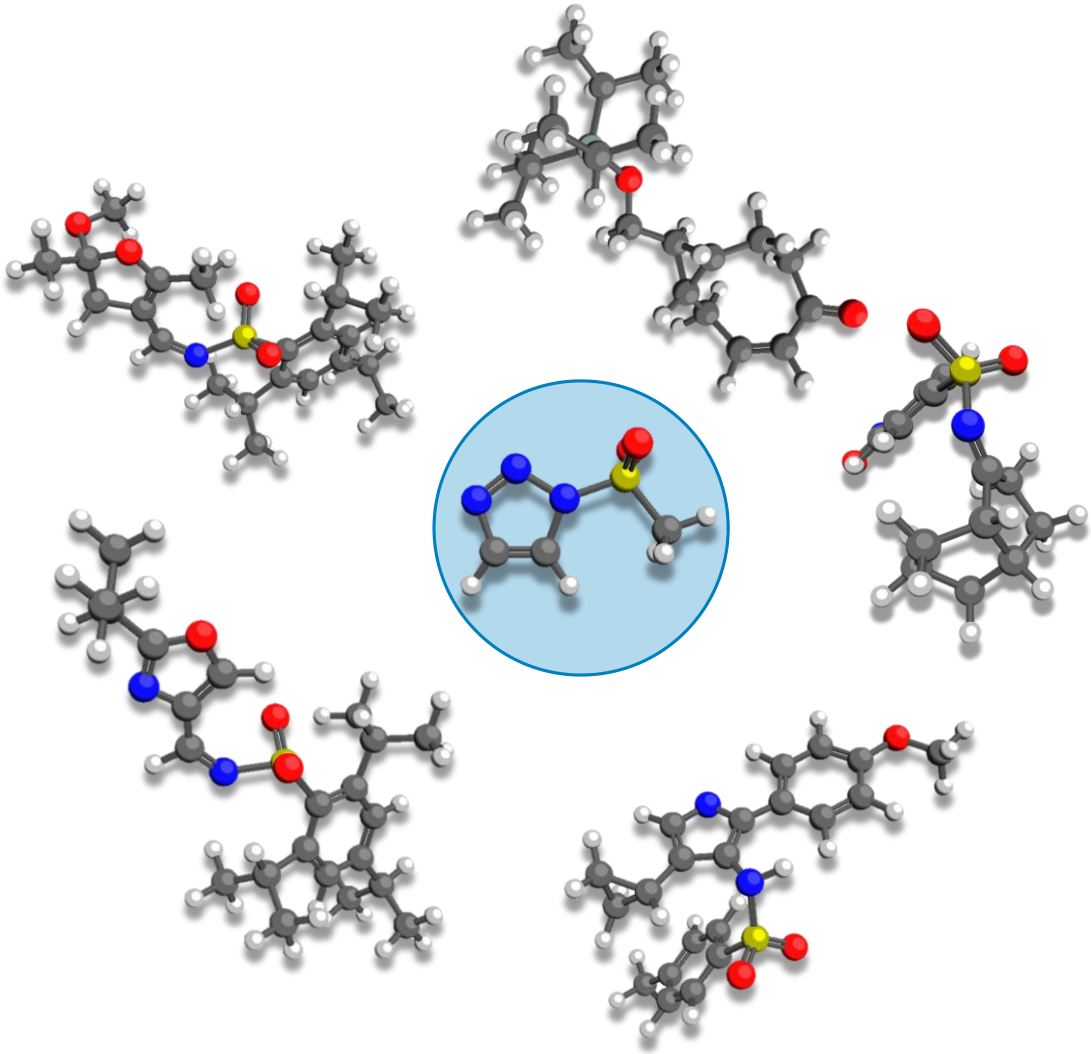
1-Sulfonyl-1,2,3-Triazoles: Versatile Carbene Precursors for the Functionalisation of Simple Building Blocks



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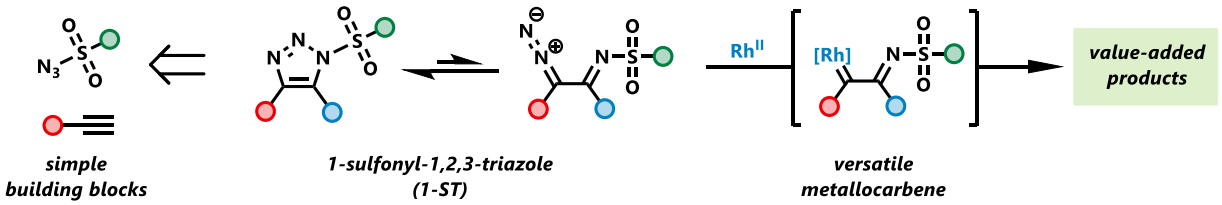
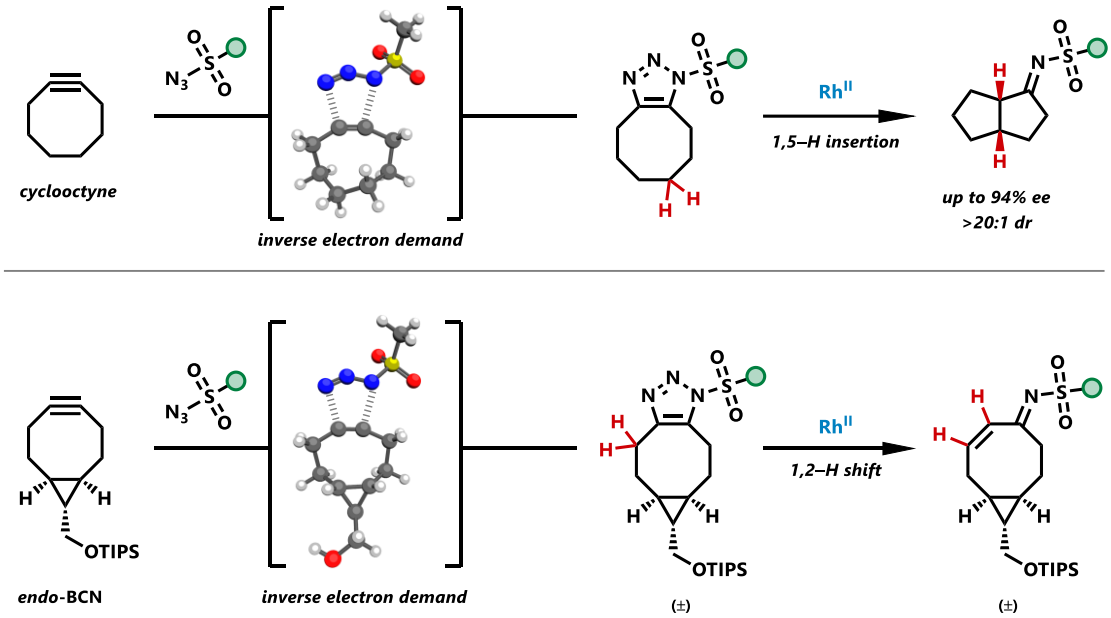
Abstract

Electronically biased 1,2,3-triazoles undergo ring–chain tautomerisation which allows access to the corresponding diazoimine intermediates. In the presence of suitable catalysts, these intermediates undergo metal-catalysed denitrogenation to generate metallocarbenes. In particular, metallocarbenes generated from 1-sulfonyl-1,2,3-triazoles (1-STs) are capable of undergoing a diverse range of synthetically useful transformations and have emerged as a new staple in metallocarbene chemistry (**Scheme A**). 1-STs with a substituent at the 4-position are commonly prepared from readily available sulfonyl azides and terminal alkynes by the copper-catalysed alkyne azide cycloaddition (CuAAC) reaction, whereas 1-STs that have 5- or 4,5-substitution are more challenging to prepare and are underutilised compared to 4-substituted 1-STs.



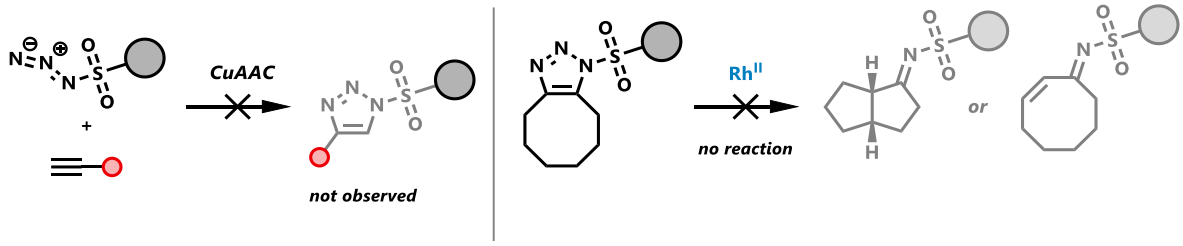
Scheme A

In this work, strained cyclic alkynes were investigated as a means of preparing 1-STs. Cyclooctyne and *exo*-BCN underwent strain-promoted alkyne azide cycloaddition (SPAAC) with sulfonyl azides, yielding the corresponding 1-sulfonylcyclooctatriazoles in excellent yield (**Scheme B**). When treated with a chiral rhodium(II) carboxylate catalyst, cyclooctyne derived 1-STs underwent a 1,5-C–H insertion reaction to generate [3.3.0]-bicyclic products diastereoselectively with good yield and very high *ee*. For 1-STs prepared from *exo*-BCN, a 1,2-H shift occurred in moderate yield. The relative rate of cycloaddition between different sulfonyl azides and these cyclic alkynes was investigated using a combination of ^{1}H NMR experiments and *in situ* reaction monitoring using IR spectroscopy, revealing that more electron poor sulfonyl azides reacted faster. The transition state structures for the cycloadditions involving mesyl azide were evaluated computationally and frontier molecular orbital analysis was carried out, showing that electron-poor sulfonyl azides were a better energy match for the strained alkynes in an inverse electron demand mechanism.



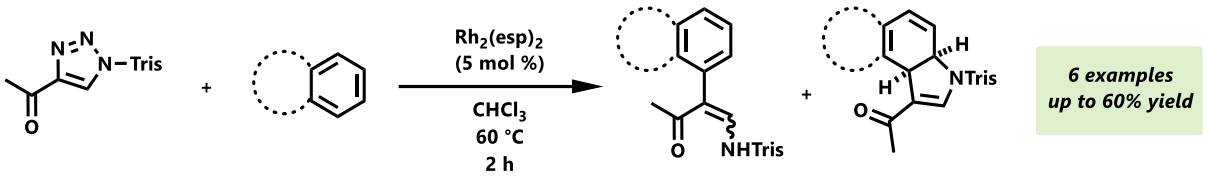
Scheme B

Separately, the use of a polymer-supported sulfonyl azide was investigated in 1-ST preparation (**Scheme C**). A polymer-supported sulfonyl azide was successfully prepared but CuAAC with terminal alkynes was very challenging. Successful cycloaddition was carried out with cyclooctyne at elevated temperatures although the polymer-supported 1-ST did not undergo any denitrogenative transformation.



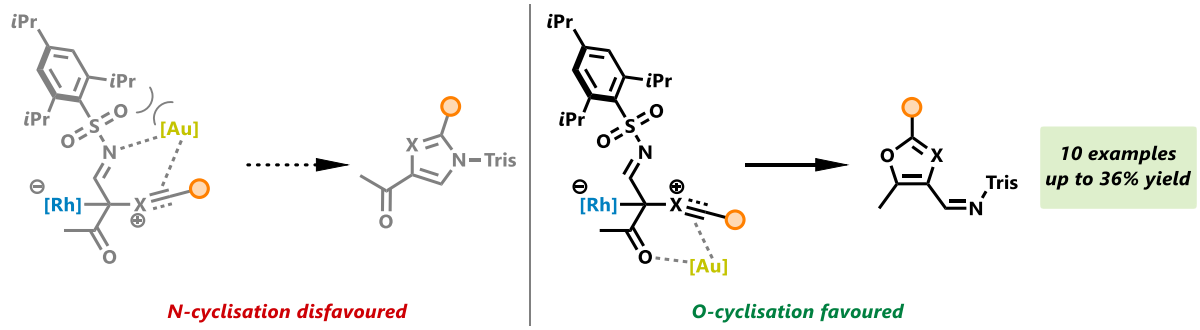
Scheme C

Additionally, the reactivity of acceptor/acceptor carbenoids generated 1-STs with a 4-acyl substituent was investigated. The 4-acyl substitution meant that the metallocarbenes were highly electrophilic and underwent insertion into aromatic C(sp^2)–H bonds (**Scheme D**). Functionalisation of polycyclic aromatic systems was investigated but the regioselectivity proved difficult to control. Functionalisation of alkene π-bonds was also investigated and similar problems with regioselectivity were encountered.



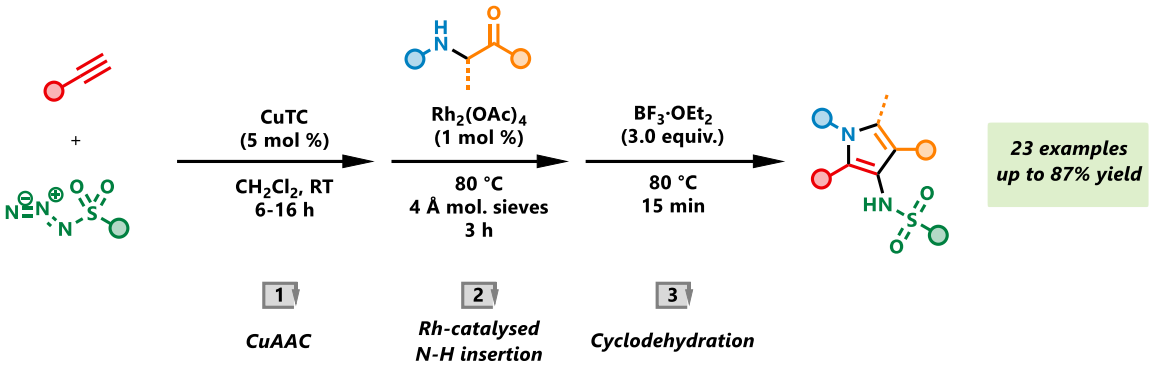
Scheme D

When electron-rich alkenes such as enol ethers were used, an interesting change in chemoselectivity was observed that gave rise to dihydrofuran motifs. This mode of reactivity was unprecedented for 1-STs and was extended to the preparation of other oxygen heterocycles including furans and oxazoles (**Scheme E**). Control over the chemoselectivity was examined by careful tuning of the stereoelectronics of both the sulfonyl group and substituent at the 4-position. Using a large sulfonyl group and gold(I) additive was important for controlling the selectivity in the transannular reaction with nitriles to afford oxazoles.



