes activated by a π-acid **206**, such as gold, are electrophilic in nature and can be trapped by various nucleophiles to form gold carbenes (Scheme 33). For the oxazole formation, this nucleophile **207** should be able to deliver the required functionality, which includes the nitrogen and the oxygen in this case, but also be able to form the carbene (**209a**/**209b** through **208**) and finally trap it leading to the heterocycle **210**. This nucleophile should also be easily modified from inexpensive starting precursors, be stable and compatible under the reaction conditions without displaying undesirable side reactivity.



Scheme 33: Synthesis design for gold-catalysed formation of oxazoles

Indeed this two component reactivity was achieved by the Davies group, in 2011 just before this PhD research was started. They used gold-activated alkynes **212** and pyridine-*N*-aminides **213** to act as acyl nitrene equivalents (Scheme 34). Some of the main advantages of these aminides are their stability in air in combination with their controlled reactivity compared to acyl nitrenes. Furthermore, they can be very easily modified by combining the commercially available *N*-aminopyridinium iodide **214** and acyl chlorides **215** under basic conditions. Literature precedent reveals that these aminides usually act as 1,3-*C,N*-dipoles by giving substitution reactions around the pyridine ring,[83],[84] however for the oxazole formation alternative reactivity as 1,3-*N,O*-dipoles is required.

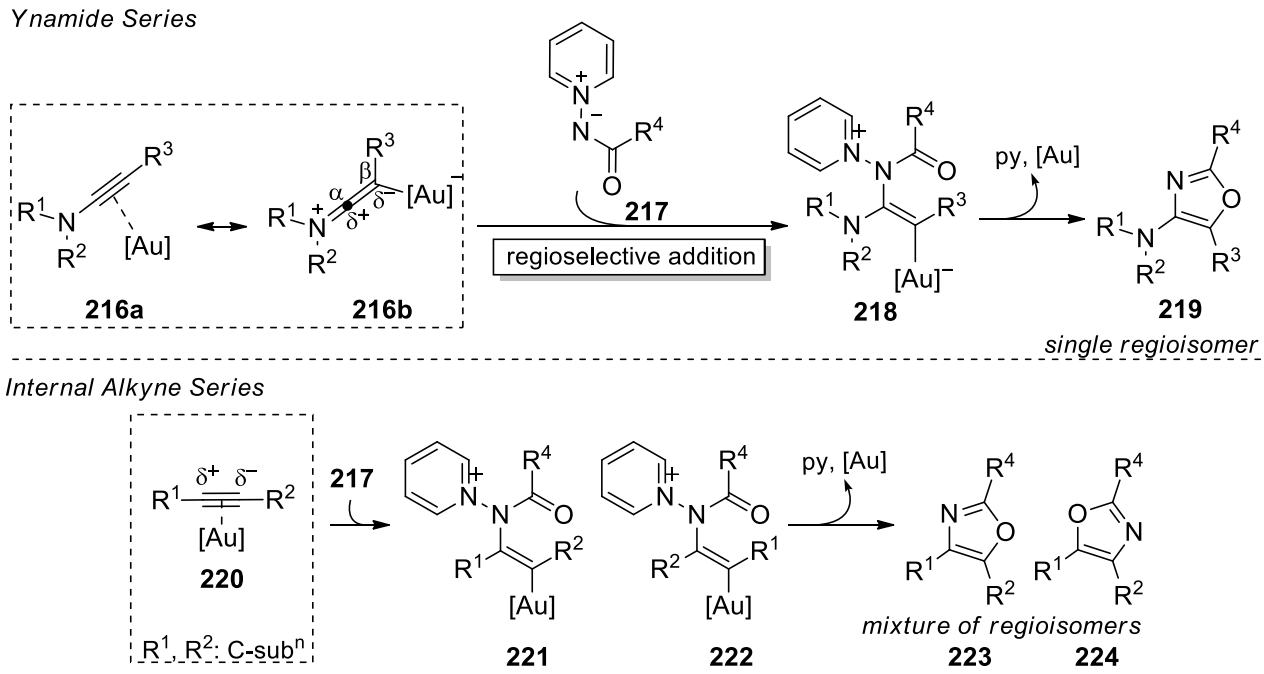


Scheme 34: Gold-catalysed formation with the use of alkynes and pyridine-*N*-aminides

In this context and as mentioned in the previous section, the Davies group reported the synthesis of fully substituted oxazoles with the use of ynamides/ynol ethers and pyridine-*N*-aminides through a regioselective [3+2]-cycloaddition (*vide infra*). Taking over this powerful transformation it would be desirable to expand the substrate scope further. Having in mind that the pyridine-*N*-aminides can be flexibly modified so as to deliver a broad spectrum of different

groups on the 2-position of the oxazole, attention was initially focused on the alterations possible at the π-system.

In the case of the ynamides and ynol ethers, the observed reactivity and regioselectivity is attributed to the nitrogen (or oxygen) lone pair of electrons that differentiates the carbons of the π-system rendering the α-carbon more electrophilic (**216a**/**216b,** Scheme 35). However, this advantage is lost when less electron-rich π-systems, such as internal alkynes **220**, are used depicting a considerable reactivity and regioselectivity challenge. On the aspect of the reactivity, there is no literature precedent reporting an intermolecular addition of a nitrenoid onto internal alkynes that are activated by a π-acid. As regards the regioselectivity, the lack of electronic control results in the potential erosion of the regioselectivity (a mixture of regioisomers **223** and **224** can likely be formed), as it is difficult to control the position of an intermolecular attack towards an unsummetrical and sterically unbiased alkyne.



Scheme 35: Reactivity and regioselectivity difference between ynamides/internal alkynes

Several attempts to further expand the substrate scope of the reaction and to find the conditions required to overcome these reactivity and regioselectivity issues are described in this chapter.

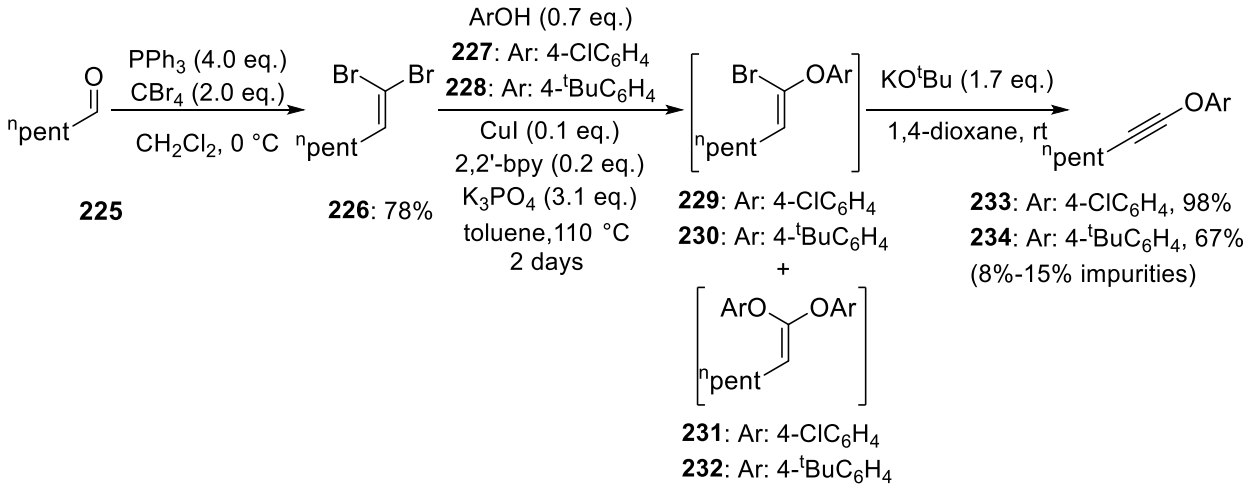
2.3.2 Expanding the substrate scope

2.3.2.1 Alkyl, aryl and silyl ynol ethers

The first attempt was to investigate different functionalised ynol ethers for the formation of the oxazoles inducing an alkoxy, aryloxy or silyloxy motif at the 4-position of the heterocycle. Although the preparation of these substrates have been recently developed, the corresponding methods proved problematic.

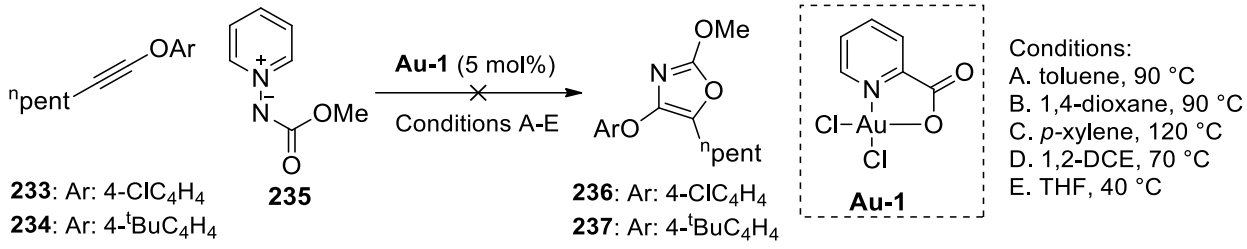
The preparation of aromatic ynol ethers from vinyl dibromides and substituted phenols through Cu-catalysed coupling in one pot process under rigorously dry conditions was reported by Evano and co-workers (Scheme 36).[85] Substituted phenols deprotonated by potassium phosphate can couple with the vinyl dibromide **226** to afford the corresponding mono-bromoalkene **229** and **230**. In the second step, treatment of the latter with potassium *tert*-butoxide gives the aromatic ynol ether **233** and **234**.

To test this, vinyl dibromide **226** was therefore prepared by Ramirez olefination from the corresponding aldehyde **225** in good yield (78%).[86] However, when **226** was treated with copper catalyst, purification of the final product was problematic. Bromoalkene derivatives (**229** and **230**) and the ketene acetal side-product **231** and **232** could not be separated from the desired product. Further purification of potassium *tert*-butoxide before use in the second step did not change the outcome of the reactions. A careful examination of the published spectra in the literature procedure indicates the presence of these impurities as well.



Scheme 36: Copper-catalysed formation of aromatic ynol ethers

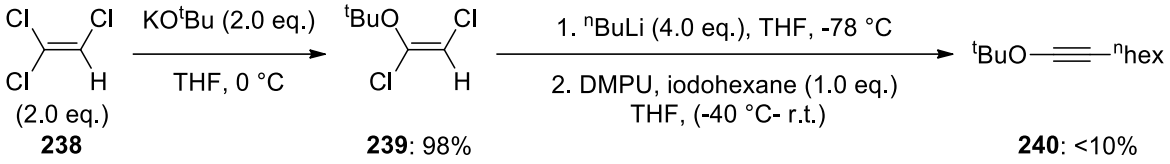
Despite the significant impurities, **233** and **234** in combination with *N*-aminide **235** were subjected under the standard gold-catalysed conditions (Conditions A, Scheme 37),[82] followed by a small study of solvent, however the desired oxazoles **236** and **237** were not formed, complicated mixtures were obtained in every case, potentially due to degradation of the starting ynol ethers.



Scheme 37: Aromatic ynol ethers for the gold-catalysed oxazole formation

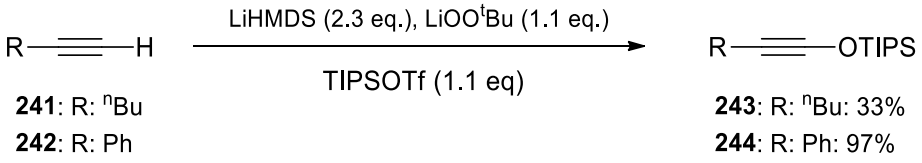
Alternative methods for the formation of analytically pure ynol ethers were then attempted. Preparation of *tert*-butyl alkynyl ether **240** was pursued by the reaction of dichloroalkene **239** with ^{n}BuLi and iodoalkane (Scheme 38).[87],[88] However, the reaction mixture was very messy

and despite several attempts to purify the crude mixture, the final product was afforded in a very low yield (10%), impure and consequently was not used for catalysis.



Scheme 38: Synthesis of *tert*-butyl alkynyl ether 240

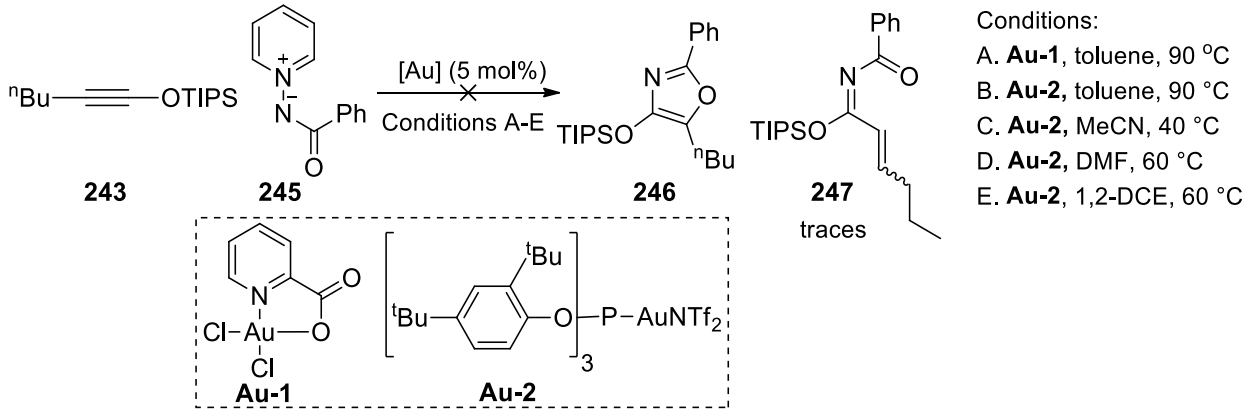
The formation of silyl ynol ethers proved similarly challenging. Silyl ynol ethers **243** and **244** have been synthesised by deprotonation of the corresponding terminal alkyne (**241** and **242** respectively) and subsequent silylation (Scheme 39).[89] These substrates are very sensitive to moisture; considerable amounts of impurities such as silanols or alkyne dimers may be formed if the base is not freshly purified or the solvent is not anhydrous (>7 ppm H_2O); thereby strictly anhydrous conditions were used for their synthesis. Moreover, purification problems were encountered as ynol ethers were easily degraded by silica (deactivated or not) or alumina (neutral or basic) gel chromatography. For this reason, bulb-to-bulb distillation proved to be the best solution for their purification.



Scheme 39: Formation of silyl ynol ethers

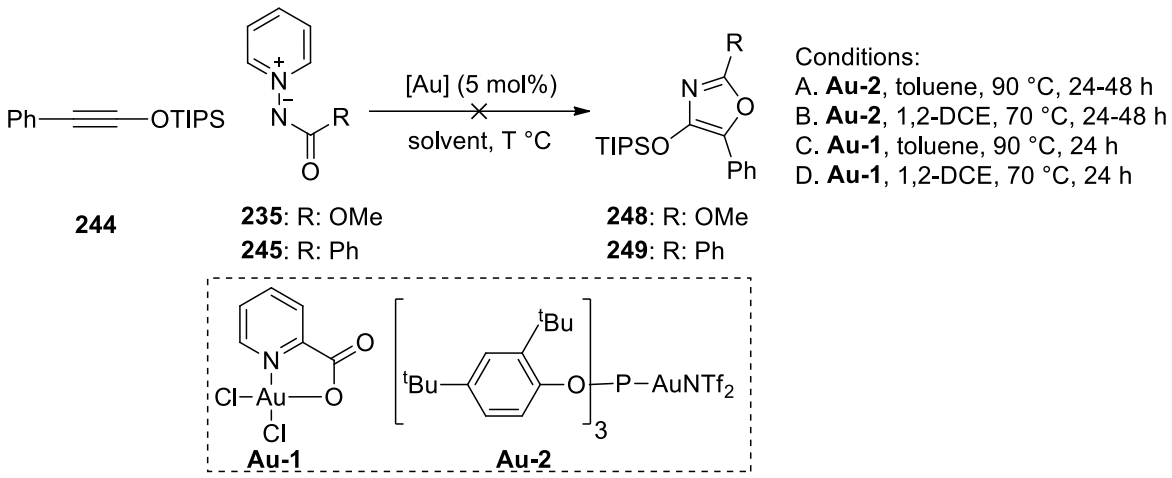
After numerous attempts to successfully furnish analytically pure ynol ethers, they were subsequently used for the formation of the oxazoles. Reaction of alkynyl silyl ynol ether **243**

with the *N*-benzoyliminopyridinium ylide **245** did not afford oxazole **246** and in every case (Conditions A-E, Scheme 40) traces of unidentifiable products have been formed along with starting material and degradation moieties. The reaction mixtures were too complex to identify each single product; however, on the basis of ^{1}H-NMR spectroscopy, traces of the acyclic **247** might be identified. The origin of this undesired product will be discussed in detail in the following section.



Scheme 40: Alkyl silyl ynol ether for the oxazole formation

Similar results were obtained when aromatic silyl ynol ether **244** was used under the catalysis conditions (Scheme 41). Complex mixtures of products and degradation of starting material were observed, the products could not be fully identified, even with the use of either Au(I) or Au(III) catalysts, different *N*-aminides, solvents and temperatures.



Scheme 41: Conditions employed for gold-catalysed reaction of aromatic silyl ynol ether

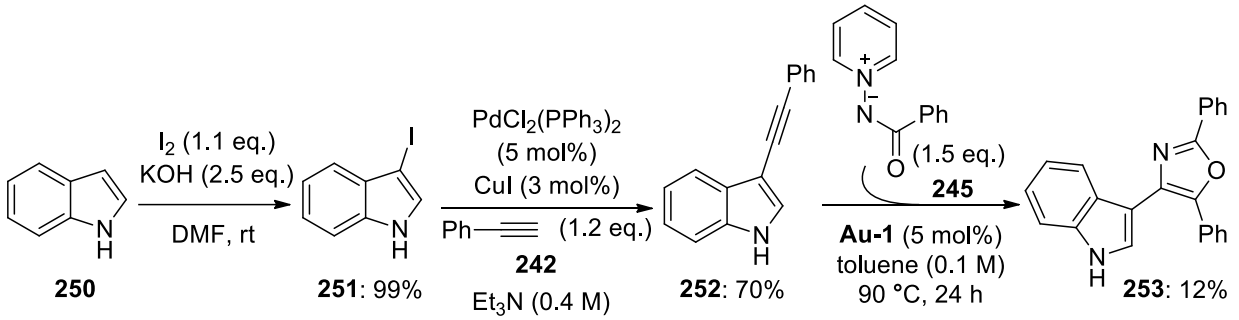
The observed inability of the silyl ynol ethers to form the corresponding oxazoles may be attributed to the increased electronegativity of the oxygen (in comparison with the nitrogen of the ynamides). Finally, the steric hindrance of the triisopropyl silyl group that blocks the cyclisation pathway might facilitate side reactions and degradation.

2.3.2.2 Indole Derivatives

Ynol ethers do not seem to be optimum substrates for the gold catalysed oxazole formation as their preparation is not straightforward in general, exhibiting uncontrollable side reactivity. In contrast, ynamides proved reactive and controllable systems which furnished the desired heterocycle in a regioselective fashion. Nitrogen-containing heterocycles, such as indoles, attached to the π-system were therefore investigated to see whether similar reactivity and regioselectivity would be displayed.

The synthesis of the indolyl alkyne included the formation of 3-iodoindole **251** followed by Sonogashira coupling with the terminal alkyne **242** (Scheme 42). These two simple steps gave

the internal alkyne **252** in good yield without problems of instability or undesired impurities. Having the alkyne in hand, the previously developed conditions for the formation of the oxazoles with the ynamides were applied. Pleasingly, the desired oxazole **253** was formed, though in low yield with significant amount of remaining starting material.



Scheme 42: Preparation of 3-phenylethynyl-1*H*-indole

Extensive optimisation studies were needed to afford the oxazole in high yields. In the following table only a small sample of these reactions, which highlights the most important issues and sheds light on the reactivity, is included (Table 1, for the complete optimisation studies please refer to the appendix). It is worthy to point out that, regardless of the conditions, only one regioisomer of the oxazole was formed, with the indole core being attached always on the 4-position of the oxazole ring, as is clearly indicated by the X-ray structure (Figure 4).

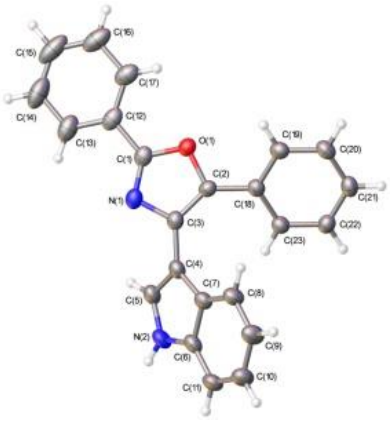
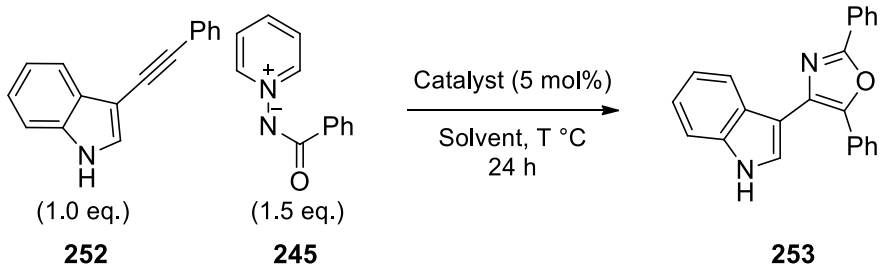


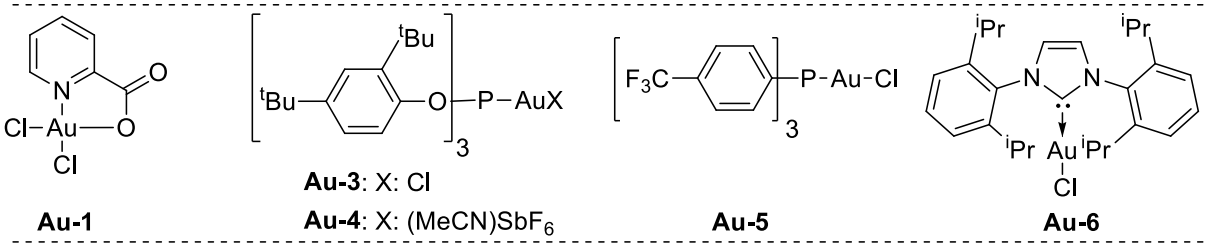
Figure 4: Crystal structure of oxazole 253 with ellipsoids drawn at the 50% probability level. X-Ray crystallography was performed and data solved by Dr Louise Male (University of Birmingham).

Table 1: Reaction optimisation screening



Entry	Catalyst	[245] (M)	Solvent	T (°C)	253 (%)[a]
1	**Au-1**	0.1	toluene	90	12
2	Ph_3PAuCl/AgOTf	0.1	toluene	90	24
3	**Au-5**/AgOTf	0.1	toluene	90	37
4	**Au-3**/AgOTf	0.1	toluene	90	38
5	**Au-6**/AgOTf	0.1	toluene	90	46
6	**Au-3**/AgOTf	0.05	toluene	90	35
7	**Au-3**/AgOTf	0.2	toluene	90	54
8	**Au-3**/$AgNTf_2$	0.2	toluene	90	44
9	**Au-3**/AgOTs	0.2	toluene	90	37
10	**Au-3**/$AgBF_4$	0.2	toluene	90	41
11	**Au-3**/$AgSbF_6$	0.2	toluene	90	58

12	**Au-6**/AgOTf	0.2	*m*-xylene	120	65
13	**Au-6**/$AgSbF_6$	0.2	*m*-xylene	120	61
14	**Au-3**/$AgSbF_6$	0.2	*m*-xylene	120	73 (64[b])
15	-	0.2	*m*-xylene	120	0
16	TfOH	0.2	*m*-xylene	120	0[c]
17	$AgSbF_6$	0.2	*m*-xylene	120	25
18	**Au-3**	0.2	*m*-xylene	120	61
19	**Au-4**	0.2	*m*-xylene	120	78[d] (48[e])
20	**Au-4**	0.2	*p*-xylene	120	63
21	**Au-4**	0.2	*o*-xylene	120	76



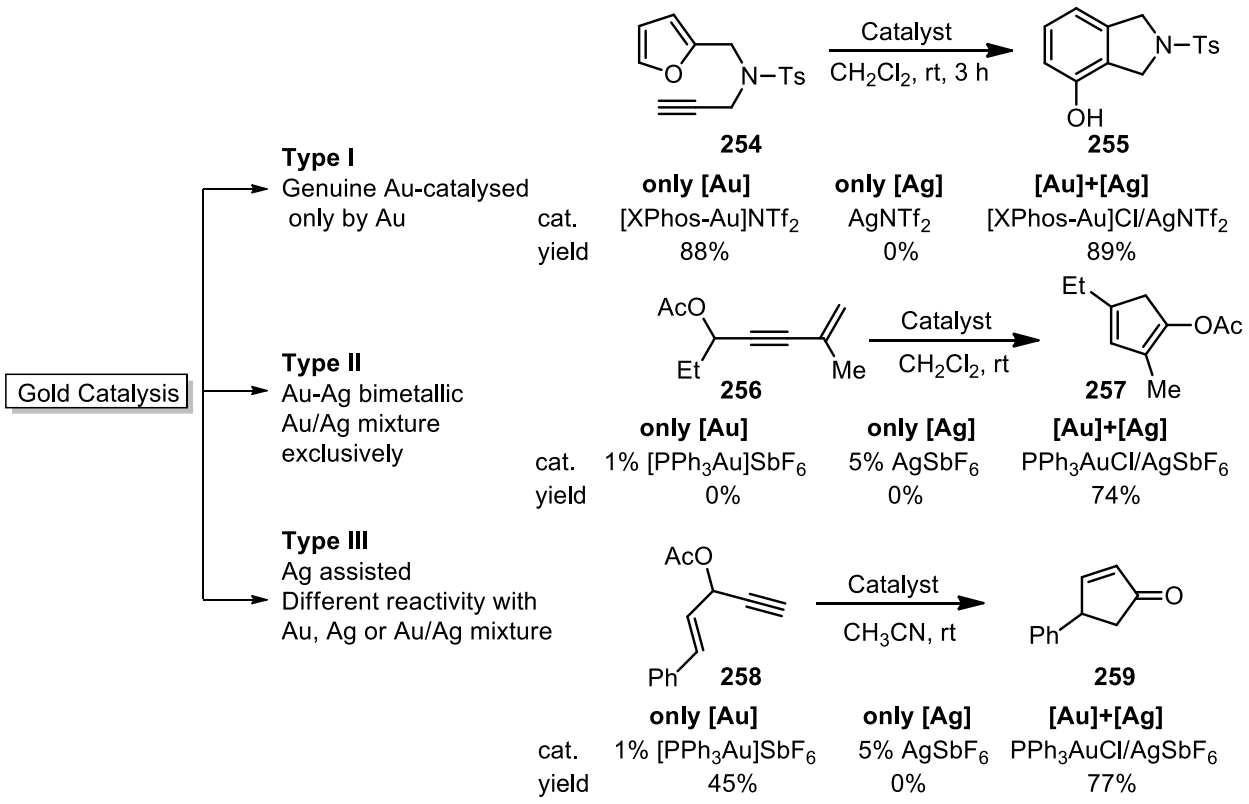
Au-1 **Au-5** **Au-6**

[a] isolated yields after flash chromatography. [b] **245** (1.0 eq). [c] immediate degradation of the starting material 5 mol% loading. [d]average yield across 3 runs[e] 1 mol% catalyst loading.

Although the Au(III) precatalyst **Au-1** showed low conversion (Entry 1, Table 1), several cationic Au(I) species, generated *in situ* with the corresponding gold chloride salts and silver triflate, promoted the reactivity (Entries 2-5). The conversion was improved by increasing the concentration of the reaction mixture (Entries 4 vs 6 and 7). Looking at different silver salts to exchange the counterion of the cationic gold-complex, different silver sources were tested and silver hexafluoroantimonate proved the most effective (Entries 7-11). The yield was increased when the gold complex **Au-3** was used in combination with higher temperature in *m*-xylene, while NHC gold complex **Au-6** did not prove as active (Entries 12-14). Changing the

stoichiometry of the reaction by decreasing the equivalents of the *N*-amide was not beneficial (Entry 14[b]). Control experiments showed no reaction in the absence of catalyst with the starting alkyne being recovered (Entry 15), while the use of Brønsted acid led to rapid degradation of the alkyne (Entry 16).

As mentioned in the previous chapter, it is generally accepted that $[L\text{-}Au]^+$ is the active π-acid in gold-catalysed reactions. This cationic species is generated through ligand exchange of [L-Au]Cl with the corresponding silver salt to form AgCl. According to recent literature, the presence of AgCl in the reaction mixture might influence the efficiency of the gold-catalysed reaction (known as 'the silver effect in gold-catalysis').[5, 90] In particular, Shi and co-workers supported that there are three main categories of gold-catalysed reactions (Scheme 43): the 'genuine' gold-catalysed reactions where silver does not contribute to the reactivity (Type I),[91] the gold/silver bimetallic catalysis where, surprisingly, only a combination of gold and silver can catalyse the relevant process (Type II)[92] and the silver-assisted gold-catalysed reactions where silver enhances the already existed reactivity of the gold (Type III).[93]



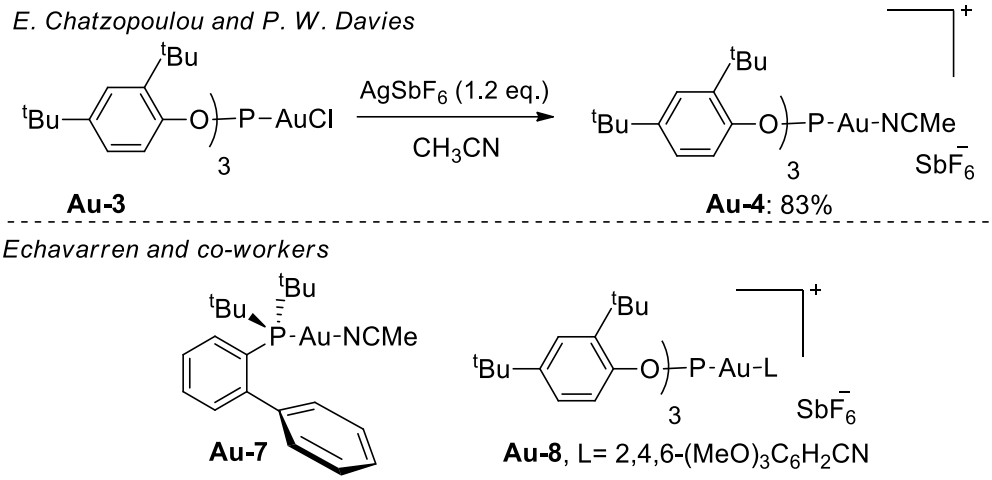
Scheme 43: Characteristic examples which demonstrate the silver effect in gold-catalysis

In order to investigate the possibility of a silver-effect in the present oxazole synthesis, silver hexafluoroantimonate was used, without the aid of a gold catalyst; the silver salt was able to catalyse the transformation, however the conversion was low (Entry 17, Table 1), highlighting the benefits of a gold complex. Gold chloride complex **Au-3** can also promote the reaction independently (Entry 18), though the cationic preformed complex **Au-4** proved more active for this transformation (Entry 19). Notably, under these conditions the oxazole could be formed in good yield even when the catalyst loading was decreased to 1 mol%. In addition, *o*-xylene gave similar results with *m*-xylene (Entry 21 vs 19), however *p*-xylene afforded less clean reactions (Entry 20). Finally, it is worth mentioning that conversion of starting material was visible by TLC

for at the first 8 hours of the reaction, indicating that the catalytic reaction was proceeding slowly (after 24 h stirring either complete consumption or traces of starting material was observed).

Preformed gold-complex **Au-4** was synthesised for the first time based on the procedure for the preparation of analogous phosphine-containing gold complexes reported by Echavarren and co-workers (Scheme 44). In particular, the Echavarren group had previously reported that gold complexes with bulky dialkylbiarylphosphine ligands and an acetonitrile adduct (**Au-7**) are stable at high temperatures, whereas the corresponding phosphite-containing complexes **Au-8** require a benzonitrile adduct to display similar stability.[94]

Despite the expected instability at the reaction temperatures the acetonitrile gold complex **Au-4** proved an effective catalyst which did not appear to undergo ready degradation in the oxazole formation. This might be explained by the presence of other Lewis-basic species in the reaction mixture which could stabilise the cationic gold species, minimising degradation pathways.

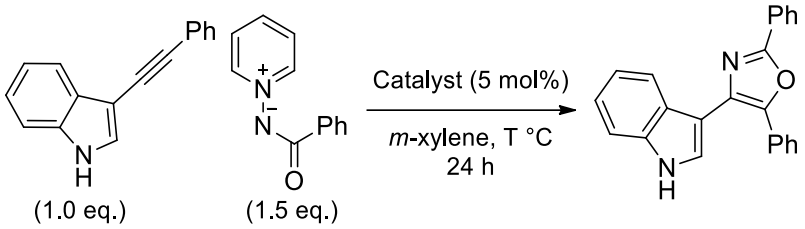


Scheme 44: Formation of gold complex Au-4

The final optimised conditions included the use of the preformed cationic complex **Au-4** in 5 mol% loading, in *m*-xylene, at 120 °C, when the concentration in respect to the alkyne is 0.2 M (Entry 19, Table 1).

Other metal complexes with the potential to activate the π-system and give the desired oxazole, were tested (Table 2).

Table 2: Other metals employed for the gold-catalysed oxazole formation



Entry	Catalyst	253 (%)[a]
1	$CuCl_2$	60
2	$Cu(MeCN)BF_4$	52
3	CuOTf	Complex mixtures
4	CuI	Complex mixtures
5	CuOAc	Complex mixtures
6	$(PPh_3)RuCl$	45
7	$[(CH_3CO_2)_2Rh]_2$	27
8	$(PPh_3)RhCl$	26

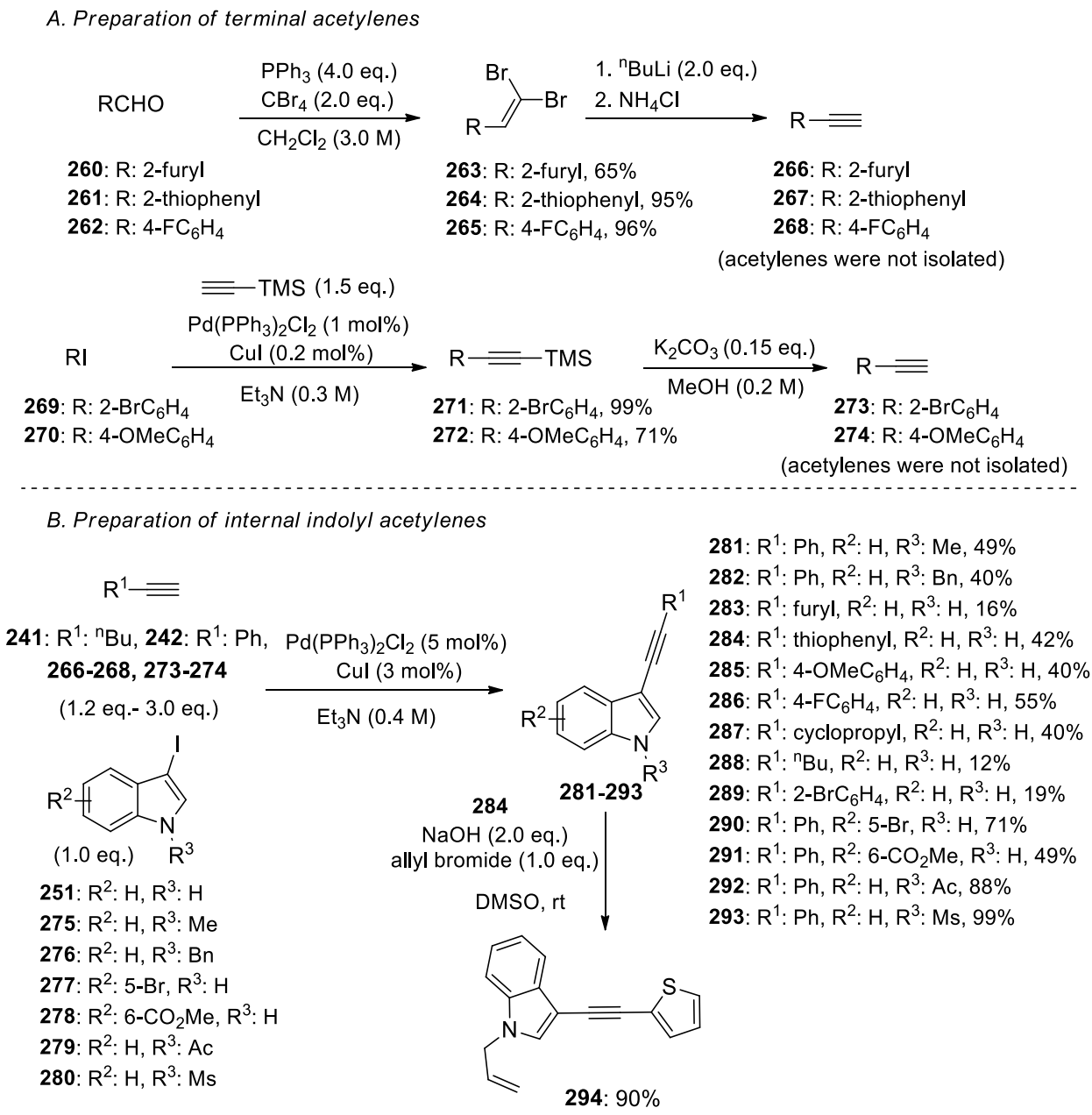
[a]isolated yield

The use of different copper salts indicated that $CuCl_2$ (Entry 1) and $Cu(MeCN)BF_4$ (Entry 2) gave the oxazole in moderate yields, whereas other copper sources afforded complex mixtures (Entries 3-5). Comparatively, the oxazole formation was not improved when ruthenium chloride

salt was used (Entry 6), while rhodium salts gave much lower yields (Entries 7 and 8). Thus, under the optimised conditions gold catalyst proved the most effective.

With the optimised conditions in hand, further investigation of the substrate scope was undertaken. Internal alkynes were prepared through Sonogashira coupling of the 3-iodoindole and the corresponding terminal acetylenes. The terminal acetylenes were accessed either from the easily prepared dibromo olefins (**263**-**265,** Scheme 45A) or *via* deprotection of the silyl protected acetylenes (**271**-**272**). Due to the low boiling point of the terminal acetylenes (**266**-**268**, **273**-**274**), they were not isolated and used as a solution for the next step, while their amount was assumed the same as the starting dibromo olefins or silyl protected alkynes. Although Sonogashira couplings have been extensively studied,[95] with many variable conditions available in the literature, reactions involved *N*-unprotected indoles are rare.[96] Despite different conditions being tested, the final yields were moderate in most of the cases (Scheme 45B). This behaviour might stem from the problematic oxidative insertion of the palladium into the bulky, electron-rich, *N*-unprotected indole.

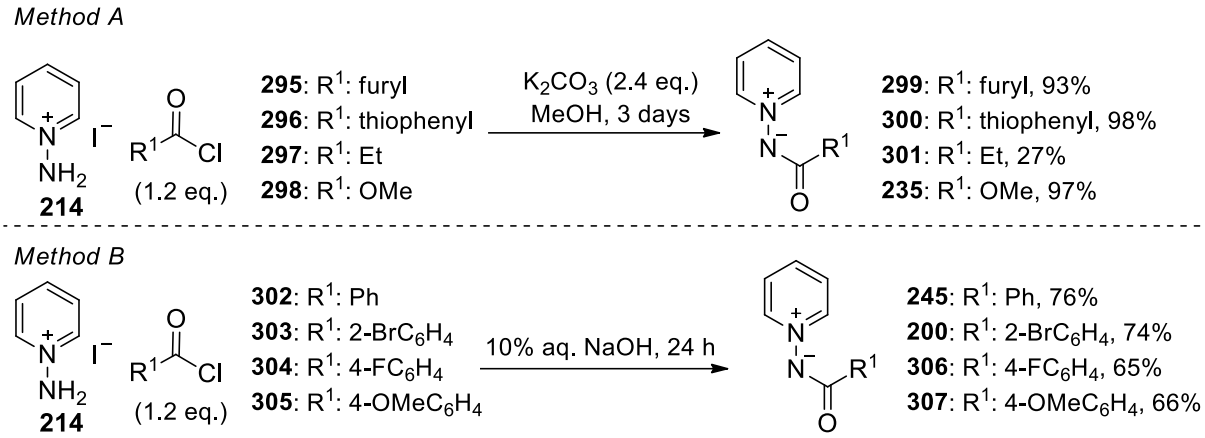
Alkyl and heteroaryl terminal alkynes, as well as substituted aryl acetylenes with electron withdrawing or electron donating substituents could be coupled with the 3-iodo-1*H*-indole derivatives (**251**, **275**-**276**) and give the corresponding internal alkynes in reasonable yields (**281**-**288**). Functionalised indole cores (**277**-**278**) gave the desired products too (**289**-**291**), while *N*-protected indoles with electron withdrawing groups (**279**-**280**) reacted much more efficiently giving the relative alkynes in high yields (**292**-**294**).



Scheme 45: Preparation of internal indolyl-acetylenes

On the other hand, the synthesis of the pyridine-*N*-aminides was straightforward.[82] Commercially available *N*-aminopyridinium iodide **214** was reacted with acid chlorides **295**-**298** and **302**-**305** under basic conditions to form the ylides **299**-**300**, **245**, **200** and **306**-**307** in high

yields (Scheme 46). An exception was the preparation of **301**, as degradation took place in the reaction mixture and gave the aminide in low yield.



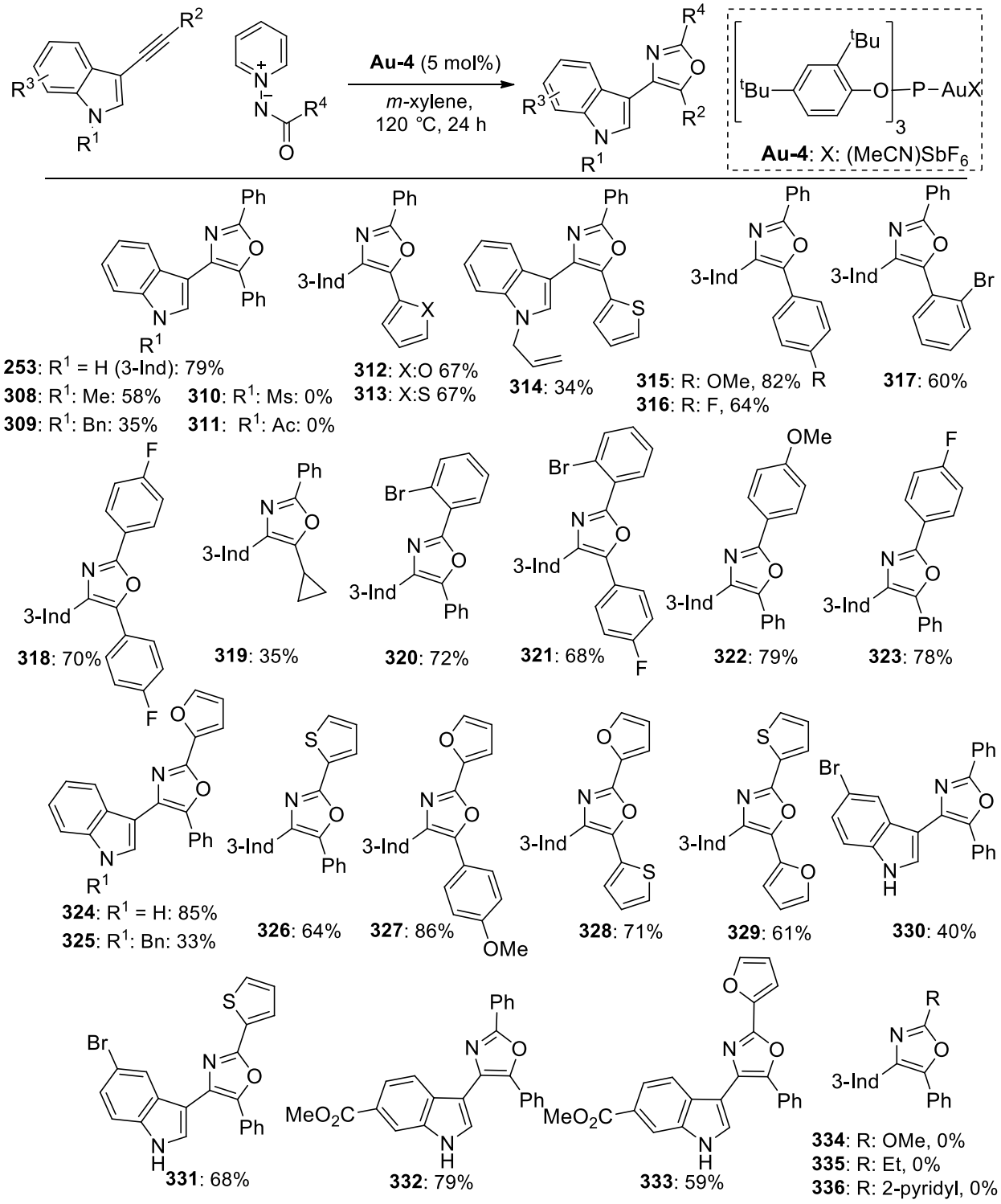
Scheme 46: Preparation of pyridine-*N*-aminides

The substrate scope for the gold catalysis was then explored. *N*-Substituted indoles with methyl (Scheme 47), benzyl or allyl groups reacted under the optimised conditions giving the desired heterocycles (**308, 309** and **314** respectively) in lower yields than the *N*-unprotected analogues (**253** and **313**). Notably, indoles with electron-withdrawing protection on their nitrogen did not show any conversion (examples **310** and **311**) under the catalytic conditions, with starting material remaining in every case. The regioselective outcome was not altered when electron-rich heterocycles and phenyl ring were attached to the alkyne (oxazoles **312**-**315**). Sterically hindered π-systems with a bulky bromide in close proximity to the coordination site of the metal, did not prove problematic, giving the oxazole **317** in good yield. Also, electron-deficient aryl group on the triple bond was well tolerated in combination with different aminides to form the oxazoles in good yields (**316** and **318**). A cyclopropyl ring can be introduced in the 5-position of the heterocycle (**319**), however other alkyl substituents were not well-tolerated affording

complex mixtures (this trend will be discussed in detail in paragraph 3.2.3). Heteroaryl groups and functionalised benzenes can also be accommodated in the 2-position of the oxazole (**320**-**327**). Direct access to the two isomers of oxazoles (**328** and **329**) could be achieved by the relevant choice of starting precursors bearing either furyl- or thiophenyl-substituents. The reactivity was not diminished even when electron-withdrawing groups in conjugation with the nitrogen lone pair were employed, giving the corresponding oxazoles in moderate yields (**330**-**333**).

Although most of the ylides proved reactive under the optimised conditions, the ylide with a methoxy group did not give the desired oxazole **334**, with complicated mixtures being instead formed. Similar results were obtained when an ethyl ylide did not form the oxazole **335** either, probably due to extensive degradation. Finally, a pyridyl group could not be induced on the 2-position of the oxazole **336** as the corresponding ylide seemed totally unreactive. Following up the previous discussion about the stability of the gold-complex and the reactive gold species in the reaction mixture (*vide supra*), this unsuccessful result can be attributed to the coordination of the metal with the pyridyl group of the ylide.

It is worth mentioning that all three ylides reacted very quickly when combined with the ynamide series giving the corresponding oxazoles in high yields. Apparently, the alternative conditions used in the case of the indoles, which involve high temperature, were not compatible with more sensitive aminides.



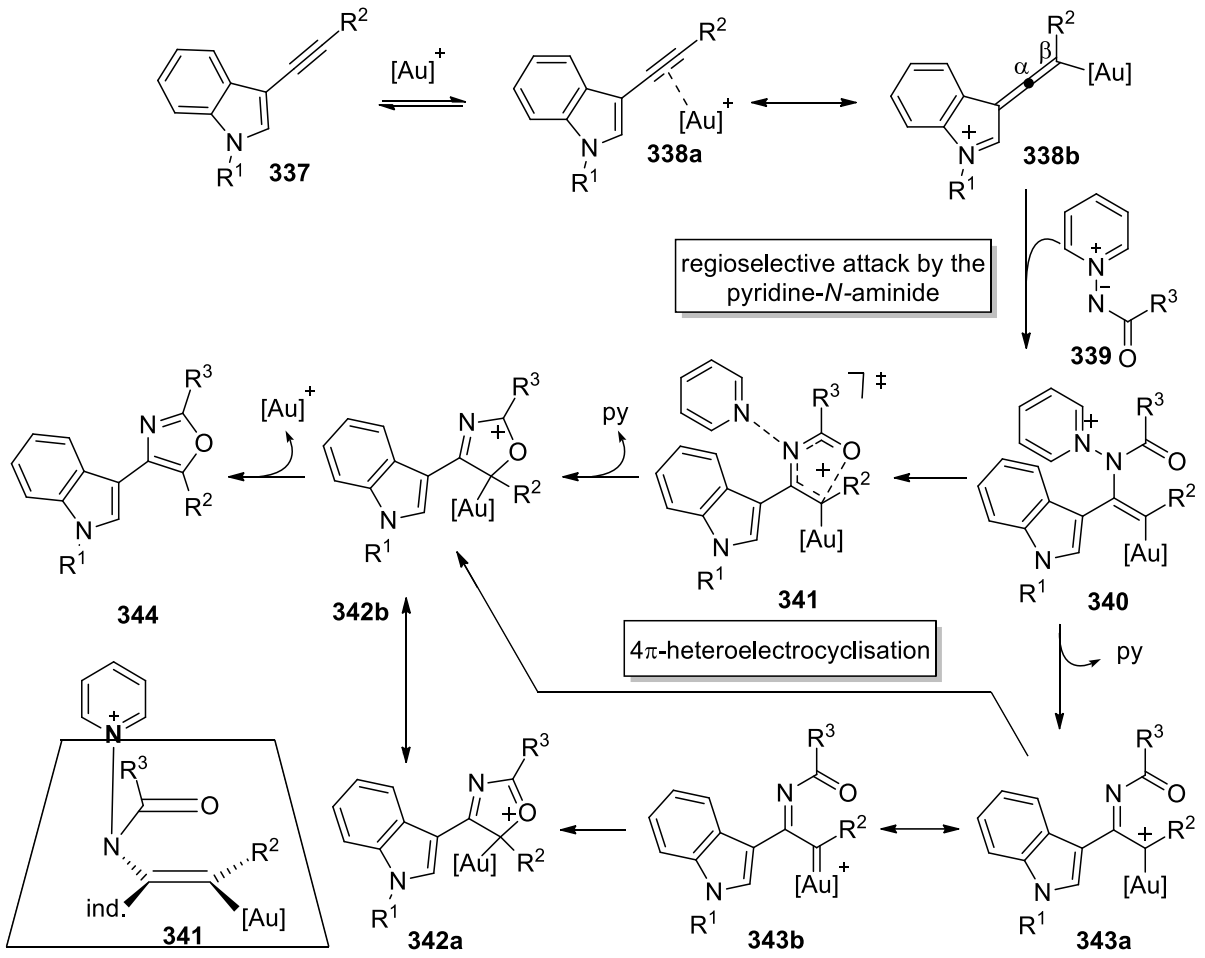
Scheme 47: Substrate scope for the formation of 4-indolyl oxazoles

2,4,5-All carbon trisubstituted oxazoles were easily accessed from readily available starting materials including many different functionalities such as bromides, fluorides, esters and heteroaryl groups. The substrate scope was further investigated by employing alternative electron-rich systems.

2.3.2.3 Proposed mechanism

The reactivity and the regioselectivity of the reaction can be explained by the following possible mechanism (Scheme 48). Upon activation of the π-system and delocalisation of the free electron pair of the nitrogen, gold-alkyne complex is formed (**337** and **338a**/**338b**). The regioselectivity of the reaction can be explained more clearly by this gold-alleniminium species intermediate **338b**, as the α-carbon is more electron deficient than the β-carbon, thus nucleophilic attack of the amide can take place selectively into the α-carbon, giving the acyclic gold carbenoid **340**. Two alternative following routes can be envisioned. Elimination of the pyridine as a good leaving group affords gold carbene (**343a** and **343b**) that can undergo 4π-heteroelectrocyclisation to give intermediate **342b**. Alternatively, attack of the oxygen lone pair of **343** on the gold carbene centre gives the same intermediate **342a**. Subsequent deaurative aromatisation leads to the desired heterocycle **344**. The alternative pathway involves a more concerted process with the elimination of the pyridine taking place simultaneously with the Nazarov-type electrocyclisation. As the N-N bond is elongating and breaking, a positive charge is developing that promotes the nucleophilic attack of the carbonyl to the carbene centre. It seems like a requirement for this cyclisation is the molecule to adopt the desired *s-cis*

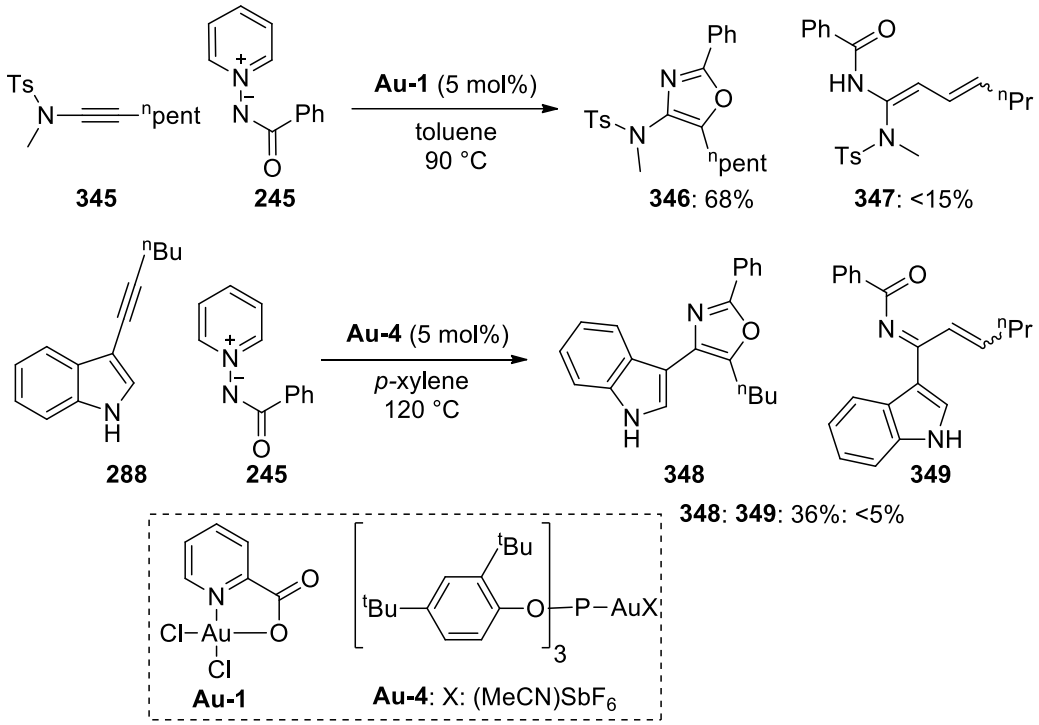
conformation with the pyridine leaving group out of the plane (3D-structure of **341**). Finally, elimination of the metal gives the final oxazole **344**.



Scheme 48: Proposed mechanism for a formal [3+2]-intermolecular cyclisation

In the cases when an alkyl group is tethered to the triple bond (R^2: alkyl), a competing pathway is possible (Scheme 49). When ynamide **345** with an alkyl group attached to the π-system was subjected into the gold-catalysed reaction, the oxazole **346** was formed as a major product along with a complicated mixture, in which one of the major component was acyclic **347** (experiment by Andrew Gillie, unpublished result). Comparatively, when alkyl-containing indolyl

alkyne **288** was used the oxazole **348** was formed as the major product, again in a complex mixture from which indicative resonances that are consistent with the structure of unsaturated acyclic byproduct **349** were present in ^{1}H-NMR. Other competing pathways, such as dimerisation of the alkyne (or ynamide),[22c] can potentially explain the observed complicated mixtures which lead to the formation of the oxazole in low yield. In addition, degradation of the relatively sensitive internal alkyne **288** at high temperature should also be considered.

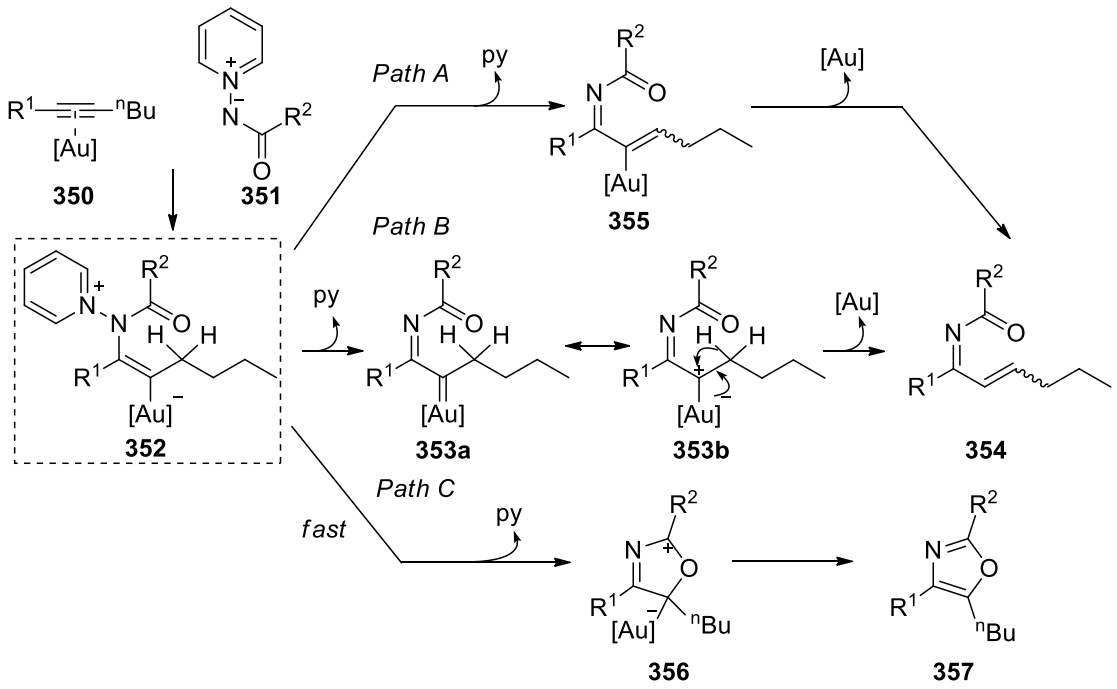


Scheme 49: 1.2-Insertion competing pathway of ynamides and indole-based alkynes

The formation of α,β-unsaturated amides can be explained as follows: the gold carbenoid **352**, which is formed through the nucleophilic attack of the amide, instead of encountering cyclisation (either through a concerted, Path A, or step-wise fashion, Path B), can evolve through insertion chemistry (product **354**, Scheme 50). Exclusion of the pyridine leads to

intermediate **353a**/**353b** followed by hydride shift onto the carbene centre as the metal eliminates. Similar reactions have been reported by Zhang and co-workers using *N*-sulphonyl ylides and gold-activated alkynes.[24]

In general, no definite conclusion can be drawn about the origin and the rational of the 1,2-insertion *versus* cyclisation pathway, as more mechanistic indications are needed. However, it can be proposed that the leaving group abilities of the pyridine, as part of the corresponding carbenoid **352**, is closely related to this 1,2-insertion process. In this context, it seems plausible that the carbenoid **352** can cyclise quickly to give the oxazole (Path C), whilst the prior formation of carbene **353a**/**353b** is very likely to facilitate the hydride shift. 1,2-Hydride shift from carbenoid **352** with simultaneous loss of the pyridine, forming intermediate **355**, should not be precluded either. Apart from this kinetic assumption, potentially, the size of the R^2 group on the ylide also contributes to the cyclisation or elimination pathway.

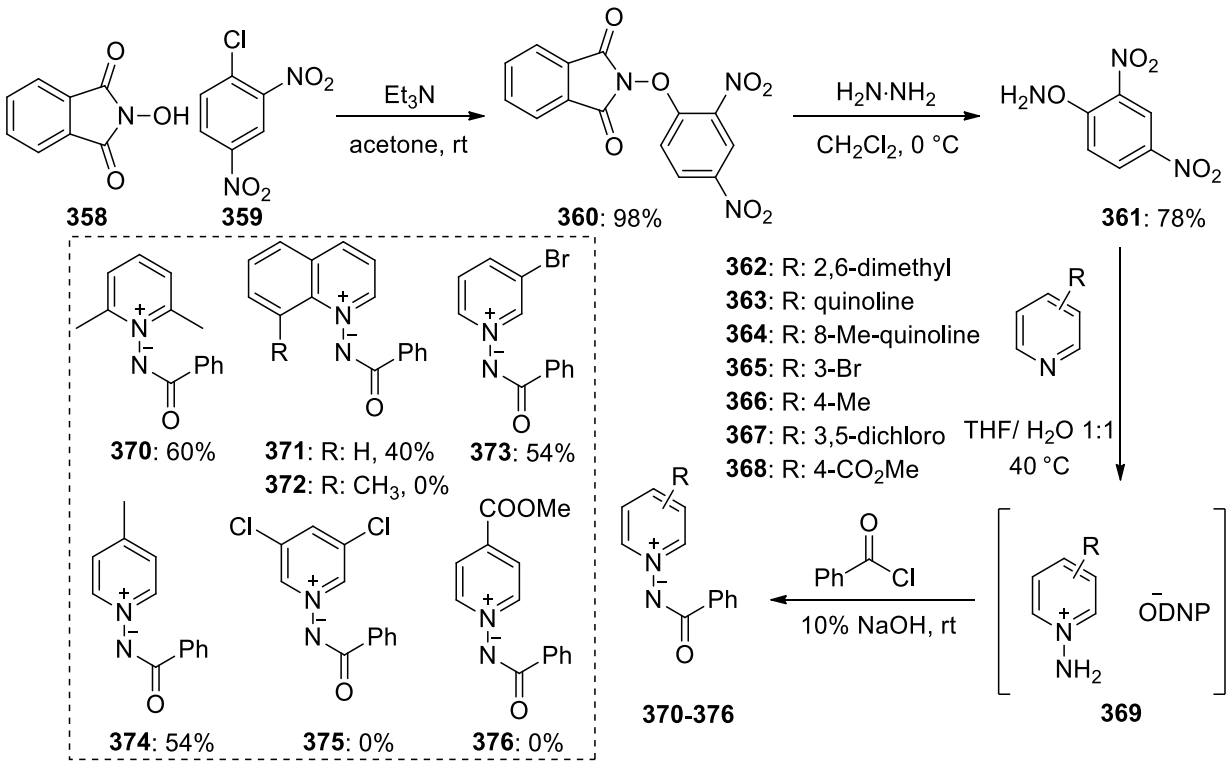


Scheme 50: Possible mechanism for the competing 1,2-insetion pathway

According to the mechanism, it becomes obvious that pyridine is released in the reaction mixture. As discussed previously, the crucial role of the pyridine as a leaving group as well as the potential interaction with the metal might affect the outcome of the reaction. In an attempt to examine this behaviour further, *N*-aminides which incorporated functionalised pyridines were prepared and tested under the optimised catalytic conditions.

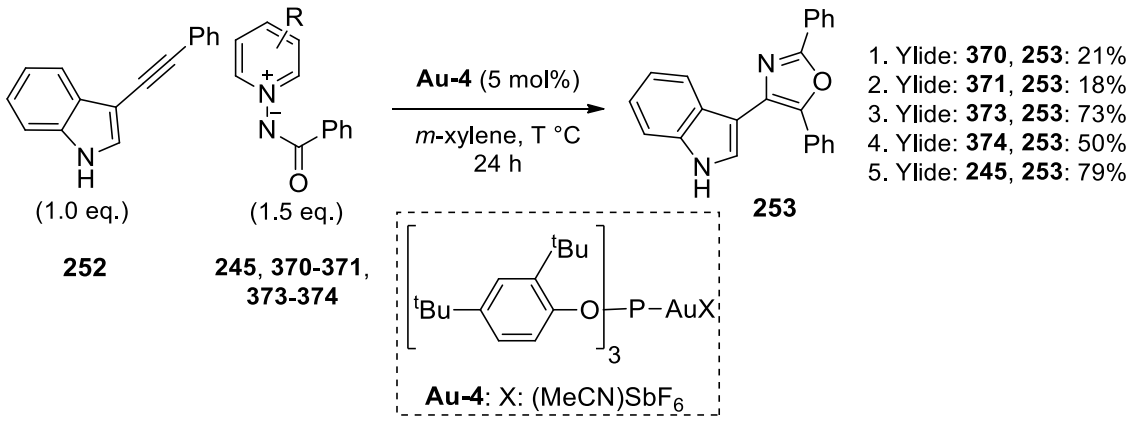
Following Charette's method,[97] the preparation of these *N*-aminides involved a two-step synthesis of *O*-(2,4-dinitrophenyl)hydroxylamine **361** which was used as an aminating reagent to form *in situ* the *N*-aminopyridinium species **369** (Scheme 51). Reaction with benzoyl chloride under basic conditions led to *N*-benzoyliminopyridimium ylides. Although the published protocol reported excellent reactivity and clean reactions, degradation occurred which, in

combination with purification problems, afforded the aminides in moderate yields **370**-**371** and **373**-**374**. Furthermore, the method does not seem to be compatible with electron deficient or hindered pyridines (**364**, **367**-**368**) as extended degradation pathways were followed and not even traces of the desired products were observed (**372**, **375**-**376**).



Scheme 51: Preparation of ylides with functionalised pyridine moieties

Ylides **370**-**371** and **373**-**374** proved much less reactive than the corresponding ylide with unsubstituted pyridine **245**, under the gold-catalysed reaction conditions (Scheme 52). Only when **373** was employed, the observed yield was comparable with the use of **245**. The lack of efficiency might not attribute only to their low reactivity but also to their insolubility as well as instability in the reaction.



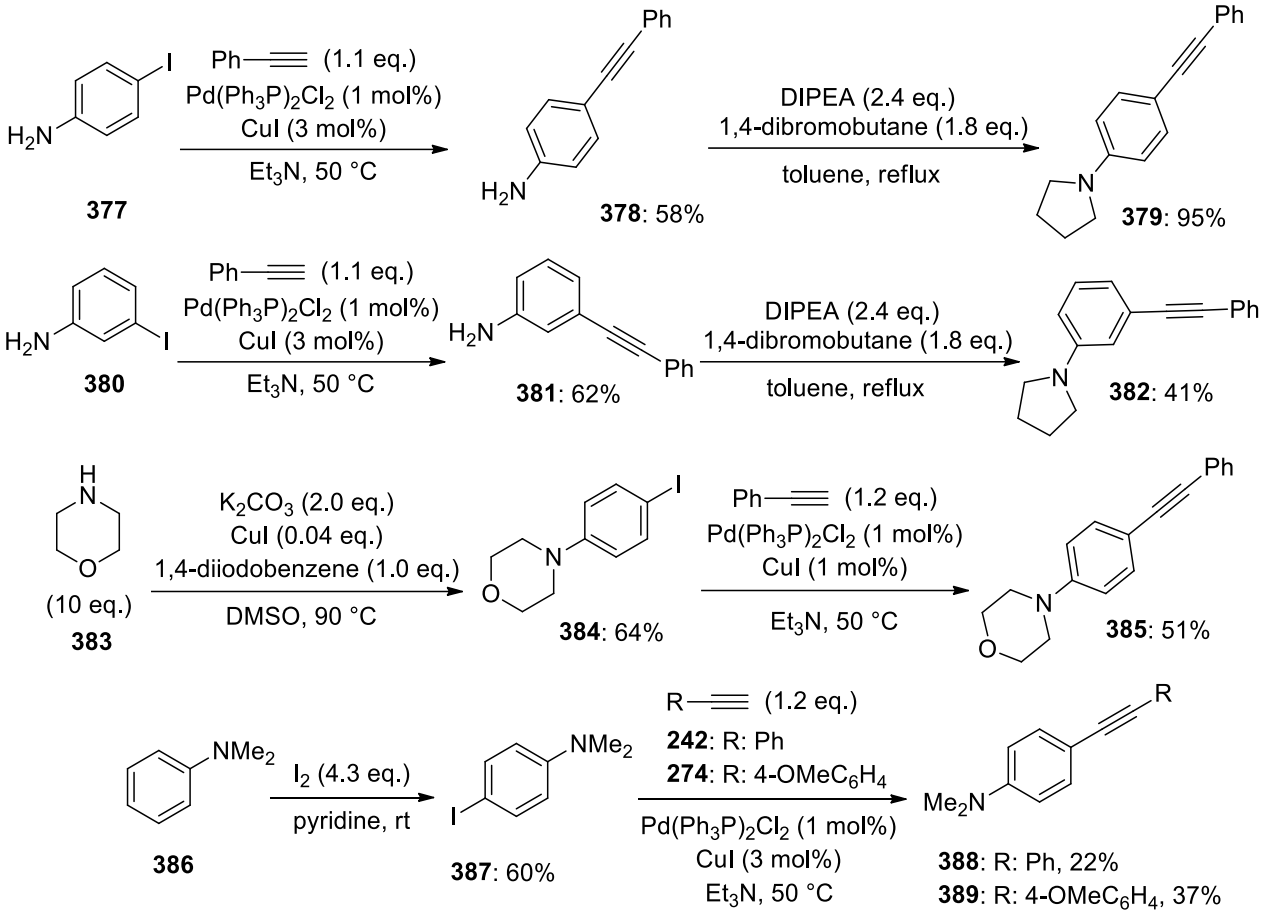
Scheme 52: Functionalised pyridine-*N*-aminides under gold-catalysis

Based on these results, no outcome can be drawn about the effect and the role of the pyridine in the catalysis. Many other factors surely interfere such as the solubility and the stability of the aminides, problems that were not encountered when **245** was used (Entry 5). Thus unsubstituted pyridine-*N*-aminides were used for the investigation of the substrate scope.

2.3.2.4 Aniline derivatives

Aniline derivatives were designed to test whether a more remote activation towards the π-system can be achieved, furnishing the corresponding oxazoles in single regiosimers.

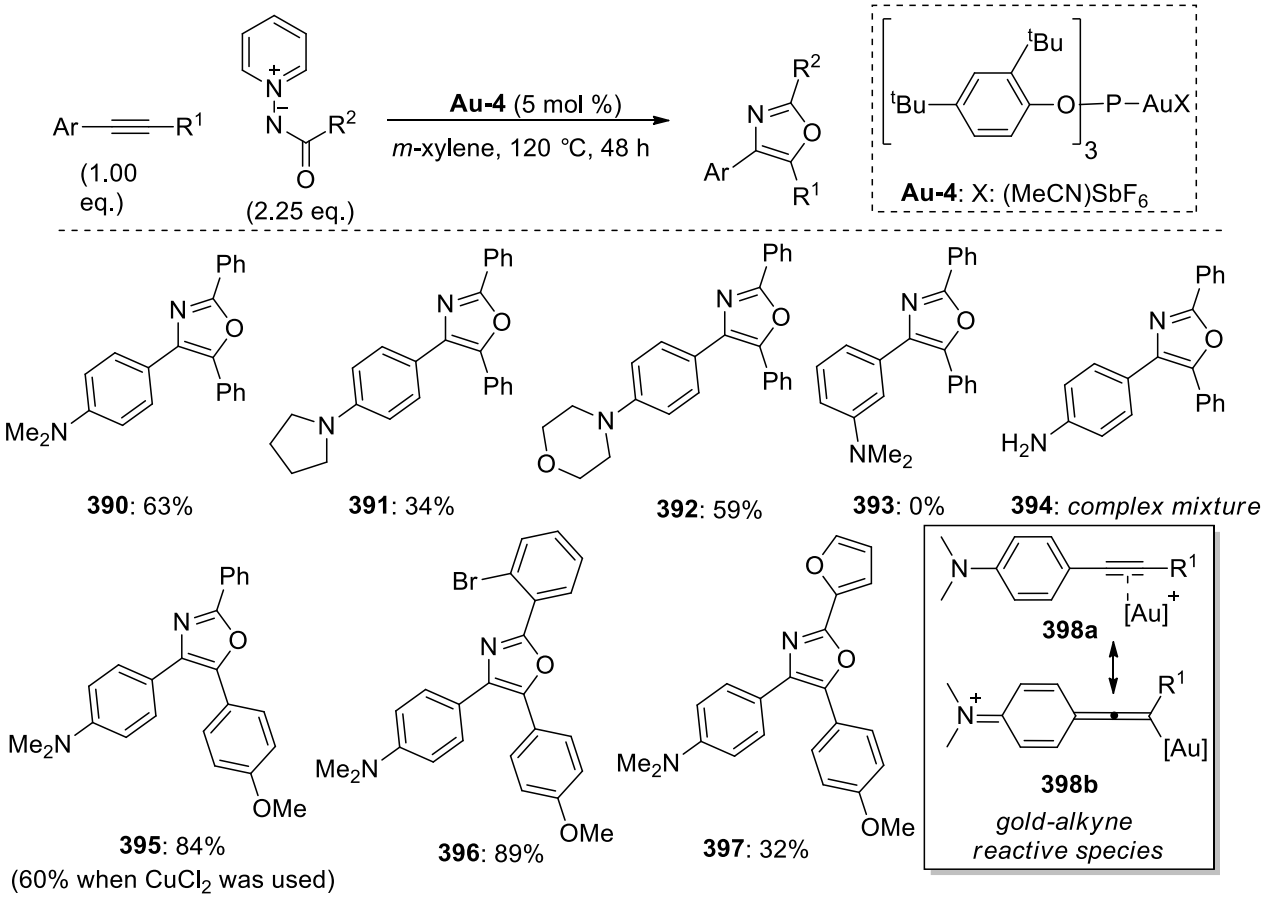
Aniline containing π-systems were formed through Sonogashira reaction and *N*-alkylation to give the internal alkynes in low to moderate yields (products **379**, **382**, **385**, **388**-**389**, Scheme 53). Then the substrates in combination with the pyridine-*N*-aminides were tested under the optimised gold-catalysed conditions.



Scheme 53: Preparation of aniline-derived internal alkynes

Pleasingly, the reaction was not only bound to indoles as the aniline derivatives exhibited the same kind of activation (Scheme 54). The regioselectivity was not diminished either, affording only one regioisomer of the oxazole with the aniline core being attached in the 4-position (**390**-**392, 395**-**397**), indicating the influence of the remote nitrogen lone pair in this case too. In comparison to the indole series, when anilines were employed the reactions proceeded more slowly and additional quantity of *N*-aminides was needed to give full conversion after 48 hours. This trend is potentially assigned to the disturbed aromaticity towards the formation of the

gold-alkyne species **398a**/**398b**, assuming that this intermediate is responsible for the observed reactivity. Comparatively, the analogous formation of the indole derived alleniminium intermediate interrupts the system's conjugation to a much lower extent. In addition, due to the extended reaction time and high temperatures, more sensitive furyl-substituted aminide gave the corresponding oxazole **397** in relatively low yield.



Scheme 54: Aniline derived alkynes for the oxazole formation

Our assumption, that the free electron pair of the nitrogen is responsible for both the reactivity and the regioselectivity, was tested by preparing an inactive alkyne **382**, with the amine *meta*-to the triple bond. When this derivative was subjected under the optimised conditions, no

conversion was observed as expected (**393**). In addition, an unprotected aniline gave very complicated mixtures, potentially due to further interaction of the amine with the metal (**394**).

Importantly, alkyne **389** with two nominally activating groups attached to the triple bond without any steric bias, when treated with different aminides, gave oxazoles **395**-**396** as single regioisomers in excellent yields. This regioselective outcome points out the significant electronic influence of the amino group towards the activation of the π-system.

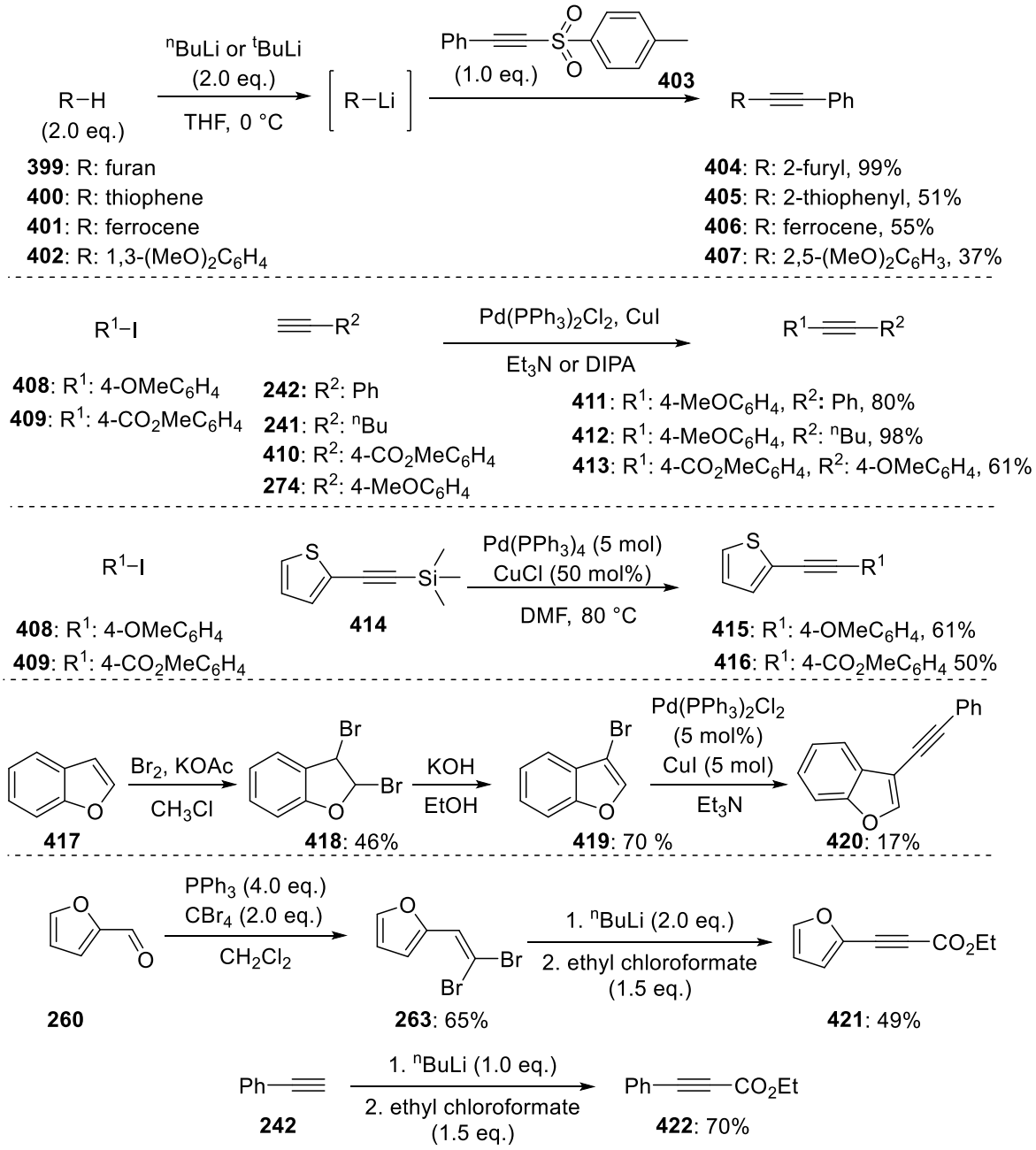
When inexpensive $CuCl_2$ was used, instead of gold, under the same conditions, oxazole **395** was formed in satisfactory yield. These encouraging, yet unoptimised results would open interesting routes for further investigation of the observed copper-activation.

2.3.2.5 Other substrates

The substrate scope was further investigated by employing alternative electron-rich π-systems (Scheme 55). Facile access to these scaffolds was achieved using Ruano and Alemán's method[98] based on alkynylation of organolithium precursors. Electron-rich aryl groups and heteroaryl groups were treated with lithium bases and the generated organolithium species were trapped by sulfonyl acetylene **403**, to give a range of alkynes in moderate to good yields (**404**-**407**).

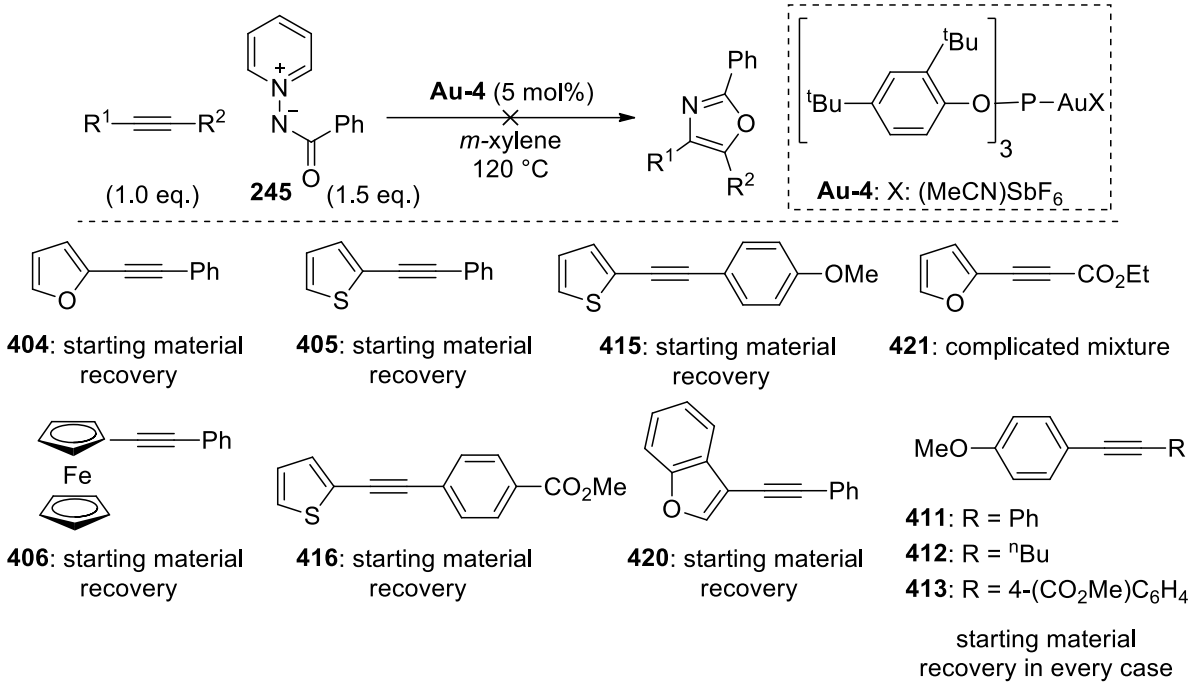
Other electron-rich substrates, accommodating anisole moiety, heteroaryl and alkyl groups were prepared through classic Sonogashira coupling between the corresponding aryl halide and the terminal alkyne (alkynes **411**-**416**). Benzofuran derivative **420** was prepared in a three-step reaction sequence in very low yield, due to degradation.

Moreover, electron-deficient π-systems were also prepared. Alkynyl lithium species were able to be captured by ethyl chloroformate to form the corresponding internal alkynes in moderate to good yields (**421**-**422**).



Scheme 55: Formation of electron-rich and electron-deficient π-systems

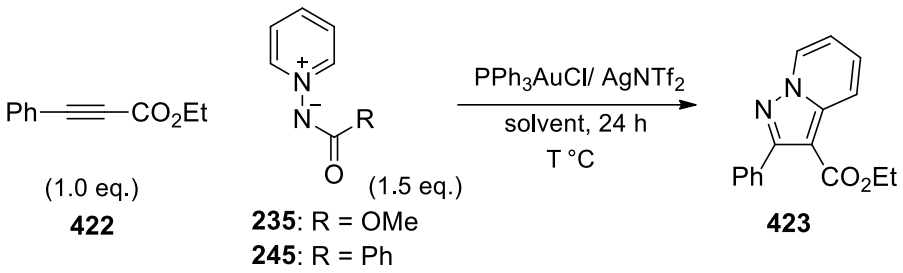
When furan **404**, thiophene **405** and **415**-**416**, ferocene **406,** benzofuran **420** and anisole **411-413** alkynyl derivatives were tested under the optimised gold-catalysed conditions, no reactivity was observed (Scheme 56). Unfortunately, in every case starting material was recovered and not even traces of the corresponding desired oxazoles were formed. It is worth mentioning that substrate **412** with an alkyl group attached to the triple bond did not form either the 1,2-hydride shift product or the oxazole. The complete lack of reactivity indicates the inefficient activation of the triple bond when non-nitrogen-containing heteroaryl groups or even electron-rich aryl groups are employed. As discussed in previous sections, the role of the nitrogen is crucial for the reactivity and regioselectivity and it looks like no other heteroatom exhibits sufficient activation, for this process, towards the π-system. Notably, these substrates also did not give any products when copper salt, instead of gold catalyst, was used under the same, optimised conditions.



Scheme 56: Other electron-rich systems under optimised, gold-catalysed conditions

When a furan-substituted alkyne with a strong electron-withdrawing group, such as an ester group **421** (Scheme 56), was utilised for the oxazole formation under either gold or copper catalysis, a complicated mixture was obtained. In contrast, an alternative reactivity was observed when the phenyl-substituted alkynyl analogue **422** was used towards the formation of the relative oxazole. As indicated in Table 3, when the more reactive ylide **235** was used with *in situ* generated PPh_3AuNTf_2, only the pyrazole derivative **423** was formed. The less reactive ylide **245** did not show any product formation.

Table 3: *N*-aminides as 1,3-*C,N*-dipoles



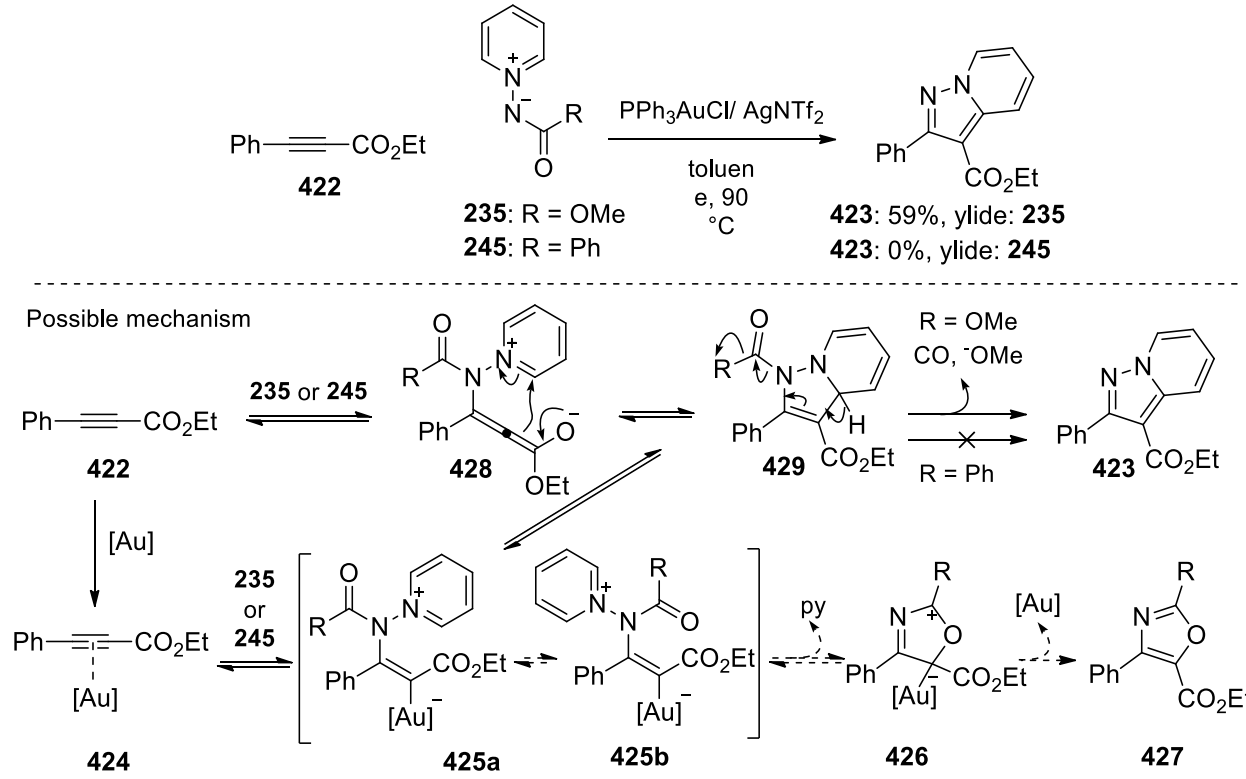
Entry	Ylide	T (°C)	Solvent	423 (%)[a]
1	**235**	90	toluene	56%
2	**235**	90	*m*-xylene	7%
3	**235**	90	1,4-dioxane	20%
4	**245**	90	toluene	0
5	**245**	90	DMF	0
6	**245**	40	THF	0

[a] isolated yield

In this process, in the presence of an electron deficient alkyne the ylide acts as a 1,3-*C,N*-dipole by giving substitution reaction around the pyridine ring. This reactivity has been previously reported using electron deficient alkynes,[99] benzynes[100] and metal acetylides.[83, 101]

A possible mechanism involves the metal acting either as a Lewis acid, stabilising intermediate **428** or as a π-acid giving vinyl gold species **425** (Scheme 57). Cyclisation of **425a** or **428** forms cyclic intermediate **429** which can evolve through decarboxylation and elimination of the R-group. Assuming that every step for the formation of both C-N and C-C bond is reversible, it can be envisioned that the reaction outcome depends on the ability of the R-group to eliminate. In this respect, ylide **235** reacted rapidly at high temperature as the methoxy group can be easily cleaved giving irreversibly the aromatised pyrazole product **423**. In contrast, the aromatic ring on ylide **245** is not a good leaving group, thus cleavage of the *N*-acyl group cannot be achieved. Additionally, it can be suggested that vinyl species **425b**, with an *s-cis* conformation leads to the

formation of the desired oxazole. However, this reactivity was not observed in none of the cases, presumably because the intermediates **425a**/**425b** are not formed. In the alternative scenario that **425a**/**425b** are formed, the inability of **425b** to cyclise is not clearly understood: the ester group does not seem to be involved in the final 4π-cyclisation as the corresponding oxazole was formed in the case of an analogous ester-containing ynamide. Potentially a high rotation barrier that interconverts **425a** and **425b** favours **425a** which leads to the starting materials when ylide **245** is employed.

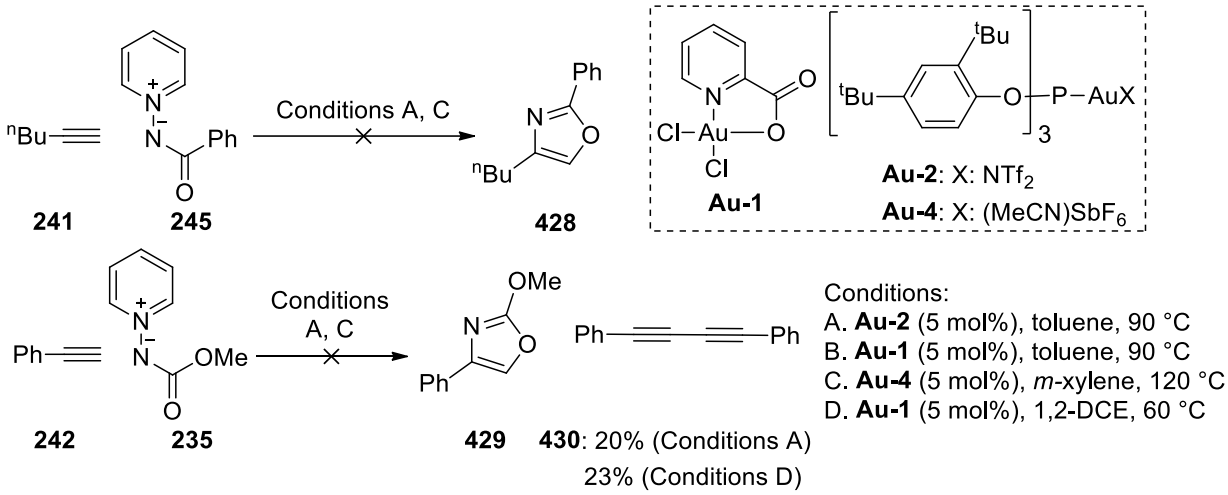


Scheme 57: Possible mechanism for the formation of pyrazole derivative

Finally, taking into account these unwanted results, no further investigation of the reaction scope was performed using electron-deficient alkynes.

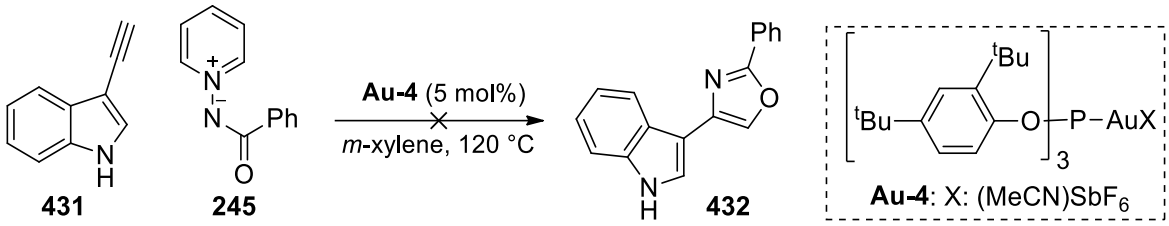
2.3.2.6 Terminal alkynes

Terminal alkynes can potentially exhibit the desired reactivity to form 2,4-disubstituted oxazoles (Scheme 58). However, simple alkyl and aromatic terminal alkynes proved unreactive when combined either with ylide **245** or with the more reactive ylide **235** under several catalytic conditions. Instead, a dimer **430** was observed derived from a Glazer-coupling. The following scheme shows only a small sample from the study.



Scheme 58: Terminal alkynes for the formation of 2,4-disubstituted oxazoles

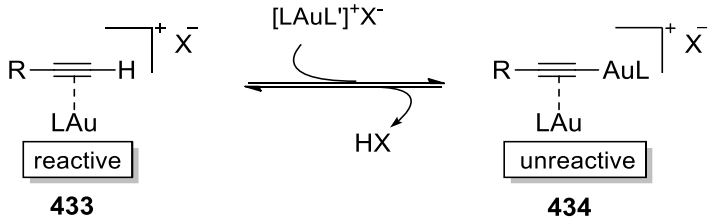
When the terminal *N*-unprotected 3-indolyl acetylene **431** was used under the optimised conditions, rapid degradation was observed and no starting material was remaining after 30 minutes (Scheme 59).



431 245 432

Scheme 59: Terminal indole-based alkyne for the formation of 2,4-disubstituted oxazoles

Echavarren and co-workers have reported that terminal acetylenes are prone to form digold σ,π-acetylide species **434**. These are unreactive and also reduce the concentration of the catalytically active π-gold mononuclear complex (Scheme 60).[102] The use of gold complexes with bulky ligands and a less basic, non-coordinating counterion seem to be a solution to the problem as the deprotonation of the acetylene is slowed down and σ-interactions are not favoured.[103]



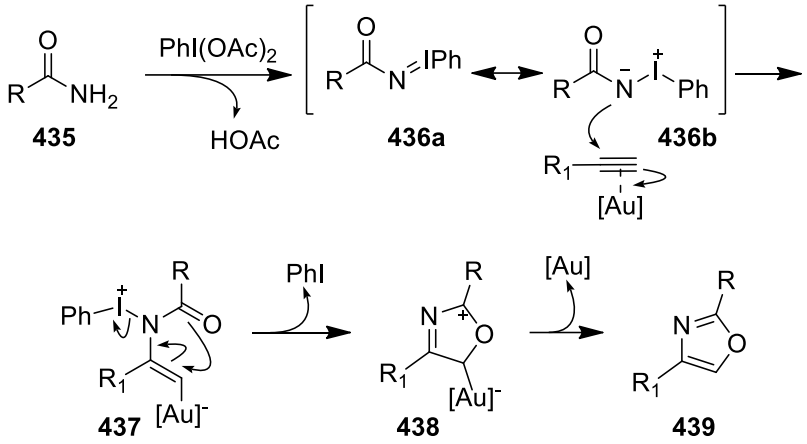
433 434

Scheme 60: Mononuclear gold complexes *versus* digold σ,π-acetylide species

These recent literature results can be potentially applied in the gold-catalysed oxazole formation as well. More activated terminal alkynes in combination with bulky gold catalysts with a non-basic counterion will probably give the corresponding oxazoles.

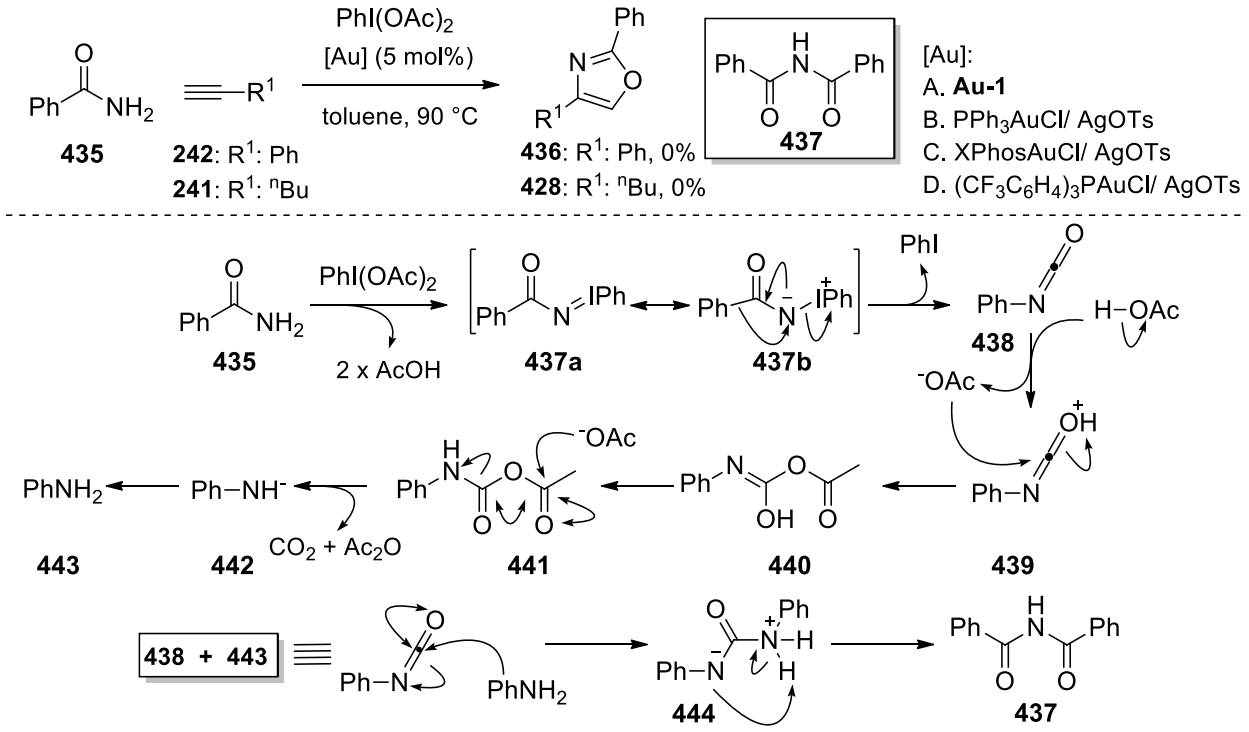
An alternative approach was then considered that might avoid gold acetylide formation promoted by the release of basic pyridine in the reaction mixture (Scheme 61). Instead of using

pyridine-*N*-aminides, iodonium-*N*-amides were considered to act as 1,3-*N,O*-dipoles for the oxazole formation. These species (**436a**/**436b**), which can be formed *in situ* by combining different amides **435** and (diacetoxyiodo)benzene, can undergo rearrangement, however the potential to proceed through the desired [3+2]-cycloaddition was further investigated.



Scheme 61: Alternative use of iodonium ylides for the formation of the oxazoles

These ylides proved incompatible with this reaction as they underwent rearrangement forming the urea product **437** almost instantly (Scheme 62). The outcome of the reaction was the same regardless the catalytic conditions used. Test reactions in the absence of the alkyne and/or the gold catalyst indicated that the acetylene does not participate in the reaction and the gold catalyst does not seem to contribute to the observed reactivity either. The formation of the urea derivative **437** with the use of benzamide **435** and (diacetoxyiodo)benzene had previously reported by the Liu and Landsberg research groups.[104],[105]



Scheme 62: Side reaction of iodonium-ylides

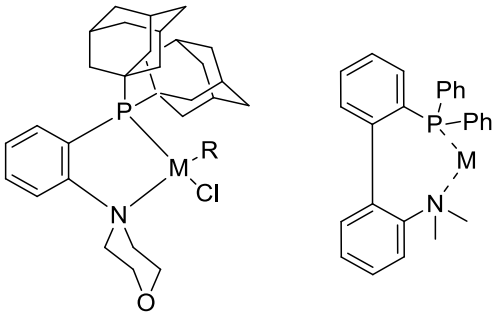
The gold-catalysed formation of disubstituted oxazoles with the use of terminal acetylenes and either pyridine or iodonium-*N*-aminides was not achieved. As regards the pyridinium ylides, although they have been proved excellent components for this method, the possible formation of gold-acetylides might be the reason why terminal alkynes does not exhibit the desired reactivity. On the other hand, iodonium ylides, as acyl-nitrene equivalents undergo uncontrollable rearrangement, forming a urea byproduct almost instantly.

2.3.3 Further reactivity

2.3.3.1 Ligand Formation

Functionalised oxazoles with bulky groups around the ring can act as building blocks for the formation of bulky ligands.[106] Catalysts with hindered ligands are advantageous and widely applied in many catalytic processes. Bulky ligands tend to ''support'' the metal being coordinated, thus the catalyst often has longer life time. Also, side reactions are usually suppressed as hindered ligands may block coordination sites of the metal. Many research groups have broadly explored this area in order to construct catalysts with the required properties.[107],[108]

The Buchwald[109] and Stradiotto[110] research groups have made major contribution to the field by reporting the synthesis of bidentate phosphine ligands, where the metal can coordinate with both the phosphorus and the nitrogen (**445**, **446**, Scheme 63).



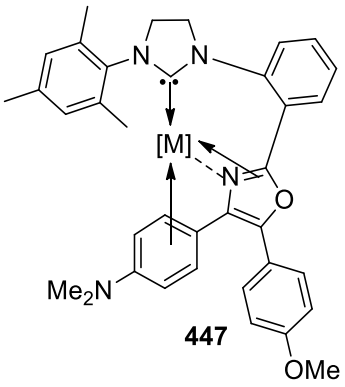
445
Mor-DalPhos
[Stradiotto]

446
PhDavePhos
[Buchwald]

Scheme 63: Stradiotto and Buchwald bidentate ligands

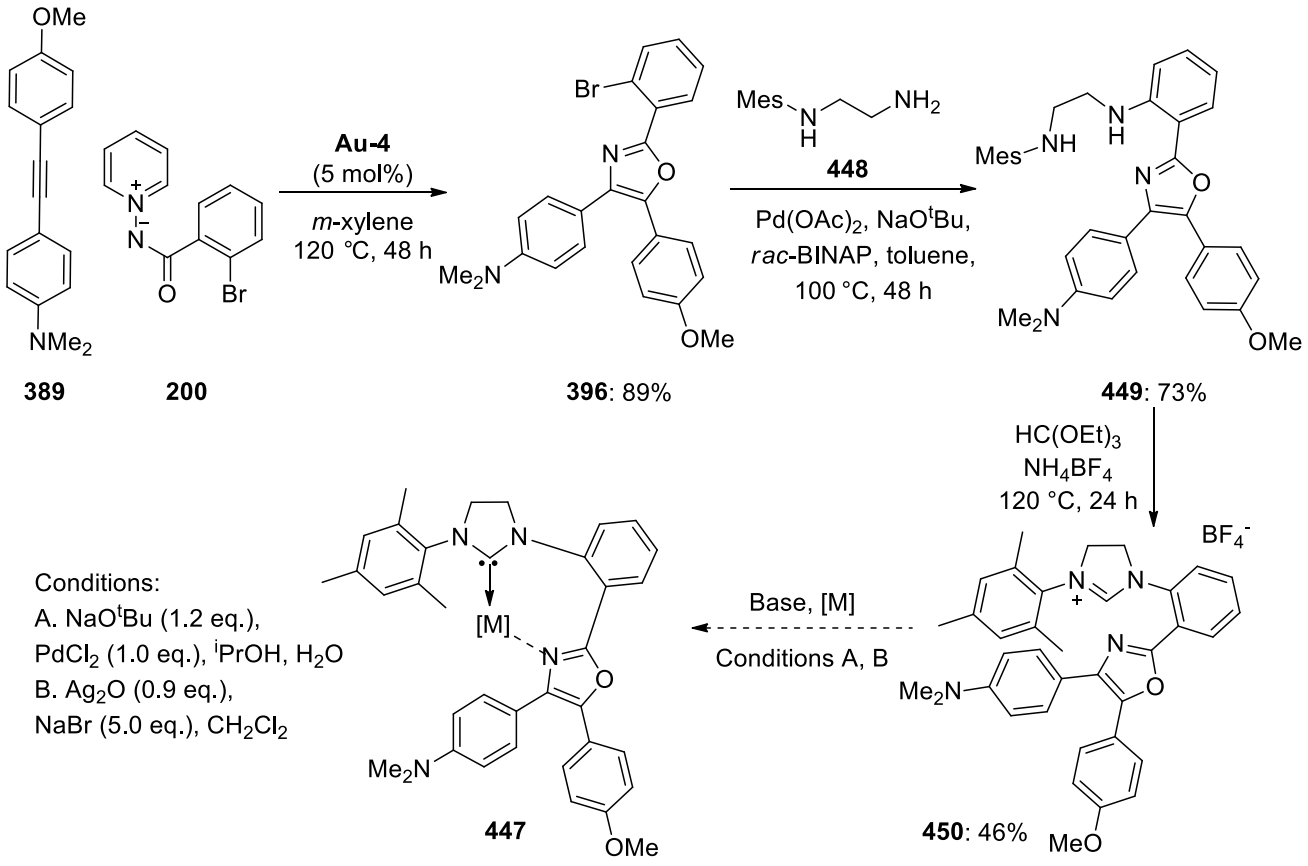
Having oxazoles with bulky aromatic substituents in hand, it was envisioned that these scaffolds could be utilised to build sterically bulky ligands which could likely bind into a metal and render interesting properties to the catalyst (Scheme 64). In analogy to Buchwald and Stradiotto ligands, an N-heterocyclic carbene **447** was designed, which has the oxazole as the main core structure and can potentially coordinate to the metal with both the carbene centre and the nitrogen of the oxazole. Furthermore, π-interactions between the metal and the oxazole ring or the aniline group attached to the oxazole might block the coordination sites of the metal avoiding side reactivity.