Scheme E

Finally, a new approach to 3-azapyrroles was established. The 3-azapyrrole scaffold makes up the core of several biologically active compounds but there are few existing synthetic approaches. A general three step sequence was developed consisting of CuAAC between sulfonyl azides and terminal alkynes, rhodium(II)-catalysed N–H bond insertion and Lewis acid promoted cyclodehydration (**Scheme F**). These three steps could be telescoped into a single pot and the method was highly efficient with good functional group tolerance. The ready availability of individual substrates means that this method represented a modular approach to pyrroles allowing each position on the product heterocycle to be customised based on judicious choice of starting materials.


CuTC
(5 mol %)
CH2Cl2, RT
6-16 h
Rh2(OAc)4
(1 mol %)
80 °C
4 Å mol. sieves
3 h
BF3·OEt2
(3.0 equiv.)
80 °C
15 min
23 examples
up to 87% yield
1
CuAAC
2
Rh-catalysed
N-H insertion
3
Cyclodehydration

Scheme F

Contents

Acknowledgements

First and foremost I would like to thank my supervisor, Dr Alistair Boyer, for his guidance and support in carrying out this project. His commitment to providing the best possible experience for me has made my time here very special.

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Outside of chemistry, I'd like to thank Jake Rivett for sharing his flat with me for all these years and keeping me sane during the pandemic. Of course I'd also like to acknowledge Rachel Clark for her love and support and making Glasgow and the rest of Scotland such a special place for me. Finally, I'd like to thank all my other friends and family who have been so supportive throughout.

Abbreviations

↑↓	heated under reflux
1-ST	1-sulfonyl-1,2,3-triazole
2-ST	2-sulfonyl-1,2,3-triazole
Ac	Acyl
acac	acetylacetonate
app	apparent
Ar	aryl
BCN	bicyclo[6.1.0]non-4-yn-9-ylmethanol
Bn	benzyl
CAN	ceric ammonium nitrate
cod	1,5-cyclooctadiene
CuAAC	copper(I)-catalysed alkyne azide cycloaddition
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
Dansyl	1-(5-Dimethylaminonaphth-1-yl)sulfonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMF	dimethyl formamide
DMDO	Dimethyldioxirane
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DOSP	*N*-(dodecylbenzenesulfonyl)prolinate
dr	diastereomeric ratio
E	electrophile
EDG	electron-donating group
ee	enantiomeric excess
Eind	1,1,3,3,5,5,7,7-octaethyl-1,2,3,5,6,7-hexahydro-s-indacene
ESI	electrospray ionisation
equiv.	molar equivalents
EWG	electron-withdrawing group
FMO	frontier molecular orbital
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionate

HFIP	hexafluoroisopropanol
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IED	inverse electron demand
IR	infrared
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
LED	light-emitting diode
LG	leaving group
Lit.	literature
LUMO	lowest unoccupied molecular orbital
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves
MW	microwave
NBS	*N*-bromosuccinimide
Ns	*p*-nitrobenzenesulfonyl
NTTL	*N*-1,2-naphthaloyl-(*S*)-*tert*-leucinate
oct	octanoate
Piv	pivaloyl
PMDETA	N,N,N′,N′′,N′′-pentamethyldiethylenetriamine
ppm	parts per million
PS	polymer-supported
PTAD	*N*-phthaloyl-(*S*)-adamantylglycine
PTSA	*p*-toluenesulfonic acid
PTTL	*N*-phthaloyl-(*S*)-*tert*-leucinate
Pybox	2,6-bis[(4*R*)-4-*tert*-butyloxazolin-2-yl]pyridine
RuAAC	Ruthenium-catalysed azide-alkyne cycloaddition
SPAAC	Strain-promoted alkyne-azide cycloaddition
TFA	trifluoroacetic acid
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TIPS	triisopropylsilyl
Tris	2,4,6-triisopropylsilyl
TS	transition state
Ts	*p*-toluenesulfonyl

Declaration

I declare that, except where explicit reference is made to the contribution of others, that this thesis is the result of my own work and has not been submitted in candidature for any other degree at the University of Glasgow or any other institution. Some sections of this thesis have been published in academic journals and are Open Access:

i) M. B. Williams and A. Boyer, *J. Org. Chem.,* 2022, **87**, 16139–16156.

ii) M. B. Williams, R. J. Wells and A. Boyer, *Chem. Comm.*, 2022, **58**, 12495–12498.

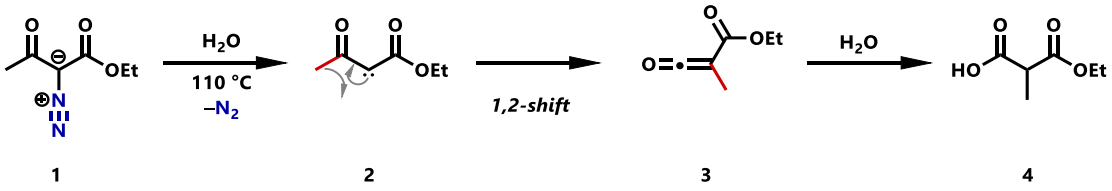
Matthew Williams – January 2023

Dr Alistair Boyer – January 2023

1 Introduction

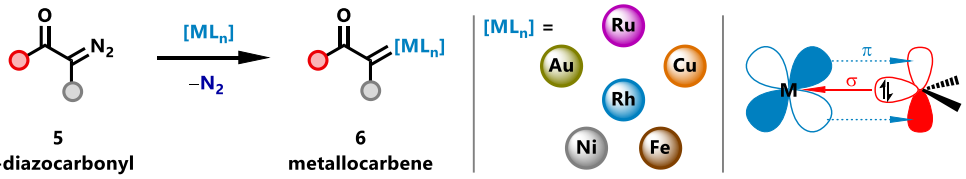
1.1 α-Diazocarbonyl Compounds as Carbene Precursors

The conversion of simple starting materials into complex value-added products is a fundamental aim of organic chemistry. An attractive approach is to exploit the energy stored within highly reactive species to create new bonds that are otherwise challenging to make.[1] Within this general strategy, α-diazocarbonyl compounds have emerged as powerful precursors to desirable compounds. α-Diazocarbonyl compounds derive most of their synthetic utility from their ability to generate a carbene by entropically favourable release of N_2.[2] For example, Wolff reported in 1902 that when heated in water, an ethyl α-diazoester **1** was converted to a carboxylic acid **4** (**Scheme 1-01**).[3] Although the exact mechanistic sequence of events is still disputed,[4] it is generally accepted that denitrogenation of the α-diazocarbonyl generated a free carbene **2** that enabled a 1,2-shift of the neighbouring methyl group to give a ketene **3.** Water then added into the ketene to give carboxylic acid **4**.[4–6] This type of transformation is now known as the "Wolff rearrangement".



Scheme 1-01: The original Wolff rearrangement.

Although free carbenes are useful for a wide selection of transformations, they are unstable and their reactivity can be difficult to control.[7] The stability of carbenes can be increased when they are bonded to transition metals to form metallocarbenes. The high stability of metallocarbenes is down to the structure, which consists of a σ-bond between the metal and carbene, as well as a π-bond between the filled d-orbitals of the metal and empty p-orbital of the carbene (π-backbonding). The degree of π-backbonding is usually low, so the metallocarbenes generated from α-diazocarbonyl compounds are highly electrophilic and undergo a range of reactions based on this functionality.[2,8–10] Metals that promote denitrogenation of α-diazo compounds include gold,[11] copper,[12] ruthenium[13] and rhodium (**Scheme 1-02**).[14]

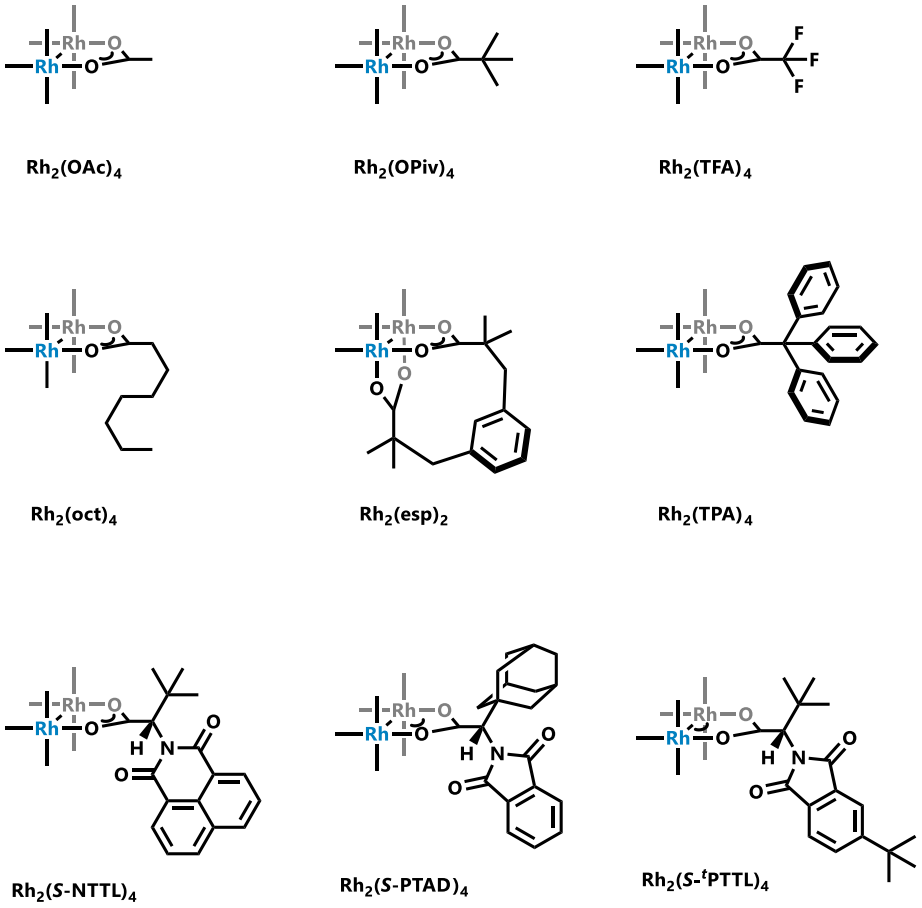


5
α-diazocarbonyl

6
metallocarbene

Scheme 1-02: Generation and structure of a metallocarbene from an α-diazocarbonyl compound.

Rhodium(II) carboxylates are highly versatile and commonly used catalysts for the denitrogenation and further reaction of diazo compounds.[15] The structure of a rhodium(II) carboxylate consists of two central rhodium atoms with a single Rh–Rh bond surrounded by four carboxylate ligands in a "paddlewheel" geometry (**Figure 1-01**).[16] The two vacant axial sites can be ligated with solvent, substrate or water to satisfy the 18 electron count.[17] Rhodium(II) tetracarboxylates can be prepared by reductive ligation of rhodium(III) chloride,[18,19] or by ligand exchange with an existing rhodium(II) carboxylate catalyst.[20]



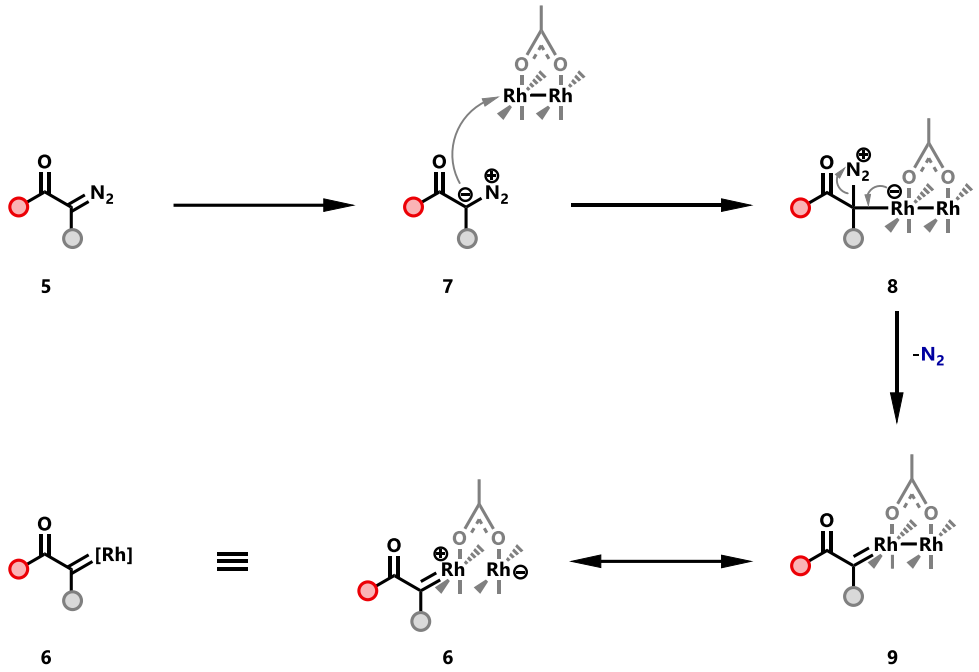
$Rh_2(OAc)_4$ $Rh_2(OPiv)_4$ $Rh_2(TFA)_4$

$Rh_2(oct)_4$ $Rh_2(esp)_2$ $Rh_2(TPA)_4$

$Rh_2(S\text{-NTTL})_4$ $Rh_2(S\text{-PTAD})_4$ $Rh_2(S\text{-}^t\text{PTTL})_4$

Figure 1-01: Some commonly used rhodium(II) carboxylate catalysts.

The generation of rhodium carbenes from α-diazocarbonyl compounds has been extensively studied.[21–23] This mechanism is initiated by complexation of the negatively polarised carbon of diazo compound **5** to an axial site of the rhodium(II) catalyst (**Scheme 1-03**).[21–23] Donation of electron density from the Rh 4d_{xz} orbital into the C–N σ* orbital promotes elimination of nitrogen to generate rhodium-carbene complex **9**. The Rh–Rh bond in the complex **9** is highly polarisable and readily breaks to form the ionic species **6**.[15] The surrounding carboxylate ligands stabilise the negative charge, and their structure can be used to tune the reactivity of the rhodium carbene **6**.[24]



Scheme 1-03: Mechanism for the formation of rhodium(II) carbenes from α-diazocarbonyl compounds.

Metallocarbenes derived from α-diazocarbonyl compounds can be broadly classified according to their substitution (**Figure 1-02**).[9,25,26] Installation of electron-withdrawing substituents (acceptors) such as keto, nitro, sulfonyl *etc.* enhance the electrophilicity of the metallocarbene and thus makes them more reactive.[27] The increase in reactivity is usually accompanied by a decrease in selectivity. Conversely, when electron-donating substituents (donors) such as vinyl, aryl, heteroaryl *etc.* are adjacent to the metallocarbene centre, the reactivity is tempered and these metallocarbenes display greater selectivity.[2]

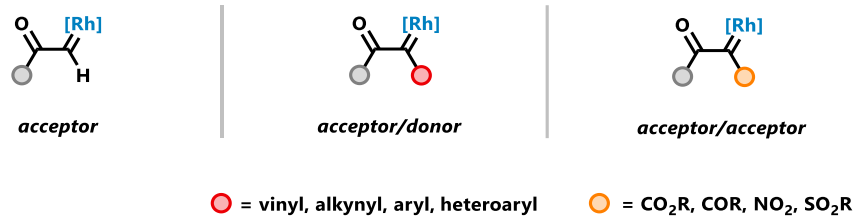


Figure 1-02: Classification of metallocarbenes

All three main classes of metallocarbenes are electrophilic and have been shown to undergo a variety of valuable transformations. These transformations can be categorised according to the type of initial nucleophilic interaction of substrate with carbene into π-bonds, σ-bonds, or lone pairs (**Figure 1-03**).

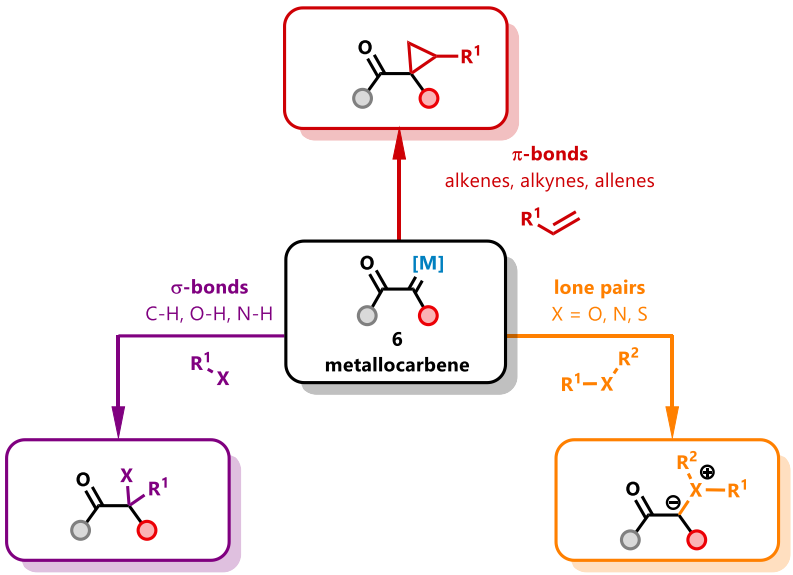
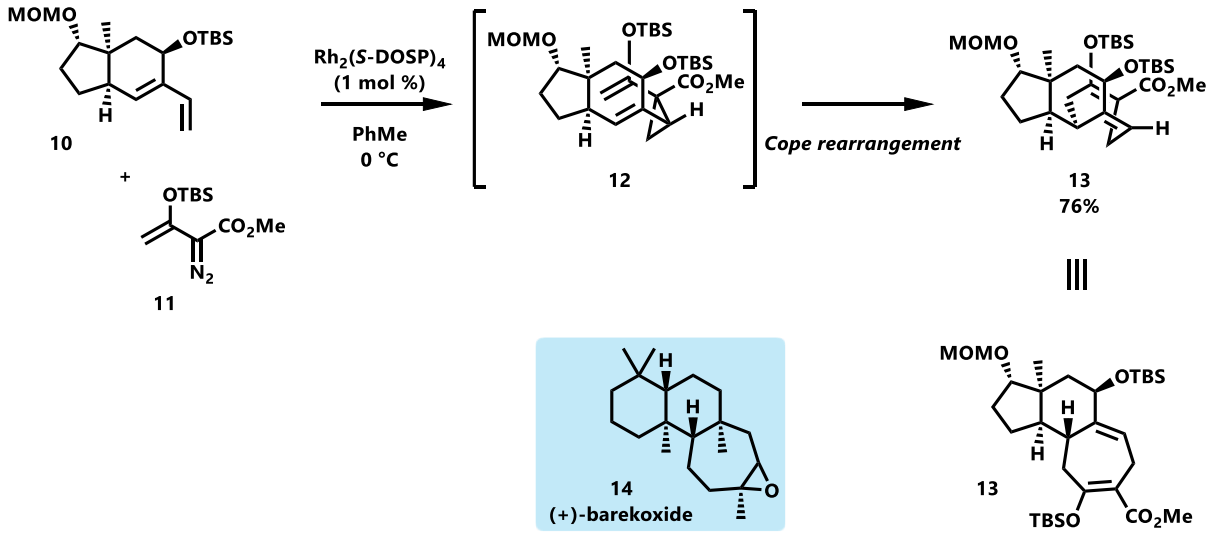


Figure 1-03: Reactions of metallocarbenes derived from α-diazocarbonyl compounds.

1.1.1 Reactions of α-diazocarbonyl compounds with π-bonds

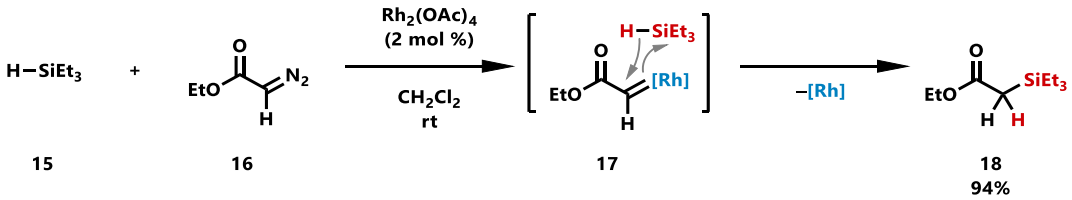
The cyclopropanation of alkenes using α-diazocarbonyl compounds is a very well-documented transformation.[28–30] The cyclopropane ring not only appears in natural products but serves as a useful intermediate for synthesis and has emerged as a valuable functional group in medicinal chemistry.[31,32] For example, Davies, Sarpong and co-workers developed a rhodium(II)-catalysed tandem cyclopropanation/Cope rearrangement that was carried out with complete diastereocontrol and applied to the total synthesis of (+)-barekoxide **14** (**Scheme 1-04**).[33] Rhodium(II) catalysed denitrogenation of a silyl enol diazoester **11** generated a metallocarbene which underwent cyclopropanation with alkene **10** to generate divinylcyclopropane **12** with complete diastereocontrol. The cyclopropane **12** underwent a Cope rearrangement through a boat transition state to give the product **13** in 76% yield. The diastereoselectivity of the cyclopropanation was rationalised by the directing influence of Rh_2(*S*-DOSP)$_4$ in combination with the siloxy group of **10** causing the metallocarbene to approach from the convex face. Interestingly, when Rh_2(*R*-PTAD)$_4$ was used, the opposite diastereoselectivity was observed, demonstrating the power of using different chiral rhodium(II) catalysts.



Scheme 1-04: Rhodium(II) catalysed tandem cyclopropanation/Cope rearrangement.

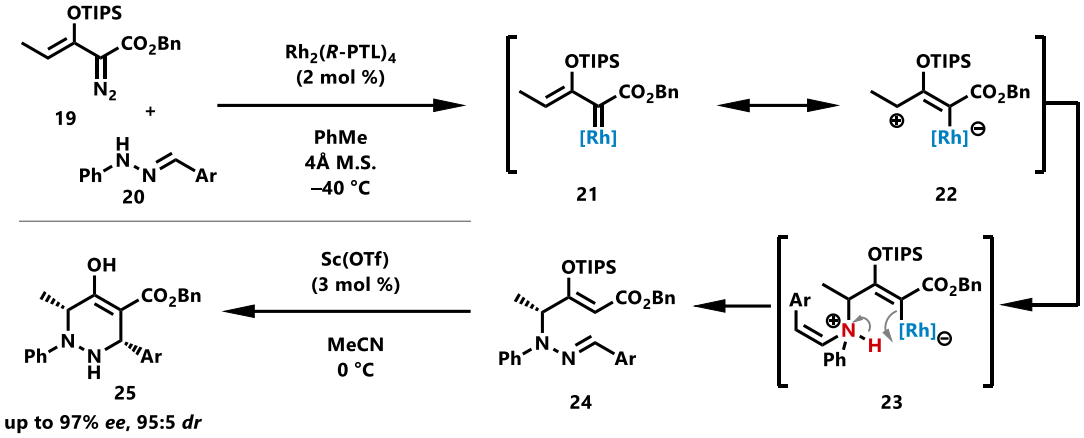
1.1.2 Reactions of α-diazocarbonyl compounds with σ-bonds

The metallocarbenes generated from α-diazocarbonyl compounds are capable of inserting into in sp^3 X–Y bonds such as C–H,[34] O–H,[35] and even C–C bonds.[36] In the majority of cases, X is a heteroatom and Y is a hydrogen atom.[37] For example, triethyl silane **15** was treated with ethyl diazoacetate **16** in the presence of rhodium(II) acetate to generate an α-silyl ester **18** (**Scheme 1-05**).[38] The reaction mechanism occurred by metal-catalysed denitrogenation to generate the rhodium(II) carbene **17**, which coordinated triethylsilane resulting in simultaneous Si–H and C–Si bond formation to form the α-silyl ester **18** in 94% yield.



Scheme 1-05: Si–H insertion of a metallocarbene derived from an α-diazocarbonyl.

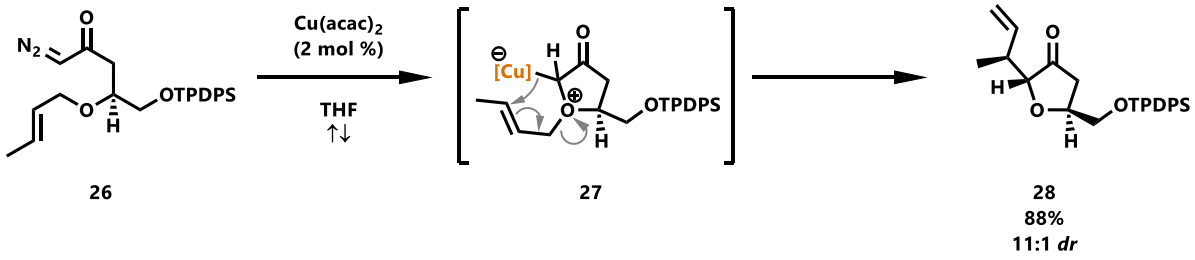
Metallocarbenes from α-diazocarbonyl compounds can also undergo N–H insertion reactions. For example, Doyle and co-workers recently reported a rhodium(II)-catalysed N–H insertion between vinyl diazoacetate **19** and hydrazones **20** (**Scheme 1-06**).[39] Vinylogous addition of the hydrazones **20** to metallocarbene **21** generated aza-ylide species **23** which underwent 1,4-H shift, rather than a concerted insertion.[40] The intermediates **24** were treated with Lewis-acid to trigger a diastereoselective Mannich addition and silyl deprotection to give tetrahydropyridazines **25** in excellent *dr* and *ee*.



Scheme 1-06: Enantioselective vinylogous N–H insertion of α-diazocarbonyls and Lewis acid-catalysed diastereoselective Mannich addition.

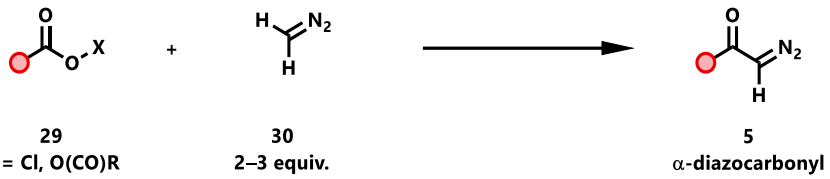
1.1.3 Reactions of α-diazocarbonyl compounds with lone pairs

One of the most characteristic reactions of metallocarbenes derived from α-diazocarbonyl compounds is the coordination to heteroatom lone pairs to generate ylide intermediates.[41–43] [2,3]-Sigmatropic rearrangements of allylic oxonium ylide species is a very useful transformation that has been applied to the total synthesis of many natural products.[42] First disclosed by Roskamp[44] and Pirrung,[45] this methodology was applied to the synthesis of the A-ring fragment **28** of gambieric acid by Clark and co-workers (**Scheme 1-07**).[46] Copper catalysed denitrogenation generated a metallocarbene that was trapped by intramolecular attack of the allylic ether moiety to generate oxonium ylide **27**. Subsequent [2,3]-sigmatropic rearrangement proceeded with high diastereocontrol to deliver the fragment **28** in 88% yield. This general approach is particularly useful for the iterative synthesis of polycyclic ethers.[42]



Scheme 1-07: Synthesis of the A-ring fragment of gambieric acid by [2,3]-sigmatropic rearrangement.

Although α-diazocarbonyl compounds are extremely versatile reagents, one of the major drawbacks is the difficulty in their synthesis. One of the most widely used routes involves acylation of diazomethane **30**, commonly referred to as the Arndt-Eistert homologation (**Scheme 1-08**).[47-49]



29
X = Cl, O(CO)R

30
2–3 equiv.

5
α-diazocarbonyl

Scheme 1-08: Generation of α-diazocarbonyl compounds.

Diazomethane **30** is an extremely toxic and explosive gas and hence the industrial applications are limited.[50] Additionally, the diazo compounds themselves are potentially explosive and must be handled with specialist care.[51] In lieu of the safety concerns associated with diazo compounds, chemists have looked towards alternative strategies for generating metallocarbenes.