- *oxazole-based NHC*
- *bulky, bidentate catalyst*
- *π-interactions from the aromatic substituent*
- *π-interactions from the oxazole ring*
- *coordination with the oxazole nitrogen*
- *potential to exhibit controlled reactivity*



Scheme 64: Oxazole-based bidentate ligand in analogy to Stradiotto and Buchwald ligands

The synthesis of the imidazolium salt was initiated the preparation of the corresponding oxazole **396** which was obtained in high yield on 0.7 mmol scale with the use of 5 mol% of the catalyst (Scheme 65). It is worth mentioning that the loading of the catalyst is important as decreased catalyst loading resulted in lower conversion (1 mmol scale, 2.5 mol% gave 44% of the oxazole).



Scheme 65: Towards the formation of oxazole-based NHC catalyst

Hartwig-Buchwald Pd-mediated C-N bond formation with amine **448** gave diamine oxazole derivative **449** in good yield, while subsequent cyclisation with triethyl orthoformate gave the saturated tetrafluoroborate imidazolium salt **450** which was constructed in overall 3 linear steps (starting from the easily prepared alkyne **389**).

Unfortunately, preliminary investigations into preparation of NHC **447** was not straightforward. Attempts to coordinate either with palladium or silver proved problematic, with different byproducts being formed in every case. Several recrystallisation trials did not afford the pure

complex either, while purification with silica or alumina chromatography gave additional degradation byproducts.

The hindered ligand, along with the potentially reduced nucleophilicity of the nitrogen of the oxazole, might be the reason of this obstructed reactivity. Thus, different methods have to be optimised in order to achieve binding of this bulky ligand with the metal.

2.3.3.2 Biological activity

As mentioned in the previous section, naturally occurring pimprinine derivatives have an indole core at the 5-position of the oxazole ring. It has been reported that isomeric pimprinine analogues with the indole attached on the 4-position of the oxazole exhibit significant cytotoxicity against various cancer cell lines, while some of them can act selectively against pancreatic and breast cancer cell lines.[111],[112]

Given the potentially interesting biological activity, the prepared 4-indolyl oxazoles were submitted to Eli Lilly's Open Innovation drug discovery program to evaluate the potency to act as lead molecules for drug discovery. The oxazoles were first passed the *in silico* test, provided by the company, that determines compounds suitable for drug applications. Further screening was conducted against phenotypic, target and tuberculosis assays.

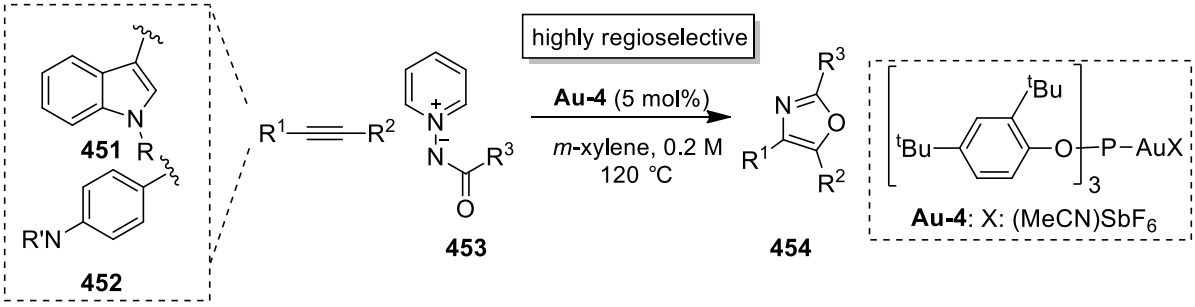
In vitro screening was performed to a variety of mouse and human cell lines. Endocrine and cardiovascular activity was tested, to stimulate GLP-1 secretion for the treatment of diabetes.[113] The compounds' ability to prevent growth of *Mycobacterium tuberculosis* (H37Rv) was also tested. Other tests involving oxazoles' behaviour against mGlu2R receptor allosteric antagonist,[114] CGRP receptor antagonist for the treatment of migraine and other neurological

diseases,[115] inhibition of EZH2 which is a protein closely related to the treatment of cancer[116] and C-Raf, a kinase which plays a major role in tumor-genesis.[117]

Further investigation upon the biological activity of these scaffolds is ongoing.

2.4 Summary

A new methodology for the formation of all-carbon fully substituted oxazoles was designed and developed, through highly regioselective gold-catalysed cycloaddition.[118] This approach is fast and convergent in comparison to classic methods for the preparation of functionalised oxazoles. All-carbon 2,4,5-substituted oxazoles were accessed *via* a novel gold-catalysed intermolecular formal [3+2]-cycloaddition across the π-system of internal alkynes (**451** and **452**) by employing conjugated *N*-ylides (**453**) as *N*-nucleophilic 1,3-*N,O*-dipole equivalents (Scheme 66).



Scheme 66: Gold-catalysed formation of all-carbon tri-substituted oxazoles

By employing electron-rich aryl/heteroaryl groups, comprising of indole and aniline derivatives, highly regioselective C-C π-system activation could be efficiently achieved. This intermolecular addition to an unsymmetrical internal alkyne represents a considerable regioselectivity and reactivity challenge, as there are no examples of intermolecular atom-transfer nitrene addition by π-acid activation of an internal alkyne. Across all the indole and aniline derivatives this

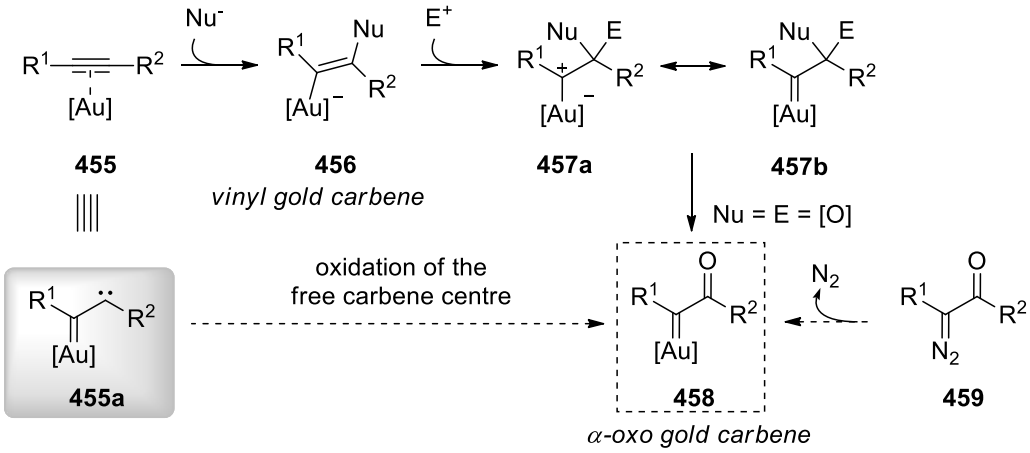
reactivity trend correlates with the ability of the nitrogen lone pair to donate electron density into the alkyne. Moreover, this 3-indole oxazole motif is found in pimprinine derivatives and provides potentially interesting framework of organic materials and medicinal compounds. Further advances are needed to extend this approach into other π-systems.

3. Chapter 3:

Intramolecular group- and atom-transfer onto π-systems

3.1 Introduction

As previously discussed in Chapter 1, gold carbenes are some of the most versatile tools in the field of gold catalysis. The generation of these intermediates from alkynes involves coordination of the gold catalyst to the π-system, which promotes nucleophilic attack giving vinyl gold species **456** (Scheme 67). These species are highly reactive and can formally react with an approaching electrophile on the β-position forming the gold stabilised carbocation **457a**. Attack on the α-carbon can also occur, leading to alternative pathways. Back donation of electron density from the metal stabilises the carbene centre rendering a gold carbene **457b**. As proposed by Fürstner and Davies, the conversion of an alkyne to gold carbene can theoretically be seen as a speculative α-carbene gold carbene **455a** exhibiting both electrophilic and nucleophilic properties at the free carbene centre.[1e]

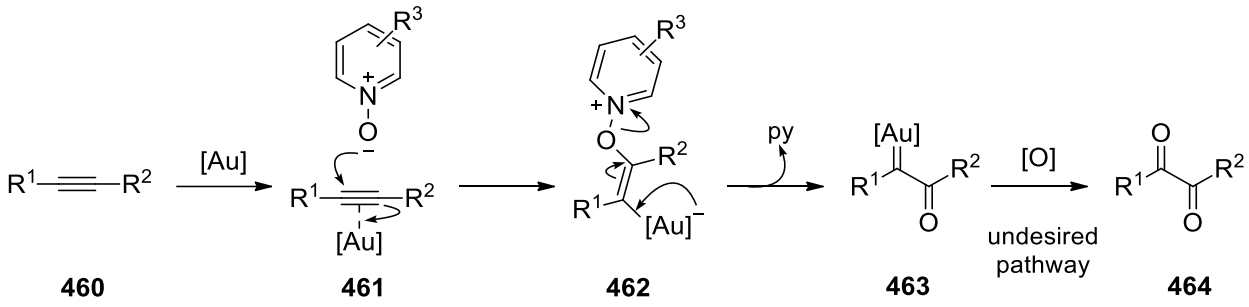


Scheme 67: Generation of gold carbenes from alkynes

In case that both the nucleophile and the electrophile are oxygen, an α-oxo gold carbene **458** is generated which can be considered as an oxidation of the carbene centre of **455a**. While vinyl

gold species **456** are usually the key intermediates for diverse transformations, α-oxo gold carbenes **458** can also show valuable reactivity.[12] It is important to highlight that classical methods for the formation of these species involve the use of hazardous and potentially explosive diazo-precursors **459** (please refer to the relative discussion in Chapter 1).

In this context, a few years ago, a breakthrough was made in the development of new synthetic methodologies *en route* to α-oxo gold carbenes **463** (Scheme 68). The method involved gold-activated alkynes and an external oxidant to transfer oxygen. Pyridine-*N*-oxides serve this purpose by adding to the triple bond **461** forming vinyl intermediate **462**, which upon elimination of pyridine as a good leaving group leads to the formation of α-oxo gold carbenes.[12]

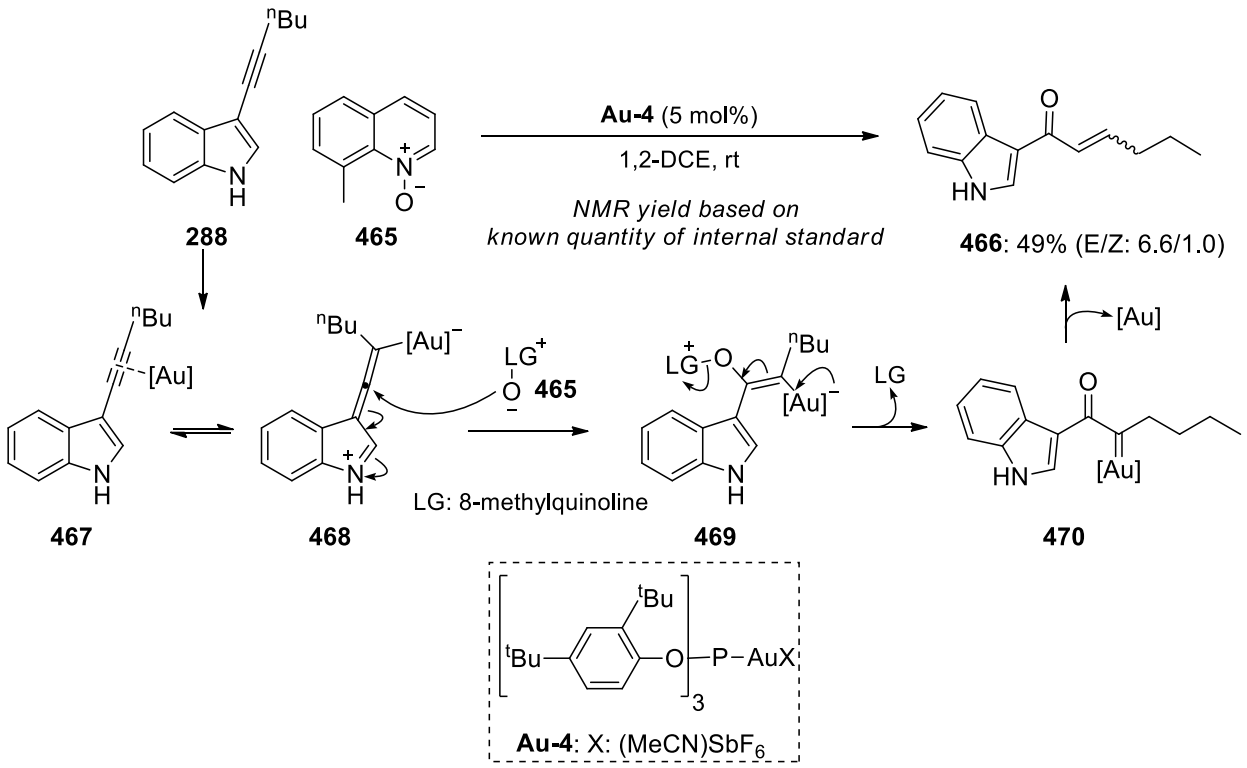


Scheme 68: Formation of α-oxo gold carbenes from pyridine-*N*-oxides

One of the main challenges of this approach is the control over the regioselectivity of the addition. Steric bias and/or conjugation of the two groups attached to the π-system can direct the regioselectivity. Furthermore, the potential for over-oxidation (**463** to **464**) introduces a fundamental challenge which must be suppressed by the use of the appropriate conditions.

In the previous chapter, the first example of a regioselective intermolecular nitrene transfer onto gold-activated, unsymmetrical internal alkynes was described. By exploring other atom-transfer processes, further studies were focused on whether the previously observed regioselectivity would be eroded when the same, sterically unbiased alkynes were employed in the intermolecular oxidation (Scheme 69).

Zhang and co-workers have reported the regioselective transformation of sterically biased internal alkynes into α,β-unsaturated carbonyls.[119] Using 8-methylquinoline-*N*-oxide **465** and gold catalyst **Au-4**, indole derivative **288** was tested for the formation of α,β-unsaturated ketones. The free electron pair of the indole nitrogen, which is in conjugation with the π-system, dictated the position of the nucleophilic attack to give the product **466** in moderate yield as a single regioisomer as a mixture of *E*- and *Z*-isomers.



Scheme 69: Intermolecular oxidation of indolyl-alkynes with 8-methylquinoline-*N*-oxide

Although intermolecular oxidation of electrophilic organogold species has been widely explored in the last five years, no examples in the literature use pyridine-*N*-oxides for the oxidation of π-systems in an intramolecular fashion. The first challenge to be overcome is the construction of the appropriate starting materials that include a pyridine-*N*-oxide tethered to the triple bond. It was hypothesized that an internal redox-system such this, would not suffer from the undesired over-oxidation pathways, whilst maintaining the required regioselectivity.

Analogous substrates with a pyridine-*N*-aminide tethered to the π-system would potentially allow controlled intramolecular nitrene transfer, giving access to a wide range of functionalised

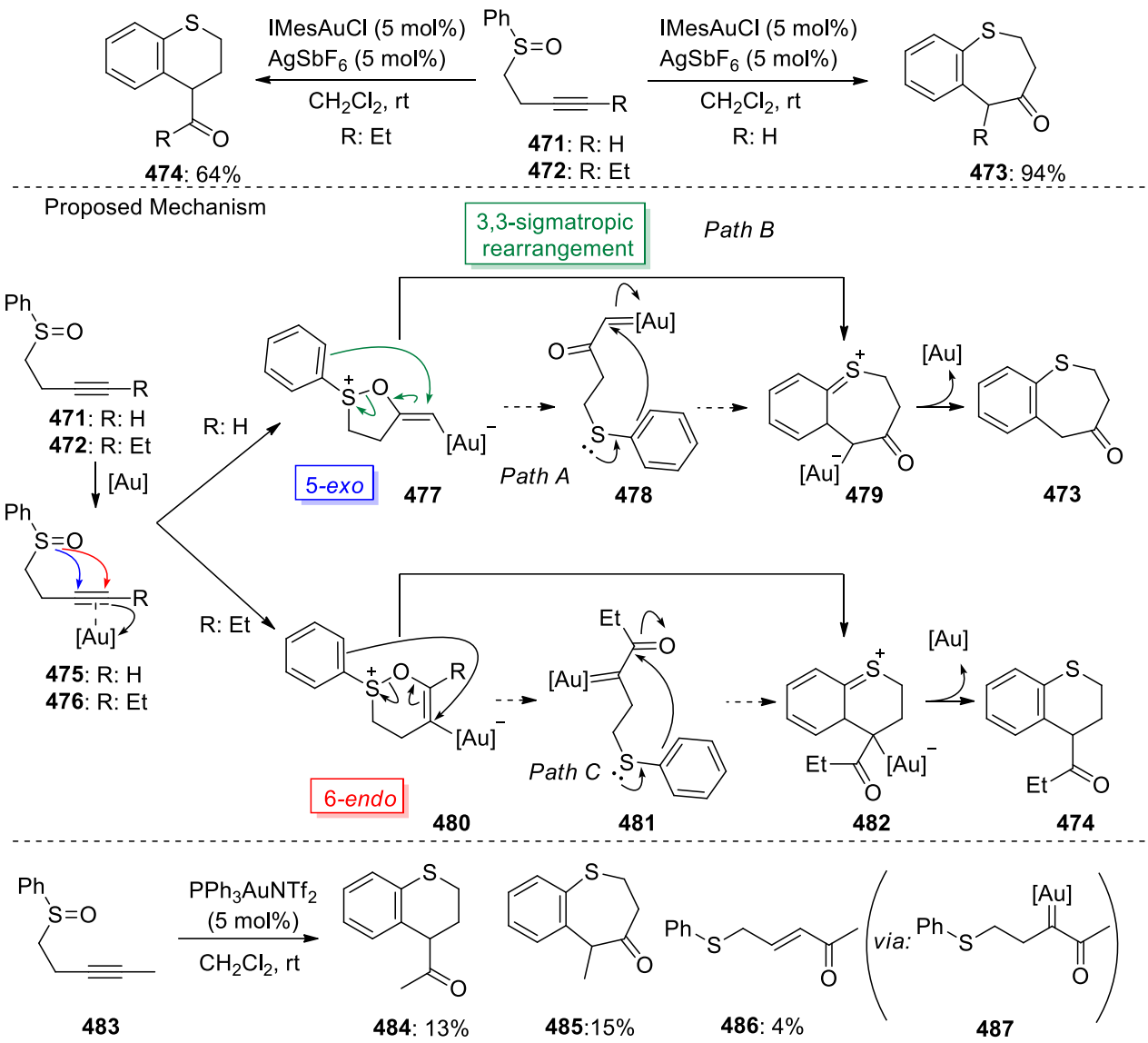
scaffolds. Further discussion about the design of these substrates, with an oxygen or nitrene attached to the triple bond, will follow in the next sections.

This chapter will be focused on selected examples of intramolecular oxygen and nitrene transfer towards gold-activated electron-rich alkynes.

3.1.1 Intramolecular oxidation of π-systems

3.1.1.1 Sulfur-containing oxidants

The research groups of Toste and Zhang have demonstrated that cascade reactions which invoke gold carbenes generated by an internal oxidant, can lead to diverse structures.



Scheme 70: Sulfoxides for intramolecular oxygen transfer onto gold-activated acetylenes

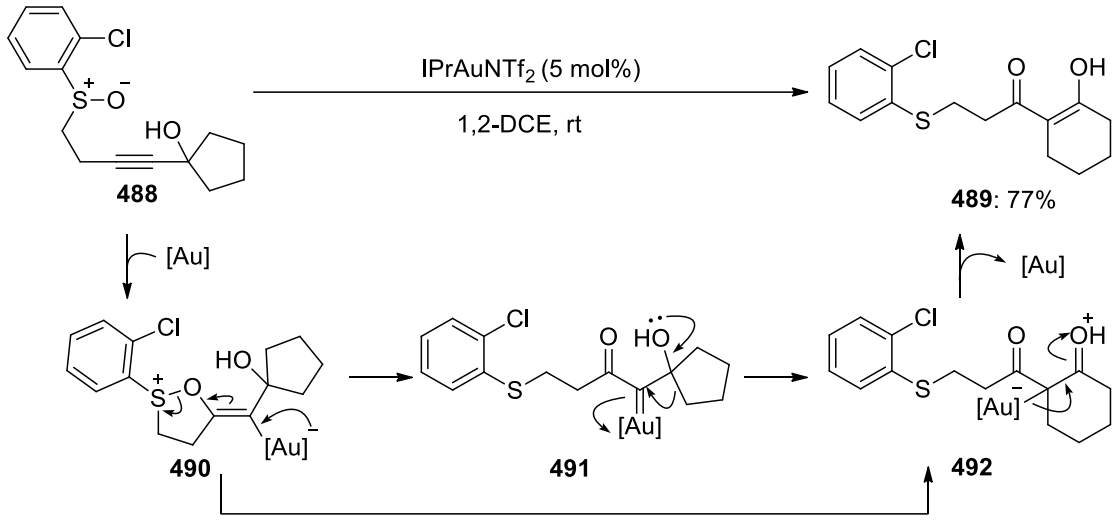
Initially, Toste and co-workers reported the first intramolecular oxygen transfer using a tethered sulfoxide as an internal redox system (Scheme 70).[120] The easily prepared terminal sulfinyl alkyne **471**, upon gold activation of the triple bond, can undergo 5-*exo-dig* cyclisation to give vinyl gold intermediate **477** (Path A). In the initial report the authors suggested that α-oxo gold carbene **478** is then formed and subsequently trapped in an electrophilic aromatic substitution

reaction, releasing the seven-membered ring derivative **473**. When an internal alkyne was used instead, the 6-*endo*-*dig* cyclisation was promoted leading to the alternative gold carbene **481**, which gave a six-membered-ring derivative **481** (Path C).

Several months later, Zhang and co-workers published similar results based on the same mechanism.[121] Crucially, mechanistic studies and DFT calculations by Maulide and co-workers[122] showed that the formation of α-oxo gold carbene is highly unlikely; instead, the vinyl gold **477** is the active species and the seven-membered ring derivative **473** is generated by a [3,3]-sigmatropic rearrangement of intermediate **477** (*vide supra,* Path B). This was supported by Zhang and co-workers later on.[123] In particular, they reported that the α-oxo gold carbene **478**, generated from terminal alkyne **475**, can suffer from side reactivity, thus the high efficiency of the reaction with the lack of any by-products can only be explained by the rearrangement pathway. Indeed, when internal alkyne **483** was employed, the formation of α-oxo gold carbene is competing with the [3,3]-sigmatropic rearrangement, however, in this case the carbene (**487**) evolves though 1,2-insertion giving the unsaturated ketone **486.**

Zhang highlighted that the mechanistic alteration, which involves the rearrangement of the vinyl gold carbenoid, should not be generalised and possibly is limited to the cases where other processes can be invoked. This was demonstrated by the formation of the β-hydroxyenones **489** (Scheme 71).[121] In this case the tethered benzene ring is *ortho*-chlorinated (**488**) which helps to suppress the [3,3]-sigmatropic rearrangement and to promote the formation of α-oxo gold carbene **491** which can undergo pinacol-type rearrangement (**491**-**492**), resulting in ring

expansion. Direct conversion of the vinyl carbenoid **490** to the intermediate **492** should also be considered.

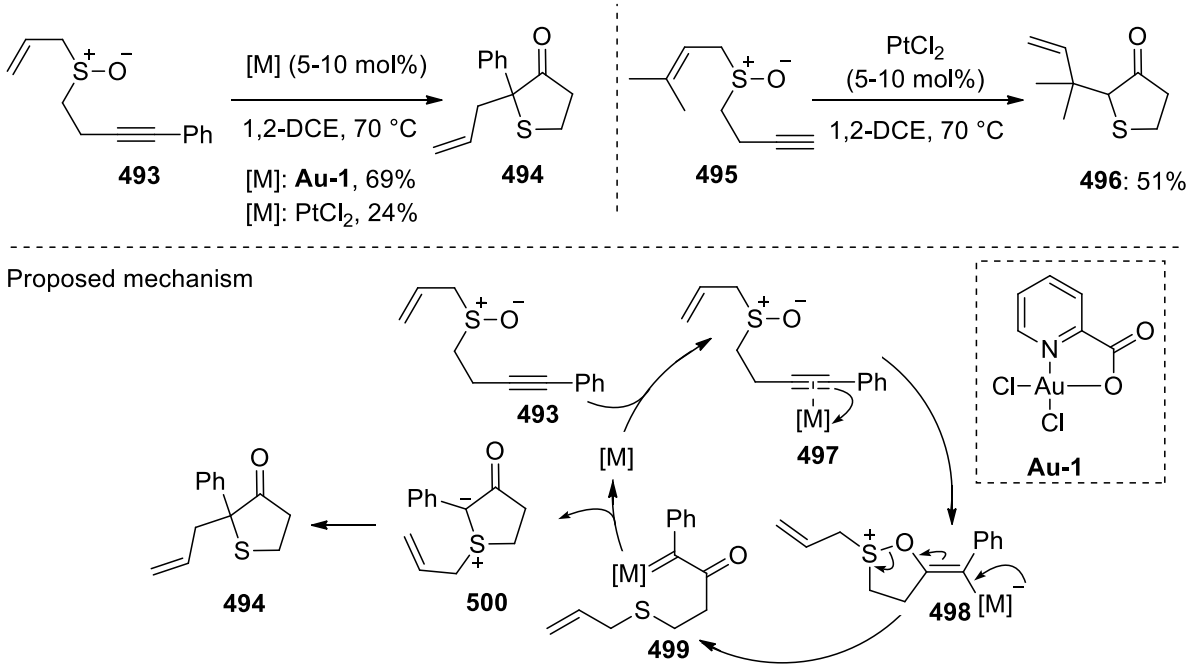


Scheme 71: Carbene formation and pinacol-type rearrangement

Based on Toste's and Zhang's powerful approach to generate carbenes masked as alkynes, Davies *et al* used alternative sulfoxides to trap the corresponding α-oxo gold carbene with a subsequent 2,3-sigmatropic rearrangement (Scheme 72).[124]

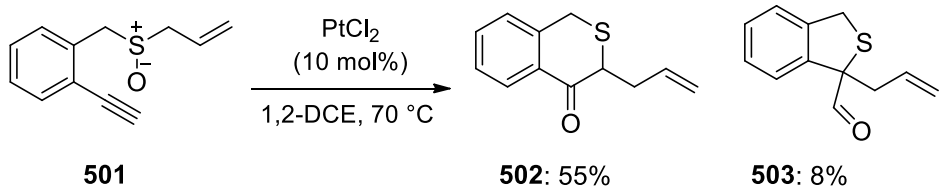
This time, the starting sulfoxide has an allyl group tethered to the sulfur, thus a [3,3]-sigmatropic rearrangement is not operative. According to the mechanism, nucleophilic attack of the sulfoxide **497** onto electrophilic organogold species forms intermediate **498** which precedes the generation of carbene **499**. The subsequently generated sulfonium ylide **500** can undergo 2,3-sigmatropic rearrangement to give heterocycle **494**. It can also be envisioned that carbene **499** is able to undergo cyclopropanation, however such product was not reported potentially due to the slow formation of the relative seven-membered ring system. Optimisation of the

reaction conditions revealed that gold(III) precatalyst was optimal when internal alkynes were used, whereas $PtCl_2$ proved more effective when terminal alkynes (such as **495**) were employed.



Scheme 72: 2,3-Sigmatropic rearrangement of sulfonium ylide

Interestingly, the regioselectivity of the initial attack by the sulfoxide was eroded when a precursor **501** with an incorporated aromatic unit between the sulfoxide and the alkyne was employed: a mixture of isomeric fused heterocycles (**502** and **503**) was formed, derived from 6-*exo*-*dig* and 7-*endo*-*dig* cyclisations respectively (Scheme 73).

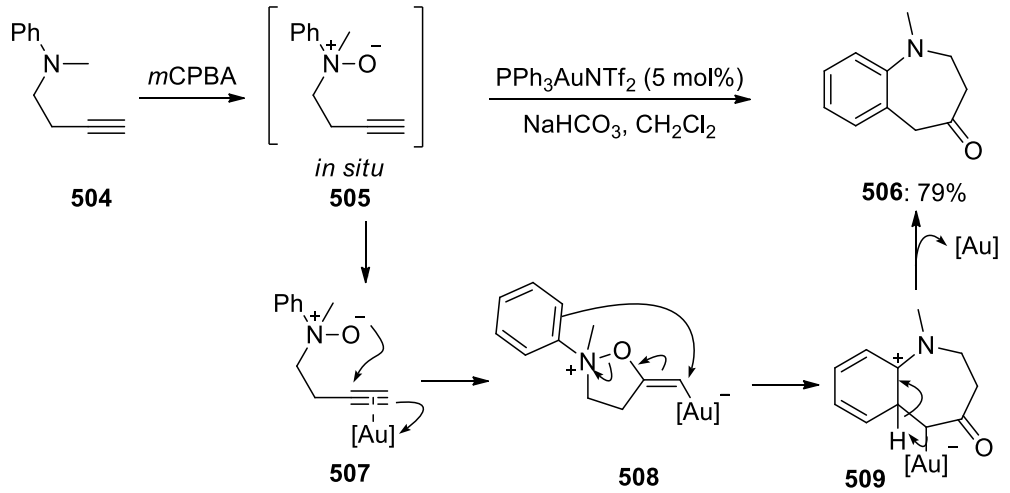


Scheme 73: Formation of sulfur-containing fused heterocycles

The above characteristic examples demonstrate the *in situ* formation of gold carbenes from the easily prepared sulfoxide tethered alkynes. The generated carbenes (either the vinyl gold species or the α-oxo gold carbenes) may be trapped by different nucleophiles, such that diverse reactivity and the formation of different products is possible.

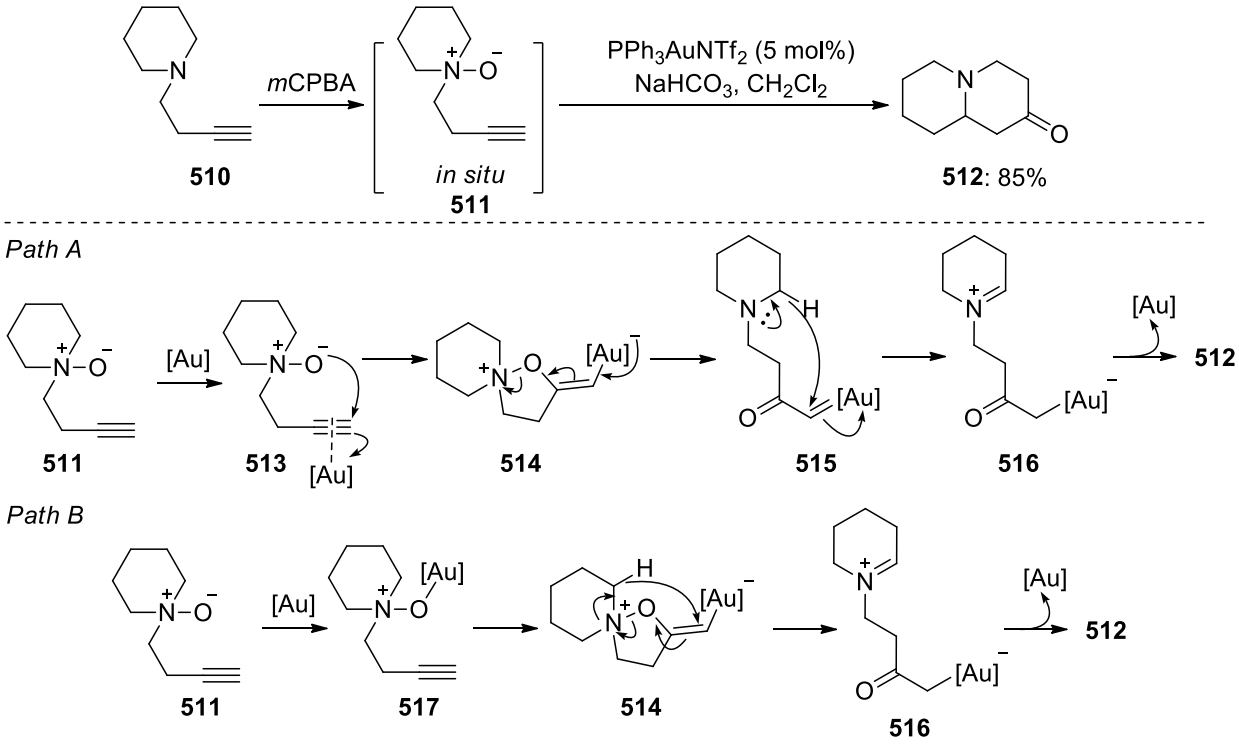
3.1.1.2 Nitrogen-containing oxidants

In analogy to the previously described substrates, *N*-oxides can be employed instead of sulfoxides as part of the internal redox system. Zhang and co-workers reported that amines tethered to an alkyne can be oxidised with *m*CPBA (Scheme 74).[125] In the initially reported mechanism, the authors suggested that the transformation evolved through the corresponding α-oxo gold carbene in a similar manner to that described previously to give functionalised azepinones **506**. However, based on the more recent advances to the field, the related [3,3]-sigmatropic rearrangement pathway (**508**-**509**) is much more likely to occur.



Scheme 74: *N*-oxides for the formation of azepinones

In an effort to expanding the substrate scope of this reaction, the same research group developed the synthesis of piperidinones **512** (Scheme 75).[126]

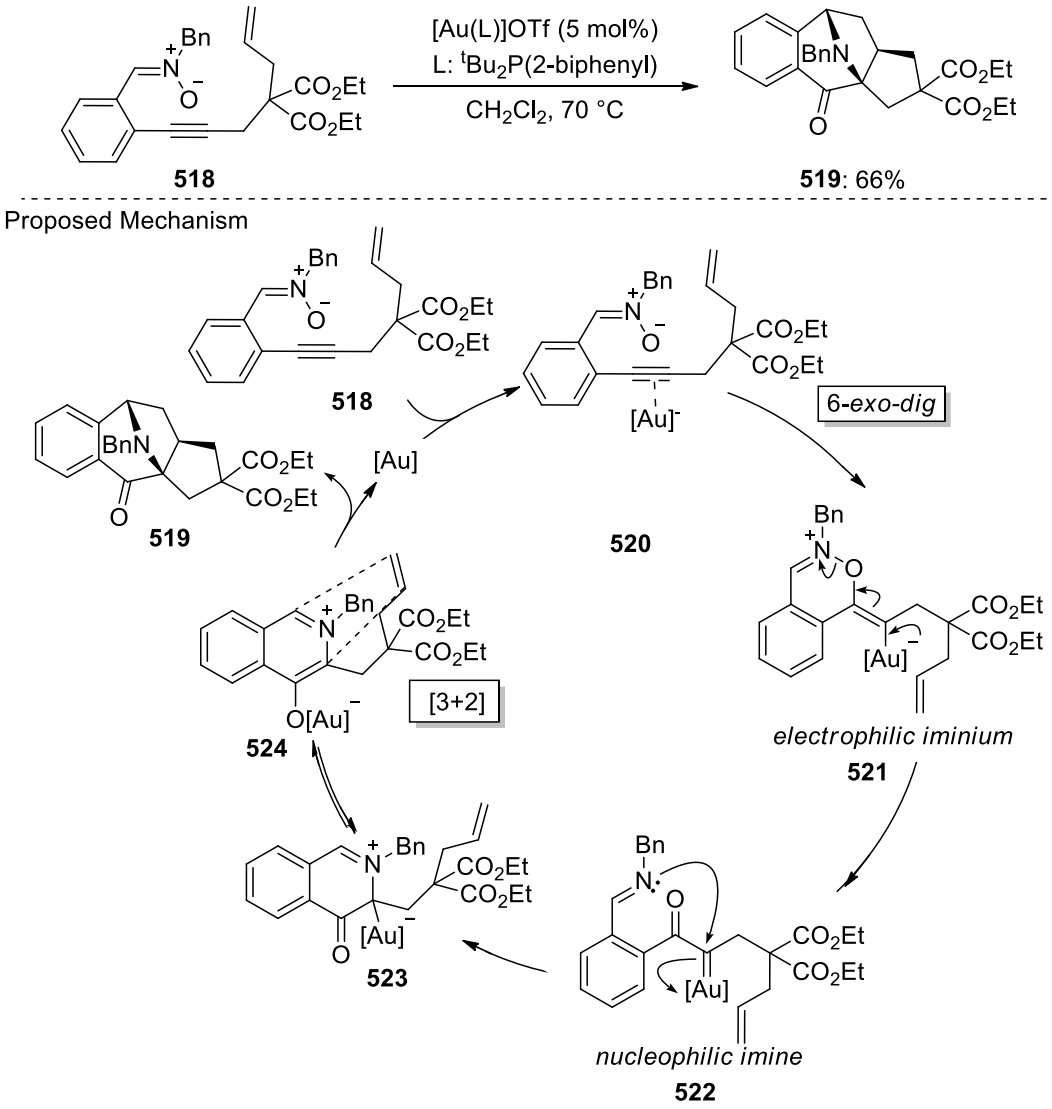


Scheme 75: Hydride shift as a means to quench the gold carbene

Originally, the authors suggested that upon oxidation of the secondary amine **510** and gold-activation of the triple bond, intramolecular attack leads to α-oxo gold carbene **515** (Path A). Subsequent 1,6-hydride migration to the carbene centre (**516**) and then cyclisation gives the cyclic derivative **512**. However, later on, an alternative and more possible mechanism was proposed based on DFT calculations (Path B).[127] Initially the cationic gold catalyst strongly coordinates to the *N*-oxide and the complex **517** formed proceeds through a *syn* addition to the alkyne. The vinyl gold carbenoid **514** undergoes a heteroarene reaction to give directly iminium **516**, avoiding the α-oxo gold carbene intermediate. Subsequent cyclisation, which was

calculated to be the rate determining step, and regeneration of the catalyst gives piperidinone **512**.

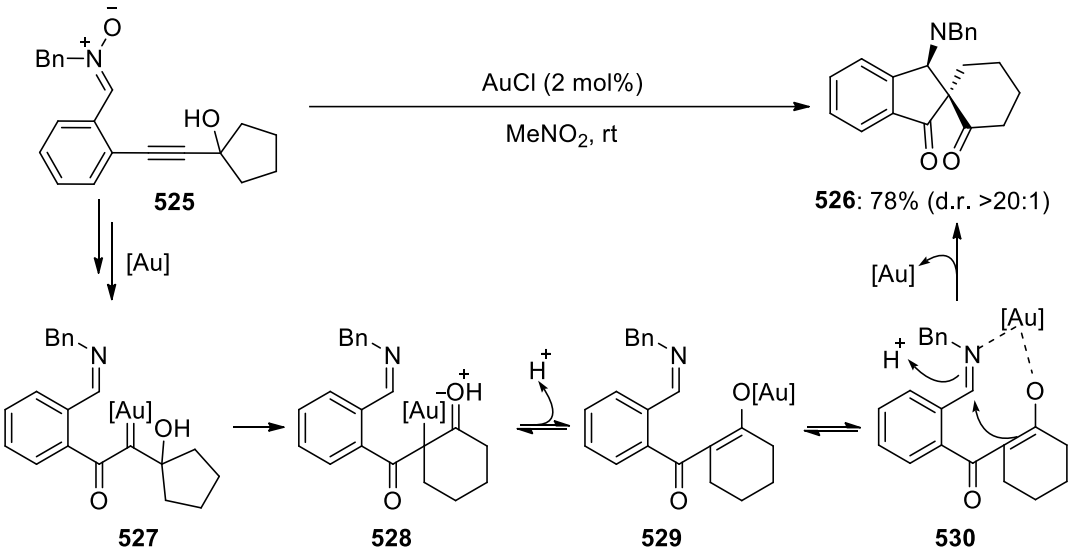
Shin and co-workers reported the use of a nitrone **518** as an internal redox system to assemble complex polycyclic systems **519** (Scheme 76).[128]



Scheme 76: Nitrones as internal redox systems for the construction of polycyclic systems

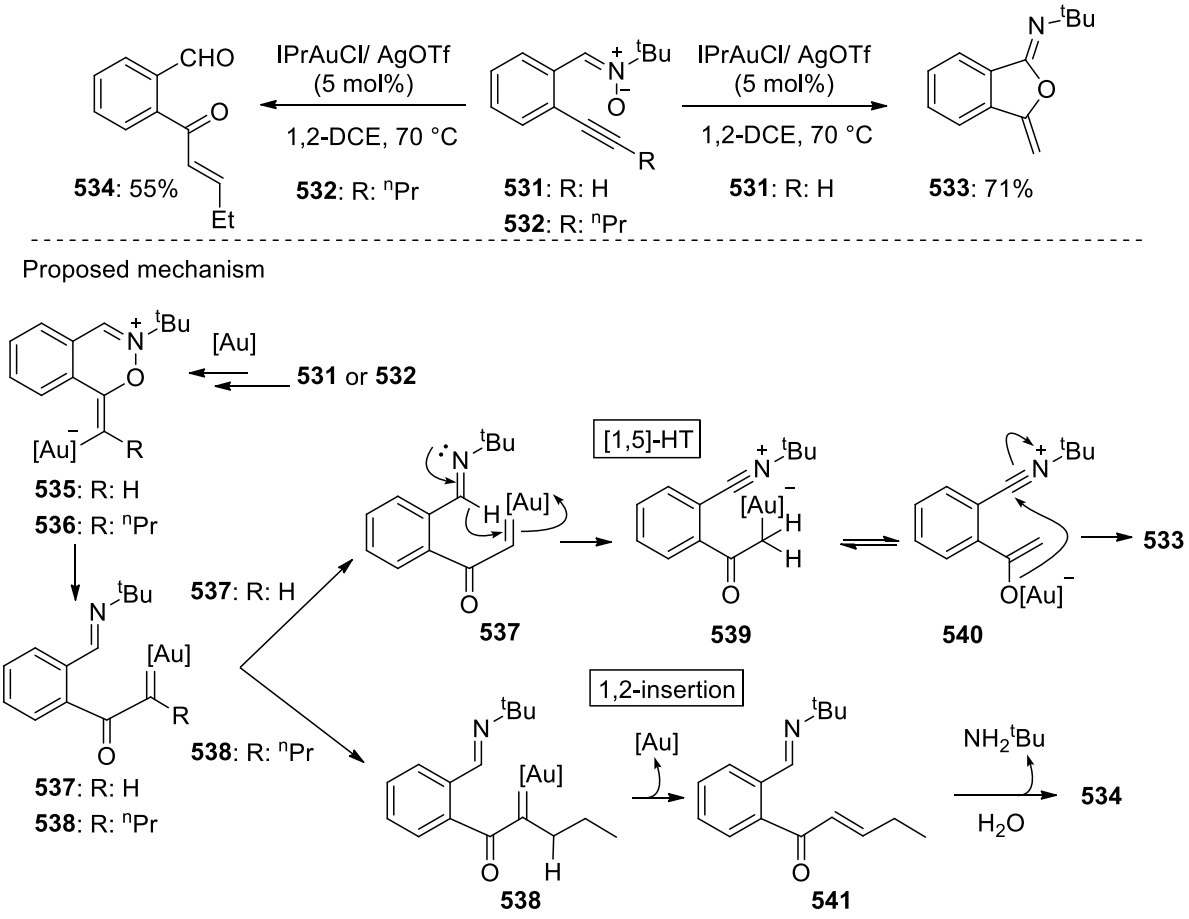
The tethered nitrogen has a dual role acting both as an electrophile and as a nucleophile (**520** and **521** respectively). First nucleophilic attack of the oxidant gives iminium **521** which forms carbene **522**. The imine can then intercept the carbene forming cyclic carbenoid **523** (in equilibrium with **524**) which can then undergo a formal intramolecular [3+2]-cycloaddition with the alkene to construct the azabicyclo[3.2.1]octane **519**.

Shin further expanded this reactivity by trapping the generated α-oxo gold carbene with an 1,2-alkyl shift (Scheme 77).[129] Instead of nucleophilic attack of the imine to the carbene centre **527**, the latter evolves through the formation of a metal enolate **529** after a 1,2-alkyl shift. Coordination of the metal with the nitrogen of the imine and the oxygen enolate (**530**) promotes a diastereoselective Mannich addition that gives spirocycle **526** as a single diastereomer. This redox-ring expansion-Mannich cascade proceeded smoothly at room temperature even with low catalyst loading.



Scheme 77: Redox-ring expansion-Mannich cascade for the formation of spirocycles

Similarly Li and co-workers were able to switch the reactivity and avoid nucleophilic attack by the imine by altering the substituent on nitrogen (Scheme 78).[130]

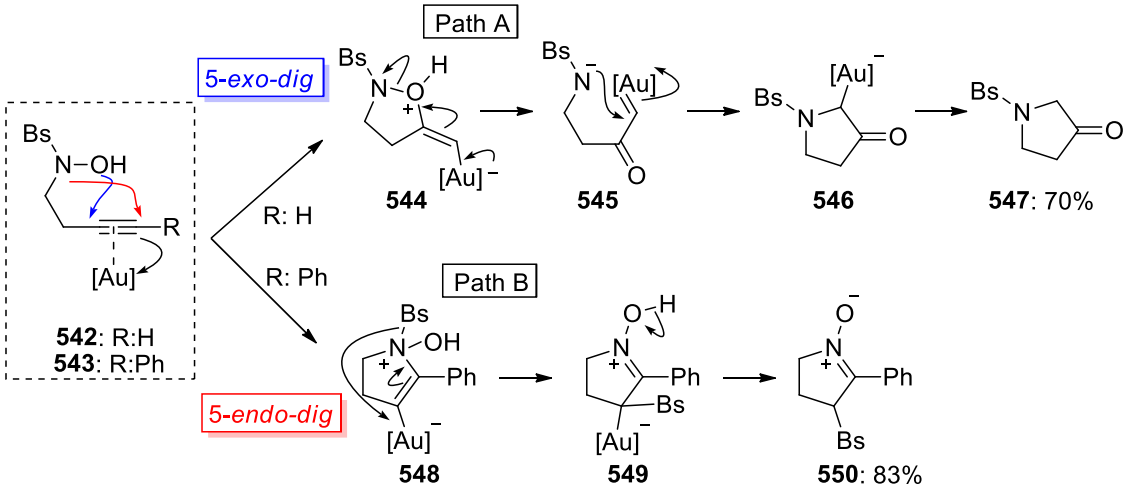


Scheme 78: 1,5-Hydride transfer as an alternative trap of the α-oxo gold carbene

In particular, the electron-donating and bulky *tert*-butyl group on nitrogen (**531**) prevents the imine trapping of the carbene **537** and instead promotes a 1,5-hydride transfer. The resulting nitrilium **539** can isomerise to give the corresponding metal enolate **540**, which cyclises to give imino ester **533**. Interestingly, when internal alkyne **532** was employed under the same conditions the alternative, acyclic product **534** was isolated. This product derived from the corresponding

α-oxo gold carbene **538** which underwent 1,2-insertion from the adjacent alkyl group and demetallation to form enone-imine **541**. Hydrolysis of the imine during the purification gave the final aromatic compound **534**. Notably, nitrones with biaryl substituted alkynes proved completely unreactive.

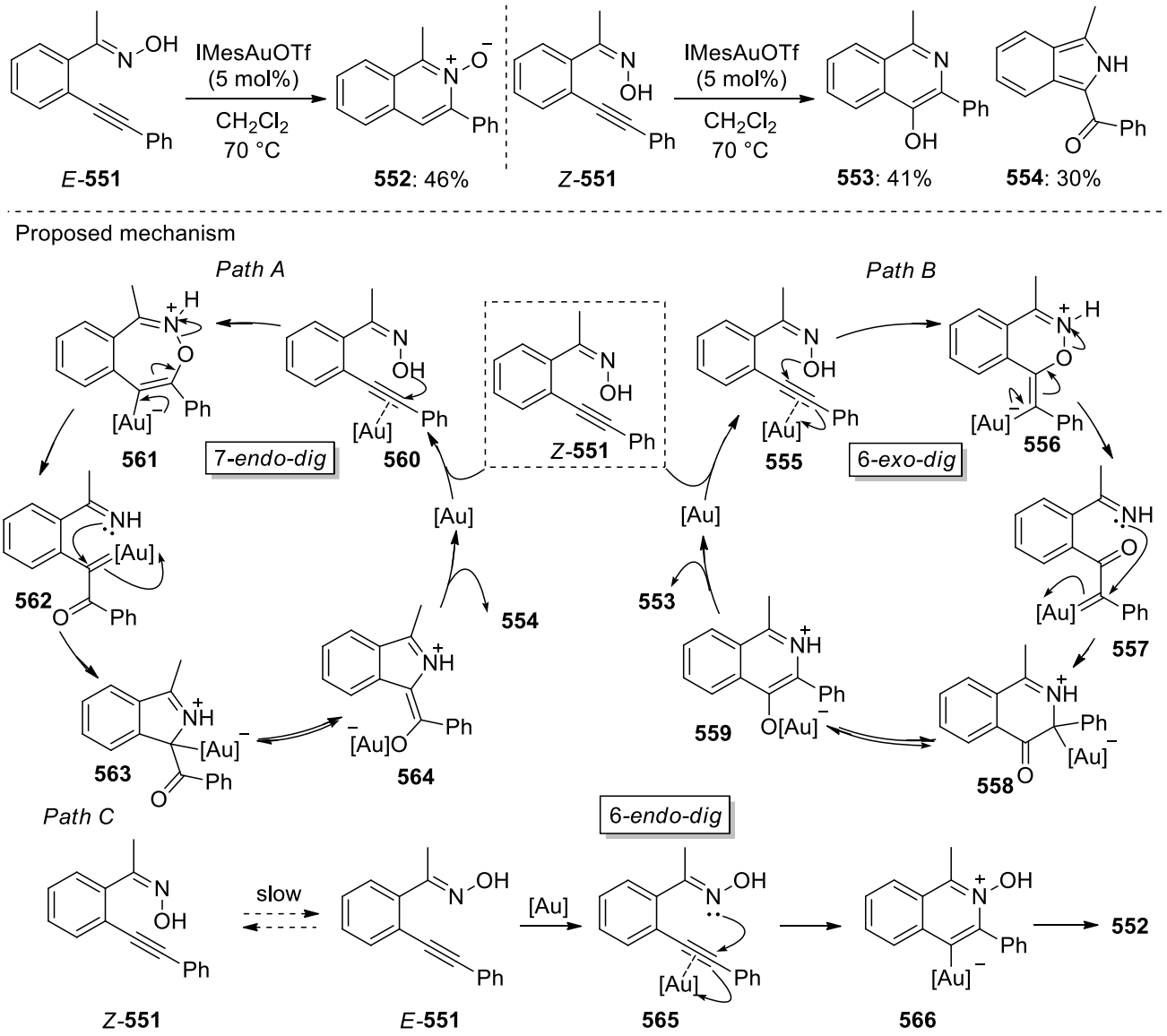
N-Sulfonylhydroxylamines were also employed for the formation of gold carbenes (Scheme 79, Path A).[131] A 5-*exo-dig* cyclisation of oxygen onto the gold-activated terminal alkyne **542** leads to the formation of carbene **545** *via* **544**. Subsequent cyclisation followed by deauration gives 3-pyrrolidinone **547**. A competing reaction is also possible as a 5-*endo-dig* cyclisation from nitrogen generates vinyl gold intermediate **548** which, *via* 1,3-*N*-sulfonyl migration, forms vinyl hydroxylamine **549**. Tautomerisation gives the final nitrone **550** (Path B).



Conditions:
Path A: IPrAuCl/ $AgSbF_6$ (5 mol%), toluene, 60 °C
Path B: (^{t}Bu)$_2$(*o*-biphenyl)PAuCl/ $AgNTf_2$ (5 mol%), MeOH, 60 °C

Scheme 79: Hydroxylamines for the formation of gold carbenes

The lack of regioselectivity of the initial nucleophilic attack was demonstrated when ketoximes were used in the formation of the respective carbenes (Scheme 80).[132]

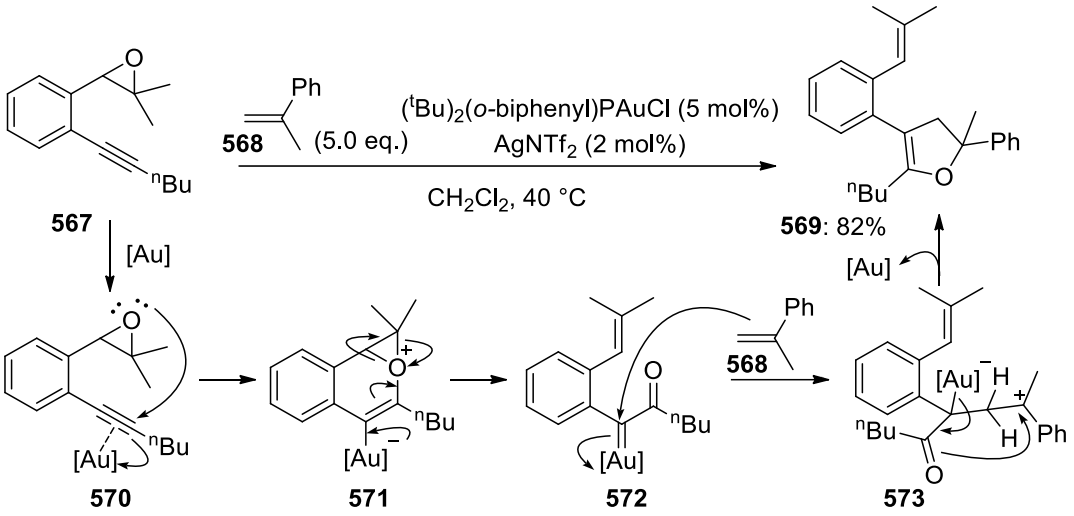


Scheme 80: E- and Z-ketoximes for the formation of gold carbenes

Z-Ketoxime *Z*-**551** can either cyclise *via* a 7-*endo-dig* (Path A) or a 6-*exo-dig* (Path B) pathway, through attack of oxygen to generate the corresponding α-oxo carbenes **562** and **557**. Nucleophilic attack from the imine and protodeauration results in the formation of either

isoindoles **554** or functionalised isoquinolines **553**. Slow isomerisation of the initial oxime to the *E*-isomer gives isoquinoline-*N*-oxide **552** *via* a *6-endo-dig* approach of the nitrogen to the gold-activated alkyne (Path C).

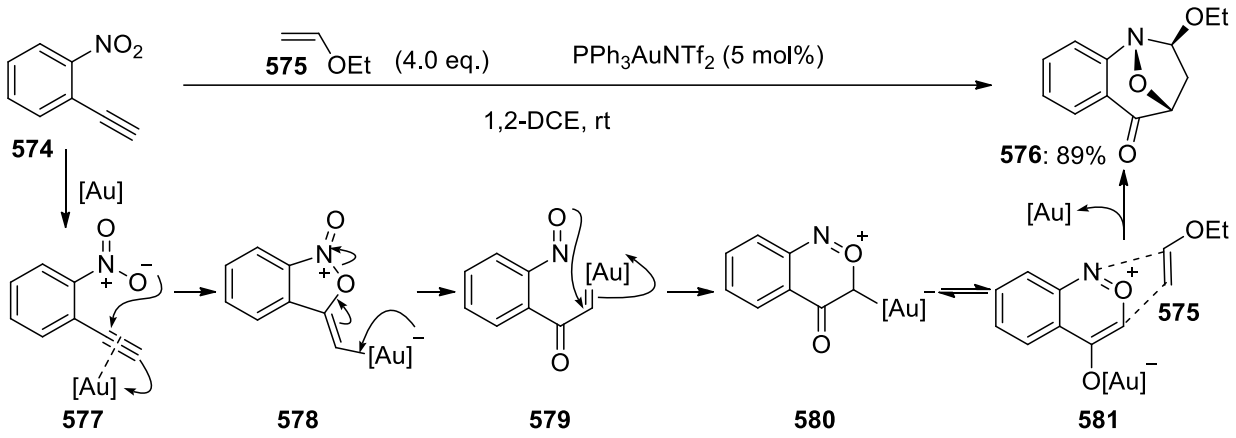
Liu and co-workers reported that epoxides **567** can function as internal redox systems which can lead to α-oxo gold carbenes (Scheme 81).[133] In this case, upon gold-activation of the triple bond, oxygen transfer of the epoxide occurs in a 6-*endo* fashion (**570**), followed by the formation of carbene **572**. The carbene is then trapped intermolecularly by a terminal alkene **568** and 2,3-dihydrofuran **569** is formed following a [3+2]-cycloaddition.



Scheme 81: The intermolecular interception of epoxide-generated gold carbenes

Nitroalkynes **574** combined with enol ethers **575** gave azacyclic compounds **576** as single diastereomers through a redox/[2+2+1]-cycloaddition cascade (Scheme 82).[134] Although the diastereoselectivity observed was not clearly understood, mechanistic studies suggested that the nitro group oxidises the alkyne, generating vinyl gold carbenoid **578**. Upon formation of α-

oxo carbene **579**, nucleophilic attack of the oxygen gives oxonium intermediate **580** which is in equilibrium with the metal enolate **581**. Finally, addition of the enol ether gives the bicyclic system **576**.



Scheme 82: Nitroalkynes for the formation of gold carbenes, followed by intermolecular trapping.

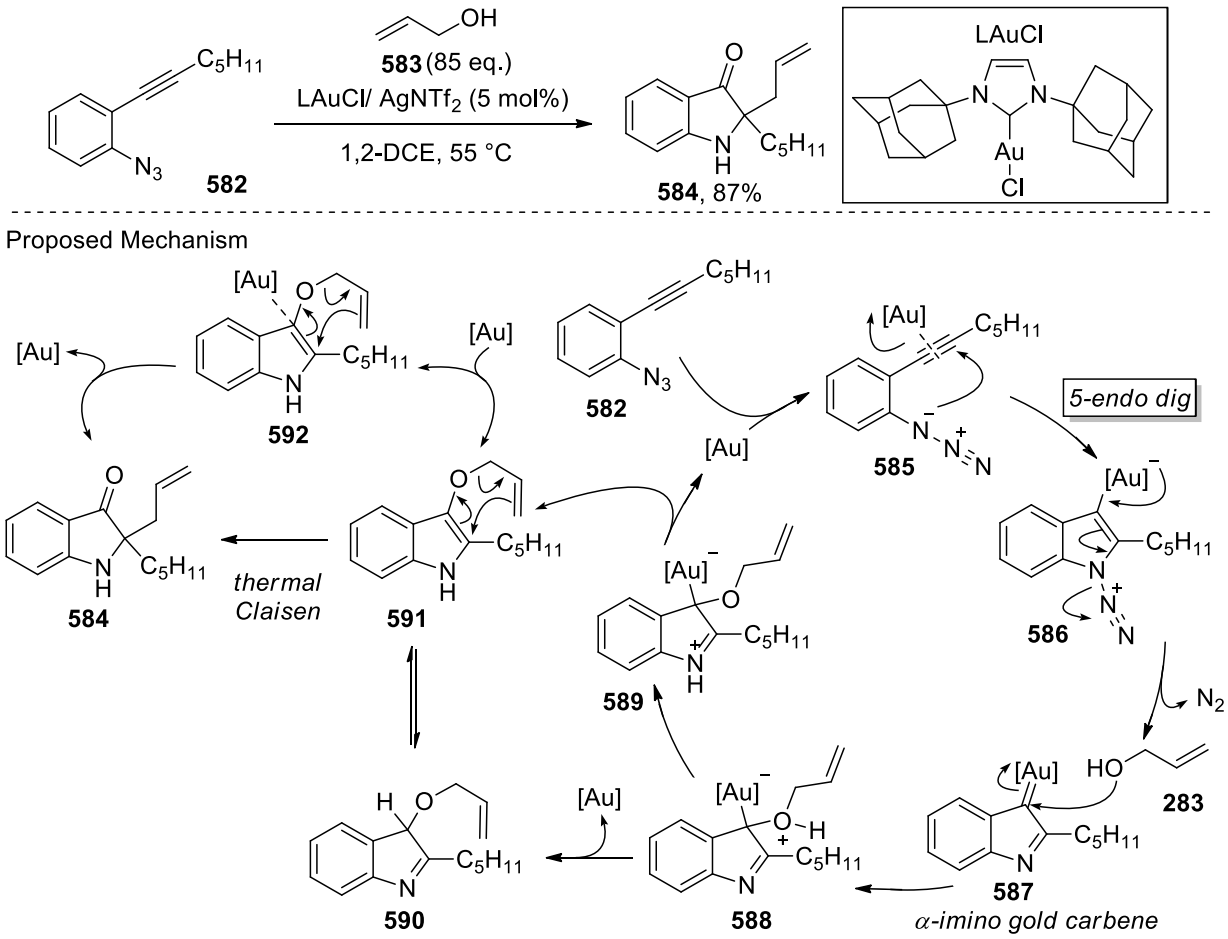
In summary, *N*-oxides, nitrones, hydroxylamines, ketoximes, epoxides and nitro groups can function as internal redox systems generating the reactivity patterns associated with an α-oxo gold carbene *in situ*, which can be captured either intramolecularly or intermolecularly, giving access to a broad range of products.

3.1.2 Intramolecular nitrene transfer

Azides, as nitrene precursors, and gold-activated alkynes can generate α-imino gold carbenes of differing reactivity. These can react further with a range of nucleophiles, which illustrates the applicability and the diverse reaction pathways the gold carbenes may undergo. The Toste,[135]

Zhang[136] and Gagosz[137] research groups have widely explored this reactivity and herein selected examples that have become major contributions to the field are included.

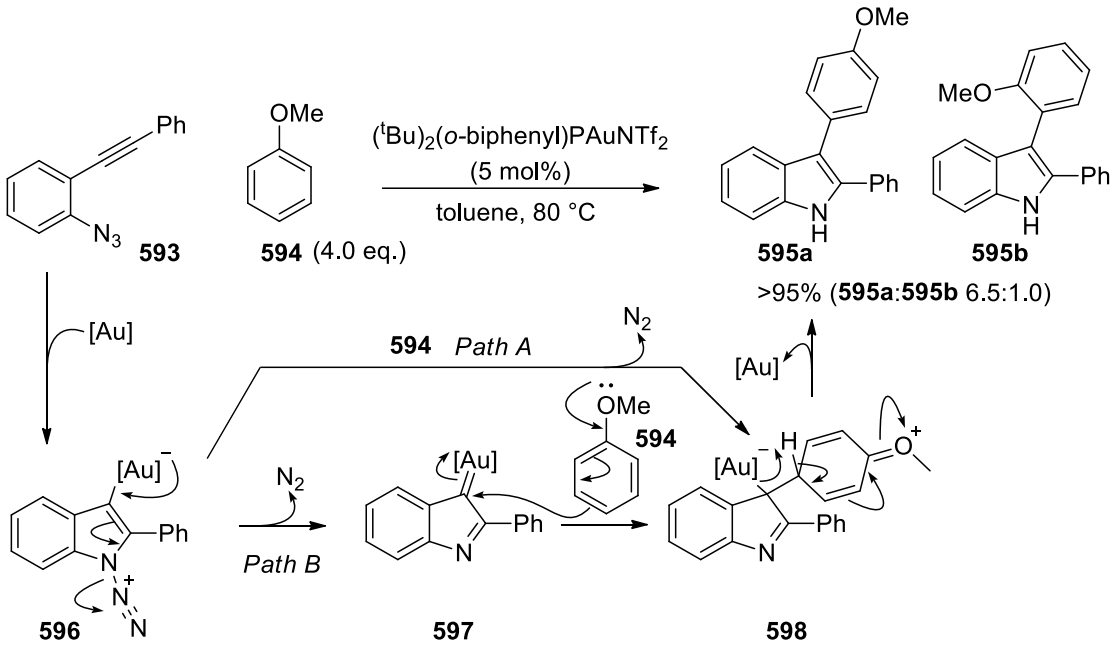
The following two examples demonstrate an exceptional umpolung reactivity of the indoles as the normally nucleophilic 3-position acts as an electrophilic centre. In particular, in 2011, Gagosz and co-workers reported that azides tethered to a π-system **582** can form functionalised indolyl frameworks **584** *via* a cascade sequence (Scheme 83).



Scheme 83: Gagosz's formation of imino gold carbenes and their intermolecular trapping

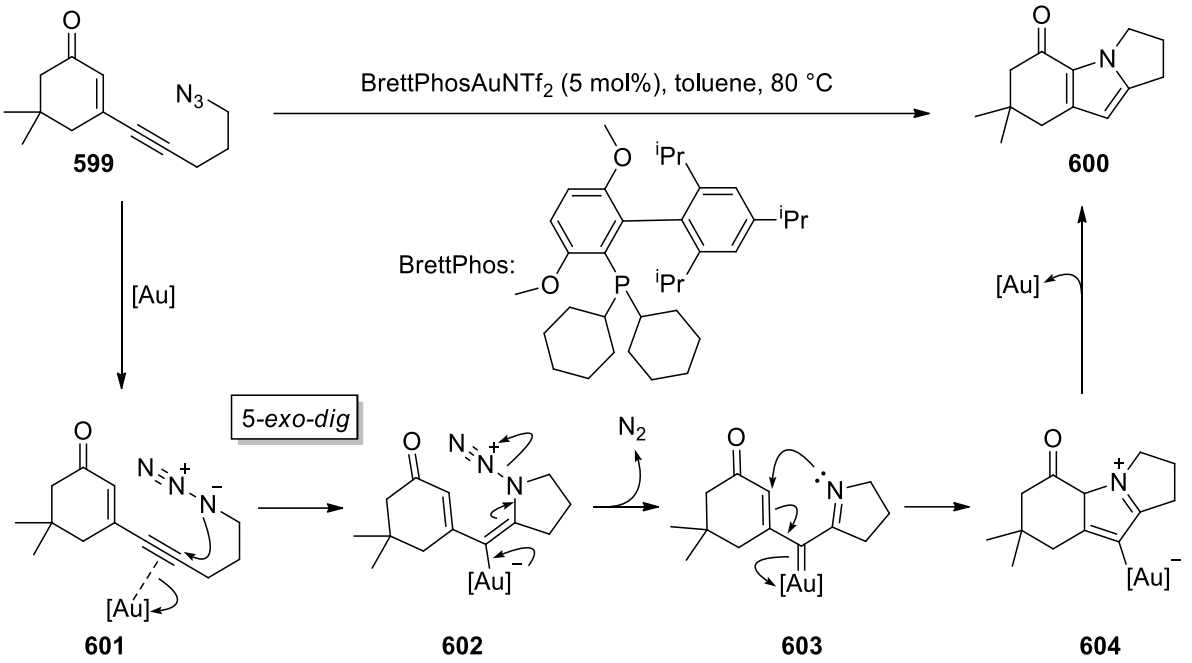
Initial intramolecular nucleophilic attack of the azide towards the gold-activated triple bond in an 5-*endo*-*dig* fashion generates intermediate **586**, which undergoes extrusion of nitrogen to form α-imino carbene **587**. Intermolecular nucleophilic attack of allylic alcohol leads to **588**. Indole **591** can be generated either by iminium **589** through deauration or through a protodemetallation/tautomerisation sequence. Finally, a thermally promoted or gold-catalysed (**592**) Claisen rearrangement gives indole derivative **584**.

A similar approach, where a tethered azide **593** undergoes a 5-*endo*-*dig* cyclisation upon gold activation of the π-system, was followed by the Zhang research group (Scheme 84).[138] In this case the α-imino gold carbene **597** was trapped by intermolecular electrophilic aromatic substitution to form functionalised indoles **595a**/**595b**. Trapping the carbene can either occur in a concerted fashion with simultaneous loss of nitrogen (**596** to **598,** Path A) or stepwise with the prior formation of gold carbene **597** (Path B).



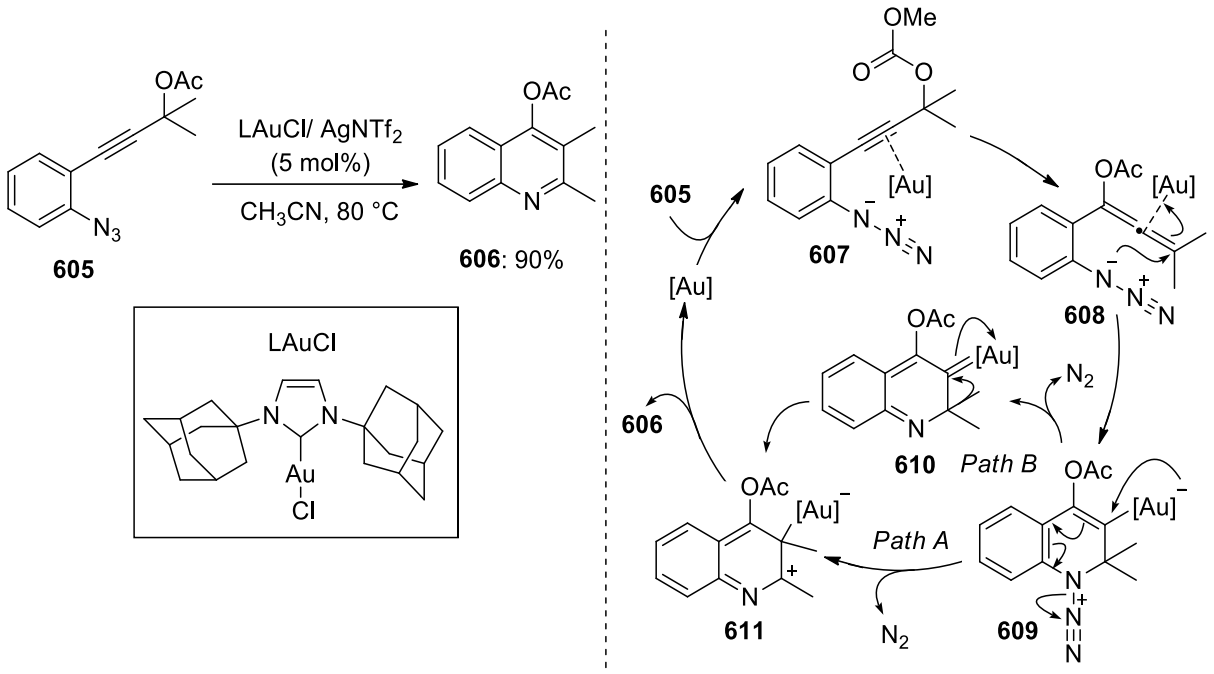
Scheme 84: α-Imino gold carbene trapped by electrophilic aromatic substitution

A year later, Zhang and co-workers reported that a 5-*exo*-*dig* cyclisation by the tethered azide is also feasible when electron withdrawing groups are attached to the triple bond (**599**) (Scheme 85).[139] Electronic bias from these groups minimize the alternative 6-*endo* cyclisation. The generated carbene **603** can undergo a Nazarov 4π-electrocyclic ring closure (**603** to **604**) to give, upon elimination of the metal, 2,3-dihydro-1*H*-pyrrolizines **600** with an electron withdrawing group at the 5-position. These scaffolds display interesting biological activity as they can potentially be used as anti-flammatory drugs and antitumor agents.[140]



Scheme 85: Formation of imino gold carbenes from a 5-*exo*-*dig* cyclisation

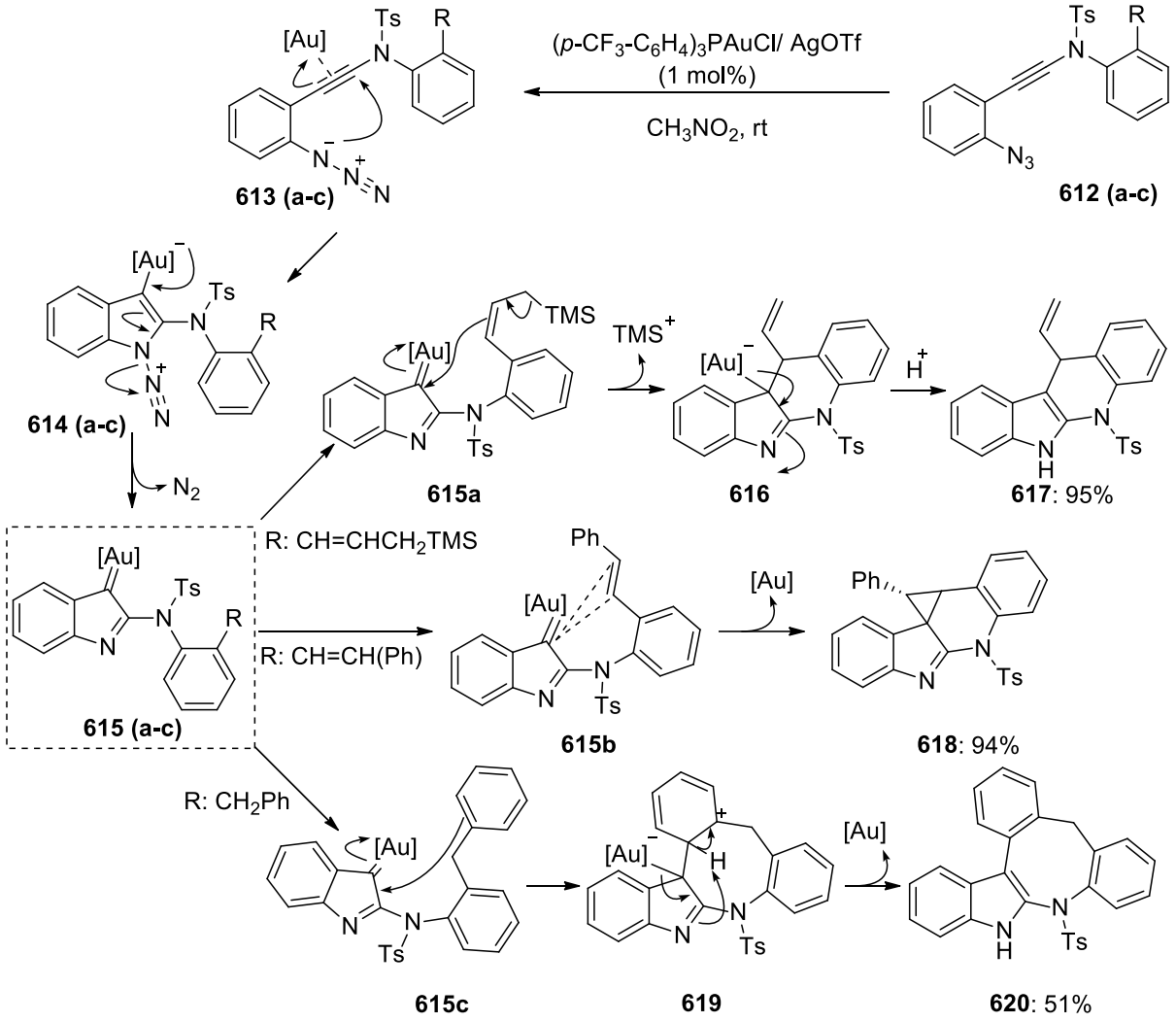
Different reaction pathway was observed when an acyloxy group was attached into the triple bond **605**, leading to the formation of highly functionalised quinolones **606** (Scheme 86).[21c]



Scheme 86: Gold-catalysed formation of quinolones *via* intramolecular nitrene transfer

Upon gold activation of the π-system (**607**), a 3,3-sigmatropic rearrangement takes place furnishing allene **608** followed by nucleophilic attack of the azide. The generated vinyl gold species **609** can undergo an 1,2-alkyl shift with loss of nitrogen (Path A) which gives the quinoline **606** after elimination of gold. An alternative mechanism involving the formation of carbene **610** is also possible (Path B).

More recently, Ohno and co-workers reported the synthesis of indoloquinolines with the use of azidoynamides (Scheme 87).[141]



Scheme 87: Diverse reactivity of α-amidino gold carbenes

α-Amidino gold carbenes **615(a-c)** were generated by azide cyclisation onto the gold activated ynamides. Intramolecular trapping by the group tethered to nitrogen can lead to a range of different products. Ynamide **613a** with an allyl silane tether can undergo intramolecular cyclisation towards the formation of gold intermediate **616** with simultaneous loss of the silyl group, followed by deauration to form quinoline **617**. When an allyl containing ynamide **613b** was employed, cyclopropanation on carbene **615b** takes place which leads to the alternative

quinoline **618**. Finally, ynamides with aryl groups **613c** evolve through electrophilic aromatic substitution to furnish tetracycle **620** after elimination of the metal.

As described in the examples above, intramolecular oxygen and nitrene transfer reactions allow facile access to a wide range of products. Whilst preparation of the starting materials (functionalised sulfoxides, nitrones, azides etc) may be challenging, this can be counterbalanced by the superb reaction control these methods exhibit.

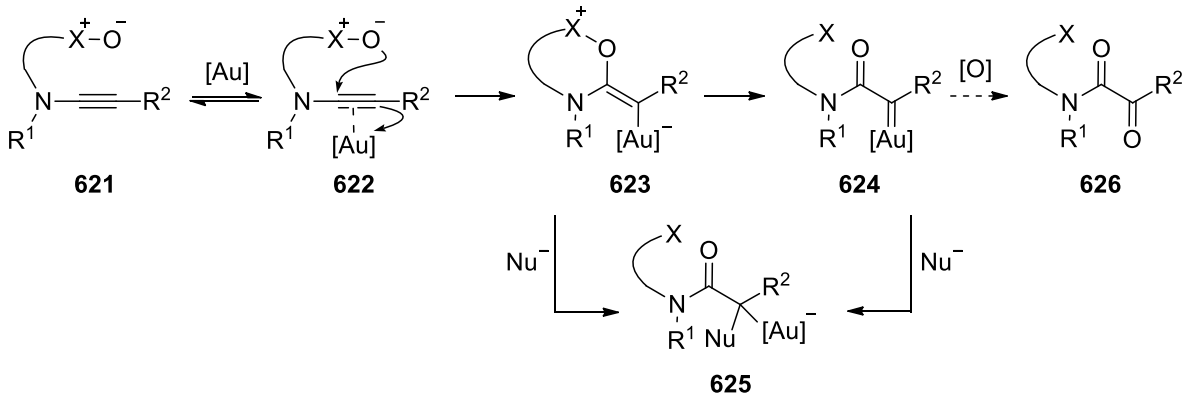
The next section of this chapter will be focused on our attempts to broaden the flexibility of these approaches, using alternative intramolecular gold activated redox and nitrene transfer systems.

3.2 Results and discussion

3.2.1 Target reactivity profile

As mentioned in Chapter 1, one of the main targets of my PhD research has been to develop the reactivity of gold carbenes by exploring novel synthetic routes towards the formation of these reactive intermediates and investigating their subsequent evolution. The development of novel reactive carbene species, derived through the intramolecular rearrangement of gold-activated ynamides was envisaged to address this goal (Scheme 88). In this context, the substrate design was based on ynamides **621** with an oxidant tether which should be capable of regioselective oxygen transfer onto the gold-activated π-system **622** to form vinyl gold intermediate **623**. These highly reactive species should be able either to react directly with nucleophiles giving

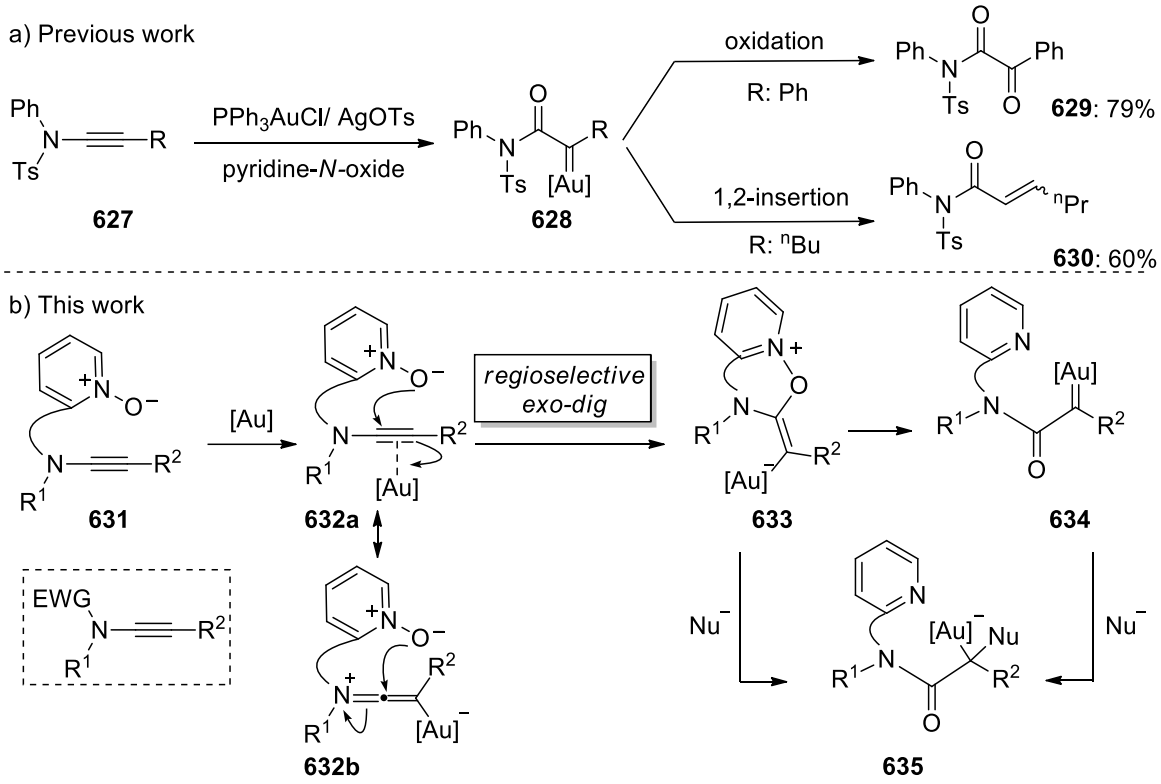
intermediates such as **625** or evolve *via* the formation of an α-oxo gold carbene **624** which can subsequently react with nucleophiles to give the same intermediates **625**.[7]



Scheme 88: General design of alternative carbene precursors

It was hypothesised that such systems would potentially provide many advantages and solve major challenges in the field of the oxidation chemistry, as double oxidation (**624** to **625**) is expected to be largely suppressed, yet still operative. It is crucial that the design and the preparation of these precursors should be carefully planned as several challenges can be involved.

Initially, the appropriate oxidant should be chosen. The tethered oxidant should be nucleophilic enough to readily react with the gold-activated ynamide and deliver the oxygen avoiding undesired pathways from the neighbouring substituents of the ynamide (ie. enynes cycloisomerisation from a tether allyl group[142]). It has been already demonstrated by the Davies group that pyridine-*N*-oxides are excellent oxidants which can be added regioselectively to gold-activated ynamides in an intermolecular fashion (Scheme 89a).[23] For this reason, pyridine-*N*-oxide was chosen as part of the internal redox system (Scheme 89b).

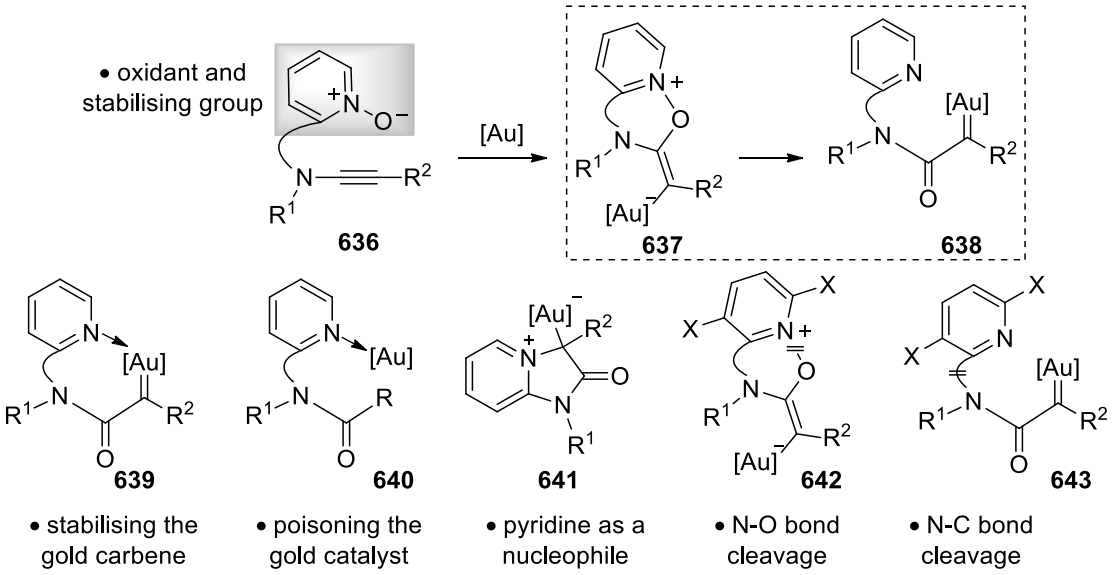


Scheme 89: Gold-catalysed intermolecular and intramolecular oxidation of ynamides

In this design, the pyridine-*N*-oxide would have a dual role acting as both an oxidant delivery system and as a surrogate, replacing the required electron-withdrawing protecting group (usually sulfonyl, acyl or phosphenyl group) which is required to stabilise the ynamide **631** (structure **636**, Scheme 90). Thus additional synthetic steps for the incorporation of a protecting group will not be needed in this case.

The pyridine unit on carbenes **637** and **638** is also prone to interact with the gold (Scheme 90). This interaction can either enhance or harm the reactivity by stabilising the carbene (**639**) or by poisoning the catalyst (**640**). According to a report by Zhang and co-workers, additional

coordination of a nitrogen substituent of a ligand with the gold provides extra stability to the metal while curbing side reactions (please refer to Scheme 30 in Chapter 2).[81, 109-110]



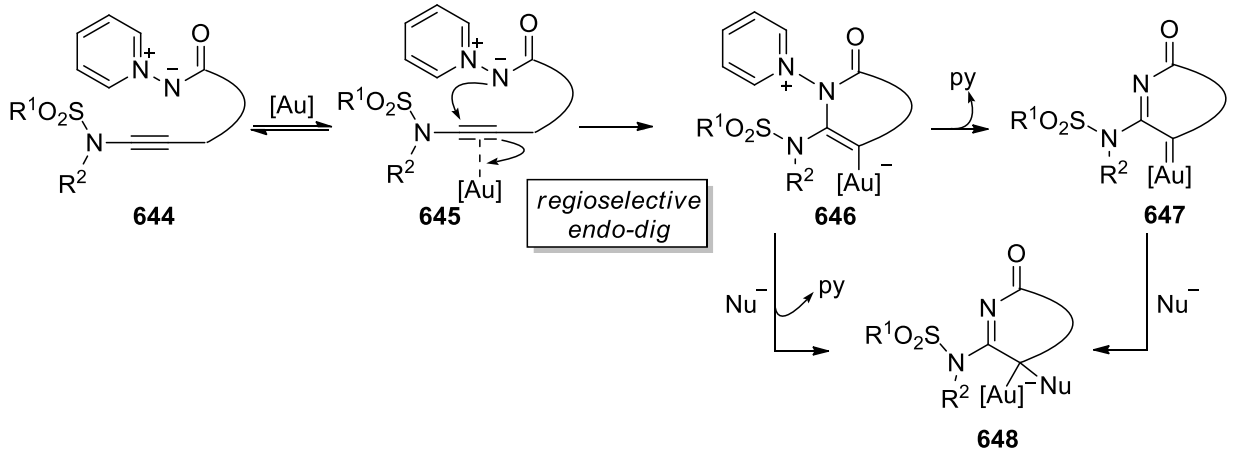
Scheme 90: The role of the pyridine-*N*-oxide and the effect of the pyridine

Finally, the pyridine will potentially play an important role to the subsequent reactivity of intermediates **637** and **638**. The free electron pair of the nitrogen can attack the electrophilic carbene centre to form pyridinium intermediate **641**. Substitution reactions around the pyridine should also be considered especially at the activated 2-position, however this can be avoided by suitable substitution. Substituents around the pyridine ring might influence the reactivity by facilitating or hindering the cleavage of the N-O bond of carbene **637** (intermediate **642**) or the N-C bond of α-oxo gold carbene **638** (intermediate **643**).

It was expected that the geometry of the molecule would also play a crucial role. The system should be flexible enough to allow efficient orbital overlap for initial nucleophilic attack and also for the cleavage of the nucleofuge in the vinyl gold intermediate **637** (cleavage of N-O bond, **637**

to **638**). In fact, the architecture of the vinyl gold intermediate **637** can potentially affect the evolution of the reaction, leading preferentially to α-oxo gold carbene **638** or to intermediate **635** (*vide supra*, Scheme 89).

Moreover, it should be mentioned that the neighbouring groups R^1 and R^2 can be involved in the reaction pathways by stabilising or quenching the gold carbenes. Thus, exceptional consideration should be taken when choosing these groups in order to avoid multiple and uncontrolled reactions (for the evolution of gold carbenes, please refer to Chapter 1). It can be envisaged that the reactivity can also be directed by the incorporation of a chiral group tethered to the ynamide (R^1).



Scheme 91: Gold-catalysed intramolecular nitrene transfer

As well as approaches involving pyridine-*N*-oxide as oxygen delivery systems, further substrate designs were investigated based on related precursors with the triple bond of the ynamide tethered to a nitrene delivery system (Scheme 91). As described in Chapter 2, pyridine-*N*-aminides attack gold-activated ynamides, electron rich indoles or aniline derivatives in a

regioselective manner to form oxazoles.[82, 118] Taking advantage of this reactivity and regioselectivity, it was envisioned that tethered pyridine-*N*-aminides **644** could be used to access vinyl gold intermediates **646** and α-imino gold carbenes **647** in an intramolecular fashion, through a related internal redox process (Scheme 91). In analogy to oxygen transfer systems, these highly electrophilic species can undergo nucleophilic attack leading to intermediate **648.** The possible pathways involve loss of the pyridine as a good leaving group through the formation of either the α-imino gold carbene **647** or the intermediate **648** from the vinyl gold species.

Similar challenges, as the previous substrates, can be considered in this case as well, with the pyridine potentially affecting the reactivity and the geometry of the systems playing an important role on the initial nitrene transfer and the subsequent evolution of intermediates **646** and **647**.

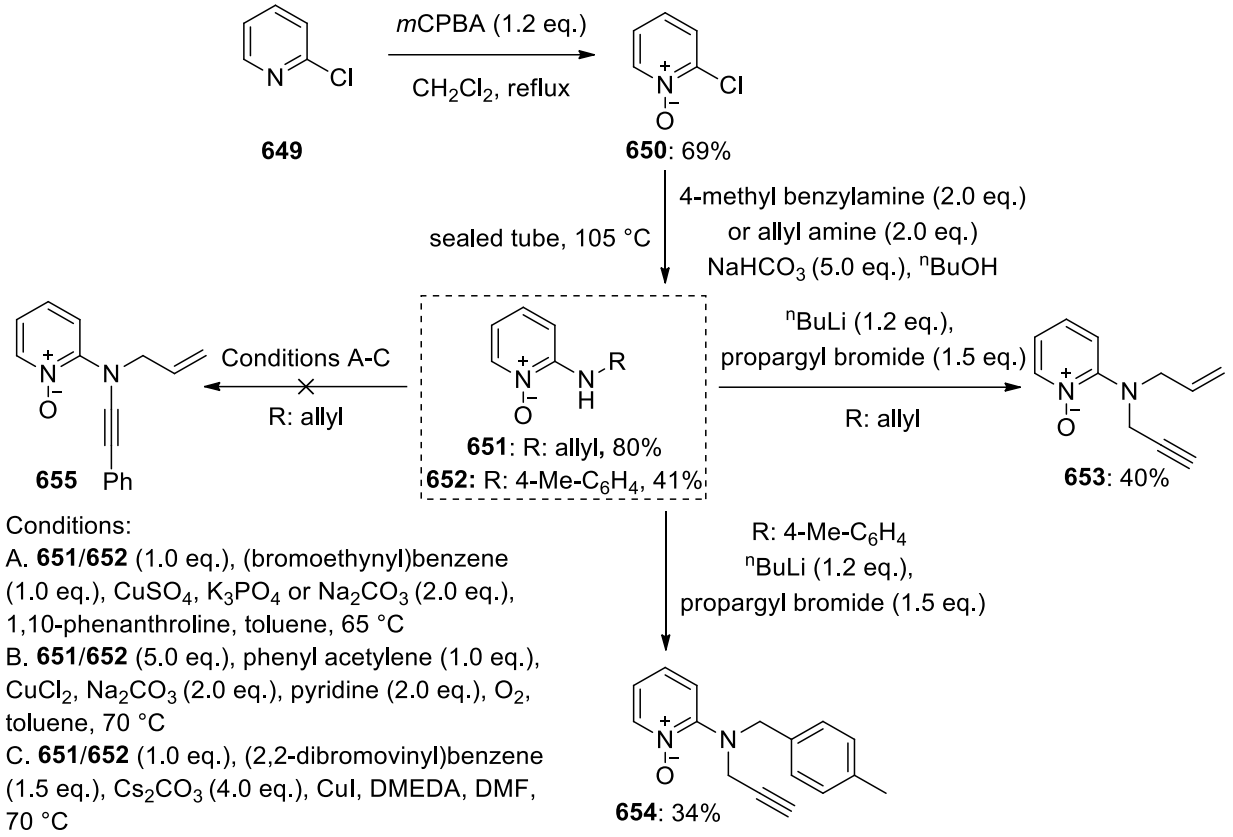
The preparation of these challenging substrates will be discussed in the next sections.

3.2.2 Pyridine-*N*-oxides as internal redox systems

3.2.2.1 Preparation of starting materials

Ideally, the preparation of ynamide systems with a pyridine-*N*-oxide tether should be based on general methodologies, compatible with different substrate variations. These methods should be elegant, avoiding multiple steps while exhibiting functional group tolerance. It was hypothesised that the pyridine-*N*-oxide might function as an ynamide stabilising group, so no additional steps will be needed for the installation of a sulfonyl protecting group.

Initially, the previously reported copper-catalysed methods for the formation of ynamides were employed (Scheme 92).[20a, 143] However, based on the above discussion, it was anticipated that the pyridine (or the pyridine-*N*-oxide) is likely to participate in unwanted intramolecular side reactivity especially in the presence of metals.



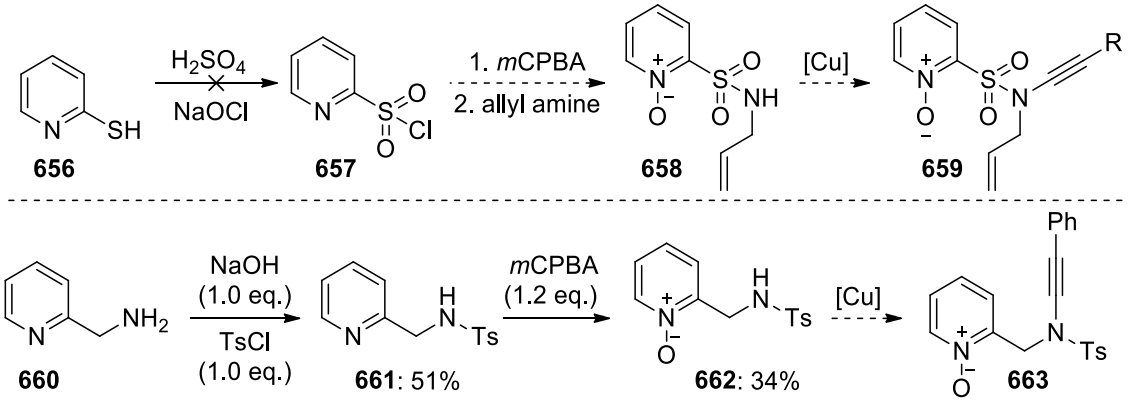
Scheme 92: Synthesis of internal redox starting materials

It was thought that established methods for the copper catalysed coupling between sulfonamides and terminal alkynes,[20a] bromoalkynes[143a] or dibromo olefins[143b] might be compatible when 2-amino-pyridine-*N*-oxides **651** and **652** were employed instead of sulfonamides (Scheme 92).

2-(Allylamino)pyridine *N*-oxide **651** was successfully prepared in two steps, however copper-catalysed coupling with alkynyl or alkenyl partners to form ynamide **655** was unsuccessful (Conditions A-C), leading to complicated mixtures. Whilst several other methods for the formation of ynamides were tested; no traces of the desired product was observed with complex mixtures obtained.

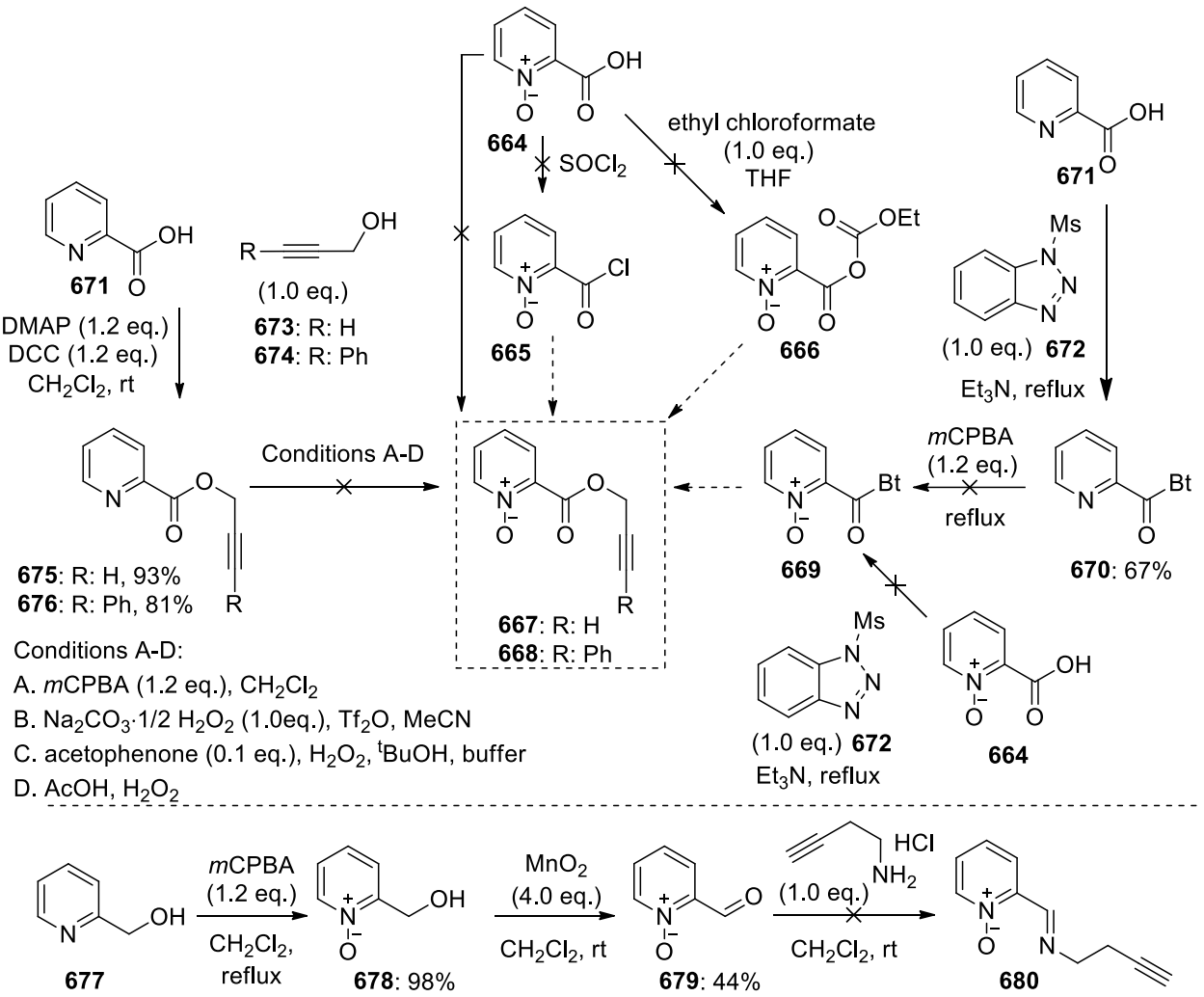
In light of these initial results, an alternative substrate **653**, with a one carbon spacer between the nitrogen and the triple bond was prepared in moderate yield following treatment of **651** with a lithium base and propargyl bromide. A modified analogue **654** bearing a 4-methyl benzyl group was also synthesised *via* the same reaction sequence.

The problems encountered during the synthesis of the starting precursor **655** might be derived from their instability under the reaction conditions. The initial hypothesis that the pyridine-*N*-oxide provides the same stabilising effect as a sulfonyl (or relevant) protecting group appears unsuitable for these substrates. In order to examine the issue of stability and test this hypothesis, the syntheses of ynamides **659** and **663** containing both a sulfonyl group and a pyridine *N*-oxide were attempted (Scheme 93).



Scheme 93: Preparation of sulfonyl-containing ynamides as internal redox substrates

Several attempts to oxidize 2-mercapto pyridine **656** proved unsuccessful with no product observed, despite the literature precedent.[144] Disappointingly, tosylated pyridine-*N*-oxide derivative **662**, which was prepared in two steps, did not undergo the desired copper-catalysed ynamide formation, with a complex mixture being obtained. These results indicate that the pyridine-*N*-oxide moiety may be incompatible with the coper-catalysed ynamide formation and so studies were directed towards simpler alkenyl systems.



Scheme 94: Challenging preparation of internal redox systems containing pyridine-*N*-oxide

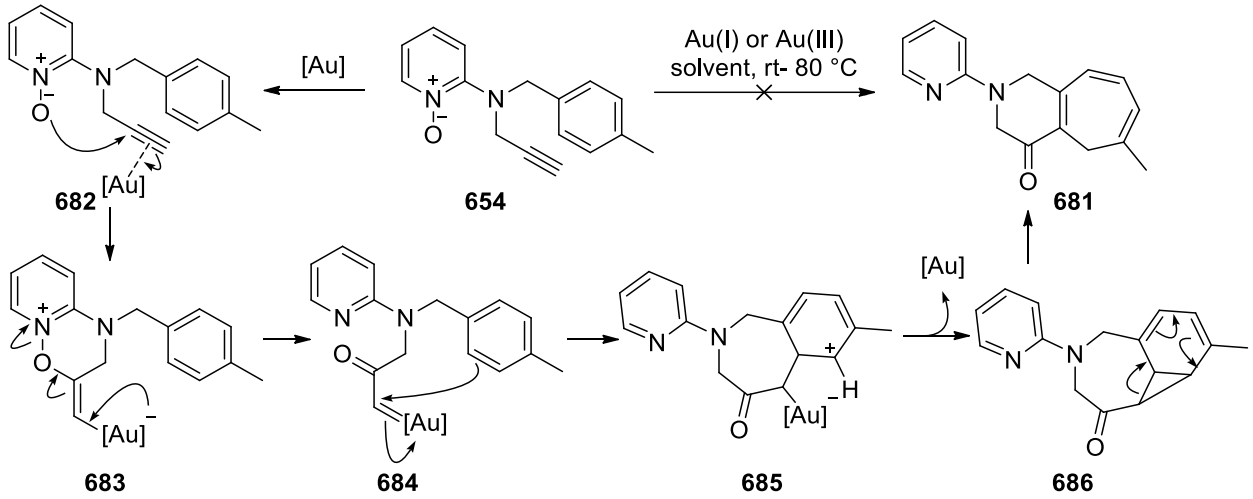
Despite forming esters **675** and **676** in excellent yields, subsequent oxidation under various conditions failed to give the desired *N*-oxides **667** and **668,** with only unreacted starting materials remaining in each case (Scheme 94). In an alternative approach with an *N*-oxide pre-installed, efforts were made to form **667** or **668** from direct esterification of picolinic acid *N*-oxide **664**, acid chloride **665**, benzotriazole derivative **669** and mixed anhydride **666**, however none were successful. Similar results were obtained when aldehyde **679** was employed for the formation of imine **680**. Complicated mixtures and degradation to a great extent was observed in all of the above cases.

In conclusion, a novel design for alternative π-systems with a tethered pyridine-*N*-oxide was investigated. The preparation of these precursors was attempted based on pre-existing methods, however they exhibited substantial limitations and did not prove compatible. New approaches, with greater compatibility have to be investigated in order to restrain the uncontrolled side reactions of these internal atom transfer systems.

3.2.2.2 Pyridine-*N*-oxides as internal redox systems under gold-catalysis

Substrates **654** and **653** were then subjected to gold catalysis. It was expected that, upon treatment with a gold catalyst, **654** would undergo a 6-*exo*-*dig* cyclisation onto the triple bond to form vinyl gold carbenoid **683** (Scheme 95). π-Back donation from the metal would lead to α-oxo gold carbene **684** which could be trapped though electrophilic aromatic substitution by the neighbouring benzyl group, giving intermediate **685**. Protodeauration followed by ring

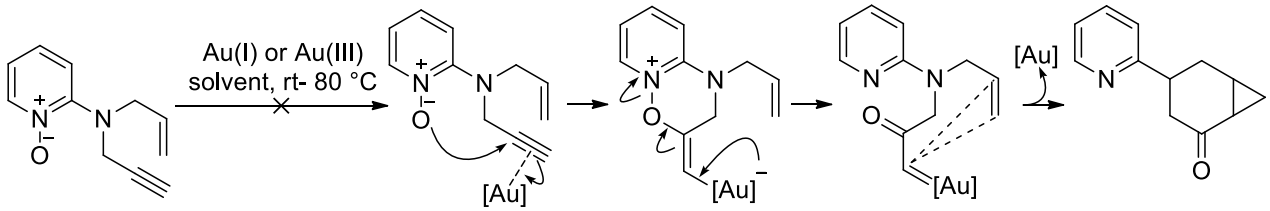
expansion would give the fused ring system **681**. Trapping the α-oxo gold carbene intramolecularly with 4-methylbenzyl group has previously developed by other members of the Davies group, giving the corresponding annulated products.



Scheme 95: Proposed formation of pyridine adduct 681 under gold catalysis

Regardless of the conditions employed, complicated mixtures were formed. Gold(III) and gold(I) precatalysts were tested in different solvents and at varied temperatures, however the same outcome was observed, indicating the high and uncontrollable reactivity of these substrates.

The analogous *N*-allyl substituted system **653** was expected to undergo intramolecular cyclopropanation following formation of the related α-oxo gold carbene **689**, to form the pyridine adduct **690** (Scheme 96).