1.2 Structure and Reactivity of 1,2,3-Triazoles

1,2,3-Triazoles are a five-membered heterocycle containing three contiguous nitrogen atoms (**Figure 1-04**).

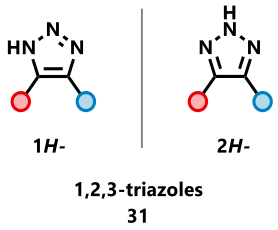
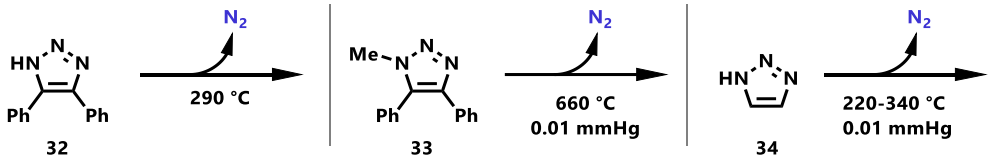


Figure 1-04: Isomeric forms of 1,2,3-triazoles and 1,2,4-triazoles.

Although they have high percentage nitrogen content, 1,2,3-triazoles are generally stable to a range of oxidative, reductive, and hydrolytic conditions and they exhibit remarkable thermal stability (**Scheme 1-09**).[52–55]



Scheme 1-09: Very forcing conditions are required to decompose 1,2,3-triazoles.

The 1,3-dipolar cycloaddition between an azide and an alkyne results in the formation of a 1,2,3-triazole (*vide infra*). Due to their ease of preparation, 1,2,3-triazoles have an extremely broad range of applications, from materials science to bioconjugation.[56–60] Additionally, their unique structure allows them to bind with enzymes and receptors in biological systems in a variety of different ways which makes them useful fragments in drug molecules (**Figure 1-05**).[61–63]

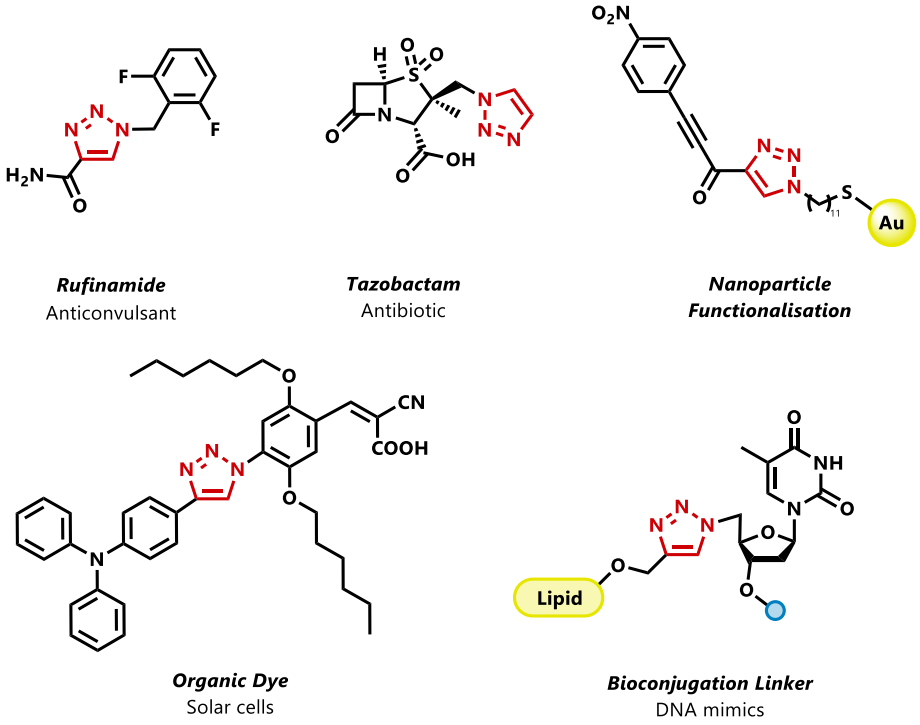
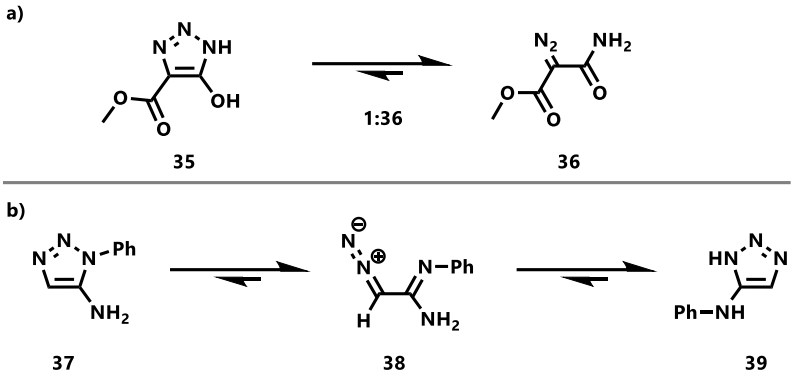


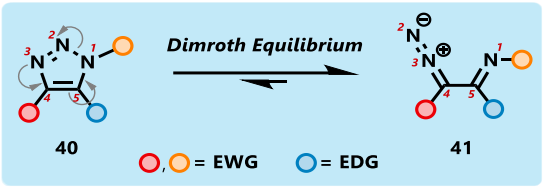
Figure 1-05: Common applications of 1,2,3-triazoles.

The behaviour of 1,2,3-triazoles can be influenced by introducing different substituents around the ring. Under certain circumstances, 1,2,3-triazoles can be made to undergo various ring transformations and rearrangements. In 1906, Piloty and Neresheimer prepared 5-oxy-1,2,3-triazole **35** and observed it to be in equilibrium with the ring opened diazodicarbonyl compound **36** (**Scheme 1-10a**).[64] Soon after, Dimroth prepared 5-aza-1,2,3-triazole **37** and reported that over time, it spontaneously rearranged to the 5-anilino-1,2,3-triazole isomer **39** (**Scheme 1-10b**).[65,66] It was suggested that these rearrangements involved a ring–chain isomerisation through an α-diazoimine intermediate **38** in a process now known as the Dimroth rearrangement.



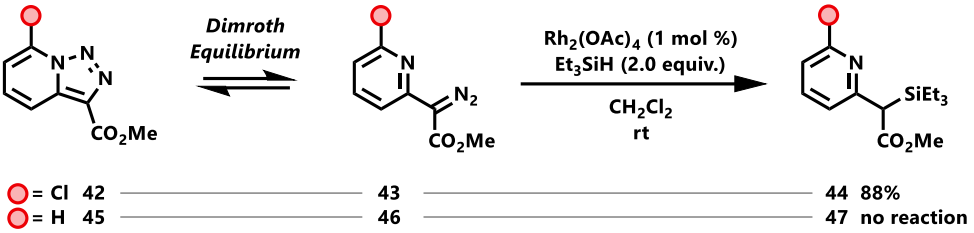
Scheme 1-10: Rearrangements of 1,2,3-triazoles.

Ring–chain isomerisation of 1,2,3-triazoles was studied further by several groups including Grünanger,[67] Harmon,[68] Marsh[69] and Bakulev.[70] It became clear that the position of the Dimroth equilibrium was highly dependent on the nature of the substituents around the ring; installing electron withdrawing groups at the *N*-1 position,[71–73] 4-position,[74,75] and/or electron-donating functional groups at the 5-position of triazoles **40** was found to push the equilibrium towards the ring-opened α-diazoimine structure **41** (**Scheme 1-11**).[67,70,76]



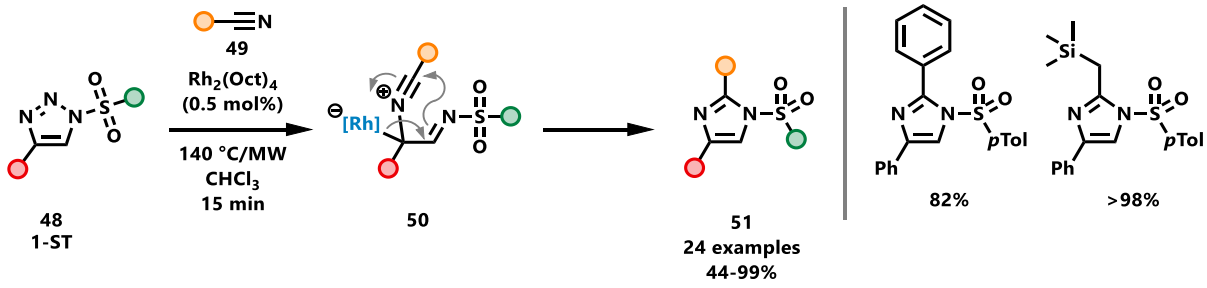
Scheme 1-11: The Dimroth equilibrium is facilitated by electron-withdrawing groups at the *N*-1, 4-position and/or electron-donating groups at the 5-position.

The potential of 1,2,3-triazoles as carbene precursors was first realised by Gevorgyan and co-workers in 2007.[75] A rhodium azavinyl carbene was generated from 7-chloropyridotriazole **42**, which underwent Si–H insertion with triethylsilane **15** to generate silane **44** in 88% yield (**Scheme 1-12**). The chlorine substituent was crucial, as hydrogen analogue **45** was unreactive, demonstrating the delicate balance between triazole stability and reactivity.



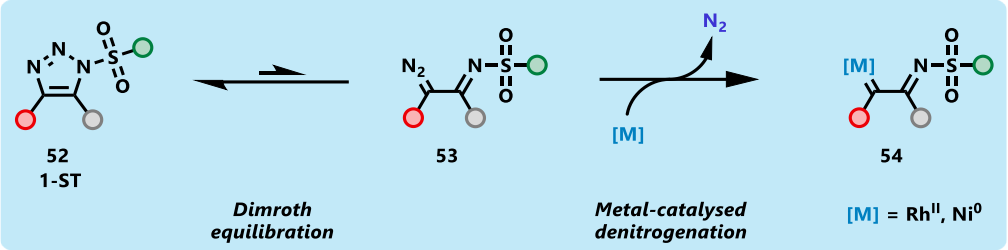
Scheme 1-12: Rhodium(II)-catalysed functionalisation of 7-chloropyridotriazole.

Following the initial report from Gevorgyan and co-workers, efforts were made to discover other functional groups that unlock this kind of behaviour. Fokin and Gevorgyan subsequently revealed 1-sulfonyl-1,2,3-triazoles **48** (1-STs) as stable metallocarbene precursors which underwent rhodium(II)-catalysed transannulation with nitriles **49** to generate imidazoles **51** (**Scheme 1-13**).[77] Rhodium(II)-catalysed denitrogenation of a 1-ST **48** generated a metallocarbene that was attacked by a nitrile (**49**) to generate an azaylide species **50** that cyclised with release of the catalyst to give imidazoles **51**.



Scheme 1-13: Rhodium(II)-catalysed transannulation of 1-sulfonyl-1,2,3-triazoles with nitriles.

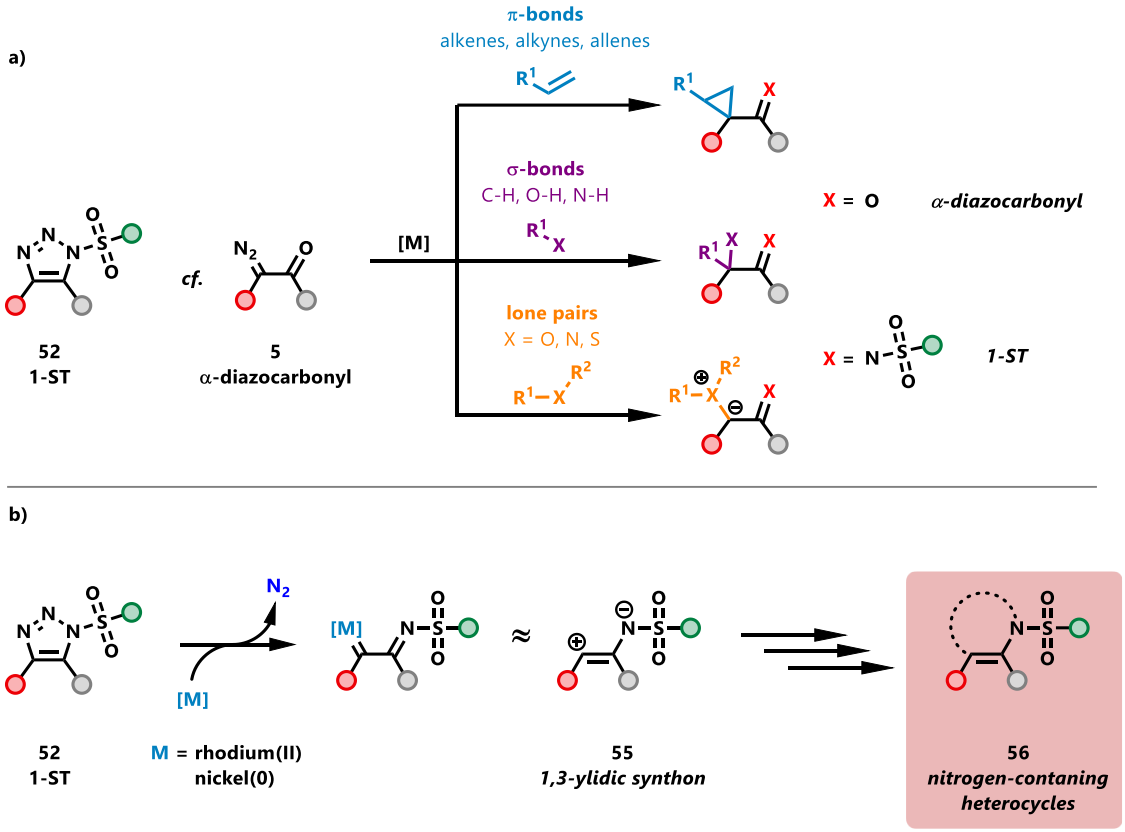
Installation of a sulfonyl group at the *N*-1 position of 1,2,3-triazoles **52** allows access to the reactive α-diazoimine species **53** whilst predominantly existing in the stable closed ring isomer (**Scheme 1-14**). This affords on-demand reactivity when treated with certain metal catalysts, generating the highly electrophilic metallocarbene species **54** which is capable of undergoing a vast wealth of transformations.[78–83] Additionally, the relative position of the equilibrium means that there is a low concentration of reactive species at any one time. This allows for exquisite chemoselectivities and overcomes the need for slow addition, which is often required when dealing with α-diazocarbonyl compounds.[51]



Scheme 1-14: 1-sulfonyl-1,2,3-triazoles as metallocarbene precursors.

1.3 Reactions of 1-STs

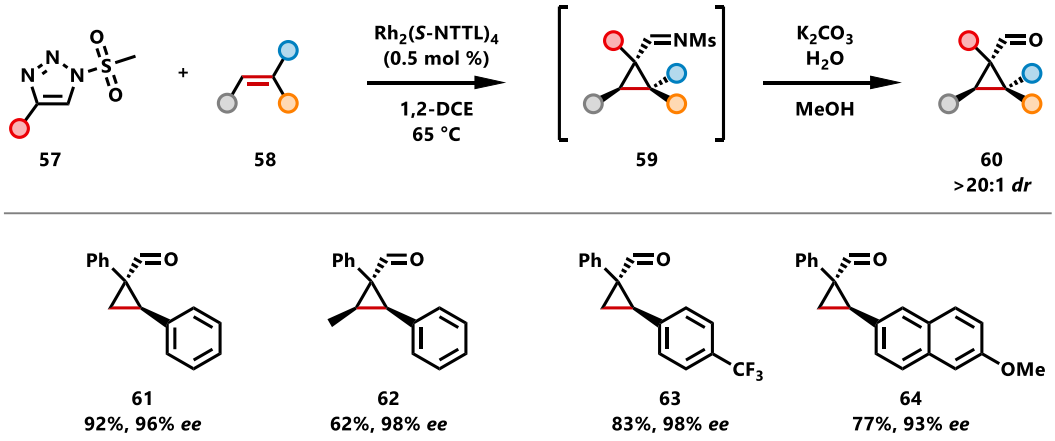
Following the pioneering work of Fokin,[77] Gevorgyan[75], Murakami,[84] Davies,[85] Boyer,[86] Anbarasan,[87] Yoo[88] and Lacour,[89] denitrogenative transformations of 1-STs have become a new staple in metallocarbene chemistry. Analogously to α-diazocarbonyl compounds **5**, 1-STs **52** can perform reactions such as cyclopropanation,[90–93] various X–H bond insertions,[94–98] and sigmatropic rearrangements with high yield and selectivity (**Scheme 1-15a**).[99–102] The key difference between 1-STs and α-diazocarbonyl compounds is the presence of the *N*-sulfonylimino group instead of the carbonyl. This group is nucleophilic and can participate in reactions (**Scheme 1-15b**). This mode of reactivity is particularly useful in the synthesis of nitrogen-containing heterocycles.



Scheme 1-15: 1-STs are excellent precursors to other nitrogen-containing heterocycles.

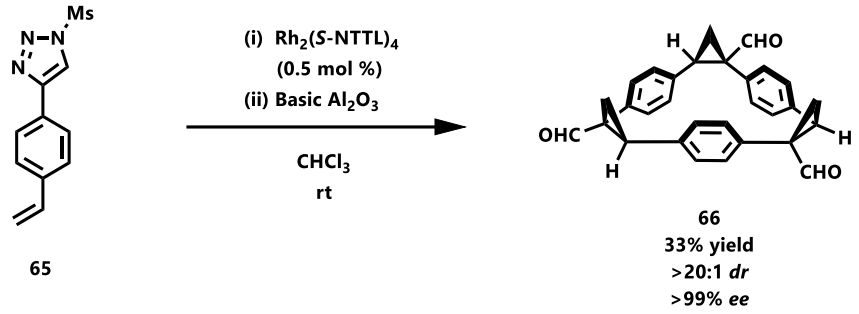
1.3.1 Functionalisation of π-bonds: cyclopropanation reactions

1-STs can be used to carry out cyclopropanation of double bonds in a similar manner to α-diazocarbonyl compounds. One of the earliest examples of 1-ST reactivity involved rhodium(II)-catalysed denitrogenation and cyclopropanation of substituted styrenes (**Scheme 1-16**).[103] In the presence of the chiral catalyst Rh_2(*S*-NTTL)$_4$, 4-aryl substituted 1-STs **57** denitrogenated to generate metallocarbenes which carried out cyclopropanation with high enantio- and diastereocontrol. Importantly, the resulting sulfonyl imines **59** were unstable and were readily converted to the corresponding aldehydes **60** by treatment with potassium carbonate, water and methanol. This type of work-up is a general strategy when a sulfonyl imine moiety is in the product. Reduction to a sulfonamide is also commonly used to prevent decomposition of the product.



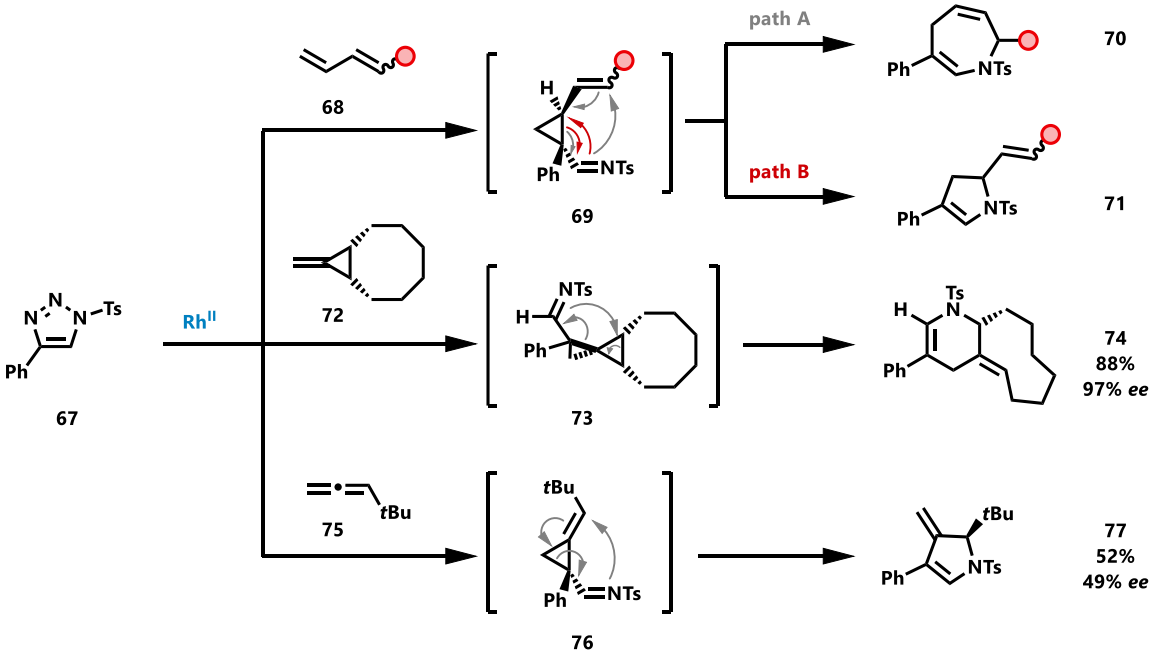
Scheme 1-16: Rhodium(II)-catalysed enantioselective cyclopropanation of styrenes.

An interesting example of cyclopropanation of alkenes using 1-STs was recently reported by Murakami and co-workers.[104] A 1-mesyl triazole **65** bearing a styryl substituent at the 4-position underwent enantioselective trimerisation in the presence of Rh_2(*S*-NTTL)$_4$ to generate C_3-symmetric macromolecule **66** which is a useful chiral building in supramolecular chemistry (**Scheme 1-17**).



Scheme 1-17: Synthesis of enantiopure C_3-symmetric macromolecules by cyclopropanation of 1-STs

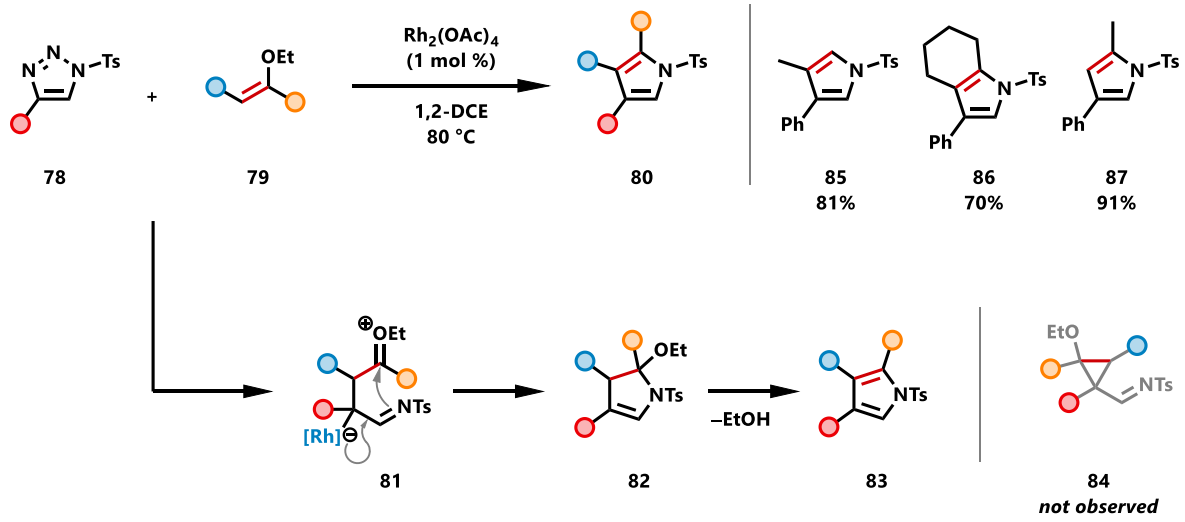
Having substrates that are able to relieve cyclopropane ring strain through pericyclic reaction allowed access to diverse nitrogen heterocycles.[82] For example, in the rhodium catalysed reaction of 1-ST **67** with 1,3-dienes **68**, the intermediate cyclopropane **69** underwent either an aza-Cope rearrangement (path A) or Cloke rearrangement (path B) to give the formal [4+3] and [3+2] cycloadducts **70** and **71** respectively.[105] Likewise, in the reaction with methylenecyclopropane **72**, cyclopropanation generated the spirocycle **73** which thermally rearranged to give the *trans*-cyclononene **74** in 88% yield and 97% *ee*.[106] In reaction with an allene **75**, initial cyclopropanation was followed by ring-opening rearrangement to furnish 2,3-dihydropyrrole **77** in 52% yield and 49% *ee*.[107]



Scheme 1-18: Rhodium(II)-catalysed cyclopropanation-rearrangement reactions of 1-STs.

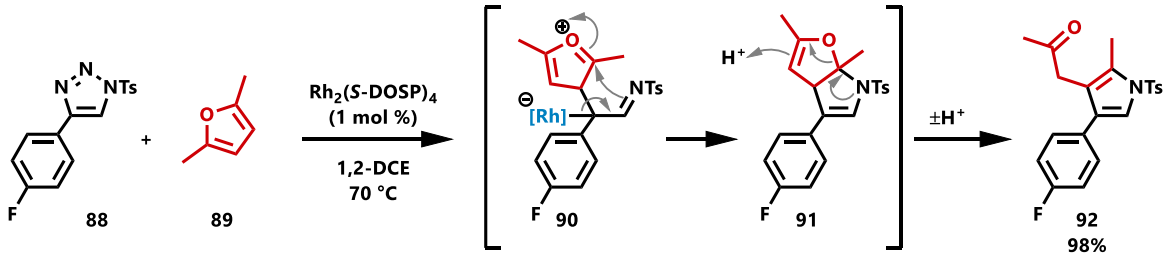
1.3.2 Functionalisation of π-bonds: transannular reactions

The conversion of a heterocyclic 1-ST into another heterocyclic product is often referred to as a transannular reaction and is most often is reported in reactions involving electron-rich π-bonds.[79] For example, Lee and co-workers reported an efficient preparation of pyrroles **80** from triazoles **78** and enol ethers **79** (**Scheme 1-19**).[108] A plausible mechanism involved denitrogenation of 1-ST **78** to generate a metallocarbene followed by nucleophilic addition of the enol ether **79** to give zwitterionic intermediate **81**. Release of electrons from the anionic rhodium into the imine moiety caused ring formation affording 2,3-dihydropyrrole **82**, which spontaneously aromatised by elimination of alcohol to give pyrrole **83**. An alternative pathway involving cyclopropanation-rearrangement was ruled out by NMR studies as the alkoxycyclopropyl imine species **84** was not detected.



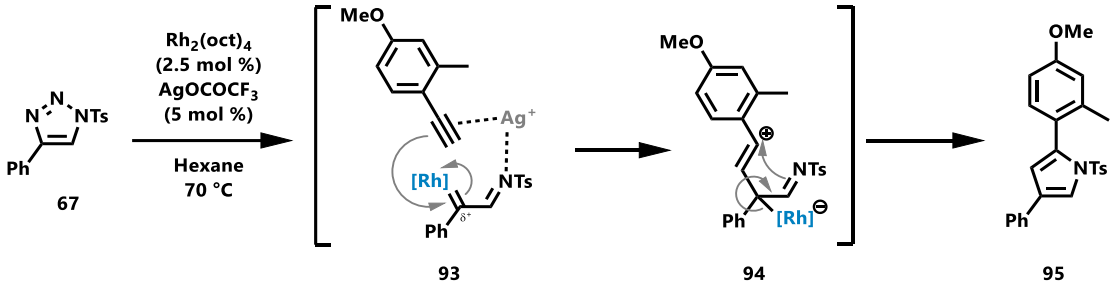
Scheme 1-19: Transannular reaction of 1-STs with enol ethers gave pyrroles.

Similar reactivity was observed when 2,5-disubstituted furans were used as pseudo-enol ethers.[109] For example, 1-ST **88** reacted with 2,5-dimethylfuran **89** in the presence of Rh_2(*S*-DOSP)$_4$ to generate ylide species **90**, which cyclised to give bicyclic hemiaminal **91** which underwent ring-opening and aromatisation to pyrrole **92** in 98% yield (**Scheme 1-20**).