Scheme 96: Proposed formation of pyridine adduct 690 under gold catalysis

Unluckily, on exposure of **653** to gold catalysts, complicated mixtures were observed in every case, regardless of the conditions used. Several trials to purify the crude samples and identify the major product formed were unsuccessful due to the complexity of the mixtures. Based on the discussion in the previous section, it is likely that the pyridine is involved in side reactions with the α-oxo gold carbene (*vide supra*, Scheme 90, intermediate **641**). The allyl group can also lead to side reactions prior to the attack of the oxidant.[142]

This side reactivity could not be removed by altering the conditions used in the catalysis.

3.2.3 Pyridine-*N*-aminides as intramolecular nitrene delivery systems

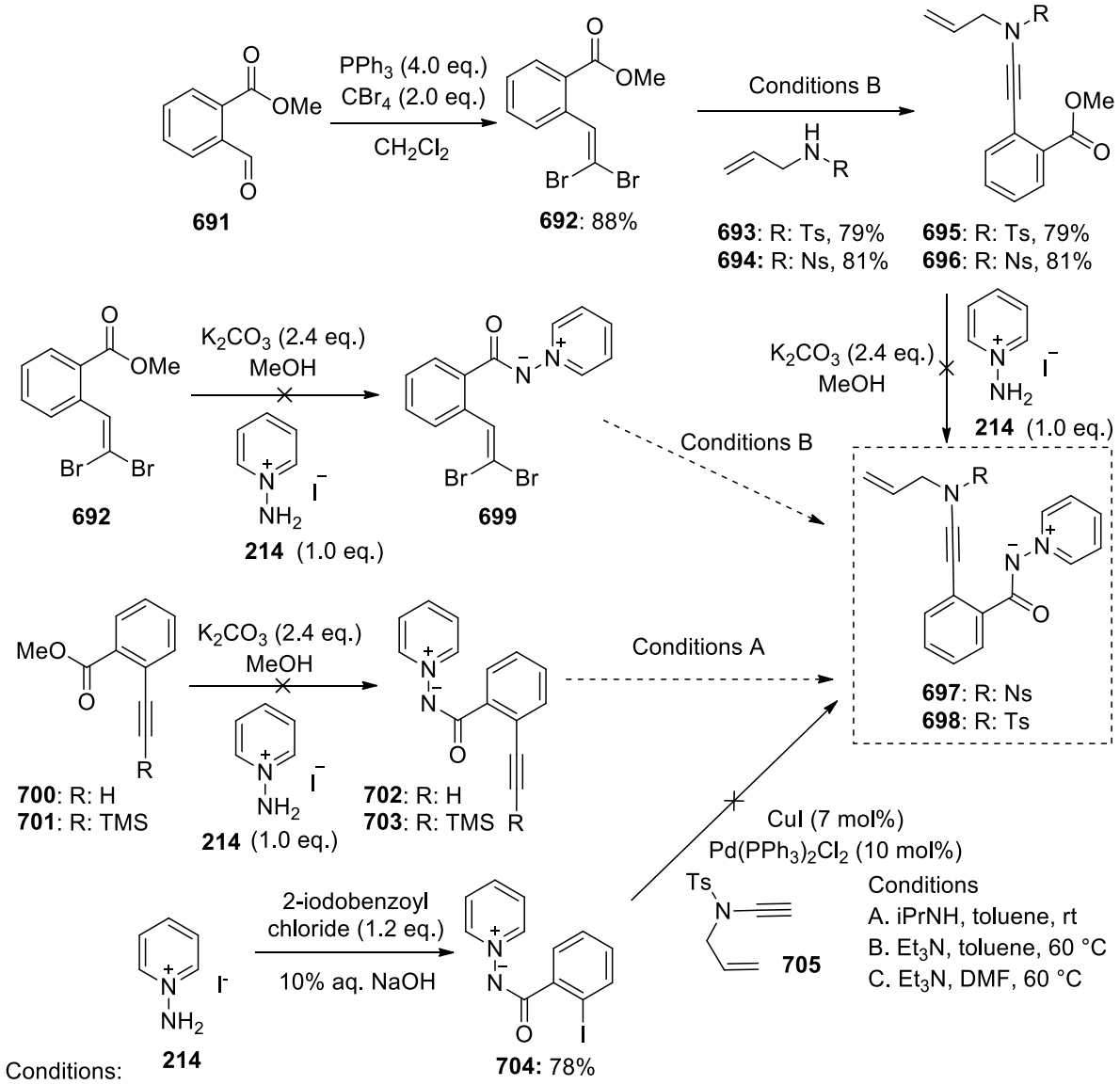
3.2.3.1 Preparation of starting materials

In analogy with the previously described precursors, the synthesis of ynamides bearing a nitrene delivery system was attempted.

In the previous chapter it was described that pyridine-*N*-aminides can be formed when *N*-aminopyridinium iodide and an acid chloride are combined under basic conditions (*vide supra*,

Scheme 46). It was proposed that ynamides with a tethered pyridine-*N*-aminide could potentially be accessed by this method, however there are no reports in the literature about compatibility of ynamides and acid chlorides. On the other side, esters instead of acid chlorides can also be used to form the ylides under the same conditions. As such, an ester group was incorporated into the ynamides **695** and **696** which were prepared using sulfonamides **693** and **694** and dibromo olefin **692**, using the standard copper-catalysed conditions (Scheme 97).[143a] Nosyl protected ynamide **696** proved unstable at room temperature and when it was subjected to the conditions for ylide formation, only degradation occurred. A similar outcome was observed when ynamide **695** substituted with a more robust tosyl group was employed; the pyridine-*N*-aminide was not formed. Later, a member of the Davies group (Andrew Gillie) discovered that electron-rich systems (such as 2-furan or 3-indole derivatives) with a conjugated ester tend to react poorly under the basic conditions to furnish the corresponding ylides.

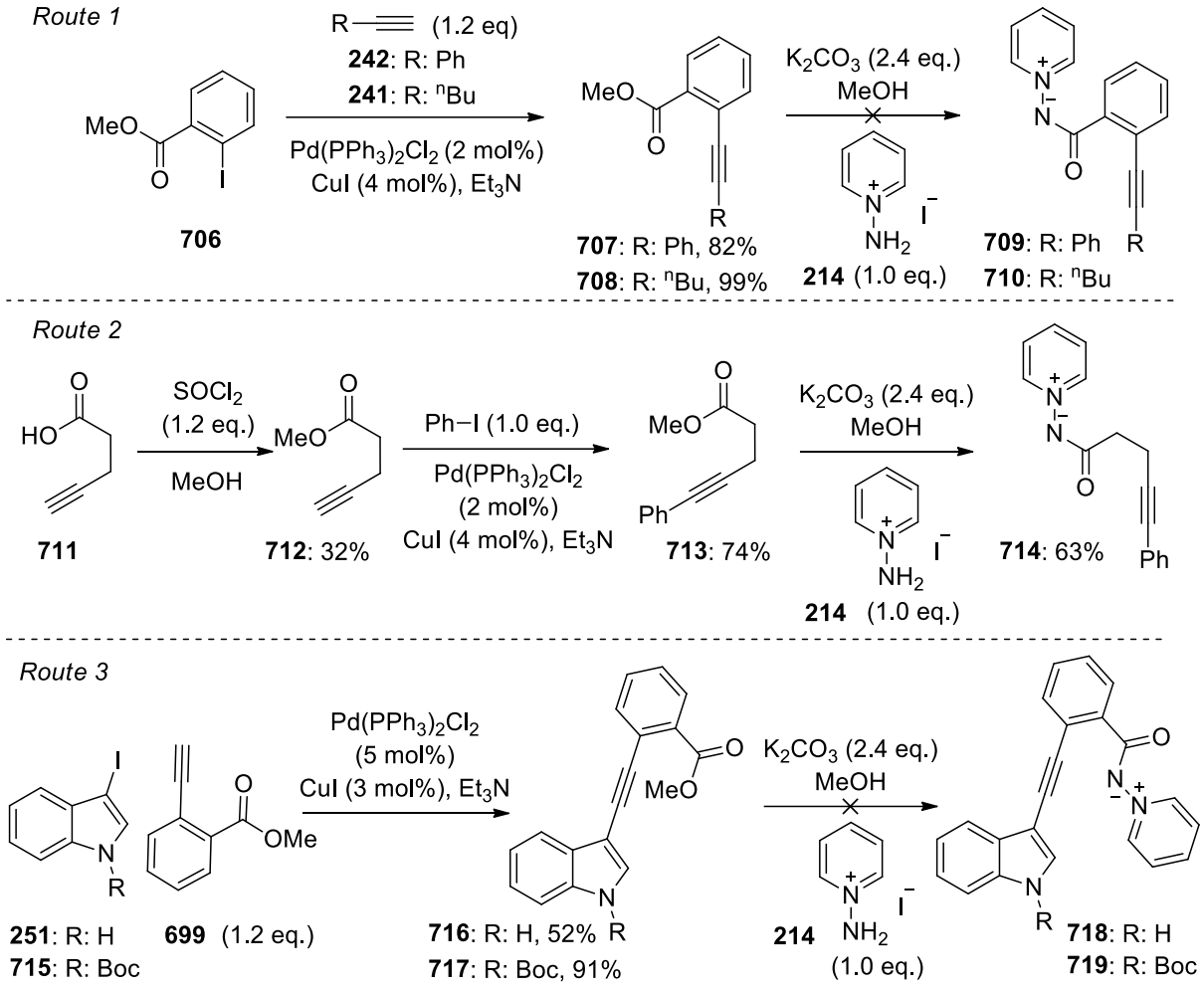
An alternative route was then envisioned, using preformed ylides to couple with a sulfonamide under copper catalysis. However, ylides with a dibromo olefin functionality **699**, terminal alkyne **702** or silyl protected alkyne **703** could not be formed, with extensive degradation observed in every case. Similarly, the Sonogashira coupling between aminide **704** and terminal ynamide **705** was unsuccessful, leading to rapid degradation even at room temperature.[145]



Scheme 97: Initial attempts to form ynamides with an internal nitrene delivery system

While the same trend was observed when esters **707** and **708** were employed for the formation of ylides **709** and **710** respectively (Route 1, Scheme 98), aminide **714** was synthesised in good

yield from ester **713** (Route 2). Finally, when unprotected **716** or Boc-protected **717** indole derivatives were taken into the ylide formation reaction to give **718** and **719**, no products were formed, with starting material remained in both cases (Route 3).

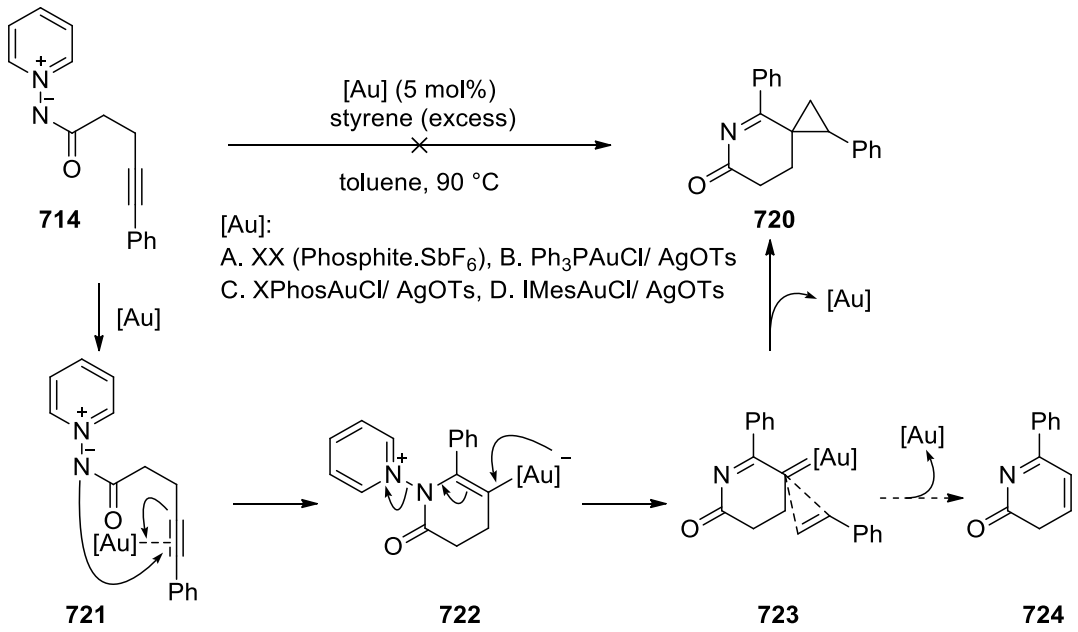


Scheme 98: Other substrates as intramolecular nitrene delivery sytems

The preparation of alternative compounds with pyridine-*N*-aminides tethered to either ynamides or π-systems is not straightforward. Alternative approaches, compatible with electron-rich systems and ynamides, should be developed for the formation of these synthetically useful compounds.

3.2.3.2 Pyridine-*N*-aminides under gold catalysis

The reactivity of aminide **714**, in the presence of a gold catalyst was then examined (Scheme 99). In analogy with the reported literature concerning intramolecular nitrene transfer, a 6-*endo-dig* cyclisation would be expected initiated by nucleophilic attack onto the triple bond forming vinyl gold carbenoid **722**. Back donation of electron density from the metal results in the elimination of pyridine and the formation of carbene **723** which could be trapped intermolecularly by an external nucleophile such as styrene to form imine **720**. Alternative trapping of the carbene by 1,2-insertion also appears possible, which would lead to hydropyridine derivative **724**.



Scheme 99: Pyridine-*N*-aminide 714 under gold-catalysed conditions.

The starting precursor **714** was insoluble in most solvents, such that solubility was only possible in toluene at high temperature. **714** reacted very slowly, under several different catalytic

conditions, with complex mixtures being formed in every case. The high polarity of the main products did not allow their isolation regardless the eluent of the purification used.

3.3 Summary

A new design of substrates incorporating an electron-rich π-system and a tethered oxidant or a nitrene delivery system was investigated. Several strategies towards the formation of these systems were proposed and the exhibiting limitations were identified. Based on the difficulties encountered above it can be concluded that the syntheses of these internal redox or nitrene transfer systems are highly challenging and not straightforward. New synthetic methods for the ynamide formation have to be developed in order to address any side reactivity; modifying the design of these precursors might be essential.

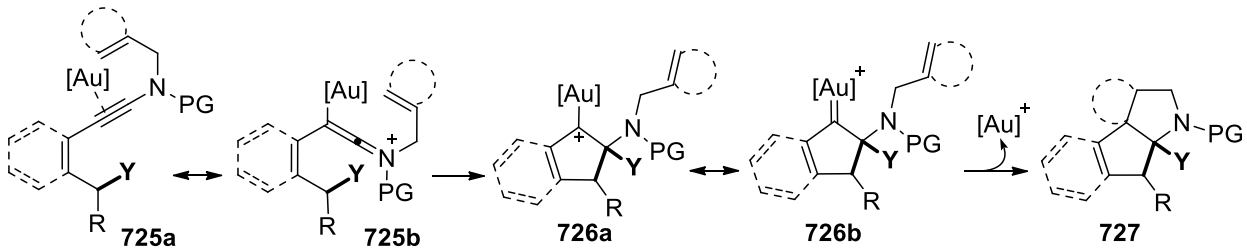
4. Chapter 4:

Gold-catalysed [1,5]-hydride transfer/cyclisation cascade of *N*-allyl ynamides

4.1 Introduction

As depicted in the previous chapters, the use of π-acids to access carbene reactivity has been an area of intense interest within contemporary organic synthesis, as it provides elegant and efficient routes to product complexity.[1e],[146],[147] In particular these advantageous synthetic tools have been successfully applied to late stage transformations in the syntheses of complex natural products, even in the presence of sensitive functional groups.[148],[149]

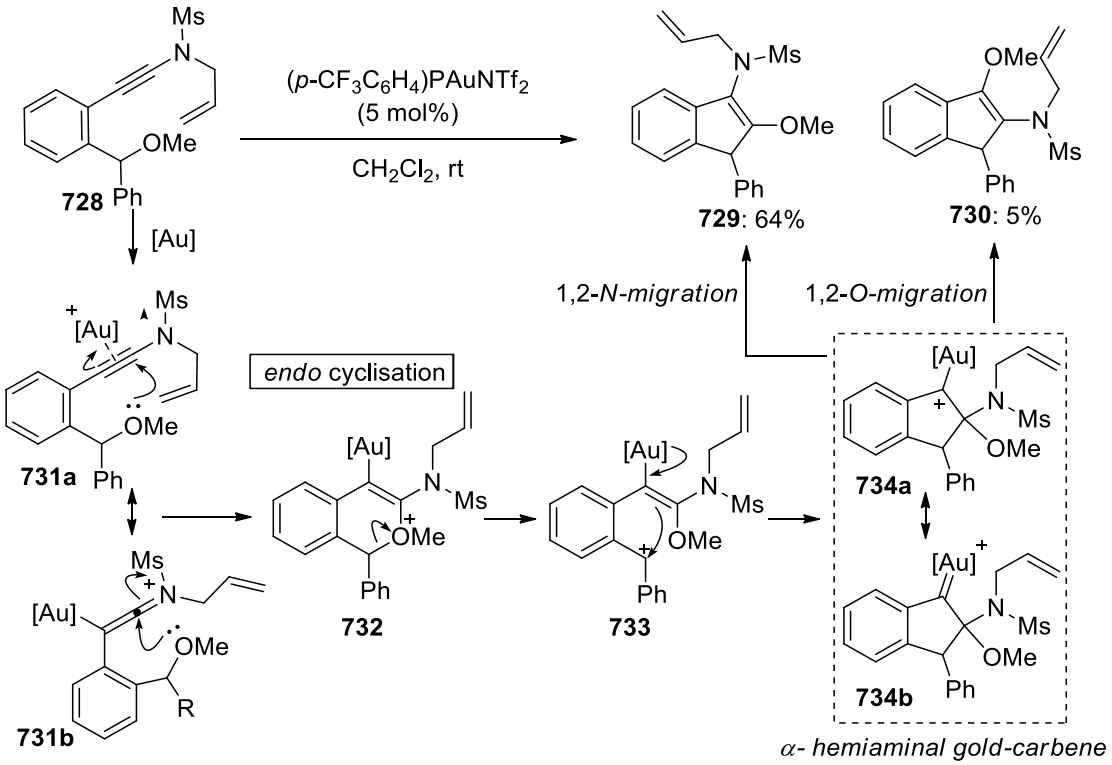
During a programme on exploring new avenues for the generation and use of gold carbenes with ynamides, a design based on regioselective intramolecular cyclisation at an activated sp^3 centre to carbene **726a**/**726b** was proposed (Scheme 100). The carbene can then be trapped by the substituent tethered to the ynamide. During this process group Y is transferred from an *ortho* or pseudo-*ortho* Csp^3 on the α-carbon attached to the ynamide followed the cascade cyclisation to give fused polycyclic ring systems **727**.



Scheme 100: Carbocyclisation strategies towards the formation of gold carbenes

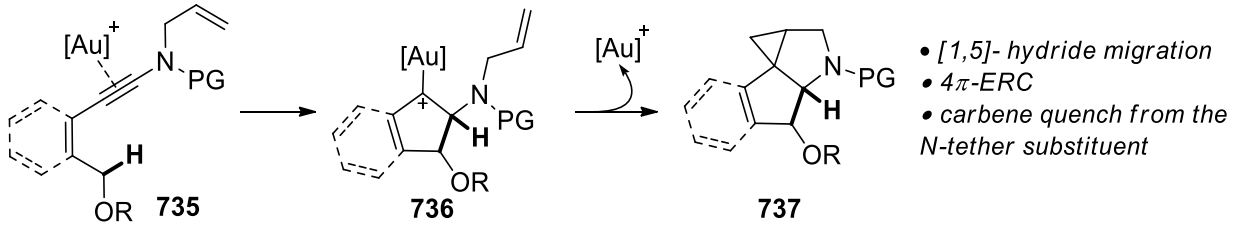
This carbocyclisation concept would provide access to novel molecular architectures, as the ynamide can represent a number of competing pathways. Thus reagent and substrate control should be established to provide selective access to divergent products.

In this context the Davies group recently reported an ynamide 1,1-carboalkoxylation strategy for the generation of unique gold carbenes adjacent to hemi-aminal ether moieties (Scheme 101).[21d] The proposed mechanism is initiated by regioselective *endo* oxygen attack to the gold activated π-system **731a**/**731b**, giving the vinyl carbenoid **732**. Subsequent fragmentation is followed by formation of gold carbene **734a**/**734b**. Cascade cyclisation does not take place in this case, carbene **734a**/**734b** instead evolves through either 1,2-*N*- or *O*-migration to form isomeric indenes **729** and **730**. Importantly, nitrogen migration is favoured over oxygen migration due to developing steric hindrance which involves the formation of indene **730**.



Scheme 101: 1,1-Carboalkoxylation followed mainly by 1,2-*N*-migration

A member of the Davies group (Holly Adcock) discovered that different pathways could be favoured by tuning the catalytic conditions which led to different products (Scheme 102). In particular an alternative hydride insertion onto the electrophilic carbon of the carbene **736** occurred. In this case cyclisation onto the *N*-tether of the ynamide was favoured, over 1,2-*H*-migration, resulting in cyclic system **737**.



Scheme 102: Alternative [1,5]-hydride migration of gold-activated ynamides

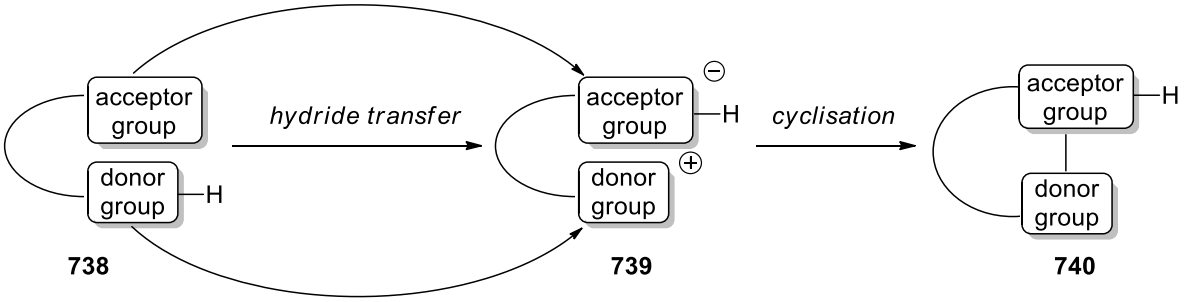
This gold catalysed process generates complex 3D structures, forming three new carbon-carbon-bonds and four new contiguous stereogenic centres in a single operation. The development of this powerful strategy, which employs relatively simple strating ynamides to furnish polycyclic systems, as well as the investigation of the substrate scope will be discussed in the next sections.

Selected examples of direct functionalization of C(sp^3)-H bonds and the challenges these processes involve will be discussed in the next section of this chapter.

4.2 [1,5]-Hydride Shift/Cyclisation Cascade

4.2.1 Reaction profile

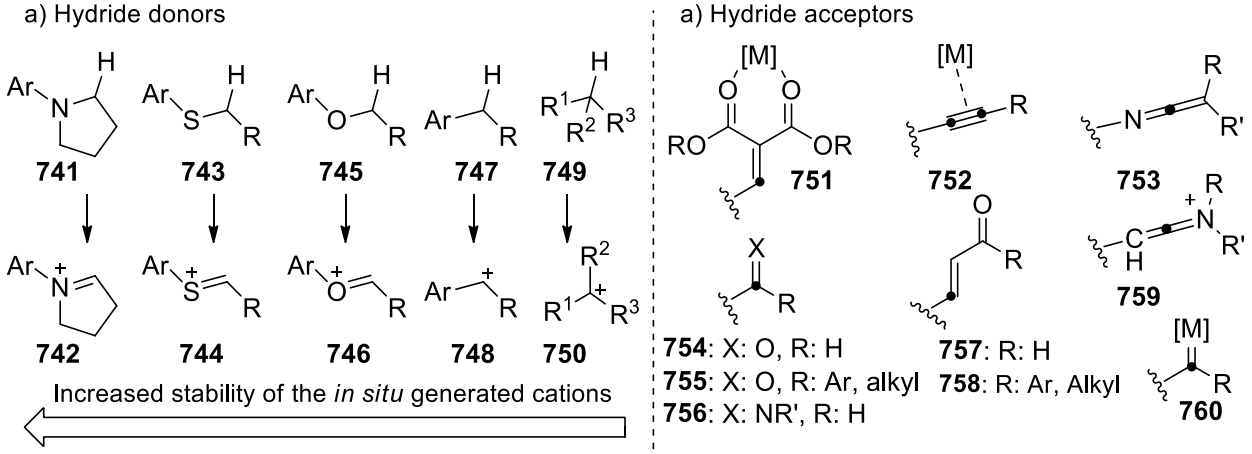
Functionalisation of C-H bonds has been a thriving area over the last few years and this significant popularity derives from the ability of these methods to promote direct formation of C-C and C-X (X: O, N, Si etc.) bonds without the need of a pre-functionalised C-C bond.[150],[151],[152] While recent advances on π-acid catalysis provide numerous methods for the functionalisation of C(sp^2)-H bonds, activation of relatively inactive C(sp^3)-H bonds still remains a challenge. The ability to activate C(sp^3)-H bonds is particularly attractive as it allows novel retrosynthetic routes to be released. In this regard, limited methods based on transition metal catalysis have only recently addressed C(sp^3)-H bond activation,[153],[154] whilst hydride transfer pathways provide powerful alternatives for this demanding reactivity.



Scheme 103: C-H Activation by 1,5-hydride transfer

Reactions proceeding *via* a [1,n]-hydride transfer (usually n= 4, 5, 6) are intramolecular, redox neutral processes which involve sequential activation of inert C(sp^3)-H bonds and the formation of C-C, C-O or C-N bonds (Scheme 103). This approach, which was initially employed in ring

closing reactions using aniline derivatives, is known as the '*tert*-amino effect'.[155] Two main components are enclosed: a hydride donor and a hydride acceptor. A hydride donor can be a C(sp^3)-H bond adjacent to a nitrogen **741/742**, sulfur **743/744**, oxygen **745/746**, benzyl **747/748**, alkyl **749/750** or other groups such as acetals and thioacetals, whereas a hydride acceptor can be a group with an electrophilic site such as activated alkylidenemalonates **751,** alkynes and allenes **752**, aldehydes **754**, ketones **755**, imines **756**, enals **757**, enones **758**, metal carbenoids **760**, ketenimines **753**, and more recently keteniminium ions **759** (Scheme 104).

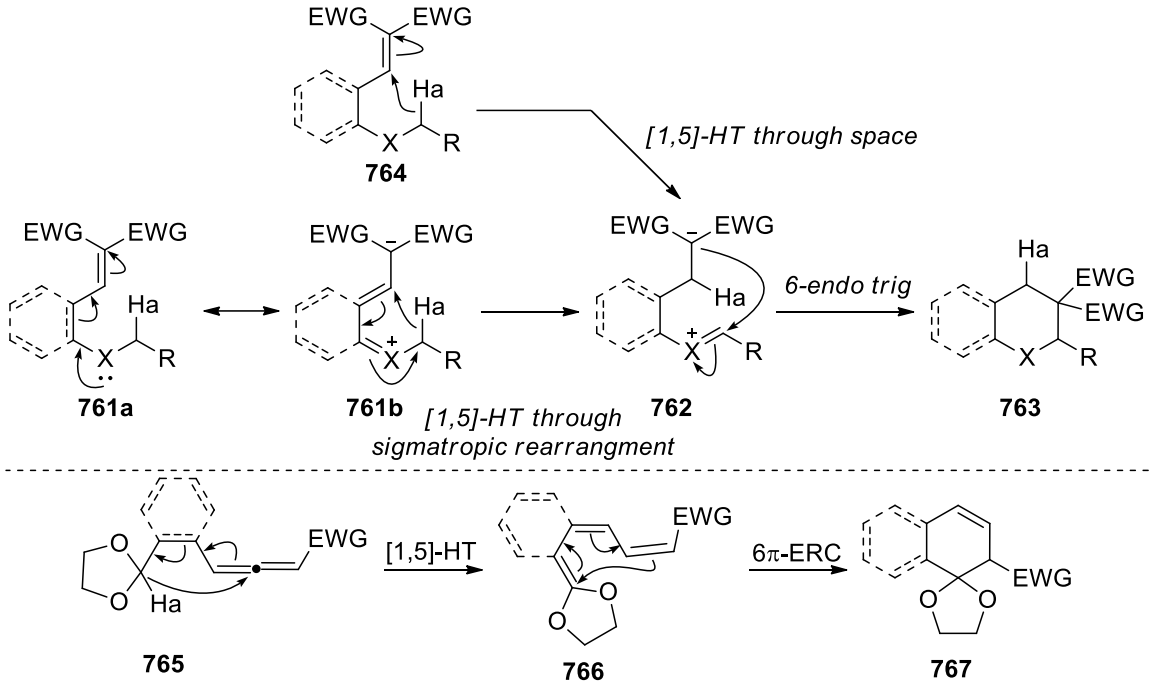


Scheme 104: Different types of hydride donors and hydride acceptors

The hydride donor mode of action is to lower the dissociation energy by polarising and weakening the C-H bond, resulting in a developing negative charge on the hydride on stabilising a carbocation which promotes the C-H cleavage.[156],[157],[158] Upon hydride abstraction, the heteroatoms at the α-position stabilise the generated carbocation by overlap of their free electron pair with the p-orbital of the cation. When aromatic or alkyl groups are adjacent to the C-H bond, the carbocation is stabilised either by the π-system or by σ-p hyperconjugation

respectively. On the other side, the hydride acceptor should be electrophilic enough to receive the hydride, otherwise the cation will capture the hydride again and no reaction will occur.

Regarding [1,5]-hydride transfer, several mechanisms can be considered. As illustrated in the example below, the transfer can occur through space from the hydride donor to the electrophilic acceptor, generating the charged intermediate **762**, which can cyclise in an 6-*endo*-*trig* fashion (Scheme 105).[159],[160],[161] Alternatively, sigmatropic rearrangement can also result in hydrogen transfer, *via* **761a**/**761b**, generating the same zwitterion **762** which participates in the same cyclisation.[162],[163],[164] This last step can proceed alternatively through a 6π electrocyclic ring closure to form cyclic product **767**, precluding the generation of potentially unstable charged intermediate **762**.[165],[166],[167] Importantly, DFT studies depict that the rate determining step is the initial hydride transfer and that the following cyclisation occurs very quickly.[168]

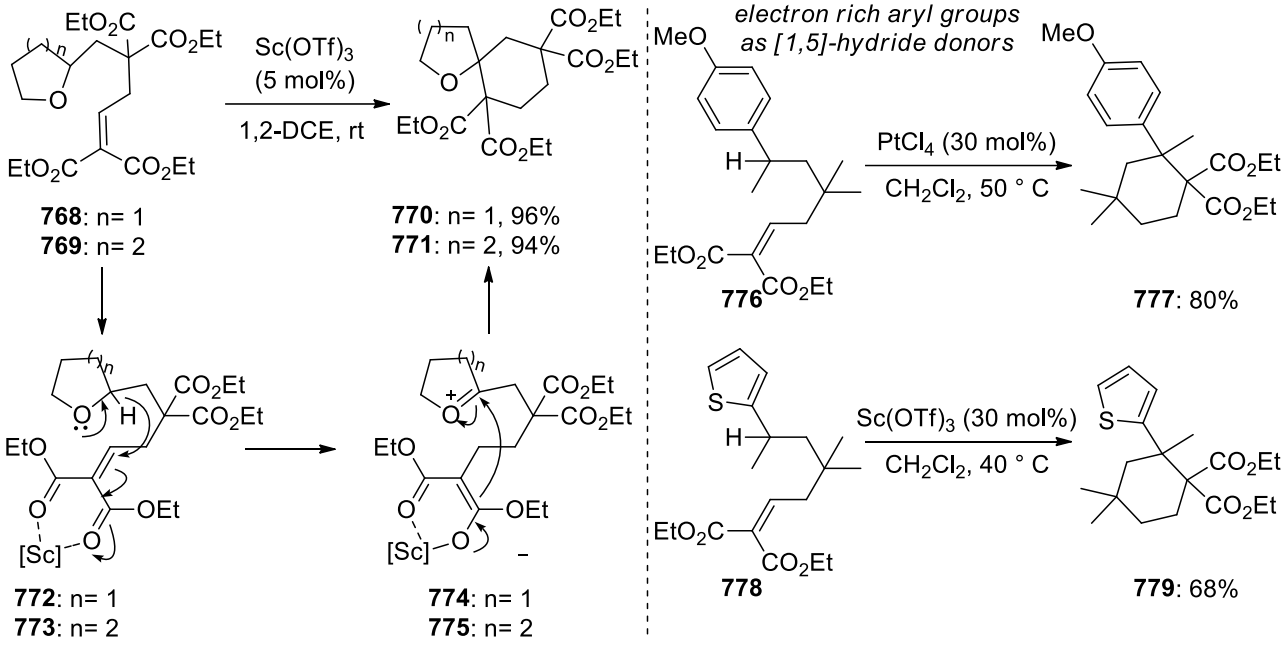


Scheme 105: 1,5-HT Mechanism either through space or *via* sigmatropic rearrangement

While chemistry involving [1,4]-[169],[170] and [1,6]-hydride transfer[171],[172],[173] is also applicable, the rest of this section will focus on [1,5]-shifts and the examples below are classified based on the hydride acceptors usually employed.

4.2.2 Benzylidinemalonates as hydride acceptors

Since 2005, the Sames research group has made a substantial contribution to the field. They first developed the Lewis acid promoted hydroalkylation of electron deficient olefins by employing tetrahydropyran **769** or tetrahydrofuran **768** as the source of hydride and α,β-unsaturated malonates as hydride acceptors (Scheme 106).[174]

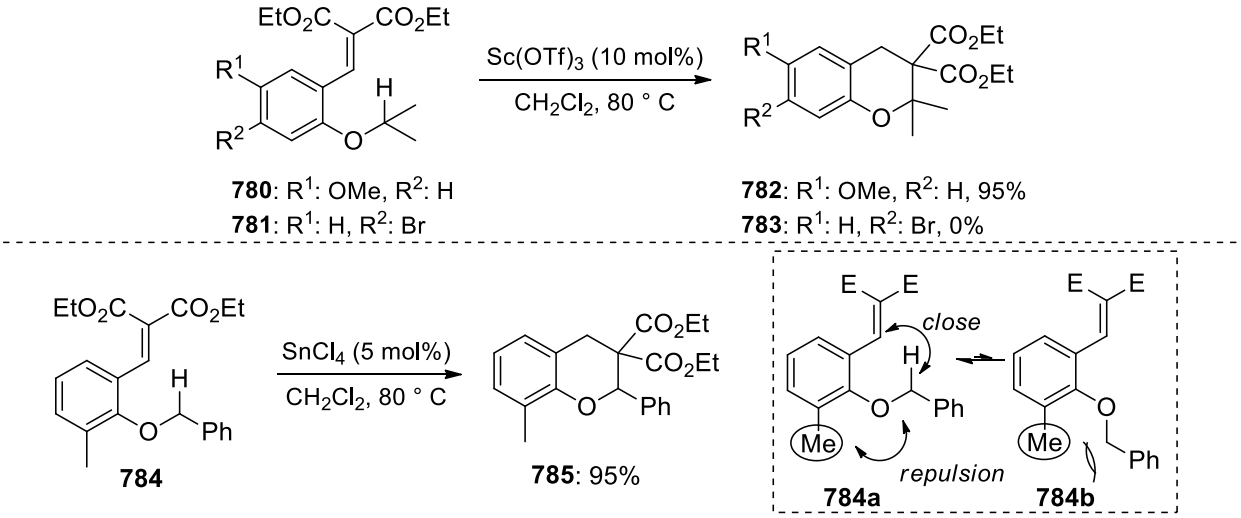


Scheme 106: Sames' initial work using malonates as hydride acceptors

The Lewis acid catalyst plays a crucial role in their strategy as following complexation with carbonyl containing compound **772**/**773** the electrophilicity of the adjacent olefin is increased. The now facile hydride shift can occur and following subsequent cyclisation yields spirocycles **770**/**771**. This method was extended to include electron-rich aromatic systems as hydride donors, such as *para*-methoxy substituted benzyl ring **776** and 2-thiophene **778**. These aromatic groups can effectively stabilise the benzylic position *via* π-p conjugation.

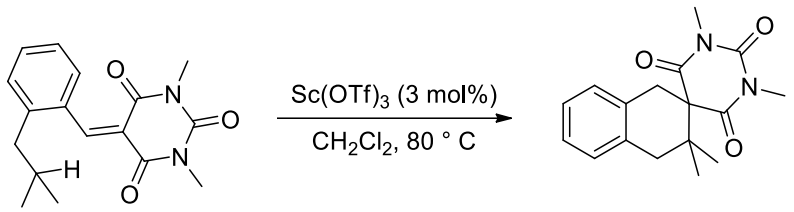
In addition, the same group reported that regardless substitution, *ortho*-substituted aryl ethers **780** can be employed for the formation of highly substituted dihydrobenzopyrans **782** (Scheme 107).[175] For these systems *iso*-propoxy groups function as hydride donors and notably the substitution around the aromatic ring exerts significant influence on the hydride migrating ability. The negative inductive effect of bromine, when *meta*- to the donor, shuts down the

reaction completely (**781** to **783**). In the same context as reported by the Akiyama group, a methyl group *ortho* to the donor enhances the reactivity greatly, allowing for the use of a lower catalyst loading (**784** to **785**).[176] A synergistic effect is responsible for this trend, the steric repulsion between the methyl and the benzyloxy group forces the molecule to adopt conformation **784a**/**784b**. This repulsion brings the two key factors (donor-acceptor) closer to one another (‘*buttressing effect’)*, facilitating the [1,5]-hydride transfer.



Scheme 107: Substituent effect when ortho-substituted aryl ethers are employed

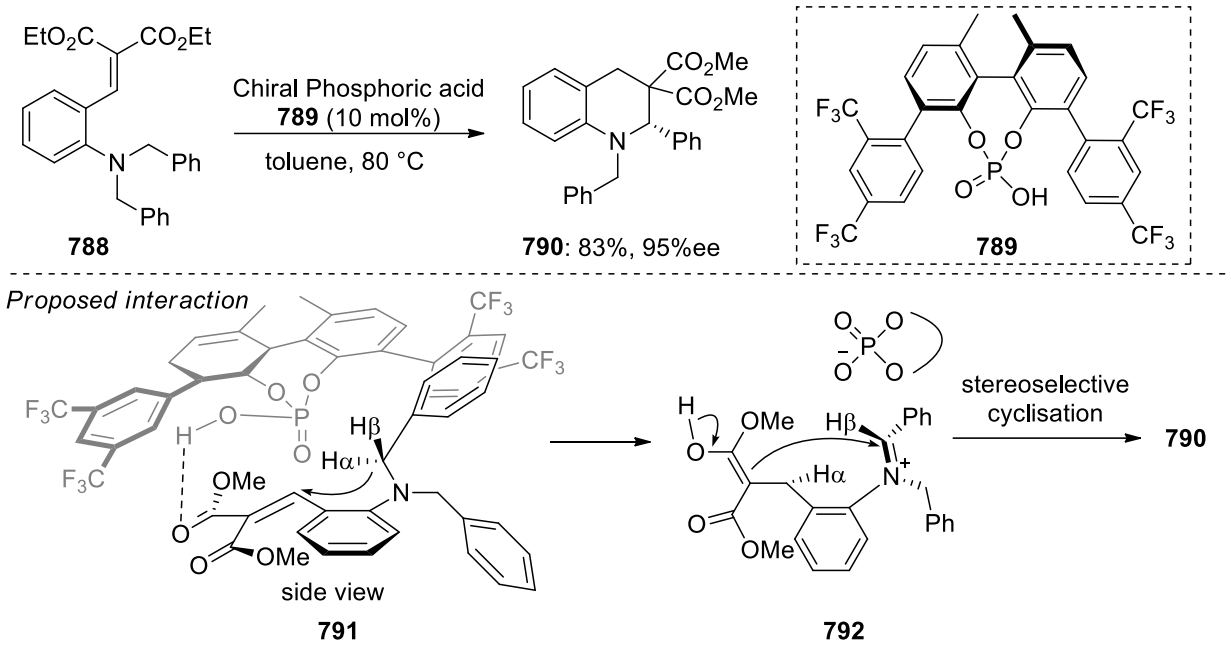
Akiyama and co-workers expanded the reaction scope further by using benzylidenebarbituric acid **786** for the construction of functionalised tetraline skeletons **787** (Scheme 108).[172] The hydride shift in this unprecedented cascade reaction originates from a normally inactive, aliphatic, non-benzylic position while in the absence of a heteroatom and interestingly proceeds efficiently under even lower catalyst loadings.



786 **787**: 96%

Scheme 108: Aliphatic, non-benzylic hydride shift

The same research group has employed a chiral phosphoric acid to catalyse an asymmetric hydride transfer/cyclisation cascade giving tetrahydroquinolines **790** in excellent enantioselectivities (Scheme 109).[177] According to the depicted mechanism, the asymmetric induction takes place during the hydride migration process. As the phosphoric acid coordinates with the acceptor moiety, steric repulsion between the aromatic ring on the catalyst and the *N*-benzyl group of the donor detains the benzyl group on the opposite side relative to the ligand (structure **791**). As a result, Hβ is too far away to undergo migration and Hα migrates instead. In addition, control experiments based on analogous chiral precursors showed that the initial chiral information was not lost when an achiral catalyst was employed. Thus the cyclisation of **792** proceeds in a stereoselective fashion to give the **790** as the major enantiomer.



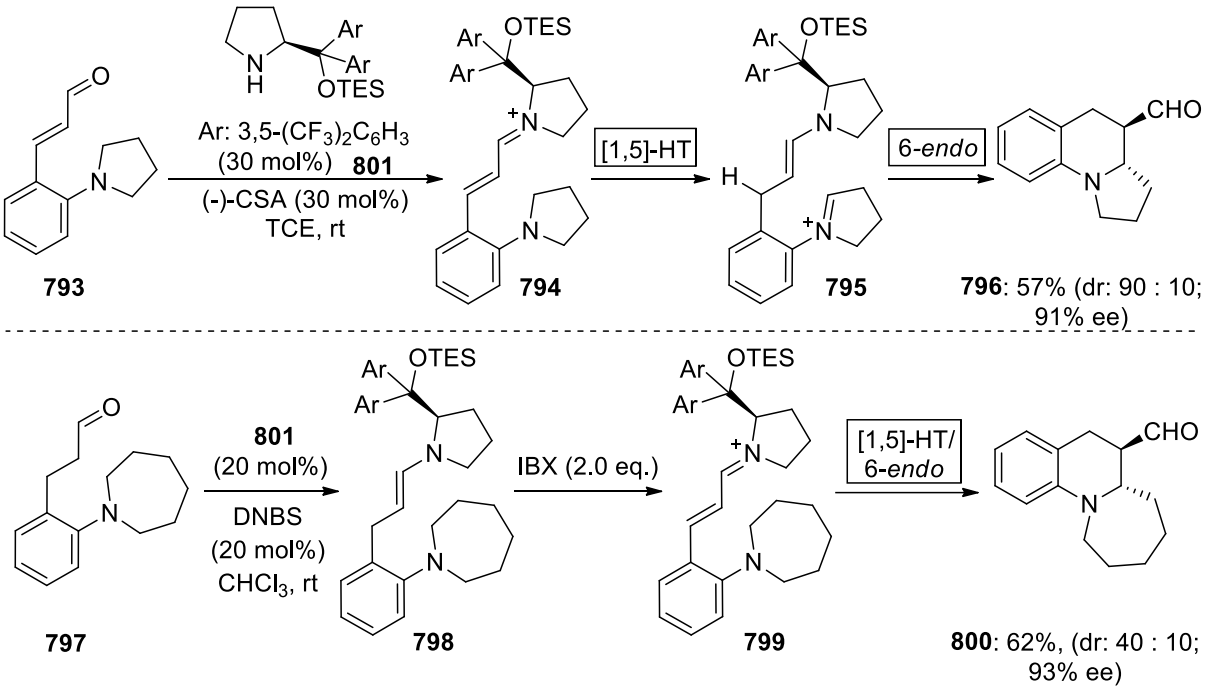
Scheme 109: Asymmetric [1,5]-HT with the use of chiral phosphoric acid

This appealing strategy, using chiral catalysts to exploit asymmetric control and promote enantioselective hydride migration was broadly applied later on by different research groups, for the formation of diverse products.[178],[179],[180],[181]

4.2.3 Aldehydes, ketones and imines as hydride acceptors

In 2010 Kim and co-workers reported the first organocatalytic, enantioselective [1,5]-hydride transfer/cyclisation cascade (Scheme 110).[182] They employed α,β-unsaturated aldehydes **793**/**797** as hydride acceptors for the formation of optically active tetrahydroquinolines **796**/**800**. The reaction is promoted by condensation of the aldehyde **797** with the chiral organocatalyst **801** to form iminium **794**. Intramolecular hydride transfer to the electron deficient alkene followed by 6-*endo* cyclisation of **795** gives the final quinoline derivative **796** in

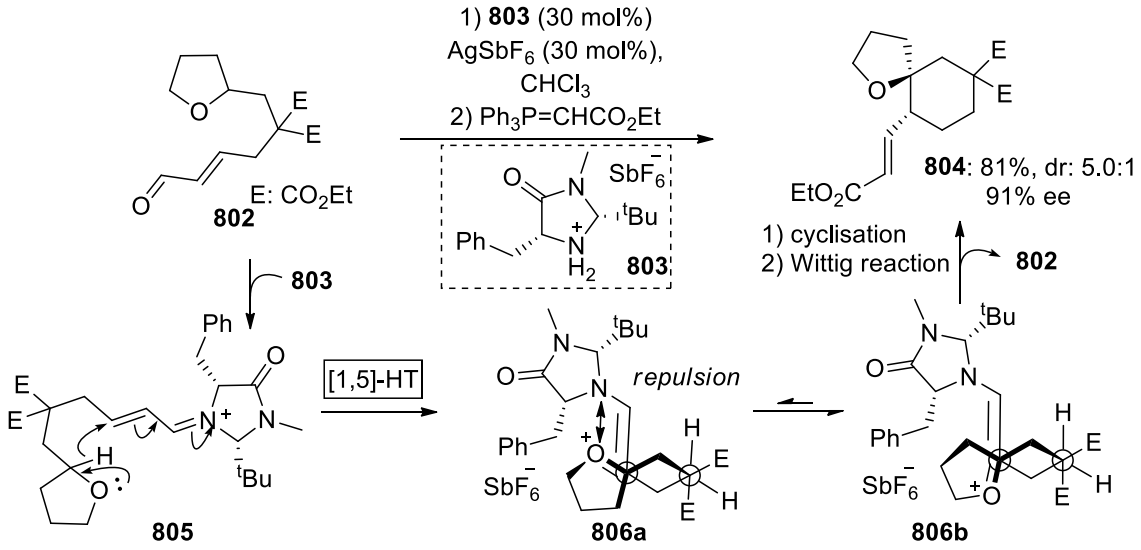
moderate yield but high enantioselectivity. An extension of this methodology is based on oxidative enamine catalysis prior to the hydride shift.[183] Although enantioselective oxidative β-functionalisation of simple aldehydes is rare, *in situ* conversion of the saturated aldehyde **797** to the enamine **798** followed by oxidation to the corresponding iminium ion **799** was achieved. The subsequent hydride migration/cyclisation cascade gives the desired products **800**.



Scheme 110: Organocatalytic 1,5-HT/cyclisation cascade

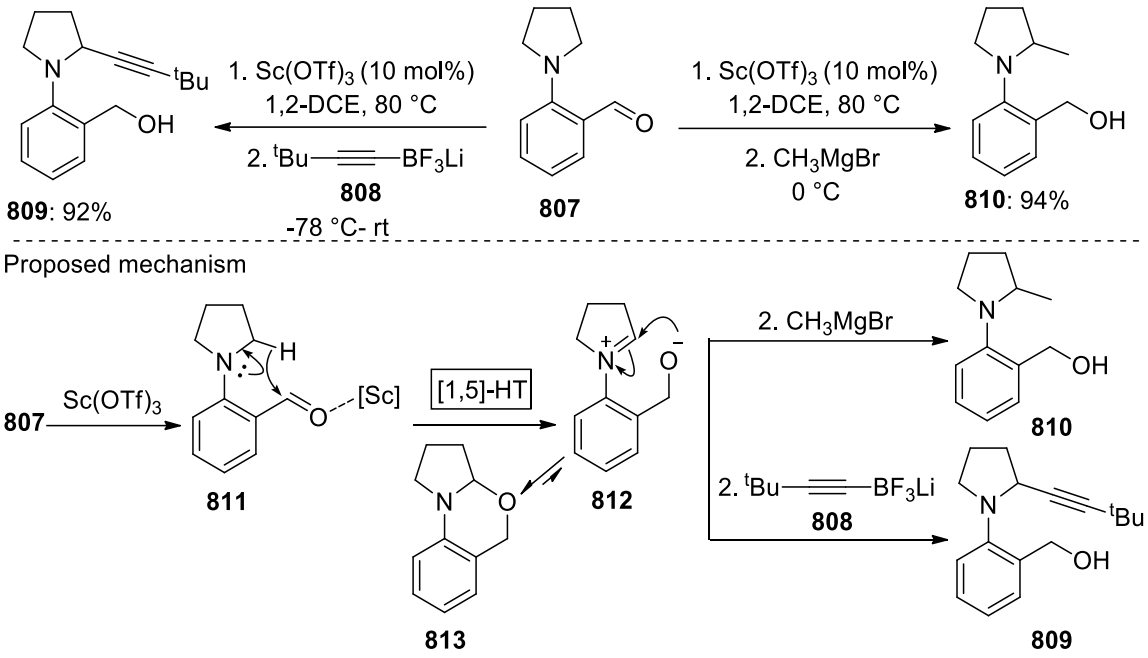
Li and co-workers reported the enantioselective formation of chiral spiroethers from proline based iminium ion catalysis (Scheme 111).[184] A possible mechanism involves the reaction of α,β-unsaturated aldehyde **802** with chiral amine **803** to form iminium ion **805**. A tetrahydrofuran moiety is used as a hydride donor to give *E*-enamine **806** selectively due to steric encumbrance from the bulky substituents of the amine. The **806b** conformation of the

enamine is favoured over **806a**, as repulsion between the oxocarbenium ion and the enamine subunit is avoided. Intramolecular cyclisation followed by Wittig reaction gave α-functionalised spiroether **804** in high yield and enantioselectivity.



Scheme 111: Organocatalytic formation of chiral spiroethers

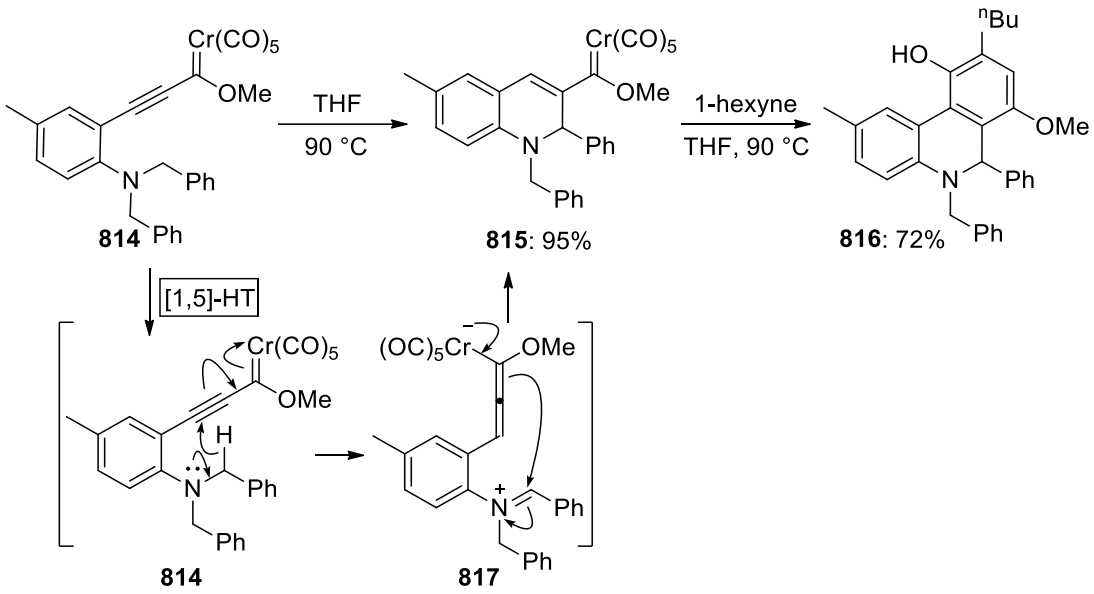
Maulide's research group reported a one-pot, scandium catalysed C-H functionalisation of tertiary amines (Scheme 112).[185] In this process the neighbouring aldehyde (**807**) is being reduced and the generated iminium ion **812** is trapped intermolecularly by the addition of Grignard reagents and lithium alkynyl trifluoroborates **808**. Extensive mechanistic investigation concluded that the reaction is under thermodynamic control. Upon [1,5]-hydride transfer iminium intermediate **812** is formed which exists in equilibrium with relatively unstable aminal **813**. Subsequent trap of **812** with more nucleophilic reagents result in the functionalised corresponding products **810** and **809** in excellent yields.



Scheme 112: Scandium catalysed C-H functionalization of tertiary amines

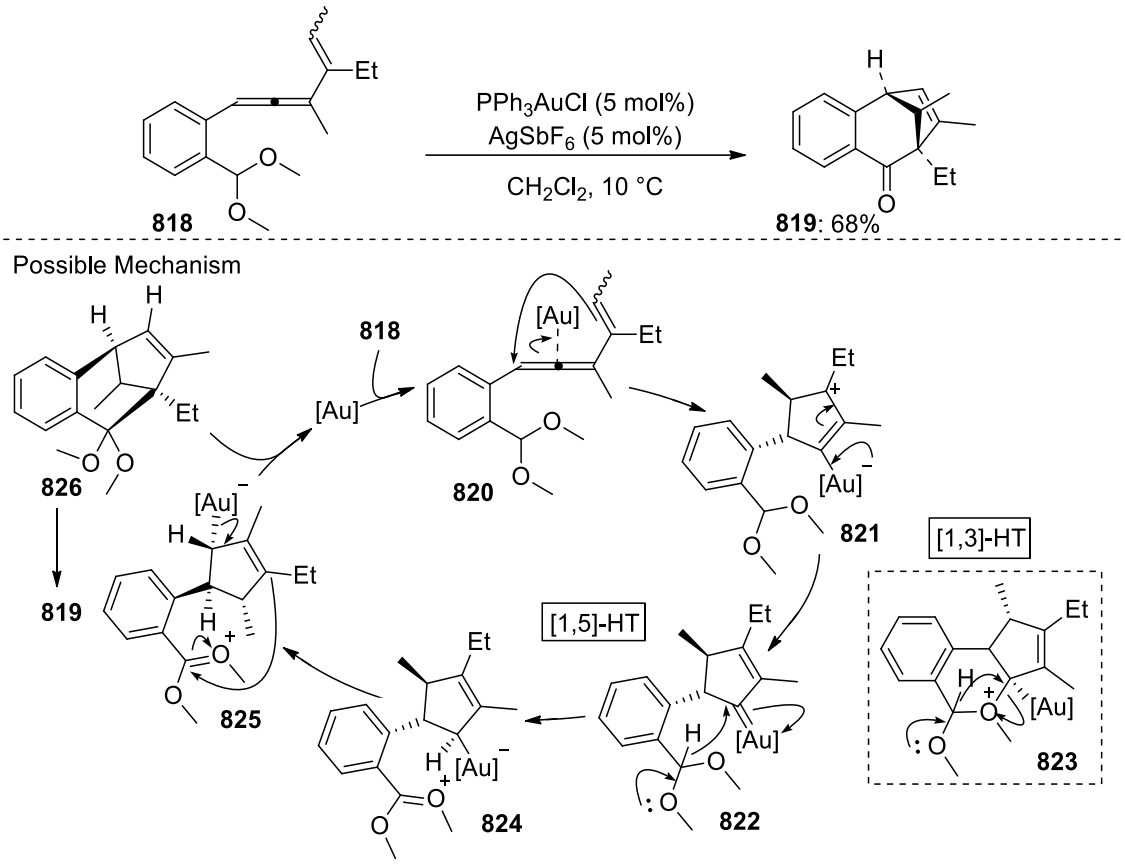
4.2.4 Activated alkynes and allenes as hydride acceptors

The first example of an alkyne acting as a hydride acceptor was reported by Barluenga *et al.* in 2008 (Scheme 113).[168] The alkyne subunit in this case is highly activated by the strongly electron withdrawing chromium pentacarbonyl Fischer carbene **814**, triggering the hydride migration. Isomeric chromium carbene **815** is formed which is stable enough to be isolated. Due to the synthetic versatility of Fischer carbenes, further treatment of **815** with 1-hexyne gives tricycle **816** *via* Dötz benzannulation.



Scheme 113: Highly electrophilic carbenes as hydride acceptors

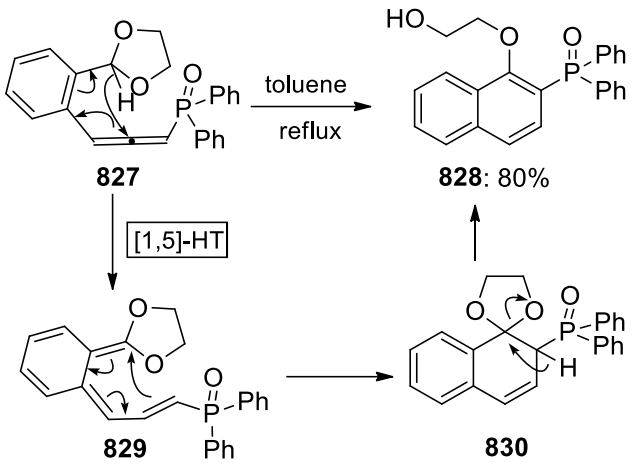
Liu's research group used gold-activated allenes **820** for the construction of complex bicyclic systems **819** with high chemo and stereoselectivity (Scheme 114).[186] Based on extensive deuterium and crossover experiments, a plausible mechanism revealed the formation of gold carbene **822** (*via* **821**), upon activation by the metal the phenyl moiety is arranged *trans* to the methyl substituent to minimize steric interactions. Subsequent [1,5]-hydride transfer traps the generated gold carbene to give oxonium intermediate **824**, the alternative intermediate **823** can also lead to oxonium **824** *via* an [1,3]-hydride transfer. Rotation of the C-C linker of the two rings allows S_E2' addition of Au-allyl moiety towards the electrophilic carbon of the oxonium, affording tetracyclic system **826**. Final acid-catalysed deprotection gives bicycle **819** as a single stereoisomer. Notably, ruthenium carbenes can also be inserted into Csp^3-H bonds resulting in a range of diverse products.[171]



Scheme 114: [1,5]-HT on gold-activated allenes for the stereoselective formation of tricycles

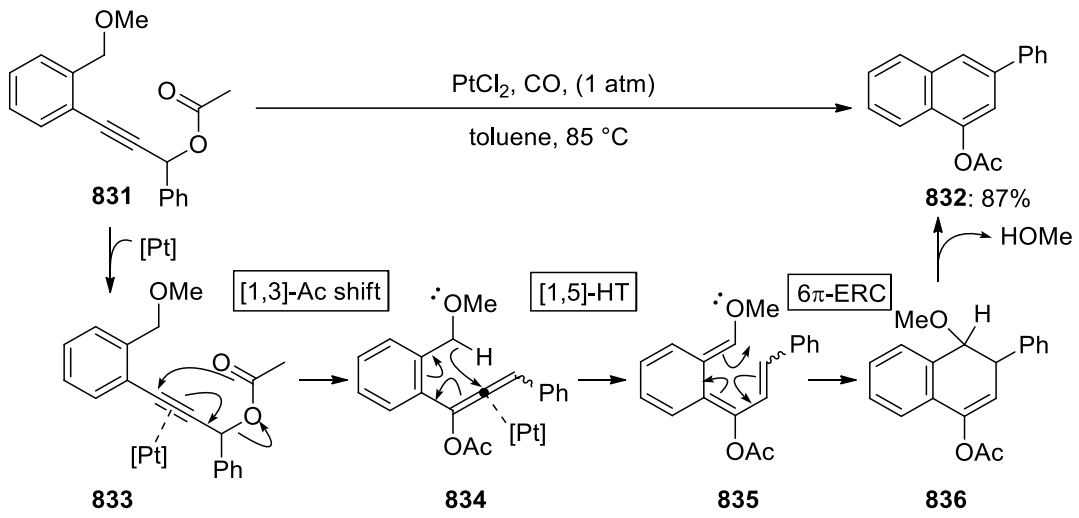
In contrast, allenes **827** can be activated by electron withdrawing groups on the carbon terminus of the π-system, without the need of a carbophilic metal (Scheme 115).[187] Recently Alajarin and co-workers reported the synthesis of highly functionalised naphthalene derivatives **828** under thermal conditions by employing electron deficient allenyl moieties bearing sulfonyl, alkoxycarbonyl or phosphinyl substituents. An acetal unit acts as a hydride donor in this case. The possible mechanism is initiated by hydride shift towards the central carbon of the allene forming hexatriene **829**, which can then undergo a 6π electrocyclic ring closure to form

spirocyclic intermediate **830**. Aromatisation with simultaneous cleavage of C-O bond gives the substituted naphthalene **828**.



Scheme 115: Thermal [1,5]-HT/cyclisation cascade for the formation of naphthalenes

Liang and co-workers developed the first platinum catalysed [1,5]-sigmatropic hydride transfer reaction of propargyl esters **831** for the formation of naphthalenyl acetate derivatives **832** (Scheme 116).[164] Deuterium labelling studies depicted that upon activation of the π-system, [1,3]-acetate shift leads to Pt-allene complex **834** which can readily undergo [1,5]-sigmatropic hydride migration. Acyclic hexatriene **835** evolves through 6π electrocyclic ring closure to give intermediate **836** which can aromatise, through elimination of the methoxy group, giving the final naphthyl derivative **832**.

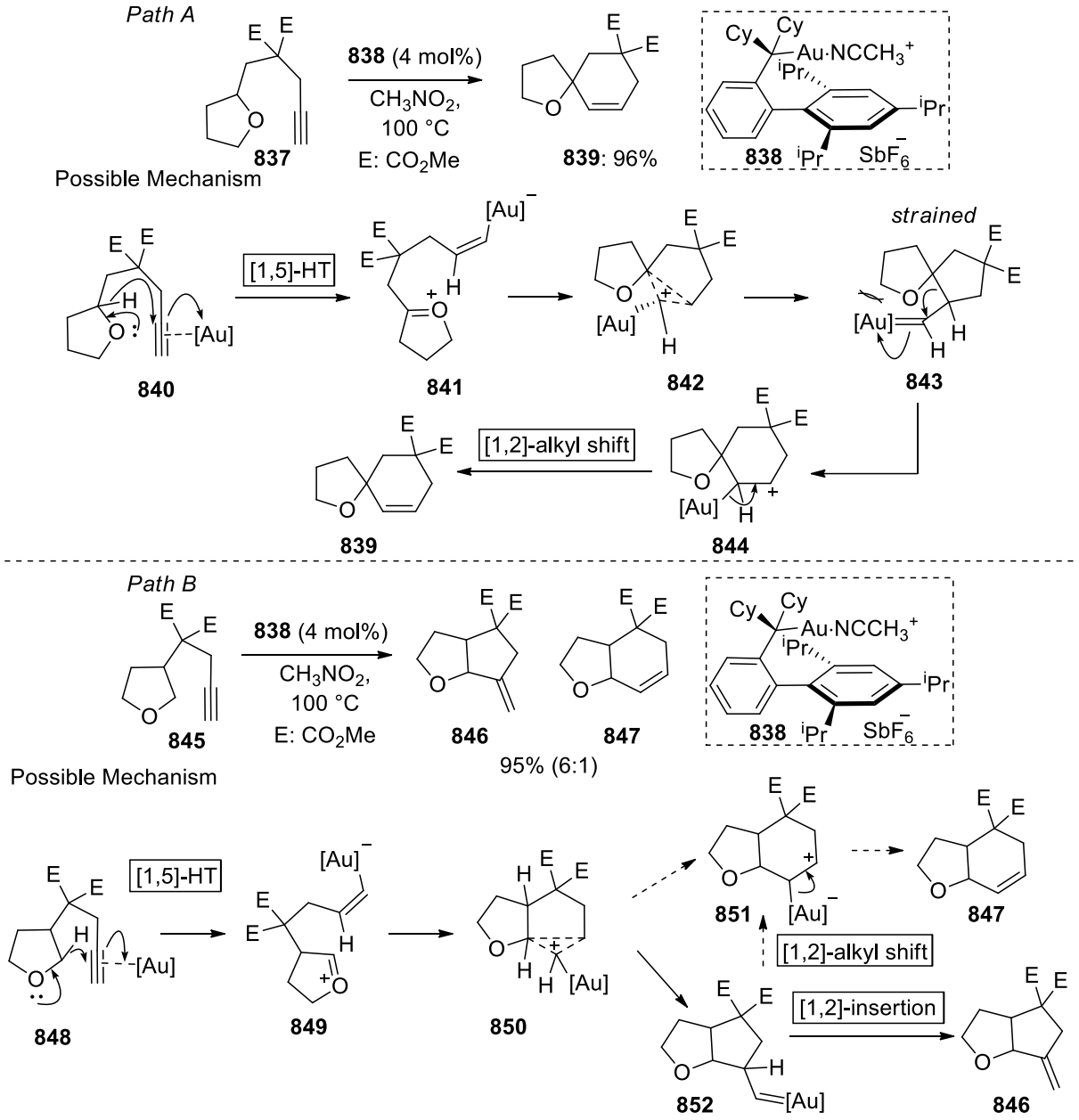


Scheme 116: Platinum-catalysed [1,3], [1,5], 6π-ERC cascade

While many other protocols have been realized based on rhodium[188] ruthenium[163],[189] and platinum[190],[189],[173] catalysed [1,5]-hydride transfer, employing mostly terminal alkynes for the formation of variable products, the next few examples will be focused on recent advances on gold-activated π-systems highlighting the synthetic versatility of these methods.

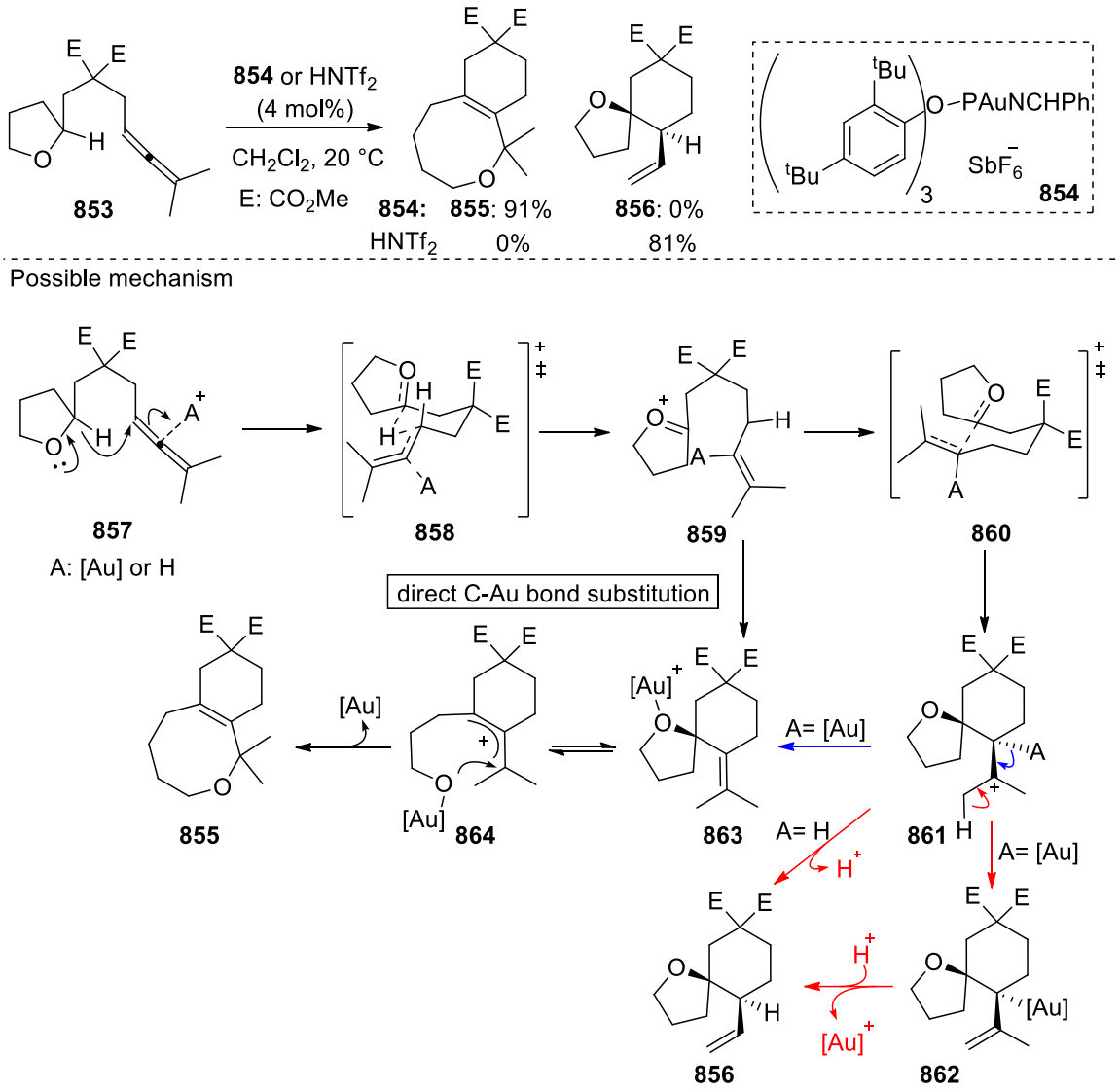
Gagosz and co-workers showed that gold activated alkynyl ethers can undergo hydride transfer leading to spiro or fused dihydrofurans (Scheme 117).[191] Based on deuterium labelling studies, utilising terminal alkyne **837** with a three-carbon spacer between the donor and the triple bond, [1,5]-hydride migration of **840** results in oxocarbenium **841**. Interaction between the vinyl gold unit and the oxonium moiety develops the cationic intermediate **842** which further collapses to form carbene **843**. 1,2-Alkyl shift/ring expansion forms 5,6-spirocycle **839**. On the other hand, when terminal alkyne **845** with a two-carbon spacer is employed, a 6:1 mixture of isomeric **846** and **847** is formed. The observed selectivity relies on the relative stability of intermediates **843** and **852**. Notably, comparing path A and path B, steric strain of spirocyclic intermediate **843**

follows alkyl shift, whereas the less strained fused intermediate **852** undergoes rapid [1,2]-hydride shift to form the *exo*-methylenecyclopentane **846** as a major product.



Scheme 117: Hydroalkylation of alkynyl ethers *via* Au-catalysed [1,5]-HT/cyclisation cascade

Further efforts provided a significant increased substrate scope in which gold-activated allenyl ethers **857** were transformed into tetrahydropyrans **855** (Scheme 118).[192] The formation of alternative product **856** was observed when a Brønsted acid was employed instead of the metal. According to the proposed mechanism, gold or acid activation of the allene triggers [1,5]-hydride migration to give oxonium **859**, a common intermediate for both products **855** and **856**. When gold is used, direct reaction of the metal with the oxonium gives intermediate **863**, which can also be formed through a step-wise process *via* carbocation **861**. Ring opening of **863** develops an allylic carbocation **864** which can further cyclise to give oxepane **855**, or contrastingly, intermediate **861** can undergo proton loss (**861** to **862**) followed by protodeauration to give the alternative product **856**. When the Brønsted acid is used, oxonium **859** is trapped through the alkene unit, forming **861** which after proton loss furnishes spirocyclic compound **856**.

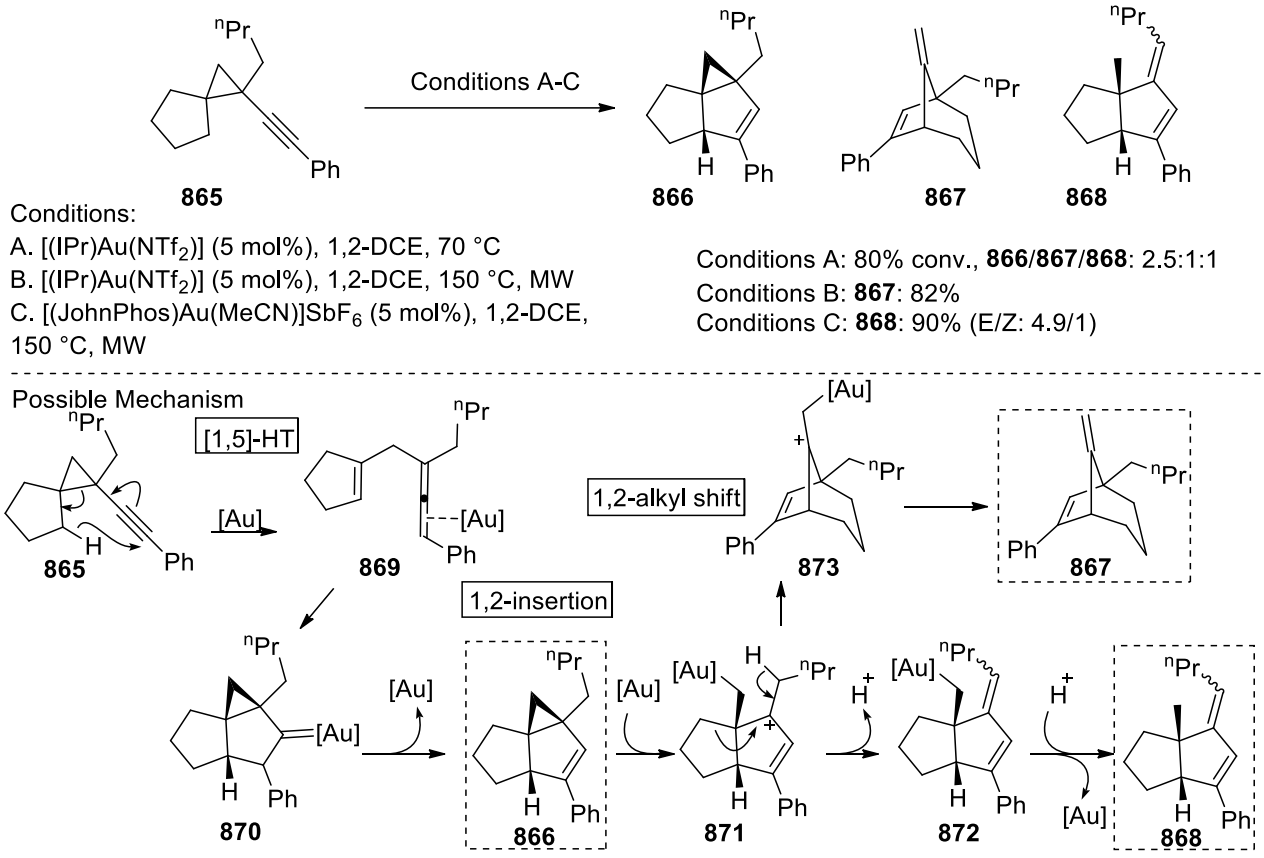


Scheme 118: Hydroalkylation of allenyl ethers *via* Au-catalysed [1,5]-HT/cyclisation cascade

Gagosz concluded that the observed product selectivity relies on the concerted or stepwise formation of **863**, when gold is used, whereas under Brønsted acid catalysis, a regiospecific proton loss (through **861**) leads instead to **856**.

Barluenga *et al.* reported a novel hydride transfer in which an inactive non-benzylic secondary carbon can function as a hydride donor towards gold-activated alkynes (Scheme 119).[193] In

particular alkynylcyclopropanes with a spirane core **865** were transformed to diverse products. This diversity can be simply controlled by tuning the catalyst, forming selectively product **866**, **867** or **868**.



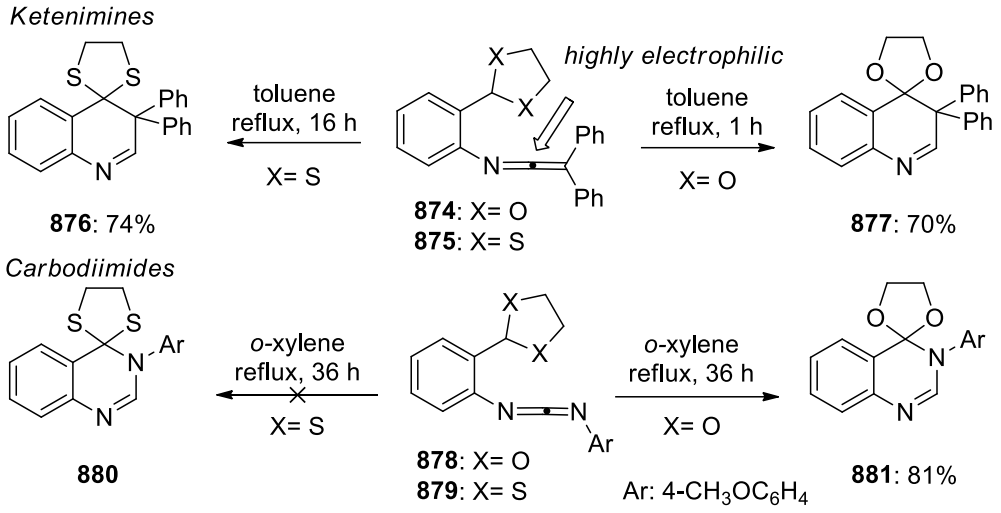
Scheme 119: Diverse reactivity of alkynylcyclopropanes with an incorporated spirane core

Assuming that the migration is a cationic process taking place through space, the cyclopropyl subunit is essential for the reactivity as it brings the donor and the acceptor closer to one another. Regarding the mechanism, upon activation of the triple bond, [1,5]-hydride transfer takes place with simultaneous ring opening of the cyclopropyl ring. 1,4-Enallenyl intermediate **869** can then undergo cyclopropanation to form carbene **870** followed by 1,2-insertion giving product **866**. Harsher conditions promote further ring opening which leads to cation **871**. 1,2-

Alkyl shift and elimination of the metal gives product **867**, whereas loss of a proton and protodeauration results in product **868**.

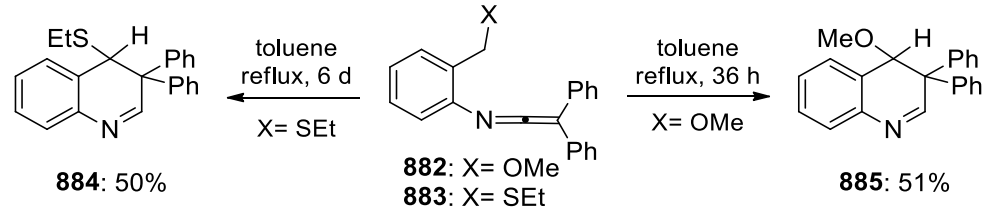
4.2.5 Ketenimines as hydride acceptors

As mentioned earlier, activated allenes can undergo thermal cascade [1,5]-hydride transfer/cyclisation when acetals are employed as an excellent source of hydride. The Alajarin and Vidal research groups have investigated this approach in detail by using active ketenimines **874**/**875** or carbodiimides **878**/**879** as hydride acceptors (Scheme 120).[157],[166] The position highlighted in the structure **874**/**875** is highly electrophilic and can readily accommodate the hydride derived from the activated acetal donor. This process generates the corresponding neutral intermediate which is expected to be relatively stable, as it contains a conjugated π-system, while the absence of any charge separation is energetically favoured. 6π-Electrocyclic ring closure gives the dihydroquinoline **877** or spirocyclic dioxolanoquinazoline **881** in good yields. Extensive experimental data revealed that carbodiimides are less reactive than the ketenimines. Additionally, when 1,3-diothiolane was used instead of the analogous 1,3-dioxolane, the reactivity of the system was decreased (**877** was furnished in 1 hour *versus* **876** in 16 hours), indicating the decreasing donating ability of the thioacetal unit. Less reactive carbodiimides **879** with an adjacent thioacetal group remained completely unreactive.



Scheme 120: Carbodiimides and ketenimines as hydride acceptors

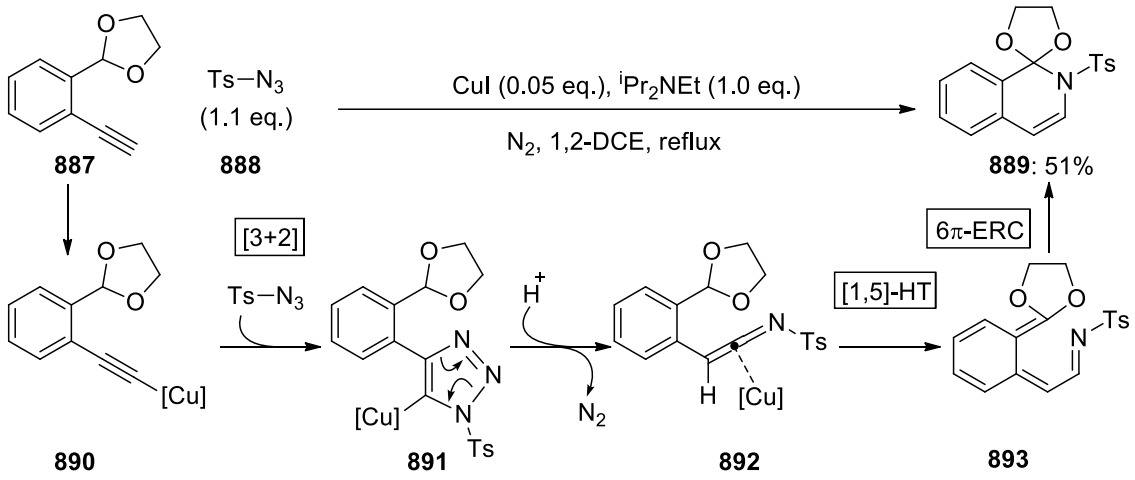
Alkoxide-containing ketenimine **882** and thioether derivative **883** can also be converted into the corresponding dihydroquinolines **885** and **884** respectively, however only in moderate yields (Scheme 121).[194]



Scheme 121: Alkoxides and thioethers as hydride donors towards ketenimine acceptors

The Lu and Wang research groups jointly reported the copper-catalysed synthesis of 1,2-dihydroisoquinolines from terminal alkynes **887** and azides **888** (Scheme 122).[195] This two-component synthesis initiates with a copper-catalysed alkyne-azide cycloaddition, forming triazolium intermediate **891**. Subsequent Dimroth rearrangement results in fragmentation of the triazolium intermediate and diazotisation gives ketenimine **892**. [1,5]-Hydride migration

from the acetal to the electrophilic carbon of the ketenimine affords sulfonyl imide **893** which undergoes 6π-electrocyclisation to form the isoquinoline **889** in moderate yield.



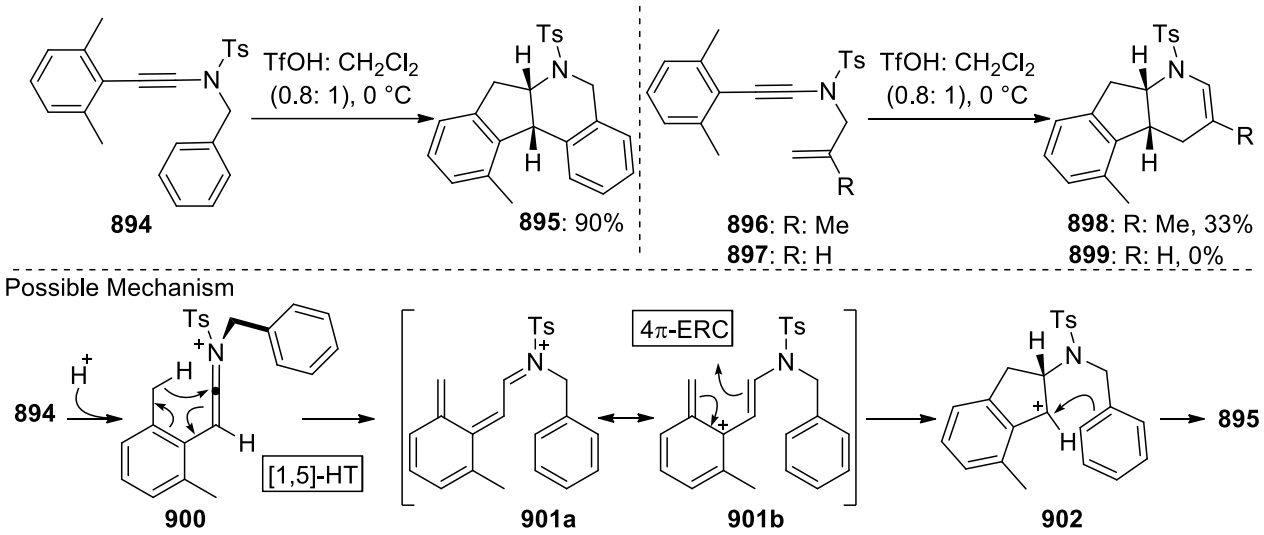
Scheme 122: Copper-catalysed formation of 1,2-dihydroisoquinolines

4.2.6 Keteniminium-ion as hydride acceptor

Recently and while we were investigating our research on [1,5]-hydride migration, the Evano and Thibaudeau research groups jointly reported a keteniminium-initiated polycyclisation, with the use of *N*-benzyl ynamides **894**, to form complex nitrogen-containing heterocycles **895** (Scheme 123).[196] The process requires either triflic acid or bistriflimide to promote the cascade cyclisation which gives scaffolds with up to three contiguous stereocentres and seven fused ring systems. According to the proposed mechanism, based on deuterium labelling studies, the use of a strong Brønsted acid is crucial for the reaction as it triggers the protonation of the π-system of the ynamide, forming *N*-sulfonyl keteniminium ion **900**. [1,5]-Sigmatropic hydride shift generates iminium **901a**/**901b** which undergoes Nazarov-type 4π-electrocyclisation to form the

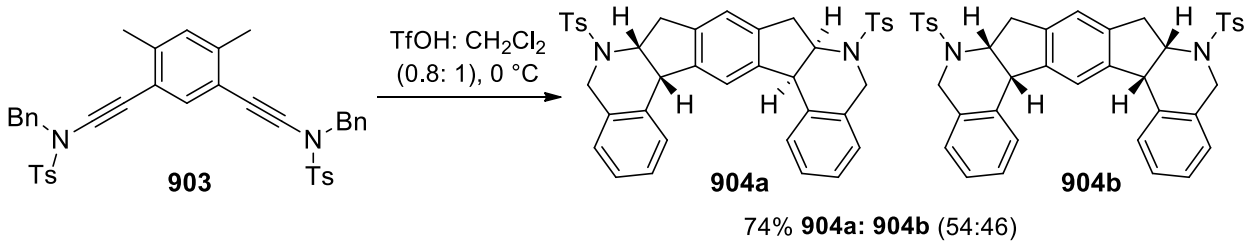
first

5-membered ring. Subsequent cyclisation of **902** from the aromatic tether gives the fused tetracycle **895**. Notably substituted *N*-allyl ynamide **896** was proved less reactive forming the desired product in low yield, whereas *N*-unsubstituted allyl ynamide **897** did not show any reactivity.



Scheme 123: Keteniminium ion as [1,5]-HT acceptor for the formation of complex polycycles

Impressively, double polycyclisation was achieved when bisynamide **903** was subjected under the acidic optimised conditions, forming the complex seven-membered fused ring systems **904** (as a mixture of diastereomers **904a** and **904b**) in high yield in a single step (Scheme 124).



Scheme 124: Bisynamides for the formation of fused polycyclic ring systems

As clearly demonstrated from the above examples, [1,5]-hydride migration of inactive Csp^3-H bonds is a powerful and elegant method which allows facile access to complex scaffolds in one step from typically readily available, simple precursors.

As mentioned in the introduction of the chapter, a [1,5]-hydride migration strategy towards gold-keteniminium acceptors was developed. In the next section details about the mechanism involved, the expansion of the substrate scope and the further reactivity of the final compounds will be discussed.

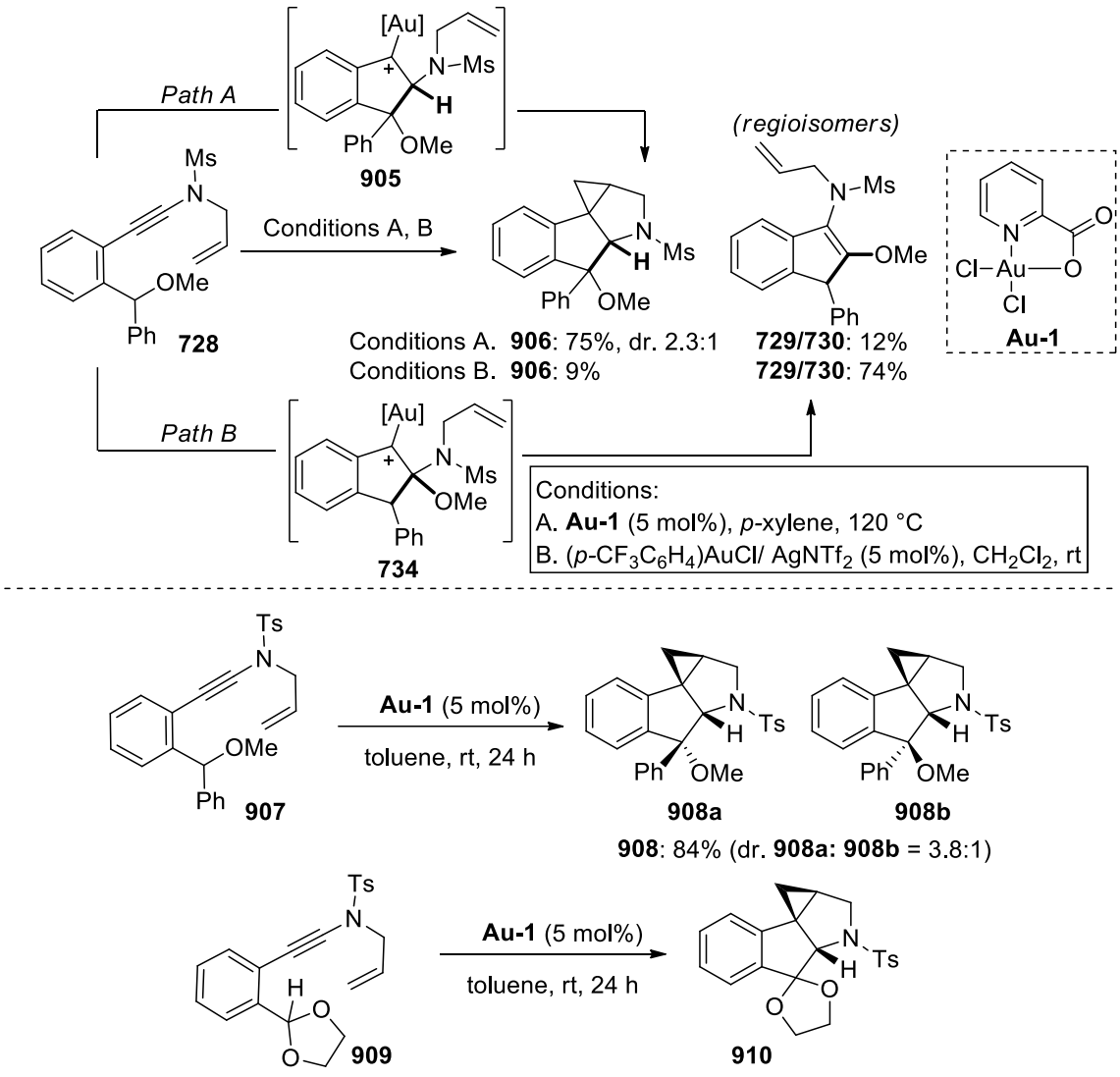
4.3 Results and discussion

4.3.1 Reaction design

No examples are known in the literature about gold-keteniminium species acting as hydride acceptors in a cascade [1,5]-hydride transfer/cyclisation process. The synthetic versatility of such a method potentially allows the construction of complex, highly functionalised heterocyclic systems, starting from simple and easily accessible *N*-substituted ynamides.

As mentioned earlier, Holly Adcock discovered that when ynamide **728** is treated with gold(III) precatalyst **Au-1**, this cascade process is followed, providing direct access to 3D structures, *via* the formation of three new Csp^3-sp^3 bonds and three (up to four) contiguous stereogenic centres (Scheme 125, Path A). In this case, the 1,5-hydride migration from a benzylic Csp^3 centre triggers the synthesis of carbene **905**. Trapping from the tethered *N*-allyl group leads to functionalised tetracyclic system **906** as a mixture of diastereomers (dr. 2.3:1).

Importantly, the carboalkoxylation pathway (Path B) which stems from *O*-insertion into the gold-keteniminium ion followed by 1,2-*N*- or *O*-migration, is greatly suppressed by choice of conditions. Much cleaner reactions were obtained when the corresponding tosyl protected ynamide **907** was employed as no trace of carboalkoxylation product was observed. In addition, ynamide **909** with an acetal unit as a hydride donor gave the corresponding tetracycle **910** as a single diastereomer.



Scheme 125: 1,5-Hydride transfer/cascade cyclisation *versus* carboalkoxylation pathway

Extensive optimisation studies revealed that the optimal conditions for the formation of the tetracycles involve the gold(III) precatalyst **Au-1** and toluene as a solvent, while the temperature can be adjusted depending on the reactivity of the substrate.

The potential of this reaction to construct diverse products led to further investigation of the substrate scope (Figure 5). Modifications on the benzylic position, alteration of the *N*-substituent of the ynamide and the donor-acceptor linker can potentially generate alternative and potentially interesting molecular architectures. These alterations, the challenges disclosed on the preparation of the starting ynamides and their subsequent reactivity are going to be discussed in the next sections.

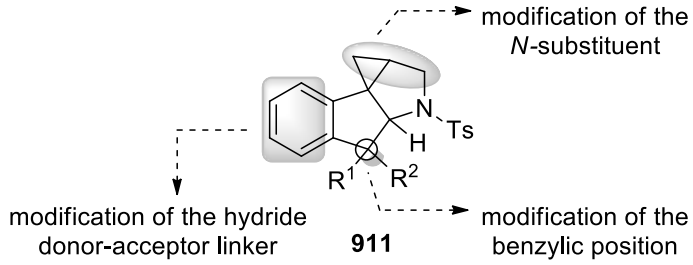
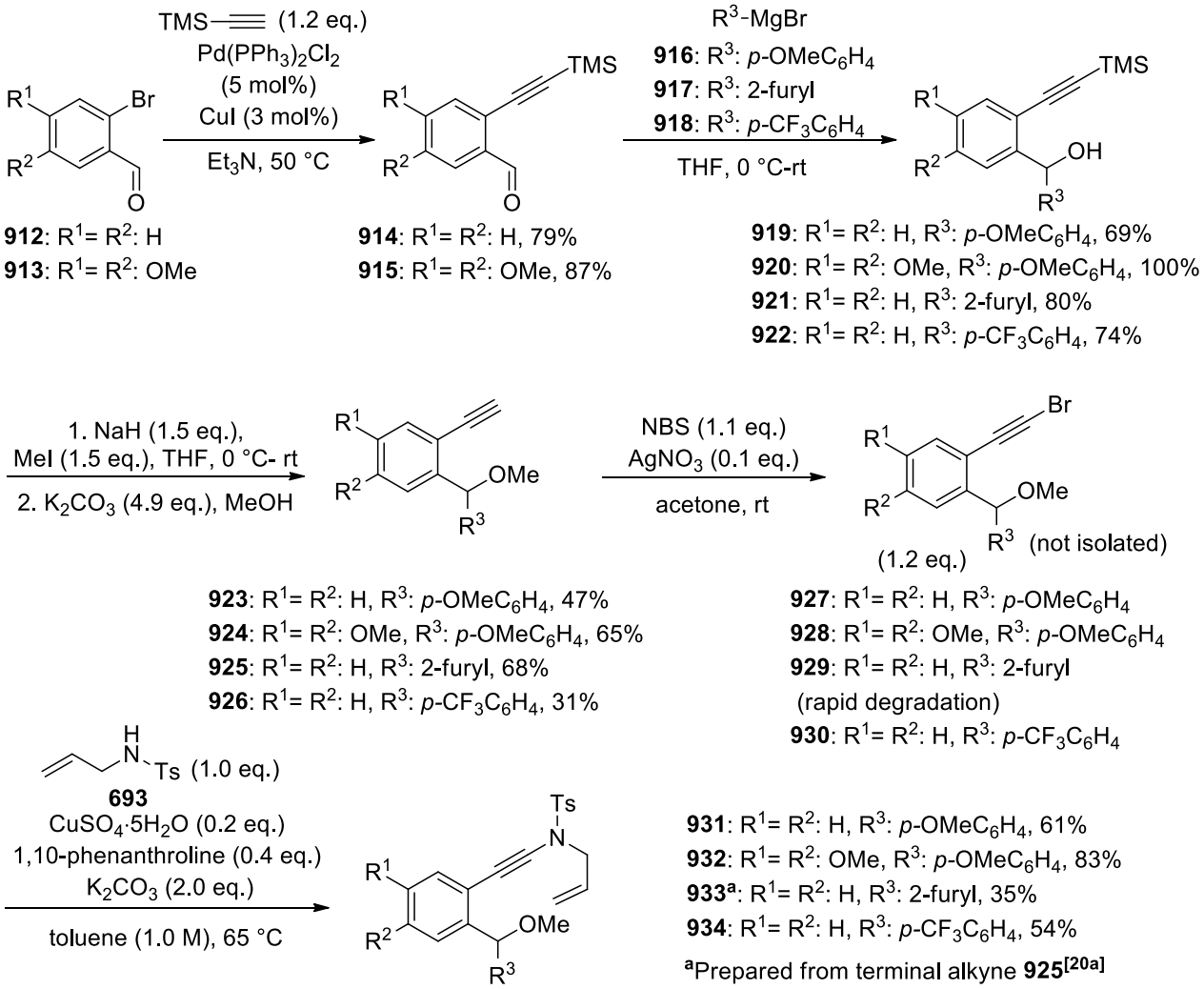


Figure 5: Investigating the substrate scope of the [1,5]-HT cascade reaction

4.3.2 Modification of the benzylic position

As shown in the above example, an unsubstituted phenyl ring at the benzylic position gave the desired polycycle in good yield. Thus, in order to further investigate the influence of the groups neighbouring the hydride donor, a series of ynamides bearing either electron-rich or electron-deficient aryl groups attached to the benzylic position were then prepared in a six-step reaction sequence (Scheme 126).

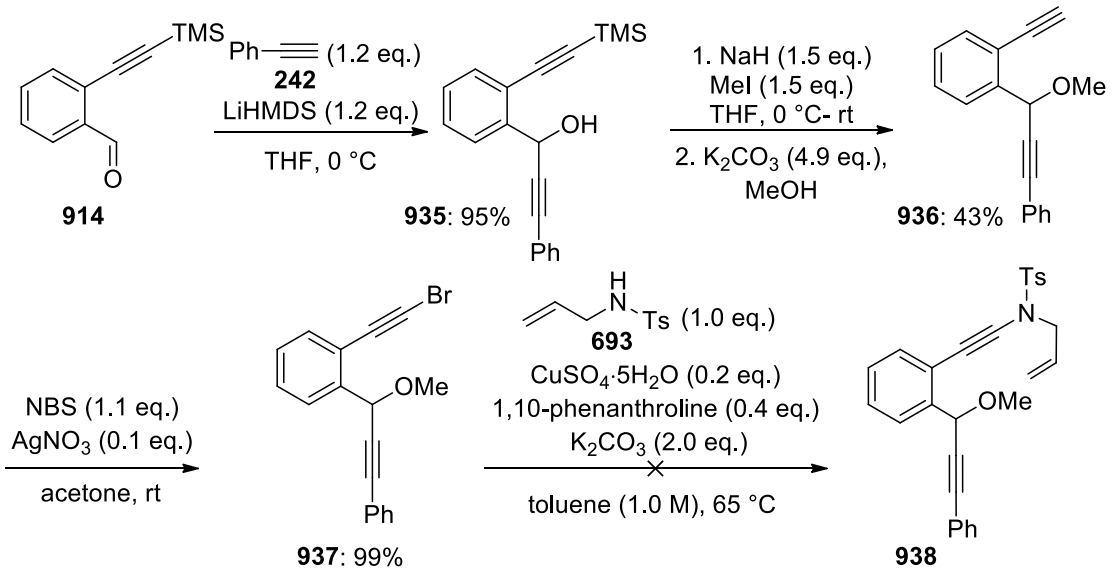
Starting from 2-bromobenzaldehydes **912** and **913**, Sonogashira coupling with trimethylsilylacetylene gave the protected alkynes **914** and **915** respectively in high yields. Freshly prepared Grignard reagents **916**-**918** were then added to the aldehydes to give the corresponding secondary alcohols **919**, **920**, **921** and **922** in good yields. Subsequent methylation of the alcohol and cleavage of the silyl group in a one pot process, as described by Toste and co-workers[197] gave the terminal alkynes **923**-**926**. Bromination of the terminal alkynes with freshly recrystallized *N*-bromosuccinamide gave the desired bromoalkynes **927**-**930** in high yields. The recrystallization of the *N*-bromosuccinamide proved crucial, as traces of impurities of the commercially available reagent led to complex mixtures. The brominated alkynes were then subjected directly to the next step without further purification, due to their lack of stability. Copper-catalysed coupling between the bromoalkynes and the tosyl-protected sulfonamide **693** gave ynamides **931**-**934** in moderate to good yields[20b] (for further details about copper catalysed ynamide syntheses, please refer to Chapter 3).



Scheme 126: Six-step reaction sequence for the preparation of the starting ynamides

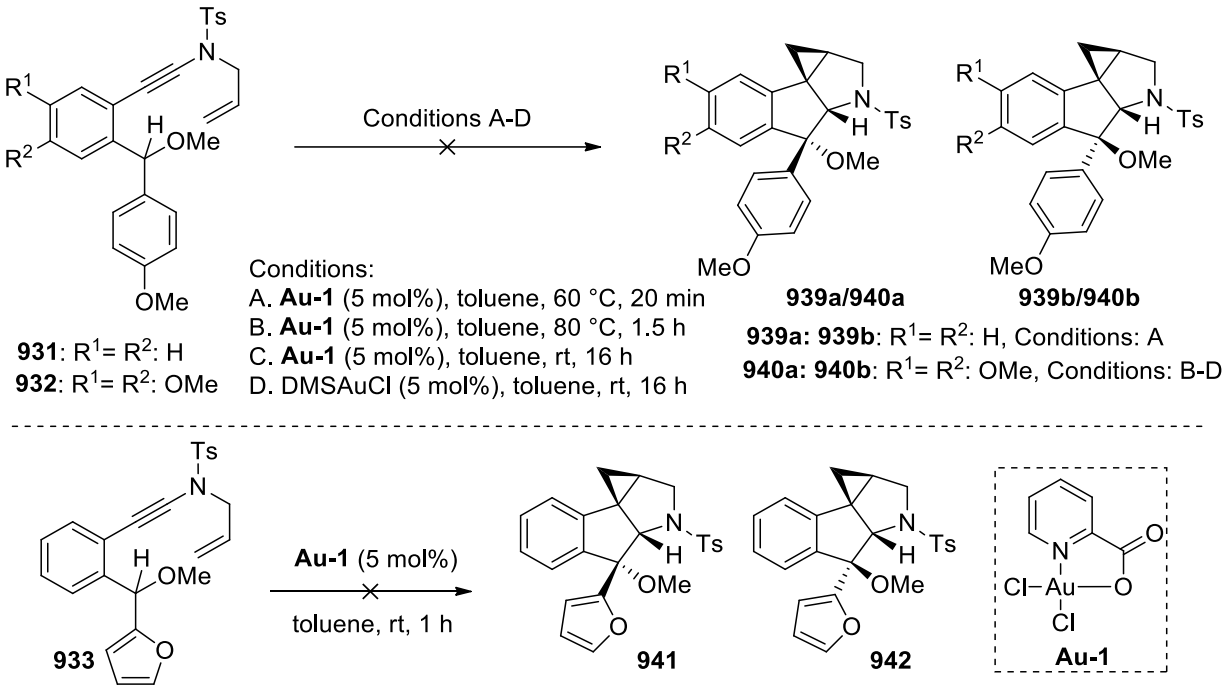
In order to investigate the reactivity of a precursor with two different in nature triple bonds, the synthesis of ynamide **938** was attempted (Scheme 127). Initially, aldehyde **914** was treated with lithiated phenyl acetylene to give diyne **935** in excellent yield. Methylation of the secondary alcohol followed by deprotection of the silylated alkyne formed alkyne **936**. Although bromination of the terminal alkyne gave the corresponding acetylene in excellent yield, further

treatment with sulfonamide **693** under copper catalysis did not form ynamide **938**. Degradation of the starting bromoalkyne was instead observed, possibly due to propargylic activation.



Scheme 127: Towards the preparation of an alkynyl-containing ynamide

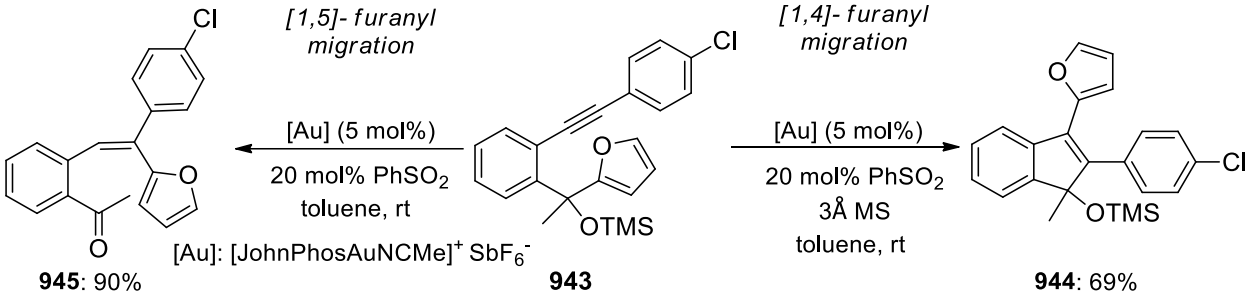
When ynamides **931** and **932** were subjected to the optimised gold-catalysed conditions for the formation of polycycles **939** and **940** respectively, complex mixtures were obtained in each case (Scheme 128). In particular, although ynamide **931** was totally unreactive at room temperature, when heated up at 60 °C consumption of starting material was observed within 20 minutes. ^{1}H-NMR analysis of the crude residue indicated a very complex mixture and attempts at purification were unsuccessful. When ynamide **932** was treated with gold(III) precatalyst or gold(I) species at room temperature or at 80 °C complicated mixtures were also formed.