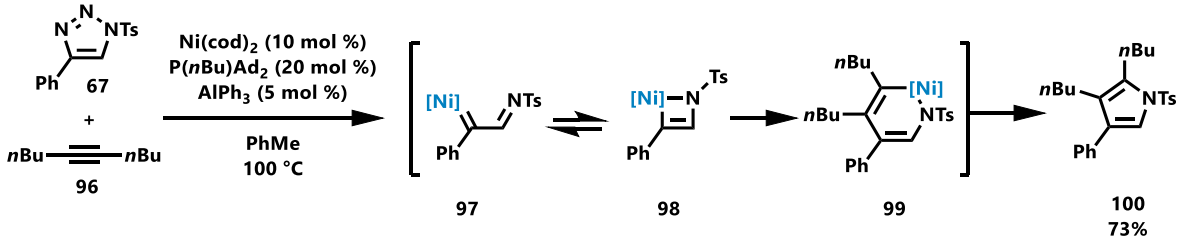
Scheme 1-20: Rhodium(II)-catalysed conversion of furans into pyrroles using 1-STs.

As well as alkenes, 1-STs are capable of reacting with the π-bonds of alkynes. Gevorgyan and co-workers reported that when treated with a $Rh_2(oct)_4$ and silver(I) trifluoroacetate catalyst system, a 4-phenyl 1-ST **67** underwent a transannular reaction with a terminal alkyne to give pyrrole **95** in 81% yield (**Scheme 1-21**). Generation of the rhodium carbene **93** followed by nucleophilic attack of the terminal alkyne generated ylide **94**, which cyclised to release the catalyst giving the 1,2,4-substituted pyrrole **95**. Although the exact role of the silver catalyst is unknown, it likely acted as a Lewis acid by coordination to the imine, activating the carbene to nucleophilic attack. Crucially, no reaction was observed without the addition of silver(I) trifluoroacetate.



Scheme 1-21: Transannulation of 1-STs and terminal alkynes to generate pyrroles.

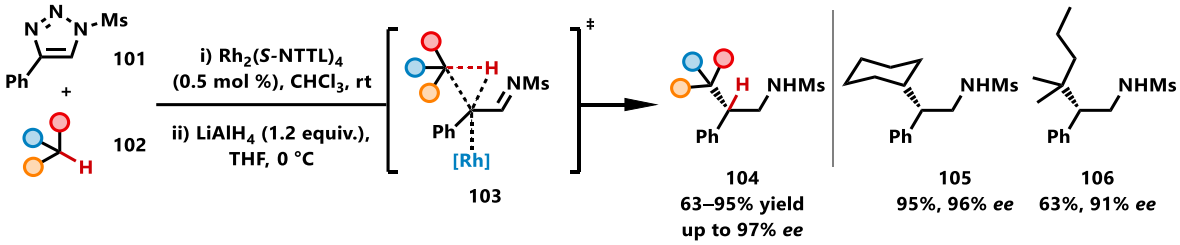
Transannulation with an internal alkyne was reported by Murakami (**Scheme 1-22**).[110] Unusually for 1-STs, the reaction was initiated with a nickel(0)/phosphine catalyst system. The 1-ST **67** denitrogenated to generate nickel carbene **97** which cyclised to form the azametallocycle **98**. Insertion of alkyne **96** into the Ni–C bond generated the six-membered azametallocycle **99**. Lewis-acid promoted reductive elimination afforded the pyrrole **100** in 73% yield.[111] Nickel(0) catalysts are scarcely used to generate metallocarbenes from 1-STs as these catalysts are very reactive and require glovebox techniques, whereas rhodium(II) tetracarboxylate catalysts are air-stable.



Scheme 1-22: Nickel-catalysed denitrogenative alkyne insertion of 1-STs.

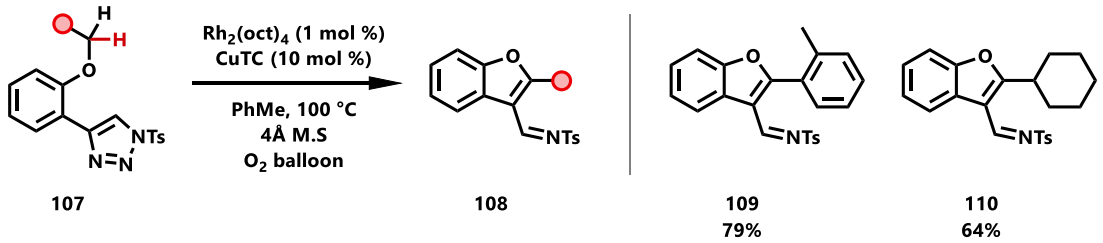
1.3.3 Functionalisation of σ-bonds: C–H insertion reactions

Similar to α-diazocarbonyl compounds, the metallocarbenes generated from 1-STs are capable of undergoing a variety of insertions into C−H σ-bonds. The first enantioselective C−H insertion reaction involving 1-STs was reported by Fokin (**Scheme 1-23**) in 2011.[112] The 1-ST **101** underwent rhodium(II)-catalysed C−H insertion into unactivated alkanes **102**. The resulting sulfonylimines were reduced to the corresponding sulfonamides **104** by treatment with lithium aluminium hydride. In this approach, the metallocarbenes inserted preferentially into tertiary C−H bonds over secondary and primary C−H bonds, and likely involved a three-membered transition state **103** with concerted bond formation.[48,95]



Scheme 1-23: Rhodium(II)-catalysed C−H bond insertion of 1-STs.

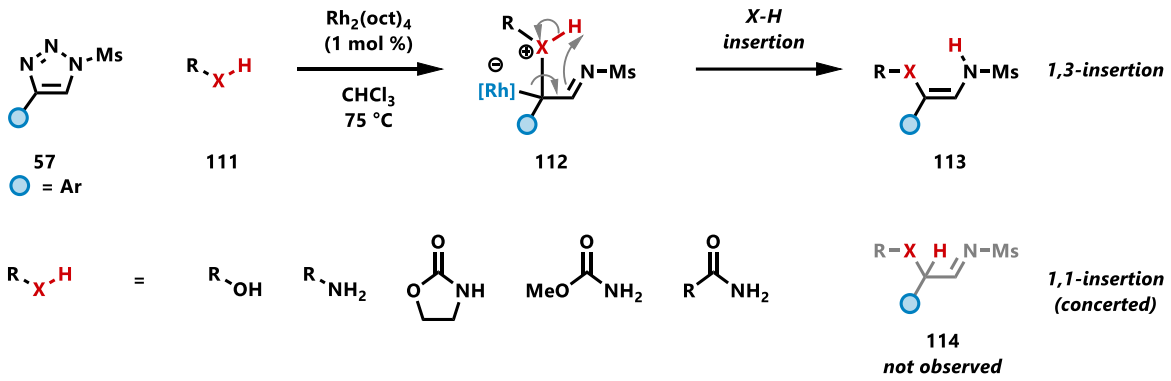
1-STs have also been employed in intramolecular C−H migration reactions. Kang and co-workers developed an approach to benzofurans **108** involving rhodium(II)-catalysed 1,5-C−H migration and *in situ* copper-catalysed aerobic oxidation (**Scheme 1-24**).[113]



Scheme 1-24: Synthesis of benzofurans by rhodium(II)-catalysed C−H migration and copper-catalysed aerobic oxidation

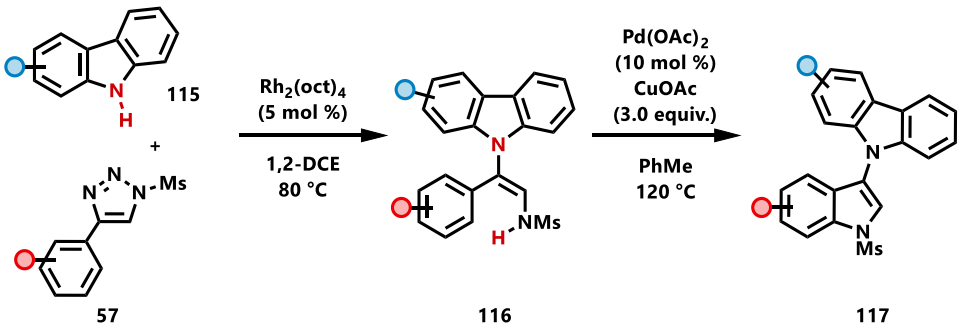
1.3.4 Functionalisation of σ-bonds: N–H and O–H insertion reactions

In contrast to C–H bonds, N–H and O–H bond insertions of azavinyl carbenes proceed with formation ylide-type species **112** followed be intra- or intermolecular proton abstraction (**Scheme 1-25**).[7,95] Fokin and co-workers demonstrated this mode of reactivity (1,3-insertion) by subjecting 4-aryl substituted 1-STs **57** to a diverse selection of N–H and O–H bonds from alcohols, amines, amides *etc.* in the presence of rhodium(II) carboxylate catalysts (**Scheme 1-25**).[95] The consistent formation of (*Z*)-enamides **113** verified that the reaction proceeded through formation of ylide species **112**.[114] Rather than ylide formation, if concerted X–H insertion took place then the product **114** would have been observed.

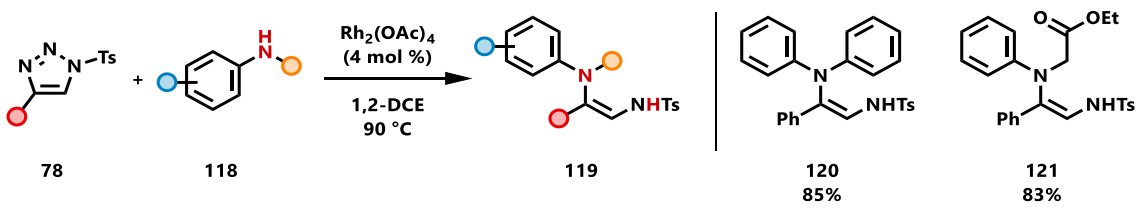


Scheme 1-25: Rhodium(II)-catalysed N–H and O–H insertions of 1-STs.

The 1,3-insertion of azavinylcarbenes into carbazoles **115** was reported by Yoo and co-workers (**Scheme 1-26a**).[115] The 1-STs **57** underwent N–H bond insertion catalysed by $Rh_2(oct)_4$ to generate substituted enamines **116**. Intramolecular C–H amination catalysed by $Pd(OAc)_2$ gave heterobiaryls **117**, which are a class of potent antibiotics.[116] A similar reaction was reported by Shang in which 1-STs **78** smoothly underwent N–H insertion with *N*-aryl amines **118** to afford a selection of substituted enamines **119** (**Scheme 1-26b**).[117]



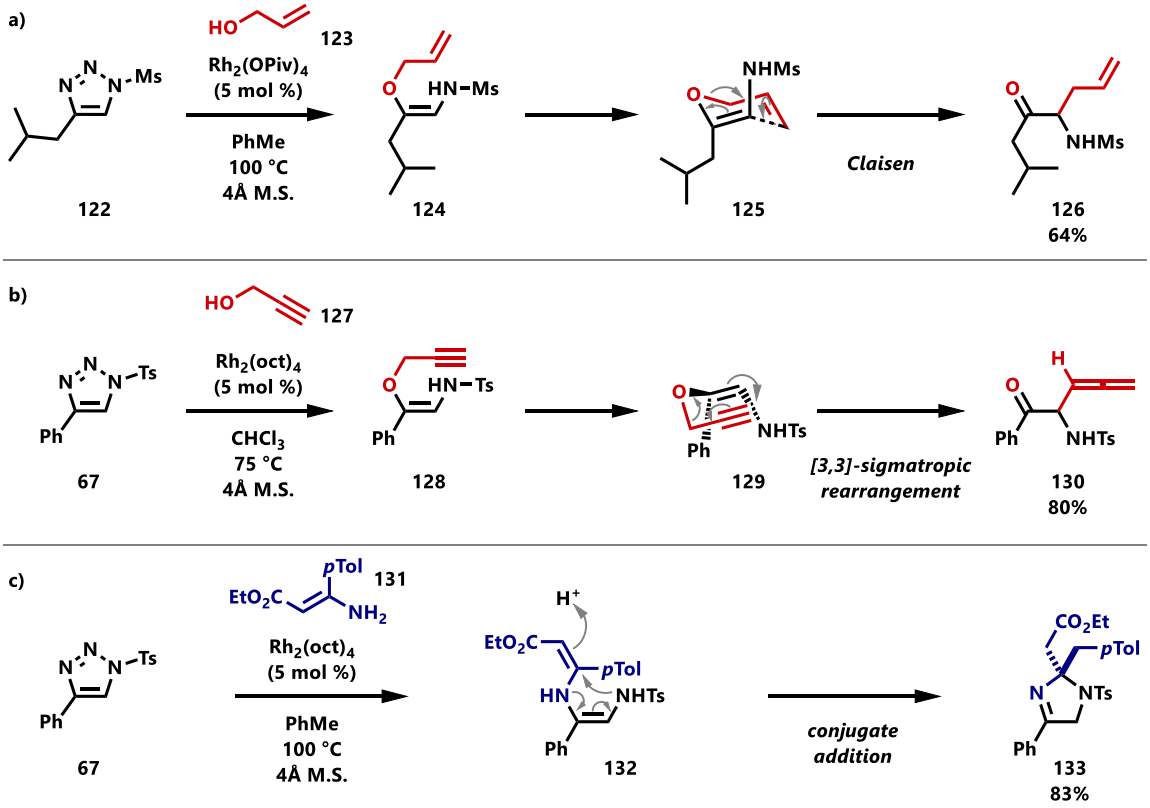
Scheme 1-26a: Rhodium(II)-catalysed N–H insertion followed by palladium-catalysed C–H amination.



Scheme 1-26b: Synthesis of substituted enamines by rhodium-catalysed N−H insertion.