Scheme 128: Electron-rich systems under gold-catalysis

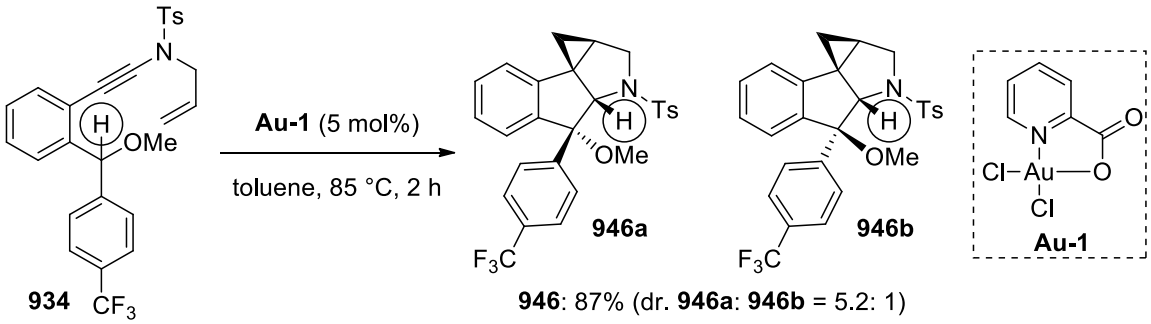
In addition, furyl-containing ynamide **933** gave similar results when treated with gold(III) precatalyst at room temperature, whereby the obtained complex mixture could not be purified (Scheme 128).

The observed, uncontrollable side reactivity of electron-rich aryl groups on the benzylic position can be explained by the propensity of these systems to act as nucleophiles, even at room temperature (Scheme 129). Very recently, and while our research was ongoing, the Li and Liu research groups reported the 1,4- or 1,5-migration of electron rich heteroaryl groups (such as furans) across gold-activated alkynes.[198] In our case, the complexity of the mixtures acquired does not allow a definite conclusion to be drawn about the formation of the corresponding byproducts, however the possibility of heteroaryl group migration should not be ruled out.



Scheme 129: Li and Liu's 1,4- and 1,5-furanyl migration towards gold-activated alkynes

On the other hand, when ynamide **934**, bearing an electron-deficient aryl group on the benzylic position was subjected to gold catalysis, it reacted cleanly forming the tetracyclic system **946** in high yield as a 5.2:1 diastereomeric mixture (Scheme 130). Elevated temperature of 85 °C is essential in this case, as at lower temperatures no conversion was observed.



Scheme 130: Electron-deficient systems under gold-catalysis

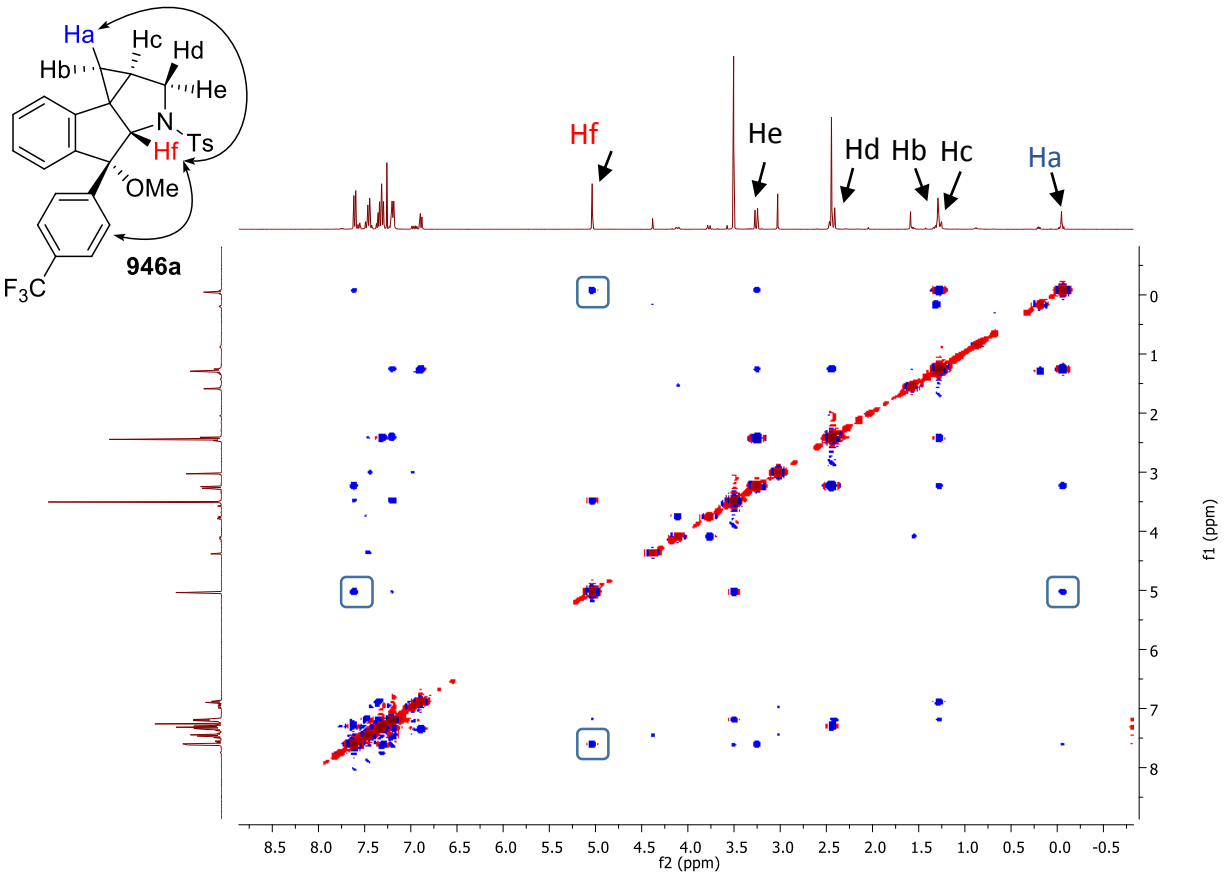
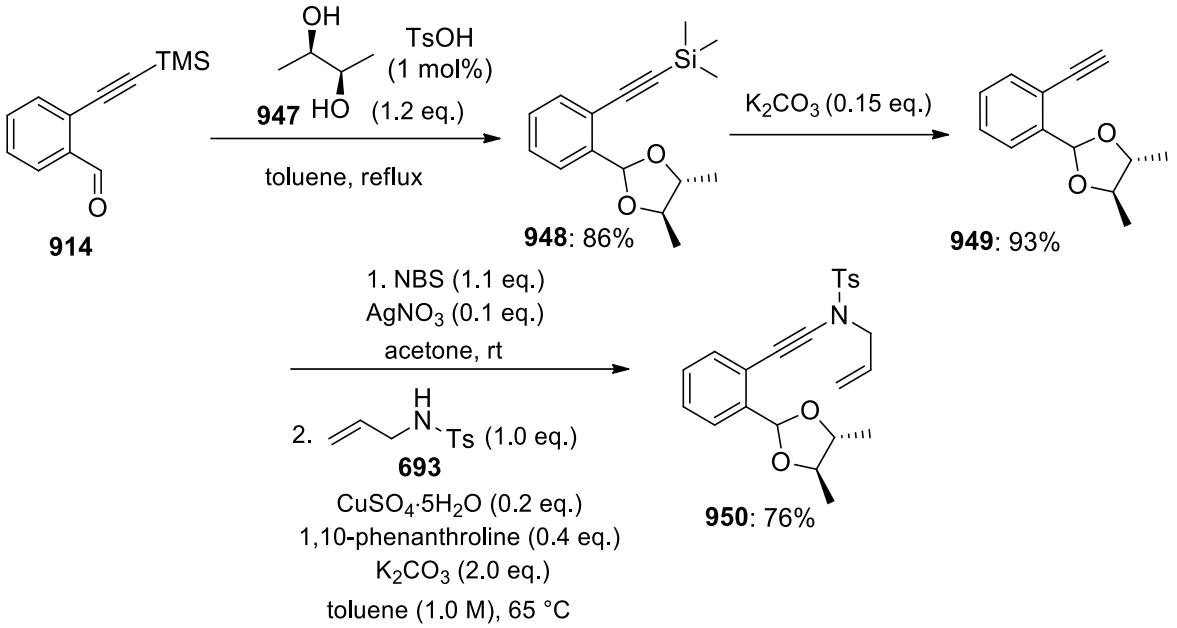


Figure 6: n*O*e experiment confirming the *syn*-relationship between the phenyl substituent, the cyclopropyl ring and the migrating hydrogen

The relative stereochemistry of the major diastereomer was clearly determined by n*O*e experiment, in which the aromatic ring is on the same side hydrogen which has been migrated (Figure 6). Notably, both stereoisomers have a fixed geometry across the junction of the two 5-membered rings: the migrating hydride is on the same side as the cyclopropyl ring. The explanation of this diastereoselectivity trend will be discussed in a following section.

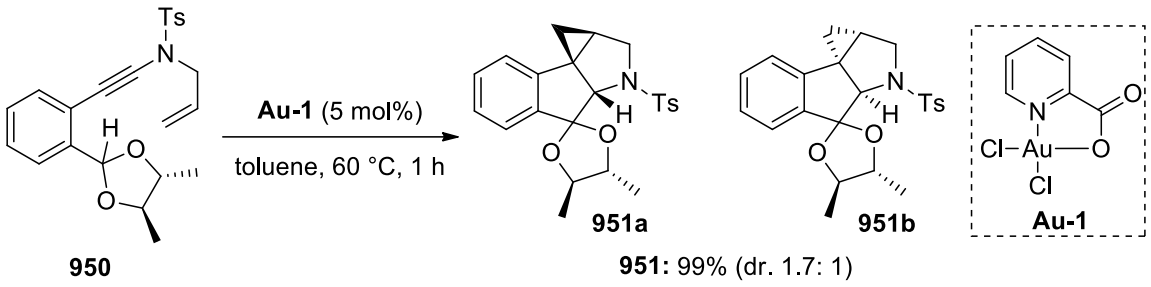
As mentioned previously, ynamide with an acetal as a hydride donor was well-tolerated under the catalysis conditions. Thus, enantiomerically pure ynamide **950** was constructed in five steps from commercially available 2-bromobenzaldehyde (Scheme 131).



Scheme 131: Reaction sequence for the formation of chiral ynamide.

Sonogashira coulpling, followed by acetal formation with the use of the chiral (*2R,3R*)-butane-2,3-diol **947**, gave silylated alkyne **948**. Deprotection of the alkyne, subsequent bromination and copper-catalysed coupling afforded ynamide **950** as a single enantiomer.

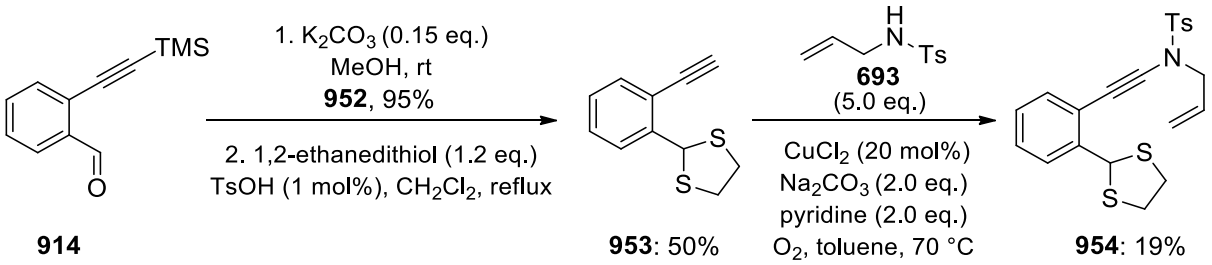
Clean and rapid reactivity was observed when ynamide **950** was employed in the gold-catalysed [1,5]-hydride shift/cyclisation cascade (Scheme 132). The tetracycle **951** was obtained in excellent yield in a mixture of two diastereomers (dr. 1.7:1). Unfortunately, the two isomers could not be separated by flash column chromatography or recrystallisation, while overlapping resonances on the ^{1}H-NMR did not allow the absolute structure determination by n*O*e experiment. Following up from the previous example, the same trend was observed with the migrating hydride adopting a *syn*-relationship with the cyclopropyl ring (for the corresponding n*O*e spectrum which indicates this relationship, please refer to the appendix).



Scheme 132: Stereoinduction using chiral acetal 950 under gold-catalysis

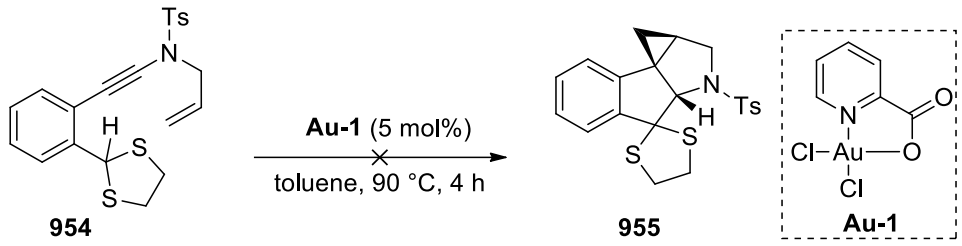
The ability to induce stereocontrol, even at a low extent, potentially opens new routes for investigation, as accessing a separable enantiopure diastereomer may be possible (eg. by modifying the substituents on the acetal and/or the catalyst employed).

Ynamide **954** with an incorporated thioacetal group was prepared in three steps (Scheme 133). In this case, deprotection of the silyl protected alkyne (**914** to **952**) is required prior to the introduction of the thioacetal subunit, as no product was formed when the bulky silylated alkyne was instead employed under the standard conditions for the formation of the corresponding silylated thioacetal. Subsequent bromination of the terminal alkyne **953** was unsuccessful, thus an alternative copper-catalysed coupling of the terminal alkyne and sulfonamide **693** was used,[20a] forming the ynamide **954** albeit in poor yield.



Scheme 133: Formation of ynamide 954, which contains a cyclic thioacetal group

However, ynamide **954** proved totally unreactive even at high temperature, leading to degradation of the starting material after 4 hours (Scheme 134). This result indicates the decreased donating ability of the cyclic thioacetal group which is in agreement with several examples in the literature, reporting that cyclic thioacetals are in general much less reactive hydride donors than acetals.[157],[166]

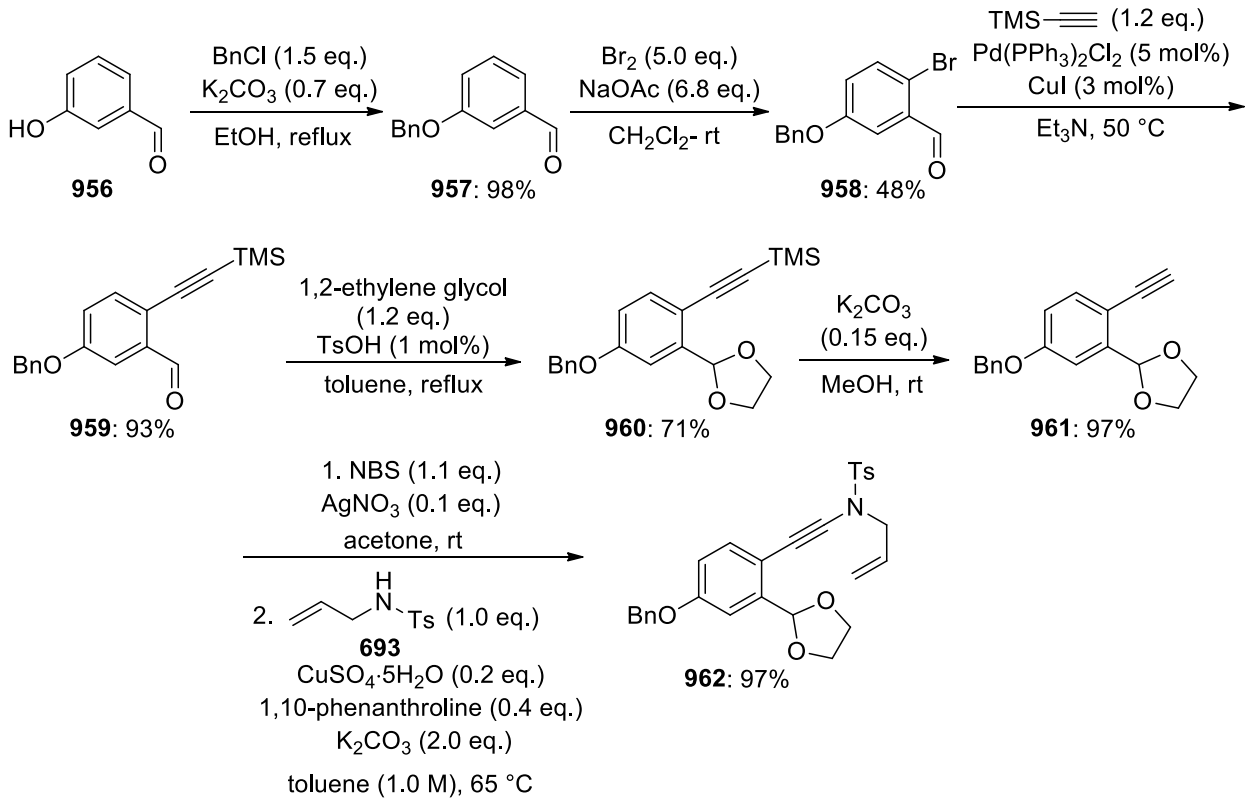


Scheme 134: Ynamide with a cyclic acetal subunit under gold-catalysis

4.3.3 Modification of the hydride donor-acceptor linker

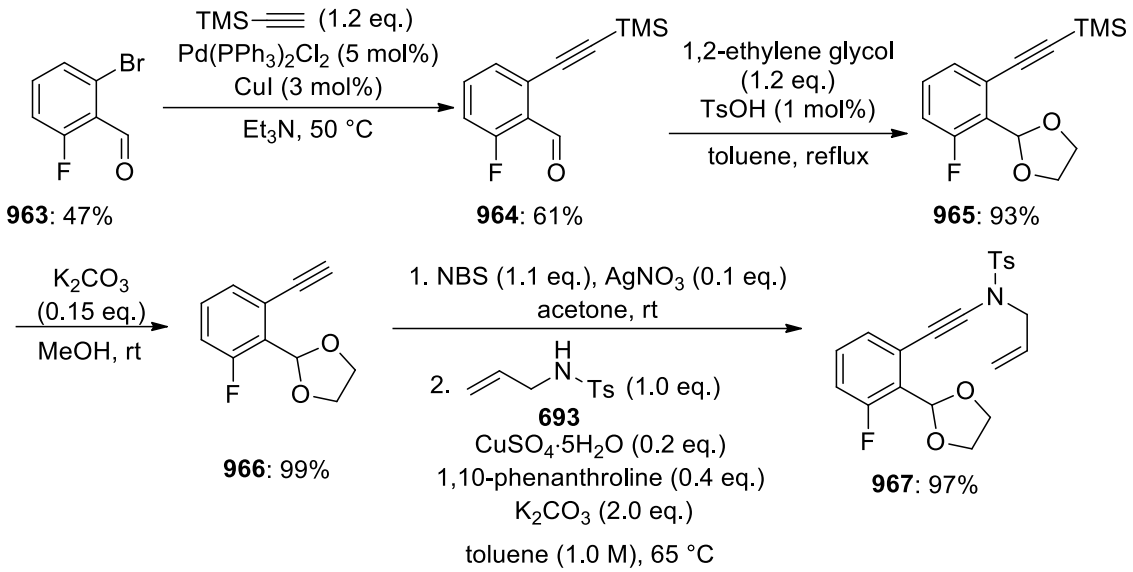
4.3.3.1 Aromatic systems

Alteration of the hydride donor-acceptor linker was then explored, in an attempt to achieve alternative functionalised complexes. A benzyl ether was incorporated into the *meta*-position relative to the acetal (Scheme 135). Initially, benzylation of 3-hydroxybenzaldehyde **956** followed by bromination gave aldehyde **958**. Sonogashira coupling furnished alkyne **959**, which was then treated with ethylene glycol under acidic conditions to form acetal **960**. Deprotection (**961**), bromination and copper-catalysed coupling with the sulfonamide **693** gave ynamide **962** in excellent yield.



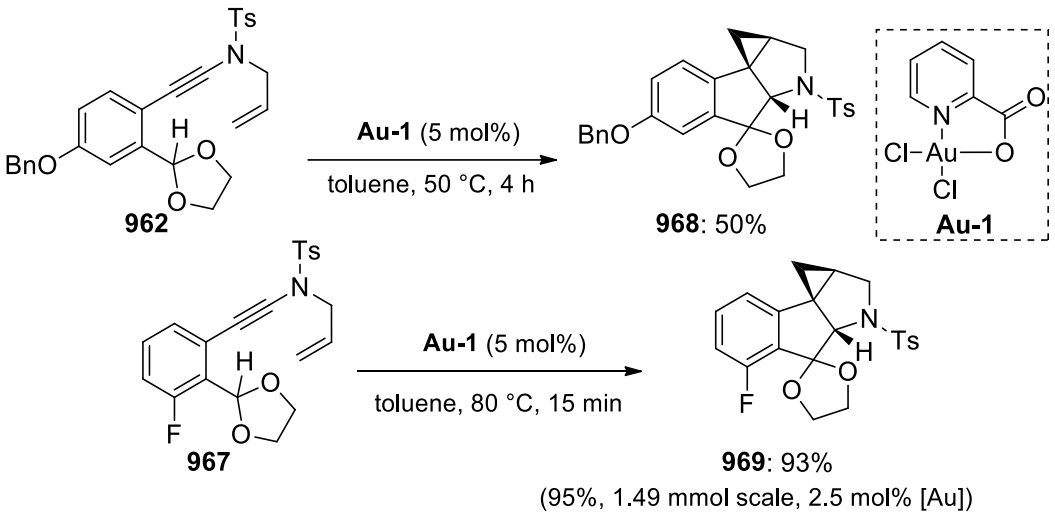
Scheme 135: Towards the formation of benzyl-substituted ynamides

The same reaction sequence was used for the preparation of fluoro-substituted ynamide **967**, starting from the commercially available 2-bromo-6-fluorobenzaldehyde **963** (Scheme 136).



Scheme 136: Incorporating a fluorine substituent in the *ortho*-relative to the acetal position

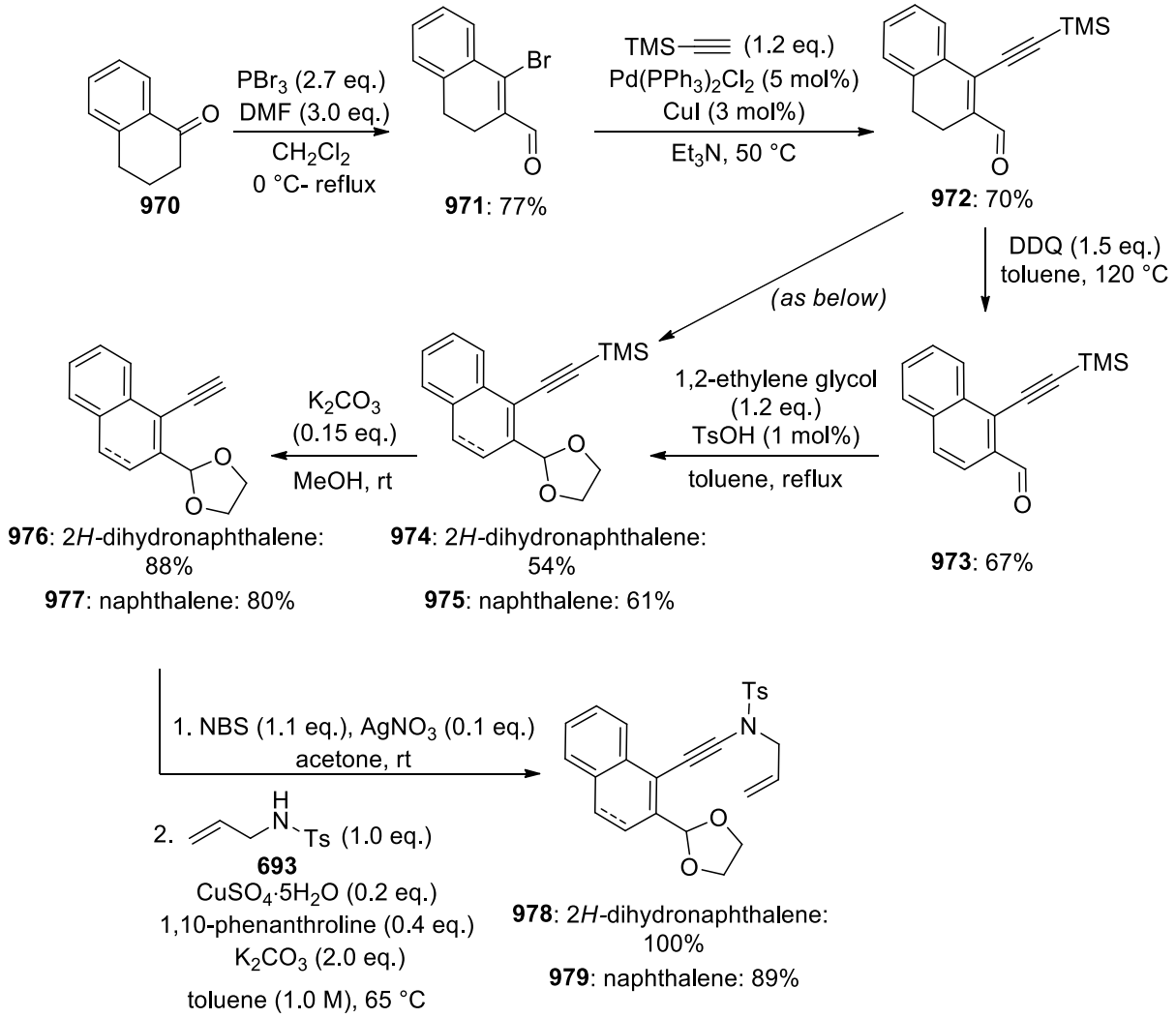
The electron donating, benzyloxy group positioned relatively *meta*- to the hydride donor and *para*- to the acceptor, was expected to decrease the 'hydricity' of the donor due to the inductive effect while, on the other hand, reduce the electrophilicity of the acceptor due to the mesomeric effect. These two synergistic effects were reflected to the reactivity of ynamide **962**, which was well-tolerated under the catalytic conditions, forming tetracycle **968** in a moderate yield (Scheme 137).



Scheme 137: Effect of EWG or EDG on the aromatic donor-acceptor linker

In the same context, the mesomeric effect of a fluoro-substituent in combination with its ability to bring the donor-acceptor components in close proximity (please refer to Scheme 107 for 'buttressing effect'), resulted in tetracycle **969** in excellent yield after 20 minutes (Scheme 137). The scalability of the reaction was demonstrated by the ability to subject 1.49 mmol of ynamide **967**, with lower catalyst loading without sacrificing the efficiency of the reaction.

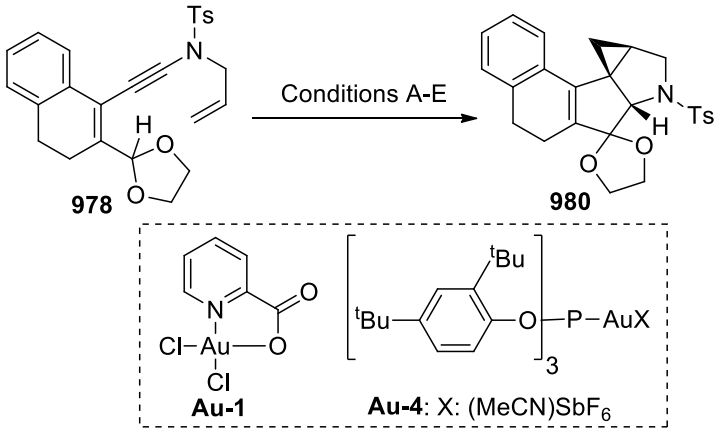
In comparison with these substrates, the effect of a substituent *ortho*- to the hydride acceptor was then explored. Thus, non-aromatic tetralone-derived ynamide **978** and naphthyl-containing ynamide **979** were prepared (Scheme 138).



Scheme 138: Preparation of tetralone- or naphthyl-containing ynamides

Starting from a Vilsmeier-Haack haloformylation reaction of α-tetralone **970**, the generated bromide was subjected to a Sonogashira coupling to give internal alkyne **972**. Aromatisation of alkyne **972** gave the corresponding naphthyl derivative **973**. The following reaction sequence, for the formation of both ynamides **978** and **979**, was the same as described in the previous examples.

Ynamide **978** reacted very slowly when subjected to the optimised conditions using a Au(III) precatalyst, giving the pentacyclic fused system **980** in low yield at high temperature (20% NMR yield, based on known quantity of internal standard, Scheme 139). It was hypothesised that a Au(I) catalyst, which adopts a linear geometry, would potentially increase the efficiency of the reaction. Indeed, when a Au(I) catalyst was employed instead, the reactivity was greatly enhanced, affording the polycycle **980** in good yield after 3 hours (Conditions B). The linear geometry of DMSAuCl, versus the square planar of Au(III), allows the acceptor to adopt the planar conformation which is required for the cascade (more aspects of the mechanism and the required geometry will be discussed in the next section). Other sources of Au(I) species bearing bulky NHC, phosphine or phosphite ligands, did not promote the reactivity, as not even traces of **980** were observed. The bulky ligands coordinated to the metal potentially do not allow activation of the π-system due to steric encumbrance with the tetralone backbone.



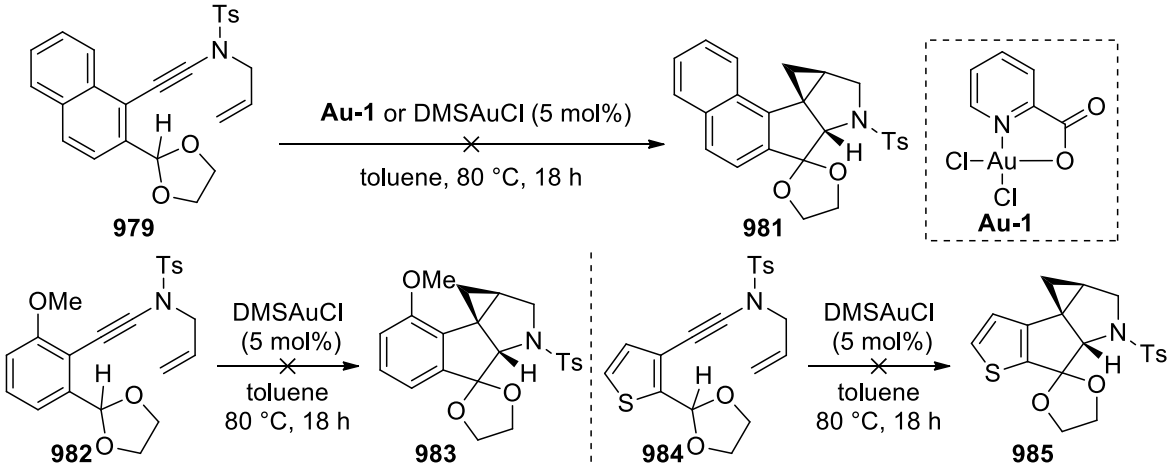
Conditions A-E:
A. **Au-1**, toluene, 80 °C, 18 h, **980**: 20%[a]
B. DMSAuCl, toluene, 80 °C, 3 h, **980**: 69%[b]
C. IPrAuCl, toluene, 80 °C, 8 h, **980**: 0%
D. PPh_3AuCl, toluene, 80 °C, 8 h, **980**: 0%
E. **Au-4**, toluene, 80 °C, 8 h, **980**: 0%
[a]NMR yield baced on a known quantity of internal standard
[b]isolated yield

Scheme 139: Tetralone-based ynamide under gold catalysis

Less flexible, hindered systems did not give the desired transformation, even when DMSAuCl was used (Scheme 140). Ynamide **979** was unreactive at room temperature and on heating to 80

°C, degradation of the starting precursor mainly occurred. Along the same lines, ynamide **982**, with a methoxy substituent 'blocking' the *ortho*-position, did not exhibit the desired reactivity either, with degradation pathways being favoured at high temperatures. Based on other gold-catalysed processes when similar *ortho* methoxy-substituted ynamides and alkynes are employed,[199],[200] it can be assumed that activation by the metal is occurring and the lack of the reactivity can be attributed to the inability of the gold keteniminium to adopt the planar geometry required for the [1,5]-hydride transfer to proceed.

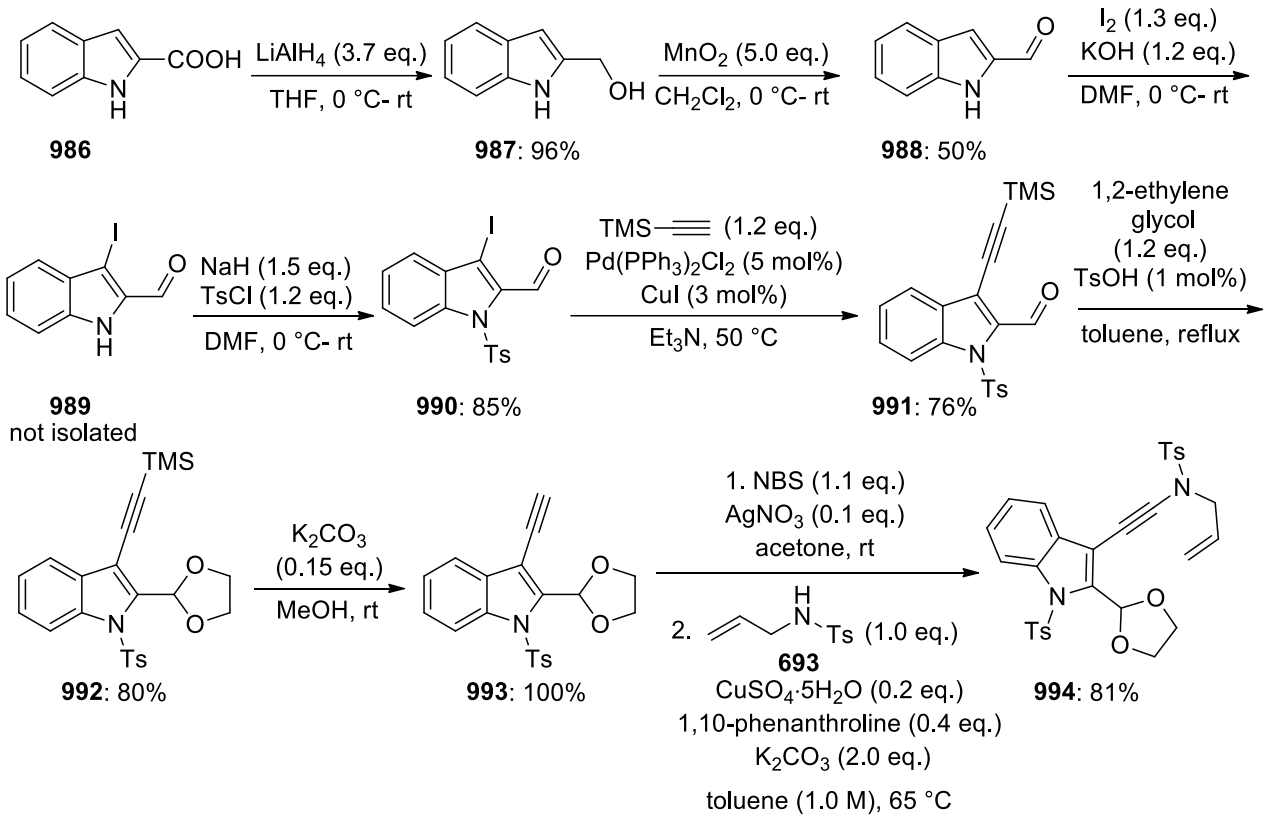
The same trend was observed when rigid, thiophene-based ynamide **984** was employed. Traces of the tetracycle **985** was formed (<1.5% NMR yield based on a known quantity of an internal standard), while only 41% of starting material was recovered. The larger dihedral angles of a five-membered ring, which push the donor-acceptor components further away from one another, might be the reason why **984** was completely inactive. Ynamides **982** and **984** were tested with Au(III)-precatalyst **Au-1** too and similar results were acquired (experiments by Holly Adcock).



Scheme 140: Effect of steric bulk around the π-system

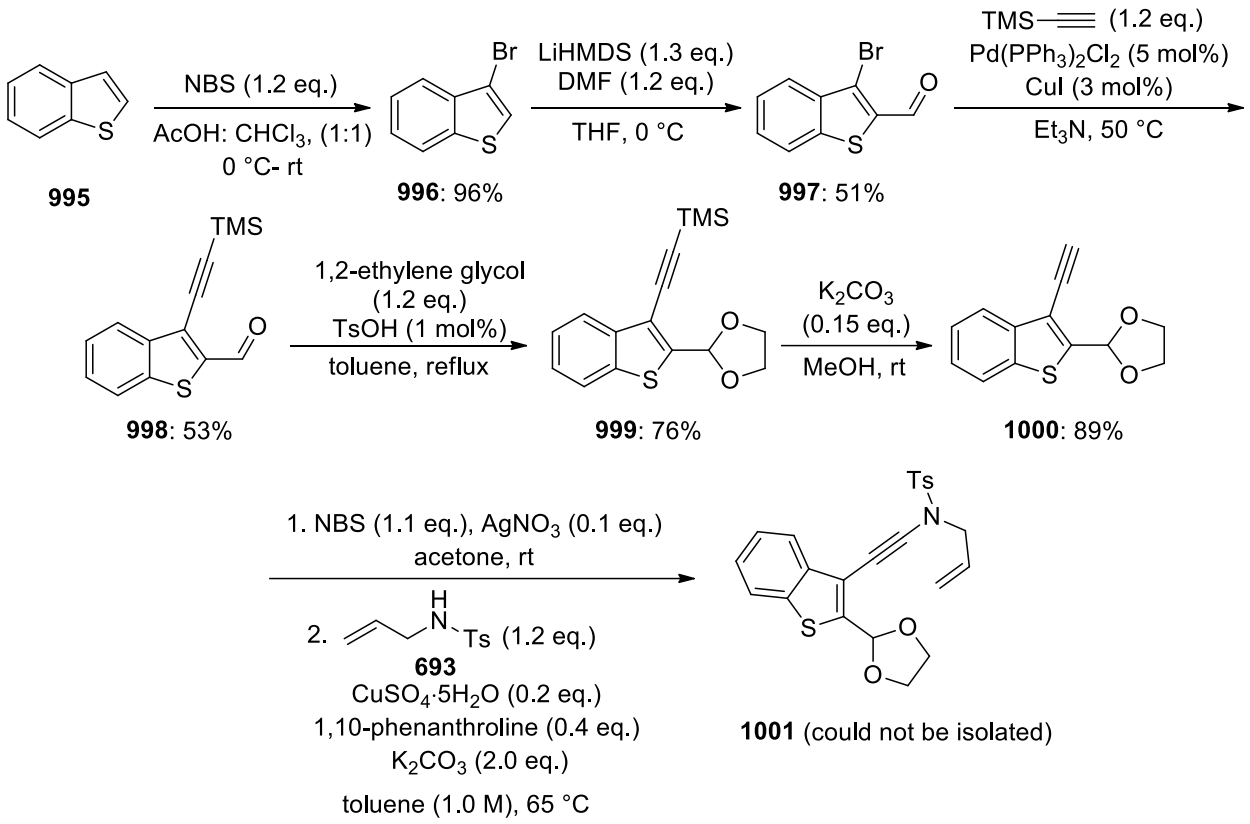
Alongside the thiophene synthesis, ynamides **994** and **1001**, containing electron-rich heteroaryl groups, such as an indole and a benzothiophene core, were prepared (Scheme 141). Indoles are abundant motifs in bioactive natural products, thus elegant methods furnishing complex indole-containing structures are particularly attractive.[111],[201]

The synthesis of this ynamide **994** was not straightforward and several test reactions based on alternative, more flexible synthetic plans proved to be unsuccessful. Herein, only the successful synthetic route is disclosed. The synthesis initiates with reduction of the commercially available indole-2-carboxylic acid **986** to form primary alcohol **987**, which was then oxidised to the corresponding aldehyde **988**. These two steps can be performed in one-pot process without isolation of the intermediate alcohol. Iodination of the 3-position of the indole gave **989** which was very unstable at room temperature, thus tosylation of the nitrogen was followed directly giving indole derivative **990**. Attempts to reverse the order of the steps and instead protect the indole before the introduction of the iodine at the 3-position, were completely unsuccessful with the iodination step showing no conversion. This is likely due to the reduced nucleophilicity of the 3-position of the indole when the nitrogen is protected with an electron withdrawing group. Furthermore, Sonogashira coupling between indole **990** and the corresponding terminal ynamide to furnish directly ynamide **994** showed complex mixtures potentially due to degradation of the relatively unstable starting indole derivative **990**. Having in hand this indole derivative, the subsequent synthetic steps are the same as the ones described in the above substrates affording the ynamide **994** in overall decent yield.



Scheme 141: Formation of indole-derived ynamide 994

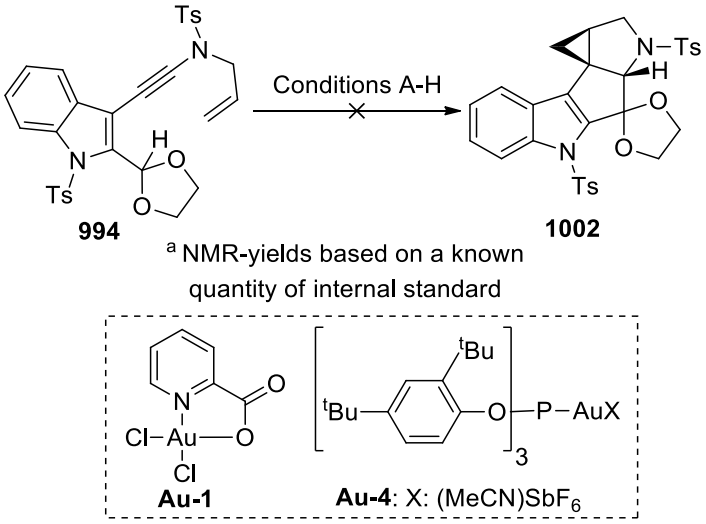
Following up the studies of electron-rich heteroaryl groups, the synthesis of the benzothiophene analogue **1001** was attempted (Scheme 142).



Scheme 142: Synthesis of thiophene-containing ynamide 1001

Starting from bromination of the 3-position of benzothiophene **995** followed by formylation of the 2-position, derivative **997** was formed in a moderate yield. Following the same reaction sequence as above, ynamide **1001** was prepared in excellent yield according to ^{1}H-NMR spectroscopy. Due to the fact that the corresponding bromoalkyne was very polar, the stoichiometry of the copper-catalysed coupling was reversed, using excess of sulfonamide **693**, to avoid co-elution of products. However, unfortunately, the product co-eluted with the excess of the sulfonamide **693** and the ynamide could not be isolated by column chromatography. Several attempts to remove **693** by basic work-up were also unsuccessful.

With the corresponding indole substrate in hand, ynamide **994** was subjected under the optimised gold-catalysed conditions for the cyclisation cascade at room temperature (Scheme 143). No reactivity was observed by TLC in this case, until the temperature was slowly increased to 90 °C, however a complex mixture was obtained at this point. Many other sources of Au(I) and Au(III) catalysts were tested in combination with different solvents and temperatures, yet the same outcomes were obtained. The desired polycycle **1002** could be observed by ^{1}H-NMR spectroscopy in most of the cases but the complexity of the mixture rendered either the isolation of the product or the characterisation of the side products impossible. The origin of the uncontrollable side reactivity cannot be clearly defined at this point, the low conversion into tetracycle **1002** can speculatively be due to the distance between the hydride donor-acceptor fragments.



Conditions[a]:
A. **Au-1**, toluene, 90 °C, 2 h, **1002**: <0.1%
B. **Au-1**, toluene, 90 °C, 5.5 h, 4Å MS, **1002**: 11%
C. **Au-1**, toluene, 90 °C, 6 h, **1002**: 23%
D. **Au-1**, 1,4-dioxane, 90 °C, 25 h, **1002**: 13%
E. **Au-4**, 1,4-dioxane, 90 °C, 25 h, **1002**: 2.5%
F. IPrAuCl/ AgOTs, 1,4-dioxane, 90 °C, 25 h, **1002**: 0%
G. (p-$CF_3Ph)_3$AuCl/ AgOTs, 1,4-dioxane, 90 °C, 25 h, **1002**: 1.5%
H. DMSAuCl, toluene, 80 °C, 18 h, **1002**: 2.8%

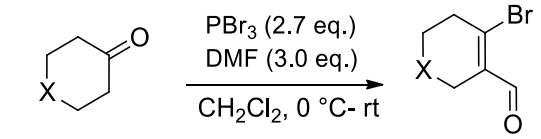
Scheme 143: Indole derivative 994 in gold-catalysis

Being discouraged by the unsuccessful results of the indole derivative **994**, no further attempt was made to repeat the synthesis of the analogous benzothiophene derived ynamide **1001**.

4.3.3.2 Aliphatic systems

In order to further explore the scope of the reaction, the interest was turned towards ynamides bearing cyclic aliphatic backbones, as these hydride donor-acceptor linkers are very rarely displayed in hydride transfer reactions. Moreover, Csp^3-rich complex, non-aromatic systems are attractive and potentially useful frameworks.

The preparation of these substrates started with the commercially available 4-tetrahydropyranone and 4-piperidinone, which was first tosylated to provide more stability and avoid side reactions in later steps. The ketones were first converted into the brominated carbaldehydes **1005** and **1006** respectively by Vilsmeier-Haack haloformylation reactions (Scheme 144). Although this reaction was first established in the late 20's and since then numerous improved modifications made this method a powerful tool for constructing 2-bromoaldehyde derivatives,[202] in the current case this first step proved very challenging.



1003: X: NTs, 99%
1004: X: O

1005: X: NTs, 8%
1006: X: O, 18%

Scheme 144: Challenging Vilsmeier-Haack haloformylation

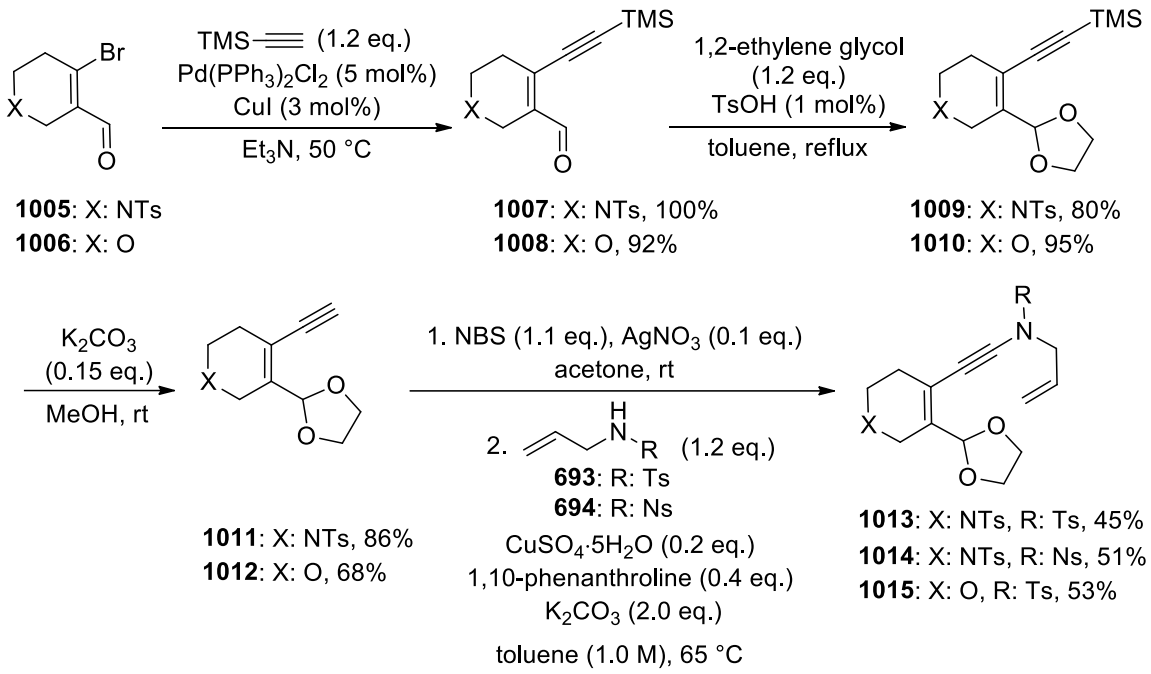
According to recent literature, the conversion of **1003** and **1004** to **1005** and **1006** respectively is quantitative when 3.0 equivalents of DMF and 2.7 equivalents of PBr_3 are used. Following very

meticulously the same experimental procedures,[203],[204] and despite the fact that the reactions were completed by TLC and sole products were formed, **1005** was acquired in 8% yield and **1006** in 18% yield. Unfortunately the source of this very poor reactivity could not be identified, despite the broad investigation, giving yields lower than 20% for both substrates in every case. Freshly acquired PBr_3, anhydrous DMF and CH_2Cl_2 or $CHCl_3$ (both checked by Karl Fischer titration), reversing the order of addition into the reaction mixture, tuning the temperature and the reaction time, alternating the solvent used on the aqueous work-up and increasing the number of the extractions, did not improve the yields. The results were the same even when the solvent was used directly from the bottle. Additionally, varying the purification by flash column chromatography or by filtration through a small silica pad did not increase the yields.

The next steps towards the synthesis of the aliphatic ynamides **1013**-**1015** involved the same reaction sequence as the one described for the aromatic substrates (Scheme 145). In these cases, the acetal products **1009** and **1010** are relatively unstable at high temperature, so the formation of these products has to be monitored very carefully by TLC, as degradation was observed in prolonged reaction times.

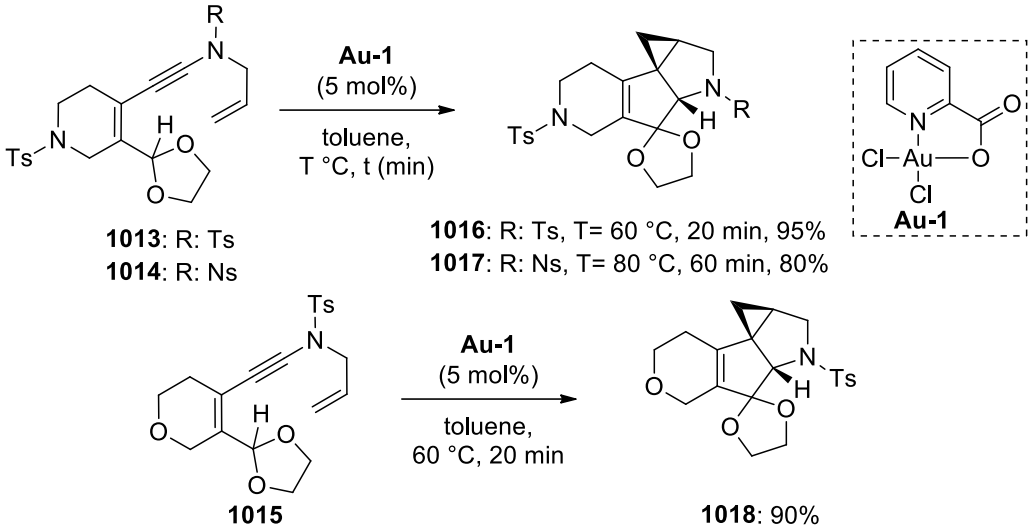
Most of the intermediate products of this reaction sequence were acquired in high yields and were purified from work-up, and so they were subjected to the following steps without further purification. The only exception being the final copper-catalysed coupling between the corresponding bromoalkynes and sulfonamides **693** and **694**, as the former are relatively unstable when heated in high temperature. Thus, tosyl or nosyl protected ynamides **1013**/**1015** and **1014** were obtained in medium yields. It should be also highlighted that the quality of the

N-bromosuccinamide is important; recrystallized reagent is essential to avoid cleavage of the sensitive acetal subunit of **1011** and **1012**.



Scheme 145: Preparation of ynamides with cyclic-aliphatic backbones

Pleasingly, these substrates proved very reactive when treated with Au(III), giving aliphatic tetracyclic fused systems in excellent yields (Scheme 146). In particular, ynamides **1013** and **1015**, although unreactive at room temperature, they were fully converted into the corresponding **1016** and **1018** as single diastereomers at 60 °C, in 20 minutes. Additionally, the formation of nosylated derivative **1017**, at higher temperature, can potentially allow selective deprotection of the different sulfonyl group leading to the corresponding secondary amine.



Scheme 146: Systems with cyclic aliphatic backbones under gold catalysis

Consistently with the previously observed relative stereochemistry, a *syn*-relationship between the cyclopropyl group and the migrating hydrogen was shown by n*O*e experiment in this case as well (Figure 7).

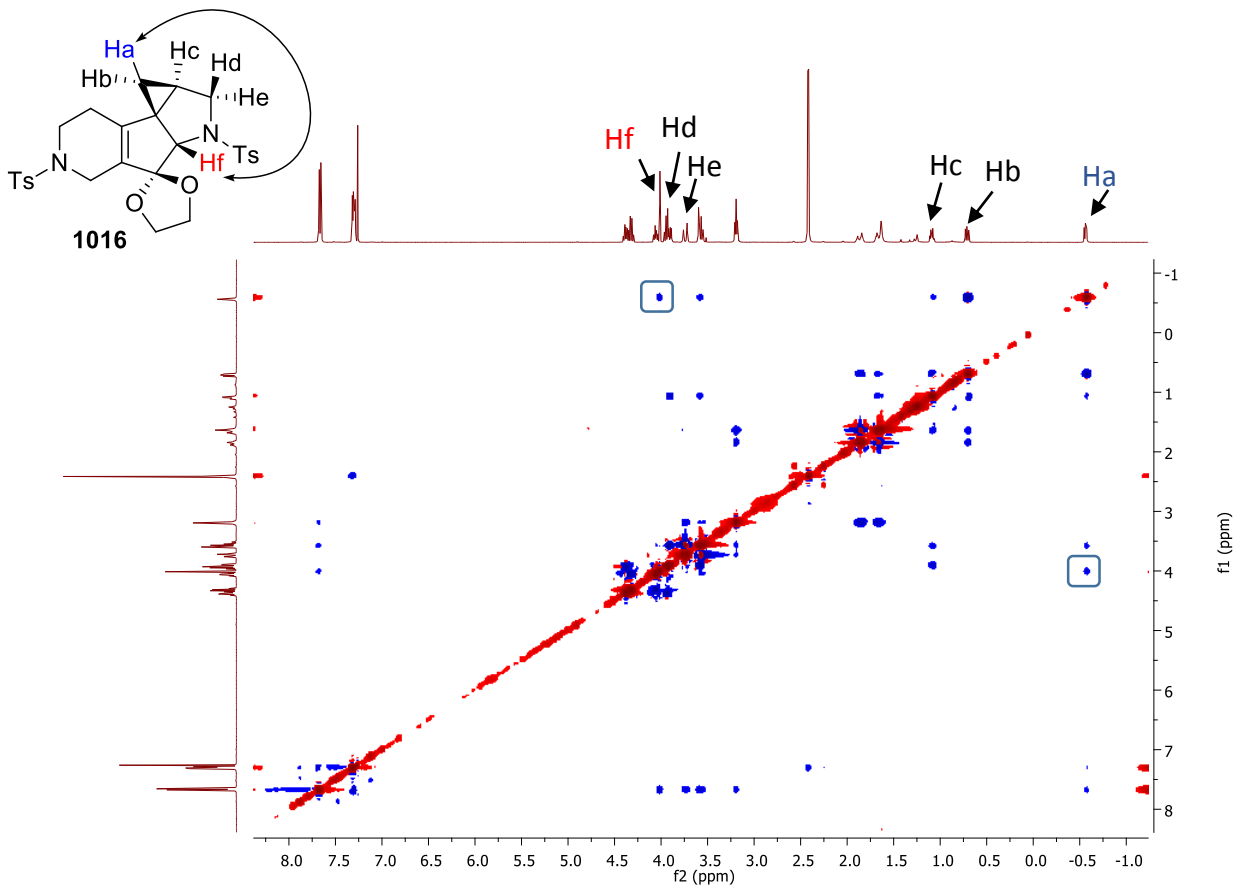
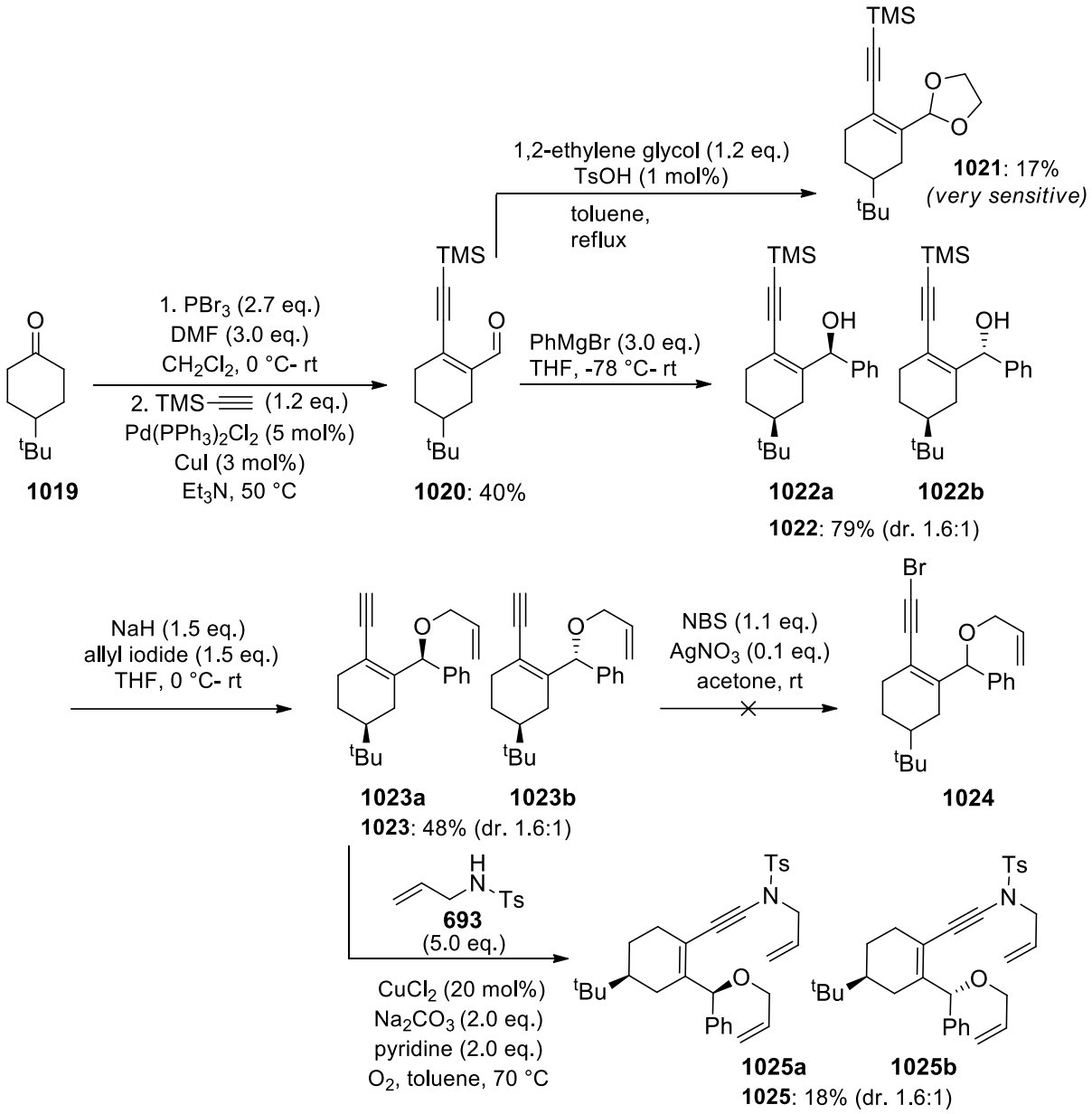


Figure 7: n*O*e experiment confirming the *syn*-relationship between the cyclopropyl ring and the migrating hydrogen

Following up these successful results, ynamide **1025** with a *tert*-butyl substituent on the aliphatic backbone was prepared (Scheme 147).

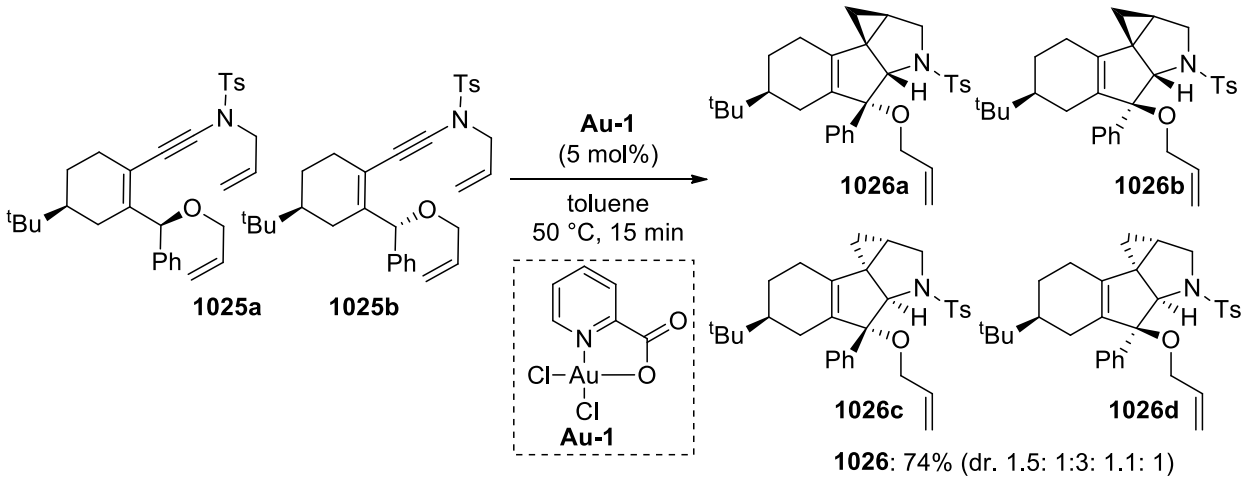


Scheme 147: Formation of cyclohexyl-based ynamide 1025 as a mixture of diastereomers

First, the internal alkyne **1020** was formed in modest yield (40% over two steps). Subsequent acetal formation gave alkyne **1021** in very low yield, which was very sensitive and prone to acetal cleavage in following steps, thus secondary alcohol **1022** was formed instead as a mixture of diastereomers. Allylation of the alcohol and deprotection of the triple bond gave terminal

alkyne **1023** which was subjected directly to the copper-catalysed coupling with sulfonamide **693** to give ynamide **1025** as a mixture of diastereomers, albeit in low yield. Unfortunately, bromination of **1023** did not give any product, thus the alternative coupling using the terminal alkyne seemed to be the only solution.

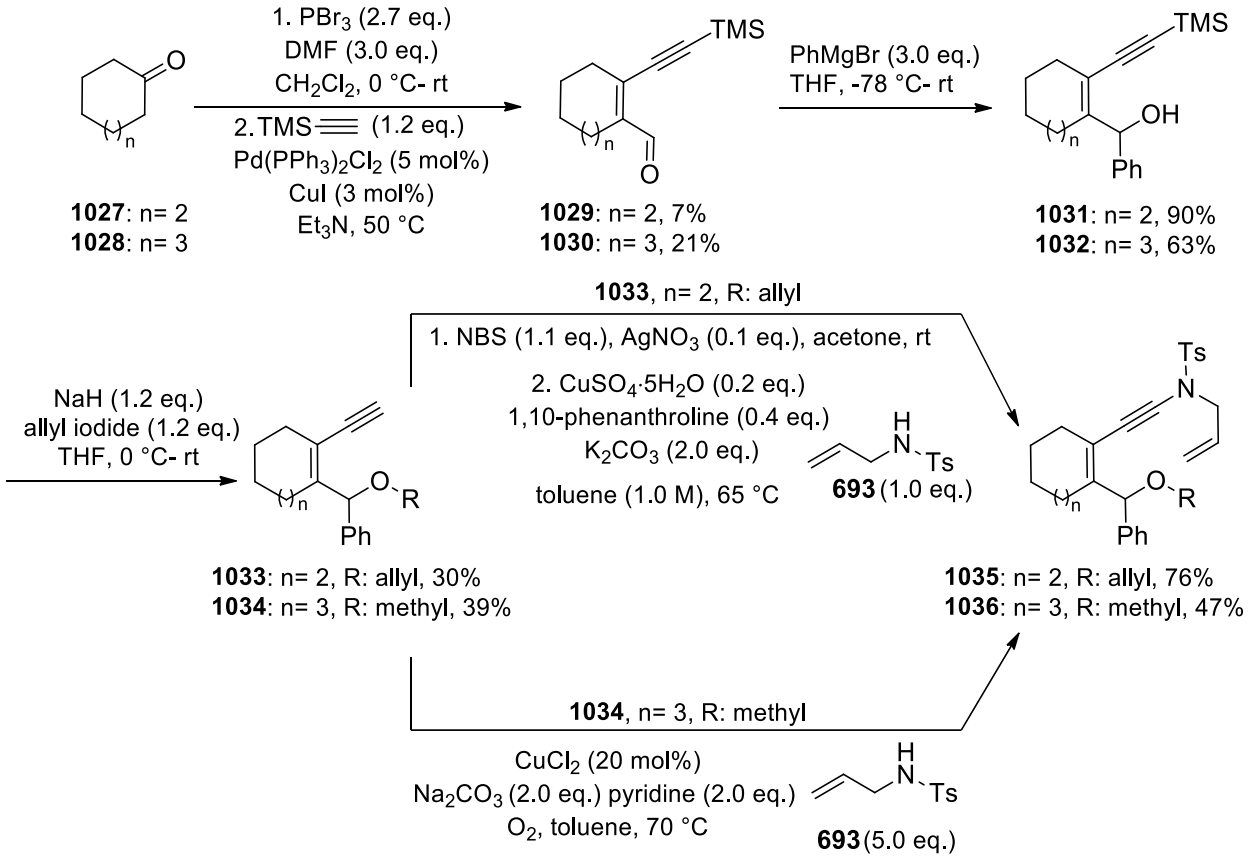
Although ynamide **1025** was very sensitive, it was well-tolerated when subjected to the gold-catalysed conditions, very rapidly giving a mixture of four diastereomers of tetracycle **1026** in good yield (Scheme 148). However, due to the high complexity of the ^{1}H-NMR spectrum, identification of the relative stereochemistry in the major diastereomer was not feasible.



Scheme 148: Cyclohexyl-based ynamide 1025 under gold-catalysis

Encouraged by these successful results, while aiming to determine the limits of this transformation, investigation of substrates bearing larger ring sizes was then followed (Scheme 149). The preparation of these precursors was similar to the above synthetic routes. The Vilsmeier-Haack reaction was problematic in both cases, forming aldehydes **1029** and **1030** in very low yields after two steps. Acetal formation from **1029** and **1030** led to many side products,

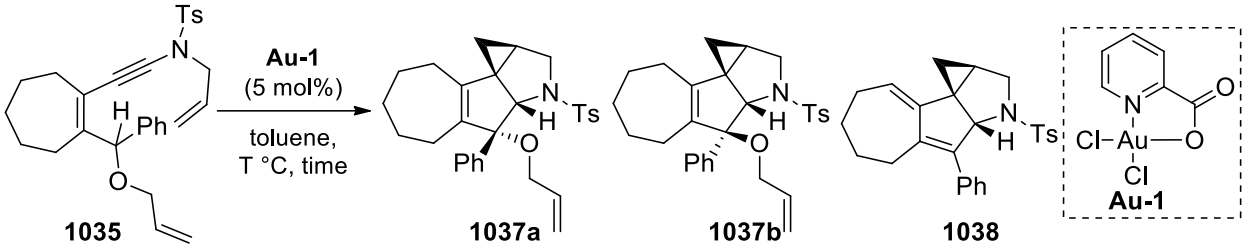
thus preparation of the secondary alcohols **1031** and **1032** were followed instead. Finally, copper-catalysed coupling of either bromoalkyne derived from **1033** or terminal alkyne **1034** with sulfonamide **693** gave ynamides **1035** and **1036** respectively in decent yields.



Scheme 149: Synthesis of ynamides containing 7- or 8-membered aliphatic cyclic system

When **1035** was treated with gold(III) precatalyst, no conversion was observed until the temperature reached 55 °C when a mixture of two products were formed very rapidly. The desired tetracycle **1037** was isolated as major product and alkene **1038** as the minor (Table 4). The stereochemistry of the major diastereomer **1037a** was assigned in analogy to other aliphatic systems (*vide infra,* n*O*e experiment for tetracycle **1042a,** Figure 8) and the selectivity observed was consistent with the aromatic systems (*vide supra*).

Table 4: Ynamide bearing a cycloheptyl group under gold-catalysis



Entry	T (°C)	Time	1037a	1037b	1038	dr. (1037a: 1037b)
1.	80	30 min	28%[a] (24%)[b]	20%[a] (7%)[b]	18%[a] (40%)[b]	1.4: 1[a] (3.3: 1)[b]
2.	55	20 min	46%[a] (40%)[b]	41%[a] (17%)[b]	4.6%[a] (17%)[b]	1.1: 1[a] (2.4: 1)[b]
3.	55	20 min	43%[a] (44%)[c]	38%[a] (23%)[c]	4.2%[a] (-)[c]	1.1: 1[a] (1.8: 1)[c]

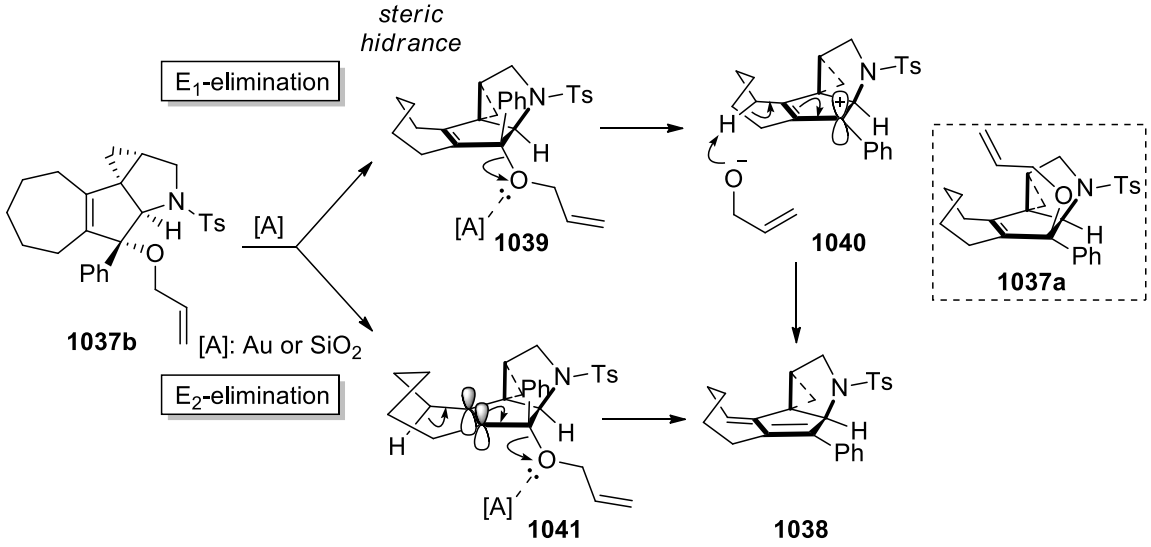
[a]Yields or diastereomeric ratio of crude mixtures, calculated by ^{1}H-NMR spectroscopy based on known quantity of internal standard (1,2,4,5-tetramethylbenzene); [b]Isolated yield (based on the diastereomeric ratio of the isolated mixture of both diasteromers) or diasteromeric ratio obtained by silica gel flash column chromatography; [c]Isolated yield (based on the diastereomeric ratio of the isolated mixture of both diasteromers) or diastereomeric ratio obtained by deactivated silica gel flash column chromatography

The formation of byproduct **1038** was increased when the reaction was run in higher temperature, in otherwise the same conditions. Surprisingly, purification of the crude mixtures with silica gel column chromatography gave alkene **1038** in much higher yields than the ones indicated by ^{1}H-NMR spectroscopy of the crude mixtures (comparing values inside and outside the parentheses). In parallel, the diastereomeric ratio of **1037** was altered through purification, by drastically decreasing the quantity of the minor diastereomer **1037b**. Isolation of diastereomers **1037a** and **1037b**, without great erosion of their ratio, was achieved when the

mixture was purified by deactivated silica gel column chromatography. In this case, isolation of alkene **1038** was not feasible. Finally, when a mixture of all three products stirred at room temperature for 18 hours in the absence of gold catalyst but in the presence of silica gel the ratio was only slightly altered (before SiO_2 treatment: **1037a**: **1037b**: **1038** = 2.4: 1: 1.1, after SiO_2 treatment: **1037a**: **1037b**: **1038** = 2.6: 1: 1.2).

Based on these experimental data, byproduct **1038** must be mainly derived from the minor diastereomer **1037b**, whereas the participation of **1037a** cannot be ruled out (inter-conversion between **1037a** and **1037b** is also possible). Co-elution of the two diastereomers hampered further investigation of the behaviour of each diastereomer separately.

An acid-catalysed E_1-elimination mechanism should be primarily considered for this process with the formation of relatively stable benzylic carbocation **1040**, however an E_2-elimination should not be excluded (Scheme 150, for clarity the enantiomer of **1037b** is shown in the scheme).

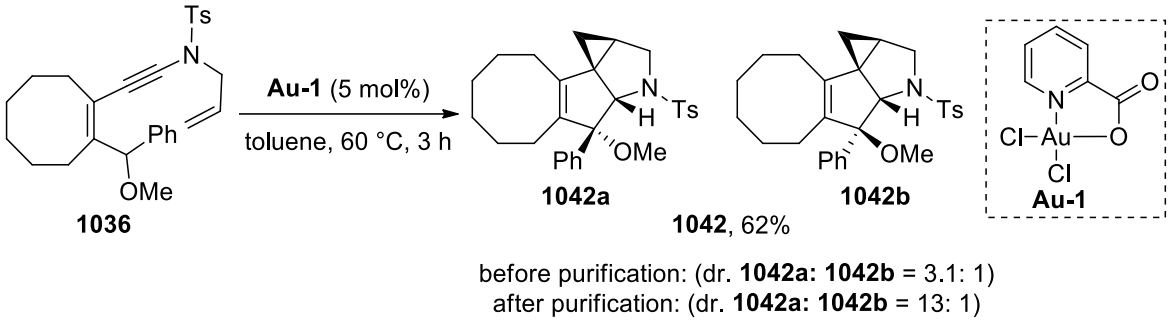


Scheme 150: Elimination of allyloxy group for the formation of alkene 1038

Steric factors can be envisaged being responsible for **1037b** undergoing allyloxy elimination. In **1037b**, the phenyl group is on the same side as the nitrogen-containing 5-membered ring; elimination of the allyloxy group results in planarization of the system (if proceeds *via* E_1 fashion), which releases this steric encumbrance as the phenyl group is no longer on the same side as the nitrogen-containing 5-membered ring. On the other hand, in **1037b**, efficient orbital overlap between the π-system and the oxygen σ* orbital can be achieved, promoting elimination of the allyloxy group in E_2-fashion.

It appears clear that the gold-catalysed conditions are sufficiently mild giving the elimination product in a low yield, while SiO_2 can promote the elimination pathway of sensitive product **1037b** in much greater extent.

Pleasingly, when the related ynamide **1036** was subjected under the gold-catalysed conditions, tetracycle **1042** was also formed, albeit in moderate yield as a mixture of two diastereomers (Scheme 151). In this case, only traces (<0.5%) of the elimination product was observed by ^{1}H-NMR spectroscopy, despite the high temperature and the prolonged time of the reaction. However, the diasteromeric ratio of the crude mixture was assigned as **1042a**: **1042b** = 1.3: 1, whereas after purification through deactivated silica gel chromatography it changed to **1042a**: **1042b** = 13.0: 1. It seemed that the same reactivity trend, as the 7-membered analogue, is followed in this case too, with the minor diastereomer **1042b** undergoing elimination side reactions. The byproducts could not be isolated due to the complexity of the mixture.



Scheme 151: Ynamide bearing a cyclooctyl group under gold-catalysis

The relative stereochemistry of the major diastereomer **1042a** was clearly confirmed by n*O*e experiment; the phenyl substituent, the cyclopropane ring and the migrating hydride are on the same side of the central cyclopentene ring (Figure 8).

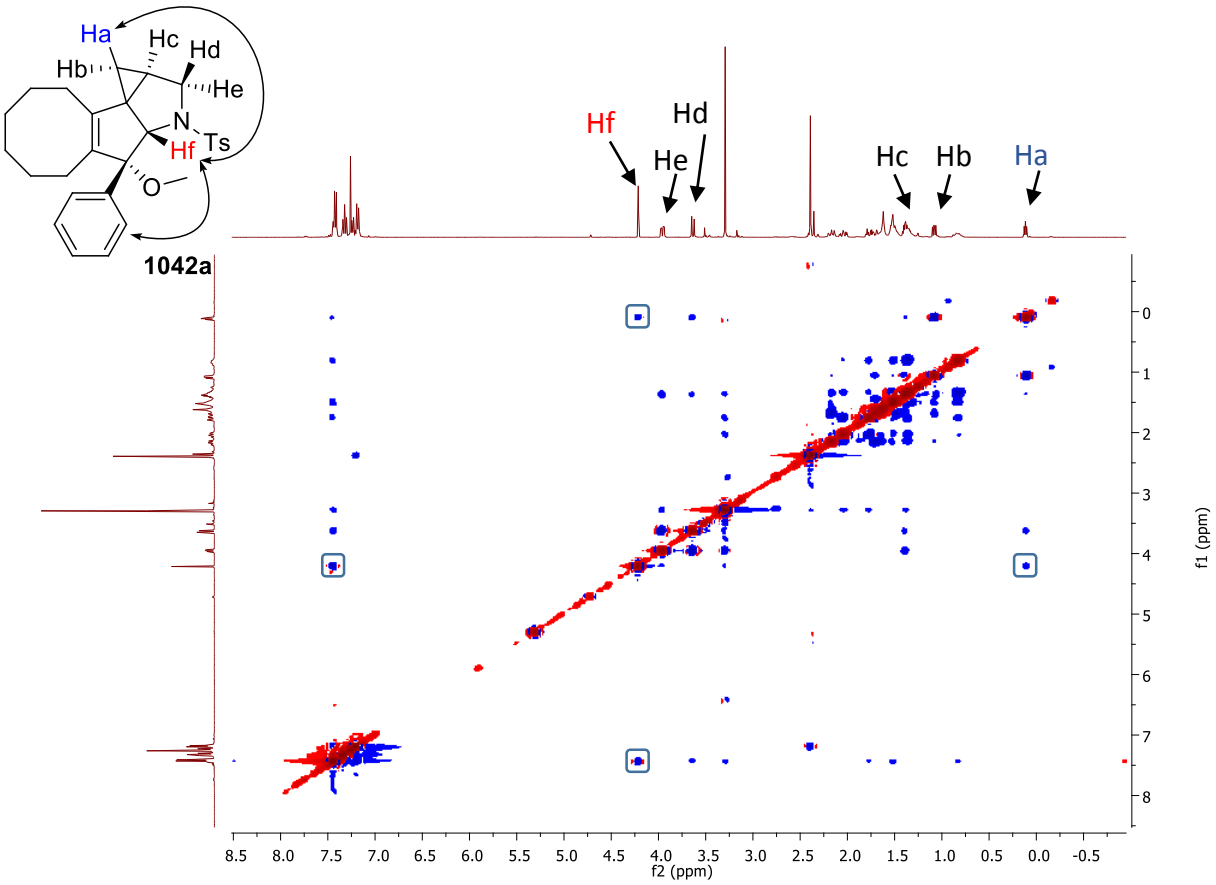
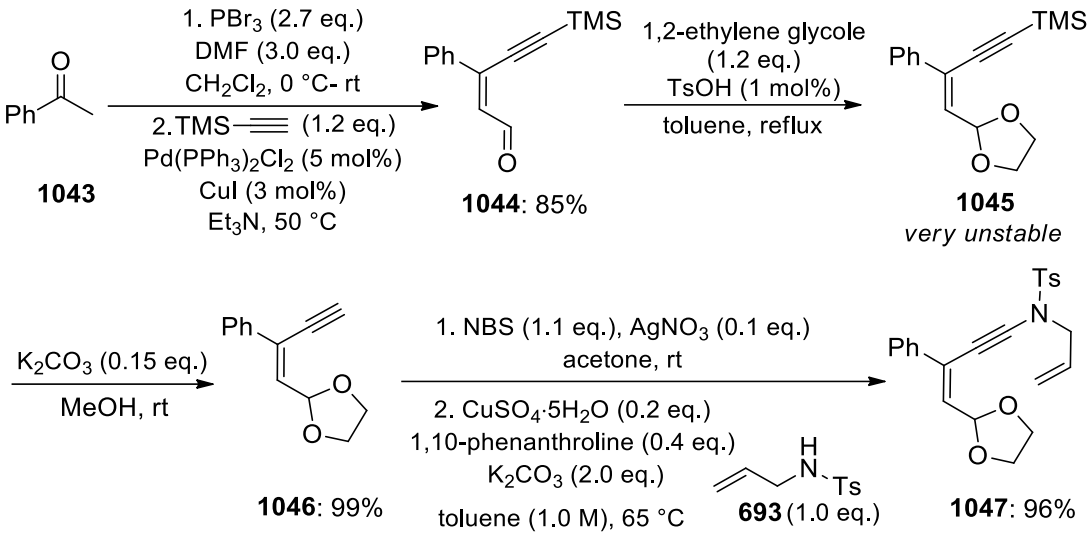


Figure 8: n*O*e experiment confirming the *syn*-relationship between the phenyl substituent, the cyclopropyl ring and the migrating hydrogen

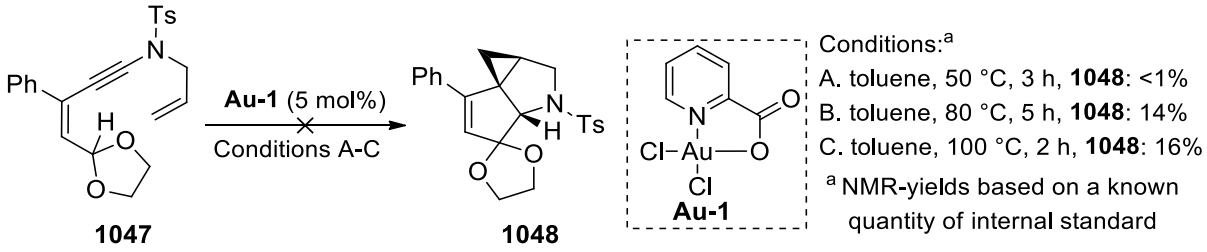
4.3.3.3 Acyclic systems

Systems with an acyclic linker between the hydride donor-acceptor fragments were then investigated, as their structural flexibility can potentially enhance the desired reactivity. The starting ynamide **1047**, which accommodates a phenyl substituent adjacent to the triple bond, was prepared under the same reaction sequence as described above for the previous substrates (Scheme 152).



Scheme 152: Preparation of ynamide 1047 with an acyclic hydride donor-acceptor linker

Ynamide **1047** proved unstable when treated with gold(III)-precatalyst (Scheme 153). Although only minor reactivity was observed at 50 °C with starting material being predominant, when the temperature was increased complicated mixtures were obtained. Based on crude ^{1}H-NMR spectroscopy, side products with aldehyde groups were mainly formed, indicating cleavage of the acetal subunit, whereas the levels of the desired alkene **1048** remained very low.



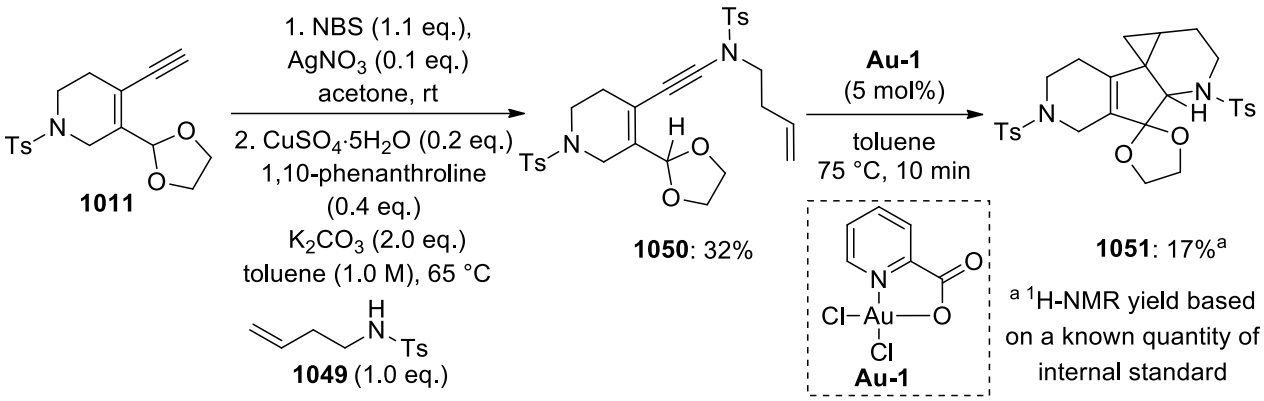
Scheme 153: Ynamide 1047 with an acyclic backbone under gold-catalysis

Due to potentially challenging syntheses of ynamides bearing an acetal group and an acyclic backbone along with the limited literature precedent for the construction of the starting precursors, no further studies on these substrates were pursued.

4.3.4 Modification of the *N*-substituent

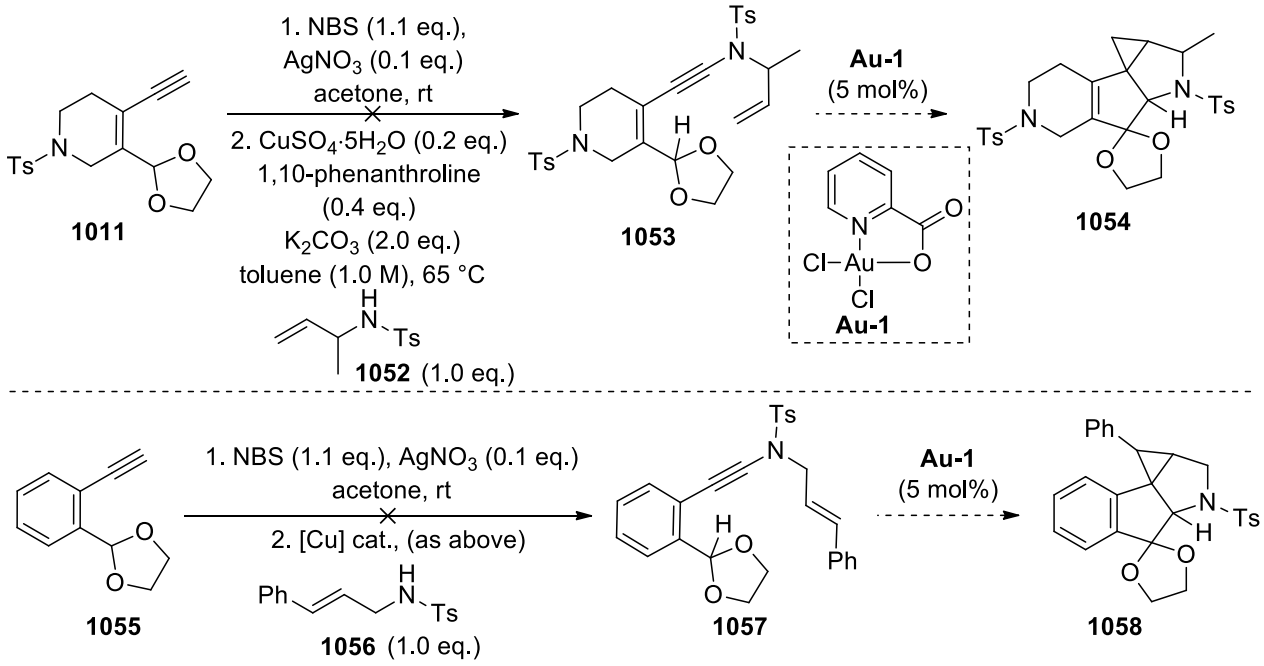
Modification of the *N*-substituent of the ynamide would broaden the product diversity, leading to heterocycles with bigger ring sizes or more highly substituted cyclopropane rings. Firstly, the related sulfonamides were constructed by combining tosyl amine with the corresponding allyl bromide under basic conditions, following known experimental protocols.[205]

The investigation started with the construction of homoallyl-based ynamide **1050** *via* copper-catalysed coupling of the corresponding bromoalkyne and homoallyl sulfonamide **1049** (Scheme 154). Ynamide **1050** proved unreactive when was subjected into the standard gold-catalysed conditions at low temperatures, whereas very rapid degradation occurred at 70 °C along with tetracycle **1051** in poor yield. Comparatively, a homoallyl ynamide with an aromatic backbone was able to react under the optimised conditions, giving the corresponding tetracycle in good yield (experiment by Holly Adcock).



Scheme 154: Homoallyl-based ynamide 1050: preparation and reactivity

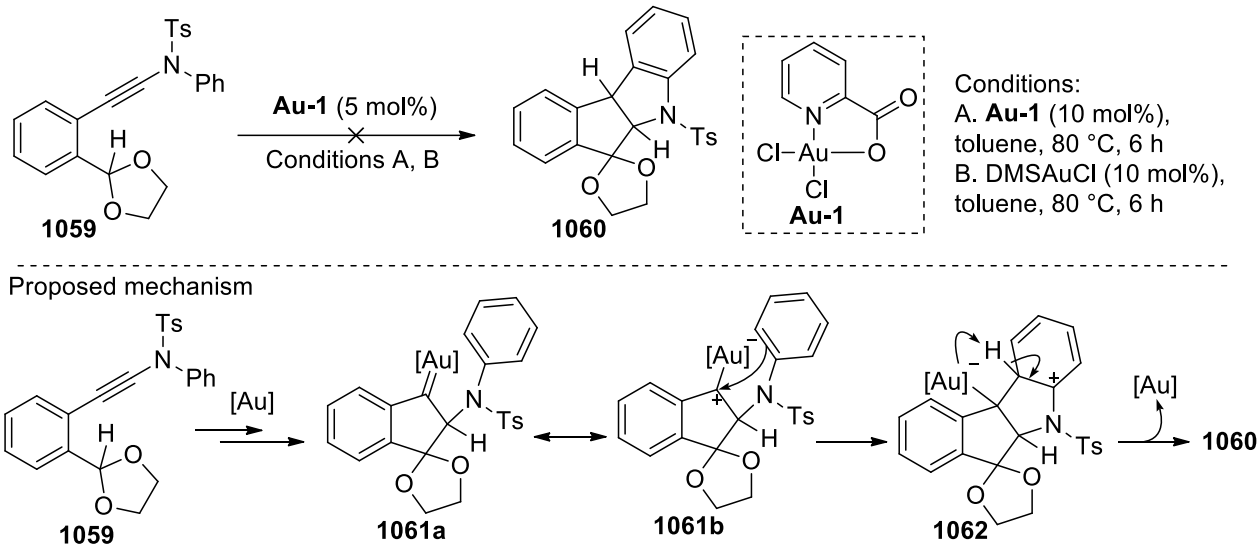
Similarly, the preparation of ynamides **1053** and **1057** was attempted, however no product was formed, due to complete degradation of the corresponding bromoalkyne in the first case and the relatively unreactive sulfonamide **1056** in the second case (Scheme 155).



Scheme 155: Attempts for construction of ynamides bearing a modified *N*-substituent

4.3.5 Alternative carbene trap

Alternative ways of capturing the intermediate carbene (*vide infra*, **726a**/**726b**, Scheme 100) were then explored, which would potentially provide the opportunity to construct alternative polycyclic systems.

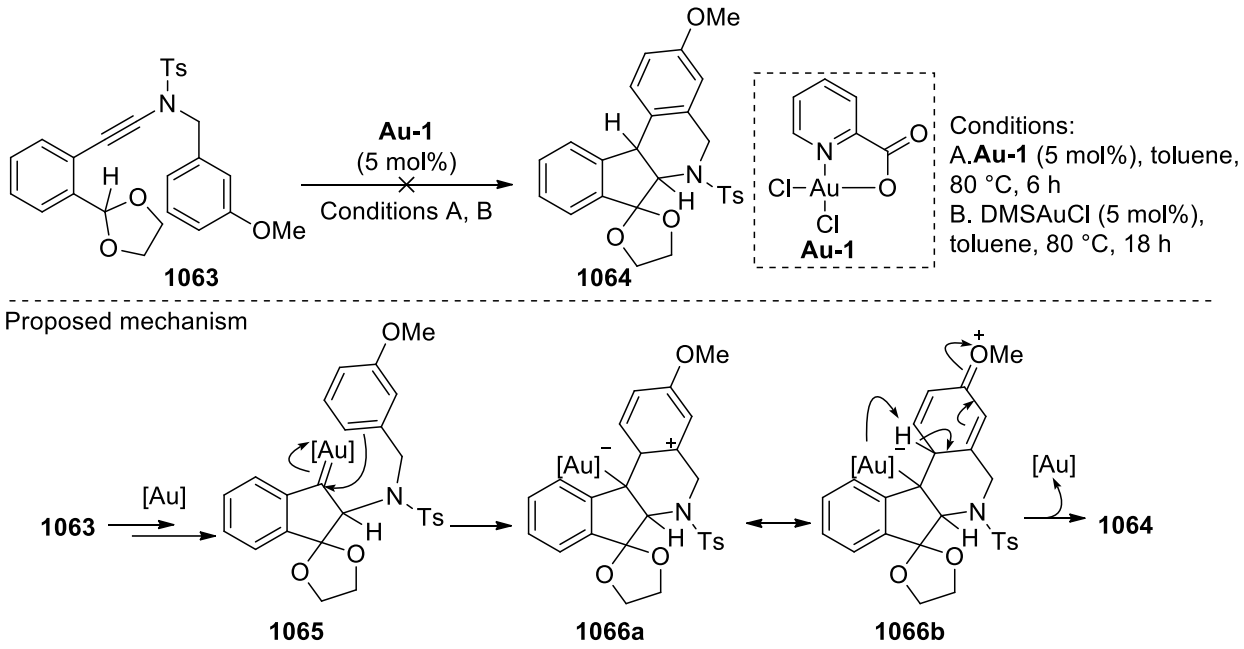


Scheme 156: Alternative carbene trap by electrophilic aromatic substitution

Ynamide **1059** was expected to undergo [1,5]-hydride transfer, forming carbene **1061a**/**1061b** which could be subsequently trapped by electrophilic aromatic substitution from the adjacent *N*-phenyl group (Scheme 156). Rearomatisation and elimination of the metal would give tetracycle **1060**. Unfortunately, the formation of **1060** was not achieved when ynamide **1059** was employed under the gold-catalysed conditions. Complicated mixtures were observed with mainly unreacted starting material even at high temperature.

In addition, studies were undertaken upon the reactivity of *N*-paramethoxybenzyl substituted ynamide **1063** (Scheme 157). The methoxy substituent, as mentioned in the previous chapter,

can exhibit extra stabilisation on the generated carbocation **1066a**. However, ynamide **1063** did not show the desired reactivity under gold catalysis in this case either, giving complicated mixtures which did not allow the products to be identified.

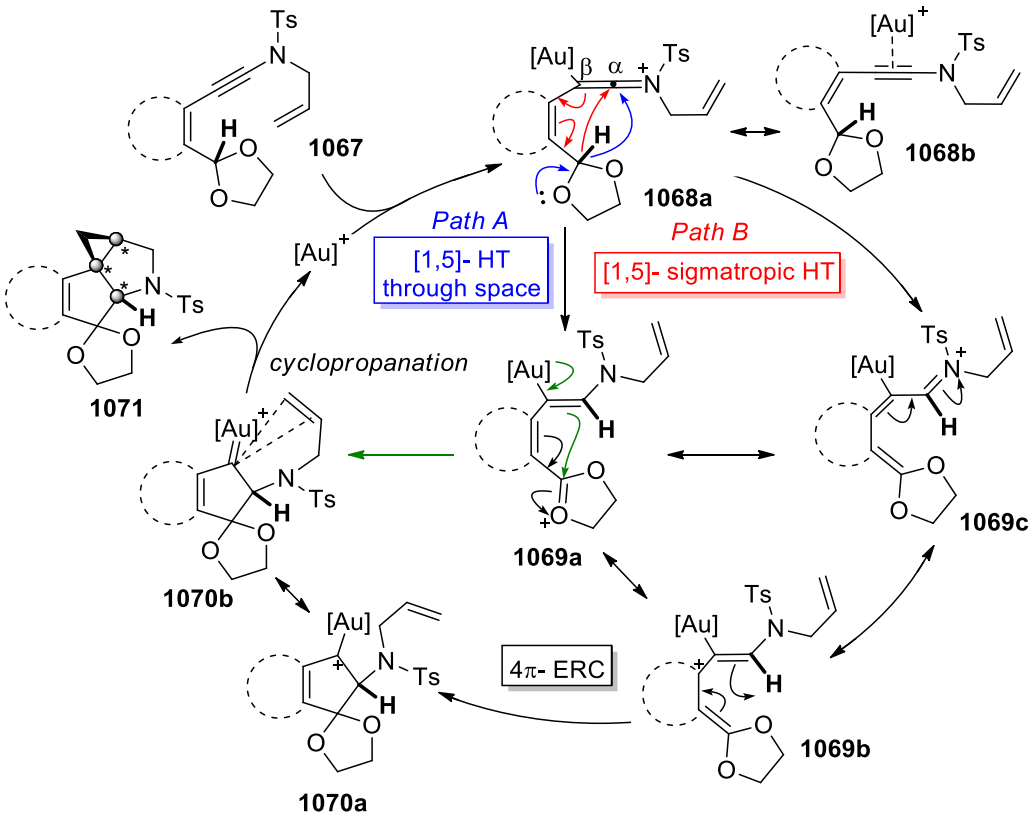


Scheme 157: Proposed formation of 6,5,6,6-fused ring systems from ynamide 1063

4.3.6 Proposed mechanism

Based on the literature and our experimental data, two possible routes towards the formation of the polycyclic scaffolds can be envisioned (Scheme 158).[195],[196] Upon gold-activation of the π-system, gold-keteniminium species **1068a** is formed. [1,5]-Hydride shift through space from the donor (either an acetal or alkoxy group) towards the more electron-deficient α-carbon takes place, giving vinyl gold intermediate **1069a** (Path A). Subsequently, **1069b**, which is a resonance structure of **1069a** and **1069c**, undergoes conrotatory 4π-electrocyclic ring closure to form

carbene **1070a** (resonance structure **1070b**). An alternative mechanism can also be considered: back donation of electron density from the metal results in nucleophilic attack to the electrophilic oxonium giving carbene **1070a**/**1070b**. Finally, the generated carbene is quenched by a cyclopropanation process with the *N*-allyl tether to give the tetracycle **1071**.



Scheme 158: Proposed mechanism for the [1,5]-hydride transfer/cyclisation cascade

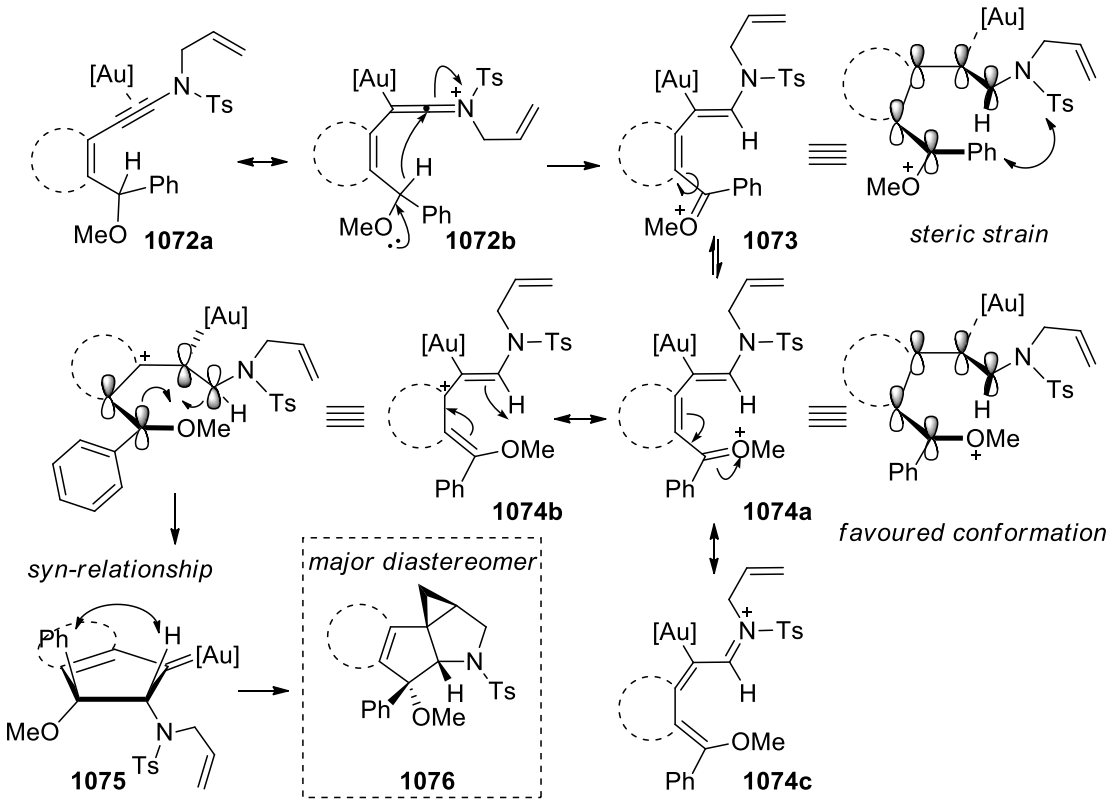
The mechanism may also be initiated by a [1,5]-sigmatropic hydride transfer, similar to those reported by Evano and Thibaudeau[196] or by Alajarin,[187] forming iminium ion **1069c** (Path B). The reasonance structure **1069b** can then evolve through the same sequence for the formation of the final product.

This powerful reaction generates three new Csp^3-Csp^3 bonds and three contiguous stereogenic centres (structure **1071**). As discussed in the previous section, tetracycles which contain an acetal subunit were formed as a single diastereomer in which the migrating proton is positioned on the same side as the cyclopropane ring. Assuming the above mechanism, this relative stereochemistry is set during the cyclopropanation step of racemic gold carbene **1070a**/**1070b**.

When an alkyloxy substituent was employed as a hydride donor, a mixture of two diastereomers was isolated. Analysis of n*O*e experiments revealed that the major diastereomer has the bulky aromatic ring on the same side as the migrating hydride and the cyclopropyl ring (Scheme 159, please note that only the major diastereomer is drawn).

In this case, the tetracycle **1076** has four neighbouring stereogenic centres, but three of them are set by the stereoselective cyclopropanation step in the same fashion discussed above. Therefore, the remaining diastereoselectivity should be induced in a previous step. Nazarov-type cyclisation, when a Csp^3-Csp^3 bond generates the first 5-membered ring, requires a fully conjugated, planar π-system, thus the diastereomeric induction must occur prior to this step. Once [1,5]-hydride transfer generates cation **1073** or **1074**, rotation of the C-C bond favours the formation of **1074** in which the bulky phenyl ring is pointing away from the *N*-allyl-tosyl group, in order to reduce the steric strain. Rotation of (Au)C-C(H)(*N*-subst.) bond (can be seen more clearly in resonance structure **1074c**) or (Au)C-C(aryl) bond (can be seen more clearly in resonance structure **1074b**) must not be precluded either. Conrotatory 4π-electrocyclisation brings the aromatic ring into a *syn*-relationship with the migrating hydride in carbene **1075**. The

remaining stereochemistry of the final molecule is set at this stage as the other two stereogenic centres are formed stereoselectively based on the relative position of the migrating hydrogen.

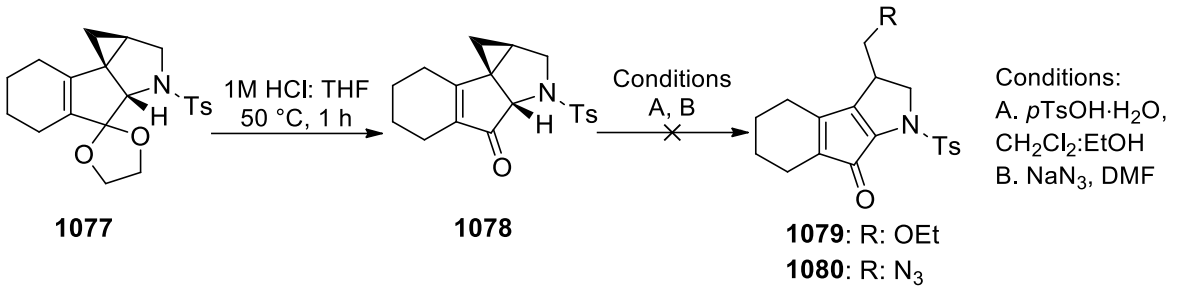


Scheme 159: Rationalising the observed diastereoselectivity

4.3.7 Further reactivity

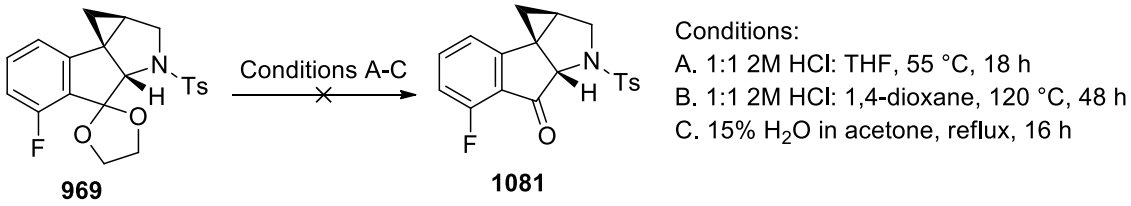
Further transformation of these tetracyclic ring systems, which would potentially lead to functionalised diverse products, was then explored (Scheme 160). Deprotection of the acetal under mild acidic conditions gave the corresponding ketone **1078** in almost quantitative yield (experiment by Holly Adcock). Following literature precedent onto similar bicyclic systems,[141] cyclopropyl ring opening was then attempted by employing several nucleophiles, however

starting material was recovered in each case. Presumably, this cyclopropane ring is not electrophilic enough to react and an extra Lewis-acid activation of the neighbouring carbonyl is required.



Scheme 160: Further functionalization: cyclopropyl ring opening

Tetracycle **969** bearing an acetal unit adjacent to an electron deficient centre proved very stable under acidic conditions (Scheme 161). Only traces of the desired ketone were observed with the starting material remaining mostly unreactive, even when harsh conditions were used. Thus, further modification of **969** was not achieved.

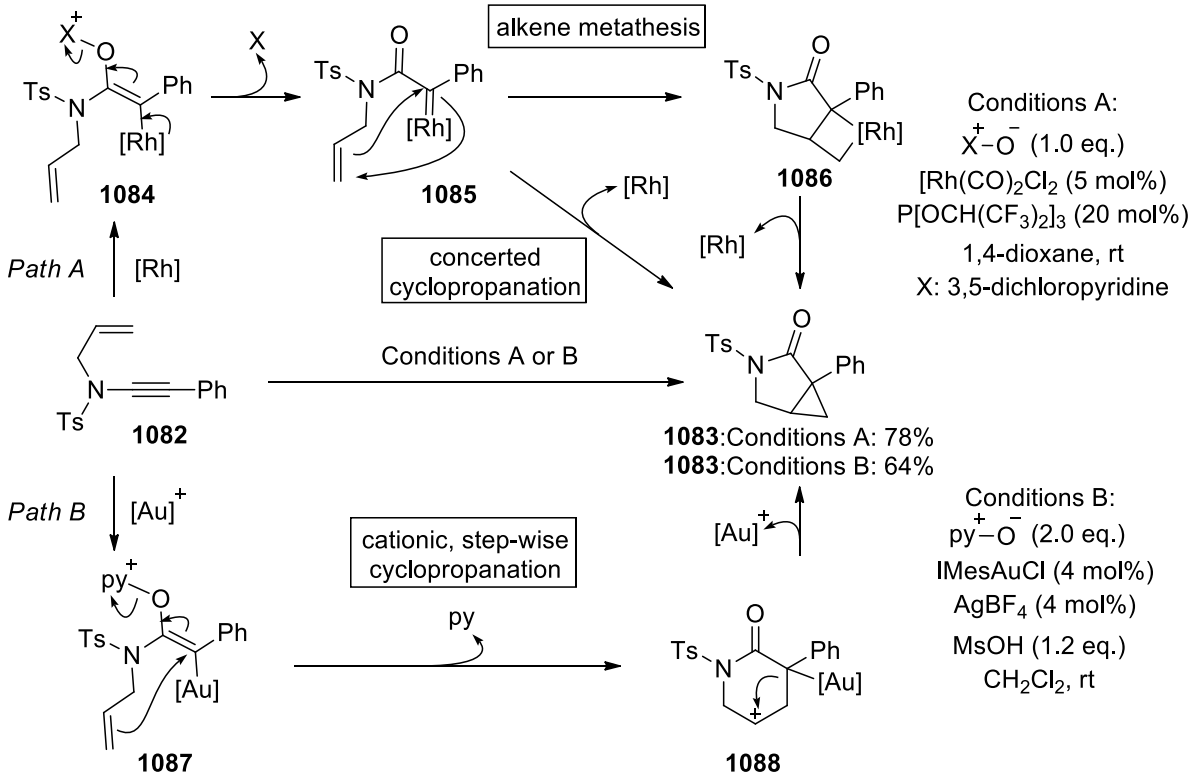


Scheme 161: Challenging acetal cleavage even under harsh conditions

4.3.8 Unexpected reactivity

In 2013 a member of the Davies group (Fernando Sánchez) discovered a new reaction for the formation of aza-bicyclic systems using gold-activated ynamides and external oxidants

(unpublished work). While this research was in progress, the Tang group reported the synthesis of these scaffolds *via* a similar approach using rhodium catalysis (Scheme 162, Path A).[206] As regards the proposed mechanism, nucleophilic attack of the oxidant onto the α-carbon of the ynamide **1082** followed by elimination of the pyridine gives rhodium carbene **1085**. Alkene metathesis, which leads to intermediate **1086** followed by reductive elimination forms the final product **1083**. However, DFT studies showed that the elimination of the metal from **1086** is relatively difficult, thus the authors suggested the concerted cyclopropanation mechanism as a more possible route (**1085** to **1083**).

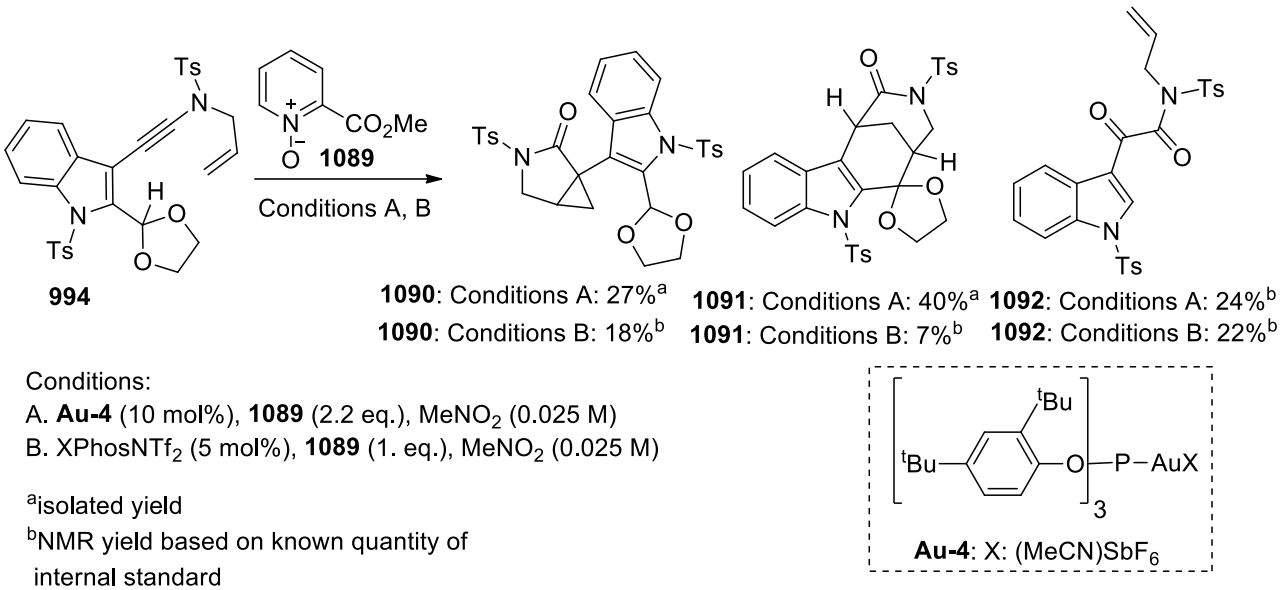


Scheme 162: Rhodium and gold-catalysed formation of aza-bicyclic scaffolds

The same transformation was reported by Li and co-workers using gold catalysis (Path B, Scheme 162).[207] Comparatively, they proposed a different, more cationic, step-wise approach. The gold-catalysed reaction is initiated by attack of the oxidant to form intermediate **1087**, which can evolve through elimination of the pyridine after intramolecular nucleophilic addition of the tether allyl group. C-C Bond formation constructs the bicyclic product **1083**.

Being intrigued by this reactivity, ynamides bearing an acetal subunit were tested under modified oxidative gold-catalysed conditions to form the corresponding aza-bicyclic compounds. Initially, indole derived ynamide **994** was treated with **Au-4** and pyridine-*N*-oxide **1089** (Scheme 163). Surprisingly, the desired product **1090** was isolated in 27% yield alongside an initially unknown product **1091** in 40% isolated yield. A double-oxidation product **1092**, derived from the addition of two equivalents of oxidant, was also observed in 22% NMR yield based on a known quantity of internal standard. Additionally, when catalyst XPhosAuNTf$_2$ was employed instead, in otherwise the same catalytic conditions, **1091** was observed in only 7% whereas **1090** and double-oxidation product **1092** were formed to more or less the same extent.

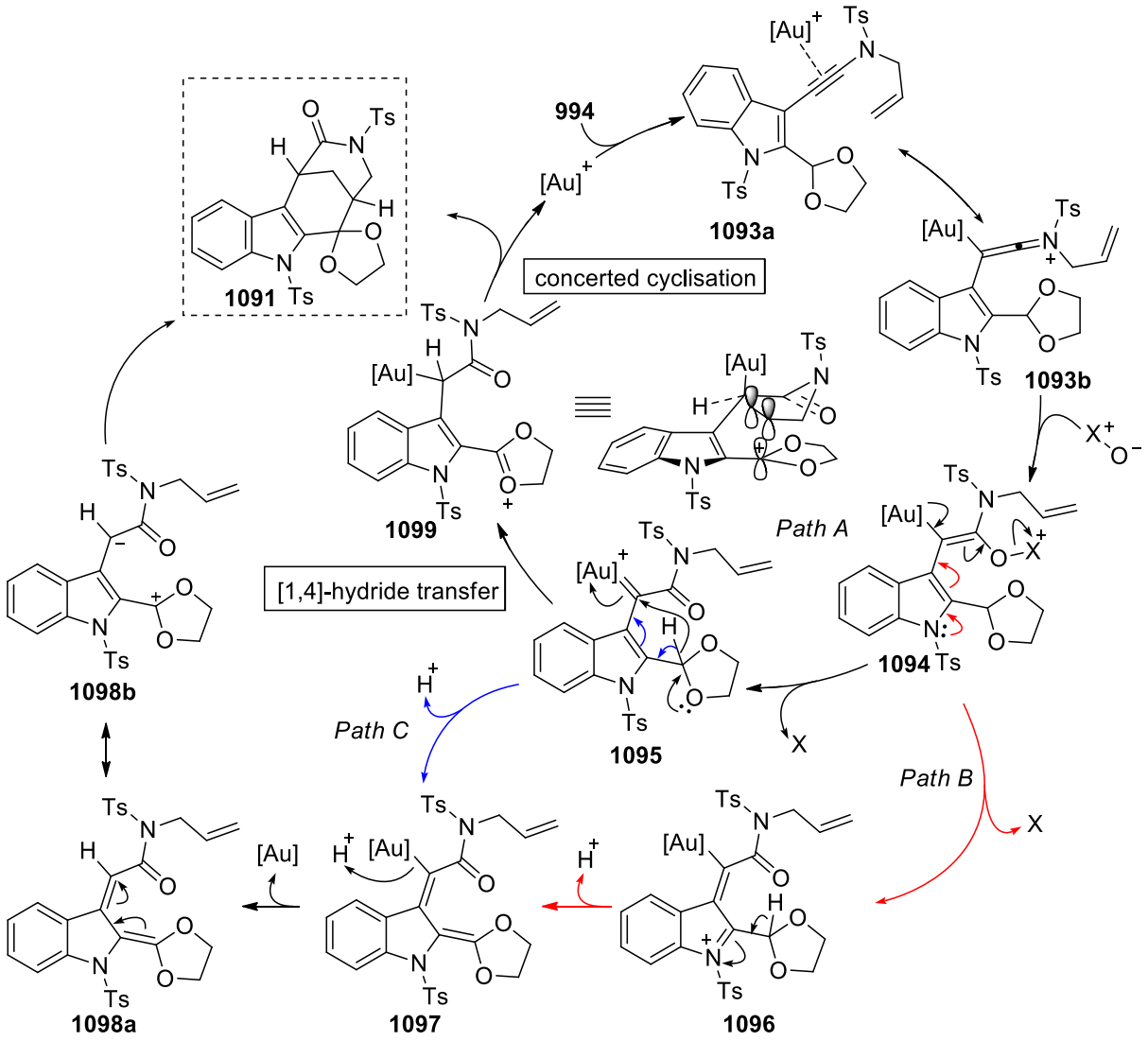
Extensive studies of the ^{1}H-, ^{13}C- and 2D-NMR spectras revealed that the most likely structure of **1091** is a tetracyclic ring system comprising of two 6-membered rings, fused to the indole. Unfortunately, the scale of the reaction did not allow crystals suitable for X-ray diffraction to be obtained and all the starting material had been consumed at that point.



Scheme 163: Indole derived ynamide 994 for the formation of polycyclic systems

A plausible mechanism for the formation of **1091**, which combines both oxidation chemistry and a hydride migration, can be envisioned (Scheme 164). Gold-activation of the π-system triggers regioselective nucleophilic attack of the oxidant to the α-carbon of the ynamide forming intermediate **1094**. Back-donation of the metal allows elimination of the pyridine and formation of gold carbene **1095**. [1,4]-Hydride transfer from the acetal donor to the electrophilic centre of the carbene forms oxonium **1099** (Path A). A concerted cyclisation can then form [6,6]-bicyclic system **1091**. An alternative mechanism can also be considered. The free electron pair of the indole nitrogen can be involved in the mechanism by promoting elimination of the pyridine forming intermediate **1096**, which potentially have the ability to lose a proton resulting in vinyl gold carbenoid **1097** (Path B). This intermediate can also derive from α-oxo gold carbene **1095** in a similar fashion (Path C). Protodeauration can then follow to generate diene **1098** which accommodates a nucleophilic and an electrophilic site, as depicted from the resonance

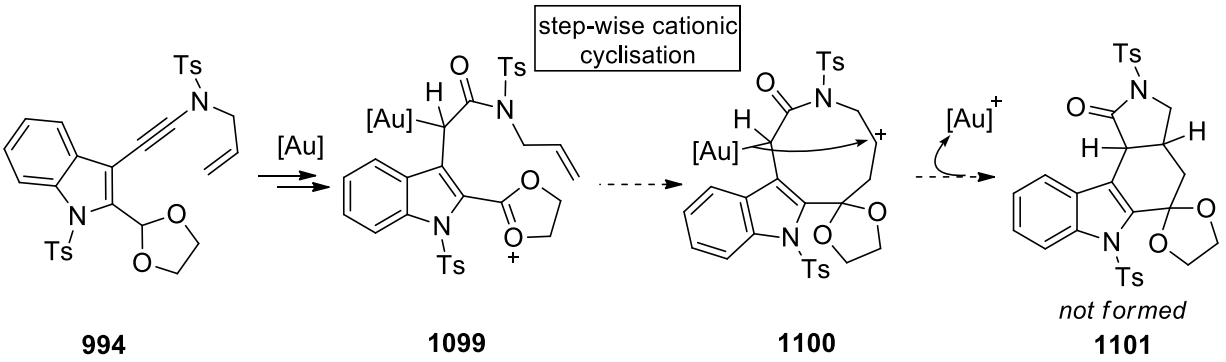
structure **1098b**. Diene **1098** can undergo concerted cyclisation from the tether *N*-allyl group to form the final product, in a similar manner as the corresponding gold species **1099**.



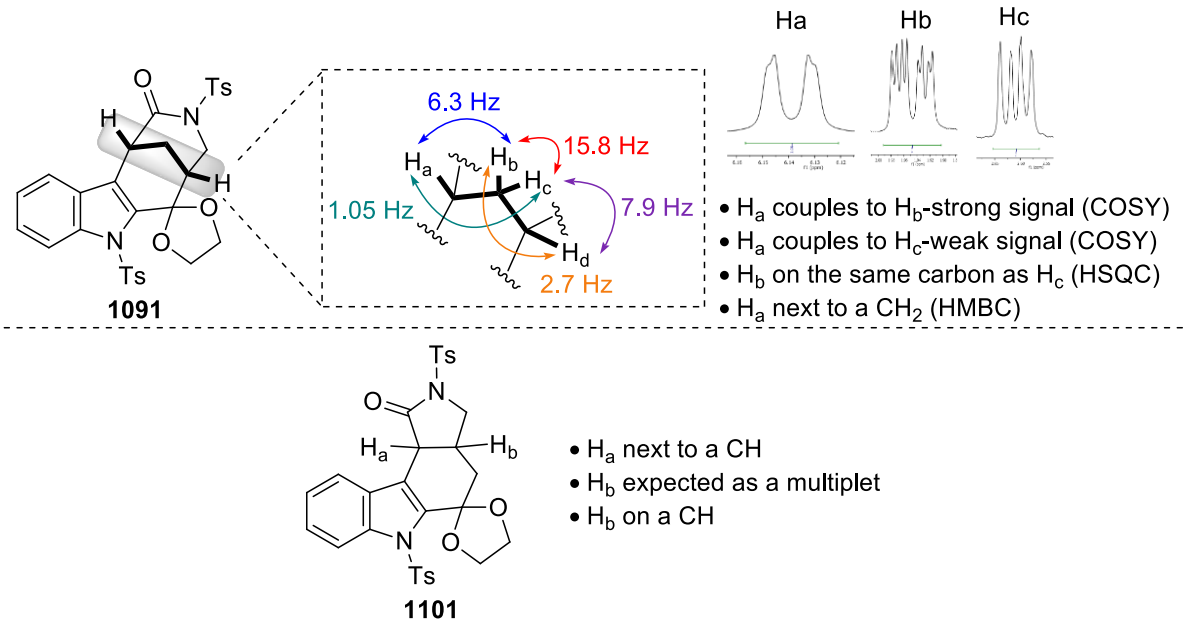
Scheme 164: Possible mechanism for the formation of bicyclic system 1091

A stepwise reaction might be expected to yield isomeric polycyclic system **1101** (Scheme 165). Stepwise cyclisation of gold intermediate **1099** would result in the relatively stable carbocation **1100**, which could then have been quenched to form a [5,6]-bicyclic system **1101**. However,

isomeric **1101** was not observed indicating that a concerted cyclisation to form **1091** is favoured over a step-wise process towards **1101**.



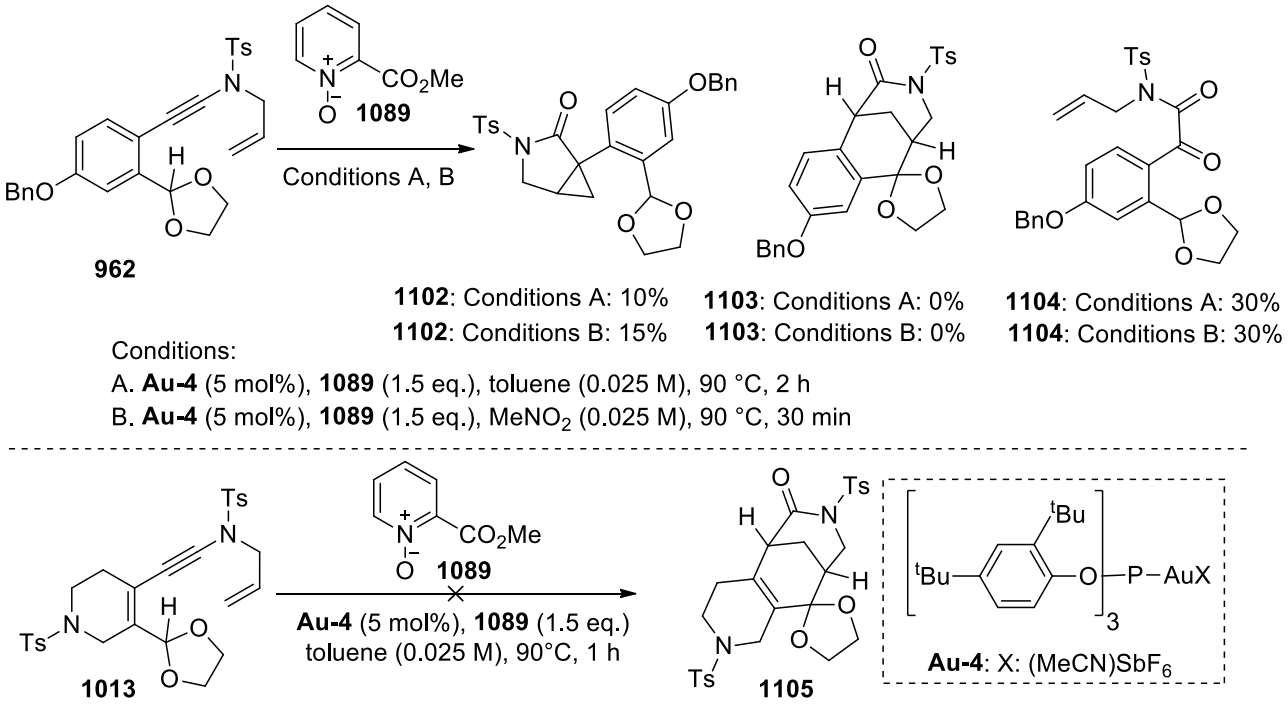
Scheme 165: Expected stepwise cyclisation of indole 994 leading to 1101



Scheme 166: Characteristic ^{1}H-NMR couplings for product 1091

The reason for this reactivity trend is not clear yet; potentially the conformation of intermediate **1099**, as it is demonstrated in the 3D-structure on the scheme 164, plays a crucial role as it allows the optimal orbitals overlap for the formation of **1091**.

Simpler aromatic and non-aromatic systems were subjected under the previously employed conditions to investigate whether similar reactivity trend would be observed (Scheme 167). On the first case, when aromatic ynamide **962** was tested, the bicyclic product **1102** was observed in 10%, double oxidation derivative **1104** in 30%, whereas the corresponding fused polycyclic system **1103** was not formed at all. Regarding the non-aromatic ynamide **1013**, although consumption of starting material was observed in one hour, a complicated mixture was afforded. Identification of the main components of the crude residue was not possible, due to the complexity of the mixture.



Scheme 167: Aromatic and non-aromatic ynamides for the formation of polycyclic systems

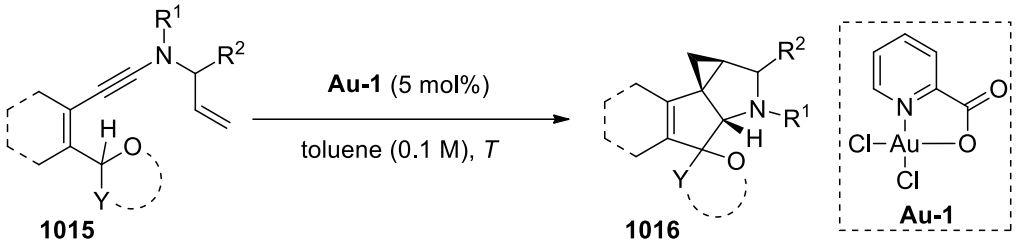
The inability of ynamides **962** and **1013** to undergo similar reactivity to **994** cannot be fully explained based on these very initial results. Potentially the indole core is essential for the

required orbital alignment and the cascade cyclisation to occur due to the free electron pair of the indole nitrogen which is likely to be involved in the reactivity (Path B, Scheme 164).

The initial results based on the indole derivative **1091** were encouraging, revealing a novel cascade oxidation/hydride shift/cyclisation sequence for the formation of complex polycycles. Further studies upon the origin of this reactivity, its limitations and the optimal conditions required may well expand the substrate scope of the reaction, while demonstrating the powerful ability of ynamides to construct complex scaffolds in a single manipulation.

4.4 Summary

The effect of structural variation on a new gold-catalysed reaction has been developed for the formation of complex polycyclic systems, which involves a [1,5]-hydride transfer/cyclisation cascade of aromatic and non-aromatic ynamides (Scheme 168). Under mild conditions, the process rapidly generates three fused ring systems by the formation of three new $C(sp^3)$-$C(sp^3)$ bonds and up to four contiguous stereogenic centres, in a single step. The observed diastereoselectivity of the compounds with an ether unit on the benzylic position was rationalised by the disfavoured steric interactions prior to the 4π-conrotatory cyclisation. This strategy can be applied to access Csp^3-rich cyclic molecular architectures as well as complex functionalised aromatic scaffolds.

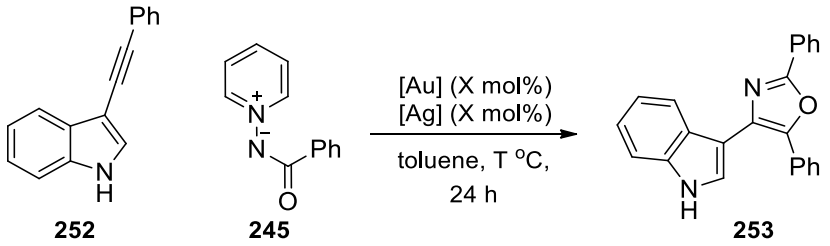


Scheme 168: Gold-catalysed formation of polycyclic systems *via* [1,5]-HT/cyclisation cascade

Finally, a new and potentially powerful reaction of an indole based ynamide was discovered for the formation of [6,6]-fused ring systems.

5. **Appendix**

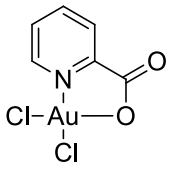
5.1 Optimisation Studies for the Formation of 253



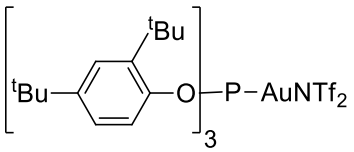
Entry	[Au]	[Ag]	[252] M	(X mol%)	Solvent	T (°C)	Yield (%) [a]
1	**Au-1**	-	0.1	5.0	toluene	90	12
2	PPh_3AuCl	AgOTf	0.1	5.0	toluene	90	24
3	AuCl	AgOTf	0.1	5.0	toluene	90	0
4	**Au-9**	-	0.1	5.0	toluene	90	23
5	**Au-2**	-	0.1	5.0	toluene	90	35
6	**Au-3**	AgOTf	0.1	5.0	toluene	90	38
7	**Au-3**	AgOTf	0.2	5.0	toluene	90	54
8	**Au-3**	AgOTf	0.05	5.0	toluene	90	35
9	**Au-3**	AgOTf	0.1	5.0	toluene	r.t.	0
10	**Au-5**	AgOTf	0.1	5.0	toluene	90	37
11	**$PtCl_2$**	-	0.1	5.0	toluene	90	25
12	**Au-6**	AgOTf	0.1	5.0	toluene	90	46
13	**Au-3**	AgOTf	0.1	5.0	toluene	90	38
14	**Au-3**	AgOTf	0.2	5.0	toluene	90	54
15	**Au-3**	$AgNTf_2$	0.2	5.0	toluene	90	44
16	**Au-3**	AgOTs	0.2	5.0	toluene	90	37

17	**Au-3**	$AgBF_4$	0.2	5.0	toluene	90	41
18	**Au-3**	$AgSbF_6$	0.2	5.0	toluene	90	58
19	**Au-3**	$AgSbF_6$	0.2	5.0	THF	40	0
20	**Au-3**	$AgSbF_6$	0.2	5.0	DCE	60	13
21	**Au-3**	$AgSbF_6$	0.2	5.0	AcCN	60	5
22	**Au-3**	$AgSbF_6$	0.2	5.0	DMF	120	78
23	**Au-3**	$AgSbF_6$	0.2	5.0	xylene	120	73
24	**Au-6**	AgOTf	0.1	5.0	toluene	90	46
25	**Au-6**	AgOTf	0.2	5.0	toluene	90	36
26	**Au-6**	AgOTf	0.2	5.0	xylene	120	65
27	**Au-6**	$AgSbF_6$	0.1	5.0	toluene	90	21
28	**Au-6**	$AgSbF_6$	0.2	5.0	toluene	90	36
29	**Au-6**	$AgSbF_6$	0.1	5.0	xylene	120	61
30	**Au-6**	$AgSbF_6$	0.2	5.0	xylene	120	61
31	**Au-3**	$AgSbF_6$	0.2	5.0	xylene	120	73
32	**Au-3**	$AgSbF_6$	0.3	5.0	xylene	120	51
33	**Au-3**	$AgSbF_6$	0.5	5.0	xylene	120	73
34	**Au-3**	$AgSbF_6$	0.2	2.5	xylene	120	63
35	**Au-3**	$AgSbF_6$	0.2	1.0	xylene	120	69
36	**Au-3**	$AgSbF_6$	0.2	5.0	xylene	120	25
37	-	-	0.2	-	xylene	120	<5
38	**Au-4**	-	0.2	5.0	xylene	120	79

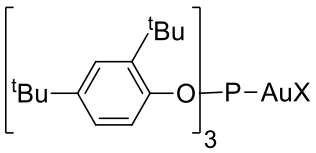
39	**Au-4**	-	0.2	2.5	xylene	120	50
40	**Au-4**	-	0.2	1.0	xylene	120	48



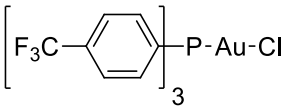
Au-1



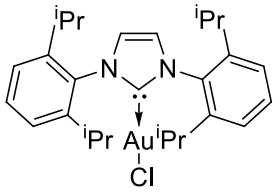
Au-2



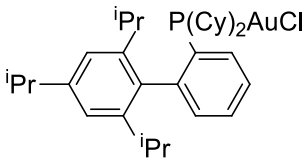
Au-3: X: Cl
Au-4: X: $(MeCN)SbF_6$



Au-5



Au-6



Au-9

[a]isolated yield

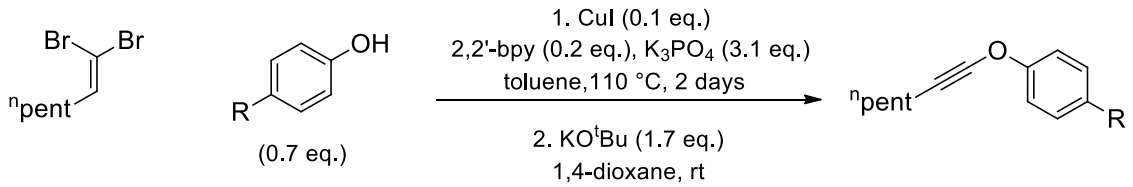
5.2 General Experimental

Flash column chromatography: Geduran (Merck) silica gel 60 (0.043-0.063 mm). Thin layer chromatography (TLC): Merck silica gel 60F254 analytical plates which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), potassium permanganate /Δ and vanillin /Δ. IR: Perkin–Elmer Spectrum 100 FTIR spectrometer (ATR). Only selected absorbencies (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 chemicals/ reagents were purchased from Sigma Aldrich, Acros, Alfa Aesar and used without further purification unless reported. All reactions in non-aqueous solvents were conducted in heat gun-dried glassware under an argon atmosphere.

The solvents used were purified using a Pure Solv-MD solvent purification system and were transferred under argon. Anhydrous *m*-xylene was dried over 4 Å molecular sieves. The following cooling baths were used: 0 °C (ice/water) and -78 °C (dry ice/acetone). NMR: Spectra were recorded on Bruker AVIII300 (^{1}H= 300 MHz) and Bruker AVIII400 (^{1}H = 400 MHz, ^{13}C = 101 MHz) in the solvents indicated; $CDCl_3$ and DMSO-d^6 purchased from Sigma Aldrich. Chemical shifts (δ) are given in ppm relative to TMS. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C \equiv 77.16$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm). Coupling constants (J) are reported in Hz. Multiplicity is denoted in ^{1}H-NMR and ^{13}C-NMR by: C (quaternary), CH (tertiary), CH_2 (secondary) and CH_3 (primary). 1D ^{13}C-NMR spectra were recorded using the UDEFT pulse sequences from the Bruker standard pulse program library. 2D HSQC, HMBC and n*O*e spectra were recorded using the Bruker standard pulse program library. Spectra were processed using MestReNova version 6.0.2.

5.3 General Procedures for Chapters 2, 3 and 4

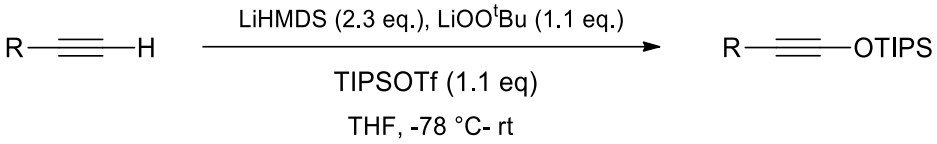
General Procedure 1 (GP1): Preparation of aromatic ynol ethers



Following a procedure reported by Evano and co-workers,[85] a 15 mL pressure tube, fitted with a rubber septum, was charged with the required phenol (1 eq.), 2,2'-bipyridine (30 mol%), K_3PO_4 (4.6 eq.) and CuI (15 mol%). The tube was evacuated under high vacuum and backfilled with a

rgon 5 times. Toluene (0.3 mL) was then added along with the 1,1-dibromo-hept-1-ene (1.5 eq.). The rubber septum was replaced by a Teflon screw cap and the heterogenous suspension was heated at 110 °C for 2 days. The solution was cooled to room temperature, diluted with dry dioxane (4 mL) and treated with potassium *tert*-butoxide (3 eq.). The resulting mixture was stirred for 18 hours at room temperature, filtered through a silica pad (ca 3 cm, washing with EtOAc) and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (hexane) afforded the desired aromatic ynol ethers.

General Procedure 2 (GP2): Preparation of silyl ynol ethers

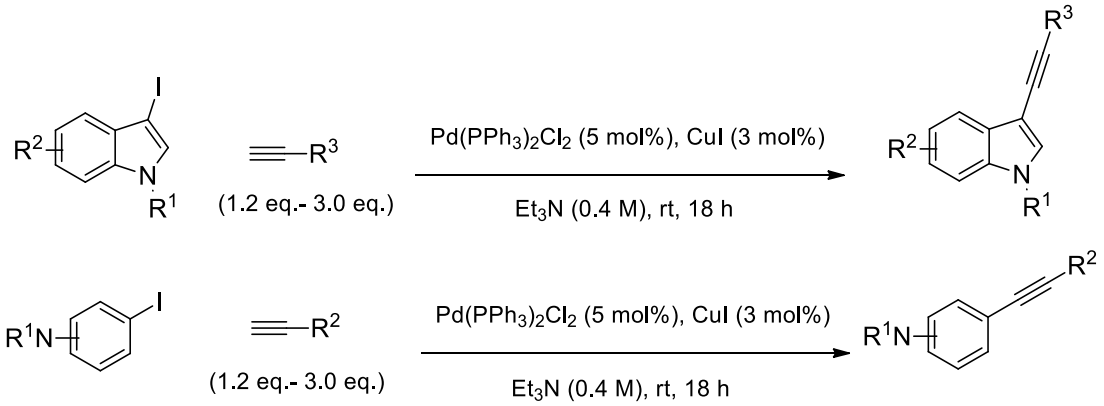


Following a modified procedure reported by Kozmin and co-workers,[89a, 89b] a mixture of the alkyne (1 eq) in THF (0.2 M) was treated with freshly prepared LiHMDS[a] in THF (1 M, 1.1 eq.) at -78 °C under argon. At the same time, a solution of Li^{t}OBu was generated by treating a solution of anhydrous *tert*-butyl hydrogen peroxide (4.93 M in toluene, 1.1 eq.) in THF with LiHMDS (1.1 eq.) at -78 °C. The solution of Li^{t}OBu was transfered to the alkynyl lithium solution *via* cannula, the resulting mixture was allowed to warm slowly to 0 °C and continued stirring at this temperature for 2 hours. The solution was cooled again to -78 °C and triisopropylsilyl trifluoromethanesulfonate (1.1 eq) was added dropwise. The reaction mixture was stirred at this temperature for 5 minutes, allowed to warm to 0 °C, stirred for 40 minutes and diluted with hexane (ca 50 mL). The final solution was washed once consecutively with saturated $NaHCO_3$ (50

mL) solution, $Na_2S_2O_3$ (50 mL), H_2O (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude oil was purified by bulb-to-bulb distillation to give the pure ynol ethers.

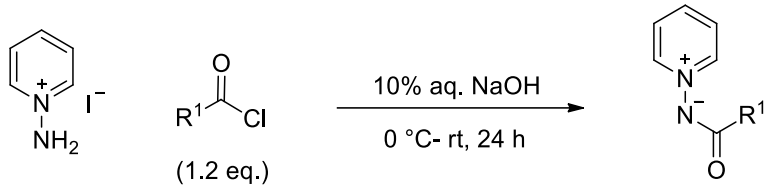
[a] Pretitrated ^nBuLi (solution in hexane, 1 eq.) was added dropwise under argon at 0 °C to a solution of freshly distilled (60 mbar/ 42 °C) HMDS (1 eq.) in THF (5 mL). After stirring at this temperature for 1 hour, the reaction mixture was cooled at -78 °C and stirring continued at this temperature for 5 minutes. The reaction was considered quantitative and the resulting LiHMDS solution was used without titration.

General Procedure 3 (GP3): Sonogashira reaction for the preparation of indole- and aniline-containing internal alkynes



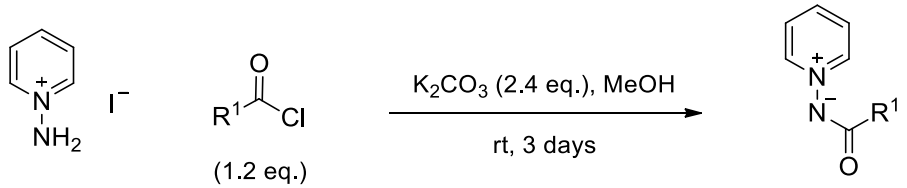
A mixture of the aryl iodide (1.0 eq.), $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (3 mol%) and the terminal alkyne (1.2- 3.0 eq.) in degassed Et_3N (0.4 M) was stirred at room temperature overnight (unless otherwise stated). The reaction mixture was then filtered through a pad of Celite® (ca 3 cm) washing with EtOAc and the solved was removed under reduced pressure. Purification by flash column chromatography afforded the internal indole- or aniline-containing alkynes.

General Procedure 4 (GP4): Preparation of pyridine-*N*-aminides



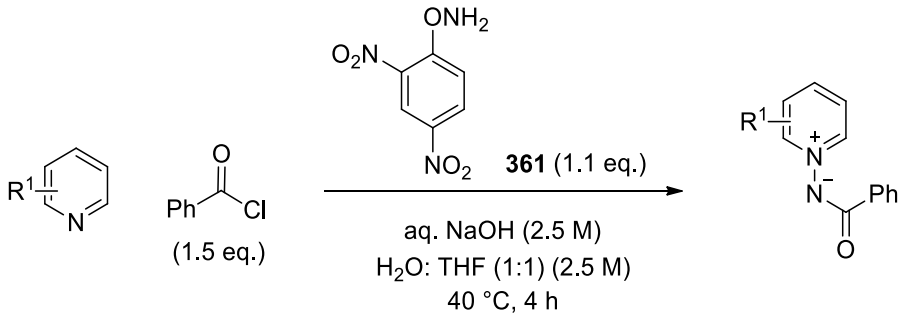
Using a procedure that has already been published by the Davies group,[82] *N*-aminopyridinium iodide (1.0 eq.) was added to an aqueous solution of 10% aq. NaOH at 0 °C and stirred for 10 minutes. Acid chloride (1.2 eq.) was added at this temperature and the mixture was stirred overnight at room temperature. The resulting suspension was then extracted with CH_2Cl_2 (3 x), the combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford the desired ylides which, if necessary, were purified by recrystallisation.

General Procedure 5 (GP5): Preparation of pyridine-*N*-aminides



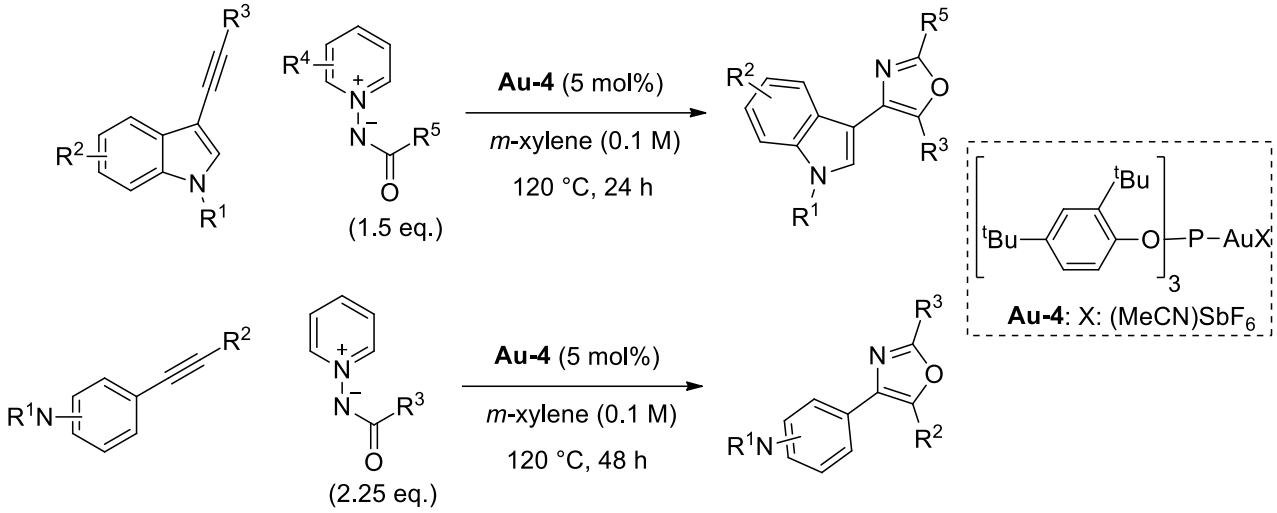
N-Aminopyridinium iodide (1.0 eq.) was suspended in MeOH, followed by addition of K_2CO_3 (2.4 eq.) and the corresponding acyl chloride (1.2 eq.). The reaction mixture was stirred at room temperature for 3 days. Undissolved salts were removed by filtration through a filter paper (washing with EtOAc) and the filtrate was evaporated under reduced pressure. Purification of the crude mixture by flash column chromatography using neutral or basic Al_2O_3 [95:5 (CH_2Cl_2:MEOH)] aforded the desired *N*-aminides.

General Procedure 6 (GP6): Preparation of *N*-aminides bearing functionalised pyridine units



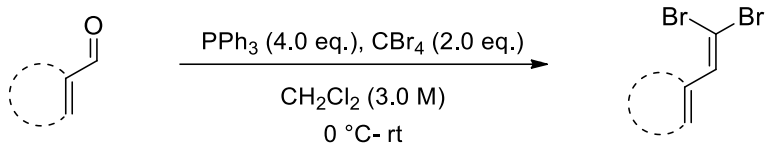
Using a modification of a known procedure,[97b] the substituted pyridine (1.0 eq.) and *O*-(2,4-dinitrophenyl)hydroxylamine **361** (1.1 eq.) were dissolved in a 1:1 mixture of THF:H_2O (2.8 M). The reaction mixture was stirred at 40 °C for 12 hours. Then, the mixture was cooled to room temperature and poured into aqueous NaOH (2.5 M). Benzoyl chloride (1.5 eq.) was added dropwise and the reaction mixture was stirred for 4 hours at room temperature. Subsequently the mixture was diluted with water and extracted (3 x) with $CHCl_3$. The organic layer was washed with aqueous NaOH (2.5 M), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography afforded the pure *N*-aminides.

General Procedure 7 (GP7): Gold-catalysed formation of oxazoles



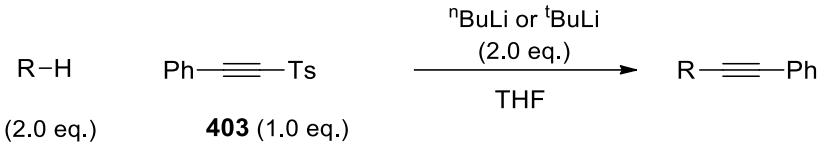
Initially, the internal alkyne (1.0 eq.), the pyridinium ylide (1.5 eq.) and the gold complex **Au-4** (5 mol%) were combined in a Schlenk tube; *m*-xylene (0.2 M) was added and the reaction mixture was stirred at 120 °C for 24 hours. The reactions were monitored by TLC until 8 hours showing the formation of the product and unreacted starting material. After 24 hours (TLC indicates either consumption of the starting material or trace of it) the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by flash column chromatography (toluene:EtOAc) afforded the pure oxazoles.[118]

General Procedure 8 (GP8): Ramirez olefination for the preparation of dibromo olefins



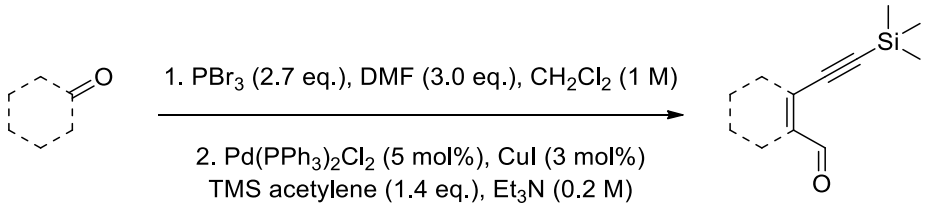
PPh_3 (4.0 eq.) and CBr_4 (2.0 eq.) were dissolved in CH_2Cl_2 (3.0 M) at 0 °C. After 40 minutes the aldehyde (1.0 eq.) was added in one portion at the same temperature and the mixture left at room temperature until consumption of starting material was indicated by TLC. Silica was then added to the mixture and the solvent was removed under reduced pressure. The resulting solid was loaded onto the top of a plug of silica (ca 2 inch) and the product was eluted with hexane to afford the desired dibromo olefins.

General Procedure 9 (GP9): Formation of electron-rich alkynes



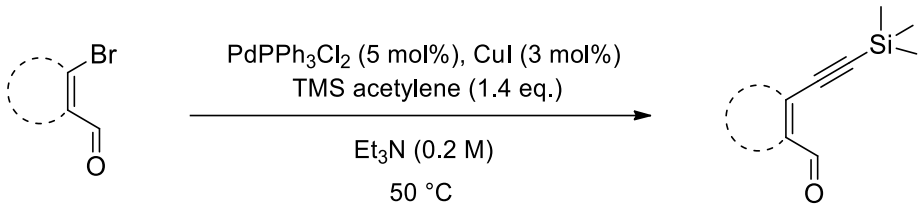
Following a procedure reported by Ruano and co-workers,[98] ^{n}BuLi or ^{t}BuLi (2.0 eq.) was added at the temperature indicated to the mixture of the aromatic compound (2.0 eq.) in THF (0.4 M). A mixture of sulfone **403** (1.0 eq.) in THF (0.2 M) was added to the solution of the organolithium at the same temperature and the reaction was stirred for 30 minutes. Saturated NH_4Cl solution (20 mL) was added and the residue was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography afforded the electron-rich alkynes.

General Procedure 10 (GP10): Two-step synthesis of silyl-protected alkynes



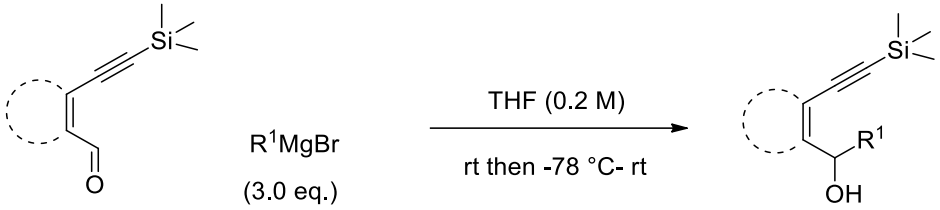
PBr_3 (2.7 eq.) was added to a solution of DMF (3.0 eq.) in CH_2Cl_2 (1.0 M) at 0 °C. The mixture was stirred at this temperature for 1 hour and the ketone (1.0 eq.) was added in one portion. After stirring for an additional 16 hours at room temperature, the reaction mixture was poured very slowly into an ice-cooled saturated $NaHCO_3$ solution and stirred until no further gas was generated (usually ca 10 min). The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was dissolved in degassed Et_3N (0.2 M), $Pd(PPh_3)_2Cl_2$ (5 mol%) and CuI (3 mol%) were added and the resulting mixture was stirred at room temperature for 10 minutes. Trimethylsilylacetylene (1.4 eq.) was then added and the mixture was heated to 50 °C until consumption of starting material was indicated by TLC. The reaction mixture was cooled to room temperature, filtered through Celite® (ca. 2 cm) washing with EtOAc and the solvent was removed under reduced pressure. Purification by flash column chromatography afforded the desired silyl-protected alkynes.

General procedure 11 (GP11): Sonogashira reaction for the formation of silyl-protected alkynes



The aldehyde (1.0 eq.), $Pd(PPh_3)_2Cl_2$ (5 mol%) and CuI (3 mol%) were suspended in degassed Et_3N (0.2 M) and the resulting mixture was stirred at room temperature for 10 minutes (in some cases THF or DMF is needed to dissolve the aldehyde). Trimethylsilylacetylene (1.2-1.4 eq.) was then added and the mixture was heated to 50 °C (unless indicated) until consumption of starting material was observed by TLC. The reaction mixture was cooled to room temperature, filtered through a pad of Celite® (ca 3 cm) washing with EtOAc and the solvent was removed under reduced pressure. Purification by flash column chromatography gave the silyl-protected alkynes.

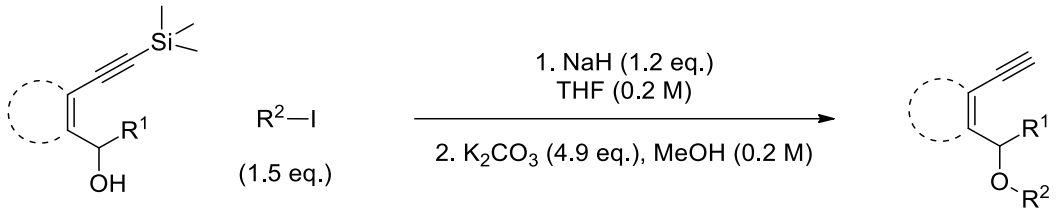
General procedure 12 (GP12): Preparation of benzhydric alcohols



Following the a modified procedure reported by Dubé and Toste,[197] magnesium turnings (3.0 eq.) were added to a double-neck flask fitted with a reflux condenser. THF (1.0 M) was then added followed by a sub-stoichiometric quantity of iodine (20-50 mg). The aryl bromide (3.0 eq.) was added slowly and the reaction was stirred for 1 hour until the magnesium turnings had

been consumed and the flask had cooled to room temperature. Stirring was stopped and the solution was used directly. The aldehyde (1.0 eq.) was dissolved in THF (0.2 M), cooled to -78 °C and the freshly prepared solution of Grignard reagent (3.0 eq.) was added dropwise. The mixture was stirred at this temperature for 30 minutes at which point consumption of starting material was indicated by TLC. The reaction mixture was then warmed to room temperature and stirring was continued for one extra hour before being quenched by addition of saturated NH_4Cl solution. The aqueous phase was extracted with Et_2O (2 x) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography afforded the desired benzhydric alcohols.

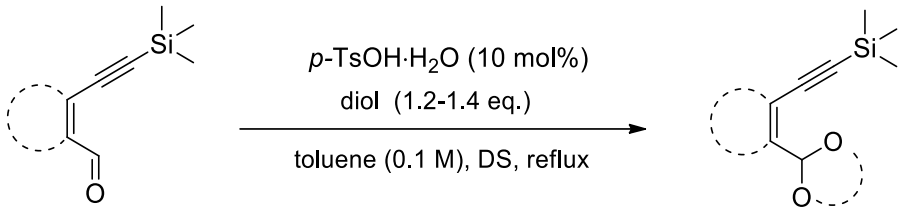
General procedure 13 (GP13): Preparation of terminal alkynes



Following a modified procedure reported by Dubé and Toste,[197] the secondary alcohol (1.0 eq.) was dissolved in THF (0.2 M) and cooled to 0 °C. NaH (1.2 eq., ca 60% oil dispersion) was added in one portion and the mixture was stirred for 30 minutes at this temperature. Alkyl iodide (1.5 eq.) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched by addition of saturated NH_4Cl solution and the aqueous phase was extracted with Et_2O (2 x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was dissolved in MeOH (0.2 M), K_2CO_3 (4.9 eq.) was added and the mixture was stirred at room temperature for 1 hour until

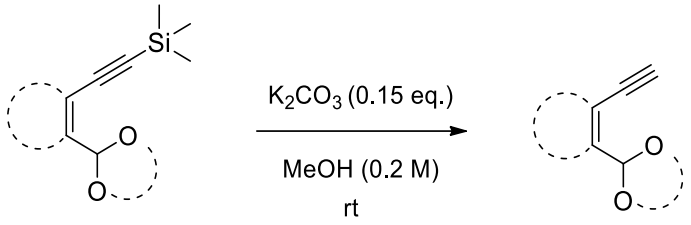
consumption of starting material was indicated by TLC. Saturated NH_4Cl solution was added to the mixture and the aqueous phase was extracted with Et_2O (2 x). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography afforded the desired terminal alkynes.

General Procedure 14 (GP14): Formation of acetals



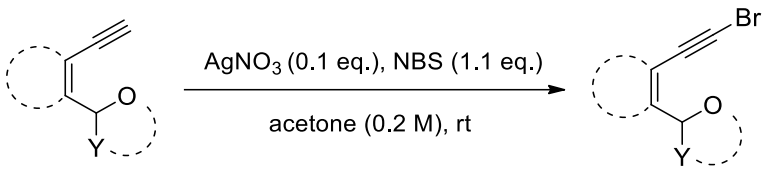
The aldehyde (1.0 eq.) was dissolved in toluene (0.1 M). *p*-TsOH·H_2O (10 mol%) and the relevant diol (1.2-1.4 eq.) were added to the reaction mixture and a Dean Stark apparatus was fitted on the top of the flask. The solution was heated to reflux until consumption of starting material was indicated by TLC. The mixture was cooled to room temperature, washed with saturated $NaHCO_3$ solution and extracted with EtOAc (2 x). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification, if required, by flash column chromatography afforded the desired acetals.

General procedure 15 (GP15): Preparation of terminal alkynes



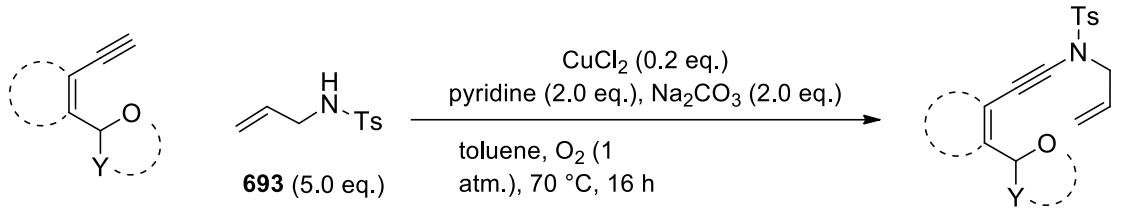
The silyl acetylene (1.0 eq.) was dissolved in MeOH (0.2 M), K_2CO_3 (0.15 eq.) was added and the reaction mixture was stirred at room temperature until consumption of starting material was indicated by TLC. Saturated NH_4Cl solution was added to the mixture and the aqueous phase was extracted with EtOAc (2 x). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification, if required, by flash column chromatography afforded the desired terminal alkynes.

General Procedure 16 (GP16): Preparation of bromoalkynes



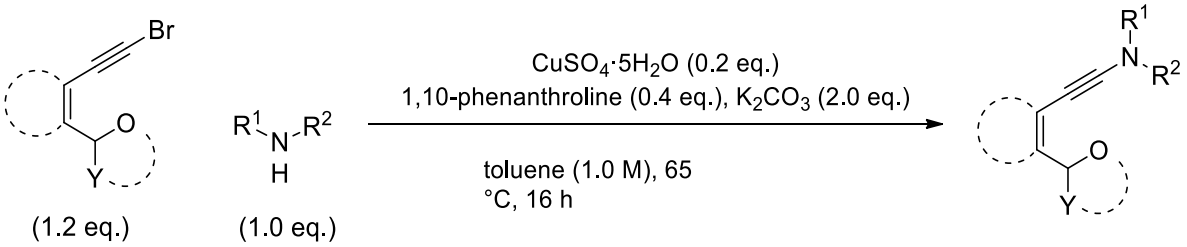
Following a procedure reported by the Davies group,[21d] $AgNO_3$ (0.1 eq.) and freshly recrystallized *N*-bromosuccinimide (1.1 eq.) were added to a solution of the terminal alkyne (1.0 eq.) in acetone (0.2 M). The reaction mixture was stirred at room temperature until consumption of starting material was indicated by TLC. 2-3 Spatulas of silica were added to the mixture and the solvent was removed under reduced pressure (if an acetal functionality was present, one drop of Et_3N was added prior to the addition of the silica). The resulting solid was loaded onto a plug of silica (ca 2 cm) and the product was eluted with [80:20 (hexane:EtOAc), 1% Et_3N]. The solvent was evaporated under reduced pressure and the resulting bromoalkyne was used immediately in the next step, without further purification.

General Procedure 17 (GP17): Preparation of ynamides



Following the procedure reported by Stahl and co-workers for the preparation of ynamides,[20a] the sulfonamide (5.0 eq.), $CuCl_2$ (0.2 eq.) and Na_2CO_3 (2.0 eq.) were combined in a 1 litre 3-necked round bottom flask. The flask was purged with O_2 while stirring for 15 minutes. A mixture of toluene (1.0 M with respect to the sulfonamide) and pyridine (2.0 eq.) were added and the mixture was heated to 70 °C. Two large balloons filled with O_2 were then attached to the flask. The terminal alkyne was dissolved in toluene (0.2 M with respect to the alkyne) and added to over 8 hours using a syringe pump and stirring was continued for 16 hours. Once cooled to room temperature, the reaction mixture was diluted with EtOAc, filtered through a pad of Celite® (ca 2 cm), eluting with EtOAc and the solvent was removed under reduced pressure. Purification by flash column chromatography afforded the pure ynamides.

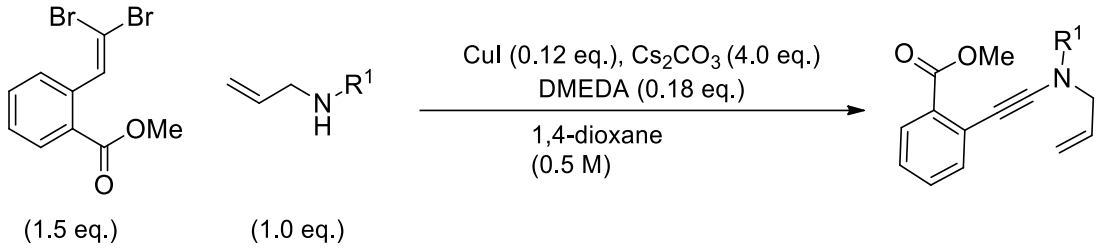
General Procedure 18 (GP18): Preparation of ynamides



Following a modified procedure of Hsung and co-workers for the preparation of ynamides,[143a] the sulfonamide (1.0 eq.), the bromoalkyne (1.2 eq.), $CuSO_4 \cdot 5H_2O$ (20 mol%), 1,10-

phenanthroline (40 mol%) and K_2CO_3 (2.0 eq.) were combined in a reaction tube which was purged with argon for 5 minutes. Toluene (1.0 M) was added and the reaction mixture was heated to 65 °C for 16 hours, at which point consumption of starting material was indicated by TLC. The reaction was cooled to room temperature, diluted with EtOAc and filtered through a pad of Celite® (ca 2 cm), eluting with EtOAc. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography to afford the pure ynamides.

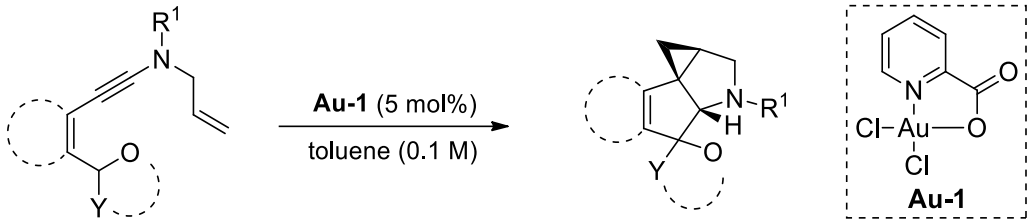
General Procedure 19 (GP19): Preparation of ynamides



(1.5 eq.) (1.0 eq.)

Following the procedure reported by Evano and co-workers for the preparation of ynamides,[143b] the sulfonamide (1.0 eq.), the dibromo olefin (1.5 eq.), CuI (0.12 eq.), Cs_2CO_3 (4.0 eq.) and DMEDA (0.18 eq.) were combined and the flask was evacuated and refilled with argon for 3 times. Then 1,4-dioxane (0.5 M) was added and the reaction was stirred at 60 °C for 18 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through Celite® (ca 2 cm). The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography to afford the pure ynamides.

General procedure 20 (GP20): Gold-catalysed cascade for the preparation of polycyles

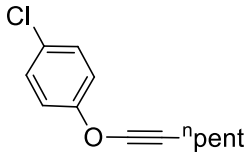


The ynamide (1.0 eq.) was dissolved in toluene (0.1 M) at room temperature. **Au-1** (5 mol%) was added and the mixture was heated on a preheated block at the temperature specified until consumption of starting material was observed by TLC. The reaction mixture was cooled to room temperature, filtered through a pipette containing a small pad of silica (ca 1 cm), eluting with EtOAc (ca 10 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography afforded the desired polycycles.

5.4 Characterisation of Compounds

5.4.1 Compounds in Chapter 2

1-Chloro-4-(hex-1-yn-1-yl)benzene 233

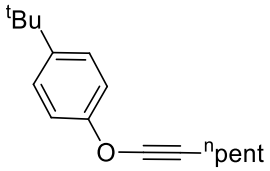


Prepared according to **GP1** using 4-chorophenol (1.3 mmol, 0.13 mL) and 1,1-dibromo-hept-1-ene (2.0 mmol, 535 mg). Purification by flash column chromatography [hexane] afforded the ynol ether **233** as a pale yellow oil (292 mg, 98%). The sample contained ca 8% impurities, which could not be separated from the desired ynol ether; IR ν_{max}/cm^{-1} 2957, 2930, 2859, 2278, 1590,

1484, 1245, 1177, 1149, 1090, 1011, 823, 726, 663; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 2.18 (t, *J* = 7.0 Hz, 2H), 1.48-1.28 (m, 6H), 0.96-0.91 (m, 3H).

Data matches that reported in the literature.[85]

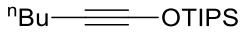
1-*Tert*-butyl-4-(hept-1-yn-1-yloxy)benzene 234



Prepared according to **GP1** using 4-*tert*-butylphenol (1.3 mmol, 0.13 mL) and 1,1-dibromo-hept-1-ene (2.0 mmol, 535 mg). Purification by flash column chromatography [hexane] afforded the ynol ether **234** as a pale yellow oil (220 mg, 67%). The sample contained ca 10% impurities, which could not be separated from the desired ynol ether; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.0 Hz, 2H), 7.20 (d, *J* = 9.0 Hz, 2H), 2.28 (t, *J* = 6.9 Hz, 2H), 1.62-1.37 (m, 6H), 1.33 (s, 9H), 0.94 (t, *J* = 6.0 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 154.3 (C), 146.8 (C), 126.3 (2 × CH), 114.3 (2 × CH), 83.7 (C), 74.1 (C), 34.3 (C), 31.5 (3 × CH_3), 31.1 (CH_2), 29.1 (CH_2), 22.2 (CH_2), 17.2 (CH_2), 14.0 (CH_3).

Data matches that reported in the literature. [85]

1-(Triisopropylsiloxy)-1-hexyne 243

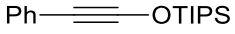


Prepared according to **GP2** using hexyne (5.0 mmol, 0.57 mL) and triisopropylsilyl trifluoromethanesulfonate (5.5 mmol, 1.48 mL). Purification by bulb-to-bulb distillation (30 mbar/136 °C) afforded the silyl ynol ether **243** as a yellow oil (470 mg, 37%); IR ν_{max}/cm^{-1} 2945,

2868, 2281; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.08 (t, *J* = 6.9 Hz, 2H), 1.46-1.38 (m, 4H), 1.30-1.25 (m, 3H), 1.14 (d, *J* = 6.6 Hz, 18H), 0.91 (t, *J* = 6.9 Hz, 3H).

Data matches that reported in the literature.[89a]

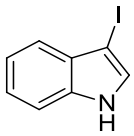
Triisopropylsilylethynyl-benzene 244



Prepared according to **GP2** using phenyl acetylene (5.0 mmol, 0.55 mL) and triisopropylsilyl trifluoromethanesulfonate (5.5 mmol, 1.48 mL). Purification by bulb-to-bulb distillation (10 mbar/90 °C) afforded the silyl ynol ether **244** as yellow oil (1.10 g, 97%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.30 (m, 2H), 7.26-7.24 (m, 2H), 7.24-7.15 (m, 1H), 1.41-1.29 (m, 3H), 1.20 (d, *J* = 6.1 Hz, 18H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 131.4 (2 × CH), 128.2 (2 × CH), 125.9 (CH), 125.2 (C), 96.8 (C), 33.5 (C), 17.3 (6 × CH_3), 11.9 (3 × CH).

Data matches that reported in the literature.[89a]

3-Iodoindole 251

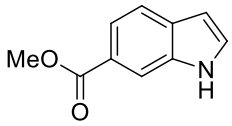


A solution of iodine (2.20 g, 8.6 mmol, 1 eq.) in DMF (15 mL, 0.6 M) was added dropwise at room temperature to a solution of indole (1.00 g, 8.5 mmol, 1.0 eq.) and KOH (1.21 g, 21.3 mmol, 2.5 eq.) in DMF (15 mL, 0.6 M). After 45 minutes stirring the reaction mixture was poured onto ice water containing ammonia (0.5%) and $Na_2S_2O_3$ (0.1%). The white precipitate was filtered and washed several times with cold water. The iodo-substituted indole **251** was isolated as a pink solid (2.00 g, 99%) and used for the next step without further purification; mp. 72-74

°C (lit. 72-73 °C) ; IR ν_{max}/cm^{-1} 3382, 3108, 1620, 1451, 1406, 1321, 1236, 1189, 1175, 1115, 1083, 1003, 957, 928, 811, 734; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.52-7.45 (m, 1H), 7.42-7.37 (m, 1H), 7.32 (m, 1H), 7.26-7.19 (m, 1H), 4.80 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 135.7 (C), 129.8 (C), 128.4 (CH), 123.2 (CH), 121.0 (CH), 120.8 (CH), 111.3 (CH), 57.6 (C).

Data matches that reported in the literature. [208]

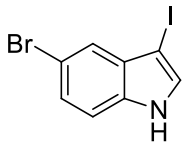
Methyl 1*H*-indole-6-carboxylate



Indole-6-carboxylic acid (800 mg, 5.0 mmol, 1.0 eq.) was dissolved in MeOH (16 mL, 0.3 M), 2-3 drops of H_2SO_4 were then added and the solution was refluxed for 16 hours. K_2CO_3 (10-15 mg) was added until the pH indicates neutral solution and the reaction mixture was stirred at the same temperature for 1 more hour. The solution was cooled to room temperature and washed with saturated $NaHCO_3$ solution (20 mL). The two phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [70:30 (hexane:EtOAc)] afforded the desired ester as a yellow solid (650 mg, 74%); mp 79-81 °C (lit. 78-80 °C); IR ν_{max}/cm^{-1} 3332, 2950, 1686, 1620, 1507, 1434, 1295, 1223, 1084, 986, 896, 774, 730; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.48 (s, NH), 8.18 (bs, 1H), 7.82 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.40-7.37 (m, 1H), 6.61 (ddd, *J* = 3.1, 2.0, 1.0 Hz, 1H), 3.94 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.3 (C), 135.3 (C), 131.7 (C), 127.6 (CH), 123.9 (C), 121.0 (CH), 120.4 (CH), 113.6 (CH), 103.2 (CH), 52.1 (CH_3).

Data matches that reported in the literature.[209]

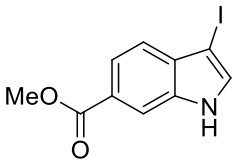
5-Bromo-3-iodo-1*H*-indole 277



A solution of iodine (157 mg, 0.8 mmol, 1.0 eq.) in DMF (3 mL, 0.3 M) was added dropwise at room temperature to a solution of 5-bromo-1*H*-indole (204 mg, 0.8 mmol, 1.0 eq.) and KOH (211 mg, 2.0 mmol, 2.5 eq.) in DMF (3 mL). After 45 minutes the reaction mixture was diluted with H_2O (10 mL), the two phases were separated and the aqueous phase was extracted with 50:50 Et_2O:EtOAc (2 × 10 mL). The combined organic extracts were washed with $Na_2S_2O_3$ (30 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford the indole derivative **277** as a brown oil (207 mg, 92%). The product was used for the next step without any further purification. (*The compound proved unstable at room temperature and no further data could be obtained as it was used directly to the next step)*; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.03 (s, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.38-7.19 (m, 2H).

Data matches that reported in the literature.[210]

Methyl 3-iodo-1*H*-indole-6-carboxylate 278

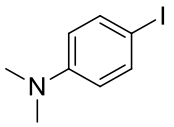


A solution of iodine (157 mg, 2.5 mmol, 1.0 eq.) in DMF (5 mL, 0.5 M) was added dropwise to a solution of methyl 1*H*-indole-6-carboxylate (430 mg, 2.5 mmol, 1.0 eq.) and KOH (383 mg, 6.3

mmol, 2.5 eq.) in DMF (5 mL) at room temperature. The reaction mixture was stirred for 1 hour, diluted with H_2O (10 mL), the two phases were separated and the aqueous phase was extracted with 50:50 Et_2O:EtOAc (2 × 10 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$ solution (30 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford the indole derivative **278** as a white solid (275 mg, 98%). The product was used for the next step without further purification; mp. 101-103 °C; IR ν_{max}/cm^{-1} 3203, 2950, 1709, 1434, 1311, 1298, 1221, 1083, 1024, 825, 769; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.66 (s, NH), 8.14 (dd, *J* = 1.3, 0.6 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 3.95 (s, 3H).

Data matches that reported in the literature.[211]

4-Iodo-*N,N*-dimethylaniline 377

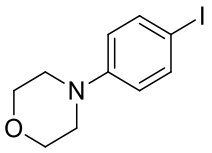


N,N-Dimethyl aniline (1.20 mL, 10.0 mmol, 1.0 eq.) was dissolved in 1,4-dioxane (60 mL, 0.2 M), followed by addition of pyridine (60 mL). The solution was then cooled to 0 °C, iodine (3.80 g, 30.0 mmol, 3.0 eq.) was added in one portion and the reaction was stirred for 1 hour at room temperature. Extra iodine (166 mg, 1.3 mmol) was added and the mixture was stirred for 1 more hour. The reaction was quenched by addition of saturated $Na_2S_2O_3$ solution (50 mL), the two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [90:10 (hexane:EtOAc)]

afforded the iodoaniline **377** as a white solid (1.50 g, 60%); mp. 82-83 °C (lit. 82-83 °C); IR ν_{max}/cm^{-1} 3064, 2957, 1591, 1523, 1465, 1331, 1248, 1181, 1081, 1026, 905, 762, 690; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 9.1 Hz, 2H), 6.49 (d, *J* = 9.1 Hz, 2H), 2.92 (s, 6H).

Data matches that reported in the literature.[212]

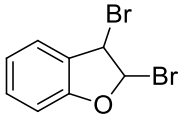
4-(4-Iodophenyl)morpholine 384



1,4-Diiodobenzene (1.70 g, 5.0 mmol, 1.0 eq.), CuI (95 mg, 0.2 mmol, 0.04 eq.), K_2CO_3 (1.40 g, 10.0 mmol, 2.0 eq.), L-proline (115 mg, 1.0 mmol, 0.2 M) and morpholine (1.3 mL, 15.0 mmol, 3.0 eq.) were suspended in DMSO (3 mL, 1.7 M) and the mixture was heated at 90 °C for 40 hours in a sealed tube. The reaction was cooled to room temperature, H_2O (10 ml) was added and the residue was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with Brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexane) gave the morpholine derivative **384** as a yellow solid (925 mg, 64%); mp. 151-152 °C (lit. 151-154 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 9.0 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 1H), 3.88-3.82 (m, 2H), 3.16-3.07 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.8 (C), 138.0 (2 × CH), 117.9 (2 × CH), 117.6 (C), 66.9 (2 × CH_2), 49.06 (2 × CH_2).

Data matches that reported in the literature.[213]

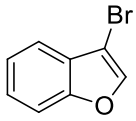
2,3-Dibromo-2,3-dihydrobenzofuran 418



Benzofuran (1.10 mL, 10.0 mmol, 1.0 eq.) and AcOK (1.46 g, 15.0 mmol, 1.5 eq.) were suspended in $CHCl_3$ (3 mL, 3.3 M) at room temperature. A solution of bromine (0.81 mL, 15.0 mmol, 1.5 eq.) in $CHCl_3$ (15 mL, 1.0 M) was added dropwise to the suspension and the mixture was stirred for 1 hour. H_2O (20 mL) was then added, the two phases were separated, the aqueous phase was extracted with $CHCl_3$ (2 × 20 mL), the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (petroleum ether) afforded the benzofuran derivative **418** as a white solid (1.3 gr, 46%); mp. 89-90 °C (lit. 88-90 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.38 (td, *J* = 8.2, 1.3 Hz, 1H), 7.16 (td, *J* = 7.5, 0.9 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 5.76 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.1 (C), 131.7 (CH), 126.3 (C), 126.0 (CH), 124.3 (CH), 112.6 (CH), 90.7 (CH), 53.1 (CH).

Data matches that reported in the literature.[214]

3-Bromobenzofuran 419



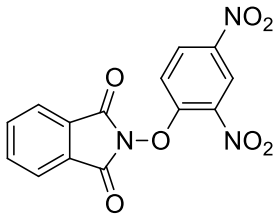
The dibrominated benzofuran derivative **418** (1.10 g, 4.0 mmol, 1.0 eq.) was suspended in EtOH (3 mL, 1.3 M) and was added dropwise to a solution of KOH (450 mg, 8.0 mmol, 2.0 eq.) in EtOH (5 mL, 1.6 M) at 0 °C. The reaction mixture was refluxed for 2 hours, then cooled to room

temperature and the solvent was removed under reduced pressure. The residue was diluted with EtOAc (10 mL) and H_2O (10 mL), the two phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the brominated benzofuran **419** as a yellow oil (545 mg, 70%). The product was used for the next step without any further purification; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.58-7.53 (m, 1H),

7.53-7.48 (m, 1H), 7.41-7.30 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 154.6 (C), 142.8 (CH), 127.3 (C), 125.6 (CH), 123.6 (CH), 119.9 (CH), 111.9 (CH), 98.1 (C).

Data matches that reported in the literature. [215]

2-(2,4-Dinitrophenoxy)isoindoline-1,3-dione 360

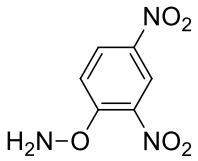


Et_3N (4.2 mL, 30.0 mmol, 1.0 eq.) was added to a suspension of *N*-hydroxyphthalimide **358** (5.0 g, 30.0 mmol, 1.0 eq.) in acetone (100 mL, 3.1 M) and the mixture was stirred for 10 minutes. Dinitrobenzene **359** (6.70 g, 30 mmol, 1.0 eq.) was added in one portion and the reaction was stirred at room temperature for 2 hours at which point a yellow solid was formed. The reaction mixture was poured into cold water (100 mL), the precipitate was filtered, washed (3 × 20 mL with cold MeOH and then 3 x 20 mL hexane) and dried under vacuum to give the *N*-protected phthalimide **360** as a yellow solid (9.90 g, 98%); mp. 185-187 °C (lit. 186-188 °C); ^{1}H-NMR (300

MHz, $CDCl_3$) δ 8.99 (d, *J* = 2.7 Hz, 1H), 8.44 (dd, *J* = 9.3, 2.7 Hz, 1H), 8.05-7.96 (m, 2H), 7.95-7.86 (m, 2H), 7.46 (d, *J* = 9.3 Hz, 1H); MS (ES): 352 (M+Na, 100%).

Data matches that reported in the literature. [97b]

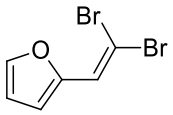
O-(2,4-Dinitrophenyl)hydroxylamine 361



The phthalimide derivative (6.60 g, 20.0 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (100 mL, 0.2 M), cooled to 0 °C and a solution of hydrazine hydrate (3.28 mL, 58.0 mmol, 2.9 eq.) in MeOH (20 mL, 2.9 M) was added in one portion. The mixture was stirred at this temperature for 8 hours (CAUTION: danger of explosion, temperature must maintain at 0 °C). Cold HCl 1 M (130 mL) was added and the flask was shaken very rapidly followed by a quick filtration. The filter cake was washed (3 × 20 mL MeCN) and the filtrate was poured into a separating funnel where the two phases were separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 100 mL), the organic extracts were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Recrystallisation with hot EtOH afforded the desired amine **361** as a yellow solid (1.09 g, 30%); mp. 112-113 °C (lit. 111-113 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.7 Hz, 1H), 8.45 (dd, *J* = 9.4, 2.7 Hz, 1H), 8.06 (d, *J* = 9.4 Hz, 1H), 6.37 (s, NH_2); MS (ES): 181 (100%).

Data matches that reported in the literature.**[97b]**

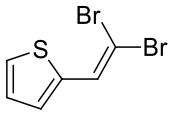
2-(2,2-Dibromovinyl)furan 263



Prepared according to **GP8** using furaldehyde **260** (0.25 mL, 3.0 mmol), PPh_3 (3.20 g, 12 mmol), CBr_4 (2.00 g, 6.0 mmol) and the reaction was complete in 40 minutes. The olefin **263** was isolated as a yellow oil (488 mg, 65%); IR ν_{max}/cm^{-1} 3239, 2964, 2929, 1740, 1476, 1363, 1333, 1148, 755, 693; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.41 (s, 1H), 6.95 (d, *J* = 3.5 Hz, 1H), 6.46 (dd, *J* = 3.5, 1.8 Hz, 1H).

Data matches that reported in the literature.[216]

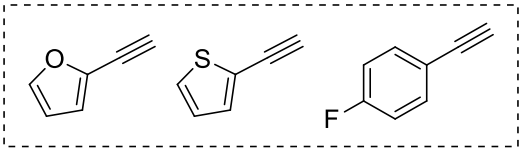
2-(2,2-Dibromovinyl)thiophene 264



Prepared according to **GP8** using thiophene carboxaldehyde **261** (0.9 mL, 10.0 mmol), PPh_3 (10.51 g, 40.0 mmol), CBr_4 (6.60 g, 20.0 mmol) and the reaction was complete in 40 minutes. The olefin **264** was isolated as a brown solid (2.60 g, 95%); mp. 55-56 °C; IR ν_{max}/cm^{-1} 3102, 3008, 1801, 1726, 1421, 1348, 1264, 1210, 1081, 1051, 855, 817, 740, 703; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (bs, 1H), 7.39 (ddd, *J* = 5.1, 1.2, 0.6 Hz, 1H), 7.26–7.24 (m, 1H), 7.04 (dd, *J* = 5.1, 3.7 Hz, 1H).

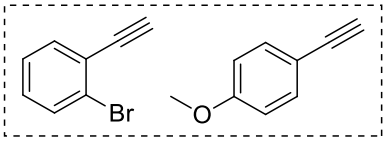
Data matches that reported in the literature.[217]

Ethynylfuran 266, 2-Ethynylthiophene 267 and-Ethynyl-4-fluorobenzene 268



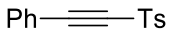
The dibromo olefines (1.0 eq.) were dissolved in dry THF (0.5 M) and the solution was cooled to -78 °C. ^{n}BuLi (1.2 eq.) was added and the mixtures were stirred at room temperature for 1 hour. Saturated NH_4Cl solution was then added and the residues were extracted with Et_2O (2 ×). The combined organic extracts were dried over $MgSO_4$, filtered and the mixtures were concentrated under reduced pressure (at 35 °C) until ca 1 mL of the solvent was remained. The final products were not isolated and the solutions were subjected to the corresponding Sonogashira reactions directly.[218],[219],[220]

1-Bromo-2-ethynylbenzene 273 and 1-Ethynyl-4-methoxybenzene 274



Prepared according to a **GP15** using the corresponding ethynyl trimethylsilane derivatives (1.0 eq.) and K_2CO_3 (0.15 eq.) in MeOH (0.2 M). After the workup described in the procedure the solvent was concentrated under reduced pressure (at 35 °C) until ca. 1 mL was remained. The final products were not isolated and the solutions were subjected to the subsequent Sonogashira reactions directly.[221],[222]

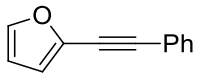
1-Methyl-4-((phenylethynyl)sulfonyl)benzene 403



K_2CO_3 (500 mg, 3.6 mmol, 1.0 eq.) was dissolved in the minimum amount of H_2O (ca 5 mL) and was added to the solution of the (*E*)-1-((2-iodo-2-phenylvinyl)sulfonyl)-4-methylbenzene (1.41 g, 3.6 mmol, 1.0 eq.) in MeOH (25 mL, 0.1 M) at room temperature. The mixture was stirred at 60 °C for 3 hours, cooled to room temperature and 2/3 of the solvent mixture was removed under reduced pressure. H_2O (20 mL) was then added to the residue and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried oven $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [50:50 (hexane:EtOAc)] gave the alkyne **403** as a white solid (577 mg, 63%); mp. 79-81 °C (lit. 79-81 °C); IR ν_{max}/cm^{-1} 2181, 1593, 1487, 1323, 1292, 1152, 1083, 1118, 849, 812, 757, 678; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.55-7.48 (m, 2H), 7.49-7.43 (m, 1H), 7.42-7.33 (m, 4H), 2.47 (s, 3H).

Data matches that reported in the literature.[223]

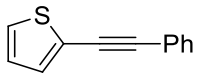
2-(Phenylethynyl)furan 404



Prepared according to **GP9** using furan (0.29 mL, 4.0 mmol) and ^{n}BuLi (2.5 M, 1.6 mL, 4.0 mmol), stirring at room temperature. Purification by flash column chromatography (hexane) afforded the alkyne **404** as a yellow oil (336 mg, 100%); IR ν_{max}/cm^{-1} 3154, 3118, 1573, 1475, 1214, 1012, 928, 889, 737, 687; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56-7.49 (m, 2H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.39-7.32 (m, 3H), 6.66 (d, *J* = 3.4 Hz, 1H), 6.43 (dd, *J* = 3.4, 1.6 Hz, 1H).

Data matches that reported in the literature.[98]

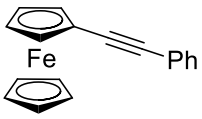
2-(Phenylethynyl)thiophene 405



Prepared according to **GP9** using thiophene (0.32 mL, 4.0 mmol) and ^{n}BuLi (2.5 M, 1.6 mL, 4.0 mmol), stirring at room temperature. Purification by flash column chromatography (hexane) afforded the alkyne **405** as a yellow oil (189 mg, 51%); IR ν_{max}/cm^{-1} 1517, 1484, 1441, 1424, 1213, 1070, 852, 832, 752, 705, 687; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.55-7.48 (m, 2H), 7.38-7.32 (m, 3H), 7.31-7.27 (m, 2H), 7.02 (dd, *J* = 5.0, 3.8 Hz, 1H).

Data matches that reported in the literature.[98]

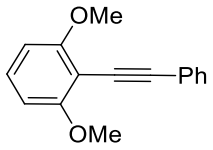
1-Ferrocenyl-2-phenylacetylene 406



Prepared according to **GP9** using ferrocene (744 mg, 4.0 mmol) and ^{t}BuLi (1.6 M, 2.5 mL, 4.0 mmol), stirring at 0 °C. Purification by flash column chromatography (hexane) afforded the alkyne **406** as an orange solid (318 mg, 55%); mp 103-105 °C (lit. 104-105 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.51-7.42 (m, 2H), 7.38-7.29 (m, 3H), 4.54-4.49 (m, 2H), 4.27-4.23 (m, 7H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 131.5 (2 × CH), 128.4 (2 × CH), 127.8 (CH), 124.1 (C), 88.4 (C), 85.9 (C), 71.6 (2 × CH), 70.1 (5 × CH), 69.0 (2 × CH), 65.5 (C).

Data matches that reported in the literature.[98]

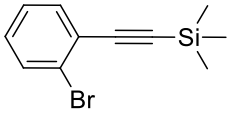
1,3-Dimethoxy-2-(phenylethynyl)benzene 407



Prepared according to **GP9** using 1,3-dimethoxybenzene (1.10 g, 8.0 mmol) and ^{n}BuLi (2.5 M, 3.2 mL, 8.0 mmol), stirring at room temperature. Purification by flash column chromatography (hexane) afforded the alkyne **407** as an off-white solid (350 mg, 37%); mp. 80-81 °C (lit. 80-82 °C); IR ν_{max}/cm^{-1} 2938, 2838, 1581, 1473, 1431, 1253, 1107, 1031, 755, 724, 690; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.63-7.57 (m, 2H), 7.37-7.26 (m, 3H), 7.25-7.21 (m, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 3.91 (s, 6H).

Data matches that reported in the literature.[98]

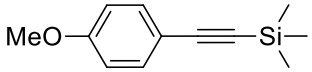
((2-Bromophenyl)ethynyl)trimethylsilane 271



Prepared according to **GP3** using 1-bromo-2-iodobenzene (1.0 mL, 7.8 mmol, 1.0 eq.), in a mixture of degassed Et_3N (5.4 mL, 39.0 mmol, 5.0 eq.) and THF (15 mL, 0.5 M), stirring at room temperature for 1 hour. Purification by flash column chromatography (hexane) afforded the silyl-protected alkyne **271** as a yellow oil (2.00 g, 99%); IR ν_{max}/cm^{-1} 2899, 2161, 1464, 1240, 890, 750, 620; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.23 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.19-7.12 (m, 1H), 0.27 (s, 9H).

Data matches that reported in the literature.[224]

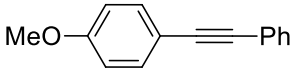
((4-Methoxyphenyl)ethynyl)trimethylsilane 272



Prepared according to a modified **GP3** using 4-iodoanisole (936 mg, 4.0 mmol), stirring for 4 hours at room temperature. Purification by flash column chromatography (hexane) afforded the silyl-protected alkyne **272** as a yellow oil (813 mg, 71%); IR ν_{max}/cm^{-1} 2927, 2854, 1603, 1513, 1254, 1177, 1027, 850; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 0.24 (s, 9H).

Data matches that reported in the literature.[225]

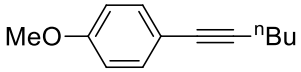
1-Methoxy-4-(phenylethynyl)benzene 411



Prepared according to a modified **GP3** using *p*-iodoanisole (1.17 g, 5.0 mmol, 1.0 eq.). Purification by flash column chromatography (hexane) afforded the alkyne **411** as a yellow solid (824 mg, 80%); mp. 54-56 °C (lit. 55-56 °C); IR ν_{max}/cm^{-1} 2994, 2217, 1594, 1508, 1439, 1243, 1178, 1027, 832, 752, 690; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47-7.43 (m, 2H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.31-7.22 (m, 3H), 6.84-6.78 (d, *J* = 8.9 Hz, 2H), 3.76 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.8 (C), 133.2 (2 × CH), 131.6 (2 × CH), 128.5 (2 × CH), 128.1 (CH), 123.8 (C), 115.6 (C), 114.2 (2 × CH), 88.5 (C), 88.2 (C), 55.5 (CH_3).

Data matches that reported in the literature.[226]

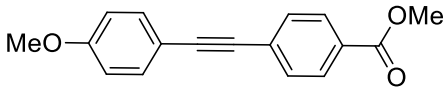
1-Butyl-2-(4-methoxyphenyl)acetylene 412



Prepared according to **GP3** using *p*-iodoanisole (468 mg, 2.0 mmol, 1 eq.), stirring at room temperature overnight. Purification by flash column chromatography [98:2 (hexane:EtOAc)] afforded the alkyne **412** as a yellow oil (307 mg, 98%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 2.41 (t, *J* = 7.0 Hz, 2H), 1.66-1.42 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 132.9 (2 × CH), 116.4 (C), 113.8 (2 × CH), 88.7 (C), 80.3 (C), 55.1 (CH_3), 31.0 (CH_2), 22.1 (CH_2), 19.1 (CH_2), 13.7 (CH_3); MS (EI): 188 (M, 90%), 145 (100), 173 (60), 159 (52).

Data matches that reported in the literature.[227]

Methyl 4-((4-methoxyphenyl)ethynyl)benzoate 413

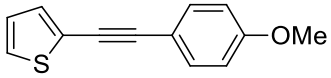


Methyl 4-iodobenzoate (345 mg, 1.3 mmol, 1.0 eq.), 1-ethynyl-4-methoxybenzene (2.5 mmol, 1.9 eq.), $Pd(PPh_3)_4$ (75 mg, 5 mol%), CuI (50 mg, 20 mol%) and *N*-ethyl-*N*,*N*-diisopropyl amine (2.5 mL) were suspended in DMF (10 mL, 0.1 M) and the mixture was heated to 80 °C for 5 hours. The reaction was cooled to room temperature, H_2O (10 mL) was added and the residue was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with H_2O (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the alkyne **413** as a yellow solid (212 mg, 61%); mp. 156-158 °C (lit. 156-158 °C); IR ν_{max}/cm^{-1} 2952,

1716, 1598, 1501, 1434, 1279, 1253, 1108, 1026, 839, 769, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.8 (C), 160.2 (C), 133.4 (2 x CH), 131.5 (2 × CH), 129.7 (2 × CH), 129.3 (C), 128.6 (C), 114.9 (C), 114.3 (2 × CH), 92.7 (C), 87.7 (C), 55.5 (CH_3), 52.3 (CH_3).

Data matches that reported in the literature.[228]

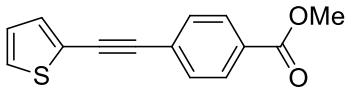
2-((4-Methoxyphenyl)ethynyl)thiophene 415



Trimethyl(thiophen-2-ylethynyl)silane (901 mg, 5.0 mmol, 2.0 eq.), *p*-iodoanisole (585 mg, 2.5 mmol, 1.0 eq.), $Pd(PPh_3)_4$ (144 mg, 5 mol%) and CuCl (124 mg, 50 mol%) were suspended in DMF (13 mL, 0.2 M) and the mixture was heated to 80 °C for 4 hours. The reaction was cooled to room temperature, H_2O (10 mL) was added and the residue was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with H_2O (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the alkyne **415** as a brown oil (161 mg, 61%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.9 Hz, 2H), 7.29-7.20 (m, 2H), 7.00 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.9 (C), 133.1 (2 × CH), 131.6 (CH), 127.2 (CH), 126.9 (CH), 123.9 (C), 115.2 (C), 114.2 (2 × CH), 93.2 (C), 81.4 (C), 55.5 (CH_3).

Data matches that reported in the literature.[18]

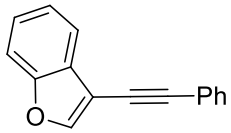
Methyl 4-(thiophen-2-ylethynyl)benzoate 416



Trimethyl(thiophen-2-ylethynyl)silane (901 mg, 5.0 mmol, 2.0 eq.), methyl 4-iodobenzoate (655 mg, 2.5 mmol, 1.0 eq.), $Pd(PPh_3)_4$ (144 mg, 5 mol%) and CuCl (124 mg, 50 mol%) were suspended in DMF (13 mL, 0.2 M) and the mixture was heated to 80 °C for 3 hours. The reaction was cooled to room temperature, H_2O (ca 10 mL) was added and the residue was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with H_2O (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [90:10 (hexane:EtOAc)] gave the alkyne **416** as a brown solid (297 mg, 50%); mp. 115-116 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.36-7.31 (m, 2H), 7.03 (dd, *J* = 5.1, 3.7 Hz, 1H), 3.92 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.5 (C), 132.7 (C), 130.2 (C), 131.4 (CH), 129.7 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 127.4 (C), 122.8 (CH), 92.5 (C), 85.8 (C), 52.4 (CH_3).

Data matches that reported in the literature.[229]

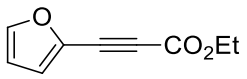
3-(Phenylethynyl)benzofuran 420



Prepared according to a modified **GP3** using 3-bromobenzofuran **419** (545 mg, 2.8 mmol, 1.0 eq.), stirring for 24 hours at room temperature. Purification by flash column chromatography [100-90:10 (pentane:EtAOc)] afforded the desired alkyne **420** as a brown viscous oil (104 mg,

17%); IR ν_{max}/cm^{-1} 3112, 3056, 1596, 1487, 1452, 1233, 1109, 1008, 856, 805, 689; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.79-7.74 (m, 1H), 7.60-7.55 (m, 2H), 7.55-7.51 (m, 1H), 7.41-7.35 (m, 5H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 154.8 (C), 147.6 (CH), 131.8 (C), 131.7 (2 × CH), 128.6 (2 × CH), 128.5 (CH), 125.4 (CH), 123.5 (CH), 123.3 (C), 120.7 (CH), 111.8 (CH), 104.8 (C), 94.0 (C), 78.9 (C).

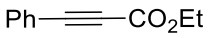
Ethyl 3-(furan-2-yl)propiolate 421



Dibromoalkene **263** (1.30 g, 5.0 mmol, 1.0 eq.) was dissolved in THF (25 mL, 0.2 M) and the mixture was cooled to -78 °C. ^{n}BuLi (2.5 M solution in hexane, 5.0 mmol, 2.0 mL, 1 eq.) was added dropwise and the reaction was stirred at this temperature for 1 hour before the addition of the ethylchloroformate (0.72 mL, 7.5 mmol, 1.5 eq.). Then the mixture was slowly warmed up to room temperature and the reaction was stirred for 3 more hours. Saturated NH_4Cl solution (20 mL) was added, the two phases were separated and the aqueus phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography afforded the alkynyl ester **421** as a yellow oil that solidifies under low pressure (ca 0.4 mbar) (401 mg, 49%); mp 89-90 °C (lit. 89-90 °C); IR ν_{max}/cm^{-1} 3136, 2996, 2211, 1701, 1475, 1365, 1282, 1201, 1025, 1016, 769, 740, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 1.8 Hz, 1H), 6.94 (d, *J* = 3.5 Hz, 1H), 6.47 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

Data matches that reported in the literature.[230]

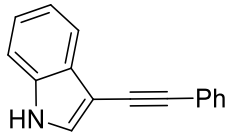
Ethyl phenylpropiolate 422



Phenyl acetylene (5.5 mL, 50.0 mmol, 1.0 eq.) was added dropwise at 0 °C to a solution of ^{n}BuLi (2.5 M solution in hexane, 50 mmol, 20 mL, 1 eq.) in ether (70 mL, 0.1 M) and the reaction mixture was stirred at this temperature for 30 minutes. The mixture was then transferred to a solution of ethyl chloroformate (14.4 mL, 150.0 mol, 3.0 eq.) in ether (50 mL) at 0 °C. After stirring for 1 hour at this temperature, the mixture was poured into ice water and extracted with ether (2 × 50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography [95:5 (hexane:EtOAc)] afforded the alkyne **422** as a colourless oil (6.20 g, 70%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64-7.58 (m, 2H), 7.51-7.35 (m, 3H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 154.1 (C), 133.0 (2 × CH), 130.6 (2 × CH), 128.6 (CH), 119.7 (C), 86.1 (C), 80.7 (C), 62.1 (CH_2), 14.1 (CH_3); MS (EI+): 174.1 (M, 32%), 129.0 (100), 102.0 (70).

Data matches that reported in the literature.[231]

3-(Phenylethynyl)-1*H*-indole 252

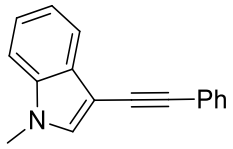


Prepared according to **GP3** using 3-iodoindole **251** (2.43 g, 1 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc)] afforded the indole derivative **252** as a brown solid (913 mg, 70%); mp. 140-142 °C (lit. 164-165 °C decomposition); IR ν_{max}/cm^{-1} 3386, 2214, 1484, 1421, 1456, 1333, 1236, 1100, 819, 744, 688; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.58 (bs, NH),

7.78 (d, *J* = 2.7 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.57-7.51 (m, 2H), 7.47-7.30 (m, 4H), 7.24-7.01 (m, 2H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 135.5 (C), 130.8 (2 × CH), 129.7 (CH), 128.5 (2 × CH), 128.1 (C), 127.7 (C), 123.9 (CH), 122.4 (CH), 120.1 (CH), 119.0 (CH), 112.2 (CH), 96.1 (C), 90.6 (C), 84.4 (C).

Data matches that reported in the literature.[98]

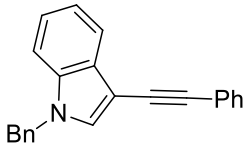
1-Methyl-3-(phenylethynyl)-1*H*-indole 281



Prepared according to **GP3** using *N*-methyl-3-iodoindole **275** (514 mg, 2.0 mmol). Purification by flash column chromatography [90:10 (hexane:toluene)] afforded the indole derivative **281** as a brown oil (228 mg, 49%); IR ν_{max}/cm^{-1} 3052, 2932, 2209, 1596, 1487, 1424, 1155, 813, 737, 689; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.60-7.51 (m, 2H), 7.38-7.33 (m, 3H), 7.33-7.28 (m, 2H), 7.25-7.19 (m, 2H), 3.80 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 136.4 (C), 132.3 (CH), 131.4 (2 × CH), 129.3 (CH), 128.4 (2 × CH), 127.5 (CH), 124.5 (C), 122.8 (C), 120.5 (CH), 120.3 (CH), 109.7 (CH), 97.2 (C), 91.2 (C), 83.3 (C), 33.2 (CH_3).

Data matches that reported in the literature. [232]

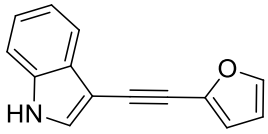
1-Benzyl-3-(phenylethynyl)-1*H*-indole 282



Prepared according to **GP3** using 1-benzyl-3-iodo-1*H*-indole **276** (1.65 g, 5.0 mmol). Purification by flash column chromatography [70:30 (hexane:EtOAc)] afforded the indole derivative **282** as a brown solid (616 mg, 40%); mp. 116-118 °C; IR ν_{max}/cm^{-1} 3388, 2216, 1598, 1496, 1214, 831, 741; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 1H), 7.59-7.52 (m, 2H), 7.42 (s, 1H), 7.39-7.27 (m, 7H), 7.25-7.21 (m, 2H), 7.18-7.12 (m, 2H), 5.33 (s, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 136.7 (C), 136.0 (C), 131.7 (CH), 131.4 (2 × CH), 129.5 (C), 129.0 (2 × CH), 128.4 (2 × CH), 128.1 (CH), 127.7 (CH), 127.1 (2 × CH), 124.4 (C), 123.0 (CH), 120.8 (CH), 120.5 (CH), 110.2 (CH), 97.9 (C), 91.4 (C), 83.1 (C), 50.4 (CH_2).

Data matches that reported in the literature. [233]

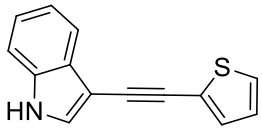
3-(Furan-2-ylethynyl)-1*H*-indole 283



Prepared according to **GP3** using 3-iodoindole **251** (729 mg, 3.0 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the indole derivative **283** as a dark brown oil (98 mg, 16%); IR ν_{max}/cm^{-1} 3376, 3059, 1615, 1514, 1488, 1239, 1114, 923, 766, 685; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (bs, NH), 7.80 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 2.7 Hz, 1H), 7.37 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.35-7.30 (m, 1H), 7.22-7.13 (m, 2H), 6.64 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.44 (dd, *J* = 3.4, 1.8 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.3 (CH), 138.1 (C), 135.3 (C), 128.7 (CH),

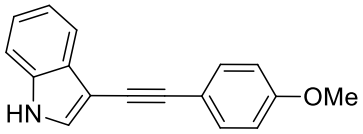
128.4 (C), 123.5 (CH), 121.1 (CH), 120.3 (CH), 114.5 (CH), 111.5 (CH), 111.1 (CH), 98.2 (C), 87.1 (C), 81.0 (C); HRMS (EI) calcd. for $C_{14}H_9NO$: 207.0684, found: 207.0686 $[M]^+$.

3-(Thiophen-2-ylethynyl)-1*H*-indole 284



Prepared according to **GP3** using 3-iodoindole **251** (729 mg, 3.0 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc)] afforded the indole derivative **284** as a dark brown solid (670 mg, 42%); mp. 69-71 °C; IR ν_{max}/cm^{-1} 3382, 2206, 1457, 1255, 1098, 815, 742, 682; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (bs, NH), 7.82 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.49 (d, *J* = 2.7 Hz, 1H), 7.42-7.38 (m, 1H), 7.31-7.27 (m, 2H), 7.25-7.20 (m, 2H), 7.02 (dd, *J* = 5.2, 3.6 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 135.3 (C), 131.2 (CH), 128.5 (C), 128.1 (CH), 127.1 (CH), 126.5 (CH), 124.5 (C), 123.4 (CH), 121.0 (CH), 120.3 (CH), 111.4 (CH), 98.8 (C), 86.8 (C), 84.1 (C); HRMS (ES) calcd. for $C_{14}H_{10}NS$: 224.0534, found: 224.0523 $[M+H]^+$.

3-[(4-Methoxyphenyl)ethynyl]-1*H*-indole 285

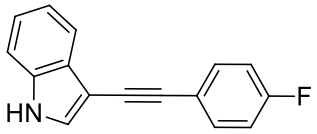


Prepared according to **GP3** using 3-iodoindole **251** (486 mg, 2.0 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc)] afforded the indole derivative **285** as a brown solid (196 mg, 40%); mp. 128-130 °C; IR ν_{max}/cm^{-1} 3379, 1456, 1242, 1028, 815, 743, 707; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.19 (bs, NH), 7.82 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 2.6 Hz, 1H), 7.40 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.29-7.19 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.84 (s,

3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.1 (C), 135.4 (C), 133.0 (2 × CH), 130.9 (C), 128.6 (C), 127.5(CH), 123.3 (CH), 120.8 (CH), 120.3 (CH), 116.5 (C), 114.1 (2 × CH), 111.4 (CH), 91.0 (C), 81.4 (C), 55.5 (CH_3).

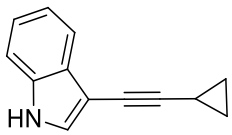
Data matches that reported in the literature.[96]

3-[(4-Fluorophenyl)ethynyl]-1*H*-indole 286



Prepared according to **GP3** using 3-iodoindole **251** (600 mg, 2.5 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc)] afforded the indole derivative **286** as a dark brown solid (323 mg, 55%); mp. 170-172 °C; IR ν_{max}/cm^{-1} 3388, 2217, 1599, 1497, 1457, 1215, 1089, 831, 741, 627; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.24 (bs, NH), 7.81 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.57-7.51 (m, 2H), 7.49 (d, *J* = 2.6 Hz, 1H), 7.41 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.28 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.25-7.21 (m, 1H), 7.08-7.02 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 162.3 (d, J_{C-F} = 250.1 Hz, C), 135.2 (C), 133.3 (d, J_{C-F} = 7.8 Hz, *meta*-2 × CH), 130.6 (C), 128.6 (C), 127.9 (CH), 123.4 (CH), 121.0 (CH), 120.2 (CH), 115.7 (d, J_{C-F} = 22.1 Hz, *ortho*-2 × CH), 112.3 (C), 111.5 (CH), 91.9 (C), 90.1 (C); HRMS (EI) calcd. for $C_{16}H_{10}NF$: 235.0797, found: 235.0796 $[M]^+$.

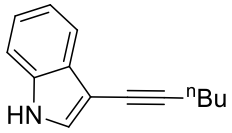
3-(Cyclopropylethynyl)-1*H*-indole 287



Prepared according to **GP3** using 3-iodoindole **251** (972 mg, 4.0 mmol). Purification by flash column chromatography [90:10 (hexane:toluene)] afforded the indole derivative **287** as a dark

brown oil (707 mg, 98%); IR ν_{max}/cm^{-1} 3380, 1607, 1485, 1432, 1174, 930, 830, 736, 697; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (bs, NH), 7.73 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.40-7.36 (m, 1H), 7.35 (d, *J* = 2.6 Hz, 1H), 7.26-7.24 (m, 1H), 7.22 (dd, *J* = 8.2, 1.5 Hz, 1H), 1.58-1.50 (m, 1H), 0.92-0.80 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 135.3 (C), 129.0 (C), 127.4 (CH), 123.0 (CH), 120.6 (CH), 120.1 (CH), 111.3 (CH), 99.5 (C), 94.8 (C), 68.6 (C), 8.8 (2 × CH_2), 0.5 (CH); HRMS (ES) calcd. for $C_{13}H_{12}N$: 182.0970, found: 182.0969 $[M+H]^+$.

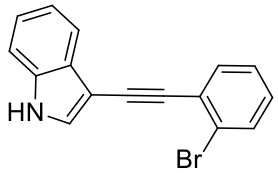
3-(Hex-1-yn-1-yl)-1*H*-indole 288



Prepared according to **GP3** using 3-iodo-1*H*-indole **251** (1.22 g, 5.0 mmol, 1.0 eq.). Purification by flash column chromatography [80:20-50:50 (hexane:toluene)] afforded the indole derivative **288** as a brown viscous oil (119 mg, 12%); IR ν_{max}/cm^{-1} 3404, 2956, 1455, 1416, 1329, 1241, 1095, 1007, 812, 739; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (bs, NH), 7.73 (d, *J* = 7.3 Hz, 1H), 7.38-7.30 (m, 2H), 7.19 (ddd, *J* = 14.4, 7.4, 1.3 Hz, 2H), 2.49 (t, *J* = 6.9 Hz, 2H), 1.70-1.48 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H).

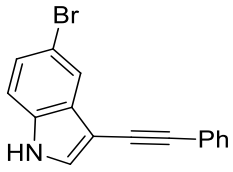
Data matches that reported in the literature.[234]

3-((2-Bromophenyl)ethynyl)-1*H*-indole 289



Prepared according to **GP3** using methyl 3-iodo-1*H*-indole **251** (729 mg, 3.0 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the indole derivative **289** as a brown oil (171 mg, 19%); IR ν_{max}/cm^{-1} 3395, 3258, 2206, 1456, 1229, 1098, 1025, 838, 739; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (bs, NH), 7.95-7.90 (m, 1H), 7.63 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.54 (d, *J* = 2.7 Hz, 1H), 7.44-7.40 (m, 1H), 7.35-7.27 (m, 3H), 7.19-7.12 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 209.7 (C), 135.4 (C), 132.9 (CH), 132.5 (CH), 128.7 (CH), 128.2 (CH), 127.1 (CH), 126.5 (C), 125.1 (C), 123.4 (CH), 121.1 (CH), 120.5 (CH), 111.5 (CH), 98.8 (C), 90.0 (C), 88.2 (C); HRMS (ES) calcd. for $C_{16}H_{11}NBr$: 296.0075, found: 296.0061 $[M+H]^+$.