1.3.5 X−H insertion reactions with unsaturated compounds

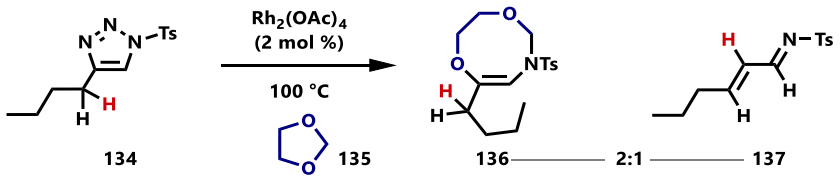
When unsaturated alcohols or amines are used in X−H insertion reactions with 1-STs, various rearrangements can occur to create products with higher complexity. For example, $Rh_2(OPiv)_4$ catalysed reaction of 1-ST **122** with allylic alcohol **123** generated O−H insertion product **124**, which underwent a Claisen rearrangement to form α-allyl ketone **126** in 64% yield (**Scheme 1-27a**).[94] Propargyl alcohol **127** underwent a similar N−H insertion followed by sigmatropic rearrangement to give allene **130** in 80% yield (**Scheme 1-27b**).[95] Rhodium(II)-catalysed N−H insertion of 1-ST **67** into enamine **131** generated the functionalised enamine **132** and spontaneous intramolecular conjugate addition delivered the 3-imidazoline **133** in 83% yield. (**Scheme 1-27c**).[118]



Scheme 1-27: Rhodium(II) catalysed X−H insertions of azavinyl carbenes with unsaturated compounds.

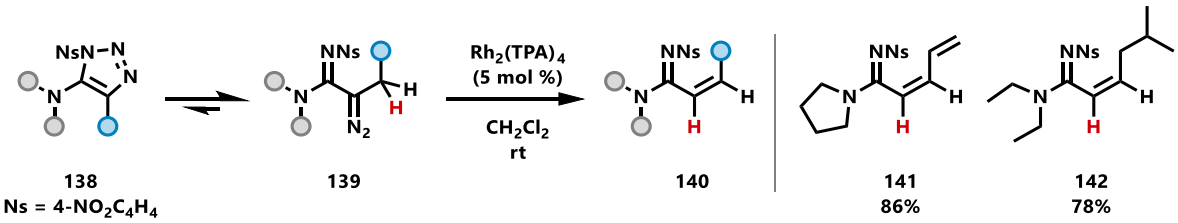
1.3.6 Rearrangements involving 1,2-shifts

For 1-STs with suitable substitution adjacent to the carbene centre, 1,2-shifts can occur to generate diverse functionality.[83] When there is an adjacent C(sp^3)-H bond, a 1,2-hydride shift can occur to introduce an alkene and this is commonly referred to as β-hydride elimination.[48] As with α-diazocarbonyl compounds, 1,2-H shifts often occur competitively with other rhodium(II)-catalysed pathways.[89,90,119,120] For example, in the attempted synthesis of 8-membered dioxazocine **136** by rhodium(II)-catalysed reaction of 1-ST **134** with dioxolane **135** as solvent, the alkene **137** arising from intramolecular 1,2-H shift was isolated as the major product alongside the desired heterocycle **136** (**Scheme 1-28**).[89]



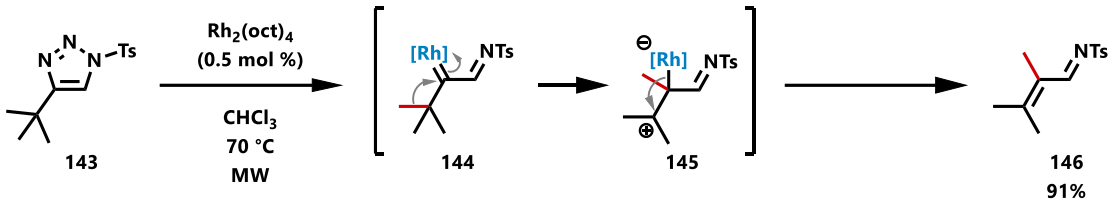
Scheme 1-28: Rhodium(II)-catalysed intramolecular 1,2-H shift of 1-STs is often competing process.

However, controlled 1,2-H shift can be used to access alkene motifs (**Scheme 1-29**).[121] A range of 5-aza substituted 1-STs **138** were allowed to react in the presence of $Rh_2(TPA)_4$ to generate a library of valuable α,β-unsaturated amidines **140** in high yield. The combination of a sterically encumbered rhodium(II) carboxylate and electron-withdrawing sulfonyl group were critically important for shutting down a competing S–O transfer reaction as well as giving rise to exclusive *Z*-selectivity.[122]



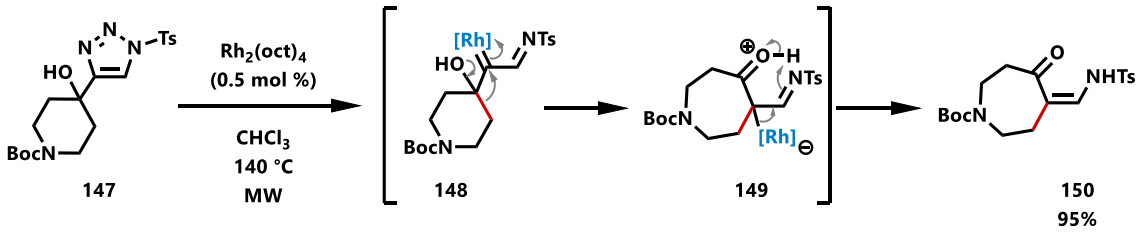
Scheme 1-29: Rhodium(II) catalysed 1,2-H shift to generate *Z*-α,β-unsaturated amidines.

As well as 1,2-H shifts, 1,2-alkyl migrations are possible using 1-STs.[83] For example, rhodium(II)-catalysed denitrogenation of 4-*tert*butyl substituted 1-ST **143** generated the metallocarbene **144** under microwave irradiation (**Scheme 1-30**).[89] A 1,2-methyl shift occurred to generate the alkene product **146** in 91% yield.



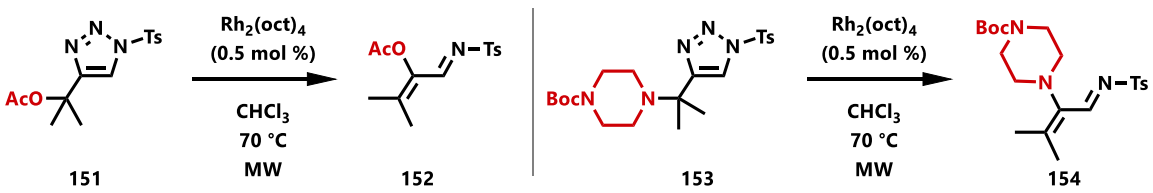
Scheme 1-30: Rhodium(II)-catalysed 1,2-methyl shift.

Murakami reported that α-hydroxy 1-ST **147** underwent rhodium(II)-catalysed denitrogenation to generate intermediate metallocarbene **148** (**Scheme 1-31**).[123] The electron-donating effect of the alkoxy group facilitated ring expansion with concomitant insertion into the metallocarbene, generating intermediate **149**. The sulfonyl imine behaved as an intramolecular base to furnish the ring expanded enaminone **150** in 95% yield.



Scheme 1-31: Rhodium(II)-catalysed migratory insertion.

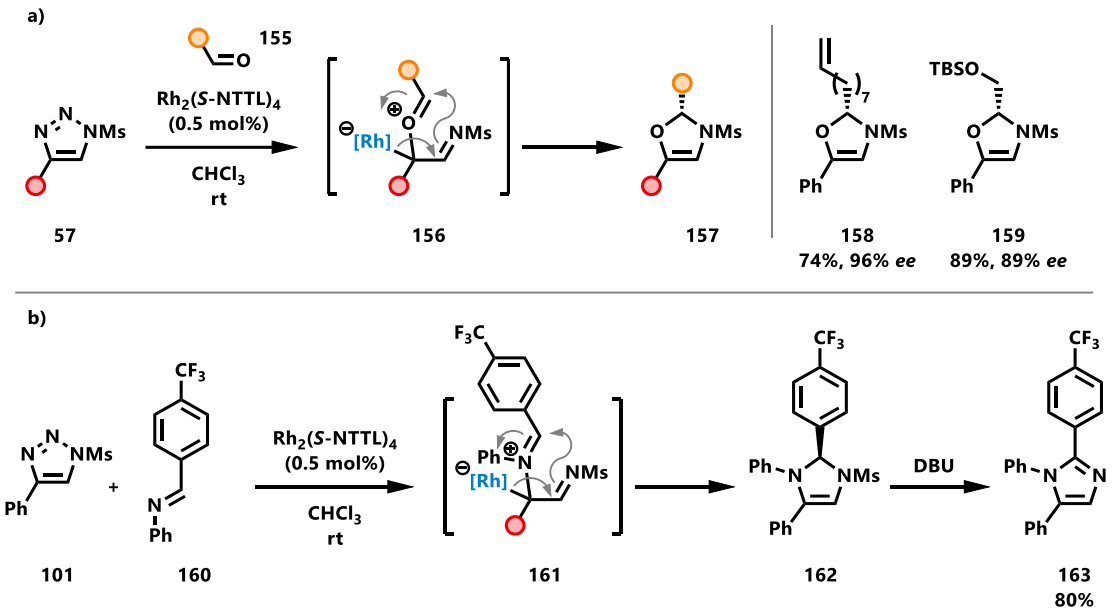
Rhodium(II)-catalysed 1,2-shifts of alkoxy and amino groups have also been reported using 1-STs (**Scheme 1-32**).[124] The acetoxy group of 1-ST **151** underwent 1,2-shift catalysed by $Rh_2(OAc)_4$ under microwave irradiation to give the enol **152** in 96% yield. Similarly, the piperazine group of 1-ST **153** underwent a 1,2-shift under the same conditions to give the olefin **154** in 71% yield.



Scheme 1-32: 1,2-O and 1,2-N shift reactions of 1-STs.

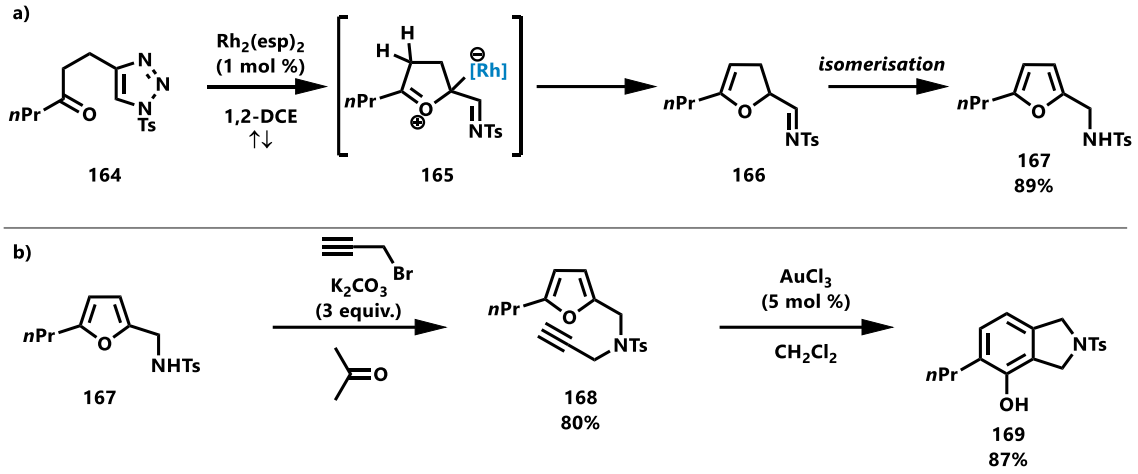
1.3.7 Rearrangements involving unsaturated ylide species

Similarly to with nitriles (*vide supra*), rhodium(II)-catalysed nucleophilic addition of aldehydes **155** and imines **160** followed by intramolecular cyclisation is an efficient route to five-membered heterocycles (**Scheme 1-33**). When using a chiral rhodium(II) catalyst, 1-STs **57** and aldehydes **155** formed the chiral ylide species **156** (**Scheme 1-33a**).[125] Ring-closure by the sulfonyl imine generated oxazolines **157** in high yield and enantioselectivity. Analogous reactivity was observed with imine **160**, which generated the imidazoline **162** (**Scheme 1-33b**). The corresponding imidazole **163** was obtained in 80% overall yield by treatment with DBU.[125]



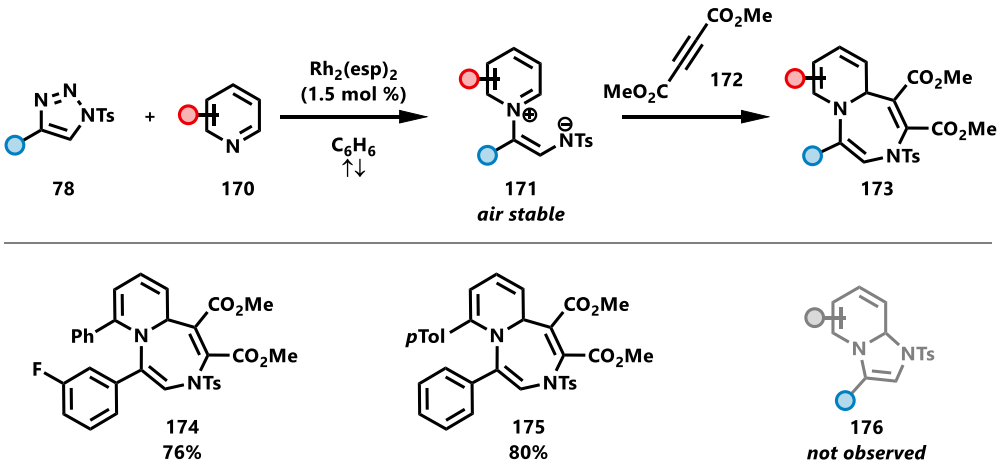
Scheme 1-33: Rhodium(II)-catalysed transannular reaction of 1-STs with aldehydes and imines.

Multi-substituted furans could be accessed by using a 1-ST **164** with a carbonyl tether (**Scheme 1-34a**).[126] When treated with $Rh_2(esp)_2$ catalyst under reflux, intramolecular trapping of the rhodium carbene by the carbonyl group generated oxonium ylide **165**. Rearrangement and aromatisation gave furan **167** in 89% yield. The furan product was *N*-alkylated with propargyl bromide to generate alkyne **168**, which underwent an $AuCl_3$-catalysed rearrangement to deliver the phenol **169** in 87% yield (**Scheme 1-34b**).



Scheme 1-34: Rhodium(II)-catalysed synthesis and derivatisation of a multi-substituted furan using a 1-ST.