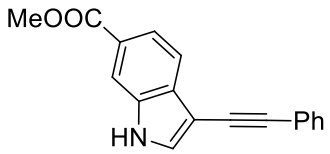
5-Bromo-3-(phenylethynyl)-1*H*-indole 290



Prepared according to **GP3** using methyl 5-bromo-3-iodo-1*H*-indole **277** (258 mg, 0.8 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the indole derivative **290** as a brown solid (169 mg, 71%); mp. 96-98 °C; IR ν_{max}/cm^{-1} 3414, 2211, 1448, 1285, 1098, 872, 757, 692; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (bs, NH), 7.95 (d, *J* = 1.6 Hz, 1H), 7.58-7.55 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.48 (d, *J* = 2.6 Hz, 1H), 7.41-7.29 (m, 5H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 134.0 (C), 131.5 (2 × CH), 130.3 (C), 128.8 (CH), 128.5 (2 × CH), 128.0 (CH), 126.3 (CH),

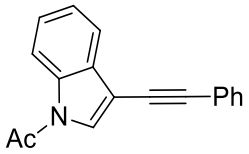
123.9 (C), 122.9 (CH), 114.4 (C), 113.0 (CH), 99.0 (C), 91.5 (C), 82.1 (C); HRMS (EI) calcd. for $C_{16}H_{10}NBr$: 294.9997, found: 294.9993 $[M]^+$.

Methyl 3-(phenylethynyl)-1*H*-indole-6-carboxylate 291



Prepared according to **GP3** using methyl 3-iodo-1*H*-indole-6-carboxylate **278** (753 mg, 2.5 mmol). Purification by flash column chromatography [70:30 (hexane:EtOAc)] afforded the indole derivative **291** as a dark brown solid (337 mg, 49%); mp. 166-168 °C; IR ν_{max}/cm^{-1} 3316, 2216, 1697, 1284, 1223, 756, 688; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.57 (bs, NH), 8.17 (dd, *J* = 1.4, 0.7 Hz, 1H), 7.92 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 2.7 Hz, 1H), 7.60-7.55 (m, 2H), 7.41-7.33 (m, 3H), 3.95 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.0 (C), 134.8 (C), 132.2 (C), 131.5 (2 × CH), 130.8 (CH), 128.5 (2 × CH), 128.0 (CH), 125.2 (C), 123.9 (C), 121.9 (CH), 120.0 (CH), 113.4 (CH), 99.7 (C), 91.7 (C), 82.1 (C), 52.2 (CH_3); HRMS (ES) calcd. for $C_{18}H_{14}NO_2$: 276.1025, found: 276.1027 $[M+H]^+$.

Methyl 3-(phenylethynyl)-1*H*-indole-1-carboxylate 292

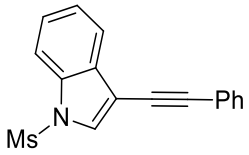


Prepared according to a modified **GP3** using methyl 3-iodo-1*H*-indole-1-carboxylate **279** (601 mg, 2.0 mmol, 1.0 eq.), in a 5/1 mixture of degassed Et_3N: DMF (0.22 M) for 24 hours at 60 °C. Purification by flash column chromatography [50:50 (hexane:toluene)] afforded the indole

derivative **292** as a brown solid (267 mg, 48%); mp. 100-101 °C; IR ν_{max}/cm^{-1} 1752, 1454, 1372, 1234, 1211, 1082, 853, 741, 682; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.85 (s, 1H), 7.80-7.74 (m, 1H), 7.61-7.53 (m, 2H), 7.42-7.32 (m, 5H), 4.07 (s, 3H).

Data matches that reported in the literature.[235]

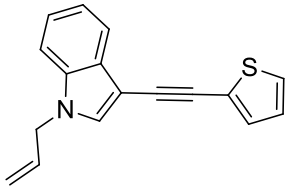
1-(Methylsulfonyl)-3-(phenylethynyl)-1*H*-indole 293



Prepared according to a modified **GP3** using 3-iodo-1-(methylsulfonyl)-1*H*-indole **280** (280 mg, 0.87 mmol, 1.0 eq.), in a 5/1 mixture of degassed Et_3N: DMF (0.22 M) for 24 hours at 60 °C. Purification by flash column chromatography [50:50 (hexane:toluene)] afforded the indole derivative **293** as a brown solid (256 mg, 99%); mp. 100-101 °C (lit. 100-102 °C); IR ν_{max}/cm^{-1} 1446, 1302, 1158, 1114, 959, 778, 752, 739, 686; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.90 (m, 1H), 7.86-7.79 (m, 1H), 7.70 (s, 1H), 7.61-7.55 (m, 2H), 7.48-7.35 (m, 5H), 3.16 (s, 3H).

Data matches that reported in the literature.[235]

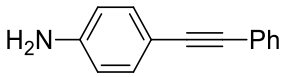
1-Allyl-3-(thiophen-2-ylethynyl)-1*H*-indole 294



Internal alkyne **284** (67 mg, 0.3 mmol, 1.0 eq.), allyl bromide (0.03 mL, 0.3 mmol, 1.0 eq.) and NaOH (25 mg, 0.6 mmol, 2.0 eq.) were dissolved in DMSO (0.3 mL, 1 M) and the reaction mixture was stirring at room temperature for 3 hours. The reaction mixture was diluted with

EtOAc (5 mL) and washed with H_2O (2 × 30 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried over Na_2SO_4. Filtration, evaporation of the solvents in reduced pressure and purification by flash column chromatography (Hexane) afforded alkyne **294** as a viscus yellow oil (71 mg, 90%); IR ν_{max}/cm^{-1} 2920, 2199, 1551, 1504, 1382, 1214, 1158, 925, 739, 701; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83-7.78 (m, 1H), 7.39 (s, 1H), 7.36-7.28 (m, 3H), 7.26-7.19 (m, 2H), 7.01 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.07-5.92 (m, 1H), 5.25 (ddd, *J* = 10.3, 2.6, 1.4 Hz, 1H), 5.12 (ddd, *J* = 17.1, 2.6, 1.7 Hz, 1H), 4.74 (dt, *J* = 5.4, 1.7 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 135.8 (C), 132.8 (CH), 131.6 (CH), 131.1 (CH), 129.3 (C), 127.1 (CH), 126.4 (CH), 124.6 (C), 123.0 (CH), 120.8 (CH), 120.5 (CH), 118.2 CH), 110.0 (CH_2), 97.4 (C), 87.0 (C), 84.1 (C), 49.2 (CH_2); HRMS (ES) calcd. for $C_{17}H_{14}NS$: 264.0847, found: 264.0846 $[M+H]^+$.

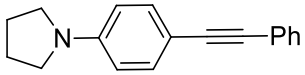
4-(Phenylethynyl)aniline 378



Prepared according to a modified **GP7** using 4-iodoaniline **377** (2.10 g, 10.0 mmol, 1.0 eq.), stirring at 50 °C for 3 hours. Purification by flash column chromatography [80:20-50:50 (hexane:EtAOc)] afforded the desired alkyne **378** as a yellow solid (1.10 gr, 58%); mp. 122-124 °C (lit. 125-126 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53-7.45 (m, 2H), 7.38-7.29 (m, 5H), 6.64 (d, *J* = 8.6 Hz, 2H), 3.82 (bs, NH_2); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 146.6 (C), 133.0 (2 × CH), 131.3 (2 × CH), 128.2 (2 × CH), 127.6 (CH), 123.9 (C), 114.7 (C), 112.7 (2 × CH), 90.1 (C), 87.3 (C).

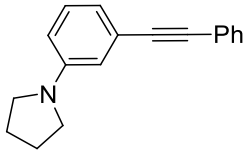
Data matches that reported in the literature.[227]

1-[4-(Phenylethynyl)phenyl]pyrrolidine 379



4-(Phenylethynyl)aniline **378** (773 mg, 4.0 mmol, 1.0 eq.) was dissolved in toluene (5 mL, 0.8 M), 1,4-dibromobutane (0.86 mL, 7.2 mmol, 1.8 eq.) and DIPEA (1.68 mL, 9.6 mmol, 2.4 eq.) were added to the reaction mixture. After refluxing for 16 hours at 120 °C, the mixture was allowed to cool and the inorganic salts formed were removed by filtration and washed with EtOAc. Evaporation of the solvent under reduced pressure and purification of the crude residue by flash column chromatography [90:10 (hexane:EtOAc)] afforded the aniline derivative **379** as an orange solid (940 mg, 95%); mp. 168-172 °C; IR ν_{max}/cm^{-1} 2962, 2869, 1608, 1518, 1159, 1026, 957, 812, 750; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.35-7.28 (m, 3H), 6.51 (d, *J* = 8.8 Hz, 2H), 3.31 (t, *J* = 6.6 Hz, 4H), 2.06-1.97 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.1 (C), 132.8 (2 × CH), 131.4 (2 × CH), 128.4 (2 × CH), 127.3 (C),127.5 (CH), 126.7 (C), 111.5 (2 × CH), 77.2 (C), 73.5 (C), 47.6 (2 × CH_2), 25.6 (2 × CH_2); HRMS (EI) calcd. for $C_{18}H_{17}N$: 247.1361, found: 247.1362 $[M]^+$.

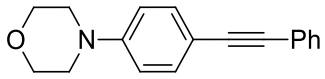
1-(3-(Phenylethynyl)phenyl)pyrrolidine 382



3-(Phenylethynyl)aniline **381** (218 mg, 1.2 mmol, 1.0 eq.) was dissolved in toluene (3 mL, 0.3 M), 1,4-dibromobutane (0.24 mL, 2.0 mmol, 1.7 M) and DIPEA (0.46 mL, 2.7 mmol, 2.3 M) were added to the reaction mixture. After refluxing for 16 hours at 120 °C, the mixture was allowed to

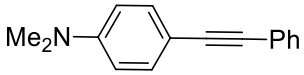
cool and the inorganic salts formed were removed by filtration and washed with EtOAc. Evaporation of the solvent under reduced pressure and purification of the crude residue by flash column chromatography (hexane) afforded the aniline derivative **382** as a yellow oil (112 mg, 41%); IR ν_{max}/cm^{-1} 2965, 2834, 1592, 1439, 1373, 1173, 1009, 837, 753, 684; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61-7.51 (m, 2H), 7.41-7.30 (m, 3H), 7.20 (t, *J* = 7.9 Hz, 1H), 6.89-6.83 (m, 1H), 6.76-6.43 (m, 1H), 6.59-6.52 (m, 1H), 3.37-3.24 (m, 4H), 2.08-1.96 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.8 (C), 131.8 (2 × CH), 129.2 (CH), 128.4 (2 × CH), 128.1 (CH), 123.7 (C), 119.0 (CH), 114.6 (CH), 112.2 (CH), 90.7 (C), 88.3 (C), 47.7 (2 × CH_2), 25.6 (2 × CH_2); HRMS (ES) calcd. for $C_{18}H_{18}N$: 248.1439, found: 247.1441 $[M+H]^+$.

4-[4-(Phenylethynyl)phenyl]morpholine 385



Prepared according to a modified **GP7** using 4-(4-iodophenyl)morpholine aniline **384** (925 mg, 3.2 mmol, 1.0 eq.), stirring at 50 °C overnight. Purification by flash column chromatography [80:20 (hexane:EtOAc)], afforded the aniline derivative **385** as a light brown solid (432 mg, 51%); mp. 178-180 °C; IR ν_{max}/cm^{-1} 2961, 2855, 2830, 2208, 1607, 1592, 1444, 1382, 1263, 1236, 1068, 818, 760; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54-7.48 (m, 2H), 7.45 (d, *J* = 8.9 Hz, 2H), 7.38-7.28 (m, 3H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.91-3.80 (m, 4H), 3.26-3.16 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 151.0 (C), 132.9 (2 × CH), 131.6 (2 × CH), 128.4 (2 × CH), 127.9 (CH), 123.9 (C), 115.0 (2 × CH), 114.0 (C), 89.9 (C), 88.1 (C), 66.9 (2 × CH_2), 48.7 (2 × CH_2); HRMS (ES) calcd. for $C_{18}H_{18}NO$: 264.1388, found: 264.1381 $[M+H]^+$.

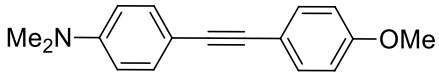
_N,N_-Dimethyl-4-(phenylethynyl)aniline 388



Prepared according to a modified **GP7** using 4-iodo-*N,N*-dimethyl aniline **387** (879 mg, 3.6 mmol, 1.0 eq.), stirring at 50 °C overnight. Purification by flash column chromatography [99:1 (hexane:EtOAc)] afforded the aniline derivative **388** as a light brown solid (175 mg, 22%); mp. 108-110 °C (lit. 108-109 °C); IR ν_{max}/cm^{-1} 3378, 2206, 1607, 1522, 1441, 1227, 1102, 1071, 745; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.35-7.27 (m, 3H), 6.66 (d, *J* = 9.0 Hz, 2H), 2.99 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 150.2 (C), 132.9 (2 × CH), 131.4 (2 × CH), 128.4 (CH), 127.6 (2 × CH), 124.3 (C), 112.0 (2 × CH), 110.0 (C), 90.6 (C), 86.9 (C), 40.4 (2 × CH_3).

Data matches that reported in the literature.[236]

4-((4-Methoxyphenyl)ethynyl)-*N,N*-dimethylaniline 389

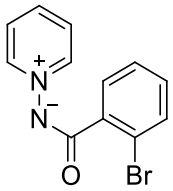


Following a procedure reported by Griego and co-workers,[32] a mixture of *p*-iodoanisole (749 mg, 3.2 mmol, 1.0 eq.), 4-ethynyl-*N,N*-dimethylaniline (3.8 mmol, 1.4 eq.), $NiCl_2(PPh_3)_2$ (105 mg, 5 mol%), CuI (61 mg, 10 mol%) and K_2CO_3 (883 mg, 6.4 mmol, 2.0 eq.) in dioxane (13 mL) and water (5 mL) was stirred under argon at reflux for 2 hours. Filtration through a silica pad, evaporation of the solvent and purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the aniline derivative **389** as a yellow solid (300 mg, 37%); mp. 118-120 °C; IR ν_{max}/cm^{-1} 3217, 1609, 1525, 1496, 1238, 1024, 817; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44

(d, *J* = 8.9 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.68 (bd, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 3.00 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.2 (C), 150.1 (C), 132.8 (2 × CH), 132.7 (2 × CH), 116.5 (C), 114.0 (2 × CH), 112.0 (2 × CH), 110.6 (C), 89.2 (C), 87.3 (C), 55.4 (CH_3), 40.4 (CH_3).

Data matches that reported in the literature.[237]

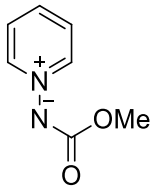
(2-Bromobenzoyl)(pyridin-1-ium-1-yl)amide 200



Prepared according to **GP4** using *N*-aminopyridinium iodide **214** (444 mg, 2.0 mmol) and 2-bromobenzoyl chloride (0.55 mL, 4.0 mmol). Recrystallisation of the crude residue from CH_2Cl_2/Et_2O afforded the desired ylide **200** as off-white needles (411 mg, 74%); mp. 102-103 °C (lit. 102-103 °C); IR ν_{max}/cm^{-1} 1584, 1465, 1347, 1256, 1022, 751; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 6.9, 1.3 Hz, 2H), 8.05-7.94 (m, 1H), 7.79-7.70 (m, 2H), 7.67-7.57 (m, 2H), 7.35 (td, *J* = 7.5, 1.3 Hz, 1H), 7.25-7.18 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 172.6 (C), 143.3 (2 × CH), 140.5 (C), 137.6 (CH), 133.1 (CH), 129.8 (CH), 129.4 (CH), 127.3 (CH), 126.4 (2 × CH), 120.9 (C).

Data matches that reported in the literature.[82]

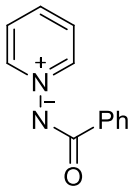
_N_-Methoxycarbonyliminopyridinium ylide 235



Prepared according to a modified **GP5** using *N*-aminopyridinium iodide **214** (1.01 g, 4.5 mmol, 1.0 eq.). Purification by filtration over a plug of Al_2O_3 (ca. 1 inch), washing (3 ×) with [95:5 (CH_2Cl_2: MeOH)], evaporation of the solvent under reduced pressure and precipitation with 50:50 hexane:ether afforded the desired ylide **235** as an off-white solid (667 mg, 97%); mp. 93-94 °C (lit. 92-94 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91-8.85 (m, 2H), 7.87-7.79 (m, 1H), 7.62 (t, *J* = 7.2 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0 (C), 142.4 (2 × CH), 135.3 (CH), 126.0 (2 × CH), 51.9 (CH_3); MS (EI): 152.1 (M, 28%), 121.0 (51), 79 (100).

Data matches that reported in the literature.[82]

Benzoyl(pyridin-1-ium-1-yl)amide 245

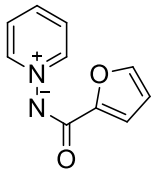


Prepared according to **GP4** using *N*-aminopyridinium iodide **214** (888 mg, 4.0 mmol). Recrystallisation of the crude residue from CH_2Cl_2/Et_2O afforded the desired ylide **245** as off-white needles (605 mg, 76%); mp. 187-189 °C (lit. 187-189 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) 8.84 (dd, *J* = 6.8, 1.2 Hz, 2H), 8.23-8.14 (m, 2H), 8.01-7.91 (m, 1H), 7.69-7.71 (m, 2H), 7.51-7.39 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.7 (C), 143.6 (2 × CH), 137.2 (C), 137.0 (CH), 130.4 (CH),

128.0 (2 × CH), 128.1 (2 × CH), 126.0 (2 × CH); HRMS (ES) calcd for $C_{12}H_{10}N_2ONa$: 221.0691, found: 221.0694 $[M+Na]^+$.

Data matches that reported in the literature.[82]

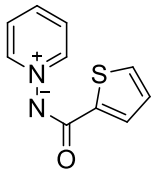
_N_-2-Furoyliminopyridinium ylide 299



Prepared according to **GP5** using *N*-aminopyridinium iodide **214** (1.11 g, 5.0 mmol). Purification by flash column chromatography using Al_2O_3 [95:5 (CH_2Cl_2:MeOH)] afforded the ylide **299** was as an off-white solid (872 mg, 93%); mp. 182-184 °C (lit. 184-186 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.86 (dd, *J* = 7.1, 1.3 Hz, 2H), 8.00-7.92 (m, 1H), 7.70 (t, *J* = 7.1 Hz, 2H), 7.51 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.11 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.50 (dd, *J* = 3.4, 1.8 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.6 (C), 151.2 (C), 143.4 (2 × CH), 143.2 (CH), 136.9 (CH), 126.0 (2 × CH), 112.8 (CH), 111.1 (CH); MS (ES): m/z 211.2 ([M+Na], 100%).

Data matches that reported in the literature.[82]

Pyridin-1-ium-1-yl(thiophene-2-carbonyl)amide 300

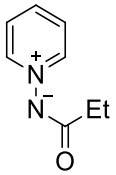


Prepared according to **GP5** using *N*-aminopyridinium iodide **214** (444 mg, 2.0 mmol). Purification by filtration over a plug of Al_2O_3, washing (3 ×) with [95:5 (CH_2Cl_2:MeOH)] and evaporation of the solvent under reduced pressure, afforded the ylide **300** as an off-white solid

(403 mg, 98%); mp. 224-226 °C; IR ν_{max}/cm^{-1} 3065, 1555, 1466, 1422, 1357, 1294, 1170, 858, 711; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 7.0, 1.3 Hz, 2H), 7.98-7.86 (m, 1H), 7.76 (dd, *J* = 3.6, 1.3 Hz, 1H), 7.66-7.57 (m, 2H), 7.38 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.08 (dd, *J* = 5.0, 3.6 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.7 (C), 143.4 (CH), 136.9 (CH), 133.6 (C), 129.2 (CH), 128.4 (CH), 127.3 (2 × CH), 126.1 (2 × CH).

Data matches that reported in the literature.[238]

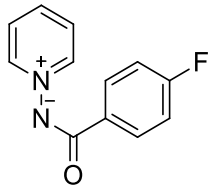
Propionyl(pyridin-1-ium-1-yl)amide 301



Prepared according to **GP5** using *N*-aminopyridinium iodide **214** (444 mg, 2.0 mmol). Purification by flash column chromatography using Al_2O_3 [95:5 (CH_2Cl_2:MeOH)] afforded the ylide **301** as a brown oil (52 mg, 27%); IR ν_{max}/cm^{-1} 3120, 3040, 2970, 2920, 2850, 1500, 1452, 1336, 1345; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 5.4, 1.2 Hz, 2H), 7.99-7.88 (m, 1H), 7.73-7.51 (m, 2H), 2.37 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H).

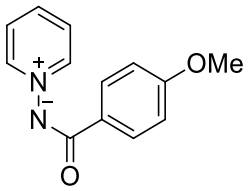
Data matches that reported in the literature.[82]

(4-Fluorobenzoyl)(pyridin-1-ium-1-yl)amide 306



Prepared according to **GP4** using *N*-aminopyridinium iodide **214** (444 mg, 2.0 mmol). Recrystallisation of the crude residue from CH_2Cl_2/Et_2O afforded the desired ylide **306** as off-white needles (280 mg, 65%); mp. 183-184 °C; IR ν_{max}/cm^{-1} 3116, 3061, 1607, 1555, 1325, 1213, 1170, 860, 765; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.84-8.79 (m, 2H), 8.20-8.12 (m, 2H), 7.99-7.92 (m, 1H), 7.74-7.66 (m, 2H), 7.13-7.04 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.0 (C), 164.4 (d, J_{C-F} = 250.1 Hz, *ipso*-$C_{q.}$), 143.4 (2 × CH), 137.0 (CH), 133.4 (d, J_{C-F} = 3.2 Hz, *para*-C), 130.3 (d, J_{C-F} = 8.4 Hz, *meta*-2 × CH), 126.2 (2 × CH), 114.8 (d, J_{C-F} = 22.4 Hz, *ortho*- 2 × CH); HRMS (ES) calcd for $C_{12}H_{10}N_2OF$: 217.0777, found: 217.0772 $[M+H]^+$.

(4-Methoxybenzoyl)(pyridin-1-ium-1-yl)amide 307

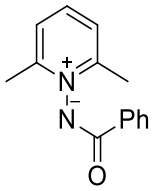


Prepared according to **GP4** using *N*-aminopyridinium iodide **214** (444 mg, 2.0 mmol). Recrystallisation of the crude residue from CH_2Cl_2/Et_2O afforded the desired ylide **307** as white needles (302 mg, 66%); mp. 148-150 °C; IR ν_{max}/cm^{-1} 3596, 3060, 1606, 1547, 1463, 1331, 1242, 1179, 1032, 843, 762; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 6.9, 1.2 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.88 (tt, *J* = 7.7, 6.9 Hz, 1H), 7.64 (app t, *J* = 7.2 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.86 (s,

3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.5 (C), 161.5 (C), 143.5 (2 × CH), 136.6 (CH), 129.7 (2 × CH, C), 126.0 (2 × CH), 113.2 (2 × CH), 55.4 (OCH_3).

Data matches that reported in the literature.[82]

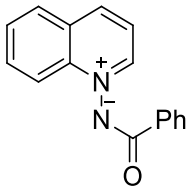
Benzoyl(2,6-dimethylpyridin-1-ium-1-yl)amide 370



Prepared according to **GP6** using 2,4-lutidine **262** (0.14 mL, 1.2 mmol). Purification by flash column chromatography [50:50 (hexane:EtOAc)-MeOH] afforded a yellow oil. Recrystallisation with hexane/Et_2O afforded the ylide **370** as yellow needles (107 mg, 60%); mp. 128-130 °C (lit. 127-129 °C) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.19-8.12 (m, 2H), 7.79-7.71 (m, 1H), 7.47-7.36 (m, 5H), 2.65 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 169.1 (C), 154.8 (C), 137.4 (CH), 130.0 (CH), 128.1 (2 × CH), 125.4 (2 × CH), 109.5 (2 × CH), 109.4 (2 × C), 20.0 (2 × CH_3); MS (ES): m/z 227.2 ([M+H], 100%).

Data matches that reported in the literature.[97b]

Benzoyl(quinolin-1-ium-1-yl)amide 371

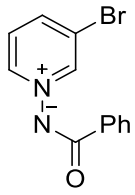


Prepared according to **GP6** using quinoline **363** (0.15 mL, 1.2 mmol). After the addition of base and benzoyl chloride (0.22 mL, 1.8 mmol) the reaction mixture was stirred for 8 hours.

Purification by flash column chromatography [50:50 (hexane:EtOAc)-MeOH] afforded the ylide **371** as a brown solid (116 mg, 40%); mp. 155-158 °C (lit. 193-194 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.16 (dd, *J* = 5.9, 1.2 Hz, 1H), 8.78 (d, *J* = 8.6 Hz, 1H), 8.42 (d, *J* = 8.6 Hz, 1H), 8.34-8.25 (m, 2H), 8.01 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.94-7.85 (m, 1H), 7.76 (ddd, *J* = 8.1, 5.7, 1.1 Hz, 1H), 7.68 (dd, *J* = 8.3, 5.9 Hz, 1H), 7.52-7.41 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.5 (C), 145.9 (CH), 139.9 (C), 138.2 (CH), 137.5 (C), 133.4 (CH), 130.2 (CH), 130.3 (C), 129.5 (CH), 128.7 (CH), 128.3 (2 × CH), 128.0 (2 × CH), 120.6 (2 × CH); MS (ES): m/z 271.1 ([M+Na], 100%).

Data matches that reported in the literature.[97b]

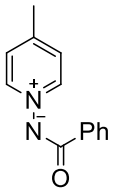
Benzoyl(3-bromopyridin-1-ium-1-yl)amide 373



Prepared according to **GP6** using 3-bromopyridine **365** (0.12 mL, 1.2 mmol). Purification by flash column chromatography [50:50 (hexane:EtOAc)-MeOH] afforded ylide **373** as a yellow solid (186 mg, 54%); mp. 121-123 °C (lit. 133-134 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.20 (bs, 1H), 8.84 (d, *J* = 6.4, 1H), 8.15 (dd, *J* = 8.0, 1.6 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.3, 6.4 Hz, 1H), 7.51-7.36 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 171.8 (C), 144.5 (CH), 141.5 (CH), 139.0 (CH), 136.9 (C), 130.6 (CH), 128.5 (2 × CH), 128.2 (2 × CH), 126.2 (CH), 120.9 (C); MS (ES): m/z 279.0 ([M+H], 100%).

Data matches that reported in the literature.[97b]

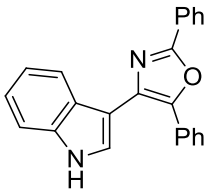
Benzoyl(4-methylpyridin-1-ium-1-yl)amide 374



Prepared according to **GP6** using 4-picoline **366** (0.12 mL, 1.2 mmol). Purification by flash column chromatography [50:50 (hexane:EtOAc)-MeOH] afforded the ylide **374** as an orange solid (150 mg, 57%); mp. 65-67 °C (lit. 65-67 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.8 Hz, 2H), 8.22-7.97 (m, 2H), 7.53-7.32 (m, 5H), 2.57 (s, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 171.2 (C), 150.2 (C), 143.0 (2 × CH), 137.4 (C), 130.2 (2 × CH), 128.1 (2 × CH), 126.5 (2 × CH), 126.6 (CH), 21.5 (CH_3); MS (ES): m/z 213.1 ([M+H], 100%).

Data matches that reported in the literature.[97b]

4-(1*H*-Indol-3-yl)-2,5-diphenyloxazole 253

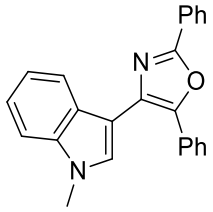


Prepared according to **GP7** using indole derivative **252** (44 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **253** as a brown solid (52 mg, 78%); mp. 150-153 °C; IR ν_{max}/cm^{-1} 3412, 2925, 2856, 1628, 1487, 1448, 1344, 1248, 1097, 1016, 934, 744, 700; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.4 (bs, 1H), 8.17-8.09 (m, 2H), 7.73-7.70 (m, 2H), 7.70 (s, 1H), 7.62-7.55 (m, 3H), 7.48 (d, J = 8.1 Hz, 1H), 7.46-7.38 (m, 3H), 7.37-7.32 (m, 1H), 7.16 (app. td, *J* = 7.5, 1.0 Hz, 1H), 7.00 (app. td, *J* = 7.5, 0.7

Hz, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 159.1 (C), 144.2 (C), 136.2 (C), 131.9 (C), 130.6 (CH), 129.2 (2 × CH), 128.7 (2 × CH), 128.6 (C), 128.1 (CH), 126.9 (C), 126.0 (2 × CH), 125.5 (2 × CH), 125.4 (C), 125.1 (CH), 121.6 (CH), 120.1 (CH), 119.3 (CH), 111.9 (CH), 106.5 (C); HRMS (ES) calcd. for $C_{23}H_{16}N_2ONa$: 359.1160, found: 359.1165 $[M+Na]^+$.

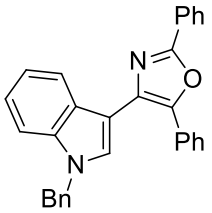
When run at 0.4 mmol scale the oxazole was afforded in 79% (106 mg).

4-(1-Methyl-1*H*-indol-3-yl)-2,5-diphenyloxazole 308



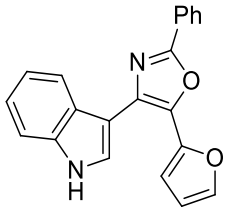
Prepared according to **GP7** using indole derivative **281** (69 mg, 0.3 mmol) and ylide **245** (89 mg, 0.45 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **308** as a brown solid (61 mg, 58%); mp. 158-160 °C; IR ν_{max}/cm^{-1} 3381, 2206, 1414, 1359, 1324, 1235, 740, 681; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.53-7.44 (m, 2H), 7.33-7.27 (m, 4H), 7.17 (m, 1H), 7.25-7.23 (d, *J* = 8.2 Hz, 5H), 6.85 (t, *J* = 7.5 Hz, 1H), 3.65 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.1 (C), 145.1 (C), 137.3 (C), 131.6 (C), 130.4 (CH), 129.4 (C), 128.9 (2 × CH), 128.8 (CH), 128.6 (2 × CH), 128.0 (CH), 127.6 (C), 126.6 (2 × CH), 126.4 (C), 126.0 (2 × CH), 122.1 (CH), 121.5 (CH), 120.0 (CH), 109.5 (CH), 107.2 (C), 33.2 (CH_3); HRMS (ES) calcd. for $C_{24}H_{19}N_2O$: 351.1497, found: 351.1486 $[M+H]^+$.

4-(1-Benzyl-1*H*-indol-3-yl)-2,5-diphenyloxazole 309



Prepared according to **GP7** using indole derivative **282** (62 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **309** as a yellow solid (30 mg, 35%); mp. 220-222 °C; IR ν_{max}/cm^{-1} 3284, 1603, 1333, 1191, 1012, 770, 739, 695; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.72 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.62 (bd, *J* = 8.2 Hz, 1H), 7.54 (s, 1H), 7.42-7.56 (m, 3H), 7.38-7.28 (m, 7H), 7.25-7.19 (m, 3H), 7.10 (app. td, *J* = 7.6, 1.0 Hz, 1H), 5.4 (s, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.1 (C), 145.2 (C), 137.2 (C), 136.8 (C), 131.8 (C), 130.3 (CH), 129.4 (C), 129.0 (2 × CH), 128.9 (2 × CH), 128.6 (2 × CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (C), 127.1 (2 × CH), 126.9 (C), 126.6 (2 × CH), 126.0 (2 × CH), 122.4 (CH), 121.6 (CH), 120.3 (CH), 110.0 (CH), 108.0 (C), 50.4 (CH_2); HRMS (ES) calcd. for $C_{30}H_{23}N_2O$: 427.1810, found: 427.1815 $[M+H]^+$.

5-(Furan-2-yl)-4-(1*H*-indol-3-yl)-2-phenyloxazole 312

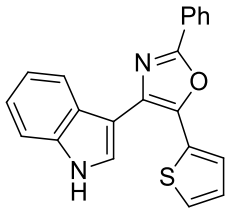


Prepared according to **GP7** using indole derivative **283** (42 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **312** as a brown solid (44 mg, 67%); mp. 180-183 °C; IR ν_{max}/cm^{-1} 3675, 2972, 2901, 1607,

1493, 1456, 1068, 746, 737; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.52 (bs, NH), 8.19-8.07 (m, 3H), 7.98 (d, *J* = 2.8 Hz, 1H), 7.92 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.66-7.56 (m, 2H), 7.50-7.45 (m, 1H), 7.24-7.23 (m, 1H), 7.17 (dd, J = 8.1, 1.2 Hz, 1H), 7.11 (dd, J = 8.1 Hz, 1.1 Hz, 1H), 6.93 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.73 (dd, *J* = 3.4, 1.8 Hz, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 159.0 (C), 143.2 (C), 143.6 (CH), 136.2 (C), 135.8 (C), 132.9 (C), 130.8 (CH), 126.5 (C), 129.2 (2 × CH), 126.1 (2 × CH), 125.9 (C), 125.2 (CH), 121.7 (CH), 121.0 (CH), 119.6 (CH), 112.0 (CH), 111.7 (CH), 109.0 (CH), 106.0 (C); HRMS (ES) calcd. for $C_{21}H_{15}N_2O_2$: 327.1134, found: 327.1144 $[M+H]^+$.

When run at 0.5 mmol scale the oxazole was afforded in 72% (166 mg).

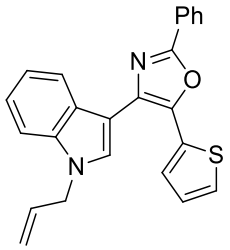
4-(1*H*-Indol-3-yl)-2-phenyl-5-(thiophen-2-yl)oxazole 313



Prepared according to **GP7** using indole derivative **284** (45 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **313** as a brown solid (46 mg, 67%); mp. 180-183 °C; IR ν_{max}/cm^{-1} 3203, 1628, 1611, 1541, 1189, 850, 744, 697 678; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.53 (bs, NH), 8.11 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.80 (d, *J* = 2.6 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.62 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.61-7.55 (m, 3H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.45 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.27-7.18 (m, 3H), 7.11 (app. td, *J* = 7.5, 0.8 Hz, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 158.8 (C), 140.2 (C), 136.2 (C), 131.7 (C), 130.7 (CH), 129.5 (C), 129.2 (2 × CH), 128.9 (C), 128.2 (C), 127.8 (CH), 126.7 (CH), 126.0 (2 × CH), 125.8 (CH),

125.3 (CH), 121.7 (CH), 120.3 (CH), 119.5 (CH), 111.7 (CH), 105.6 (C); HRMS (ES) calcd. for $C_{21}H_{14}N_2OSNa$: 365.0725, found: 365.0724 $[M+Na]^+$.

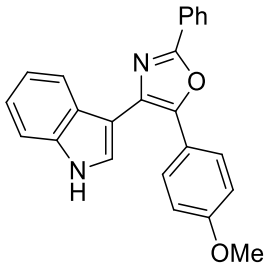
4-(1-Allyl-1*H*-indol-3-yl)-2-phenyl-5-(thiophen-2-yl)oxazole 314



Prepared according to **GP7** using indole derivative **294** (53 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography (toluene) afforded the oxazole **314** as yellow viscous oil (26 mg, 34%, ~90% purity); IR ν_{max}/cm^{-1} 3079, 2921, 1637, 1468, 1186, 923, 744, 690; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 7.6, 2.1 Hz, 2H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.57 (s, 1H), 7.54-7.49 (m, 3H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.32-7.27 (m, 2H), 7.14 (app. td, *J* = 7.5, 0.9 Hz, 1H), 7.02 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.05 (ddt, *J* = 17.0, 10.5, 5.4 Hz, 1H), 5.26 (dd, *J* = 10.5, 1.2 Hz, 1H), 5.18 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.81 (dt, *J* = 5.4 Hz, 1.4 Hz, 2H);^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.8 (C), 141.3 (C), 137.9 (C), 136.7 (C), 133.3 (CH), 130.8 (C), 130.4 (CH), 128.9 (2 × CH), 128.0 (CH), 127.5 (CH), 126.9 (C), 126.6 (2 × CH), 126.2 (C), 125.4 (CH), 125.3 (CH), 122.3 (CH), 121.5 (CH), 120.2 (CH), 117.9 (CH_2), 109.9 (CH), 106.9 (C), 49.2 (CH_2); HRMS (ES) calcd. for $C_{24}H_{19}N_2OS$: 383.1218, found: 383.1225 $[M+H]^+$.

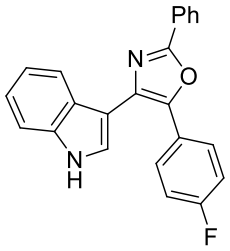
*Attempts to remove final traces of toluene led to degradation of the product.

4-(1*H*-Indol-3-yl)-5-(4-methoxyphenyl)-2-phenyloxazole 315



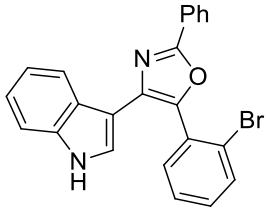
Prepared according to **GP7** using indole derivative **285** (50 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **315** isolated as a brown solid (60 mg, 82%); mp. 110-115 °C; IR ν_{max}/cm^{-1} 3376, 2207, 1607, 1337, 1241, 1228, 1170, 743; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 11.45 (bs, NH), 8.12 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.67 (d, *J* = 2.6 Hz, 1H), 7.62 (d, J = 8.9 Hz, 2H), 7.60-7.53 (m, 3H), 7.50-7.45 (m, 2H), 7.17 (app. td, *J* = 7.5, 0.9 Hz, 1H), 7.02-6.98 (m, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.78 (s, 3H); ^{13}C-NMR (101 MHz, DMSO-d$_6$) δ 159.2 (C), 158.5 (C), 144.4 (C), 136.2 (C), 130.6 (C), 130.4 (CH), 129.2 (2 × CH), 127.3 (2 × CH), 127.0 (C), 125.9 (2 × CH), 125.6 (C), 124.8 (CH), 121.6 (CH), 121.2 (C), 120.2 (CH), 119.3 (CH), 114.3 (2 × CH), 111.8 (CH), 106.6 (C)., 55.2 (OCH_3); HRMS (ES) calcd. for $C_{24}H_{19}N_2O_2$: 367.1447, found: 367.1442 $[M+H]^+$.

5-(4-Fluorophenyl)-4-(1*H*-indol-3-yl)-2-phenyloxazole 316



Prepared according to **GP7** using indole derivative **286** (47 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **316** as a brown solid (48 mg, 64%); mp. 158-160 °C; IR ν_{max}/cm^{-1} 3254, 3062, 1491, 1228, 936, 838, 724; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 8.45 (bs, NH), 8.22-8.14 (m, 2H), 7.70-7.63 (m, 2H), 7.56 (d, *J* = 2.6 Hz, 1H), 7.54-7.41 (m, 5H), 7.25-7.17 (m, 1H), 7.13-7.08 (m, 1H), 7.08-7.00 (m, 2H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 163.7 (d, J_{C-F} = 245.9 Hz, *ipso*-C), 160.1 (C), 144.6 (C), 136.4 (C), 131.4 (C), 130.4 (CH), 128.9 (2 × CH), 127.9 (d, J_{C-F} = 8.1 Hz, *meta*-2 × CH), 127.7 (C), 126.6 (2 × CH), 125.9 (C), 125.6 (C), 124.1 (CH), 122.8 (CH), 121.2 (CH), 120.5 (CH), 115.7 (d, J_{C-F} = 22.1 Hz, *ortho*-2 × CH), 111.4 (CH), 108.8 (C); HRMS (ES) calcd. for $C_{23}H_{16}N_2OF$: 355.1247, found: 355.1243 $[M+H]^+$.

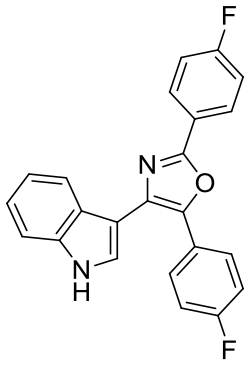
5-(2-Bromophenyl)-4-(1*H*-indol-3-yl)-2-phenyloxazole 317



Prepared according to **GP7** using indole derivative **289** (60 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the

oxazole **317** as a brown solid (50 mg, 60%); mp. 56-58 °C; IR ν_{max}/cm^{-1} 3403, 3057, 1484, 1335, 1092, 1026, 930, 742, 688; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.32 (bs, NH), 8.25-8.19 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.75-7.71 (m, 1H), 7.52-7.46 (m, 3H), 7.34-7.25 (m, 4H), 7.22-7.16 (m, 2H), 7.11-7.06 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.9 (C), 142.9 (C), 136.2 (C), 134.6 (C), 133.7 (CH), 132.5 (CH), 131.1 (C), 130.7 (CH), 130.4 (CH), 128.9 (2 × CH), 127.8 (C), 127.5 (CH), 126.7 (2 × CH), 125.9 (C), 124.2 (C), 123.4 (CH), 122.5 (CH), 121.4 (CH), 120.4 (CH), 111.2 (CH), 108.5 (C); HRMS (ES) calcd. for $C_{23}H_{16}N_2OBr$: 415.0446, found: 415.0439 $[M+H]^+$.

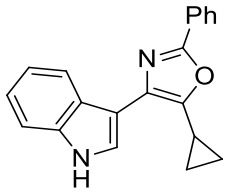
2,5-Bis(4-fluorophenyl)-4-(1*H*-indol-3-yl)oxazole 318



Prepared according to **GP7** using indole derivative **286** (47 mg, 0.2 mmol) and ylide **306** (65 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **318** as a brown solid (53 mg, 70%); mp. 192-194 °C; IR ν_{max}/cm^{-1} 3415, 1601, 1499, 1219, 1088, 928, 756, 663; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.53 (bs, NH), 8.27-8.12 (m, 2H), 7.78-7.68 (m, 3H), 7.52-7.38 (m, 4H), 7.31-7.22 (m, 2H), 7.19-7.18 (m, 1H), 7.00 (t, *J* = 7.5 Hz, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 163.8 (d, $J_{C\text{-}F}$ = 250.1 Hz, *ipso*-C), 161.3 (d, $J_{C\text{-}F}$ = 250.5 Hz, *ipso*-C), 143.5 (C), 136.2 (C), 131.7 (C), 129.1 (C), 128.5 (d, $J_{C\text{-}F}$ = 8.0 Hz, *meta*-2 × CH), 128.0 (d, $J_{C\text{-}F}$ = 8.0 Hz, *meta*-2 × CH), 126.0 (d, $J_{C\text{-}F}$ = 3.0 Hz, *para*-C), 125.4 (C), 125.0 (CH), 123.5 (d, $J_{C\text{-}F}$ = 3.0 Hz,

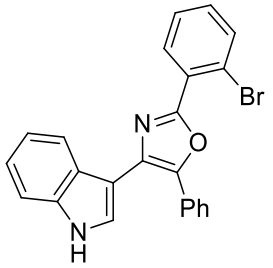
para-C), 121.6 (CH), 120.0 (CH), 119.4 (CH), 116.3 (d, $J_{C\text{-}F}$ = 21.9 Hz, *meta*-2 × CH), 115.8 (d, $J_{C\text{-}F}$ = 22.0 Hz, *meta*-2 × CH), 111.9 (CH), 106.2 (C); HRMS (ES) calcd. for $C_{23}H_{15}N_2OF_2$: 373.1152, found: 373.1153 $[M+H]^+$.

5-Cyclopropyl-4-(1*H*-indol-3-yl)-2-phenyloxazole 319



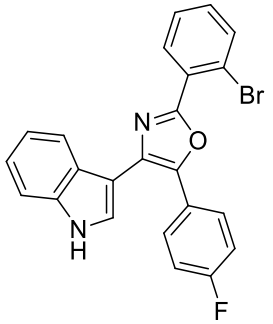
Prepared according to **GP7** using indole derivative **287** (56 mg, 0.3 mmol) and ylide **245** (89 mg, 0.45 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **319** as a brown solid (31 mg, 35%); mp. 150-152 °C; IR ν_{max}/cm^{-1} 3377, 3058, 1615, 1514, 1445, 1238, 766, 685; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.46 (bs, NH), 8.18 (dd, *J* = 6.9, 1.9 Hz, 1H), 8.08 (dd, *J* = 7.9, 1.9 Hz, 2H), 7.52-7.45 (m, 2H), 7.44-7.37 (m, 3H), 7.26-7.20 (m, 2H), 2.13 (tt, J = 7.2, 6.2 Hz, 1H), 1.21-1.02 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.7 (C), 147.5 (C), 136.3 (C), 131.8 (C), 129.8 (CH), 128.7 (2 × CH), 128.1 (C), 126.6 (C), 126.2 (2 × CH), 122.9 (CH), 122.6 (CH), 121.3 (CH), 120.3 (CH), 111.2 (CH), 108.9 (C), 7.5 (2 × CH_2), 7.4 (CH); HRMS (ES) calcd. for $C_{20}H_{17}N_2O$: 301.1341, found: 301.1343 $[M+H]^+$.

2-(2-Bromophenyl)-4-(1*H*-indol-3-yl)-5-phenyloxazole 320



Prepared according to **GP7** using indole derivative **252** (44 mg, 0.2 mmol) and ylide **200** (83 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **320** as a brown solid (60 mg, 72%); mp. 198-200 °C; IR ν_{max}/cm^{-1} 3170, 2836, 1607, 1494, 1432, 1250, 1174, 1020, 831, 688; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.42 (bs, NH), 8.18 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.78-7.67 (m, 3H), 7.64-7.33 (m, 7H), 7.21-7.13 (m, 1H), 7.05-6.98 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.6 (C), 145.9 (C), 136.2 (C), 134.6 (CH), 131.4 (CH), 131.4 (C), 131.0 (CH), 129.1 (C), 128.6 (2 × CH), 128.4 (C), 128.1 (CH), 127.4 (CH), 126.0 (2 × CH), 125.9 (C), 124.0 (CH), 122.6 (CH), 121.3 (CH), 121.0 (C), 120.4 (CH), 111.2 (CH), 108.7 (C); HRMS (ES) calcd. for $C_{23}H_{16}N_2OBr$: 415.0446, found: 415.0447 $[M+H]^+$.

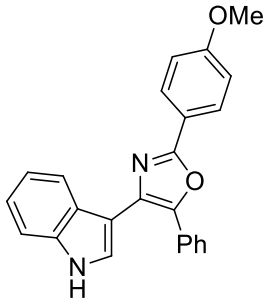
2-(2-Bromophenyl)-5-(4-fluorophenyl)-4-(1*H*-indol-3-yl)oxazole 321



Prepared according to **GP7** using indole derivative **286** (47 mg, 0.2 mmol) and ylide **200** (83 mg, 0.3 mmol). Purification with flash column chromatography [90:10 (toluene:EtOAc)] afforded the

oxazole **321** as a light brown solid (59 mg, 68%); mp. 176-178 °C; IR ν_{max}/cm^{-1} 3257, 1627, 1492, 1228, 1163, 936, 838, 763, 724; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 11.53 (bs, NH), 8.14 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.86 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.77-7.75 (m, 1H), 7.75-7.70 (m, 2H), 7.59 (td, *J* = 7.6, 1.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.52-7.45 (m, 2H), 7.31-7.25 (m, 2H), 7.14-7.19 (m, 1H), 7.02 (dd, *J* = 7.8, 7.2 Hz, 1H); ^{13}C-NMR (101 MHz, DMSO-d$_6$) δ 161.9 (d, J_{C-F} = 249.7 Hz, *ipso*-C), 157.7 (C), 143.7 (C), 136.2 (C), 134.5 (CH), 132.0 (CH), 131.6 (C), 131.3 (CH), 128.9 (C), 128.1 (CH), 128.0 (d, J_{C-F} = 8.4 Hz, *meta*-2 × CH), 127.5 (C), 125.5 (C), 125.1 (CH), 121.7 (CH), 120.2 (CH), 120.1 (C), 119.5 (CH), 115.9 (d, J_{C-F} = 21.5 Hz, *ortho*-2 × CH), 111.9 (CH), 105.9 (C); HRMS (ES) calcd. for $C_{23}H_{15}N_2OFBr$: 433.0352, found: 433.0354 $[M+H]^+$.

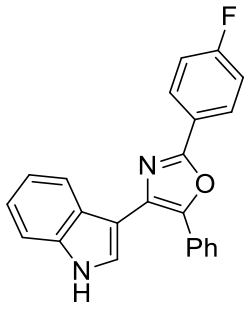
5-(4-Bromophenyl)-4-(1*H*-indol-3-yl)-2-(4-methoxyphenyl)oxazole 322



Prepared according to **GP7** using indole derivative **252** (44 mg, 0.2 mmol) and ylide **307** (69 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **322** as a yellow solid (58 mg, 79%); mp. 194-196 °C; IR ν_{max}/cm^{-1} 3079, 2920, 1637, 1465, 1186, 845, 743, 620; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 8.44 (bs, NH), 8.15 (d, *J* = 8.9 Hz, 2H), 7.68 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.38-7.28 (m, 3H), 7.25-7.19 (m, 1H), 7.12-7.05 (m, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.5 (C), 160.2 (C), 157.6 (C), 144.9 (C), 142.6 (C), 136.4 (C), 129.5

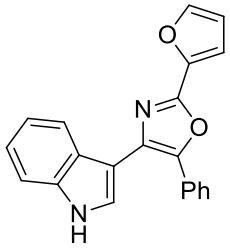
(C), 128.6 (2 × CH), 128.3 (2 × CH), 127.9 (CH), 126.1 (C), 125.9 (2 × CH), 124.2 (CH), 122.8 (C), 122.6 (CH), 121.3 (CH), 120.4 (CH), 114.4 (2 × CH), 111.3 (CH), 108.9 (C), 55.6 (OCH_3); HRMS (ES) calcd. for $C_{24}H_{19}N_2O_2$: 367.1447, found: 367.1441 $[M+H]^+$.

5-(2-Bromophenyl)-2-(4-fluorophenyl)-4-(1*H*-indol-3-yl)oxazole 323



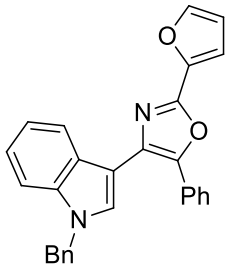
Prepared according to **GP7** using indole derivative **252** (44 mg, 0.2 mmol) and ylide **306** (65 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **323** as a brown solid (55 mg, 78%); mp. 162-164 °C; IR ν_{max}/cm^{-1} 3254, 2962, 1624, 1466, 1440, 1260, 1172, 737, 696; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.43 (bs, NH), 8.23-8.15 (m, 2H), 7.71-7.69 (m, 2H), 7.58-7.54 (m, 2H), 7.43 (d, *J* = 8.2, Hz, 1H), 7.39-7.27 (m, 3H), 7.27-7.16 (m, 3H), 7.10 (app. td, *J* = 7.5, 0.8 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 162.7 (d, J_{C-F} = 250.5 Hz, *ipso*-C), 159.3 (C), 145.4 (C), 136.4 (C), 131.7 (C), 129.3 (2 × C), 128.8 (C), 128.7 (d, J_{C-F} = 8.1 Hz, *meta*-2 × CH), 128.7 (2 × CH), 128.1 (CH), 126.0 (2 × CH), 124.1 (CH), 122.7 (CH), 121.3 (CH), 120.5 (CH), 116.2 (d, J_{C-F} = 22.3 Hz, *ortho*-2 × CH) , 111.4 (CH), 108.9 (C); HRMS (ES) calcd. for $C_{23}H_{16}N_2OF$: 355.1247, found: 355.1251 $[M+H]^+$.

2-(Furan-2-yl)-4-(1*H*-indol-3-yl)-5-phenyloxazole 324



Prepared according to **GP7** using indole derivative **252** (65 mg, 0.3 mmol) and ylide **299** (84 mg, 0.45 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **324** as a brownish solid (81 mg, 85%); mp. 138-140 °C; IR ν_{max}/cm^{-1} 3398, 3057, 2924, 1625, 1447, 1067, 1010, 930, 739, 690; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.49 (bs, 1H), 7.66 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.60 (d, *J* = 1.3 Hz, 1H), 7.60 (d, *J* = 2.6 Hz, 1H), 7.42 (t, *J* = 8.3 Hz, 2H), 7.35-7.27 (m, 3H), 7.21 (app. td, *J* = 7.6, 0.9 Hz, 1H), 7.14 (dd, *J* = 3.4, 0.5 Hz, 1H), 7.06 (app. td, *J* = 7.6, 0.8 Hz, 1H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.1 (C), 144.9 (C), 144.5 (CH), 143.3 (C), 136.3 (C), 131.4 (C), 129.0 (C), 128.6 (2 × CH), 128.2 (CH), 126.1 (2 × CH), 125.8 (C), 124.5 (CH), 122.6 (CH), 121.3 (CH), 120.4 (CH), 112.1 (CH), 111.6 (CH), 111.4 (CH), 108.6 (C); HRMS (ES) calcd. for $C_{21}H_{15}N_2O_2$: 327.1134, found: 327.1137 $[M+H]^+$.

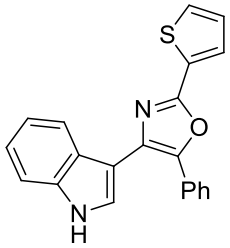
4-(1-Benzyl-1*H*-indol-3-yl)-5-phenyl-2-(thiophen-2-yl)oxazole 325



Prepared according to **GP7** using indole derivative **282** (62 mg, 0.2 mmol) and ylide **299** (56 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the

oxazole **325** as a brown solid (27 mg, 33%); mp. 124-126 °C; IR ν_{max}/cm^{-1} 3255, 1624, 1528, 1469, 1442, 1099, 725, 690; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.60 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.56 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.36-7.31 (m, 3H), 7.32-7.27 (m, 4H), 7.23-7.16 (m, 3H), 7.13 (dd, *J* = 3.5, 0.6 Hz, 1H), 7.05 (app. td, *J* = 7.5, 1.0 Hz, 1H), 6.58 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.37 (s, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.2 (C), 144.8 (C), 143.3 (C), 137.3 (C), 136.8 (C), 131.6 (C), 129.1 (C), 128.7 (2 × CH), 128.6 (2 × CH), 128.2 (CH), 128.0 (CH), 127.2 (2 × CH), 126.6 (C), 126.2 (2 × CH), 122.4 (CH), 121.7 (CH), 121.1 (CH), 120.3 (CH), 112.1 (CH), 111.7 (CH), 110.1 (CH), 144.6 (CH), 107.7 (C), 50.6 (CH_2); HRMS (ES) calcd. for $C_{28}H_{21}N_2O_2$: 417.1603, found: 417.1607 $[M+H]^+$.

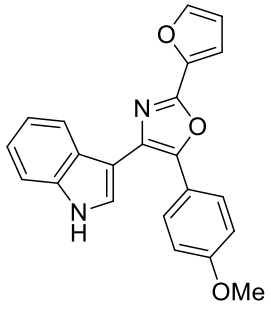
4-(1*H*-Indol-3-yl)-5-phenyl-2-(thiophen-2-yl)oxazole 326



Prepared according to **GP7** using indole derivative **252** (44 mg, 0.2 mmol) and ylide **300** (61 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **326** as a brownish solid (44 mg, 64%); mp. 167-170 °C; IR ν_{max}/cm^{-1} 3376, 3058, 1614, 1488, 1445, 1239, 825, 690; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.53 (bs, NH), 7.91 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.88 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.71 (d, *J* = 2.5 Hz, 1H), 7.67-7.61 (m, 2H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.43-7.33 (m, 4H), 7.28 (dd, *J* = 5.0, 4.0 Hz, 1H), 7.14 (app. td, *J* = 7.5, 1.0 Hz, 1H), 6.98 (app. td, *J* = 7.5, 1.0 Hz, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 155.5 (C), 143.6 (C), 136.2 (C), 131.8 (C), 129.7 (CH), 129.1 (C), 128.9 (C), 128.7 (2 × CH), 128.6 (C), 128.4 (CH), 128.2 (2 × CH),

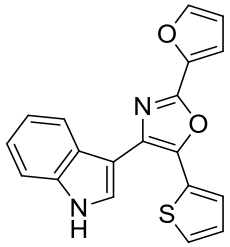
125.5 (2 × CH), 125.3 (CH), 121.6 (CH), 120.1 (CH), 119.4 (CH), 111.9 (CH), 106.2 (C); HRMS (ES) calcd. for $C_{21}H_{14}N_2ONaS$: 365.0725, found: 365.0720 $[M+Na]^+$.

2-(Furan-2-yl)-4-(1*H*-indol-3-yl)-5-(4-methoxyphenyl)oxazole 327



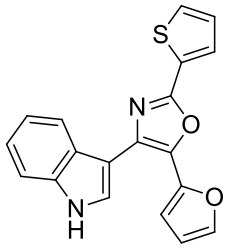
Prepared according to **GP7** using indole derivative **285** (50 mg, 0.2 mmol) and ylide **299** (56 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **327** as a brown solid (61 mg, 86%); mp. 90-93 °C; IR ν_{max}/cm^{-1} 3373, 2107, 1407, 1236, 1222, 1215, 1170, 842, 750; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (bs, NH), 7.63-7.53 (m, 4H), 7.44-7.38 (m, 2H), 7.21 (app t, *J* = 7.7 Hz, 1H), 7.11 (dd, *J* = 3.4, 0.7 Hz, 1H), 7.05 (app t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 2H), 6.57 (d, *J* = 3.4, 1.7 Hz, 1H), 3.80 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.6 (C), 152.6 (C), 145.0 (C), 144.3 (CH), 143.4 (C), 136.3 (C), 130.0 (C), 127.8 (2 × CH), 125.8 (C), 124.4 (CH), 122.5 (CH), 121.7 (C), 121.3 (CH), 120.3 (CH), 114.1 (2 × CH), 112.4 (CH), 112.0 (CH), 111.3 (CH), 108.8 (C), 55.4 (OCH_3); HRMS (ES) calcd. for $C_{22}H_{17}N_2O_3$: 357.1239, found: 357.1229 $[M+H]^+$.

2-(Furan-2-yl)-4-(1*H*-indol-3-yl)-5-(thiophen-2-yl)oxazole 328



Prepared according to **GP7** using indole derivative **284** (45 mg, 0.2 mmol) and ylide **299** (56 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **328** as a yellow powder (47 mg, 71%); mp. 197-200 °C; IR ν_{max}/cm^{-1} 3143, 1613, 1523, 1455, 1071, 971, 743, 692; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 11.54 (bs, NH), 8.00 (d, *J* = 1.0 Hz, 1H), 7.79 (bd, *J* = 2.3 Hz, 1H), 7.65-7.58 (m, 2H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.37 (dd, *J* = 3.5, 1.0 Hz, 1H), 7.28 (d, *J* = 3.5 Hz, 1H), 7.21-7.11 (m, 2H), 7.04 (app td, *J* = 7.4, 0.5 Hz, 1H), 6.77 (dd, *J* = 3.5, 1.8 Hz, 1H); ^{13}C-NMR (101 MHz, DMSO-d$_6$) δ 151.8 (C), 145.7 (CH), 141.9 (C), 139.4 (C), 136.2 (C), 131.5 (C), 129.2 (C), 127.8 (CH), 126.9 (CH), 125.9 (CH), 125.6 (C), 125.5 (CH), 121.7 (CH), 120.2 (CH), 119.5 (CH), 112.5 (CH), 112.3 (CH), 111.9 (CH), 105.3 (C); HRMS (ES) calcd. for $C_{19}H_{12}N_2O_2NaS$: 355.0517, found: 355.0518 $[M+Na]^+$.

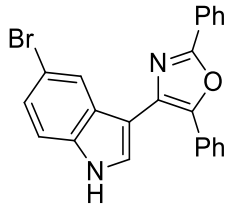
5-(Furan-2-yl)-4-(1*H*-indol-3-yl)-2-(thiophen-2-yl)oxazole 329



Prepared according to **GP7** using indole derivative **283** (42 mg, 0.2 mmol) and ylide **300** (61 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the

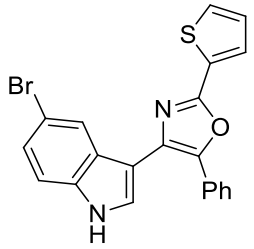
oxazole **329** as a brown solid (40 mg, 61%); mp. 157-160 °C; IR ν_{max}/cm^{-1} 3379, 3145, 2929, 1607, 1455, 1242, 1072, 884, 742; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 11.51 (bs, NH), 7.97 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 2.7 Hz, 1H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.87-7.83 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 5.0, 3.5 Hz, 1H), 7.17 (app. td, *J* = 7.5, 1.0 Hz, 1H), 7.08 (app. td, *J* = 7.5, 1.0 Hz, 1H), 6.85 (d, *J* = 3.6 Hz, 1H), 6.71 (dd, *J* = 3.5, 1.5 Hz, 1H); ^{13}C-NMR (101 MHz, DMSO-d$_6$) δ 155.4 (C), 143.7 (CH), 143.0 (C), 136.1 (C), 135.2 (C), 132.8 (C), 130.1 (CH), 128.7 (C), 128.7 (CH), 128.4 (CH), 125.8 (C), 125.3 (CH), 121.7 (CH). 120.7 (CH), 119.6 (CH), 112.0 (CH), 111.8 (CH), 109.1 (CH), 105.3 (C); HRMS (ES) calcd. for $C_{19}H_{13}N_2O_2S$: 333.0698, found: 333.0695 $[M+H]^+$.

4-(5-Bromo-1*H*-indol-3-yl)-2,5-diphenyloxazole 330



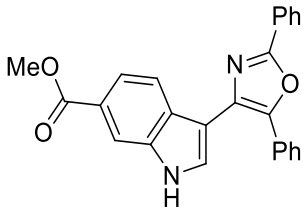
Prepared according to **GP7** using indole derivative **290** (59 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **330** as a yellow solid (33 mg, 40%); mp. 78-80 °C; IR ν_{max}/cm^{-1} 2922, 2852, 1592, 1447, 1260, 1070, 796, 690; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 11.70 (bs, NH), 8.14 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.77 (d, *J* = 2.6 Hz, 1H), 7.72-7.68 (m, 2H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.61-7.56 (m, 2H), 7.48-7.41 (m 3H), 7.27 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.26-7.21 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.3 (C), 145.7 (C), 135.0 (C), 131.0 (C), 130.5 (CH), 129.8 (C), 129.1 (C), 129.0 (2 × CH), 128.9 (2 × CH), 128.4 (CH), 127.6 (C), 126.6 (2 × CH), 126.1 (2 × CH), 125.7 (CH), 125.0 (CH), 123.9 (CH), 113.4 (C), 112.8 (CH), 108.7 (C); HRMS (ES) calcd. for $C_{23}H_{16}N_2OBr$: 415.0446, found: 415.0454 $[M+H]^+$.

4-(5-Bromo-1*H*-indol-3-yl)-5-phenyl-2-(thiophen-2-yl)oxazole 331



Prepared according to **GP7** using indole derivative **290** (59 mg, 0.2 mmol) and ylide **300** (61 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **331** as a yellow solid (57 mg, 68%); mp. 180-182 °C; IR ν_{max}/cm^{-1} 3165, 2922, 1583, 1450, 1106, 884, 799, 705; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 11.70 (bs, NH), 7.88-7.84 (m, 1H), 7.83 (bs, 1H), 7.76 (d, *J* = 1.6 Hz, 1H), 7.65 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.56 (bs, 1H), 7.47-7.38 (m, 4H), 7.30-7.25 (m, 2H); ^{13}C-NMR (101 MHz, DMSO-d$_6$) δ 155.7 (C), 143.8 (C), 134.9 (C), 131.1 (C), 129.8 (CH), 129.0 (C), 128.8 (2 × CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.7 (C), 127.2 (C), 126.7 (CH), 125.7 (2 × CH), 124.2 (CH), 122.4 (CH), 114.0 (CH), 112.0 (C), 105.9 (C); HRMS (ES) calcd. for $C_{21}H_{14}N_2OSBr$: 421.0010, found: 421.0018 $[M+H]^+$.

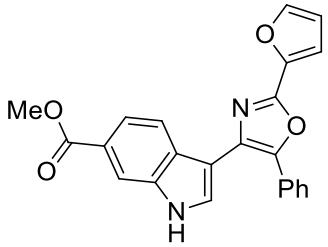
Methyl 3-(2,5-diphenyloxazol-4-yl)-1*H*-indole-6-carboxylate 332



Prepared according to **GP7** using indole derivative **291** (55 mg, 0.2 mmol) and ylide **245** (59 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **332** as a brown solid (62 mg, 79%); mp. 188-190 °C; IR ν_{max}/cm^{-1} 3376, 3231, 1712, 1504,

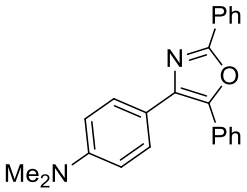
1290, 1248, 1028, 745, 690; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.99 (bs, NH), 8.22-8.18 (m, 2H), 8.17 (d, *J* = 1.1 Hz, 1H), 7.77 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.69 (d, *J* = 2.7 Hz, 1H), 7.68-7.64 (m, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.36-7.28 (m, 3H), 3.93 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.2 (C), 160.3 (C), 145.7 (C), 135.8 (C), 131.0 (C), 130.5 (CH), 129.5 (C), 129.1 (C), 129.0 (2 × CH), 128.8 (2 × CH), 128.3 (CH), 127.5 (CH), 127.6 (C), 126.6 (2 × CH), 126.1 (2 × CH), 124.4 (C), 121.4 (CH), 120.9 (CH), 113.9 (CH), 109.3 (C), 52.1 (CH_3); HRMS (ES) calcd. for $C_{25}H_{19}N_2O_3$: 395.1396, found: 395.1397 $[M+H]^+$.

Methyl 3-(2-(furan-2-yl)-5-phenyloxazol-4-yl)-1*H*-indole-6-carboxylate 333



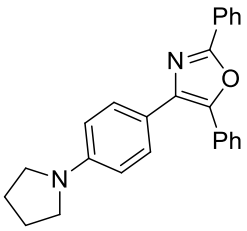
Prepared according to **GP7** using indole derivative **291** (55 mg, 0.2 mmol) and ylide **299** (56 mg, 0.3 mmol). Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **333** as a brown solid (45 mg, 59%); mp. 122-124 °C; IR ν_{max}/cm^{-1} 3219, 1704, 1437, 1290, 933, 741, 688; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.92 (bs, NH), 8.15 (s, 1H), 7.94-7.76 (m, 2H), 7.70-7.56 (m, 3H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.44-7.33 (m, 3H), 7.31 (bs, 1H), 6.77 (bs, 1H), 3.86 (s, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 167.1 (C), 152.3 (C), 145.7 (CH), 143.8 (C), 142.0 (C), 135.5 (C), 130.9 (C), 129.1 (CH), 128.9 (2 × CH and C), 128.5 (CH), 128.1 (C), 125.7 (2 × CH), 122.8 (C), 120.0 (2 × CH), 114.0 (CH), 112.4 (CH), 112.3 (CH), 106.8 (C), 51.8 (CH_3); HRMS (ES) calcd. for $C_{23}H_{17}N_2O_4$: 385.1188, found: 385.1186 $[M+H]^+$.

4-(2,5-Diphenyloxazol-4-yl)-*N,N*-dimethylaniline 390



Prepared according to a modified **GP7** using aniline derivative **388** (44 mg, 0.2 mmol, 1.0 eq.) and ylide **245** (90 mg, 0.45 mmol, 2.25 eq.). The reaction mixture was quenched after 48 hours. Purification by flash column chromatography (toluene) afforded the oxazole **390** as a yellow powder (43 mg, 63%); mp. 128-130 °C; IR ν_{max}/cm^{-1} 3691, 3619, 2919, 2852, 1607, 1455, 1242, 1008, 911, 692; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20-8.13 (m, 2H), 7.78-7.68 (m, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.51-7.45 (m, 3H), 7.43-7.30 (m, 3H), 6.76 (d, *J* = 8.6 Hz, 2H), 3.00 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.0 (C), 150.5 (C), 144.3 (C), 137.5 (C), 130.2 (CH), 129.7 (C), 129.1 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.1 (CH), 127.8 (C), 126.6 (2 × CH), 126.4 (2 × CH), 120.5 (C), 112.4 (2 × CH), 40.6 (2 × CH_3); HRMS (ES) calcd. for $C_{23}H_{20}N_2ONa$: 363.1473, found: 363.1469 $[M+Na]^+$.

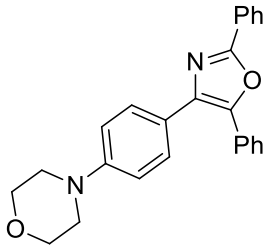
2,5-Diphenyl-4-(4-(pyrrolidin-1-yl)phenyl)oxazole 391



Prepared according to a modified **GP7** using aniline derivative **379** (50 mg, 0.2 mmol, 1.0 eq.) and ylide **245** (90 mg, 0.45 mmol, 2.25 eq.). The reaction mixture was quenched after 48 hours. Purification by flash column chromatography (toluene) afforded the oxazole **391** as a brown

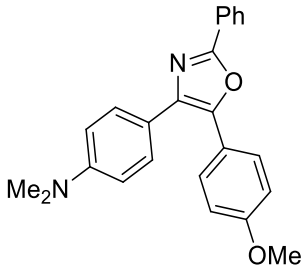
solid (25.8 mg, 34%); mp. 130-135 °C; IR ν_{max}/cm^{-1} 2851, 1614, 1378, 1112, 765, 686; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21-8.17 (m, 2H), 7.77-7.70 (m, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.52-7.43 (m, 3H), 7.40-7.35 (m, 2H), 7.36-7.31 (m, 1H), 6.59 (d, *J* = 8.7 Hz, 2H), 3.34 (t, *J* = 6.6, 4H), 2.06-2.02 (m, 4H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 159.9 (C), 147.9 (C), 144.1 (C), 137.7 (C), 130.1 (CH), 129.8 (C), 129.2 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.0 (CH), 127.9 (C), 126.6 (2 × CH), 126.4 (2 × CH), 119.4 (C), 111.7 (2 × CH), 47.7 (2 × CH_2), 25.6 (2 × CH_2); HRMS (ES) calcd. for $C_{25}H_{23}N_2O$: 367.1810, found: 367.1812 $[M+H]^+$.

4-(4-(2,5-Diphenyloxazol-4-yl)phenyl)morpholine 392



Prepared according to a modified **GP7** using aniline derivative **385** (53 mg, 0.2 mmol, 1.0 eq.) and ylide **245** (90 mg, 0.45 mmol, 2.25 eq.). The reaction mixture was quenched after 48 hours. Purification by flash column chromatography [90:10 (toluene:EtOAc)] afforded the oxazole **392** as a yellow powder (45 mg, 59%); mp. 140-142 °C; IR ν_{max}/cm^{-1} 3377, 3059, 1615, 1514, 1445, 1260, 1239, 923, 824, 740, 685; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.13-8.06 (m, 2H) 7.72-7.66 (m, 2H), 7.61- 7.53 (m, 4H), 7.53-7.38 (m, 4H), 7.01 (d, *J* = 8.6 Hz, 2H), 3.79-3.70 (m, 4H), 3.22-3.14 (m, 4H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 159.2 (C), 150.9 (C), 144.0 (C), 136.3 (C), 130.7 (CH), 129.1 (2 × CH), 128.9 (2 × CH), 128.7 (CH), 128.6 (C), 128.4 (2 × CH), 126.7 (C), 126.2 (2 × CH), 126.0 (2 × CH), 122.0 (C), 114.6 (2 × CH), 66.0 (2 × CH_2), 47.8 (2 × CH_2); HRMS (ES) calcd. for $C_{25}H_{23}N_2O_2$: 383.1760, found: 383.1764 $[M+H]^+$.

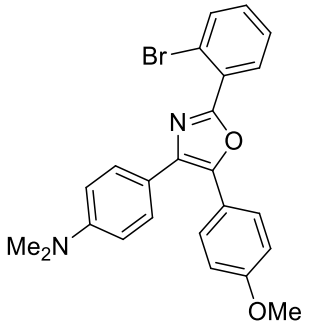
4-(5-(4-Methoxyphenyl)-2-phenyloxazol-4-yl)-*N,N*-dimethylaniline 395



Prepared according to a modified GP7 using aniline derivative **389** (50 mg, 0.2 mmol, 1.0 eq.) and ylide **245** (90 mg, 0.45 mmol, 2.25 eq.). The reaction mixture was quenched after 48 hours. Purification by flash column chromatography (toluene) afforded the oxazole **395** as a yellow powder (63 mg, 84%); mp. 117-120 °C; IR ν_{max}/cm^{-1} 2902, 1615, 1500, 1250, 1174, 1029, 827, 686; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18 (m, 2H), 7.65 (d, *J* = 8.9 Hz, 2H), 7.60 (d, *J* = 8.9 Hz, 2H), 7.51-7.41 (m, 3H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 3.00 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.6 (C), 159.5 (C), 150.4 (C), 144.4 (C), 136.2 (C), 130.1 (CH), 129.0 (2 × CH), 128.8 (2 × CH), 128.1 (2 × CH), 127.9 (C), 126.5 (2 × CH), 122.4 (C), 120.7 (C), 114.2 (2 × CH), 112.5 (2 × CH), 55.5 (OCH_3), 40.6 (2 × CH_3); HRMS (ES) calcd. for $C_{24}H_{23}N_2O_2$: 371.1760, found: 371.1755 $[M+H]^+$.

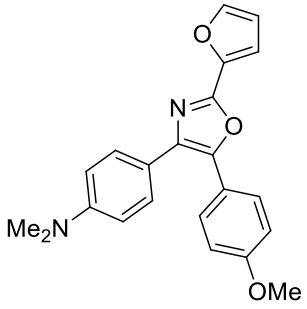
When $CuCl_2$ (5 mol%, 1 mg) was used instead of **Au-4**, the oxazole was afforded in 60% (45 mg).

4-(2-(2-Bromophenyl)-5-(4-methoxyphenyl)oxazol-4-yl)-*N,N*-dimethylaniline 396



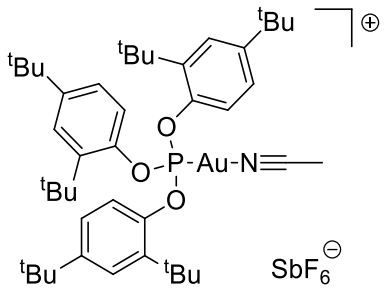
Prepared according to a modified **GP7** using aniline derivative **389** (50 mg, 0.2 mmol, 1.0 eq.) and ylide **200** (125 mg, 0.45 mmol, 2.25 eq.). The reaction mixture was quenched after 48 hours. Purification by flash column chromatography [100-90:10 (toluene:EtOAc)] afforded the oxazole **396** as a yellow solid (75 mg, 89%); mp. 162-164 °C; IR ν_{max}/cm^{-1} 2891, 2831, 1614, 1524, 1499, 1437, 1248, 1178, 1030, 829, 725; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.72 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 2H), 7.62 (d, *J* = 8.9 Hz, 2H), 7.41 (app. td, *J* = 7.8, 1.1 Hz, 1H), 7.28 (app. td, *J* = 7.6, 2.0 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 3.85 (s, 3H), 3.00 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.7 (2 × C), 158.1 (C), 150.4 (C), 145.1 (C), 135.8 (C), 134.6 (CH), 131.5 (CH), 130.9 (CH), 129.0 (2 x CH), 128.7 (C), 128.1 (2 × CH), 127.4 (CH), 122.2 (C), 120.9 (C), 114.2 (2 × CH), 112.5 (2 × CH), 55.5 (CH_3), 40.6 (2 × CH_3); HRMS (ES) calcd. for $C_{24}H_{22}N_2O_2Br$: 449.0865, found: 449.0871 $[M+H]^+$.

4-(2-(Furan-2-yl)-5-(4-methoxyphenyl)oxazol-4-yl)-*N,N*-dimethylaniline 397



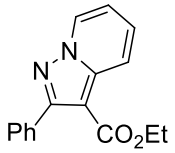
Prepared according to a modified **GP7** using aniline derivative **389** (33 mg, 0.13 mmol, 1.0 eq.) and ylide **299** (38 mg, 0.30 mmol, 2.25 eq.). The reaction mixture was quenched after 48 hours. Purification by flash column chromatography [100-90:10 (toluene:EtOAc)] afforded the oxazole **397** as a yellow oil (15 mg, 32%); IR ν_{max}/cm^{-1} 2896, 1612, 1482, 1258, 1168, 1032, 734, 711; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63–7.56 (m, 5H), 7.06 (dd, *J* = 3.5, 0.6 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 7.8 Hz, 2H), 6.55 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.84 (s, 3H), 2.99 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.8 (C), 152.6 (C), 150.4 (C), 144.3 (CH), 143.4 (C), 138.0 (C), 129.2 (C), 129.0 (2 × CH), 128.3 (2 × CH), 125.4 (C), 122.0 (C), 114.2 (2 × CH), 112.4 (2 × CH), 111.9 (CH), 111.1 (CH), 55.5 (CH_3), 40.6 (2 × CH_3); HRMS (ES) calcd. for $C_{22}H_{21}N_2O_3$: 361.1552, found: 361.1562 $[M+H]^+$.

Gold Catalyst Au-4



Following Echavarren's procedure,[239] a double-neck, round-bottom flask covered with aluminium foil was charged with $AgSbF_6$ (61 mg, 0.18 mmol, 1.2 eq.) dissolved in MeCN (10 mL). **Au-3** (132 mg, 0.15 mmol, 1.0 eq.) was added at room temperature to the reaction mixture forming a white suspension. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the white solid residue was redissolved in CH_2Cl_2 (15 mL). After filtration through a plug of silica, evaporation of the solvent and drying in the high vaccuum line for at least 3 hours, the gold complex **Au-4** was afforded as a white powder (140 mg, 83%); mp. 78-80 °C; IR ν_{max}/cm^{-1} 3379, 2206, 1615, 1499, 1415, 1097, 1071, 740, 683; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50-7.46 (m, 3H), 7.37 (dd, *J* = 8.5, 1.5 Hz, 3H), 7.25 (dd, *J* = 8.5, 1.5 Hz, 3H), 2.50 (s, 3H), 1.46 (s, 27H), 1.32 (s, 27H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 149.2 (3 × C), 147.1 (3 × C), 139.1 (3 × C), 125.9 (3 × CH), 124.7 (3 × CH), 119.2 (3 × CH), 35.3 (3 × C), 34.7 (3 × C), 31.4 (9 × CH_3), 30.5 (9 × CH_3), 2.9 (CH_3) ($C_{q.}$ of the CH_3CN is not obvious in the spectra); ^{31}P NMR (300 MHz, $CDCl_3$) δ 87.5; HRMS (ES) calcd. for $C_{44}H_{66}NO_3PAu$: 884.446, found: 884.4436 $[M]^+$.

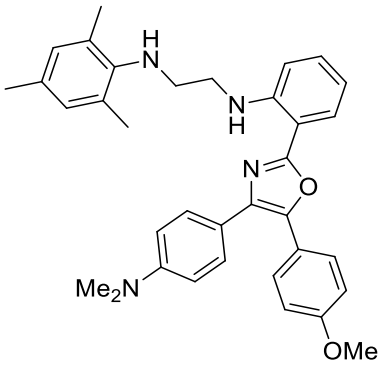
2-Phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester 423



Prepared according to a modified **GP7** using alkyne **422** (17 mg, 0.1 mmol, 1.0 eq.), ylide **235** (22 mg, 0.15 mmol, 1.5 eq.), PPh_3AuCl (2.8 mg, 5 mol%) and $AgNTf_2$ (1.9 mg, 5 mol%) in toluene (1 mL, 0.1 M) for 14 hours at 90 °C. Purification by flash column chromatography [88:12 (toluene: EtOAc)] afforded the heterocycle **423** as a white solid (56%, 13 mg); mp. 82-83 °C (lit. 82-84 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 6.9 Hz, 1H), 8.25 (d, *J* = 9.0 Hz, 1H), 7.82-7.79 (m, 1H), 7.52-7.40 (m, 5H), 6.99 (td, *J* = 6.9, 1.3 Hz, 1H), 4.34 (q, *J* = 7.1, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); MS (ES): 289.3 ([M+Na]$^+$, 100%).

Data matches that reported in the literature.[240]

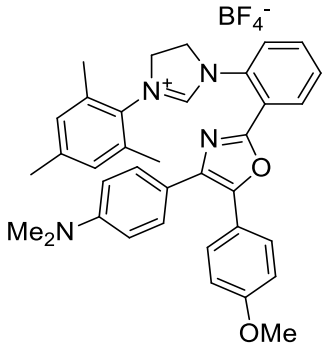
***N*1-(2-(4-(4-(Dimethylamino)phenyl)-5-(4-methoxyphenyl)oxazol-2-yl)phenyl)-*N*2-mesitylethane-1,2-diamine 449**



The oxazole **396** (449 mg, 1.0 mmol, 1.0 eq.) and the diamine **448** (178 mg, 1.0 mmol, 1.0 eq.) were added to a solution of $Pd(OAC)_2$ (2.2 mg, 0.01 mmol, 0.01 eq.), BINAP (13 mg, 0.02 mmol, 0.02 eq.) and NaO^tBu (192 mg, 2.0 mmol, 2.0 eq.) in toluene (3 mL) that had been stirred

together at room temperature for 20 minutes. The reaction mixture was heated at 100 °C for 2 days at which point consumption of the starting material was observed by TLC. The reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with H_2O (10 mL). The organic layer was collected and dried over $MgSO_4$. After filtration, evaporation of the solvent under reduced pressure and purification by flash column chromatography [80:20 (hexane:EtOAc)] the diamine **449** was isolated as a yellow solid (401 mg, 73%); mp 187-188 °C; IR ν_{max}/cm^{-1} 3284, 2909, 2837, 1611 1523, 1502, 1441, 1249, 1176, 1029, 946, 821, 740, 713, 701; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H, NH), 7.99 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.65 (d, *J* = 8.9 Hz, 2H), 7.56 (d, *J* = 8.9 Hz, 2H), 7.34-7.27 (m, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.83-6.69 (m, 4H), 6.62 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.53 (t, *J* = 5.7 Hz, 2H), 3.35 (t, *J* = 5.7 Hz, 2H), 3.01 (s, 3H), 2.97 (s, 6H), 2.22 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.7 (C), 147.2 (C), 144.7 (C), 134.6 (C), 131.5 (C), 131.4 (CH), 129.9 (C), 129.7 (2 × CH), 129.0 (C), 128.8 (2 × CH), 128.3 (2 × CH), 128.1 (C), 127.8 (CH), 127.8 (C), 122.4 (C), 121.2 (C), 115.5 (CH), 114.2 (2 × CH), 111.0 (CH), 112.4 (2 × CH), 109.8 (2 × C), 55.5 (2 × CH_3), 47.6 (CH_3), 43.5 (CH_2), 40.6 (CH_2), 20.7 (CH_3), 18.6 (2 × CH_3). HRMS (ES) calcd for $C_{35}H_{39}N_4O_2$: 547.3073, found: 547.3057 $[M+H]^+$.

1-(2-(4-(4-(Dimethylamino)phenyl)-5-(4-methoxyphenyl)oxazol-2-yl)phenyl)-3-mesityl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate salt 450

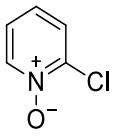


A 5mL round-bottom flask was charged with the NHC-precursor **449** (150 mg, 0.27 mmol, 1.0 eq.), NH_4BF_4 (35 mg, 0.34 mmol, 1.3 eq.) and $HC(OEt)_3$ (0.8 mL) and directly attached to a bubbler. The reaction mixture was heated at 120 °C. Insoluble solid residue remained throughout the course of the reaction and after 16 hours consumption of starting material was indicated by TLC. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and purified by flash column chromatography [95:5 (CH_2Cl_2:MeOH)] to afford the NHC-salt **450** as a yellow solid (74.0 mg, 46%); mp. 176-178 °C; IR ν_{max}/cm^{-1} 2925, 1630, 1601, 1252, 1053, 1025, 830, 772; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21-8.14 (m, 1H), 8.08-8.01 (m, 1H), 7.94 (s, 1H), 7.64-7.56 (m, 4H), 7.39 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.84 (s, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 4.49-4.39 (m, 2H), 4.93-4.84 (m, 2H), 3.85 (s, 3H), 3.02 (s, 6H), 2.25 (s, 3H), 2.10 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.2 (C), 158.1 (CH-imidazole), 155.4 (C), 150.5 (C), 145.5 (C), 140.3 (C), 136.7 (C), 135.8 (2 × C), 132.1 (CH), 132.0 (C), 130.9 (CH), 130.5 (C), 129.9 (3 × CH), 129.1 (3 × CH), 128.1 (2 × CH), 123.1 (C), 121.1 (C), 114.4 (2 × CH), 112.3 (2 × CH),

55.5 (CH_3), 53.1 (CH_2), 51.8 (CH_2), 40.5 (2 × CH_3), 21.1 (CH_3), 17.5 (2 × CH_3); HRMS (ES) calcd for $C_{36}H_{37}N_4O_2$: 557.2917, found: 557.2906 $[M]^+$.

5.4.2 Compounds in Chapter 3

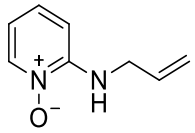
2-Chloropyridine *N*-oxide 650



*m*CPBA (30% of H_2O, 3.30 .g, 12.0 mmol, 1.2 eq.) was dissolved in CH_2Cl_2 (100 mL, 0.1 M) and 2-chloropyridine **649** (0.94 mL, 10.0 mmol, 1.0 eq.) was added successively at room temperature. After 18 hours stirring at reflux, the reaction mixture was cooled to room temperature and saturated $NaHCO_3$ solution (100 mL) was added. The residue was extracted with CH_2Cl_2 (3 × 100 mL), the extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography [94:6 (EtOAc:MeOH)] afforded the *N*-oxide **650** as a yellowish viscous oil (898 mg, 69%); IR ν_{max}/cm^{-1} 3095, 3064, 3033, 2994, 1417, 1276, 1082, 846, 763, 670; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.38-8.33 (m, 1H), 7.56-7.47 (m, 1H), 7.25-7.17 (m, 2H).

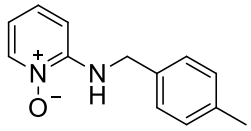
Data matches that reported in the literature.[241]

2-(Allylamino)pyridine *N*-oxide 651



2-Chloropyridine-*N*-oxide **650** (518 mg, 4.0 mmol, 1.0 eq.), $NaHCO_3$ (1.68 g, 20.0 mmol, 5.0 eq.) and allyl amine (0.60 mL, 8.0 mmol, 2.0 eq.) were suspended in 1-butanol (4 ml, 1.0 M) in a sealed tube. The reaction mixture was heated at 105 °C for 24 hours, then it was cooled to room temperature, the salts were filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography [80:20 (EtOAc:MeOH)] afforded the *N*-oxide **651** as a viscous oil (425 mg, 80%); IR ν_{max}/cm^{-1} 3268, 1624, 1540, 1529, 1454, 1195, 1130, 914, 836, 749; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.1, 1.5 Hz, 1H), 7.18-7.10 (m, 1H), 6.98 (bs, NH), 6.58-6.49 (m, 2H), 5.86 (ddt, *J* = 17.2, 10.2, 5.1 Hz, 1H), 5.26 (ddd, *J* = 17.2, 3.0, 1.7 Hz, 1H), 5.18 (ddd, *J* = 10.2, 3.0, 1.5 Hz, 1H), 3.94-3.87 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 150.4 (C), 137.5 (CH), 133.2 (CH), 128.4 (CH), 117.0 (CH), 111.7 (CH), 106.2 (CH_2), 44.6 (CH_2).

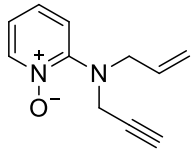
2-((4-Methylbenzyl)amino)pyridine *N*-oxide 652



2-Chloropyridine-*N*-oxide **650** (648 mg, 5.0 mmol, 1.0 eq.), $NaHCO_3$ (2.10 g, 25.0 mmol, 5.0 eq.) and 4-methyl-benzylamine (1.30 ml, 10.0 mmol, 2.0 eq.) were suspended in 1-butanol (4.5 mL) in a sealed tube. The reaction mixture was heated at 105 °C for 24 hours, then it was cooled to room temperature, the salts were filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography [94:6 (EtOAc:MeOH)] afforded the

substituted *N*-oxide **652** as a viscous oil (438 mg, 41%); IR ν_{max}/cm^{-1} 3231, 1621, 1450, 1515, 1120, 1114, 850, 752; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 6.5, 1.2 Hz, 1H), 7.27-7.05 (m, 6H), 6.56-6.46 (m, 1H), 4.44 (d, *J* = 6.1 Hz, 2H), 2.31 (s, 3H) *(the NH is not obvious in the spectrum)*; ^{13}C-NMR (101 MHz, $CDCl_3$) δ 150.45 (C), 137.42 (C, CH), 134.06 (C), 129.55 (2 × CH), 128.24 (CH), 127.04 (2 × CH), 111.80 (CH), 106.24 (CH), 46.00 (CH_2), 21.13 (CH_3); HRMS calcd. for $C_{13}H_{15}N_2O$: 215.1184, found: 215.1186 $[M+H]^+$.

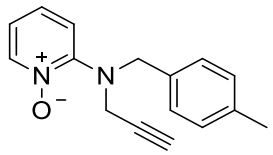
2-(Allyl(prop-2-yn-1-yl)amino)pyridine *N*-oxide 653



2-(Allylamino)pyridine-*N*-oxide **651** (300 mg, 2.0 mmol, 1.0 eq.) was dissolved in THF (10 mL, 0.2 M) and the mixture was cooled to -78 °C. ^{n}BuLi (2.33 M in hexane, 0.90 mL, 1.0 eq.) was added and the reaction mixture was stirred for 20 minutes before propargyl bromide (0.33 mL, 3.0 mmol, 1.5 eq.) was added at the same temperature. The reaction was stirred for 18 hours, then saturated NH_4Cl solution (15 mL) was added and the residue was extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and the mixture was concentrated under reduced pressure. Purification by flash column chromatography [(94:6 (EtOAc:MeOH)] afforded the *N*-oxide **653** as a yellowish viscous oil (151 mg, 40%); IR ν_{max}/cm^{-1} 3147, 2097, 1608, 1499, 1231, 920, 739; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 5.7 Hz, 1H), 7.28-7.20 (m, 1H), 7.05 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.99-6.85 (m, 1H), 5.94 (ddt, *J* = 17.0, 10.1, 6.4 Hz, 1H), 5.38 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.27 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.38 (d, *J* = 2.3 Hz, 2H), 3.97 (d, *J* = 6.4 Hz, 2H), 2.2 (t, *J* = 2.3 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.3 (C), 140.6 (CH), 133.4

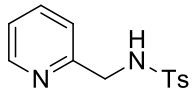
(CH), 126.8 (CH), 119.4 (CH), 118.5 (CH), 117.3 (CH), 78.7 (C), 72.8 (CH_2), 52.6 (CH_2), 37.7 (CH_2); HRMS calcd. for $C_{11}H_{13}N_2O$: 189.1028, found: 189.1022 $[M+H]^+$.

2-((4-Methylbenzyl)(prop-2-yn-1-yl)amino)pyridine *N*-oxide 654



2-((4-Methylbenzyl)amino)pyridine *N*-oxide **652** (360 mg, 1.7 mmol, 1.0 eq.) was dissolved in THF (8 mL, 0.2 M) and the mixture was cooled to -78 °C. ^{n}BuLi (0.85 mL, 2.0 mmol, 1.2 eq.) was added and the reaction mixture was stirred for 20 minutes before propargyl bromide (0.28 mL, 2.5 mmol, 1.5 eq.) was added at the same temperature. The reaction was stirred for 18 hours, then saturated NH_4Cl solution (10 mL) was added and the residue was extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography [94:6 (EtOAc:MeOH)] afforded the *N*-oxide **654** as a dark yellow viscous oil (143 mg, 34%); IR ν_{max}/cm^{-1} 1646, 1600, 1495, 1430, 1227, 1198, 747, 662; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 6.4, 0.8 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.24-7.19 (m, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.93 (td, *J* = 7.4, 1.7 Hz, 1H), 4.51 (s, 2H), 4.24 (d, *J* = 2.3 Hz, 2H), 2.33 (s, 3H), 2.25 (t, *J* = 2.3 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.6 (C), 140.8 (CH), 137.6 (C), 133.2 (C), 129.4 (2 × CH), 129.0 (2 × CH), 127.1 (CH), 118.7 (CH), 117.6 (CH), 78.9 (CH), 73.3 (C), 52.8 (CH_2), 37.8 (CH_2), 21.3 (CH_3); HRMS calcd. for $C_{16}H_{16}N_2O$: 253.1369, found: 253.1359 $[M+H]^+$

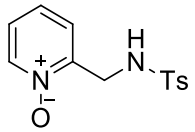
4-Methyl-*N*-(pyridin-2-ylmethyl)benzenesulfonamide 661



A solution of tosyl chloride (381 mg, 2.0 mmol, 1.0 eq.) in THF (2.0 mL, 1.0 M) was added dropwise to a solution of pyridin-2-ylmethanamine **660** (0.2 mL, 2.0 mmol, 1.0 eq.) and NaOH (80 mg, 2.0 mmol, 1.0 eq.) in H_2O (2.0 mL, 1.0 M) at room temperature and the reaction mixture was stirred for 2 hours. The THF was then removed under reduced pressure at which point a white precipitate was formed which was collected by filtration (washed with H_2O, ca. 10 mL). The tosylated derivative **661** was isolated as a white solid and used for the next step without any further purification (266 mg, 51%); mp. 96-97 °C (lit. 92-94 °C); IR ν_{max}/cm^{-1} 3045, 1599, 1330, 1162, 1113, 1091, 1008, 819, 763, 664; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 5.3, 0.7 Hz, 1H), 7.85 (app. td, *J* = 7.8, 1.7 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 6.8, 5.3 Hz, 1H), 7.30-7.20 (m, 2H), 6.25 (t, *J* = 5.8 Hz, 1H), 4.39 (d, *J* = 5.8 Hz, 2H), 2.39 (s, 3H).

Data matches that reported in the literature.[242]

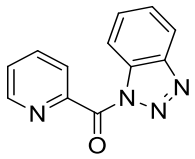
2-((4-Methylphenylsulfonamido)methyl)pyridine *N*-oxide 662



*m*CPBA (30% of H_2O, 207 mg, 1.2 mmol, 1.2 eq.) was dissolved in CH_2Cl_2 (10 mL, 0.1 M) and 4-methyl-*N*-(pyridin-2-ylmethyl)benzenesulfonamide **661** (262 mg, 1.0 mmol, 1.0 eq.) was added successively at room temperature. After 18 hours stirring at reflux, the reaction mixture

was cooled to room temperature and saturated $NaHCO_3$ solution (10 mL) was added. The residue was extracted with CH_2Cl_2 (3 × 10 mL), the extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography [95:5 (CH_2Cl_2:MeOH)] afforded the *N*-oxide **662** as a white oil (206 mg, 74%); IR ν_{max}/cm^{-1} 2994, 2767, 2688, 1432, 1328, 1150, 1090, 814, 774, 659; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 3.2 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.36-7.09 (m, 5H), 6.56 (bs, 1H), 4.33 (bs, 2H), 2.37 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.6 (C), 139.7 (C), 137.1 (C), 134.2 (CH), 129.8 (2 × CH), 127.4 (CH), 127.0 (2 × CH), 126.4 (CH), 125.4 (CH), 44.0 (CH_2), 21.6 (CH_3); HRMS (ES) calcd. for $C_{13}H_{15}O_3SN_2$: 279.0803, found: 279.0805 $[M+H]^+$.

(1*H*-Benzo[d][1,2,3]triazol-1-yl)(pyridin-2-yl)methanone 670



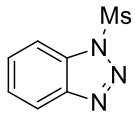
Following a procedure reported by Katritzky and co-workers,[243] picolinic acid (246 mg, 2.0 mmol, 1.0 eq.) and 1-(methylsulfonyl)-1*H*-benzo[d][1,2,3]triazole **672** (394 mg, 2.0 mmol, 1.0 eq.) were dissolved in THF (5 mL, 0.4 M)*. Et_3N (0.4 mL, 2.9 mmol, 1.4 eq.) was then added and the reaction mixture was refluxed for 18 hours. The solution was cooled to room temperature and the solvent was evaporated under reduced pressure. Then the residue was dissolved in $CHCl_3$ (20 mL) and washed with H_2O (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Recrystallisation from $CHCl_3$:hexane afforded the pyridine derivative **670** as a beige solid (300 mg, 67%); mp. 99-100 °C (lit. 9 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.89 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.40 (dt, *J* = 8.3, 0.9 Hz, 1H), 8.19 (dt,

J = 8.3, 0.9 Hz, 1H), 8.14 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.98 (td, *J* = 7.8, 1.7 Hz, 1H), 7.74 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.64-7.60 (m, 1H), 7.60-7.54 (m, 1H).

*Gradient THF was used; no conversion was observed when dry THF was used instead.

Data matches that reported in the literature.[243]

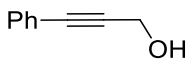
1-(Methylsulfonyl)-1*H*-benzo[d][1,2,3]triazole 672



Following a procedure reported by Katritzky and co-workers,[243] a solution of benzotriazole (1.19 g, 10.0 mmol, 1.0 eq.) and pyridine (1.20 g, 16.0 mmol, 1.6 eq.) in toluene (12 mL, 0.8 M) was cooled to 0 °C. A solution of mesyl chloride (0.90 mL, 12.0 mmol, 1.2 eq.) in toluene (3 mL) was then added dropwise and the reaction mixture was stirred at room temperature for 24 hours. H_2O (10 mL) was then added, the organic residue was extracted with EtOAc (10 mL), washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Recrystallisation from toluene afforded the triazole derivative **672** as colourless crystals (1.08 g, 55%); mp 111-112 °C (lit. 112-113 °C); IR ν_{max}/cm^{-1} 1380, 1310, 1274, 1178, 1152, 1040, 942, 911, 765, 747; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17 (dt, *J* = 8.3, 0.9 Hz, 1H), 8.02 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.69 (ddd, *J* = 8.4, 7.1, 1.1 Hz, 1H), 7.54 (ddd, *J* = 8.3, 7.1, 1.0 Hz, 1H), 3.51 (s, 3H).

Data matches that reported in the literature.[243]

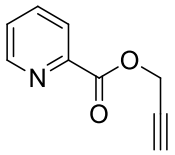
3-Phenylprop-2-yn-1-ol 674



The alkyne was prepared according to **GP3** using iodobenzene (0.33 mL, 3.0 mmol) and propargyl alcohol (0.21 mL, 3.6 mmol), stirring for 16 hours. Purification by flash column chromatography [90:10- 80:20 (hexane: EtOAc) afforded the alkyne **674** as an orange oil (397 mg, 99%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49-7.40 (m, 2H), 7.37-7.28 (m, 3H), 4.50 (s, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 131.8 (2 × CH), 128.7 (CH), 128.5 (2 × CH), 122.7 (C), 87.3 (C), 85.9 (C), 51.8 (CH_2).

Data matches that reported in the literature.[244]

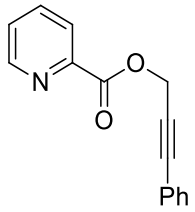
Prop-2-yn-1-yl picolinate 675



A solution of propargyl alcohol **673** (0.95 mL, 4.2 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) was added dropwise to a solution of picolinic acid (616 mg, 5.0 mmol, 1.2 eq.), DCC (1.0 g, 5.0 mmol, 1.2 eq.) and DMAP (611 mg, 5.0 mmol, 1.2 eq.) in CH_2Cl_2 (5 mL, 1.0 M) at room temperature. The reaction mixture was stirred at room temperature for 18 hours, then diluted with hexane (10 mL) and filtered through a pad of Celite® (ca 2 cm, washing with EtOAc). Purification by flash column chromatography [50:50 (hexane:EtOAc)] afforded the ester **675** as a thick, colourless oil (632 mg, 93%); IR ν_{max}/cm^{-1} 3155, 2933, 2119, 1739, 1306, 1239, 1133, 1084, 960, 737, 693; ^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.78 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.86 (td, *J* = 7.8, 1.7 Hz, 1H), 7.51 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 5.00 (d, *J* = 2.5 Hz, 2H), 2.53 (t, *J* = 2.5

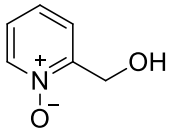
Hz, 1H); ^{13}C-NMR ($CDCl_3$, 101MHz): δ 164.5 (C), 150.1 (CH), 147.5 (C), 137.2 (CH), 127.4 (CH), 125.6 (CH), 77.4 (C), 75.6 (CH), 53.3 (CH_2); HRMS (ES) calcd. for $C_9H_8O_2N$: 162.0555, found: 162.0553 $[M+H]^+$.

3-Phenylprop-2-yn-1-yl picolinate 676



A solution of 3-phenylprop-2-yn-1-ol **674** (264 mg, 2.0 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) was added dropwise at room temperature to a solution of picolinic acid (295 mg, 2.4 mmol, 1.2 eq.), DCC (495 mg, 2.4 mmol, 1.2 eq.) and DMAP (293 mg, 2.4 mmol, 1.2 eq.) in CH_2Cl_2 (2.4 mL, 1.0 M). The reaction mixture was stirred at room temperature for 18 hours, then diluted with hexane (10 mL) and filtered through a pad of Celite® (ca 2 cm, washing with EtOAc). Purification by flash column chromatography [50:50 (hexane:EtOAc)] afforded the ester **676** as a yellow oil (460 mg, 81%); IR ν_{max}/cm^{-1} 1721, 1443, 1308, 1287, 1247, 1115, 952, 752, 691; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.79 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.20 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.87 (td, *J* = 7.8, 1.8 Hz, 1H), 7.54-7.50 (m, 1H), 7.50-7.44 (m, 2H), 7.37-7.30 (m, 3H), 5.25 (s, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.7 (C), 150.1 (CH), 147.8 (C), 137.2 (CH), 132.1 (2 × CH), 128.9 (CH), 128.4 (2 × CH), 127.3 (CH), 125.6 (CH), 122.3 (C), 87.1 (C), 82.8 (C), 54.3 (CH_2); HRMS (ES) calcd for $C_{15}H_{12}NO_2$: 238.0868, found: 238.0856 $[M+H]^+$.

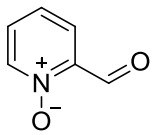
2-(Hydroxymethyl)pyridine *N*-oxide 678



Following a procedure reported by Ubink and co-workers,[245] *m*CPBA (3.00 g, 12.0 mmol, 1.2 eq.) and pyridin-2-ylmethanol **677** (1.00 mL, 10.0 mmol, 1.0 eq.) were dissolved in $CHCl_3$ (16 mL, 0.6 M) at 0 °C and the mixture was stirred at room temperature for 18 hours. Paraformaldehyde (220 mg, 7.0 mmol, 0.7 eq.) was added to quench the remaining *m*CPBA and the mixture was continued stirring for 2 hours. Ammonia gas was then bubbled through the solution for 15 minutes followed by treatment with $MgSO_4$. Then, a continuous extraction cartridge was applied, the residue was washed with CH_2Cl_2 (100 mL) and extracted over 2 days. The combined organic fractions were concentrated under reduced pressure and the crude mixture was purified with flash column chromatography [95:5 (CH_2Cl_2:MeOH)] to afford the *N*-oxide **678** as a white solid (1.25 g, 98%); mp. 132-133 °C (lit 130-132 °C); IR ν_{max}/cm^{-1} 3080, 2831, 1485, 1436, 1422, 1352, 1280, 1211, 1195, 1106, 1066, 841, 751, 694; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 6.3 Hz, 1H), 7.44-7.37 (m, 2H), 7.37-7.27 (m, 1H), 4.83 (s, 2H).

Data matches that reported in the literature.[245]

2-Formylpyridine *N*-oxide 679

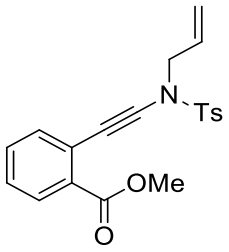


Following a procedure reported by Jørgensen and co-workers,[246] *N*-oxide **678** (500 mg, 4.0 mmol, 1.0 eq.) and MnO_2 (3.00.g, 34.0 mmol, 8.6 eq.) were suspended in 1,4-dioxane (34 mL,

0.1 M) and the reaction was heated at 90 °C for 2 hours. The mixture was filtered through a pad of Celite® (ca 5 cm) and the filter cake was washed with hot 1,4-dioxane (20 mL) and hot EtOH (20 mL). The filtrate was concentrated under reduced pressure, the resulting residue was redissolved in $CHCl_3$ (20 mL) and treated with Amberlyst 15 for 10 minutes. The resin was filtered and the filtrate was evaporated under reduced pressure to give the desired aldehyde **679** as a yellow solid (216 mg, 44%); mp. 76-78 °C (lit. 75-77 °C); IR ν_{max}/cm^{-1} 1690, 1601, 1432, 1294, 1233, 1182, 1013, 851, 766, 701; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.22 (d, *J* = 6.4 Hz, 1H), 7.83 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.54-7.41 (m, 1H), 7.33 (app. t, *J* = 7.8 Hz, 1H).

Data matches that reported in the literature.[246]

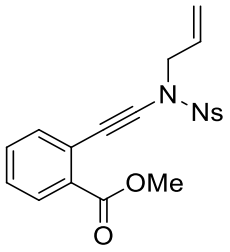
Methyl 2-(((*N*-allyl-4-methylphenyl)sulfonamido)ethynyl)benzoate 695



Prepared according to **GP19** using methyl 2-(2,2-dibromovinyl)benzoate (700 mg, 2.2 mmol) **692** and sulfonamide **693** (317 mg, 1.5 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the ynamide **695** as a light yellow oil (440 mg, 79%); IR ν_{max}/cm^{-1} 2226, 1717, 1362, 1251, 1167, 1075, 925, 755, 667; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97-7.85 (m, 3H), 7.43-7.38 (m, 2H), 7.37-7.28 (m, 3H), 5.85 (ddt, *J* = 16.8, 10.1, 6.3 Hz, 1H), 5.33 (dd, *J* = 16.8, 1.1 Hz, 1H), 5.25 (dd, *J* = 10.1, 1.1 Hz, 1H), 4.10 (d, *J* = 6.3 Hz, 2H), 3.92 (s, 3H), 1.56 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.4 (C), 124.3 (C), 124.0 (C), 144.8 (C), 135.1 (C), 132.9 (CH), 131.7 (CH), 131.1 (CH), 130.5 (CH), 129.9 (2 × CH), 127.9 (2 × CH), 126.8 (CH), 120.2 (CH_2), 77.4 (C), 71.2 (C),

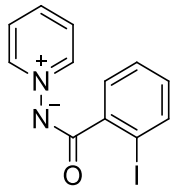
54.7 (CH_2), 52.4 (CH_3), 21.8 (CH_3); HRMS (ES) calcd for $C_{20}H_{19}NO_4SNa$: 392.0932, found: 392.0927.

Methyl 2-(((*N*-allyl-4-nitrophenyl)sulfonamido)ethynyl)benzoate 696



Prepared according to **GP19** using methyl 2-(2,2-dibromovinyl)benzoate **692** (1.40 g, 4.5 mmol) and sulfonamide **694** (724 mg, 3.0 mmol). Purification by flash column chromatography afforded the desired ynamide **696** as a light yellow oil (968 mg, 81%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.0 Hz, 2H), 8.29 (d, *J* = 9.0 Hz, 2H), 7.99-7.92 (m, 1H), 7.47-7.41 (m, 2H), 7.32 (ddd, *J* = 8.0, 6.5, 2.3 Hz, 1H), 5.83 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H), 5.35 (ddd, *J* = 16.9, 2.5, 1.2 Hz, 1H), 5.27 (ddd, *J* = 10.1, 2.5, 1.2 Hz, 1H), 4.18 (dt, *J* = 6.4, 1.2 Hz, 2H), 3.93 (s, 3H). *(The ynamide proved unstable at room temperature and was degraded very quickly. No further data could be acquired.)*

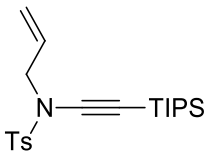
(2-Iodobenzoyl)(pyridin-1-ium-1-yl)amide 704



Prepared according to **GP4** using *N*-aminopyridinium iodide **214** (444 mg, 2.0 mmol). The ylide **704** was afforded as yellow crystals (507 mg, 78%) and used for the next step without further purification; IR ν_{max}/cm^{-1} 3105, 3071, 1574, 1548, 1471, 1321, 1171, 1015, 899, 763, 741, 668;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.93-8.85 (m, 2H), 8.02-7.94 (m, 1H), 7.87 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.78-7.70 (m, 2H), 7.60 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.37 (td, *J* = 7.6, 1.1 Hz, 1H), 7.08-7.00 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.9 (C), 144.2 (C), 143.2 (CH), 139.7 (CH), 137.7 (CH), 129.9 (CH), 128.8 (2 × CH), 128.1 (CH), 126.4 (2 × CH), 94.7 (C); HRMS (ES) calcd. for $C_{12}H_{10}ON_2I$: 324.9838, found: 324.9841 $[M+H]^+$.

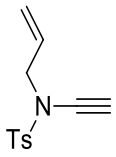
_N_-Allyl-4-methyl-_N_-((triisopropylsilyl)ethynyl)benzenesulfonamide 705a



Prepared according to **GP19** using (bromoethynyl)triisopropylsilane (1.40 g, 5.5 mmol) and sulfonamide **693** (1.10 g, 5.0 mmol). Purification by flash column chromatography [95:5 (hexane:EtOAc)] afforded the ynamide as a white solid (1.80 g, 93%); mp. 34-35 °C (lit. 46-48 °C); IR ν_{max}/cm^{-1} 2943, 2865, 2166, 1370, 1170, 1090, 883, 751, 663; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.73 (ddt, *J* = 16.5, 10.1, 6.4 Hz, 1H), 5.27-5.17 (m, 2H), 3.96 (dt, *J* = 6.4, 1.2 Hz, 2H), 2.45 (s, 3H), 1.55-1.52 (m, 3H), 1.02 (s, 18H).

Data matches that reported in the literature.[247]

_N_-Allyl-_N_-ethynyl-4-methylbenzenesulfonamide 705

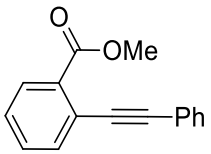


TBAF (1 M solution in THF, 9.3 mL, 9.3 mmol, 2.0 eq.) was added to the solution of ynamide **705a** (1.83 g, 4.7 mmol, 1.0 eq.) in THF (47 mL, 0.1 M) at -78 °C and the mixture was stirred at

room temperature for 2 hours. Brine (50 mL) was then added and the residue was extracted with Et_2O (3 × 50 mL). The solvent was removed under reduced pressure to give the terminal ynamide **705** as off-white crystals (728 mg, 67%) and used for the next step without further purification; mp. 64-66 °C (lit. 68-70 °C); IR ν_{max}/cm^{-1} 3272, 2140, 1593, 1352, 1159, 1087, 920, 739, 710, 660; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.72 (ddt, *J* = 16.5, 11.5, 6.3 Hz, 1H), 5.26 (ddd, *J* = 11.5, 2.3, 1.2 Hz, 1H), 5.21 (ddd, *J* = 16.5, 2.3, 1.2 Hz, 1H), 3.96 (dt, *J* = 6.3, 1.2 Hz, 2H), 2.73 (s, 1H), 2.46 (s, 3H).

Data matches that reported in the literature.[247]

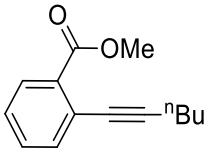
Methyl 2-(phenylethynyl)benzoate 707



Prepared according to **GP3** using methyl 2-iodobenzoate **706** (786 mg, 3.0 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the alkyne **707** as a brown liquid (584 mg, 82%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00-7.95 (m, 1H), 7.68-7.63 (m, 1H), 7.61-7.56 (m, 2H), 7.50 (app. td, *J* = 7.6, 1.5 Hz, 1H), 7.42-7.34 (m, 4H), 3.97 (s, 3H).

Data matches that reported in the literature.[248]

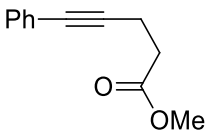
Methyl 2-(hex-1-yn-1-yl)benzoate 708



Prepared according to **GP3** using methyl 2-iodobenzoate **706** (786 mg, 3.0 mmol). Purification by flash column chromatography [90:10- 80:20 (hexane:EtOAc)] afforded the alkyne **708** as a brown liquid (648 mg, 99%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.42 (td, *J* = 7.7, 1.1 Hz, 1H), 7.32 (td, *J* = 7.8, 1.2 Hz, 1H), 3.92 (s, 3H), 2.48 (t, *J* = 7.0 Hz, 2H), 1.69-1.44 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.5 (C), 134.2 (CH), 132.0 (C), 131.4 (CH), 130.1 (CH), 127.1 (CH), 124.5 (C), 96.0 (C), 79.2 (C), 52.0 (CH_3), 30.8 (CH_2), 22.0 (CH_2), 19.5 (CH_2), 13.7 (CH_3).

Data matches that reported in the literature.[249]

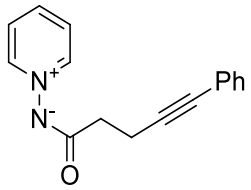
Methyl 5-phenylpent-4-ynoate 713



Prepared according to **GP3** using iodobenzene (0.16 mL, 1.5 mmol, 1.0 eq.). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the alkyne **713** as an orange oil (200 mg, 74%); IR ν_{max}/cm^{-1} 2962, 2854, 1690, 1590, 1478, 1239, 1121, 886, 815; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41-7.35 (m, 2H), 7.31-7.26 (m, 3H), 3.72 (s, 3H), 2.78-2.70 (m, 2H), 2.68-2.61 (m, 2H).

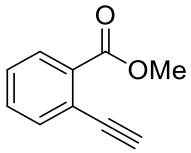
Data matches that reported in the literature.[250]

(5-Phenylpent-4-ynoyl)(pyridin-1-ium-1-yl)amide 714



Prepared according to **GP4** using *N*-aminopyridinium iodide **214** (178 mg, 0.8 mmol). Purification by flash column chromatography [95:5 (CH_2Cl_2:MeOH)] afforded the ylide **714** as a brown solid (100 mg, 50%); mp. 114-116 °C; IR ν_{max}/cm^{-1} 1556, 1470, 1368, 1259, 757, 732, 671, 691; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 5.7 Hz, 2H), 7.99 (t, *J* = 7.7 Hz, 1H), 7.76-7.65 (m, 2H), 7.46-7.37 (m, 2H), 7.33-7.15 (m, 3H), 2.84 (t, *J* = 7.3 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (C), 143.5 (2 × CH), 138.2 (CH), 131.6 (2 × CH), 128.1 (2 × CH), 127.5 (CH), 126.3 (2 × CH), 119.2 (C), 90.2 (C), 80.7 (C), 35.3 (CH_2), 16.6 (CH_2); HRMS (ES) calcd. for $C_{16}H_{15}ON_2$: 251.1184, found: 251.1178 $[M+H]^+$.

Methyl 2-ethynylbenzoate 669

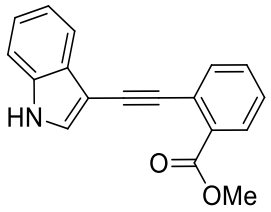


Prepared according to a modified **GP15** using methyl 2-((trimethylsilyl)ethynyl)benzoate (2.30 gr, 9.1 mmol, 1.0 eq.) and K_2CO_3 (690 mg, 5.0 mmol, 0.5 eq.), stirring for 20 minutes. The terminal alkyne **669** was isolated as a colourless liquid (770 mg, 51%) and used for the next step without further purification; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.48 (app. td, *J* = 7.8, 1.5 Hz, 1H), 7.41 (app. td, *J* = 7.7, 1.4 Hz, 1H), 3.93 (s,

3H), 3.40 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.8 (C), 135.1 (CH), 132.7 (C), 131.9 (CH), 130.4 (CH), 128.6 (CH), 122.8 (C), 82.4 (CH), 82.2 (C), 52.3 (CH_3).

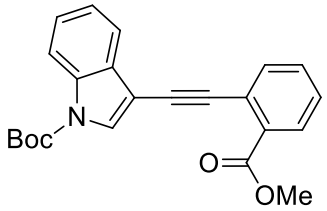
Data matches that reported in the literature.[251]

Methyl 2-((1*H*-indol-3-yl)ethynyl)benzoate 716



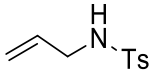
Prepared according to **GP3** using 3-iodo-1*H*-indole **251** (972 mg, 4.0 mmol). Purification by flash column chromatography [85:25 (hexane:EtOAc)] afforded the indole derivative **716** as a brown viscous oil (574 mg, 52%); IR ν_{max}/cm^{-1} 1722, 1597, 1493, 1443, 1291, 1249, 1077, 963, 752, 689; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.34 (bs, NH), 7.98 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.96-7.91 (m, 1H), 7.68 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.53 (d, *J* = 2.7 Hz, 1H), 7.48 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.43-7.36 (m, 2H), 7.28-7.24 (m, 2H), 3.99 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.1 (C), 135.4 (C), 133.4 (CH), 131.8 (CH), 131.4 (C), 130.6 (CH), 128.8 (C), 128.4 (CH), 127.2 (CH), 124.9 (C), 123.3 (CH), 121.1 (CH), 120.4 (CH), 111.5 (CH), 99.9 (C), 90.4 (C), 88.8 (C), 52.3 (CH_3); HRMS (ES) calcd for $C_{18}H_{13}NO_2Na$: 298.0844, found: 298.0842.

Tert-butyl 3-((2-(methoxycarbonyl)phenyl)ethynyl)-1_H_-indole-1-carboxylate 717



Prepared according to a **GP3** using *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate **715** (686 mg, 2.0 mmol, 1.0 eq.). Purification by flash column chromatography [80:20 (hexane: EtOAc) afforded the alkyne **717** as an orange oil (681 mg, 91%); IR ν_{max}/cm^{-1} 2210, 1723, 1453, 1369, 1237, 1154, 1087, 1071, 755, 702; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.6 Hz, 1H), 8.00 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.91-7.85 (m, 2H), 7.70 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.52 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43-7.31 (m, 3H), 3.98 (s, 3H), 1.69 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.9 (C), 144.8 (C), 137.4 (C), 134.6 (CH), 131.6 (CH), 131.3 (C), 131.2 (C), 131.1 (CH), 130.9 (C), 129.6 (C), 129.3 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 126.9 (C), 126.4 (CH), 121.0 (C), 111.7 (CH), 52.4 (CH_3), 29.9 (C), 25.6 (3 × CH_3); HRMS (ES) calcd for $C_{23}H_{21}NO_4Na$: 398.1368, found: 398.1366.

_N_-Allyl-4-methylbenzenesulfonamide 693

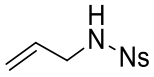


Allyl amine (2.20 mL, 30.0 mmol, 1.5 eq.), tosyl chloride (3.80 g, 20.0 mmol, 1.0 eq.) and pyridine (3.20 mL, 40.0 mmol, 2.0 eq.) were dissolved in CH_2Cl_2 (50 mL, 0.25 M) at 0 °C and the mixture was stirred at room temperature for 24 hours. H_2O (50 mL)was then added, the two phases were separated and the organic fraction was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the sulfonamide **693** as a pale yellow solid (5.01 g, 79%) which was used without further purification; mp. 66-68 °C (lit 66-67 °C); IR ν_{max}/cm^{-1} 3246,

1423, 1317, 1157, 1093, 876, 810, 665; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.72 (ddt, *J* = 16.8, 10.2, 5.8 Hz, 1H), 5.17 (ddd, *J* = 16.8, 2.8, 1.6 Hz, 1H), 5.10 (ddd, *J* = 10.2, 2.8, 1.3 Hz, 1H), 4.36 (bs, NH), 3.59 (bt, *J* = 4.7 Hz, 2H), 2.43 (s, 3H).

Data matches that reported in the literature.[252]

_N_-Allyl-4-nitrobenzenesulfonamide 694

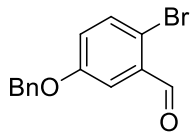


Allyl amine (1.50 mL, 20.0 mmol, 1.0 eq.), nosyl chloride (4.90 g, 22 mmol, 1.2 eq.) and pyridine (1.77 mL, 22.0 mmol, 1.2 eq.) were dissolved in CH_2Cl_2 (50 mL, 0.4 M) at 0 °C and the mixture was stirred at room temperature for 18 hours. 6.0 M NaOH solution (20 mL) was then added, the two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL).The aqueous layer was collected, acidified by slow addition of conc. HCl until the pH = 2 at which point a yellow solid crashed out. The solid was collected by filtration, washed with H_2O (ca 10 mL) and dried under reduced pressure (0.4 mbar) to give the sulfonamide **694** as a yellow solid (3.15 gr, 65%) that was used without further purification; mp. 113-114 °C (lit. 113-114 °C); IR ν_{max}/cm^{-1} 3255, 1521, 1345, 1310, 1158, 1088, 1047, 851, 739, 681; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.06 (d, *J* = 9.0 Hz, 2H), 5.71 (ddt, *J* = 17.0, 10.2, 5.8 Hz, 1H), 5.23–5.09 (m, 2H), 4.68 (t, *J* = 5.9 Hz, 1H), 3.69 (tt, *J* = 6.1, 1.5 Hz, 2H).

Data matches that reported in the literature.[253]

5.4.3 Compounds in Chapter 4

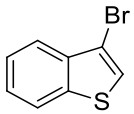
5-(Benzyloxy)-2-bromobenzaldehyde 958



A suspension of 3-(benzyloxy)benzaldehyde **957** (1.40 g, 6.6 mmol, 1.0 eq.) and NaOAc (3.71 g, 44.8 mmol, 6.8 eq.) in CH_2Cl_2 (20 mL, 0.3 M) was cooled to 0 °C. Bromine (1.7 mL, 33.4 mmol, 5.0 eq.) was added dropwise over 4 minutes and the reaction mixture was stirred at room temperature for additional 5 hours. The mixture was then cooled to 0 °C, water (ca. 10 mL) and saturated $Na_2S_2O_3$ solution (ca. 10 mL) were added until the solution turned light yellow. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x ca. 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (ca. 60 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography [95:5 (hexane:EtOAc)] afforded the bromide **958** as a white solid (900 mg, 48%); mp. 44-46 °C; IR ν_{max}/cm^{-1} 3012, 2940, 2864, 1678, 1590, 1465, 1384, 1310, 1233, 1162, 1005, 740, 701; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 3.2 Hz, 1H), 7.44-7.33 (m, 5H), 7.10 (dd, *J* = 8.8, 3.2 Hz, 1H), 5.10 (s, 2H).

Data matches that reported in the literature.[254]

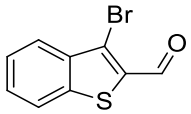
3-Bromobenzo[b]thiophene 996



Benzothiophene **995** (0.6 mL, 5.0 mmol, 1.0 eq.) was suspended between AcOH (5 mL) and $CHCl_3$ (5 mL) and the mixture was cooled to 0 °C. NBS (1.1 g, 6.0 mmol, 1.2 eq.) was added in one portion and the reaction was stirred at room temperature for 16 hours. Saturated $Na_2S_2O_3$ solution (10 mL) was added, the two phases were separated and the aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic fractions were washed with saturated Na_2CO_3 solution (1 × 30 mL), H_2O (1 × 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was dissolved in Hexane and filtered through a pad of silica (ca 5 cm, eluting with hexane). The filtrate was concentrated under reduced pressure to give the brominated benzothiophene **996** as a pale yellow oil (956 mg, 96%) which was used in the next step without further purification; IR ν_{max}/cm^{-1} 3105, 3060, 1421, 1317, 1254, 1061, 929, 751, 725, 699; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92-7.87 (m, 1H), 7.86-7.81 (m, 1H), 7.47-7.43 (m, 1H), 7.36 (s, 1H), 7.38-7.32 (m, 1H).

Data matches that reported in the literature.[255]

3-Bromobenzo[b]thiophene-2-carbaldehyde 997

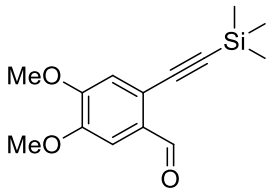


3-Bromobenzo[b]thiophene **996** (426 mg, 2.0 mmol, 1.0 eq.) was added to a solution of LiHMDS in THF (2.6 mL, 2.6 mmol, 1.0 M, 1.3 eq.) at 0 °C and the resulting mixture was stirred at this

temperature for 30 minutes. Dry DMF (175 mg, 2.4 mmol, 1.2 eq.) was added and the reaction was stirred at room temperature for 3 hours. Saturated NH_4Cl solution (3 mL) was added, the two phases were separated and the aqueous phase was extracted with Hexane (3 × 5 mL). The combined organic extracts were washed with Brine (1 × 20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] afforded the aldehyde **997** as an orange solid (245 mg, 51%); mp. 123-124 °C (lit. 123-124 °C); IR ν_{max}/cm^{-1} 1458, 1420, 1316, 1253, 1060, 1017, 928, 820, 149, 722, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.05-8.00 (m, 1H), 7.91-7.86 (m, 1H), 7.61-7.56 (m, 1H), 7.56-7.50 (m, 1H).

Data matches that reported in the literature.[256]

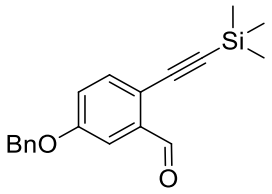
4,5-Dimethoxy-2-((trimethylsilyl)ethynyl)benzaldehyde 915



Prepared according to **GP11** using 2-bromo-4,5-dimethoxybenzaldehyde **913** (2.2 g, 9.0 mmol), stirring at 50 °C for 20 minutes. Purification by flash column chromatography [95:5 (hexane:EtOAc)] afforded the internal alkyne **915** as a brown solid (2.1 g, 87%); mp. 114-115 °C (lit. 115-116 °C); IR ν_{max}/cm^{-1} 2960, 2151, 1684, 1592, 1506, 1281, 1220, 1108, 1001, 845; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.38 (s, 1H), 6.98 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 0.28 (s, 9H).

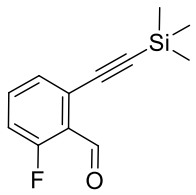
Data matches that reported in the literature.[257]

5-(Benzyloxy)-2-((trimethylsilyl)ethynyl)benzaldehyde 959



Prepared according to **GP11** using 5-(benzyloxy)-2-bromobenzaldehyde **958** (880 mg, 3.0 mmol), stirring at 50 °C for 2 hours. Purification by flash column chromatography [95:5 (hexane:EtOAc)] afforded the internal alkyne **959** as a brown solid (860 mg, 93%); mp. 120-122 °C; IR ν_{max}/cm^{-1} 2960, 2845, 2154, 1694, 1600, 1489, 1277, 1250, 1025, 842, 760; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.45-7.32 (m, 5H), 7.16 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.12 (s, 2H), 0.27 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 191.8 (CH), 159.1 (C), 137.8 (C), 136.1 (C), 135.1 (CH), 128.8 (2 × CH), 128.4 (CH), 127.7 (2 × CH), 122.2 (CH), 119.9 (C), 110.8 (CH), 100.8 (C), 100.2 (C), 70.4 (CH_2), 0.01 (3 × CH_3); HRMS (ES) calcd. for $C_{19}H_{21}O_2Si$: 309.1311, found: 309.1298 $[M+H]^+$.

2-Fluoro-6-((trimethylsilyl)ethynyl)benzaldehyde 964

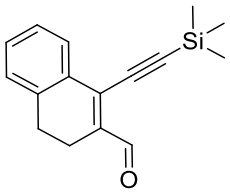


Prepared according to **GP11** using 2-bromo-6-fluorobenzaldehyde **963** (406 mg, 2.0 mmol), stirring at 65 °C for 2 hours. Purification by flash column chromatography [100:0- 95:5 (hexane:EtOAc)] afforded the internal alkyne **964** as a colourless oil (268 mg, 61%); IR ν_{max}/cm^{-1}

2961, 1788, 1706, 1601, 1465, 1251, 1006, 846; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.53-7.45 (m, 2H), 7.38 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.15-7.08 (m, 1H), 0.28 (s, 9H).

Data matches that reported in the literature.[258]

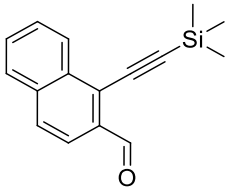
1-((Trimethylsilyl)ethynyl)-3,4-dihydronaphthalene-2-carbaldehyde 972



Prepared according to a **GP11** using 3,4-dihydronaphthalen-1(2*H*)-one **971** (4.0 mL, 30.0 mmol), stirring at 60 °C for 3 hours. Purification by flash column chromatography (hexane) afforded the internal alkyne **972** as a yellow oil (4.11 g, 70%); IR ν_{max}/cm^{-1} 2949, 2840, 2150, 1659, 1364, 1290, 1242, 1160, 867, 840, 761, 729; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.85-7.80 (m, 1H), 7.36-7.30 (m, 2H), 7.22-7.17 (m, 1H), 2.81 (t, *J* = 8.0 Hz, 2H), 2.59 (t, *J* = 8.0 Hz, 2H), 0.31 (s, 9H).

Data matches that reported in the literature.[259]

1-((Trimethylsilyl)ethynyl)-2-naphthaldehyde 973

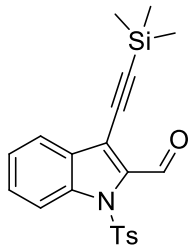


1-((Trimethylsilyl)ethynyl)-3,4-dihydronaphthalene-2-carbaldehyde **972** (1.3 g, 5.0 mmol, 1.0 eq.) and DDQ (1.7 g, 7.0 mmol, 1.7 eq.) were dissolved in dry toluene (25 mL, 0.2 M) and the mixture was heated to reflux at 120 °C for 30 hours under an argon atmosphere. The mixture

was cooled to room temperature, filtered through a silica pad (ca. 5 cm) and the filtrate was washed thoroughly with saturated Na_2CO_3 solution (2 ×) and finally with water (2 ×). The organic layer was collected, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [98:2 (hexane:EtOAc)] gave the internal alkyne **973** as a pink solid (844 mg, 67%); mp. 92-93 °C; IR ν_{max}/cm^{-1} 2960, 2152, 1681, 1331, 1250, 1230, 1069, 870, 840, 736; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.79 (d, *J* = 0.8 Hz, 1H), 8.54-8.47 (m, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.91-7.84 (m, 2H), 7.70-7.63 (m, 2H), 0.37 (s, 9H).

Data matches that reported in the literature.[258]

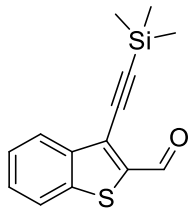
1-Tosyl-3-((trimethylsilyl)ethynyl)-1*H*-indole-2-carbaldehyde 991



Prepared according to a modified **GP11** using 3-iodo-1-tosyl-1H-indole-2-carbaldehyde **990** (1.3 g, 3.0 mmol, 1.0 eq.), in a mixture of degassed Et_3N (7 mL) and dry DMF (1.5 mL) stirring for 1 hour at room temperature. Purification by flash column chromatography [95:5- 90:10 (hexane:EtOAc)] afforded the internal alkyne **991** as an orange solid (902 mg, 76%); mp. 120-122 °C; IR ν_{max}/cm^{-1} 1682, 1523, 1265, 1175, 1089, 844, 735, 701, 672; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 7.77-7.69 (m, 3H), 7.56 (ddd, *J* = 8.6, 7.2, 1.3 Hz, 1H), 7.41-7.34 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 2.35 (s, 3H), 0.30 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 181.2 (CH), 145.8 (C), 137.9 (C), 137.7 (C), 135.0 (C), 130.1 (2 × CH), 129.7 (CH), 129.6 (C), 127.2 (2 ×

CH), 125.1 (C), 125.0 (CH), 122.5 (CH), 115.6 (CH), 107.0 (C), 95.0 (C), 21.8 (CH_3), -0.04 (3 × CH_3); HRMS (ES^+) calcd. for $C_{21}H_{22}NO_3SiS$: 396.1090, found: 396.1093 $[M+H]^+$.

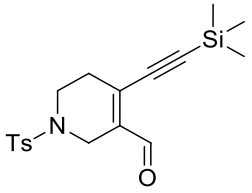
3-((Trimethylsilyl)ethynyl)benzo[b]thiophene-2-carbaldehyde 998



Prepared according to a modified **GP11** using 3-bromobenzo[b]thiophene-2-carbaldehyde **997** (241 mg, 1.0 mmol, 1.0 eq.), stirring at 50 °C for 2 hours. Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the internal alkyne **998** as an orange solid (137 mg, 53%); mp. 80-82 °C (lit. 79-80 °C); IR ν_{max}/cm^{-1} 2960, 1719, 1395, 1251, 985, 843, 733, 701; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.08-8.04 (m, 1H), 7.89-7.84 (m, 1H), 7.58-7.52 (m, 1H), 7.52-7.47 (m, 1H), 0.34 (s, 9H).

Data matches that reported in the literature.[260]

1-Tosyl-4-((trimethylsilyl)ethynyl)-1,2,5,6-tetrahydropyridine-3-carbaldehyde 1007

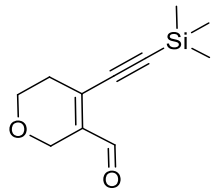


Prepared according to a modified **GP10** using 1-tosylpiperidin-4-one **1003** (7.6 gr, 30.0 mmol). Purification by flash column chromatography [85:15 (Hexane:EtOAc)] afforded the internal alkyne **1007** as an orange oil (852 mg, 8% over 2 steps); IR ν_{max}/cm^{-1} 2960, 2850, 2143, 1672, 1347, 1252, 1162, 992, 961, 843, 735; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.69 (d, *J* = 8.3

Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 3.77 (t, *J* = 2.4 Hz, 2H), 3.19 (t, *J* = 5.7 Hz, 2H), 2.64-2.55 (m, 2H), 2.43 (s, 3H), 0.17 (s, 9H).

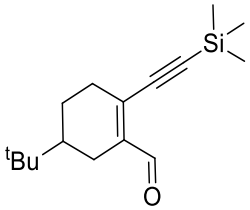
Data matches that reported in the literature.[258]

4-((Trimethylsilyl)ethynyl)-5,6-dihydro-2*H*-pyran-3-carbaldehyde 1008



Prepared according to a modified **GP10** using dihydro-2*H*-pyran-4(3H)-one **1004** (2.8 mL, 30 mmol). Purification by flash column chromatography [100:0- 90:10 (hexane:EtOAc)] afforded the internal alkyne **1008** as a brown oil (700 mg, 11% over two steps); IR ν_{max}/cm^{-1} 2962, 2836, 2143, 1675, 1389, 1252, 1156, 986, 839, 761, 693; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 4.36 (t, *J* = 2.5 Hz, 2H), 3.78 (t, *J* = 5.5 Hz, 2H), 2.48 (tt, *J* = 5.5, 2.5 Hz, 2H), 0.22 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 190.8 (CH), 141.6 (C), 136.6 (C), 106.4 (C), 99.7 (C), 63.6 (CH_2), 63.5 (CH_2), 31.1 (CH_2), 0.23 (3 × CH_3); HRMS (EI) calcd. for $C_{11}H_{17}O_2Si$: 209.0998, found: 209.0993 $[M+H]^+$.

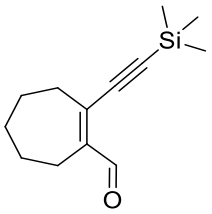
5-(*Tert*-butyl)-2-((trimethylsilyl)ethynyl)cyclohex-1-ene-1-carbaldehyde 1020



Prepared according to **GP10** using 4-(*tert*-butyl)cyclohexanone **1019** (2.30 g, 15 mmol). Purification by flash column chromatography [100:0- 95:5 (hexane:EtOAc)] afforded the terminal alkyne **1020** as an orange oil (1.5 g, 40% over two steps); IR ν_{max}/cm^{-1} 2961, 2140, 1774,

1679, 1250, 845, 761; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 2.48-2.46 (m, 2H), 2.45-2.33 (m, 1H), 1.93-1.69 (m, 2H), 1.25-1.10 (m, 2H), 0.89 (s, 9H), 0.22 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.4 (CH), 144.2 (C), 139.9 (C), 105.1 (C), 101.4 (C), 43.1 (CH_2), 33.8 (CH_2), 32.5 (C), 27.3 (3 × CH_3), 23.9 (CH), 23.4 (CH_2), -0.12 (3 × CH_3); HRMS (ES) calcd. for $C_{16}H_{27}OSi$: 263.1831, found: 263.1838 $[M+H]^+$.

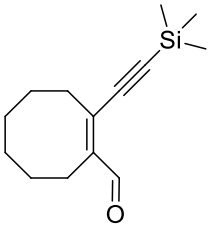
2-((Trimethylsilyl)ethynyl)cyclohept-1-enecarbaldehyde 1029



Prepared according to **GP10** using cycloheptanone **1027** (3.5 mL, 30.0 mmol). Purification by flash column chromatography (hexane) afforded the internal alkyne **1029** as a pale yellow oil (491 mg, 7% over two steps); IR ν_{max}/cm^{-1} 2959, 1288, 2150, 1404, 1249, 1101, 1064, 842 759; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 2.63-2.55 (m, 2H), 2.51-2.44 (m, 2H), 1.84-1.74 (m, 2H), 1.68-1.59 (m, 2H), 1.48-1.39 (m, 2H), 0.22 (s, 9H).

Data matches that reported in the literature.[261]

(Z)-2-((Trimethylsilyl)ethynyl)cyclooct-1-enecarbaldehyde 1030

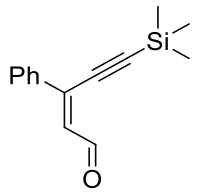


Prepared according to **GP10** using cyclooctanone **1028** (3.8 g, 30.0 mmol). Purification by flash column chromatography (hexane) afforded the internal alkyne **1030** as a pale yellow oil (1.5 g,

21% over two steps); IR ν_{max}/cm^{-1} 2927, 2855, 2140, 1673, 1292, 1250, 1209, 934, 860, 840, 760; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 2.59-2.52 (m, 2H), 2.47-2.39 (m, 2H), 1.83-1.69 (m, 2H), 1.54-1.49 (m, 2H), 1.47-1.40 (m, 4H), 0.22 (s, 9H).

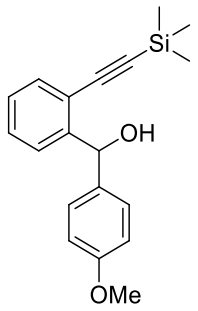
Data matches that reported in the literature.[262]

(*Z*)-3-phenyl-5-(trimethylsilyl)pent-2-en-4-ynal 1044



Prepared according to **GP10** using acetophenone **1043** (0.6 mL, 5.0 mmol), stirring at room temperature for 24 hours (second step). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the internal alkyne **1044** as a colourless oil (968 mg, 85%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.29 (d, *J* = 8.0 Hz, 1H), 7.82-7.73 (m, 2H), 7.49-7.40 (m, 3H), 6.77 (d, *J* = 8.0 Hz, 1H), 0.31 (s, 9H); MS (ES): m/z 229.1 ([M+H], 100%).

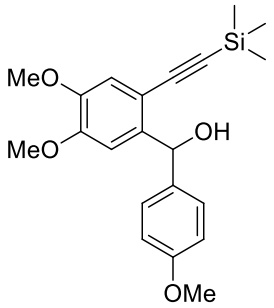
(4-Methoxyphenyl)(2-((trimethylsilyl)ethynyl)phenyl)methanol 919



Prepared according to **GP12** using 2-((trimethylsilyl)ethynyl)benzaldehyde **914** (608 mg, 3.0 mmol) and (4-methoxyphenyl)magnesium bromide **916** (9.0 mmol, 1M solution in THF). Purification by flash column chromatography [95:5 (hexane:EtOAc)] afforded the internal alkyne

919 as a yellow, viscous oil (643 mg, 69%); IR ν_{max}/cm^{-1} 2958, 2154, 1612, 1250, 1173, 1036, 871, 843, 760; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.38-7.30 (m, 3H), 7.21 (app. td, *J* = 7.6, 1.3 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.23 (d, *J* = 4.0 Hz, 1H), 3.78 (s, 3H), 2.50 (d, *J* = 4.0 Hz, 1H), 0.23 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.2 (C), 146.5 (C), 135.5 (C), 133.0 (CH), 129.2 (CH), 128.3 (2 × CH), 127.4 (CH), 126.3 (CH), 121.2 (C), 113.9 (2 × CH), 103.4 (C), 100.4 (C), 73.9 (CH), 55.5 (CH_3), 0.1 (3 × CH_3); HRMS (ES^+) calcd. for $C_{19}H_{22}O_2NaSi$: 333.1279, found: 333.1287 $[M+Na]^+$.

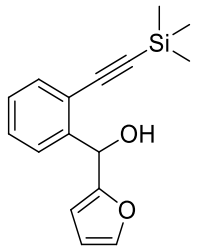
(4,5-Dimethoxy-2-((trimethylsilyl)ethynyl)phenyl)(4-methoxyphenyl)methanol 920



Prepared according to **GP12** using 4,5-dimethoxy-2-((trimethylsilyl)ethynyl)benzaldehyde **915** (786 mg, 3.0 mmol) and (4-methoxyphenyl)magnesium bromide **916** (9.0 mmol, 1M solution in THF). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the internal alkyne **920** as a yellow, viscous oil (1.1 g, 100%); IR ν_{max}/cm^{-1} 3508, 2957, 2146, 1605, 1509, 1249, 1104, 998, 888, 844, 759; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 2H), 7.05 (s, 1H), 6.91 (s, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.21 (d, *J* = 2.9 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 2.47 (d, *J* = 2.9 Hz, 1H), 0.23 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 150.0 (C), 147.8 (C), 140.2 (C), 135.7 (C), 127.9 (2 × CH), 114.9 (CH), 113.8 (2 × CH), 112.8 (C), 109.0 (CH), 103.4 (C),

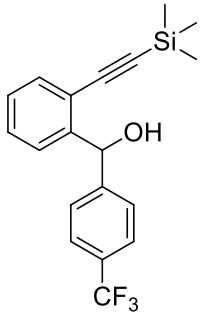
98.4 (C), 73.4 (CH), 56.1 (CH_3), 56.1 (CH_3), 55.4 (CH_3), 0.1 (3 × CH_3); HRMS (ES) calcd. for $C_{21}H_{26}O_4NaSi$: 393.1498, found: 393.1486 $[M+Na]^+$.

Furan-2-yl(2-((trimethylsilyl)ethynyl)phenyl)methanol 921



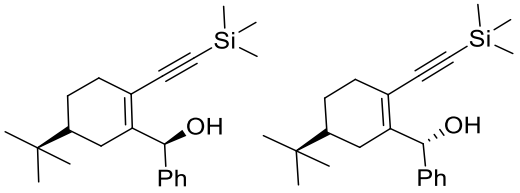
A solution of furan (0.2 mL, 2.5 mmol, 1.0 eq.) in THF (14 mL, 0.2M) was cooled to -78 °C. ^{n}BuLi (1.1 mL, 2.8 mmol, 2.47M in hexane, 1.1 eq.) was added dropwise and the resulting solution was stirred at this temperature for 20 minutes. 2-((Trimethylsilyl)ethynyl)benzaldehyde **914** (576 mg, 2.8 mmol, 1.1 eq.) was added and the reaction mixture was warmed to room temperature and stirred for an additional 2 hours. Saturated NH_4Cl solution (20 mL) was added, the two phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the internal alkyne **921** as a yellow oil (541 mg, 80%); IR ν_{max}/cm^{-1} 3365, 2960, 2156, 1249, 1220, 1009, 864, 838, 757, 734; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62-7.55 (m, 1H), 7.46 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.43-7.34 (m, 2H), 7.30-7.21 (m, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 (d, *J* = 5.1 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 2.72 (d, *J* = 5.1 Hz, 1H), 0.20 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 155.4 (C), 143.1 (C), 142.5 (CH), 132.7 (CH), 129.1 (CH), 127.8 (CH), 126.5 (CH), 121.3 (C), 110.4 (CH), 107.8 (CH), 102.5 (C), 100.6 (C), 68.6 (CH), 0.1 (3 × CH_3); HRMS (EI^+) calcd. for $C_{16}H_{18}O_2Si$: 270.1076, found: 270.1083 $[M]^+$.

(4-(Trifluoromethyl)phenyl)(2-((trimethylsilyl)ethynyl)phenyl)methanol 922



Prepared according to **GP12** using 2-((trimethylsilyl)ethynyl)benzaldehyde **914** (606 mg, 3.0 mmol) and (4-(trifluoromethyl)phenyl)magnesium bromide **918** (9.3 mmol, 1.0 M solution in THF). Purification by flash column chromatography [100:0- 90:10 (hexane:EtOAc)] afforded the internal alkyne **922** as a yellow oil (774 mg, 74%); IR ν_{max}/cm^{-1} 3342, 2962, 2156, 1325, 1165, 1126, 1068, 1017, 843, 760; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.57 (bs, 4H), 7.50-7.42 (m, 2H), 7.35 (app. td, *J* = 7.6, 1.4 Hz, 1H), 7.28-7.21 (m, 1H), 6.32 (d, *J* = 4.4 Hz, 1H), 2.71 (d, *J* = 4.4 Hz, 1H), 0.23 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 146.1 (J_{C-F} = 168.4 Hz, C), 133.0 (CH), 129.2 (CH), 127.7 (CH), 126.8 (2 × 2CH), 126.4 (CH), 125.3 (C), 125.2 (J_{C-F} = 3.6 Hz, C), 125.1 (C), 121.1 (C), 102.9 (C), 100.6 (C), 73.5 (CH), -0.21 (3 × CH_3); HRMS (ES) calcd. for $C_{19}H_{19}OF_3SiNa$: 371.1055, found: 371.1042 $[M+Na]^+$.

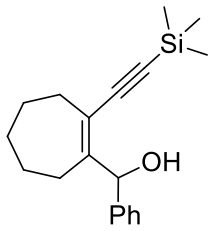
(5-(*Tert*-butyl)-2-((trimethylsilyl)ethynyl)cyclohex-1-en-1-yl)(phenyl)methanol 1022



Prepared according to **GP12** using 5-(*tert*-butyl)-2-((trimethylsilyl)ethynyl)cyclohex-1-ene-1-carbaldehyde **1020** (845 mg, 3.2 mmol,) and PhMgBr (9.66 mmol, 1.0 M solution in THF).

Purification by flash column chromatography [100:0- 98:2 (hexane:EtOAc)] afforded the benzylic alcohol **1022** as an orange oil (740 mg, 79%, dr. 1.6: 1); IR ν_{max}/cm^{-1} 2959, 2138, 1676, 1366, 1249, 1027, 840, 759, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50-7.41 (2 × m, 2H), 7.37-7.30 (2 × m, 2H), 7.28-7.19 (2 × m, 1H), 6.13 and 6.09 (2 × s, 1H), 2.42-2.27 (2 × m, 2H), 2.27-2.13 (2 × m, 1H), 1.27-0.83 (2 × m, 4H), 0.80 (2 × s, 9H), 0.20 and 0.196 (2 x s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 148.1, 148.0 (1 × C), 142.6 and 142.4 (1 × C), 128.2 (2 × s, 2 × CH), 127.1 (2 × s, 1 × CH), 125.6 and 125.4 (2 × CH), 117.1 and 117.0 (1 × C), 105.1 and 105.0 (1 × C), 98.0 and 97.9 (1 × C), 74.9 and 74.5 (1 × CH), 43.7 and 43.5 (1 × CH), 32.3 (2 × s, 1 × C), 31.6 and 31.55 (1 × CH_2), 27.2 and 27.1 (3 × CH_3), 24.6 and 24.5 (1 × CH_2), 23.8 and 23.7 (1 × CH_2), 0.1 (2 × s, 3 × CH_3); HRMS (ES) calcd. for $C_{22}H_{33}OSi$: 341.2301, found: 341.2306 $[M+H]^+$.

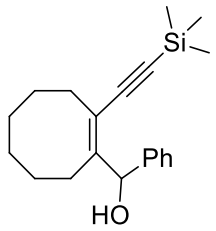
Phenyl(2-((trimethylsilyl)ethynyl)cyclohept-1-en-1-yl)methanol 1031



Prepared according to **GP12** using 2-((trimethylsilyl)ethynyl)cyclohept-1-enecarbaldehyde **1029** (853 mg, 3.9 mmol) and PhMgBr (11.6 mmol, 1M solution in THF). Purification by flash column chromatography [98:2 (hexane:EtOAc)] afforded the internal alkyne **1031** as a yellow oil (1.10 g, 90%); IR ν_{max}/cm^{-1} 3398, 2923, 2851, 2131, 1449, 1248, 837, 757, 698; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.5 Hz, 2H), 7.36-7.29 (m, 2H), 7.27-7.21 (m, 1H), 6.17 (d, *J* = 3.2 Hz, 1H), 2.47-2.32 (m, 2H), 2.26-2.17 (m, 1H), 2.13-2.04 (m, 1H), 1.97 (d, *J* = 3.2 Hz, 1H), 1.77-1.66 (m, 1H), 1.66-1.58 (m, 1H), 1.55-1.49 (m, 2H), 1.35-1.24 (m, 1H), 1.22-1.11 (m, 1H), 0.21 (s, 9H); ^{13}C-NMR (101

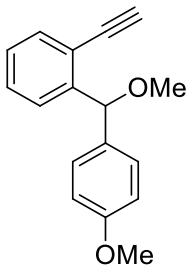
MHz, $CDCl_3$) δ 153.8 (C), 142.2 (C), 128.3 (2 × CH), 127.1 (CH), 125.5 (2 × CH), 122.9 (C), 106.6 (C), 98.1 (C), 75.1 (CH), 34.9 (CH_2), 32.6 (CH_2), 27.7 (CH_2), 27.0 (CH_2), 26.3 (CH_2), 0.24 (3 × CH_3); HRMS (ES) calcd. for $C_{19}H_{26}ONaSi$: 321.1651, found: 321.1643 $[M+Na]^+$.

_(Z)_-Phenyl(2-((trimethylsilyl)ethynyl)cyclooct-1-en-1-yl)methanol 1032



Prepared according to **GP12** using *(Z)*-2-ethynylcyclooct-1-enecarbaldehyde **1030** (1.5 g, 6.2 mmol) and PhMgBr (18.6 mmol, 1 M solution in THF). Purification by flash column chromatography [98:2 (hexane:EtOAc)] afforded the internal alkyne **1032** as a yellow oil (1.20 g, 63%); IR ν_{max}/cm^{-1} 2829, 2862, 1703, 1471, 1414, 1205, 1131, 1019, 722; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52-7.46 (m, 2H), 7.36-7.29 (m, 2H), 7.24-7.20 (m, 1H), 6.24 (d, *J* = 3.3 Hz, 1H), 2.43-2.21 (m, 3H), 2.18-2.07 (m, 1H), 2.04 (d, *J* = 3.3 Hz, 1H), 1.72-1.58 (m, 2H), 1.50-1.39 (m, 2H), 1.38-1.27 (m, 3H), 0.98-0.83 (m, 1H), 0.21 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 150.5 (C), 142.8 (C), 128.2 (2 × CH), 127.2 (CH), 125.5 (2 × CH), 128.5 (C), 105.8 (C), 97.7 (C), 75.2 (CH), 31.4 (CH_2), 31.2 (CH_2), 28.6 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 0.3 (3 × CH_3); HRMS (ES) calcd. for $C_{20}H_{28}ONaSi$: 335.1807, found: 335.1801 $[M+Na]^+$.

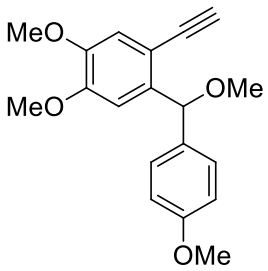
1-Ethynyl-2-(methoxy(4-methoxyphenyl)methyl)benzene 923



Prepared according to **GP13** using (4-methoxyphenyl)(2-((trimethylsilyl)ethynyl)-phenyl)methanol **919** (630 mg, 2.0 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the terminal alkyne **923** as a yellow oil (239 mg, 47% over two steps); IR ν_{max}/cm^{-1} 3284, 2933, 1610, 1509, 1462, 1244, 1172, 1081, 1032, 810, 758; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.48 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.38 (app. td, *J* = 7.6, 1.2 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.21 (app. td, *J* = 7.6, 1.3 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.75 (s, 1H), 3.77 (s, 3H), 3.38 (s, 3H), 3.33 (s, 1H).

Data matches that reported in the literature.[263]

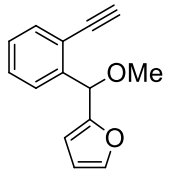
1-Ethynyl-4,5-dimethoxy-2-(methoxy(4-methoxyphenyl)methyl)benzene 924



Prepared according to **GP13** using (4,5-dimethoxy-2-((trimethylsilyl)ethynyl)phenyl)(4-methoxyphenyl)methanol **920** (1.0 g, 2.8 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc)] afforded the terminal alkyne **924** as a yellow oil (557 mg, 65%);

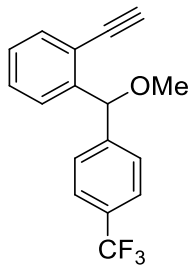
IR ν_{max}/cm^{-1} 3278, 2934, 2834, 1602, 1507, 1462, 1245, 1213, 1095, 860, 665; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.98 (s, 1H), 6.94 (s, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.72 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.78 (s, 3H), 3.37 (s, 3H), 3.26 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 150.5 (C), 147.9 (C), 138.6 (C), 134.1 (C), 128.1 (2 × CH), 114.9 (CH), 113.8 (2 × CH), 112.9 (C), 108.8 (CH), 82.2 (C), 81.7 (CH), 80.7 (CH), 57.1 (CH_3), 56.1 (2 × CH_3), 55.4 (CH_3); HRMS (ES) calcd. for $C_{19}H_{20}O_4Na$: 335.1259, found: 355.1251 $[M+Na]^+$.

2-((2-Ethynylphenyl)(methoxy)methyl)furan 925



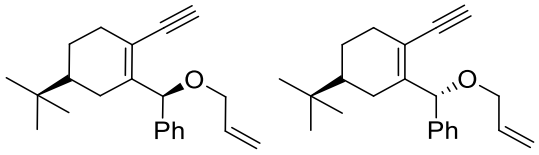
Prepared according to **GP13** using furan-2-yl(2-((trimethylsilyl)ethynyl)phenyl) methanol **921** (535 mg, 2.8 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc)] afforded the terminal alkyne **925** as a yellow oil (285 mg, 68%); IR ν_{max}/cm^{-1} 3290, 2935, 2823, 1480, 1189, 1079, 1012, 964, 761, 741; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70-7.62 (m, 1H), 7.50 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.46-7.36 (m, 2H), 7.29 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.11 (d, *J* = 3.2 Hz, 1H), 5.82 (s, 1H), 3.41 (s, 3H), 3.30 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (C), 142.9 (CH), 141.4 (C), 132.9 (CH), 129.4 (CH), 127.9 (CH), 126.8 (CH), 121.3 (C), 110.2 (CH), 108.8 (CH), 82.4 (CH), 81.2 (C), 76.3 (CH), 57.3 (CH_3); HRMS (EI) calcd. for $C_{14}H_{12}O_2$: 212.0837, found: 212.0841 $[M]^+$.

1-Ethynyl-2-(methoxy(4-(trifluoromethyl)phenyl)methyl)benzene 926



Prepared according to **GP13** using (4-(trifluoromethyl)phenyl)(2-((trimethylsilyl)ethynyl)phenyl)methanol **922** (770 mg, 2.2 mmol). Purification by flash column chromatography [95:5- 90:10 (hexane:EtOAc)] afforded the terminal alkyne **926** as a yellow oil (200 mg, 31% over two steps); IR ν_{max}/cm^{-1} 3302, 2937, 1619, 1415, 1324, 1164, 1123, 1067, 1018, 760; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56 (bs, 4H), 7.51 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.41-7.26 (m, 1H), 7.27-7.21 (m, 1H), 5.88 (s, 1H), 3.40 (s, 3H), 3.37 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.8 (J_{C-F} = 195.3 Hz, C), 133.2 (CH), 129.7 (CH), 127.8 (CH), 127.1 (2 × 2CH), 126.4 (CH), 125.5 (C), 125.40 (J_{C-F} = 3.9 Hz, C), 125.39 (C), 121.2 (C), 82.5 (C), 81.9 (CH), 81.6 (CH), 57.3 (CH_3); HRMS (EI) calcd. for $C_{17}H_{13}OF_3$: 290.0918, found: 290.0921 $[M]^+$.

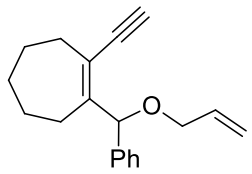
((Allyloxy)(5-(tert-butyl)-2-ethynylcyclohex-1-en-1-yl)methyl)benzene 1023



Prepared according to **GP13** using (5-(*tert*-butyl)-2-((trimethylsilyl)ethynyl)cyclohex-1-en-1-yl)(phenyl)methanol **1022** (740 mg, 2.2 mmol). Purification by flash column chromatography [100:0- 95:5 (hexane:EtOAc)] afforded the terminal alkyne **1023** as an orange oil (323 mg, 48% over two steps, dr. 1.6: 1); IR ν_{max}/cm^{-1} 2962, 1727, 1451, 1367, 1261, 1067, 751, 701; ^{1}H-NMR

(300 MHz, $CDCl_3$) δ 7.46-7.39 (2 × m, 2H), 7.36-7.29 (2 × m, 2H), 7.25-7.19 (2 × m, 1H), 6.07-5.91 (2 × m, 1H), 5.79 and 5.77 (2 × s, 1H), 5.37 and 5.31 (2 × td, *J* = 3.4, 1.7 Hz, 1H), 5.22-5.19 and 5.19-5.15 (2 × m, 1H), 4.06-3.95 (2 × m, 2H), 3.17 and 3.16 (2 × s, 1H), 2.43-2.20 (2 × m, 2H), 2.01-1.91 (2 × m, 1H), 1.85-1.71 (2 × m, 2H), 1.28-1.02 (2 × m, 2H), 0.80 and 0.79 (2 × s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.1 and 146.8 (1 × C), 135.0 and 134.89 (1 × CH), 128.1 (2 × s, 2 × CH), 127.0 (2 × s, 1 × CH), 125.9 and 125.8 (2 × CH), 117.8 and 117.6 (1 × C), 116.8 and 116.6 (1 × CH), 83.6 (2 × s, 1 × C), 80.8 and 80.76 (1 × CH_2), 80.6 and 80.5 (1 × C), 69.3 and 69.1 (1 × CH_2), 43.7 and 43.5 (1 × CH), 32.3 (2 × s, 1 × C), 31.7 and 31.67 (1 × CH_2), 27.2 and 27.1 (3 × CH_3), 24.4 (2 × s, 1 × CH_2), 23.9 (2 × s, 1 × CH), 23.9 and 23.8 (1 × CH_2); HRMS (ES) calcd. for $C_{22}H_{29}O$: 309.2210, found: 309.2218 $[M+H]^+$.

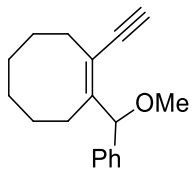
1-((Allyloxy)(phenyl)methyl)-2-ethynylcyclohept-1-ene 1033



Prepared according to **GP13** using (phenyl(2-((trimethylsilyl)ethynyl)cyclohept-1-en-1-yl)methanol **1031** (1.0 g, 3.4 mmol). Purification by flash column chromatography [95:5- 90:10 (hexane:EtOAc)] afforded the terminal alkyne **1033** as a colourless oil (274 mg, 30% over two steps); IR ν_{max}/cm^{-1} 2922, 2853, 1450, 1261, 1067, 920, 753, 704; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.46-7.41 (m, 2H), 7.35-7.27 (m, 2H), 7.25-7.17 (m, 1H), 5.98 (ddt, *J* = 17.1, 10.5, 5.3 Hz, 1H), 5.78 (s, 1H), 5.35 (app. dq, *J* = 17.1, 1.5 Hz, 1H), 5.18 (app. dq, *J* = 10.5, 1.5 Hz, 1H), 4.08 (ddt, *J* = 13.1, 5.3, 1.5 Hz, 1H), 4.01 (ddt, *J* = 13.1, 5.6, 1.5 Hz, 1H), 3.25 (s, 1H), 2.54-2.35 (m, 2H), 2.22-2.04 (m, 2H), 1.77-1.60 (m, 2H), 1.58-1.68 (m, 2H), 1.37-1.24 (m, 1H), 1.13-0.99 (m, 1H); ^{13}C-

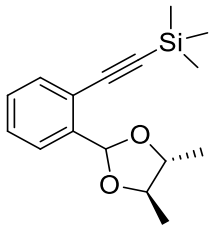
NMR (101 MHz, $CDCl_3$) δ 152.7 (C), 140.9 (C), 135.2 (CH), 128.2 (2 × CH), 127.2 (CH), 126.0 (2 × CH), 123.7 (C), 116.7 (CH_2), 83.5 (C), 81.4 (CH), 81.1 (CH), 69.5 (CH_2), 35.1 (CH_2), 32.6 (CH_2), 27.8 (CH_2), 26.6 (CH_2), 26.5 (CH_2); HRMS (ES) calcd. for $C_{19}H_{23}O$: 267.1740, found: 267.1749 $[M+H]^+$.

(*Z*)-1-Ethynyl-2-(methoxy(phenyl)methyl)cyclooct-1-ene 1034



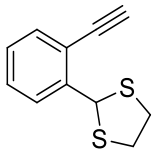
Prepared according to **GP13** using *(Z)*-phenyl(2-((trimethylsilyl)ethynyl)cyclooct-1-en-1-yl)methanol **1032** (1.2 g, 3.7 mmol). Purification by flash column chromatography [95:5- 90:10 (hexane:EtOAc)] afforded the terminal alkyne **1034** as a yellow oil (367 mg, 39% over two steps); IR ν_{max}/cm^{-1} 3307, 2926, 2857, 1451, 1093, 973, 749, 705; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47-7.41 (m, 2H), 7.34-7.27 (m, 2H), 7.25-7.19 (m, 1H), 5.73 (s, 1H), 3.40 (s, 3H), 3.18 (s, 1H), 2.45 (ddd, *J* = 13.7, 8.7, 5.3 Hz, 1H), 2.38-2.29 (m, 1H), 2.23 (ddd, *J* = 13.7, 7.3, 3.5 Hz, 1H), 2.07 (ddd, *J* = 10.4, 8.1, 3.2 Hz, 1H), 1.73-1.61 (m, 2H), 1.47-1.36 (m, 2H), 1.35-1.24 (m, 3H), 0.76-0.61 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 149.4 (C), 141.3 (C), 128.3 (2 × CH), 128.1 (CH), 125.8 (2 × CH), 120.9 (C), 84.3 (C), 83.6 (CH), 80.5 (CH), 56.8 (CH_3), 31.3 (CH_2), 30.8 (CH_2), 28.5 (CH_2), 26.8 (CH_2), 25.9 (CH_2), 25.6 (CH_2); HRMS (ES) calcd. for $C_{18}H_{23}O$: 255.1749, found: 255.1738 $[M+H]^+$.

((2-((4*R*,5*R*)-4,5-Dimethyl-1,3-dioxolan-2-yl)phenyl)ethynyl)trimethylsilane 948



Prepared according to **GP14** using 2-((trimethylsilyl)ethynyl)benzaldehyde **914** (202 mg, 1.0 mmol) and (*2R,3R*)-butane-2,3-diol (0.1 mL, 1.2 mmol) **947** refluxing for 1 hour. The internal alkyne **948** was isolated as a colourless oil (226 mg, 86%) and used in the next step without further purification; IR ν_{max}/cm^{-1} 2966, 2899, 2158, 1379, 1249, 1083, 980, 863, 840, 757; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.34 (app. td, *J* = 7.5, 1.2 Hz, 1H), 7.31-7.25 (m, 1H), 6.31 (s, 1H), 3.90-3.79 (m, 2H), 1.41 (d, *J* = 5.8 Hz, 3H), 1.33 (d, *J* = 5.8 Hz, 3H), 0.25 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 140.0 (C), 132.9 (CH), 128.9 (CH), 128.8 (CH), 126.5 (CH), 122.4 (C), 102.4 (C), 100.8 (CH), 99.3 (C), 80.7 (CH), 79.0 (CH), 17.5 (CH_3), 17.1 (CH_3), 0.1 (3 × CH_3); HRMS (EI) calcd. for $C_{16}H_{22}O_2Si$: 274.1386, found: 274.1389 $[M]^+$.

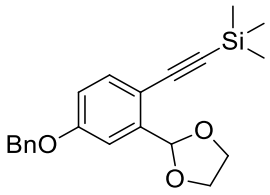
2-(2-Ethynylphenyl)-1,3-dithiolane 953



2-Ethynylbenzaldehyde **952** (371 mg, 2.9 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (23 mL, 0.1 M). *p*-TsOH H_2O (ca 15 mg), 1,2-ethanedithiol (0.27 mL, 3.4 mmol, 1.2 eq.) and silica gel (4.6 g) were added and the reaction was heated at reflux for 16 hours at which point consumption of starting material was observed by TLC. The reaction mixture was cooled to room temperature,

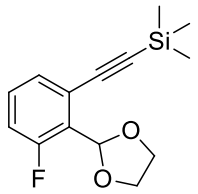
filtered and the filter cake was washed with CH_2Cl_2 (ca 30 mL). The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography [90:10 hexane:EtOAc] to afford the diol **953** as an orange oil (295 mg, 50%); IR ν_{max}/cm^{-1} 3282, 2921, 1472, 1444, 1275, 1040, 849, 753; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.36 (app. td, *J* = 7.8, 1.4 Hz, 1H), 7.21 (app. td, *J* = 7.6, 1.3 Hz, 1H), 6.22 (s, 1H), 3.53-3.43 (m, 2H), 3.41 (s, 1H), 3.40-3.33 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.6 (C), 132.7 (CH), 129.3 (CH), 127.7 (CH), 127.5 (CH), 121.1 (C), 83.2 (CH), 81.3 (C), 53.2 (CH), 40.0 (2 × CH_2); HRMS (ES) calcd. for $C_{11}H_{10}S_2$: 206.0224, found: 206.0225 $[M+Na]^+$.

((4-(Benzyloxy)-2-(1,3-dioxolan-2-yl)phenyl)ethynyl)trimethylsilane 960



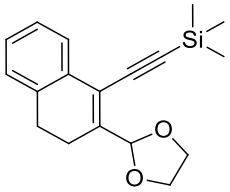
Prepared according to **GP14** using 5-(benzyloxy)-2-((trimethylsilyl)ethynyl)benzaldehyde **959** (836 mg, 2.7 mmol) refluxing for 1.5 hour. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] afforded the internal alkyne **960** as a yellow oil (681 mg, 71%); IR ν_{max}/cm^{-1} 2958, 2892, 2154, 1607, 1381, 1294, 1250, 1067, 1025, 841, 760; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44-7.31 (m, 6H), 7.17 (d, *J* = 2.7 Hz, 1H), 6.89 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.15 (s, 1H), 5.07 (s, 2H), 4.21-4.10 (m, 2H), 4.10-4.00 (m, 2H), 0.24 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.1 (C), 141.3 (C), 136.6 (C), 134.5 (CH), 128.8 (2 × CH), 128.2 (CH), 127.7 (2 × CH), 115.8 (CH), 115.0 (C), 112.5 (CH), 102.3 (C), 102.0 (CH), 97.7 (C), 70.2 (CH_2), 65.7 (2 × CH_2), 0.17 (3 × CH_3); HRMS (ES) calcd. for $C_{21}H_{25}O_3Si$: 353.1557, found: 353.1573 $[M+H]^+$.

((2-(1,3-Dioxolan-2-yl)-3-fluorophenyl)ethynyl)trimethylsilane 965



Prepared according to **GP14** using 2-fluoro-6-((trimethylsilyl)ethynyl)benzaldehyde **964** (260 mg, 1.2 mmol), refluxing for 3 hours. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] afforded the internal alkyne **965** as a colourless oil (294 mg, 93%); IR ν_{max}/cm^{-1} 2960, 2898, 2154, 1573, 1468, 1250, 1095, 1004, 838, 795, 734; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 1H), 7.24-7.18 (m, 1H), 7.02 (ddd, *J* = 10.5, 7.6, 1.9 Hz, 1H), 6.35 (d, *J* = 0.6 Hz, 1H), 4.29-4.22 (m, 2H), 4.09-4.02 (m, 2H), 0.25 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.6 (d, J_{C-F} = 251.7 Hz, C), 130.5 (d, J_{C-F} = 9.8 Hz, CH), 129.8 (d, J_{C-F} = 3.2 Hz, CH), 126.6 (d, J_{C-F} = 11.6 Hz, C), 124.8 (d, J_{C-F} = 5.1 Hz, C), 116.9 (d, J_{C-F} = 22.6 Hz, CH), 101.5 (d, J_{C-F} = 3.8 Hz, C), 100.2 (d, J_{C-F} = 3.5 Hz, CH), 100.1 (C), 66.3 (2 × CH_2), 0.05 (3 × CH_3); HRMS (EI) calcd. for $C_{14}H_{17}O_2SiF$: 264.0982, found: 264.0976 $[M]^+$.

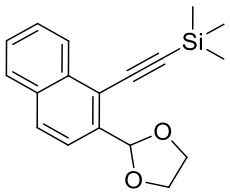
((2-(1,3-Dioxolan-2-yl)-3,4-dihydronaphthalen-1-yl)ethynyl)trimethylsilane 974



Prepared according to **GP14** using 1-((trimethylsilyl)ethynyl)-3,4-dihydronaphthalene-2-carbaldehyde **972** (1.27 g, 5.0 mmol), refluxing for 5 hours. Purification by flash column chromatography [98:2 (hexane:EtOAc), 1% Et_3N] afforded the internal alkyne **974** as an orange

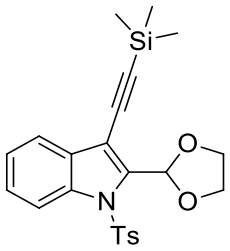
oil (800 mg, 54%); IR ν_{max}/cm^{-1} 2958, 2898, 1664, 1557, 1364, 1289, 1249, 1181, 1071, 866, 839, 760; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67-7.59 (m, 1H), 7.26-7.16 (m, 2H), 7.14-7.07 (m, 1H), 6.06 (s, 1H), 4.13-4.06 (m, 2H), 4.05-3.96 (m, 2H), 2.79 (t, *J* = 8.0 Hz, 2H), 2.39 (t, *J* = 8.0 Hz, 2H), 1.56 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 141.3 (C), 137.7 (C), 136.0 (C), 132.1 (C), 130.9 (CH), 127.9 (CH), 127.4 (CH), 127.1 (CH), 108.0 (C), 98.0 (C), 65.9 (CH), 63.9 (2 × CH_2), 26.8 (CH_2), 19.9 (CH_2), -0.09 (3 × CH_3); HRMS (EI) calcd. for $C_{18}H_{22}O_2Si$: 298.1389, found: 298.1388 $[M]^+$.

((2-(1,3-Dioxolan-2-yl)naphthalen-1-yl)ethynyl)trimethylsilane 975



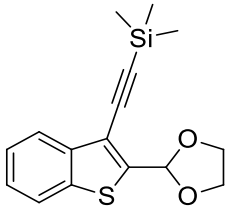
Prepared according to **GP14** using 1-((trimethylsilyl)ethynyl)-2-naphthaldehyde **973** (844 mg, 3.4 mmol), refluxing for 4 hours. Purification by flash column chromatography [98:2 (hexane:EtOAc), 1% Et_3N] afforded the internal alkyne **975** as a yellow oil (660 mg, 61%); IR ν_{max}/cm^{-1} 3252, 2924, 2854, 1673, 1592, 1232, 814, 660; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.43-8.34 (m, 1H), 7.87-7.80 (m, 2H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.62-7.56 (m, 1H), 7.56-7.49 (m, 1H), 6.45 (s, 1H), 4.41-4.22 (m, 2H), 4.10-3.98 (m, 2H), 0.34 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 138.1 (C), 133.6 (C), 133.4 (C), 129.1 (CH), 128.3 (CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 123.2 (CH), 120.6 (C), 105.50 (C) 102.5 (CH), 99.8 (C), 65.9 (2 × CH_2), 0.2 (3 × CH_3); HRMS (ES) calcd. for $C_{18}H_{21}O_2Si$: 297.1311, found: 297.1318 $[M+H]^+$.

2-(1,3-Dioxolan-2-yl)-1-tosyl-3-((trimethylsilyl)ethynyl)-1*H*-indole 992



Prepared according to **GP14** using 1-tosyl-3-((trimethylsilyl)ethynyl)-1*H*-indole-2-carbaldehyde **991** (791 mg, 2.0 mmol), refluxing for 1 hour. Purification by flash column chromatography [90:10 (hexane:EtOAc), 1% Et_3N] afforded the internal alkyne **992** as a viscous, yellow oil (698 mg, 80%); IR ν_{max}/cm^{-1} 2974, 2901, 1379, 1253, 1175, 1103, 844, 749, 667; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.64-7.58 (m, 1H), 7.40-7.35 (m, 1H), 7.34-7.28 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.87 (s, 1H), 4.27-4.16 (m, 2H), 4.16-4.06 (m, 2H), 2.32 (s, 3H), 0.28 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.3 (C), 140.7 (C), 136.1 (C), 135.4 (C), 130.2 (C), 129.8 (2 × CH), 129.8 (C), 127.3 (2 × CH), 126.4 (CH), 124.2 (CH), 120.7 (CH), 115.0 (CH), 102.1 (C), 97.8 (CH), 96.1 (C), 65.7 (2 × CH_2), 21.7 (CH_3), 0.3 (3 × CH_3); HRMS (ES) calcd. for $C_{23}H_{25}NO_4SiNaS$: 462.1171, found: 462.1176 $[M+Na]^+$.

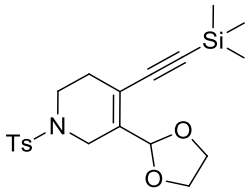
((2-(1,3-Dioxolan-2-yl)benzo[b]thiophen-3-yl)ethynyl)trimethylsilane 999



Prepared according to **GP14** using 3-((trimethylsilyl)ethynyl)benzo[b]-thiophene-2-carbaldehyde **998** (134 mg, 0.52 mmol), refluxing for 1 hour. Purification by flash column chromatography

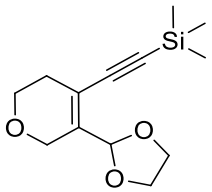
[95:5 (hexane:EtOAc), 1% Et_3N] afforded the internal alkyne **999** as an orange oil (120 mg, 76%); IR ν_{max}/cm^{-1} 2958, 2869, 2154 1248, 1199, 1098, 932, 837, 753, 733, 680; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91-7.86 (m, 1H), 7.81-7.77 (m, 1H), 7.46-7.41 (m, 1H), 7.40-7.35 (m, 1H), 6.43 (s, 1H), 4.26-4.15 (m, 2H), 4.15-4.04 (m, 2H), 0.30 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 146.3 (C), 139.7 (C), 138.3 (C), 125.9 (CH), 124.9 (CH), 123.5 (CH), 122.7 (CH), 118.1 (C), 101.6 (C), 99.6 (CH), 96.5 (C), 65.8 (2 × CH_2), 0.2 (3 × CH_3); HRMS (ES) calcd. for $C_{16}H_{19}O_2SSi$: 303.0875, found: 303.0869 $[M+H]^+$.

5-(1,3-Dioxolan-2-yl)-1-tosyl-4-((trimethylsilyl)ethynyl)-1,2,3,6-tetrahydropyridine 1009



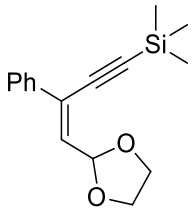
Prepared according to **GP14** using 1-tosyl-4-((trimethylsilyl)ethynyl)-1,2,5,6-tetrahydropyridine-3-carbaldehyde **1007** (852 mg, 2.4 mmol), refluxing for 2.5 hours. Purification by flash column chromatography [90:10- 80:20 (hexane:EtOAc), 1% Et_3N] afforded the internal alkyne **1009** as a yellow oil (780 mg, 80%); IR ν_{max}/cm^{-1} 2959, 2893, 2145, 1343, 1251, 1163, 1085, 957, 843, 757, 684; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.79 (s, 1H), 4.03-3.99 (m, 2H), 3.96-3.87 (m, 2H), 3.71 (t, *J* = 2.4 Hz, 2H), 3.14 (t, *J* = 5.8 Hz, 2H), 2.42 (s, 3H), 2.37-2.30 (m, 2H), 0.16 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 136.9 (C), 133.6 (C), 129.9 (2 × CH), 127.8 (2 × CH), 120.7 (C), 101.7 (CH), 101.0 (C), 100.9 (C), 65.7 (2 × CH_2), 42.5 (CH_2), 42.4 (CH_2), 30.2 (CH_2), 21.7 (CH_3), 0.05 (3 × CH_3); HRMS (ES) calcd. for $C_{20}H_{27}NO_4NaSSi$: 428.1328, found: 428.1330 $[M+Na]^+$.

((5-(1,3-Dioxolan-2-yl)-3,6-dihydro-2*H*-pyran-4-yl)ethynyl)trimethylsilane 1010



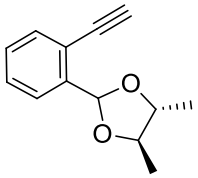
Prepared according to **GP14** using 4-((trimethylsilyl)ethynyl)-5,6-dihydro-2H-pyran-3-carbaldehyde **1008** (700 mg, 3.4 mmol), refluxing for 20 minutes. The internal alkyne **1010** was isolated as a colourless oil (807 mg, 95%) and used in the next step without further purification; IR ν_{max}/cm^{-1} 3422, 2958, 1721, 1683, 1251, 1077, 843, 761, 703; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1H), 4.24 (t, *J* = 2.5 Hz, 2H), 3.99-3.95 (m, 2H), 3.94-3.90 (m, 2H), 3.75 (t, *J* = 5.5 Hz, 2H), 2.28 (tt, *J* = 5.5, 2.5 Hz, 2H), 0.19 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 140.0 (C), 120.0 (C), 101.9 (CH), 101.4 (C), 99.8 (C), 65.7 (2 × CH_2), 63.9 (CH_2), 63.3 (CH_2), 29.8 (CH_2), 0.05 (3 × CH_3); HRMS (EI) calcd. for $C_{13}H_{20}O_3Si$: 252.1182, found: 252.1178 $[M]^+$.

(*Z*)-(4-(1,3-Dioxolan-2-yl)-3-phenylbut-3-en-1-yn-1-yl)trimethylsilane 1045



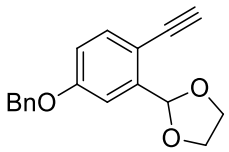
Prepared according to **GP14** using (*Z*)-3-phenyl-5-(trimethylsilyl)pent-2-en-4-ynal **1044** (969 mg, 4.3 mmol), refluxing for 2 hours. The internal alkyne proved unstable and used directly for the next.

(4*R*,5*R*)-2-(2-Ethynylphenyl)-4,5-dimethyl-1,3-dioxolane 949



Prepared according to **GP15** using internal alkyne **948** (225 mg, 0.82 mmol), stirring for 30 minutes. The terminal alkyne **949** was isolated as a colourless oil (154 mg, 93%) and used in the next step without further purification; IR ν_{max}/cm^{-1} 3279, 2975, 2880, 1717, 1380, 1280, 1081, 981, 761; ^{1}H-NMR (400 MHz, $CDCl_3$) *(spectrum recorded with 3% CH_2Cl_2 and 2% EtOAc present as extended drying time led to product degradation)* δ 7.61 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.39 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.31 (dt, *J* = 7.5, 1.4 Hz, 1H), 6.35 (s, 1H), 3.87-3.81 (m, 2H), 3.31 (s, 1H), 1.40 (d, *J* = 5.8 Hz, 3H), 1.34 (d, *J* = 5.8 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 140.5 (C), 133.3 (CH), 129.2 (CH), 129.0 (CH), 126.5 (CH), 121.3 (C), 100.8 (CH), 82.0 (CH), 81.1 (C), 80.7 (CH), 79.0 (CH), 17.4 (CH_3), 16.9 (CH_3); HRMS (EI) calcd. for $C_{13}H_{14}O_2$: 202.0998, found: 202.0994 $[M]^+$.

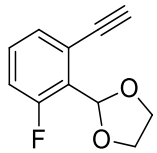
2-(5-(Benzyloxy)-2-ethynylphenyl)-1,3-dioxolane 961



Prepared according to **GP15** using ((4-(benzyloxy)-2-(1,3-dioxolan-2-yl)phenyl)ethynyl)trimethylsilane **960** (681 mg, 1.9 mmol), stirring for 1.5 hour. The terminal alkyne **961** was isolated as a yellow oil (514 mg, 97%) and used in the next step without further purification; IR ν_{max}/cm^{-1} 3283, 2887, 1607, 1493, 1380, 1294, 12312, 1064, 1022, 940, 818, 733,

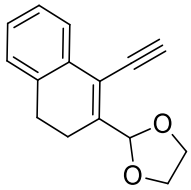
695; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 1H), 7.44-7.32 (m, 5H), 7.22 (d, *J* = 2.7 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.20 (s, 1H), 5.09 (s, 2H), 4.19-4.10 (m, 2H), 4.10-4.01 (m, 2H), 3.25 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.4 (C), 141.6 (C), 136.6 (C), 134.8 (CH), 128.8 (2 × CH), 128.3 (CH), 127.7 (2 × CH), 115.8 (CH), 113.8 (C), 112.4 (CH), 101.7 (CH), 81.0 (C), 80.6 (CH), 70.2 (CH_2), 65.7 (2 × CH_2); HRMS (ES) calcd. for $C_{18}H_{17}O_3$: 281.1178, found: 281.1170 $[M+H]^+$.

2-(2-Ethynyl-6-fluorophenyl)-1,3-dioxolane 966



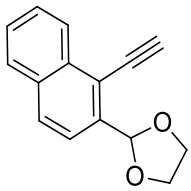
Prepared according to **GP15** using ((2-(1,3-dioxolan-2-yl)-3-fluorophenyl)ethynyl)trimethylsilane **965** (290 mg, 1.1 mmol), stirring for 30 minutes. The terminal alkyne **966** was isolated as a colourless oil (209 mg, 99%) and used in the next step without further purification; IR ν_{max}/cm^{-1} 3289, 2897, 1576, 1467, 1255, 1213, 1093, 957, 940, 796, 735; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H), 7.11-7.03 (m, 1H), 6.37 (d, *J* = 0.7 Hz, 1H), 4.29-4.21 (m, 2H), 4.09-4.02 (m, 2H), 3.33 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.6 (d, J_{C-F} = 252.1 Hz, C), 130.7 (d, J_{C-F} = 9.8 Hz, CH), 129.8 (d, J_{C-F} = 3.3 Hz, CH), 127.0 (d, J_{C-F} = 11.9 Hz, C), 123.8 (d, J_{C-F} = 5.1 Hz, CH), 117.3 (d, J_{C-F} = 22.5 Hz, C), 100.2 (d, J_{C-F} = 3.5 Hz, CH), 82.6 (2 × CH_2), 80.4 (d, J_{C-F} = 4.0 Hz, C), 66.3 (CH); HRMS (EI) calcd. for $C_{11}H_9O_2F$: 192.0587, found: 192.0584 $[M]^+$.

2-(1-Ethynyl-3,4-dihydronaphthalen-2-yl)-1,3-dioxolane 976



Prepared according to **GP15** using ((2-(1,3-dioxolan-2-yl)-3,4-dihydronaphthalen-1-yl)ethynyl)trimethylsilane **974** (800 mg, 2.7 mmol), stirring for 30 minutes. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] afforded the terminal alkyne **976** as a yellow solid (549 mg, 88%); mp. 70-71 °C; IR ν_{max}/cm^{-1} 3277, 2839, 1660, 1600, 1557, 1366, 1286, 1181, 771, 735; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.1, 1.9 Hz, 1H), 7.26-7.20 (m, 2H), 7.15-7.10 (m, 1H), 6.07 (s, 1H), 4.14-4.08 (m, 2H), 4.07-3.98 (m, 2H), 3.39 (s, 1H), 2.82 (t, *J* = 8.0 Hz, 2H), 2.42 (t, *J* = 8.0 Hz, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.8 (C), 135.7 (C), 132.5 (C), 128.5 (CH), 127.5 (CH), 126.8 (CH), 126.0 (CH), 121.4 (C), 102.9 (CH), 84.6 (CH), 78.5 (C), 66.0 (2 × CH_2), 27.4 (CH_2), 21.2 (CH_2); HRMS (ES) calcd. for $C_{15}H_{15}O_2$: 227.1072, found: 227.1069 $[M+H]^+$.

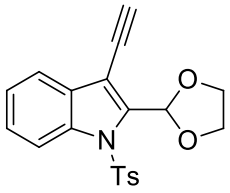
2-(1-Ethynylnaphthalen-2-yl)-1,3-dioxolane 977



Prepared according to **GP15** using ((2-(1,3-dioxolan-2-yl)naphthalen-1-yl)ethynyl)trimethylsilane **975** (583 mg, 2.0 mmol), stirring for 1.5 hours. The terminal alkyne was isolated **977** as a yellow oil (351 mg, 80%) and used in the next step without further purification; IR ν_{max}/cm^{-1} 3287, 2887, 1243, 1097, 1051, 945, 823, 751; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.46-8.38 (m, 1H), 7.92-7.81

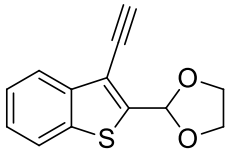
(m, 2H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.63-7.51 (m, 2H), 6.49 (s, 1H), 4.31-4.22 (m, 2H), 4.19-4.09 (m, 2H), 3.76 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 138.6 (C), 133.5 (C), 133.5 (C), 129.4 (CH), 128.2 (CH), 127.2 (CH), 127.1 (CH), 126.5 (CH), 122.9 (CH), 119.4 (C), 102.3 (CH), 87.5 (CH), 78.6 (C), 65.9 (2 × CH_2); *(no HRMS was acquired due to compound's instability).*

2-(1,3-Dioxolan-2-yl)-3-ethynyl-1-tosyl-1*H*-indole 993



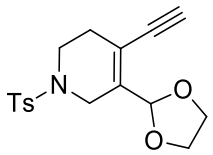
Prepared according to **GP15** using 2-(1,3-dioxolan-2-yl)-1-tosyl-3-((trimethylsilyl)ethynyl)-1*H*-indole **992** (695 mg, 1.6 mmol), stirring for 1 hour. The terminal alkyne **993** was isolated as a viscus, brown oil (586 mg, 100%) and used in the next step without further purification; IR ν_{max}/cm^{-1} 3285, 2955, 2891, 1375, 1173, 1142, 1086, 942, 911, 813, 747, 661; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.66-7.61 (m, 1H), 7.41-7.34 (m, 1H), 7.30 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.88 (s, 1H), 4.26-4.16 (m, 2H), 4.16-4.05 (m, 2H), 3.48 (s, 1H), 2.33 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.3 (C), 141.3 (C), 136.0 (C), 135.3 (C), 130.1 (C), 129.8 (2 × CH), 127.3 (2 × CH), 126.4 (CH), 124.2 (CH), 120.5 (CH), 114.9 (CH), 105.8 (C), 97.7 (CH), 84.3 (CH), 75.2 (C), 65.6 (2 × CH_2), 21.7 (CH_3); HRMS (ES) calcd. for $C_{20}H_{17}NO_4NaS$: 390.0776, found: 390.0778 $[M+Na]^+$.

2-(3-Ethynylbenzo[b]thiophen-2-yl)-1,3-dioxolane 1000



Prepared according to **GP15** using ((2-(1,3-dioxolan-2-yl)benzo[b]thiophen-3-yl)ethynyl)trimethylsilane **999** (121 mg, 0.4 mmol), stirring for 1 hour. The terminal alkyne **1000** was isolated as an orange oil (82 mg, 89%) and used in the next step without further purification; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95-7.89 (m, 1H), 7.84-7.79 (m, 1H), 7.47-7.37 (m, 2H), 6.45 (s, 1H), 4.25-4.15 (m, 2H), 4.15-4.05 (m, 2H), 3.51 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.3 (C), 139.8 (C), 138.2 (C), 125.9 (CH), 125.0 (CH), 123.3 (CH), 122.7 (CH), 116.7 (C), 99.5 (CH), 83.8 (CH), 75.8 (C), 65.9 (2 × CH_2); HRMS (ES) calcd. for $C_{13}H_{11}O_2S$: 231.0480, found: 231.0483 $[M+H]^+$.

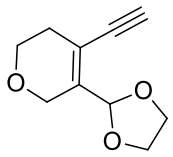
5-(1,3-Dioxolan-2-yl)-4-ethynyl-1-tosyl-1,2,3,6-tetrahydropyridine 1011



Prepared according to **GP15** using 5-(1,3-dioxolan-2-yl)-1-tosyl-4-((trimethylsilyl)ethynyl)-1,2,3,6-tetrahydropyridine **1009** (734 mg, 1.8 mmol), stirring for 30 minutes. The terminal alkyne **1011** was isolated as a colourless oil (515 mg, 86%) and used in the next step without further purification; IR ν_{max}/cm^{-1} 3270, 2890, 1340, 1257, 1160, 1082, 953, 816, 736, 659; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.80 (s, 1H), 4.03-3.99 (m, 2H), 3.94-3.90 (m, 2H), 3.74 (t, *J* = 2.2 Hz, 2H), 3.20-3.12 (m, 3H), 2.43 (s, 3H), 2.38-2.32 (m,

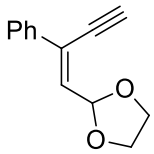
2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 148.3 (C), 138.0 (C), 133.5 (C), 129.9 (2 × CH), 127.8 (2 × CH), 129.7 (C), 101.6 (CH), 83.4 (CH), 79.9 (C), 65.7 (2 × CH_2), 42.5 (CH_2), 42.4 (CH_2), 30.1 (CH_2), 21.7 (CH_3); HRMS (ES) calcd. for $C_{17}H_{19}NO_4NaS$: 356.0932, found: 356.0926 $[M+Na]^+$.

5-(1,3-Dioxolan-2-yl)-4-ethynyl-3,6-dihydro-2*H*-pyran 1012



Prepared according to **GP15** using ((5-(1,3-dioxolan-2-yl)-3,6-dihydro-2*H*-pyran-4-yl)ethynyl)trimethylsilane **1010** (798 mg, 3.2 mmol), stirring for 1 hour. The terminal alkyne **1012** was isolated as a colourless oil (385 mg, 68%) and used in the next step without further purification; IR ν_{max}/cm^{-1} 3266, 2889, 1720, 1673, 1389, 1259, 1075, 1040; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 1H), 4.25 (t, *J* = 2.5 Hz, 2H), 4.00-3.95 (m, 2H), 3.95-3.90 (m, 2H), 3.77 (t, *J* = 5.5 Hz, 2H), 3.18 (s, 1H), 2.30 (tt, *J* = 5.5, 2.5 Hz, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 141.1 (C), 118.9 (C), 100.7 (CH), 82.5 (CH), 80.3 (C), 65.7 (2 × CH_2), 63.7 (CH_2), 63.3 (CH_2), 29.7 (CH_2); HRMS (EI) calcd. for $C_{10}H_{12}O_3$: 180.0786, found: 180.0783 $[M]^+$.

(*E*)-2-(2-Phenylbut-1-en-3-yn-1-yl)-1,3-dioxolane 1046

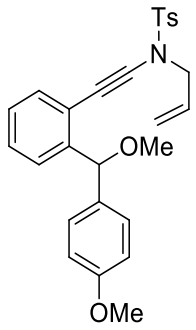


Prepared according to **GP15** using *(Z)*-(4-(1,3-dioxolan-2-yl)-3-phenylbut-3-en-1-yn-1-yl)trimethylsilane **1045** (664 mg, 2.4 mmol), stirring for 2.5 hours. The terminal alkyne **1046** was isolated as a pale yellow oil (234 mg, 99%) and used in the next step without further

purification; IR ν_{max}/cm^{-1} 3286, 2891, 2094, 1670, 1562, 1140, 765, 689; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.71-7.67 (m, 2H), 7.39-7.28 (m, 3H), 6.38 (d, *J* = 7.3 Hz, 1H), 5.97 (d, *J* = 7.3 Hz, 1H), 4.43-4.03 (m, 4H), 3.45 (s, 1 H).

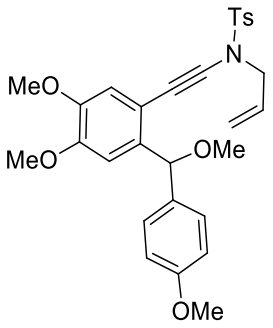
Data matches that reported in the literature.[264]

_N_-Allyl-_N_-((2-(methoxy(4-methoxyphenyl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide 931



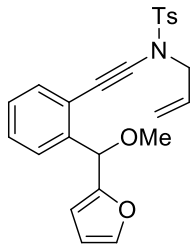
Prepared according to **GP18** using the freshly prepared bromoalkyne 1-(bromoethynyl)-2-(methoxy(4-methoxyphenyl)methyl) benzene **927** (**GP16**, 311 mg, 0.9 mmol) and sulfonamide **693** (116 mg, 0.8 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the ynamide **931** as a pale yellow oil (360 mg, 61%); IR ν_{max}/cm^{-1} 2928, 2854, 1348, 1325, 1160, 1097, 1069, 975, 814, 750, 666; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.52-7.46 (m, 1H), 7.32-7.24 (m, 6H), 7.20-7.14 (m, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.76 (ddt, *J* = 16.4, 10.1, 6.3 Hz, 1H), 5.63 (s, 1H), 5.30-5.18 (m, 2H), 4.08-4.03 (m, 2H), 3.77 (s, 3H), 3.34 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 144.9 (C), 143.6 (C), 134.9 (C), 134.0 (C), 132.1 (CH), 131.1 (CH), 130.0 (2 × CH), 128.4 (3 × CH), 127.9 (2 × CH), 127.2 (CH), 126.3 (CH), 121.8 (C), 120.3 (CH_2), 113.8 (2 × CH), 86.8 (C), 82.1 (CH), 69.4 (C), 57.1 (CH_3), 55.4 (CH_3), 54.6 (CH_2), 21.8 (CH_3); HRMS (ES) calcd. for $C_{27}H_{28}NO_4S$: 462.1739, found: 462.1732 $[M+H]^+$.

_N_-Allyl-_N_-((4,5-dimethoxy-2-(methoxy(4-methoxyphenyl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide 932



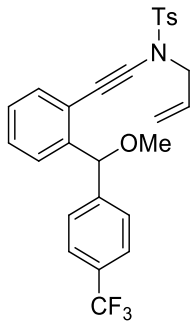
Prepared according to **GP18** using the freshly prepared bromoalkyne 1-(bromoethynyl)-4,5-dimethoxy-2-(methoxy(4-methoxyphenyl) methyl)benzene **928** (**GP16**, 530 mg, 1.4 mmol) and sulfonamide **693** (186 mg, 0.9 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] gave the ynamide **932** as a yellow oil (383 mg, 83%); IR ν_{max}/cm^{-1} 2934, 2835, 2234, 1601, 1509, 1360, 1245, 1169, 1089, 1033, 749, 663; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.30-7.25 (m, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.94 (s, 1H), 6.83-6.77 (m, 3H), 5.74 (ddt, *J* = 16.8, 10.1, 6.3 Hz, 1H), 5.57 (s, 1H), 5.23 (dd, *J* = 16.8, 1.3 Hz, 1H), 5.19 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.11-4.05 (m, 1H), 4.05-3.98 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.31 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C), 150.0 (C), 147.9 (C), 144.8 (C), 137.6 (C), 134.9 (C), 134.3 (C), 131.2 (CH), 129.9 (2 × CH), 128.1 (2 × CH), 127.9 (2 × CH), 120.2 (CH_2), 114.7 (CH), 113.7 (2 × CH), 113.6 (C), 108.9 (CH), 85.1 (C), 81.8 (CH), 69.0 (C), 57.0 (CH_3), 56.1 (2 × CH_3), 55.4 (CH_3), 54.6 (CH_2), 21.8 (CH_3); HRMS (ES) calcd. for $C_{29}H_{31}NO_6NaS$: 544.1770, found: 544.1768 $[M+Na]^+$.

***N*-Allyl-*N*-((2-(furan-2-yl(methoxy)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide 933**



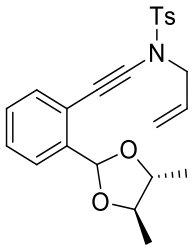
Prepared according to **GP17** using the freshly prepared terminal alkyne 2-((2-ethynylphenyl)(methoxy)methyl)furan **925** (280 mg, 1.3 mmol) and sulfonamide **693** (810 mg, 6.6 mmol). Purification by flash column chromatography [80:20- 70:30 (hexane:EtOAc)] afforded the ynamide **933** as a yellow oil (190 mg, 35%); IR ν_{max}/cm^{-1} 2932, 2234, 1366, 1171, 1090, 1013, 926, 760, 664; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.63 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.38 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.37-7.29 (m, 4H), 7.26-7.17 (m, 1H), 6.28 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.08 (d, *J* = 3.2 Hz, 1H), 5.79-5.67 (m, 1H), 5.70 (s, 1H), 5.28-5.19 (m, 2H), 4.03 (dd, *J* = 2.5, 1.2 Hz, 1H), 4.02 (dd, *J* = 2.5, 1.2 Hz, 1H), 3.36 (s, 3H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.9 (C), 144.9 (C), 142.7 (CH), 140.1 (C), 134.9 (C), 131.7 (CH), 131.0 (CH), 130.0 (2 × CH), 128.2 (CH), 127.9 (2 × CH), 127.8 (CH), 126.8 (CH), 122.1 (C), 120.2 (CH_2), 110.2 (CH), 108.9 (CH), 87.1 (C), 76.4 (CH), 68.8 (C), 57.2 (CH_3), 54.5 (CH_2), 21.8 (CH_3); HRMS (ES) calcd. for $C_{24}H_{23}NO_4NaS$: 444.1245, found: 444.1252 $[M+Na]^+$.

_N_-Allyl-_N_-((2-(methoxy(4-(trifluoromethyl)phenyl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide 934



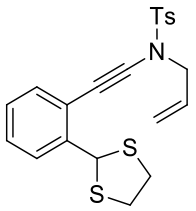
Prepared according to **GP18** using the freshly prepared bromoalkyne 1-(bromoethynyl)-2-(methoxy(4-(trifluoromethyl)phenyl)methyl)benzene **930** (**GP16**, 216 mg, 0.6 mmol) and sulfonamide **693** (103 mg, 0.5 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc)] afforded the ynamide **934** as a colourless oil (132 mg, 54%); IR ν_{max}/cm^{-1} 2232, 1368, 1325, 1169, 1123, 1067, 1018, 813, 760, 663; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.55-7.48 (m, 4H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.34-7.27 (m, 4H), 7.20 (app. td, *J* = 7.5, 1.3 Hz, 1H), 5.82-5.71 (m, 2H), 5.26 (dd, *J* = 17.1, 1.3 Hz, 1H), 5.22 (br. dd, *J* = 10.1, 1.3 Hz, 1H), 4.07 (br. dd, *J* = 6.3, 1.3 Hz, 2H), 3.37 (s, 3H), 2.42 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.8 (C), 143.6 (q, J_{C-F} = 258.1 Hz, C), 138.8 (J_{C-F} = 28.2 Hz, C), 134.8 (C), 130.9 (CH), 131.9 (CH), 129.9 (2 × CH), 128.5 (CH), 127.59 (2 × CH), 127.57 (C), 127.5 (CH), 127.0 (2 × CH), 126.2 (CH), 125.2 (J_{C-F} = 3.6 Hz, 2 × CH), 121.9 (C), 120.3 (CH_2), 87.1 (C), 81.6 (CH), 69.2 (C), 57.1 (CH_3), 54.4 (CH_2), 21.7 (CH_3); HRMS (ES) calcd. for $C_{27}H_{24}NO_3SNaF_3$: 522.1327, found: 522.1313 $[M+Na]^+$.

_N_-Allyl-_N_-((2-((4R,5R)-4,5-dimethyl-1,3-dioxolan-2-yl)phenyl)ethynyl)4-methylbenzenesulfonamide 950



Prepared according to **GP18** using the freshly prepared bromoalkyne (4*R*,5*R*)-2-(2-(bromoethynyl)phenyl)-4,5-dimethyl-1,3-dioxolane (**GP16**, 192 mg, 0.69 mmol) and sulfonamide **693** (123 mg, 0.58 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc), 1% Et_3N)] afforded the enantiopure ynamide **950** as a colourless oil (181 mg, 76%); $[\alpha]_D^{19}$ = 26 (c 0.1, $CHCl_3$); IR ν_{max}/cm^{-1} 2975, 2876, 2233, 1364, 1169, 1078, 922, 759, 661; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.63-7.59 (m, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.31-7.25 (m, 3H), 6.28 (s, 1H), 5.79 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H), 5.28 (app. dq, *J* = 16.9, 1.1 Hz, 1H), 5.23 (app. dq, *J* = 10.1, 1.1 Hz, 1H), 4.05 (app. dt, *J* = 6.3, 1.1 Hz, 2H), 3.85-3.79 (m, 2H), 2.44 (s, 3H), 1.42-1.37(m, 3H), 1.34-1.30 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 138.8 (C), 135.0 (C), 131.3 (CH), 131.1 (CH), 129.9 (2 × CH), 128.9 (CH), 128.0 (2 × CH), 127.9 (CH), 126.1 (CH), 122.4(C), 120.3 (CH_2), 100.6 (CH), 86.9 (C), 80.5 (CH), 78.9 (CH), 69.9 (C), 54.3 (CH_2), 21.8 (CH_3), 17.5 (CH_3), 17.1 (CH_3); HRMS (ES) calcd. for $C_{23}H_{25}NO_4NaS$: 434.1390, found: 434.1402 $[M+Na]^+$.

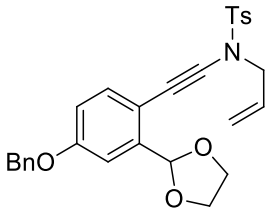
_N_-((2-(1,3-Dithiolan-2-yl)phenyl)ethynyl)-_N_-allyl-4-methylbenzenesulfonamide 954



Prepared according to **GP17** using the freshly prepared terminal alkyne 2-(2-ethynylphenyl)-1,3-dithiolane **953** (147 mg, 0.71 mmol) and sulfonamide **693** (750 mg, 3.6 mmol). Purification by flash column chromatography [50:50 (hexane:toluene), 1%Et_3N] afforded the ynamide **954** as an orange oil (55 mg, 19%); IR ν_{max}/cm^{-1} 2926, 2350, 1363, 1169, 1089, 755, 662; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.31-7.24 (m, 2H), 7.17 (app. td, *J* = 7.5, 1.3 Hz, 1H), 6.03 (s, 1H), 5.81 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.33 (br. dd, *J* = 16.8, 1.2 Hz, 1H), 5.27 (br. dd, *J* = 10.1, 1.2 Hz, 1H), 4.09 (app. dt, *J* = 6.4, 1.1 Hz, 2H), 3.50-3.42 (m, 2H), 3.37-3.29 (m, 2H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 142.3 (C), 134.8 (C), 131.6 (CH), 131.0 (CH), 130.1 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 127.7 (CH), 127.6 (CH), 122.1 (C), 120.5 (CH_2), 77.6 (C), 69.1 (C), 54.5 (CH_2), 53.6 (CH), 39.9 (2 × CH_2), 21.9 (CH_3); HRMS (ES) calcd. for $C_{21}H_{22}NO_2S3$: 416.0813, found: 416.0808 $[M+H]^+$.

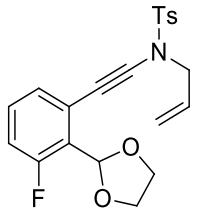
_N_-Allyl-_N_-((4-(benzyloxy)-2-(1,3-dioxolan-2-yl)phenyl)ethynyl)-4-methylbenzenesulfonamide

962



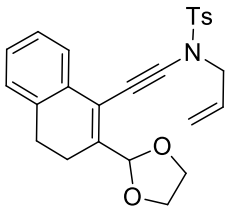
Prepared according to **GP18** using the freshly prepared bromoalkyne 2-(5-(benzyloxy)-2-(bromoethynyl)phenyl)-1,3-dioxolane (**GP16**, 513 mg, 1.4 mmol) and sulfonamide **693** (252 mg, 1.2 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc), 1% Et_3N] afforded the ynamide **962** as a yellow oil (564 mg, 97%); IR ν_{max}/cm^{-1} 2884, 2235, 1607, 1360, 1167, 1061, 1018, 813, 735, 661; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.9 Hz, 2H), 7.45-7.27 (m, 8H), 7.23-7.17 (m, 1H), 6.88 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.05 (s, 1H), 5.78 (ddt, *J* = 17.2, 10.1, 6.2 Hz, 1H), 5.35-5.17 (m, 2H), 5.07 (s, 2H), 4.18-4.10 (m, 2H), 4.07-3.98 (m, 4H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.7 (C), 144.7 (C), 140.4 (C), 136.7 (C), 135.0 (C), 133.6 (CH), 131.1 (CH), 129.9 (2 × CH), 128.7 (2 × CH), 128.8 (2 × CH), 128.0 (CH), 127.7 (2 × CH), 120.1 (CH_2), 116.0 (CH), 114.7 (C), 112.2 (CH), 101.8 (CH), 85.4 (C), 70.3 (CH_2), 68.2 (C), 65.5 (2 × CH_2), 54.5 (CH_2), 21.8 (CH_3); HRMS (ES) calcd. for $C_{28}H_{28}NO_5S$: 490.1688, found: 490.1704 $[M+H]^+$.

_N_-((2-(1,3-Dioxolan-2-yl)-3-fluorophenyl)ethynyl)-_N_-allyl-4-methylbenzenesulfonamide 967



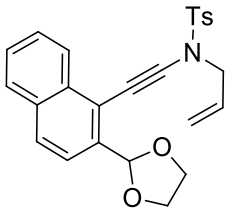
Prepared according to **GP18** using the freshly prepared bromoalkyne 2-(2-(bromoethynyl)-6-fluorophenyl)-1,3-dioxolane (**GP16**, 542 mg, 2.0 mmol) and sulfonamide **693** (352 mg, 1.6 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc), 1% Et_3N)] afforded the ynamide **967** as a white solid (625 mg, 97%); mp. 72-74 °C; IR ν_{max}/cm^{-1} 2232, 1573, 1363, 1213, 1167, 1089, 938, 732, 661; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.25-7.18 (m, 1H), 7.10 (dd, J_{H-H} = 7.7, J_{H-F} = 0.8 Hz, 1H), 6.97 (ddd, J_{H-F} = 10.6 Hz, J_{H-H} = 8.2, 1.1 Hz, 1H), 6.26 (d, J_{H-F} = 0.8 Hz, 1H), 5.77 (ddt, J = 16.5, 10.1, 6.4 Hz, 1H), 5.34-5.28 (m, 2H), 4.31-4.23 (m, 2H), 4.10-3.99 (m, 4H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.6 (d, J_{C-F} = 252.2 Hz, C), 144.9 (C), 134.7 (C), 130.9 (CH), 130.4 (d, J_{C-F} = 10.0 Hz, CH), 129.9 (2 × CH), 127.9 (d, J_{C-F} = 3.2 Hz, CH), 127.8 (2 × CH), 125.2 (d, J_{C-F} = 11.9 Hz, C), 124.8 (d, J_{C-F} = 5.6 Hz, C), 120.4 (CH_2), 115.8 (d, J_{C-F} = 22.5 Hz, CH), 100.7 (d, J_{C-F} = 2.2 Hz, CH), 87.6 (C), 68.7 (d, J_{C-F} = 4.2 Hz, C), 66.0 (2 × CH_2), 54.4 (CH_2), 21.7 (CH_3); HRMS (ES) calcd. for $C_{21}H_{20}NO_4SNaF$: 424.0995, found: 424.0987 $[M+Na]^+$.

_N_-((2-(1,3-Dioxolan-2-yl)-3,4-dihydronaphthalen-1-yl)ethynyl)-_N_-allyl-4-methylbenzenesulfonamide 978



Prepared according to **GP18** using the freshly prepared bromoalkyne 2-(1-(bromoethynyl)-3,4-dihydronaphthalen-2-yl)-1,3-dioxolane (**GP16**, 540 mg, 1.8 mmol) and sulfonamide **693** (313 mg, 1.5 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc), 1% Et_3N] afforded the ynamide **978** as an orange oil (654 mg, 100%); IR ν_{max}/cm^{-1} 2885, 2229, 1366, 1168, 1087, 935, 832, 814, 767, 733, 661; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.51-7.46 (m, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 7.13-7.09 (m, 1H), 5.93 (s, 1H), 5.80 (ddt, *J* = 16.5, 10.1, 6.4 Hz, 1H), 5.35-5.23 (m, 2H), 4.11-4.05 (m, 4H), 3.99-3.94 (m, 2H), 2.80 (t, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 2.40 (t, *J* = 8.0 Hz, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 139.5 (C), 135.8 (C), 134.8 (C), 132.8 (C), 131.2 (CH), 130.0 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 127.3 (CH), 126.6 (CH), 126.0 (CH), 121.7 (C), 120.5 (CH_2), 103.1 (CH), 88.9 (C), 66.9 (C), 65.8 (2 × CH_2), 54.4 (CH_2), 27.6 (CH_2), 21.8 (CH_3), 21.1 (CH_2); HRMS (ES) calcd. for $C_{25}H_{26}NO_4S$: 436.1583, found: 436.1585 $[M+H]^+$.

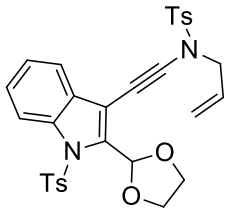
_N_-((2-(1,3-Dioxolan-2-yl)naphthalen-1-yl)ethynyl)-_N_-allyl-4-methylbenzenesulfonamide 979



Prepared according to **GP18** using the freshly prepared bromoalkyne *(Z)*-2-(4-bromo-1-phenylbut-1-en-3-yn-1-yl)-1,3-dioxolane (**GP16**, 453 mg, 1.5 mmol) and sulfonamide **693** (264 mg, 1.3 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc), 1% Et_3N] afforded the ynamide **979** as a viscous, orange oil (479 mg, 89%); IR ν_{max}/cm^{-1} 2887, 2231, 1364, 1169, 1090, 943, 819, 749, 663; ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27-8.20 (m, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.84-7.81 (m, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.55-7.47 (m, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.35 (s, 1H), 5.88 (ddt, *J* = 16.5, 10.1, 6.4 Hz, 1H), 5.39 (app. dq, *J* = 16.5, 1.2 Hz, 1H), 5.32 (app. dq, *J* = 10.1, 1.2 Hz, 1H), 4.28-4.21 (m, 2H), 4.20-4.14 (m, 2H), 4.12-4.07 (m, 2H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 136.1 (C), 134.9 (C), 133.6 (C), 132.7 (C), 131.2 (CH), 130.1 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 127.9 (CH), 126.9 (CH), 126.9 (CH), 126.7 (CH), 123.1 (CH), 120.64 (C), 120.6 (CH_2), 102.4 (CH), 92.3 (C), 67.3 (C), 65.8 (2 × CH_2), 54.5 (CH_2), 21.7 (CH_3); HRMS (ES) calcd. for $C_{25}H_{23}NO_4SNa$: 456.1245, found: 456.1244 $[M+Na]^+$.

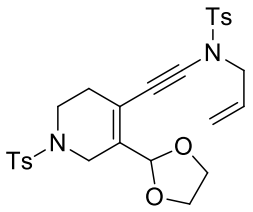
_N_-((2-(1,3-Dioxolan-2-yl)-1-tosyl-1_H_-indol-3-yl)ethynyl)-_N_-allyl-4-methylbenzenesulfonamide

994



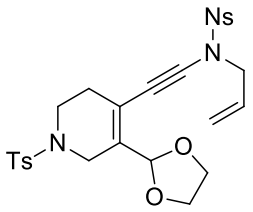
Prepared according to **GP18** using the freshly prepared bromoalkyne 3-(bromoethynyl)-2-(1,3-dioxolan-2-yl)-1-tosyl-1*H*-indole (**GP16**,443 mg, 1.0 mmol) and sulfonamide **693** (169 mg, 0.8 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc), 1% Et_3N] afforded the ynamide **994** as a white foam (372 mg, 81%); mp. 71-73 °C; IR ν_{max}/cm^{-1} 2890, 2233, 1596, 1364, 1168, 1089, 927, 787, 679, 659; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 4H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.35-7.30 (m, 3H), 7.25-7.22 (m, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.81 (s, 1H), 5.81 (ddt, *J* = 16.8, 10.2, 6.2 Hz, 1H), 5.32 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.26 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.24-4.20 (m, 2H), 4.15-4.07 (m, 2H), 4.06-4.00 (m, 2H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.1 (C), 144.9 (C), 138.4 (C), 136.1 (C), 135.5 (C), 135.0 (C), 131.2 (C), 130.3 (CH), 130.0 (2 × CH), 129.8 (2 × CH), 127.9 (2 × CH), 127.4 (2 × CH), 126.3 (CH), 124.0 (CH), 120.6 (CH), 120.2 (CH_2), 115.0 (CH), 106.5 (C), 98.0 (CH), 89.1 (C), 65.6 (2 × CH_2), 63.0 (C), 54.7 (CH_2), 21.8 (CH_3), 21.7 (CH_3); HRMS (ES) calcd. for $C_{30}H_{28}N_2O_6NaS_2$: 599.1286, found: 599.1280 $[M+Na]^+$.

_N_-((5-(1,3-Dioxolan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridin-4-yl)ethynyl)-_N_-allyl-4-methylbenzenesulfonamide 1013



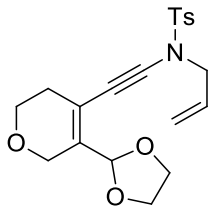
Prepared according to **GP18** using the freshly prepared bromoalkyne 4-(bromoethynyl)-5-(1,3-dioxolan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine (**GP16**, 574 mg, 1.4 mmol) and sulfonamide **693** (246 mg, 1.2 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc), 1% Et_3N] afforded the ynamide **1013** as a yellow oil (285 mg, 45%); IR ν_{max}/cm^{-1} 2888, 2229, 1343, 1165, 1128, 1086, 937, 815, 733, 659; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 5.73-5.62 (m, 2H), 5.20 (br. dd, *J* = 17.1, 1.2 Hz, 1H), 5.18 (dd, *J* = 10.1, 1.1, 1H), 4.03-3.99 (m, 2H), 3.95 (br. d, *J* = 6.4 Hz, 2H), 3.90-3.85 (m, 2H), 3.69 (t, *J* = 2.2 Hz, 2H), 3.13 (t, *J* = 5.7 Hz, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.31-2.24 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 143.7 (C), 134.5 (C), 133.3 (C), 133.0 (C), 130.7 (CH), 129.9 (2 × CH), 129.8 (2 × CH), 127.74 (2 × CH), 127.71 (2 × CH), 120.3 (CH_2), 119.9 (C), 101.9 (CH), 88.2 (C), 68.4 (C), 65.4 (2 × CH_2), 54.1 (CH_2), 42.5 (CH_2), 42.4 (CH_2), 30.0 (CH_2), 21.7 (CH_3), 21.6 (CH_3); HRMS (ES) calcd. for $C_{27}H_{30}N_2O_6S_2Na$: 565.1443, found: 565.1448 $[M+Na]^+$.

_N_-((5-(1,3-Dioxolan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridin-4-yl)ethynyl)-_N_-allyl-4-nitrobenzenesulfonamide 1014



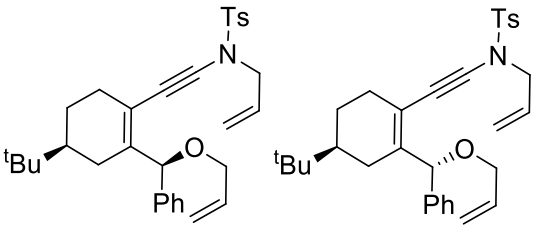
Prepared according to **GP18** using the freshly prepared bromoalkyne 4-(bromoethynyl)-5-(1,3-dioxolan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine (**GP16**, 411 mg, 1.0 mmol) and sulfonamide **694** (202 mg, 0.8 mmol). Purification by flash column chromatography [80:20- 70:30 (hexane:EtOAc), 1% Et_3N] afforded the ynamide **1014** as a bright yellow oil (243 mg, 51%); IR ν_{max}/cm^{-1} 2889, 2233, 1533, 1374, 1349, 1166, 1087, 942, 736, 659; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.9 Hz, 2H), 8.08 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 5.72-5.61 (m, 2H), 5.25 (dd, *J* = 7.5, 0.9 Hz, 1H), 5.21 (bs, 1H), 4.05-4.01 (m, 4H), 3.91-3.87 (m, 2H), 3.70 (t, *J* = 2.2 Hz, 2H), 3.14 (d, *J* = 5.7 Hz, 2H), 2.43 (s, 3H), 2.31-2.26 (m,2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 150.7 (C), 143.8 (C), 142.9 (C), 134.9 (C), 133.2 (C), 130.0 (CH), 129.8 (2 × CH), 129.1 (2 × CH), 127.7 (2 × CH), 124.5 (2 × CH), 121.0 (CH_2), 119.3 (C), 101.8 (CH), 86.8 (C), 69.0 (C), 65.5 (2 × CH_2), 54.6 (CH_2), 42.6 (CH_2), 42.3 (CH_2), 30.0 (CH_2), 21.6 (CH_3); HRMS (ES) calcd. for $C_{26}H_{27}N_3O_8S_2Na$: 596.1137, found: 596.1140 $[M+Na]^+$.

_N_-((5-(1,3-Dioxolan-2-yl)-3,6-dihydro-2_H_-pyran-4-yl)ethynyl)-_N_-allyl-4-methylbenzenesulfonamide 1015



Prepared according to **GP18** using the freshly prepared bromoalkyne 4-(bromoethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydro-2*H*-pyran (**GP16**, 272 mg, 1.0 mmol) and sulfonamide **693** (185 mg, 0.9 mmol). Purification by flash column chromatography [80:20 (hexane:EtOAc), 1% Et_3N] afforded the ynamide **1015** as a colourless oil (181 mg, 53%); IR ν_{max}/cm^{-1} 2886, 2228, 1597, 1365, 1168, 1112, 1077, 935, 837, 815, 760, 663; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.79-5.63 (m, 2H), 5.24 (dd, *J* = 11.7, 1.2 Hz, 1H), 5.23-5.21 (m, 1H), 4.23 (t, *J* = 2.4 Hz, 2H), 4.00-3.92 (m, 4H), 3.91-3.86 (m, 2H), 3.75 (t, *J* = 5.5 Hz, 2H), 2.45 (s, 3H), 2.25-2.19 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 136.3 (C), 134.7 (C), 131.0 (CH), 130.0 (2 × CH), 127.9 (2 × CH), 120.3 (CH_2), 119.3 (C), 102.1 (CH), 87.4 (C), 68.7 (C), 65.5 (2 × CH_2), 63.9 (CH_2), 63.4 (CH_2), 54.3 (CH_2), 29.7 (CH_2), 21.8 (CH_3); HRMS (ES) calcd. for $C_{20}H_{23}NO_5NaS$: 412.1195, found: 412.1198 $[M+Na]^+$.

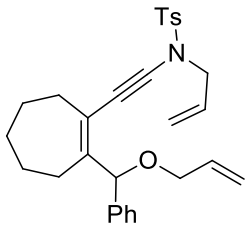
_N_-Allyl-_N_-((2-((allyloxy)(phenyl)methyl)-4-(tert-butyl)cyclohex-1-en-1-yl)ethynyl)-4-methylbenzenesulfonamide 1025



Prepared according to **GP17** using the freshly prepared terminal alkyne ((allyloxy)(5-(tert-butyl)-2-ethynylcyclohex-1-en-1-yl)methyl)benzene **1023** (227 mg, 0.74 mmol) and sulfonamide **693** (777 mg, 3.7 mmol). Purification by flash column chromatography [98:2 (hexane:EtOAc)] afforded the ynamide **1025** as a yellow oil (68 mg, 18%, dr. 1.6:1); IR ν_{max}/cm^{-1} 2925, 1704, 1363, 1167, 1088, 926, 703, 665; ^{1}H-NMR (400 MHz, $CDCl_3$) *(the major diasteroisomer is highlighted in bold, the minor diastereomer is in plain and underlined values refer to overlapping resonances from both diastereomers)* δ 7.79 (2 × d, *J* = 8.4 Hz, 2 x 2H), 7.75 (2 × d, *J* = 8.4 Hz, 2 x 2H), 7.41-7.29 (2 × m, 2 × 3H), 7.28-7.21 (2 × m, 2 × 2H), 6.05-5.90 (2 × m, 2 × 1H), 5.84-5.69 (2 × m, 2 × 1H), 5.58 (s, 1H), **5.57 (s, 1H)**, 5.36-5.12 (2 × m, 2 × 2H), 4.07-4.00 (2 × m, 2 × 2H), 3.95-3.87 (2 × m, 2 × 2H), 2.43 (2 × s, 2 × 3H), 0.81 (s, 9H), **0.80 (s, 9H)**, 2.31-2.24 (2 × m, 2 × 2H), 2.00-1.72 (2 × m, 2 × 2H), 1.53-1.41 (2 × m, 2 × 2H), 1.35-0.83 (2 × m, 2 × 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.71 (C), **144.68 (C)**, 143.4 (C), **143.0 (C)**, **141.2 (C)**, 141.1 (C), 135.1 (C), **135.0 (C)**, 134.7 (CH), **134.8 (CH)**, 131.20 (CH), **131.15 (CH)**, 129.9 (2 × CH), **129.8 (2 × CH)**, 128.1 (2 × s, 2 × 2CH), 127.8 (2 × s, 2 × 2CH), 127.0 (CH), **126.9 (CH)**, 126.0 (2 × CH), **125.9 (2 × CH)**, 120.2 (2 × s, 2 × CH_2), **118.2 (C)**, 118.0 (C), **116.7 (CH_2)**, 116.4 (CH_2), **85.7 (C)**, 85.5 (C), **81.3 (CH)**, 81.0 (CH), 70.7 (2 × s, 2 × C), **69.3 (CH_2)**, 69.1 (CH_2), 54.5 (2 × s, 2 × CH_2), 43.9 (CH), **43.7 (CH)**, 32.3 (2 × s, 2 × C), **32.1**

(CH_2), 32.0 (CH_2), 27.3 (3 × CH_3), **27.1 (3 × CH_3)**, 24.4 (CH_2), **24.0 (CH_2)**, **23.90 (CH_2)**, 23.88 (CH_2), 21.7 (2 × s, 2 × CH_3); HRMS (ES) calcd. for $C_{32}H_{39}NO_3SNa$: 540.2548, found: 540.2558 $[M+Na]^+$.

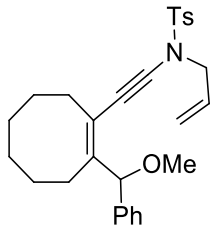
_N_-Allyl-_N_-((2-((allyloxy)(phenyl)methyl)cyclohept-1-en-1-yl)ethynyl)-4-methylbenzenesulfonamide 1035



Prepared according to **GP18** using the freshly prepared bromoalkyne 1-((allyloxy)(phenyl)methyl)-2-(bromoethynyl)cyclohept-1-ene (**GP16**, 219 mg, 0.63 mmol) and sulfonamide **693** (111 mg, 0.53 mmol). Purification by flash column chromatography [95:5 (hexane:EtOAc)] afforded the ynamide **1035** as a colourless oil (192 mg, 76%); IR ν_{max}/cm^{-1} 2923, 2220, 1449, 1367, 1169, 1089, 924, 813, 704, 662; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.31-7.26 (m, 2H), 7.26-7.20 (m, 3H), 5.94 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.76 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.52 (s, 1H), 5.29 (ddt, *J* = 17.2, 1.8, 1.7 Hz, 1H), 5.23 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.18 (dd, *J* = 10.1, 1.0 Hz, 1H), 5.12 (app. dq, *J* = 10.5, 1.5 Hz, 1H), 4.05-3.97 (m, 3H), 3.85 (app. ddt, *J* = 13.1, 5.5, 1.5 Hz, 1H), 2.46-2.40 (m, 1H), 2.39 (s, 3H), 2.37-2.29 (m, 1H), 2.15-1.98 (m, 2H), 1.73-1.45 (m, 4H), 1.32-1.23 (m, 1H), 1.09-0.98 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 148.3 (C), 144.7 (C), 141.1 (C), 135.2 (CH), 134.8 (C), 131.3 (CH), 129.9 (2 × CH), 128.0 (2 × CH), 127.9 (2 × CH), 126.9 (2 × CH), 125.9 (2 × CH), 124.0 (C), 120.2 (CH_2), 116.4 (CH_2), 86.0 (C), 81.7 (CH), 72.5 (C), 69.3 (CH_2), 54.6 (CH_2), 35.4 (CH_2), 35.2 (CH_2),

27.5 (CH_2), 26.64 (CH_2), 26.55 (CH_2), 21.8 (CH_3); HRMS (ES) calcd. for $C_{29}H_{33}NO_3SNa$: 498.2079, found: 498.2070 $[M+Na]^+$.

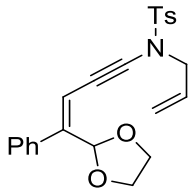
(*Z*)-*N*-allyl-*N*-((2-(Methoxy(phenyl)methyl)cyclooct-1-en-1-yl)ethynyl)-4-methylbenzenesulfonamide 1036



Prepared according to **GP17** using the freshly prepared terminal alkyne *(Z)*-1-ethynyl-2-(methoxy(phenyl)methyl)cyclooct-1-ene **1034** (530 mg, 2.1 mmol) and sulfonamide **693** (2.2 g, 10.4 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the ynamide **1036** as an orange oil (453 mg, 47%); IR ν_{max}/cm^{-1} 2926, 2220, 1450, 1366, 1167, 1089, 1029, 813, 703, 661; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.38-7.33 (m, 2H), 7.31-7.18 (m, 5H), 5.79 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.48 (s. 1H), 5.26 (app. dq, *J* = 16.8, 1.3 Hz, 1H), 5.23-5.19 (m, 1H), 4.05 (app. dt, *J* = 6.4, 1.3 Hz, 2H), 3.32 (s, 3H), 2.41 (s, 3H), 2.40-2.33 (m, 1H), 2.30-2.13 (m, 2H), 2.08-1.97 (m, 1H), 1.64-1.58 (m, 1H), 1.47-1.20 (m, 6H), 0.72-0.57 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.3 (C), 144.8 (C), 141.4 (C), 134.8 (C), 131.3 (CH), 129.9 (2 × CH), 128.1 (2 × CH), 127.9 (2 × CH), 127.0 (CH), 125.6 (2 × CH), 121.2 (C), 120.3 (CH_2), 85.4 (C), 83.9 (CH), 71.7 (C), 56.7 (CH_3), 54.6 (CH_2), 31.5 (CH_2), 30.9 (CH_2), 28.6 (CH_2), 26.9 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 21.8 (CH_3); HRMS (ES) calcd. for $C_{28}H_{33}NO_3SNa$: 486.2079, found: 486.2081 $[M+Na]^+$.

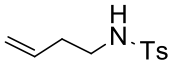
(*Z*)-*N*-(4-(1,3-Dioxolan-2-yl)-4-phenylbut-3-en-1-yn-1-yl)-*N*-allyl-4-methylbenzenesulfonamide

1047



Prepared according to **GP18** using the freshly prepared bromoalkyne *(Z)*-2-(4-bromo-1-phenylbut-1-en-3-yn-1-yl)-1,3-dioxolane (**GP16**, 409 mg, 1.5 mmol) and sulfonamide **693** (254 mg, 1.2 mmol). Purification by flash column chromatography [95:5- 70:30 (hexane:EtOAc), 1% Et_3N] afforded the ynamide **1047** as a yellow oil (470 mg, 96%); IR ν_{max}/cm^{-1} 2886, 2228, 1367, 1169, 1089, 941, 762, 664; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.61-7.55 (m, 2H), 7.35-7.29 (m, 5H), 6.17 (d, *J* = 7.5 Hz, 1H), 5.83 (d, *J* = 7.5 Hz, 1H), 5.86-5.72 (m, 1H), 5.34-5.28 (m, 1H), 5.26 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.10-4.02 (m, 2H), 4.01-3.65 (m, 2H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 136.7 (C), 134.7 (C), 131.1 (CH), 130.1 (2 × CH), 128.9 (C), 128.8 (CH), 128.5 (2 × CH), 128.2 (CH), 127.9 (2 × CH), 126.6 (2 × CH), 120.6 (CH_2), 102.1 (CH), 90.2 (C), 68.4 (C), 65.3 (2 × CH_2), 54.36 (CH_2), 21.81 (CH_3); HRMS (ES) calcd. for $C_{23}H_{24}NO_4S$: 410.1426, found: 410.1407 $[M+H]^+$.

N-(But-3-en-1-yl)-4-methylbenzenesulfonamide 1049

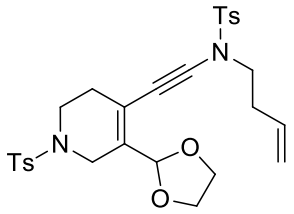


Tosyl amine (1.37 g, 8.0 mmol, 1.0 eq.) was dissolved in acetone (8 mL, 1.0 M) followed by addition of K_2CO_3 (2.21 g, 16.0 mmol, 2.0 eq.) and 4-bromobutene (0.81 mL, 8.0 mmol, 1.0 eq.). The solution was stirred at 60 °C for 24 hours and then the reaction was quenched by addition

of saturated NH_4Cl solution (10 mL). The residue was extracted with Et_2O (2 × 10 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography [80:20 (hexane:EtOAc)] afforded the sulfonamide **1049** as a pale yellow oil (998 mg, 55%); IR ν_{max}/cm^{-1} 3284, 2927, 1426, 1324, 1159, 1094, 919, 815, 663; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.62 (ddt, *J* = 17.1, 10.4, 6.9 Hz, 1H), 5.10-4.99 (m, 2H), 4.39 (t, *J* = 6.5 Hz, 1H), 3.02 (dd, *J* = 12.9, 6.5 Hz, 1H), 2.43 (s, 3H), 2.25-2.15 (m, 2H).

Data matches that reported in the literature.[205]

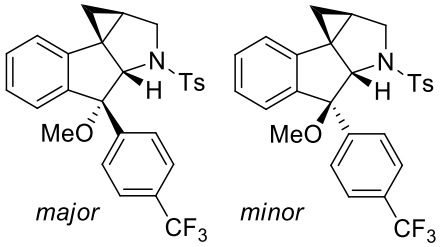
_N_-((5-(1,3-Dioxolan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridin-4-yl)ethynyl)-_N_-(but-3-en-1-yl)-4-methylbenzenesulfonamide 1050



Prepared according to **GP18** using the freshly prepared bromoalkyne 4-(bromoethynyl)-5-(1,3-dioxolan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine (**GP16**, 411 mg, 1.0 mmol) and sulfonamide **1049** (187 mg, 0.8 mmol). Purification by flash column chromatography [80:20- 70:30 (hexane:EtOAc), 1% Et_3N] afforded the ynamide **1050** as a colourless oil (141 mg, 32%); IR ν_{max}/cm^{-1} 2888, 2227, 1366, 1343, 1163, 1128, 1085, 932, 735, 659; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 5.73-5.61 (m, 1H), 5.69 (s, 1H), 5.08-5.03 (m, 1H), 5.03-5.00 (m, 1H), 4.04-3.99 (m, 2H), 3.92-3.87 (m, 2H), 3.71 (t, *J* = 2.2 Hz, 2H), 3.38 (t, *J* = 7.3 Hz, 2H), 3.15 (t, *J* = 5.7 Hz, 2H), 2.45 (s, 3H), 2.42

(s, 3H), 2.36-2.28 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 143.8 (C), 134.5 (C), 133.6 (CH), 133.4 (C), 133.3 (C), 130.0 (2 × CH), 129.9 (2 × CH), 127.8 (2 × CH), 127.8 (2 × CH), 120.0 (C), 118.0 (CH_2), 102.0 (CH), 88.3 (C), 68.6 (C), 65.5 (2 × CH_2), 50.8 (CH_2), 42.7 (CH_2), 42.5 (CH_2), 32.4 (CH_2), 30.2 (CH_2), 21.81 (CH_3), 21.7 (CH_3); HRMS (ES) calcd. for $C_{28}H_{32}N_2O_6NaS_2$: 579.1599, found: 579.1602 $[M+Na]^+$.

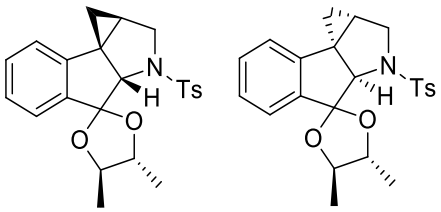
4-Methoxy-3-tosyl-4-(4-(trifluoromethyl)phenyl)-1,1a,2,3,3a,4-hexahydrocyclopropa[c]indeno[2,1-b]pyrrole 946



Prepared according to **GP20** using ynamide **934** (100.1 mg, 0.2 mmol), stirring at 85 °C for 2 hours. Purification by flash column chromatography [90:10 (hexane:EtOAc)] afforded the polycycle **946** as a white solid (87.1 mg, 87%, dr. 5.2: 1); mp. 186-188 °C; IR ν_{max}/cm^{-1} 2928, 1348, 1326, 1160, 1098, 814, 750, 708, 666; ^{1}H-NMR (400 MHz, $CDCl_3$) *(the major diasteroisomer is highlighted in bold, the minor diastereomer is in plain and underlined values refer to overlapping resonances from both diastereomers)* δ **7.61 (d, *J* = 8.3 Hz, 2H),** 7.56 (d, *J* = 8.1 Hz, 2H), 7.50-7.40 (2 × m, **2H** and 4H), 7.38-7.28 (2 × m, **4H** and 2H), 7.22-7.17 (2 × m, **3H** and 2H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), **6.91-6.87 (m, 1H)**, **5.04 (s, 1H),** 4.38 (s, 1H), 4.11 (dd, *J* = 10.6, 4.2 Hz, 1H), 3.77 (d, *J* = 10.6 Hz, 1H), **3.50 (s, 3H)**, **3.26 (d, *J* = 11.3 Hz, 1H)**, 3.03 (s, 3H), **2.48-2.45 (m, 1H), 2.44 (s, 3H),** 2.41 (s, 3H), 1.58-1.54 (m, 1H), **1.33-1.27 (m, 2H),** 1.28-1.24 (m, 1H), 0.20 (dd, *J* = 5.8, 5.2 Hz, 1H), **-0.01- (-0.08) (m, 1H)**; ^{13}C-NMR (101 MHz, $CDCl_3$)

δ **146.11 (C),** 146.10 (C), **143.42 (C),** 143.41 (C), 142.7 (C), **142.4 (C),** 141.7 (C), **141.1 (C),** 137.3 (C), **136.8 (C), 129.90 (2 × CH),** 129.91 (2 × CH), 129.7 (2 × s, CH and **CH**), **129.6 (q, J_{C-F} = 34.2 Hz, C),** 129.3 (q, J_{C-F} = 35.0 Hz, C), **128.4 (2 × CH), 128.1 (CH),** 128.0 (2 × CH), 127.6 (CH), 127.2 (2 × CH), **127.17 (2 × CH),** 126.4 (CH), **125.7 (CH),** 125.0 (q, J_{C-F} = 3.8 Hz, 2 × CH), **124.5 (q, J_{C-F} = 3.8 Hz, 2 × CH),** 120.1 (CH), **119.7 (CH), 91.6 (C),** 88.6 (C), 79.8 (CH), **72.9 (CH),** 54.7 (CH_2), **53.1 (CH_2),** 52.1 (CH_3), **52.0 (CH_3),** 38.7 (C), **38.0 (C),** 29.8 (CH), **27.1 (CH),** 26.8 (CH_3), **21.7 (CH_3), 12.1 (CH_2),** 11.2 (CH_2), *(resonances corresponding to the quaternary carbon of the CF_3 group are not visible for either diastereomer)*; HRMS (ES) calcd. for $C_{27}H_{24}NO_3NaSF_3$: 522.1327, found:522.1326 $[M+Na]^+$.

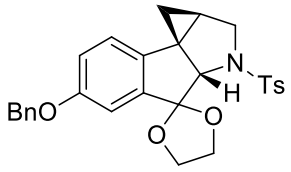
(4'*R*,5'*R*)-4',5'-Dimethyl-3-tosyl-1a,2,3,3a-tetrahydro-1*H*-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] 951



Prepared according to **GP20** using ynamide **950** (82.2 mg, 0.2 mmol), stirring at 60 °C for 1 hour. Purification by flash column chromatography [80:20 (hexane:EtOAc), 1% Et_3N] afforded the polycycle **951** as a white solid (81.0 mg, 99%, dr. 1.7: 1); mp. 120-122 °C; IR ν_{max}/cm^{-1} 2973, 1349, 1270, 1163, 1086, 912, 668; ^{1}H-NMR (400 MHz, $CDCl_3$) *(the major diasteroisomer is highlighted in bold, the minor diastereomer is in plain and underlined values refer to overlapping resonances from both diastereomers)* δ 7.74 (2 × d, *J* = 8.2 Hz, 2 × 2H), 7.41-7.35 (2 × m, 2 × 1H), 7.33 (2 × d, *J* = 8.0 Hz, 2 × 2H), 7.28-7.23 (2 × m, 2 × 2H), 6.78-6.73 (m, 1H), **6.73-6.69 (m, 1H)**,

4.46-4.41 (m, 1H), 4.41 (s, 1H), **4.32 (s, 1H), 4.31-4.26 (m, 1H), 4.09 (dd, *J* = 11.5, 4.4 Hz, 1H)**, 4.05-3.95 (2 × m, 2 × 1H), 3.90-3.84 (m, 1H), **3.66 (d, *J* = 11.5 Hz, 1H),** 3.64 (d, *J* = 11.3 Hz, 1H), 2.44 (2 × s, 2 × 3H), **1.50 (d, *J* = 6.0 Hz, 3H),** 1.43-1.37 (m, 2 × 1H and 6H), **1.33 (d, *J* = 6.0 Hz, 3H)**, 1.20-1.13 (2 × m, 2 × 1H), -0.24 (dd, *J* = 6.0, 5.1 Hz, 1H), **-0.39 (dd, *J* = 6.0, 5.2 Hz, 1H)**; ^{13}C-NMR (101 MHz, $CDCl_3$) δ **143.8 (C)**, 143.7 (C), **142.5 (C)**, 142.3 (C), **139.8 (C)**, 139.6 (C), 136.9 (C), **136.2 (C)**, 130.2 (2 × s, 2 × CH), 129.98 (2 × CH), **130.0 (2 × CH)**, **127.9 (CH)**, 127.7 (CH), **127.3 (2 × CH)**, 127.2 (2 × CH), **123.8 (CH)**, 123.6 (CH), 119.6 (CH), **119.3 (CH)**, 112.7 (C), **112.4 (C)**, 81.4 (2 × s, 2 × CH), 79.7 (CH), **79.2 (CH)**, **74.7 (CH)**, 74.5 (CH), **53.9 (CH_2)**, 54.3 (CH_2), **37.6 (C)**, 37.4 (C), 26.4 (2 × s, 2 × CH), 21.7 (2 × s, 2 × CH_3), 16.9 (CH_3), 16.6 **(CH_3)**, 16.4 (CH_3), **16.0 (CH_3)**, **11.4 (CH_2)**, 11.2 (CH_2); HRMS (ES) calcd. for $C_{23}H_{25}NO_4NaS$: 434.1402, found: 434.1397 $[M+Na]^+$.

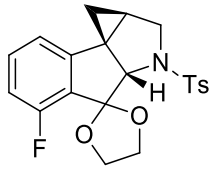
6-(Benzyloxy)-3-tosyl-1a,2,3,3a-tetrahydro-1*H*-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] 968



Prepared according to **GP20** using ynamide **962** (98.0 mg, 0.2 mmol), stirring at 50 °C for 4 hours. Purification by flash column chromatography [98:2 (toluene:Et_2O), 1% Et_3N)] and recrystallisation from [CH_2Cl_2:hexane] afforded the polycycle **968** as a white solid (48.1 mg, 50%); mp. 132-134 °C; IR ν_{max}/cm^{-1} 2892, 1596, 1500, 1345, 1184, 1161, 1102, 1006, 736, 114; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.44-7.29 (m, 7H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.89 (d, *J* = 8.3, 2.4 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.04 (s, 2H), 4.58-4.50 (m, 1H), 4.48-4.38 (m, 1H), 4.35 (s, 1H), 4.30-4.15 (m, 2H), 4.06 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.65 (d, *J* = 11.3 Hz, 1H), 2.44

(s, 3H), 1.40-1.32 (m, 1H), 1.13 (dd, *J* = 8.0, 6.4 Hz, 1H), -0.29- (-0.35) (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.1 (C), 143.8 (C), 142.5 (C), 137.0 (C), 136.3 (C), 132.3 (C), 130.0 (2 × CH), 128.7 (2 × CH), 128.2 (CH), 127.7 (2 × CH), 127.3 (2 × CH), 120.4 (CH), 118.1 (CH), 113.4 (C), 109.6 (CH), 74.7 (CH), 70.5 (CH_2), 66.8 (CH_2), 66.1 (CH_2), 54.3 (CH_2), 37.2 (C), 25.7 (CH), 21.7 (CH_3), 11.4 (CH_2); HRMS (ES) calcd. for $C_{28}H_{27}NO_5NaS$: 512.1508, found: 512.1499 $[M+Na]^+$.

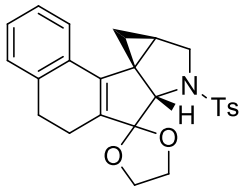
5-Fluoro-3-tosyl-1a,2,3,3a-tetrahydro-1*H*-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] 969



Prepared according to **GP20** using ynamide **967** (80.3 mg, 0.2 mmol), stirring at 80 °C for 15 minutes. Purification by flash column chromatography [70:30 (hexane:EtOAc), 1% Et_3N)] afforded the polycycle **969** as a white solid (74.9 mg, 93%). Alternatively on a larger scale reaction, ynamide **967** (597.0 mg, 1.49 mmol) and **Au-1** (14.5 mg, 2.5 mol%) were stirred in toluene (14.9 mL) at 80 °C for 15 minutes. The crude mixture was purified as described above to give the polycycle **969** as a white solid (567.4 mg, 95%); mp. 134-136 °C; IR ν_{max}/cm^{-1} 2899, 1589, 1479, 1342, 1241, 1164, 1003, 785, 665; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.25-7.19 (m, 1H), 6.88 (t, *J* = 8.9 Hz, 1H), 6.53 (d, J_{H-F} = 7.5 Hz, 1H), 4.38 (s, 1H), 4.37-4.29 (m, 2H), 4.27-4.20 (m, 2H), 4.04 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.68 (d, *J* = 11.3 Hz, 1H), 2.44 (s, 3H), 1.46-1.41 (m, 1H), 1.26 (dd, *J* = 8.0, 6.4 Hz, 1H), -0.09- (-0.13) (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.1 (d, J_{C-F} = 253.2 Hz, C), 143.8 (C), 143.4 (d, J_{C-F} = 5.0 Hz, C), 136.5 (C), 132.3 (d, J_{C-F} = 8.0 Hz, CH), 130.0 (2 × CH), 127.5 (d, J_{C-F} = 19.8 Hz, C), 127.2 (2 × CH), 115.2

(d, $J_{C\text{-}F}$ = 3.2 Hz, CH), 115.0 (d, $J_{C\text{-}F}$ = 20.8 Hz, CH), 113.0 (C), 74.2 (CH), 66.31 (CH_2), 66.29 (CH_2), 53.8 (CH_2), 37.5 (d, $J_{C\text{-}F}$ = 2.0 Hz, C), 27.0 (CH), 21.7 (CH_3), 12.2 (CH_2); HRMS (ES) calcd. for $C_{21}H_{21}NO_4FS$: 402.1175, found: 402.1178 $[M+H]^+$.

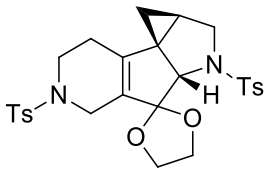
3-Tosyl-1a,2,3,3a,5,6-hexahydro-1*H*-spiro[benzo[6,7]indeno[2,1-b]cyclopropa[c]pyrrole-4,2'-[1,3]dioxolane] 980



Prepared according to a modified **GP20** using ynamide **978** (87.3 mg, 0.2 mmol), DMSAuCl (5.6 mg, 10 mol%), stirring at 80 °C for 3 hours. Purification by flash column chromatography [98:2 (toluene:Et_2O), 1% Et_3N)] afforded the polycycle **980** as a white solid (60.1 mg, 69%); mp. 161-163 °C; IR ν_{max}/cm^{-1} 2889, 1346, 1267, 1162, 1020, 950, 813, 732, 664; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.20-7.08 (m, 2H), 7.04 (app. td, *J* = 7.4, 1.9 Hz, 1H), 6.59 (d, *J* = 7.4 Hz, 1H), 4.45-4.39 (m, 1H), 4.34 (dd, *J* = 14.2, 7.0 Hz, 1H), 4.20 (s, 1H), 4.13-3.98 (m, 3H), 3.75 (d, *J* = 11.4 Hz, 1H), 2.87-2.77 (m, 2H), 2.44 (s, 3H), 2.41-2.33 (m, 1H), 2.21 (ddd, *J* = 16.6, 12.1, 8.6 Hz, 1H), 1.71-1.64 (m, 1H), 1.52-1.46 (m, 1H), -0.42 (dd, *J* = 6.1, 5.3 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.8 (C), 138.9 (C), 137.4 (C), 136.1 (C), 135.2 (C), 131.1 (C), 130.0 (2 × CH), 128.3 (CH), 127.9 (CH), 127.3 (2 × CH), 126.4 (CH), 122.2 (CH), 114.6 (C), 74.7 (CH), 66.5 (CH_2), 66.3 (CH_2), 54.4 (CH_2), 38.1 (C), 28.7 (CH), 21.7 (CH_3), 20.1 (CH_2), 19.4 (CH_2), 11.7 (CH_2); HRMS (ES) calcd. for $C_{25}H_{25}NO_4NaS$: 458.1402, found: 458.1400 $[M+Na]^+$.

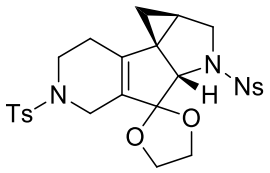
3,6-Ditosyl-1a,2,3,3a,5,6,7,8-octahydro-1*H*-

spiro[cyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridine-4,2'-[1,3]dioxolane] 1016



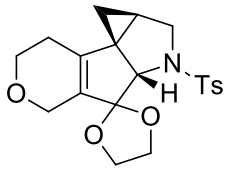
Prepared according to **GP20** using ynamide **1013** (108.1 mg, 0.2 mmol), stirring at 60 °C for 20 minutes. Purification by flash column chromatography [60:40 (hexane:EtOAc), 1% Et_3N)] afforded the polycycle **1016** as a white solid (102.1 mg, 95%); mp. 76-78 °C; IR ν_{max}/cm^{-1} 2924, 1341, 1160, 1007, 940, 816, 730, 665; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 4H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.43-4.37 (m, 2H), 4.10-4.03 (m, 1H), 4.01 (s, 1H), 3.98-3.87 (m, 2H), 3.74 (dt, *J* = 15.9, 2.4 Hz, 1H), 3.62-3.52 (m, 2H), 3.20 (t, *J* = 5.7 Hz, 2H), 2.41 (s, 3H), 2.42 (s, 3H), 1.93-1.80 (m, 1H), 1.72-1.64 (m, 1H), 1.35-1.05 (m, 1H), 0.71 (dd, *J* = 8.2, 6.2 Hz, 1H), -0.55 (dd, *J* = 6.2, 5.2 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 143.7 (C), 137.5 (C), 135.8 (C), 134.0 (C), 131.0 (C), 130.0 (2 × CH), 129.8 (2 × CH), 127.8 (2 × CH), 127.3 (2 × CH), 114.6 (C), 77.9 (CH), 66.24 (CH_2), 66.17 (CH_2), 54.1 (CH_2), 42.6 (CH_2), 41.8 (CH_2), 40.0 (C), 22.2 (CH_2), 21.7 (CH_3), 21.6 (CH_3), 20.0 (CH), 11.1 (CH_2); HRMS (ES) calcd. for $C_{27}H_{30}N_2O_6NaS_2$: 565.1443, found: 565.1453 $[M+Na]^+$.

3-((4-Nitrophenyl)sulfonyl)-6-tosyl-1a,2,3,3a,5,6,7,8-octahydro-1*H*-spiro[cyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridine-4,2'-[1,3]dioxolane] 1017



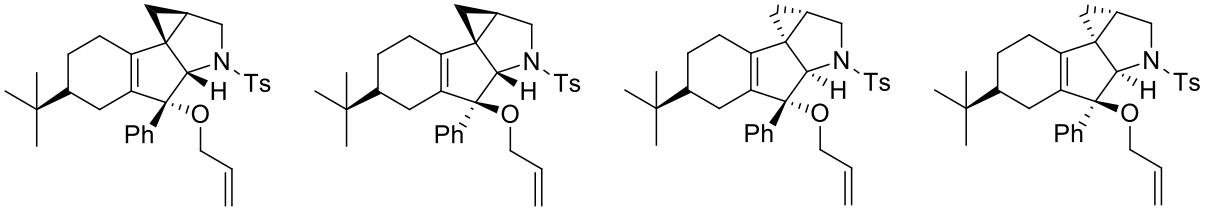
Prepared according to **GP20** using ynamide **1014** (111.0 mg, 0.2 mmol), stirring at 80 °C for 1 hour. Purification by flash column chromatography [70:30- 50:50 (hexane:EtOAc), 1% Et_3N)] afforded the polycycle **1017** as a white solid (88.8 mg, 80%); decomposition at 180 °C; IR ν_{max}/cm^{-1} 2901, 1523, 1346, 1159, 1108, 940, 816, 734, 684; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8, Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2Hz, 2H), 4.34 (app. td, *J* = 6.9, 4.5 Hz, 1H), 4.25 (dd, *J* = 14.2, 7.0 Hz, 1H), 4.08 (app. td, *J* = 6.9, 4.5 Hz, 1H), 4.02 (s, 1H), 4.01-3.93 (m, 2H), 3.72 (dt, *J* = 16.1, 2.2 Hz, 1H), 3.62-3.55 (m, 2H), 3.27-3.13 (m, 2H), 2.42 (s, 3H), 1.94-1.84 (m, 1H), 1.74-1.66 (m, 1H), 1.20-1.14 (m, 1H), 0.83 (dd, *J* = 8.1, 6.2 Hz, 1H), -0.55 (dd, *J* = 6.2, 5.3 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 150.3 (C), 144.4 (C), 143.8 (C), 137.1 (C), 134.0 (C), 131.4 (C), 129.8 (2 × CH), 128.4 (2 × CH), 127.8 (2 × CH), 124.7 (2 × CH), 114.5 (C), 74.0 (CH), 66.4 (CH_2), 66.3 (CH_2), 54.3 (CH_2), 42.5 (CH_2), 41.8 (CH_2), 39.8 (C), 22.2 (CH_2), 21.6 (CH_3), 19.8 (CH), 11.4 (CH_2); HRMS (ES) calcd. for $C_{26}H_{27}N_3O_8NaS_2$: 596.1137, found: 596.1145 $[M+Na]^+$.

3-Tosyl-1,1a,2,3,3a,5,7,8-octahydrospiro[cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-4,2'-[1,3]dioxolane] 1018



Prepared according to **GP20** using ynamide **1015** (78.0 mg, 0.2 mmol), stirring at 60 °C for 20 minutes. Purification by flash column chromatography [70:30- 50:50 (hexane:EtOAc), 1% Et_3N)] afforded the polycycle **1018** as a white solid (70.2 mg, 90%); mp. 163-164 °C; IR ν_{max}/cm^{-1} 2893, 1347, 1278, 1163, 1107, 1026, 816, 665; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 4.41-4.28 (m, 2H), 4.23 (dt, *J* = 15.6, 2.4 Hz, 1H), 4.11-4.05 (m, 1H), 4.08 (s, 1H), 4.05-3.99 (m, 1H), 3.99 (dd, *J* = 11.2, 3.8 Hz, 1H), 3.88 (q, *J* = 3.8 Hz, 1H), 3.81-3.68 (m, 2H), 3.63 (d, *J* = 11.2 Hz, 1H), 2.43 (s, 3H), 1.91-1.82 (m, 1H), 1.71-1.61 (m, 1H), 1.29-1.23 (m, 1H), 0.79 (dd, *J* = 8.1, 5.1 Hz, 1H), -0.51 (dd, *J* = 6.3, 5.1 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.8 (C), 136.8 (C), 135.9 (C), 134.0 (C), 130.0 (2 × CH), 127.3 (2 × CH), 115.0 (C), 73.9 (CH), 66.2 (CH_2), 66.1 (CH_2), 63.7 (CH_2), 62.5 (CH_2), 54.3 (CH_2), 40.4 (C), 22.6 (CH_2), 21.7 (CH_3), 19.8 (CH), 11.0 (CH_2); HRMS (ES) calcd. for $C_{20}H_{23}NO_5NaS$: 412.1195, found: 412.1192 $[M+Na]^+$.

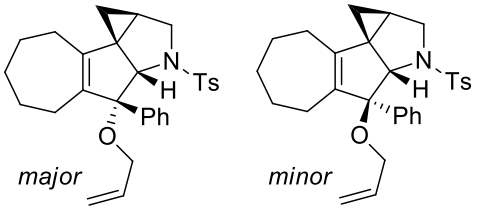
4-(Allyloxy)-6-(*tert*-butyl)-4-phenyl-3-tosyl-1,1a,2,3,3a,4,5,6,7,8-decahydrocyclopropa[c]indeno[2,1-b]pyrrole 1026



Prepared according to **GP20** using the ynamide **1025** (67.0 mg, 0.13 mmol), stirring at 50 °C for 15 minutes. Purification by flash column chromatography [98:2 (hexane:EtOAc), 1% Et_3N)] afforded the tetracycle **1026** as a yellow solid (50 mg, 74%, dr. 1.5: 1.3: 1.1: 1); mp. 74-76 °C; IR ν_{max}/cm^{-1} 2960, 1349, 1159, 1096, 1043, 812, 782; 664; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56-7.50 (m, 4 × 1H), 7.50-7.45 (m, 4 × 2H), 7.44-7.39 (m, 4 × 1H), 7.39-7.34 (m, 4 × 2H), 7.32-7.22 (m, 4 × 2H), 7.19-7.12 (m, 4 × 1H), 6.10 (ddt, *J* = 17.1, 10.4, 5.2 Hz, 2 x 1H), 5.52-5.40 (m, 2 × 1H and 4 × 1H), 5.28-5.18 (m, 2 × 1H and 4 × 1H), 4.68 (s, 1H), 4.65 (s, 1H), 4.39-4.32 (m, 2 × 1H), 4.06 (ddt, *J* = 12.7, 5.2, 1.6 Hz, 1H), 3.94 (ddt, *J* = 12.4, 5.4, 1.5 Hz, 1H), 3.58 (d, *J* = 3.6 Hz, 2 × 1H), 3.56 (d, *J* = 11.8 Hz, 2 × 1H), 3.35 (d, *J* = 4.4 Hz, 1H), 3.32 (d, *J* = 4.4 Hz, 1H), 3.23 (d, *J* = 8.6 Hz, 1H), 3.20 (d, *J* = 8.5 Hz, 1H), 2.76-2.48 (m, 4 × 1H), 2.41 (s, 3H), 2.38 (s, 3H), 2.36 (s, 2 × 3H), 2.30-2.14 (m, 4 × 1H), 2.11-2.00 (m, 8 × 1H), 2.00-1.87 (m, 4 × 2H), 1.83-1.70 (m, 4 × 1H), 1.55-1.09 (m, 4 × 1H), 0.92-0.88 (m, 2H), 0.86 (s, 9H), 0.85 (s, 9H), 0.84 (s, 9H), 0.83 (s, 9H), 0.43 (t, *J* = 5.7 Hz, 2 × 1H), 0.06-0.05 (m, 6H), -0.25 --0.30 (m, 1H), -0.33 --0.38 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.2 (4 × s, C), 141.5, 141.3, 141.6, 140.8 (C), 138.88, 138.90, 138.4, 138.3 (C), 137.83, 138.78, 137.6, 137.5 (C), 137.13, 137.12, 137.0, 136.9 (C), 135.8, 135.2 (2 × s, CH), 129.7, 129.6, 129.3, 129.1 (2 × CH), 129.3, 129.1 (2 × s, 2 × CH), 128.0, 129.95, 127.91, 127.90 (2 × CH), 127.43, 127.40,

127.30, 127.29 (2 × CH), 127.3, 127.2 (2 × s), 127.1 (CH), 116.0, 115.9, 113.8, 113.0 (CH_2), 94.3, 94.0 (2 × s, C), 74.1, 73.2, 71.8 (2 × s) (CH), 65.0, 64.8 (2 × s, CH_2), 53.39, 53.37, 50.3, 50.0 (CH_2), 45.6, 45.1, 44.8, 44.7 (CH), 40.9, 40.7, 36.8, 36.4 (C), 32.53, 32.50, 32.49 (2 × s) (C), 27.7, 27.6, 27.5, 27.4 (3 × CH_3), 26.3, 26.1, 26.0, 25.5 (CH_2), 24.8, 24.3 (2 × s, CH_2), 23.9, 23.8, 23.5, 23.3 (CH_2), 21.7, 21.6 (2 × s, CH_3), 20.2, 20.0 (2 × s, CH), 11.4, 11.0, 10.95, 10.9 (CH_2); HRMS (ES) calcd. for $C_{32}H_{39}NO_3NaS$: 540.2548, found: 540.2557 $[M+Na]^+$.

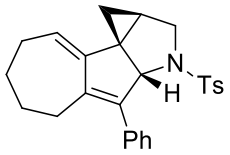
4-(Allyloxy)-4-phenyl-3-tosyl-1a,2,3,3a,4,5,6,7,8,9-decahydro-1*H*-azuleno[2,1-b]cyclopropa[c]pyrrole 1037



Prepared according to **GP20** using ynamide **1035** (95.1 mg, 0.2 mmol), stirring at 55 °C for 20 minutes. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] afforded the polycycle **1037** as a white solid (63.5 mg, 67%, dr. 1.8: 1); mp. 32-34 °C; IR ν_{max}/cm^{-1} 2922, 1350, 1161, 1099, 917, 813, 752, 663; ^{1}H-NMR (400 MHz, $CDCl_3$) *(the major diasteroisomer is highlighted in bold, the minor diastereomer is in plain and underlined values refer to overlapping resonances from both diastereomers)* δ **7.48 (d, *J* = 8.3 Hz, 2H)**, **7.40 (d, *J* = 8.3 Hz, 2H)**, 7.42-7.26 (m, 5H and **2H**), 7.25-7.21 (m, 2H and **3H**), 7.16 (d, *J* = 8.0 Hz, 2H), **6.09 (ddt, *J* = 17.2, 10.4, 5.1 Hz, 1H)**, 5.98 (ddt, *J* = 17.2, 10.5, 4.7 Hz, 1H), **5.45 (app. dq, *J* = 17.2, 1.7 Hz, 1H)**, 5.39 (app. dq, *J* = 17.2, 1.9 Hz, 1H), **5.20 (app. dq, *J* = 10.4, 1.6 Hz, 1H)**, 5.15 (app. dq, *J* = 10.5, 1.9 Hz, 1H), **4.63 (s, 1H)**, **4.36 (app. dt, *J* = 5.0, 1.6 Hz, 1H)**, **4.32 (app. dt, *J* = 5.0, 1.6 Hz, 1H)**, 4.08 (s, 1H), 3.98-

3.96 (m, 1H), 3.96-3.93 (m, 2H), 3.90 (dd, J = 10.6, 4.7 Hz, 1H), 3.64 (d, *J* = 10.6 Hz, 1H), **3.26 (d, *J* = 11.0 Hz, 1H)**, **2.70 (dd, *J* = 11.0, 4.3 Hz, 1H)**, **2.41 (s, 3H)**, 2.37 (s, 3H), 2.06-1.41 (m, **9H** and 10H), **1.36-1.29 (m, 1H)**, **1.15-1.10 (m, 1H)**, 1.06 (dd, *J* = 8.2, 5.9 Hz, 1H), **0.94 (dd, *J* = 8.3, 6.0 Hz, 1H)**, 0.03- (-0.02) (m, 1H), **-0.22 (dd, *J* = 6.0, 5.1 Hz, 1H)**; ^{13}C-NMR (101 MHz, $CDCl_3$) δ **144.5 (C)**, **143.2 (C)**, 143.0 (C), 142.7 (C), 140.6 (2 × C), 140.5 (C), **140.4 (C)**, **137.0 (C)**, 136.3 (C), 136.0 (CH), **135.8 (CH)**, **129.6 (2 × CH)**, 129.4 (2 × CH), 127.8 (2 × CH), **127.7 (2 × CH)**, **127.50 (2 × CH)**, 127.45 (2 × CH), **127.3 (2 × CH)**, 127.2 (2 × CH), 126.6 (CH), **126.5 (CH)**, **115.6 (CH_2)**, 115.0 (CH_2), **95.0 (C)**, 91.0 (C), 77.4 (CH), **72.1 (CH)**, 65.2 (CH_2), **64.5 (CH_2)**, 54.7 (CH_2), **53.3 (CH_2)**, 43.9 (C), **42.1 (C)**, 31.2 (CH_2), **31.1 (CH_2)**, 28.9 (CH_2), **27.22 (CH_2)**, 27.20 (CH_2), **27.1 (CH_2)**, 26.7 (2 × CH_2), **26.3 (CH_2)**, 26.2 (CH_2), 21.6 (2 × CH_3), 20.41 (CH), **20.37 (CH)**, 13.2 (CH_2), **11.4 (CH_2)**; HRMS (ES) calcd. for $C_{29}H_{33}NO_3NaS$: 498.2079, found: 498.2100 $[M+Na]^+$.

(1aR,3aS,9bS)-4-Phenyl-3-tosyl-1a,2,3,3a,5,6,7,8-octahydro-1*H*-azuleno[2,1-b]cyclopropa[c]pyrrole 1038

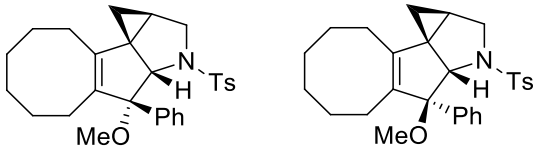


Prepared according to **GP20** using ynamide **1035** (95.1 mg, 0.2 mmol), stirring at 80 °C for 30 minutes. Purification by flash column chromatography [99:1 (hexane:EtOAc)] afforded the alkene **1038** as a yellow oil (38.1 mg, 40%); IR ν_{max}/cm^{-1} 2923, 1736, 1445, 1346, 1240, 1158, 1098, 913, 814, 730, 699, 663; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.33-7.28 (m, 3H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.24 (s, 1H), 5.12 (t, *J* = 4.7 Hz, 1H), 3.52 (d, *J* = 11.5 Hz, 1H), 3.43-3.38 (m, 1H), 2.64 (ddd, *J* = 16.0, 6.3, 2.6 Hz, 1H), 2.36 (s, 3H), 2.32-2.17 (m, 2H), 1.94-1.84 (m, 1H),

1.80-1.71 (m, 1H), 1.63-1.52 (m, 2H), 1.45-1.34 (m, 1H), 1.19-1.11 (m, 2H), 0.22 (app. t, *J* = 4.1 Hz, 1H); ^{13}C-NMR (101 MHz, CDCl3) δ 143.3 (C), 143.1 (2 × C), 140.7 (C), 137.4 (C), 136.1 (C), 129.6 (2 × CH), 129.6 (2 × CH), 127.9 (2 × CH), 127.3 (2 × CH), 127.3 (CH), 116.9 (CH), 71.8 (CH), 49.8 (CH_2), 39.5 (C), 30.54 (CH_2), 30.0 (CH_2), 29.1 (CH_2), 27.6 (CH), 26.7 (CH_2), 21.6 (CH_3), 10.6 (CH_2); HRMS (ES) calcd. for $C_{26}H_{27}NO_2NaS$: 440.1660, found: 440.1656 $[M+Na]^+$.

4-Methoxy-4-phenyl-3-tosyl-1,1a,2,3,3a,4,5,6,7,8,9,10-

dodecahydrocycloocta[3,4]cyclopenta[1,2-b]cyclopropa[c]pyrrole 1042

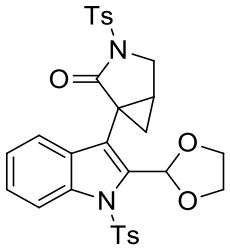


Prepared according to **GP20** using ynamide **1036** (92.6 mg, 0.2 mmol), stiring at 60 °C for 3 hours to give **1042** as a mixture of two diastereomers (dr. 3.1: 1). Purification by flash column chromatography [80:20 (hexane:EtOAc), 1% Et_3N] afforded the polycycle **1042** as a yellow solid (57.5 mg, 62%, dr. 13.0: 1); mp. 26-27 °C; IR ν_{max}/cm^{-1} 2926, 1446, 1349, 1161, 1096, 811, 701, 663; ^{1}H-NMR (400 MHz, $CDCl_3$) *(^{1}H- and ^{13}C- spectra refer to the major diasteromer from a mixture of both diastereomers; traces of the minor diastereomer do not allow further assignment)* δ 7.46-7.39 (m, 4H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.25-7.22 (m, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.21 (s, 1H), 3.96 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.63 (d, *J* = 10.7 Hz, 1H), 3.29 (s, 3H), 2.39 (s, 3H), 2.22-2.12 (m, 1H), 2.10-1.99 (m, 1H), 1.84-1.67 (m, 2H), 1.66-1.58 (m, 2H), 1.57-1.45 (m, 3H), 1.43-1.32 (m, 3H), 1.08 (dd, *J* = 6.2, 5.9 Hz, 1H), 0.90-0.79 (m, 1H), 0.13-0.03 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 143.1 (C), 139.8 (C), 138.2 (C), 135.8 (C), 129.4 (2 × CH), 127.6 (2 ×

CH), 127.5 (2 × CH), 126.5 (3 × CH), 89.9 (C), 76.0 (CH), 54.9 (CH_2), 52.7 (CH_3), 43.9 (C), 29.0 (CH_2), 27.4 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 23.5 (CH_2), 21.7 (CH_3), 20.6 (CH), 14.8 (CH_2); HRMS (ES) calcd. for $C_{28}H_{33}NO_3NaS$: 486.2079, found: 486.2061 $[M+Na]^+$.

A flame-dried Radley tube was charged with *N*-((2-(1,3-dioxolan-2-yl)-1-tosyl-1*H*-indol-3-yl)ethynyl)-*N*-allyl-4-methylbenzenesulfonamide **994** (29 mg, 0.05 mmol, 1.0 eq.) and 2-(methoxycarbonyl)pyridine *N*-oxide **1089** (17 mg, 0.11 mmol, 2.2 eq.), $MeNO_2$ (2.0 mL, 0.025 M) was added at room temperature and the solution was stirred for 10 minutes. **Au-4** (2.0 mg, 10 mol%) was then added and the reaction mixture was heated to 90 °C for 4 hours. The solution was cooled to room temperature, diluted with EtOAc (5 mL) and filtered through a pad of silica (ca 0.5 inch, washed with EtOAc, 5 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography [80:20 (hexane:EtOAc), 1% Et_3N] to give **1090** as a colourless oil (8.0 mg, 27%) and **1091** as a colourless oil (11.8 mg, 40%).

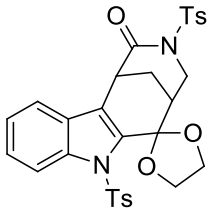
3,7-Ditosyl-3,4,5,7-tetrahydrospiro[1,5-methanoazocino[5,4-b]indole-6,2'-[1,3]dioxolan]-2(1*H*)-one 1090



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.63-7.46 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.28 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.17-7.22 (m, 3H),

6.45 (s, 1H), 4.03 (d, *J* = 9.9 Hz, 1H), 3.93 (dd, *J* = 9.9, 5.6 Hz, 1H), 3.82-3.39 (m, 4H), 2.43 (s, 3H), 2.34 (s, 3H), 2.17-2.09 (m, 1H), 1.5-1.54 (m, 1H), 1.45-1.38 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (C), 144.9 (C), 136.3 (C), 135.3 (C), 130.2 (C), 129.7 (3 × CH), 129.71 (2 × CH), 128.4 (2 × CH), 127.4 (2 × CH), 126.7 (C), 125.8 (CH), 123.8 (CH), 120.1 (C), 120.0 (C), 115.0 (CH), 98.3 (CH), 65.3 (CH_2), 47.8 (2 × CH_2), 29.9 (C), 26.61 (CH), 21.8 (CH_3), 21.7 (CH_3), 14.4 (CH_2) *(The carbonyl C is not obvious). (HRMS was not possible to obtain as the compounds showed cleavage of the sensitive acetal moiety)*

3,7-Ditosyl-3,4,5,7-tetrahydrospiro[1,5-methanoazocino[5,4-b]indole-6,2'-[1,3]dioxolan]-2(1*H*)-one 1091

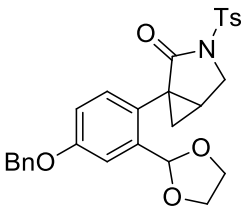


^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.32 (ddd, *J* = 8.5, 7.3, 1.1 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.04 (app t, *J* = 7.5 Hz, 1H), 6.14 (dd, *J* = 6.3, 1.05 Hz, 1H), 4.13-4.06 (m, 1H), 3.64 (dt, *J* = 14.9, 6.4 Hz, 2H), 3.47 (dd, *J* = 15.0, 6.2 Hz, 1H), 3.14 (dd, *J* = 14.7, 7.4 Hz, 1H), 2.96-2.82 (m, 2H), 2.61 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 1.95 (ddd, *J* = 15.8, 6.3, 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (C), 145.7 (C), 145.6 (C), 139.7 (C), 136.7 (C), 135.1 (C), 134.6 (C), 129.8 (4 × CH), 128.2 (2 × CH), 127.4 (2 × CH), 126.0 (C), 125.9 (CH), 124.4 (CH), 121.0 (CH), 114.7 (CH), 112.8 (C), 77.8 (C), 68.0 (CH_2), 66.6 (CH_2), 63.1 (CH), 50.6 (CH_2), 37.8 (CH), 28.8

(CH_2), 21.8 (CH_3), 21.7 (CH_3). *(Due to low quantity of the sample, not further data could be obtained)*

A flame-dried Radley tube was charged with *N*-allyl-*N*-((4-(benzyloxy)-2-(1,3-dioxolan-2-yl)phenyl)ethynyl)-4-methylbenzenesulfonamide **962** (98.0 mg, 0.2 mmol, 1.0 eq.) and 2-(methoxycarbonyl)pyridine 1-oxide **1089** (46.0 mg, 0.3 mmol, 2.2 eq.), $MeNO_2$ (8.0 mL, 0.025 M) was added at room temperature and the solution was stirred for 10 minutes. **Au-4** (10.4 mg, 10 mol%) was then added and the reaction mixture was heated up to 90 °C for 30 minutes at which point consumption of starting material was observed by TLC. The solution was cooled to room temperature, diluted with EtOAc (5 mL) and filtered through a pad of silica (ca 0.5 inch, washed with EtOAc, 5 mL). The filtrate was concentrated under reduced pressure. Crude 1H-NMR based on a known quantity of an internal standard showed **1102** (15%) and **1104** (30%).

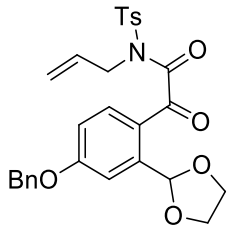
1-(4-(Benzyloxy)-2-(1,3-dioxolan-2-yl)phenyl)-3-tosyl-3-azabicyclo[3.1.0]hexan-2-one 1102



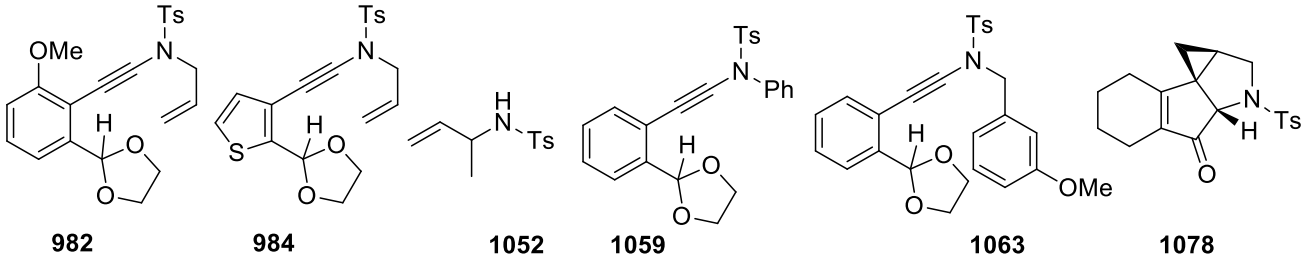
IR ν_{max}/cm^{-1} 2953, 1721, 1432, 1307, 1246, 1128, 1089, 824, 748, 706; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.42-7.34 (m, 4H), 7.34-7.29 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 2.7 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.82 (s, 1H), 5.03 (s, 2H), 4.05 (d, *J* = 9.7 Hz, 1H), 3.99 (dd, *J* = 9.7, 5.1 Hz, 1H), 3.85-3.73 (m, 2H), 3.40 (dd, *J* = 14.0, 7.3 Hz, 1H), 3.25 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.45 (s, 3H), 2.13 (dt, *J* = 7.8, 4.6 Hz, 1H), 1.54 (dd, *J* = 7.8, 4.9 Hz, 1H), 1.29 (t, *J* = 4.7 Hz,

1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.3 (C), 158.9 (C), 144.8 (C), 139.9 (C), 136.9 (C), 135.5 (C), 133.8 (CH), 129.6 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.1 (CH), 127.6 (2 × CH), 124.7 (C), 115.1 (CH), 112.8 (CH), 101.2 (CH), 70.2 (CH_2), 64.8 (CH_2), 64.7 (CH_2), 47.9 (CH_2), 34.0 (C), 21.8 (CH_3), 20.2 (CH), 18.5 (CH_2); HRMS (ES) calcd for $C_{28}H_{27}NO_6SNa$: 528.1457, found: 528.1453.

_N_-Allyl-2-(4-(benzyloxy)-2-(1,3-dioxolan-2-yl)phenyl)-2-oxo-_N_-tosylacetamide 1104

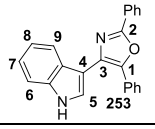
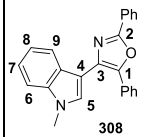
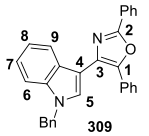
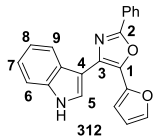
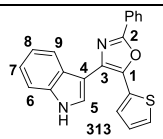
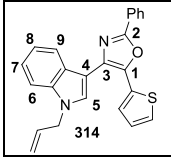


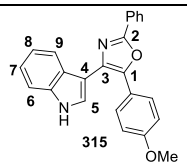
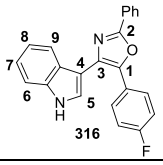
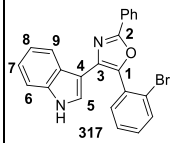
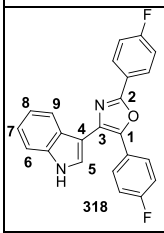
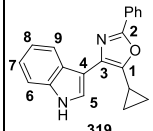
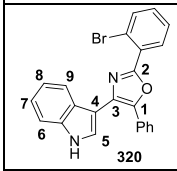
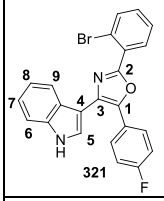
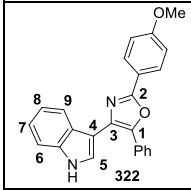
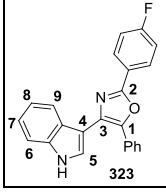
IR ν_{max}/cm^{-1} 1675, 1598, 1568, 1366, 1291, 1207, 1167, 1126, 1024, 892, 735, 702, 666; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.48 (d, *J* = 2.6 Hz, 1H), 7.45–7.32 (m, 7H), 7.01 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.69 (s, 1H), 5.73 (ddt, *J* = 16.5, 10.3, 5.9 Hz, 1H), 5.21 (dd, *J* = 16.5, 1.1 Hz, 1H), 5.17 (s, 2H), 5.12 (dd, *J* = 10.3, 1.1 Hz, 1H), 4.32 (d, *J* = 5.9 Hz, 2H), 4.07 (bs, 4H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 187.2 (C), 166.9 (C), 163.1 (C), 145.7 (C), 143.3 (C), 136.0 (C), 135.9 (CH), 134.8 (C), 131.0 (CH), 130.01 (2 × CH), 128.9 (4 × CH), 128.5 (CH), 127.7 (2 × CH), 124.1 (C), 119.4 (CH_2), 114.4 (CH), 114.2 (CH), 100.04 (CH), 70.5 (CH_2), 65.47 (2 × CH_2), 47.5 (CH_2), 21.9 (CH_3); HRMS (ES) calcd for $C_{28}H_{27}NO_7SNa$: 544.1406, found: 544.1403.

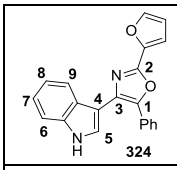
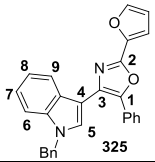
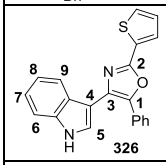
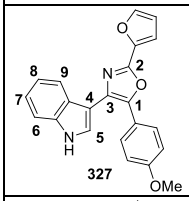
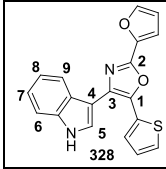
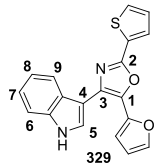
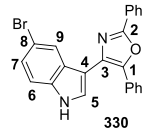
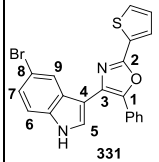
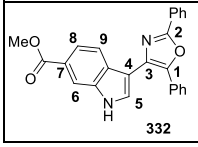


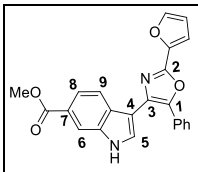
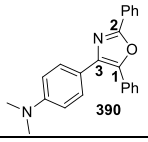
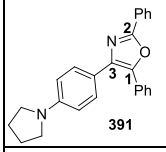
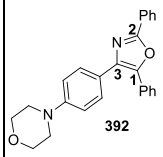
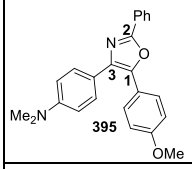
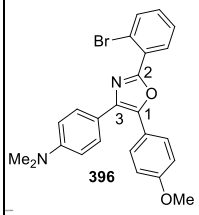
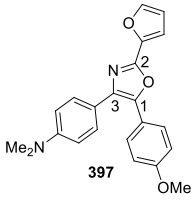
The compounds above were donated by Holly Adcock.

5.4.4 ^{13}C-NMR comparison table for characteristic peaks of oxazoles

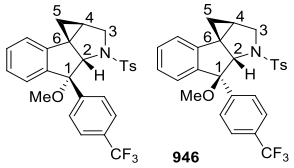
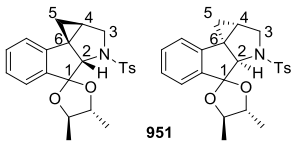
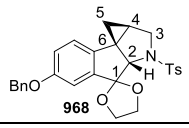
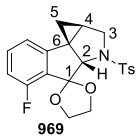
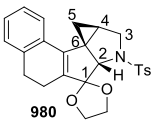
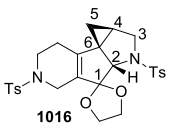
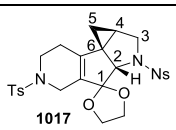
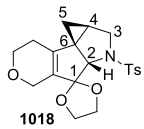
Compound	NMR solvent	C1	C2	C3	C4	C5	C6	C7	C8	C9
 253	DMSO-d_6	144.2	159.1	136.2	106.5	125.1	111.9	121.6	119.3	120.1
 308	$CDCl_3$	145.1	160.1	137.3	107.2	128.0	109.5	122.1	120.0	121.5
 309	$CDCl_3$	145.2	160.1	136.7	108.0	127.9	110.0	122.4	120.3	121.6
 312	DMSO-d_6	143.2	159.0	136.2	106.0	125.2	112.0	121.7	119.6	121.0
 313	DMSO-d_6	140.2	158.8	136.2	105.6	125.3	111.7	121.7	119.5	120.3
 314	$CDCl_3$	145.1	160.1	137.3	107.2	128.0	109.5	122.1	120.0	121.5

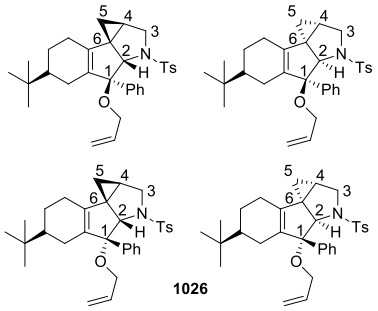
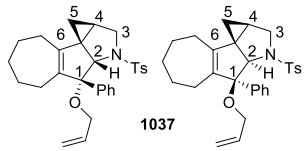
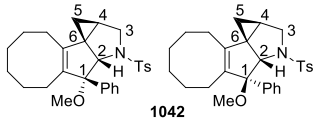
 315	DMSO-d_6	144.4	159.2	136.2	106.6	124.8	111.8	121.6	119.3	120.2
 316	$CDCl_3$	144.6	160.1	136.4	108.8	124.1	111.4	122.8	120.5	121.2
 317	$CDCl_3$	142.9	160.9	136.2	108.5	127.5	111.2	122.5	120.4	121.4
 318	DMSO-d_6	143.5	163.5	136.2	106.2	125.0	111.9	121.6	119.4	120.0
 319	$CDCl_3$	147.5	158.7	136.3	108.9	122.6	111.2	122.6	120.3	121.3
 320	$CDCl_3$	145.9	158.6	136.2	108.7	124.0	111.2	122.6	120.4	121.3
 321	DMSO-d_6	143.7	157.7	136.2	105.9	125.1	111.9	121.7	119.5	120.2
 322	DMSO-d_6	144.9	160.2	136.4	108.9	124.2	111.3	122.6	120.4	121.3
 323	$CDCl_3$	145.4	159.3	136.4	108.9	124.1	111.4	122.7	120.5	121.3

 324	$CDCl_3$	144.9	153.1	136.3	108.6	124.5	111.4	122.6	120.4	121.3
 325	$CDCl_3$	144.8	153.2	136.8	107.7	126.6	111.7	122.4	120.3	121.7
 326	DMSO-d_6	143.6	155.5	136.2	106.2	125.3	111.9	121.6	119.4	120.1
 327	$CDCl_3$	144.3	159.3	136.3	108.8	124.4	111.3	122.5	120.3	121.3
 328	DMSO-d_6	141.9	151.8	136.2	105.3	125.5	111.9	121.7	119.5	120.2
 329	DMSO-d_6	143.0	155.4	136.1	105.3	125.3	111.8	121.7	119.6	120.7
 330	$CDCl_3$	145.7	160.3	135.0	108.7	125.9	112.8	123.9	128.4	130.5
 331	DMSO-d_6	143.8	155.7	134.9	105.9	126.7	114.0	128.6 or 128.5	127.7	129.8
 332	$CDCl_3$	145.7	160.3	135.8	109.3	127.5	113.9	131.0	120.9	121.4

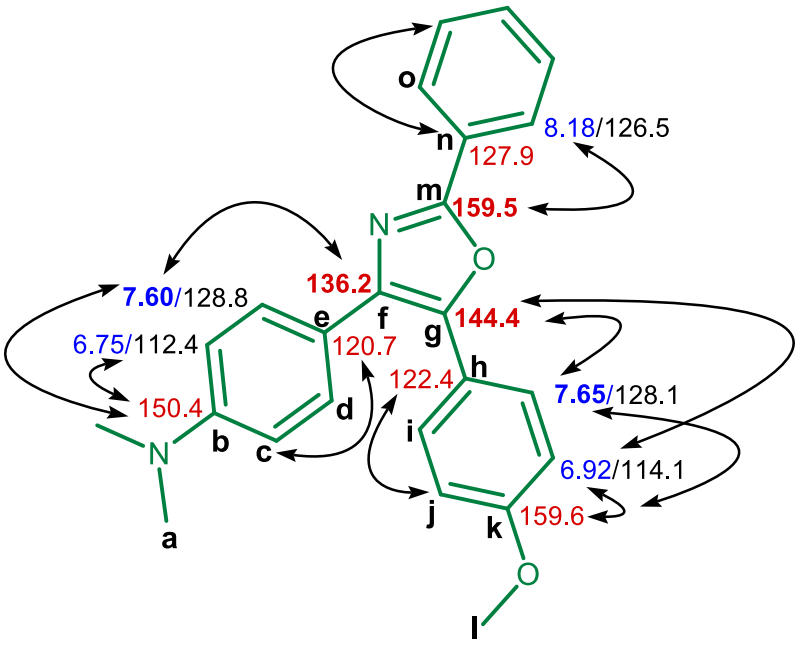
 333	DMSO-d_6	143.8	152.3	135.5	106.8	128.5	112.3	130.9	128.5	120.0
 390	$CDCl_3$	144.3	160.0	137.5	-	-	-	-	-	-
 391	$CDCl_3$	144.1	159.9	137.7	-	-	-	-	-	-
 392	DMSO-d_6	144.0	159.2	136.3	-	-	-	-	-	-
 395	$CDCl_3$	144.4	159.5	136.2	-	-	-	-	-	-
 396	$CDCl_3$	145.1	159.7	135.8	-	-	-	-	-	-
 397	$CDCl_3$	143.4	159.8	138.0	-	-	-	-	-	-

5.4.5 ^{13}C-NMR comparison table for characteristic peaks of polycyclic systems

Compound	C1	C2	C3	C4	C5	C6
 946	**91.6,** 88.6	79.8, **72.9**	54.7, **53.1**	29.8, **27.1**	**12.1,** 11.2	38.7, **38.0**
 951	112.7, **112.4**	**74.7**, 74.5	**53.9,** 54.3	26.4	**11.4,** 11.2	**37.6,** 37.4
 968	113.4	74.7	54.3	25.7	11.4	37.2
 969	113.0	74.2	53.8	27.0	12.2	37.5
 980	114.6	74.7	54.4	28.7	11.7	38.1
 1016	114.6	77.9	54.1	20.0	11.1	40.0
 1017	114.5	74.0	54.3	19.8	11.4	39.8
 1018	115.0	73.9	54.3	19.8	11.0	40.4

 1026	94.3, 94.0	74.1, 73.2, 71.8	53.39, 53.37, 50.3, 50.0	20.2, 20.0	11.4, 11.0, 10.95, 10.9	40.9, 40.7, 36.8, 36.4
 1037	**95.0** 91.0	77.4 **72.1**	54.7 **53.3**	20.41, **20.37**	13.2, **11.4**	43.9, **42.1**
 1042	89.9	76.0	54.9	20.6	14.8	43.9

5.4.6 2D-Spectra Analysis of oxazole 395

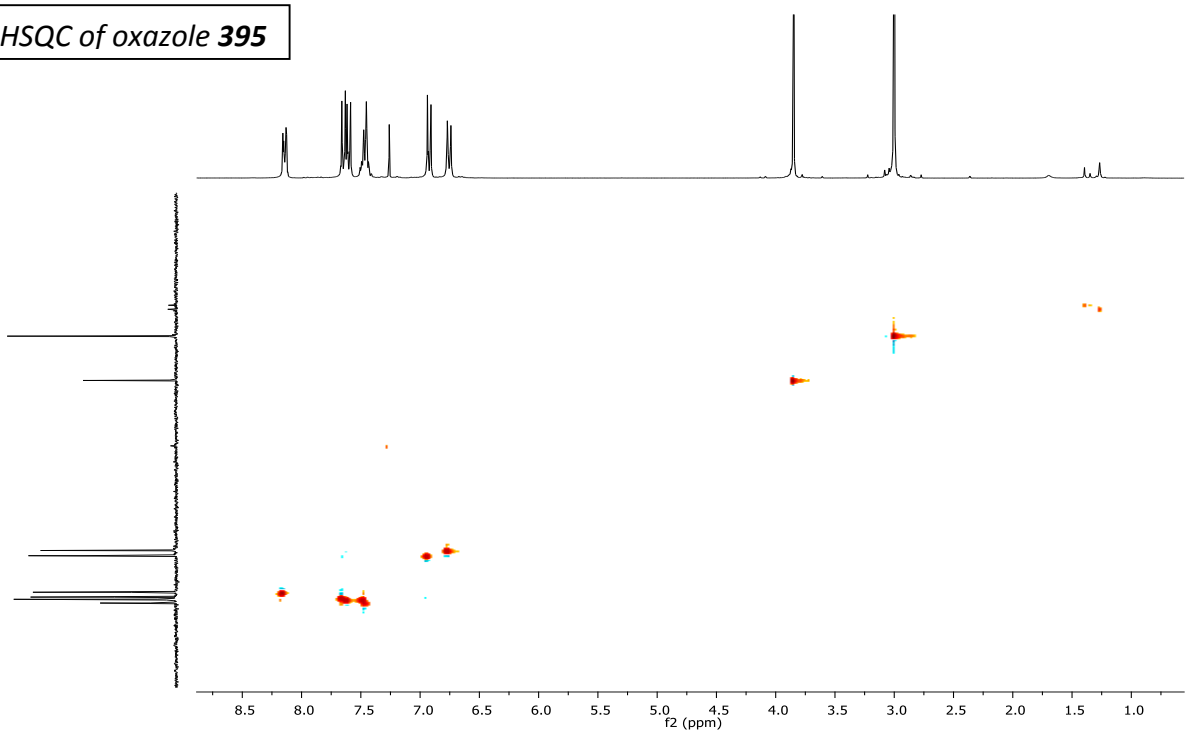


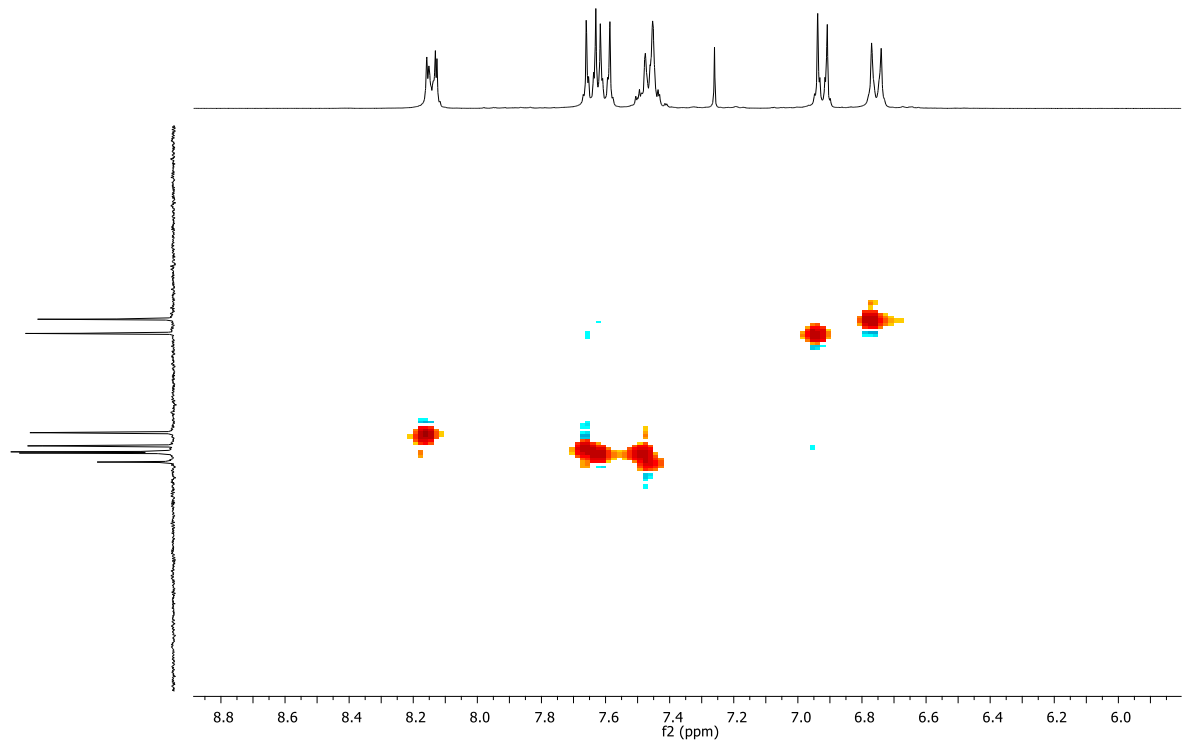
Key correlations from HMBC and HSQC studies for the determination of structure **395** are described below (Chemical shifts are shown in blue (H), black (C) and red (quaternary carbon):

- For the substituent at the 4-position of the oxazole ring: H_a is coupled with the quaternary C_b which in turn is coupled with H_c. H_d is coupled with C_c and the quaternary C_f through a ^{3}J-coupling.
- For the substituent at the 5-position of the oxazole ring: H_l is coupled with the quaternary C_k which in turn is coupled with H_j. H_i is coupled with C_j and the quaternary Cg_f through a ^{3}J-coupling.
- For the substituent at the 2-position of the oxazole ring: H_o is coupled with C_m.

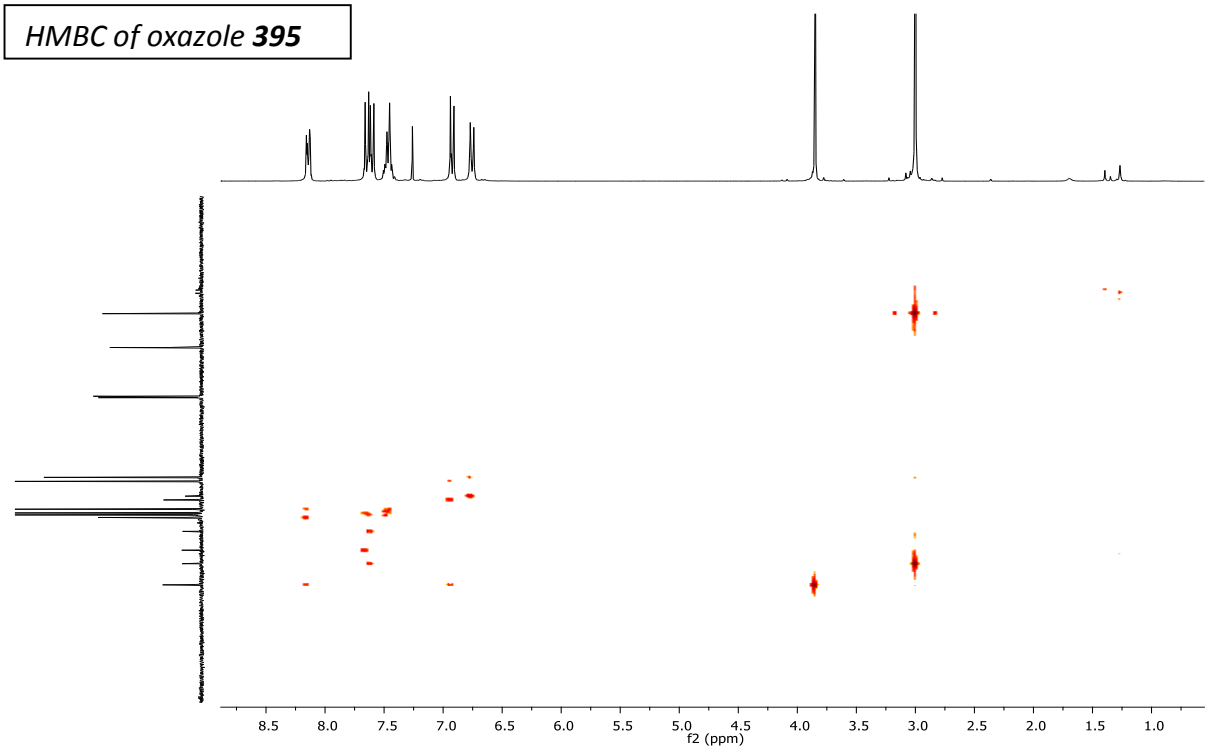
The assignment of the quaternary carbons at the oxazole ring (C_f, C_g, C_m) is in agreement with data reported in the literature.[261]

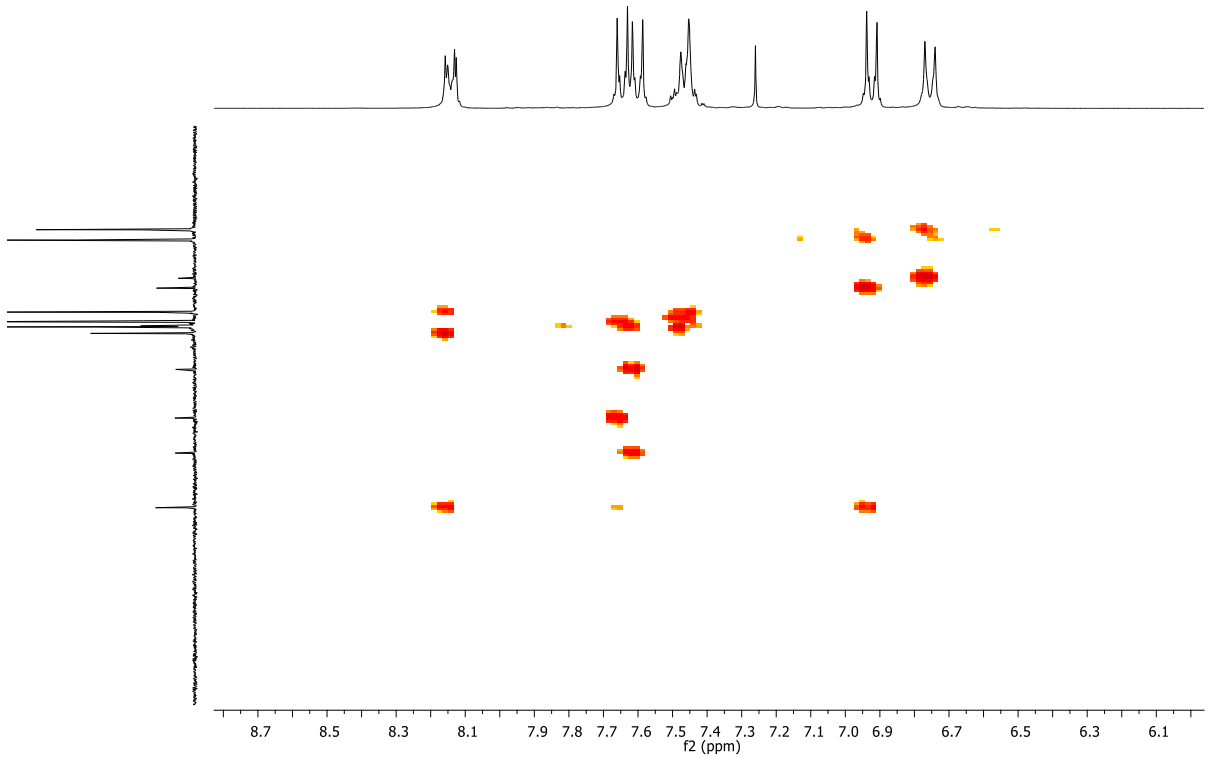
*HSQC of oxazole **395***



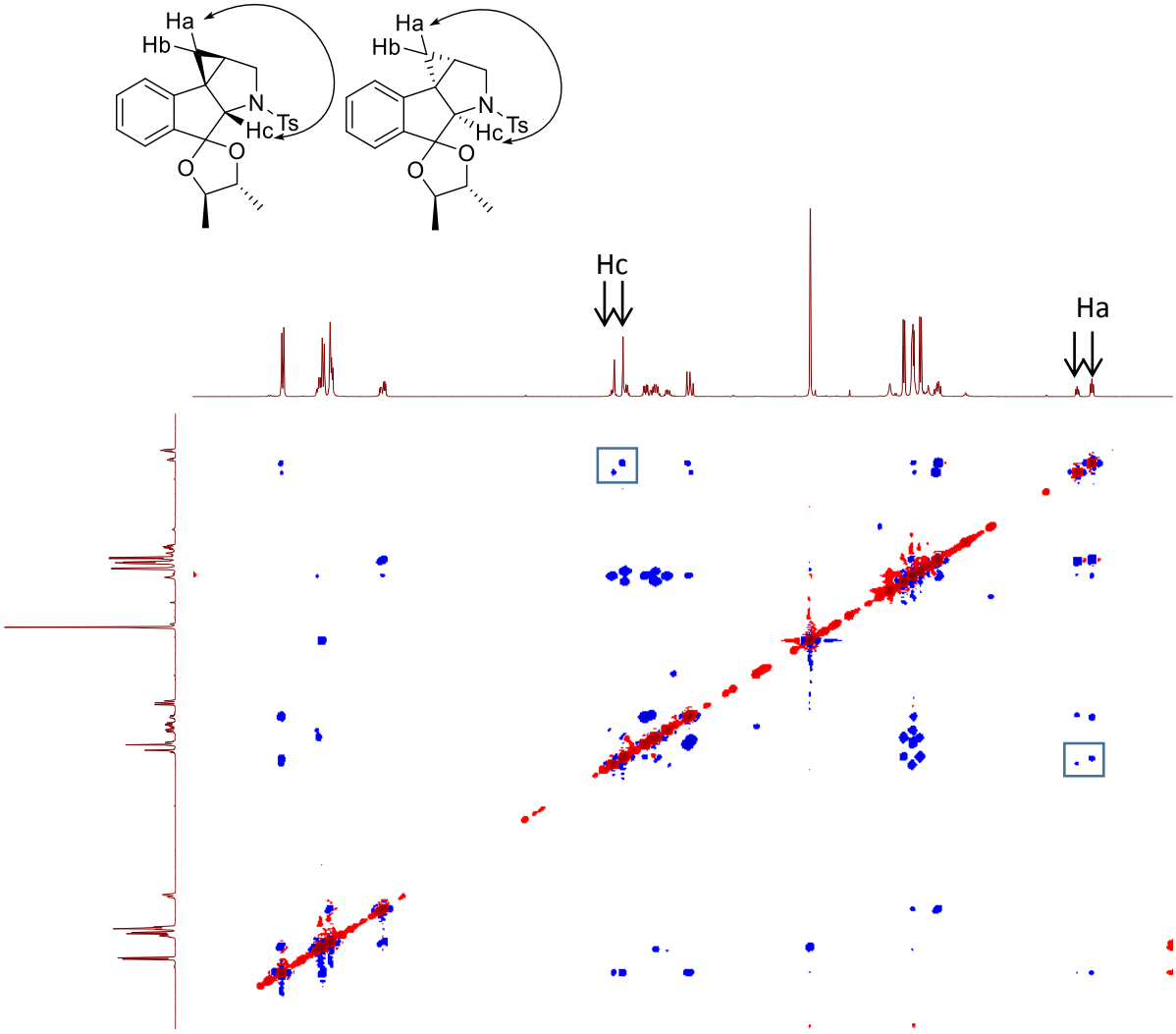


*HMBC of oxazole **395***



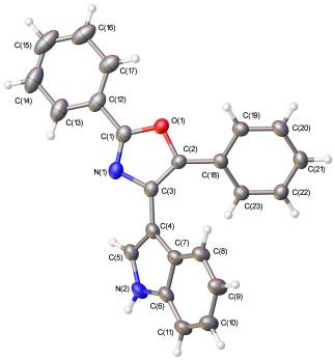


5.4.7 n*O*e Experiment for polycyclic system 951



5.4.8 Crystallographic Data for Oxazole 253

Table 1. Crystal data and structure refinement for Oxazole.



Identification code Oxazole

Empirical formula $C_{23}H_{16}N_2O$

Formula weight 336.38

Temperature 120(2) K

Wavelength 1.54184 Å

Crystal system Monoclinic

Space group P 2(1)/c

Unit cell dimensions a = 12.0222(2) Å α= 90°.

b = 7.23960(10) Å β= 106.4820(10)°.

c = 20.9825(3) Å γ = 90°.

Volume 1751.19(5) $Å^3$

Z 4

Density (calculated) 1.276 Mg/m^3

Absorption coefficient 0.623 mm^{-1}

F(000) 704

Crystal size 0.26 x 0.12 x 0.12 mm^3

Theta range for data collection 6.50 to 66.58°.

Index ranges -14<=h<=14, -8<=k<=7, -23<=l<=24

Reflections collected 11907

Independent reflections	3042 [R(int) = 0.0655]
Completeness to theta = 66.58°	98.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9290 and 0.8548
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3042 / 0 / 238
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0525, wR2 = 0.1455
R indices (all data)	R1 = 0.0575, wR2 = 0.1537
Largest diff. peak and hole	0.309 and -0.232 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Oxazole. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5314(1)	7177(2)	682(1)	32(1)
C(2)	7036(1)	7332(2)	1381(1)	28(1)
C(3)	6266(1)	6739(2)	1704(1)	29(1)
C(4)	6417(1)	6113(2)	2387(1)	31(1)
C(5)	5857(1)	4597(2)	2546(1)	35(1)
C(6)	6968(1)	5674(2)	3517(1)	34(1)
C(7)	7121(1)	6848(2)	3008(1)	32(1)

C(8)	7850(2)	8390(2)	3189(1)	37(1)
C(9)	8403(2)	8697(3)	3853(1)	43(1)
C(10)	8247(2)	7507(3)	4348(1)	43(1)
C(11)	7530(2)	5978(2)	4187(1)	39(1)
C(12)	4444(1)	7279(2)	34(1)	38(1)
C(13)	3332(2)	6609(3)	-26(1)	48(1)
C(14)	2505(2)	6669(3)	-644(1)	60(1)
C(15)	2785(2)	7373(3)	-1190(1)	64(1)
C(16)	3882(2)	8039(3)	-1131(1)	55(1)
C(17)	4722(2)	7988(2)	-520(1)	44(1)
C(18)	8294(1)	7547(2)	1541(1)	28(1)
C(19)	8797(1)	8646(2)	1151(1)	32(1)
C(20)	9999(1)	8793(2)	1298(1)	36(1)
C(21)	10707(1)	7828(2)	1830(1)	35(1)
C(22)	10213(1)	6731(2)	2220(1)	33(1)
C(23)	9018(1)	6590(2)	2078(1)	31(1)
N(1)	5164(1)	6660(2)	1244(1)	33(1)
N(2)	6193(1)	4315(2)	3216(1)	38(1)
O(1)	6426(1)	7636(2)	722(1)	31(1)

Table 3. Bond lengths [Å] and angles [°] for Oxazole.

C(1)-N(1)	1.299(2)	C(11)-H(11)	0.9500
C(1)-O(1)	1.3559(19)	C(12)-C(17)	1.394(3)
C(1)-C(12)	1.464(2)	C(12)-C(13)	1.395(3)
C(2)-C(3)	1.363(2)	C(13)-C(14)	1.392(3)
C(2)-O(1)	1.3871(18)	C(13)-H(13)	0.9500
C(2)-C(18)	1.461(2)	C(14)-C(15)	1.379(4)
C(3)-N(1)	1.4025(19)	C(14)-H(14)	0.9500
C(3)-C(4)	1.463(2)	C(15)-C(16)	1.377(4)
C(4)-C(5)	1.377(2)	C(15)-H(15)	0.9500
C(4)-C(7)	1.440(2)	C(16)-C(17)	1.389(3)
C(5)-N(2)	1.364(2)	C(16)-H(16)	0.9500
C(5)-H(5)	0.9500	C(17)-H(17)	0.9500
C(6)-N(2)	1.378(2)	C(18)-C(19)	1.396(2)
C(6)-C(11)	1.393(2)	C(18)-C(23)	1.397(2)
C(6)-C(7)	1.418(2)	C(19)-C(20)	1.393(2)
C(7)-C(8)	1.403(2)	C(19)-H(19)	0.9500
C(8)-C(9)	1.380(2)	C(20)-C(21)	1.386(2)
C(8)-H(8)	0.9500	C(20)-H(20)	0.9500
C(9)-C(10)	1.402(3)	C(21)-C(22)	1.388(2)
C(9)-H(9)	0.9500	C(21)-H(21)	0.9500
C(10)-C(11)	1.385(3)	C(22)-C(23)	1.387(2)
C(10)-H(10)	0.9500	C(22)-H(22)	0.9500

C(23)-H(23) 0.9500

N(2)-H(2) 0.91(2)

N(1)-C(1)-O(1) 113.81(13)

N(1)-C(1)-C(12) 127.70(15)

O(1)-C(1)-C(12) 118.47(15)

C(3)-C(2)-O(1) 107.71(13)

C(3)-C(2)-C(18) 136.39(14)

O(1)-C(2)-C(18) 115.62(13)

C(2)-C(3)-N(1) 108.26(14)

C(2)-C(3)-C(4) 132.22(14)

N(1)-C(3)-C(4) 119.38(14)

C(5)-C(4)-C(7) 106.13(14)

C(5)-C(4)-C(3) 123.44(15)

C(7)-C(4)-C(3) 130.42(15)

N(2)-C(5)-C(4) 110.29(15)

N(2)-C(5)-H(5) 124.9

C(4)-C(5)-H(5) 124.9

N(2)-C(6)-C(11) 130.27(15)

N(2)-C(6)-C(7) 107.32(14)

C(11)-C(6)-C(7) 122.41(15)

C(8)-C(7)-C(6) 118.51(15)

C(8)-C(7)-C(4) 134.53(15)

C(6)-C(7)-C(4) 106.94(14)

C(9)-C(8)-C(7) 119.14(15)

C(9)-C(8)-H(8) 120.4

C(7)-C(8)-H(8) 120.4

C(8)-C(9)-C(10) 121.38(16)

C(8)-C(9)-H(9) 119.3

C(10)-C(9)-H(9) 119.3

C(11)-C(10)-C(9) 121.02(16)

C(11)-C(10)-H(10) 119.5

C(9)-C(10)-H(10) 119.5

C(10)-C(11)-C(6) 117.53(15)

C(10)-C(11)-H(11) 121.2

C(6)-C(11)-H(11) 121.2

C(17)-C(12)-C(13) 120.20(17)

C(17)-C(12)-C(1) 121.07(17)

C(13)-C(12)-C(1) 118.71(18)

C(14)-C(13)-C(12) 119.1(2)

C(14)-C(13)-H(13) 120.5

C(12)-C(13)-H(13) 120.5

C(15)-C(14)-C(13) 120.5(2)

C(15)-C(14)-H(14)	119.8	C(22)-C(21)-H(21)	120.1
C(13)-C(14)-H(14)	119.8	C(23)-C(22)-C(21)	120.39(15)
C(16)-C(15)-C(14)	120.55(18)	C(23)-C(22)-H(22)	119.8
C(16)-C(15)-H(15)	119.7	C(21)-C(22)-H(22)	119.8
C(14)-C(15)-H(15)	119.7	C(22)-C(23)-C(18)	120.45(15)
C(15)-C(16)-C(17)	120.0(2)	C(22)-C(23)-H(23)	119.8
C(15)-C(16)-H(16)	120.0	C(18)-C(23)-H(23)	119.8
C(17)-C(16)-H(16)	120.0	C(1)-N(1)-C(3)	105.36(13)
C(16)-C(17)-C(12)	119.7(2)	C(5)-N(2)-C(6)	109.28(14)
C(16)-C(17)-H(17)	120.1	C(5)-N(2)-H(2)	124.3(12)
C(12)-C(17)-H(17)	120.1	C(6)-N(2)-H(2)	126.4(12)
C(19)-C(18)-C(23)	118.81(14)	C(1)-O(1)-C(2)	104.85(12)
C(19)-C(18)-C(2)	121.22(14)		
C(23)-C(18)-C(2)	119.93(14)		
C(20)-C(19)-C(18)	120.51(15)		
C(20)-C(19)-H(19)	119.7		
C(18)-C(19)-H(19)	119.7		
C(21)-C(20)-C(19)	120.10(15)		
C(21)-C(20)-H(20)	119.9		
C(19)-C(20)-H(20)	119.9		
C(20)-C(21)-C(22)	119.74(15)		
C(20)-C(21)-H(21)	120.1		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$)for Oxazole. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	32(1)	27(1)	36(1)	-6(1)	7(1)	6(1)
C(2)	31(1)	28(1)	26(1)	-1(1)	7(1)	5(1)
C(3)	27(1)	27(1)	33(1)	-4(1)	9(1)	3(1)
C(4)	28(1)	34(1)	35(1)	-2(1)	14(1)	1(1)
C(5)	31(1)	41(1)	37(1)	-4(1)	15(1)	-4(1)
C(6)	33(1)	36(1)	39(1)	0(1)	20(1)	-1(1)
C(7)	33(1)	35(1)	32(1)	-1(1)	15(1)	2(1)
C(8)	44(1)	36(1)	34(1)	0(1)	16(1)	-6(1)
C(9)	53(1)	42(1)	36(1)	-7(1)	16(1)	-11(1)
C(10)	51(1)	51(1)	31(1)	-3(1)	15(1)	-5(1)
C(11)	44(1)	46(1)	33(1)	3(1)	21(1)	-1(1)
C(12)	38(1)	29(1)	40(1)	-9(1)	0(1)	10(1)
C(13)	40(1)	36(1)	57(1)	-12(1)	-1(1)	5(1)
C(14)	44(1)	42(1)	75(2)	-19(1)	-12(1)	5(1)
C(15)	71(2)	43(1)	53(1)	-16(1)	-22(1)	21(1)
C(16)	71(1)	43(1)	39(1)	-9(1)	-6(1)	20(1)

C(17)	54(1)	36(1)	37(1)	-7(1)	3(1)	14(1)
C(18)	30(1)	28(1)	28(1)	-4(1)	11(1)	1(1)
C(19)	37(1)	33(1)	31(1)	1(1)	13(1)	5(1)
C(20)	39(1)	36(1)	38(1)	-1(1)	19(1)	-2(1)
C(21)	29(1)	37(1)	41(1)	-7(1)	13(1)	-1(1)
C(22)	30(1)	35(1)	31(1)	-3(1)	7(1)	3(1)
C(23)	32(1)	30(1)	31(1)	0(1)	11(1)	1(1)
N(1)	28(1)	32(1)	36(1)	-6(1)	8(1)	3(1)
N(2)	38(1)	41(1)	41(1)	1(1)	21(1)	-8(1)
O(1)	30(1)	33(1)	30(1)	-2(1)	7(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Oxazole.

	x	y	z	U(eq)
H(5)	5315	3853	2233	42
H(8)	7961	9212	2860	44
H(9)	8900	9736	3977	52
H(10)	8640	7754	4800	52
H(11)	7425	5166	4521	47
H(13)	3140	6119	349	57
H(14)	1744	6221	-690	72

H(15)	2216	7398	-1610	76
H(16)	4065	8533	-1509	66
H(17)	5482	8435	-480	53
H(19)	8317	9298	782	39
H(20)	10334	9556	1033	43
H(21)	11526	7916	1928	42
H(22)	10698	6073	2586	39
H(23)	8688	5837	2348	37
H(2)	5914(18)	3400(30)	3424(10)	46

Table 6. Torsion angles [°] for Oxazole.

O(1)-C(2)-C(3)-N(1)	0.32(16)
C(18)-C(2)-C(3)-N(1)	-172.94(16)
O(1)-C(2)-C(3)-C(4)	175.93(15)
C(18)-C(2)-C(3)-C(4)	2.7(3)
C(2)-C(3)-C(4)-C(5)	-136.57(18)
N(1)-C(3)-C(4)-C(5)	38.7(2)
C(2)-C(3)-C(4)-C(7)	43.3(3)
N(1)-C(3)-C(4)-C(7)	-141.44(16)
C(7)-C(4)-C(5)-N(2)	-1.82(18)
C(3)-C(4)-C(5)-N(2)	178.10(13)
N(2)-C(6)-C(7)-C(8)	178.03(14)

C(11)-C(6)-C(7)-C(8)	-1.2(2)
N(2)-C(6)-C(7)-C(4)	-0.90(17)
C(11)-C(6)-C(7)-C(4)	179.86(14)
C(5)-C(4)-C(7)-C(8)	-177.03(18)
C(3)-C(4)-C(7)-C(8)	3.0(3)
C(5)-C(4)-C(7)-C(6)	1.65(17)
C(3)-C(4)-C(7)-C(6)	-178.27(15)
C(6)-C(7)-C(8)-C(9)	0.9(2)
C(4)-C(7)-C(8)-C(9)	179.47(17)
C(7)-C(8)-C(9)-C(10)	-0.3(3)
C(8)-C(9)-C(10)-C(11)	0.0(3)
C(9)-C(10)-C(11)-C(6)	-0.3(3)
N(2)-C(6)-C(11)-C(10)	-178.17(17)
C(7)-C(6)-C(11)-C(10)	0.9(2)
N(1)-C(1)-C(12)-C(17)	175.48(15)
O(1)-C(1)-C(12)-C(17)	-5.7(2)
N(1)-C(1)-C(12)-C(13)	-6.1(2)
O(1)-C(1)-C(12)-C(13)	172.69(14)
C(17)-C(12)-C(13)-C(14)	-0.4(3)
C(1)-C(12)-C(13)-C(14)	-178.78(15)
C(12)-C(13)-C(14)-C(15)	0.3(3)
C(13)-C(14)-C(15)-C(16)	-0.4(3)
C(14)-C(15)-C(16)-C(17)	0.6(3)

C(15)-C(16)-C(17)-C(12) -0.7(3)

C(13)-C(12)-C(17)-C(16) 0.5(2)

C(1)-C(12)-C(17)-C(16) 178.93(15)

C(3)-C(2)-C(18)-C(19) -163.07(17)

O(1)-C(2)-C(18)-C(19) 24.1(2)

C(3)-C(2)-C(18)-C(23) 19.3(3)

O(1)-C(2)-C(18)-C(23) -153.61(14)

C(23)-C(18)-C(19)-C(20) -0.4(2)

C(2)-C(18)-C(19)-C(20) -178.10(14)

C(18)-C(19)-C(20)-C(21) 0.8(2)

C(19)-C(20)-C(21)-C(22) -0.7(2)

C(20)-C(21)-C(22)-C(23) 0.3(2)

C(21)-C(22)-C(23)-C(18) 0.1(2)

C(19)-C(18)-C(23)-C(22) 0.0(2)

C(2)-C(18)-C(23)-C(22) 177.68(14)

O(1)-C(1)-N(1)-C(3) -1.11(17)

C(12)-C(1)-N(1)-C(3) 177.74(15)

C(2)-C(3)-N(1)-C(1) 0.45(16)

C(4)-C(3)-N(1)-C(1) -175.82(14)

C(4)-C(5)-N(2)-C(6) 1.30(18)

C(11)-C(6)-N(2)-C(5) 178.95(16)

C(7)-C(6)-N(2)-C(5) -0.20(18)

N(1)-C(1)-O(1)-C(2) 1.30(16)

C(12)-C(1)-O(1)-C(2) -177.66(13)

C(3)-C(2)-O(1)-C(1) -0.93(15)

C(18)-C(2)-O(1)-C(1) 173.92(12)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for Oxazole [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...N(1)#1	0.91(2)	2.07(2)	2.9478(19)	163.7(18)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z+1/2

6. References

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