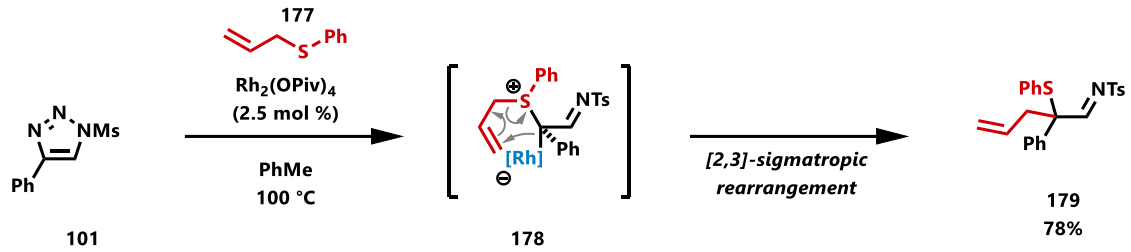
It is possible to isolate some ylide species derived from 1-STs. For example, Yoo and co-workers reported the isolation of air-stable azomethine ylides **171** when 1-STs **78** underwent a rhodium(II)-catalysed reaction with pyridines **170** (**Scheme 1-35**).[127] Remarkably, the ylides **171** were isolable by column chromatography and fully characterised by x-ray crystallography.[128,129] The azomethine ylides **171** were allowed to react with electron-poor alkyne **172** to generate 1,4-diazepine compounds **173**.[127] Interestingly, the product **176** arising from intramolecular dearomative electrocyclisation of the ylide **171** was never observed.



Scheme 1-35: Rhodium(II)-catalysed synthesis of azomethine ylides and 1,4-diazepines from 1-STs.

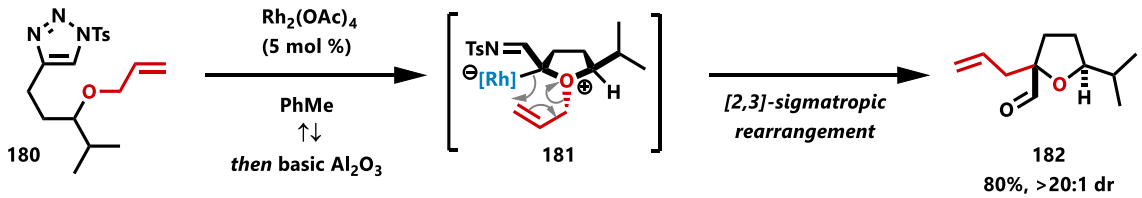
1.3.8 [2,3]-Sigmatropic rearrangements

Reactions with allylic ether species such as sulfide **177** generated an unsaturated ylide intermediate **178**, which was poised to undergo a Doyle-Kirmse reaction (**Scheme 1-36**).[99,102,130] [2,3]-Sigmatropic rearrangement of the sulfur ylide generated the α-allyl-α-sulfonylimine **179** in 78% yield.[99]



Scheme 1-36: Doyle-Kirmse reaction of a 1-ST.

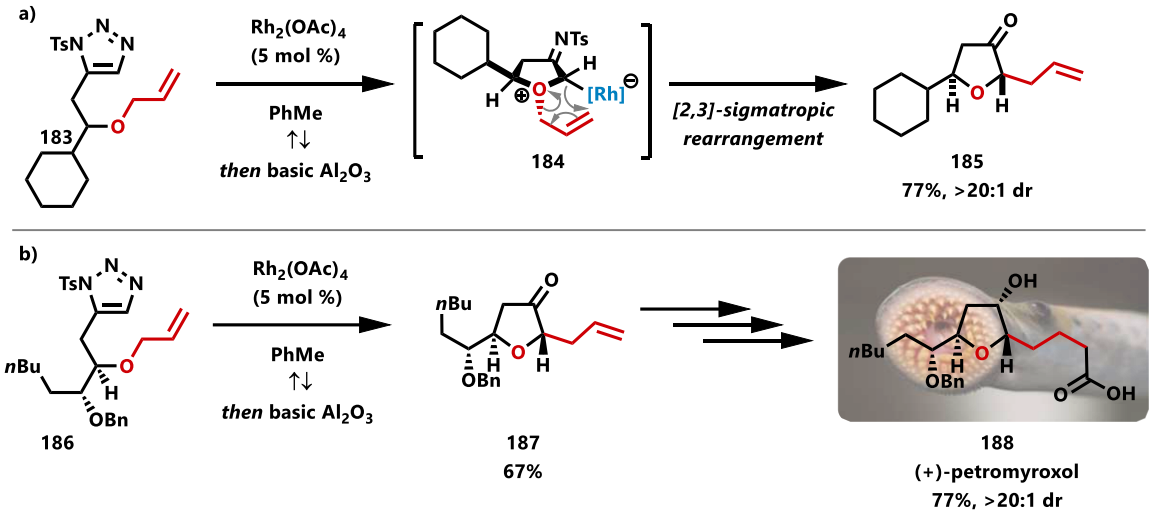
A comparable [2,3]-sigmatropic rearrangement was carried out in an intramolecular fashion using 1-ST **180** bearing a tethered allyl ether at the 4-position (**Scheme 1-37**).[101] Rhodium(II)-catalysed denitrogenation followed by oxonium ylide formation generated the intermediate **181**. Stereocontrolled [2,3]-sigmatropic rearrangement transferred the allyl group to generate a new C–C bond. Treatment with basic alumina *in situ* generated the 2-tetrasubstituted furan **182** in 80% yield and high diastereoselectivity. The *anti*-diastereoselectivity was proposed to arise from minimisation of the steric clash between the migrating allyl group and the bulk of the isopropyl group. The improvement in diastereoselectivity over the related reaction using an α-diazocarbonyl compound in place of a 1-ST **180** (see α-diazocarbonyl reactivity, **Scheme 1-07**) was ascribed to the increased steric demand of the *N*-sulfonyl group relative as well as electronic factors.[86]



Scheme 1-37: Rhodium(II)-catalysed intramolecular [2,3]-sigmatropic rearrangement of 1-ST.

When the allylic ether was tethered to the 5-position of a 1-ST **183**, a similar stereoselective rearrangement occurred to generate dihydrofuran-3-one **185** in 77% yield and high diastereoselectivity following hydrolysis with basic alumina (**Scheme 1-38a**). This methodology

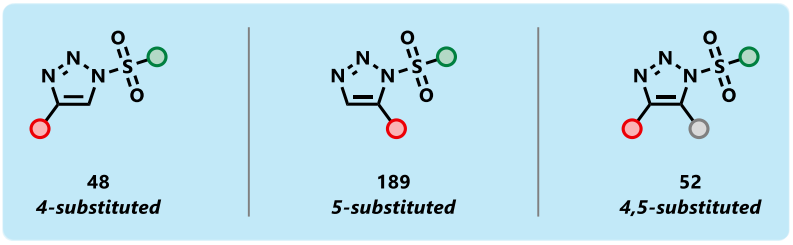
was used as the key step in the total synthesis of (+)-petromyroxol **188**, a bioactive molecule linked to the migration of the sea lamprey (**Scheme 1-38b**).[131]



Scheme 1-38: Rhodium(II)-catalysed [2,3]-sigmatropic rearrangement of 1-STs allowed access to dihydrofuran-3-ones and was used in the total synthesis of (+)-petromyroxol.

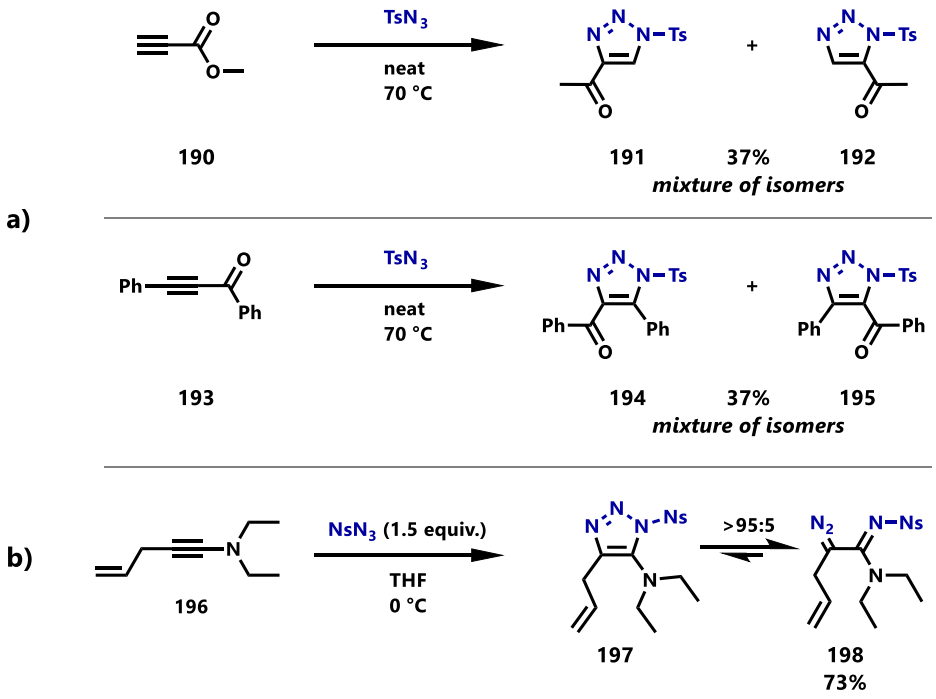
1.4 Synthesis of 1-STs

1-STs have three points of variation and can be categorised according to their substitution pattern: 4-substituted 1-STs **48**, 5-substituted 1-STs **189**, and 4,5-substituted 1-STs **52** (**Scheme 1-39**).[79–83]



Scheme 1-39: The three main types of 1-STs.

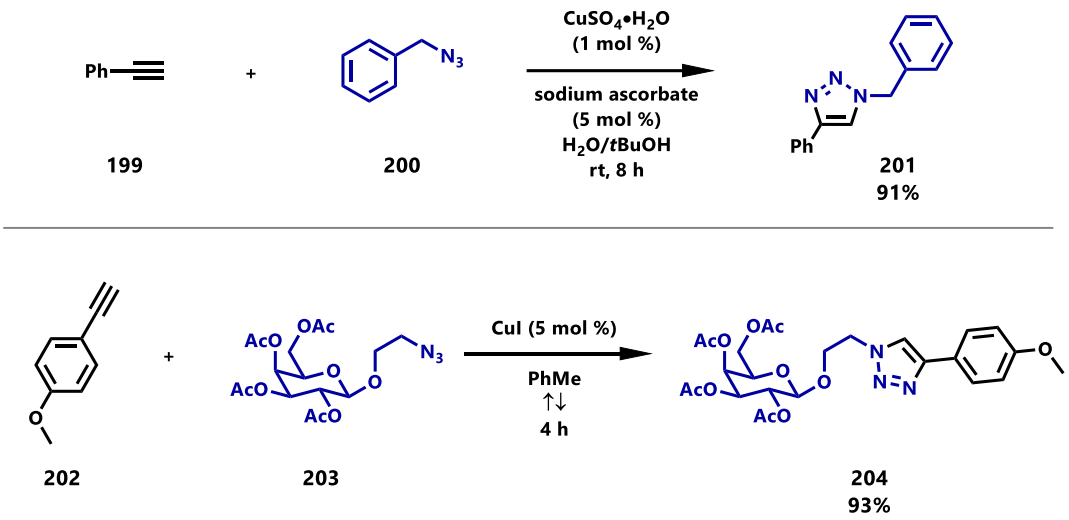
The thermal 1,3-dipolar cycloaddition between an alkyne and an azide results in formation of a 1,2,3-triazole (**Scheme 1-40a**).[132] This reaction was first reported[133] by Rolf Huisgen and is sometimes referred to as a "Huisgen cycloaddition".[134–136] However, the selectivity can be poor when the azide and alkyne are unsymmetrical or electronically mismatched. Additionally, because sulfonyl azides are electron-poor, the reaction can proceed very slowly.[137,138] However, when paired with an electron-rich reaction partner such as alkynyl amine **196**, 4-nitrobenzenesulfonyl azide (NsN_3) underwent rapid and selective cycloaddition at 0 °C to deliver 5-amino-1-ST **197** which existed predominantly in the α-diazoamidine form **198** (**Scheme 1-40b**).[139]



Scheme 1-40: Thermal 1,3-dipolar cycloaddition between alkynes and sulfonyl azides.

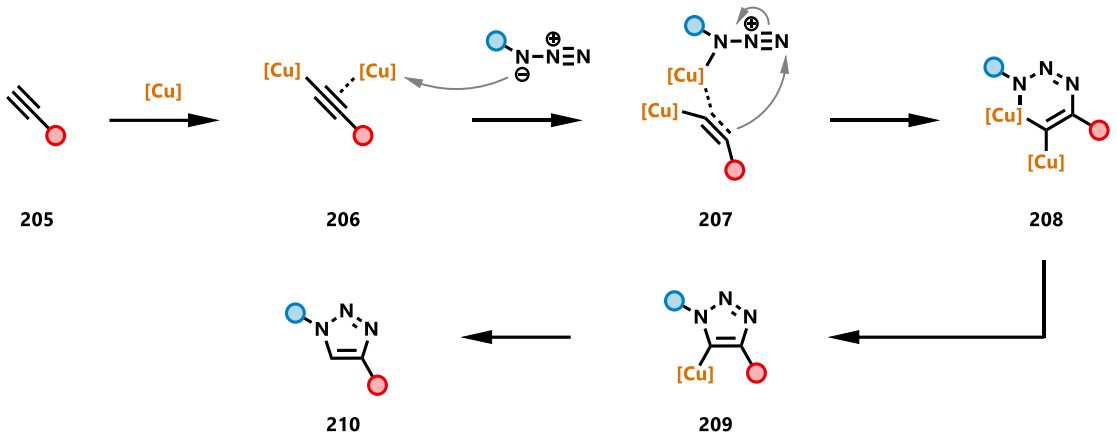
1.4.1 Preparation of 4-substituted 1-STs

The breakthrough discovery that copper(I) can catalyse the regioselective cycloaddition between an alkyne and azide to form 1,2,3-triazoles was reported independently and simultaneously by Sharpless[140] and Meldal[141] who have contributed to the area of click chemistry[142] and recently recognised with the 2022 Nobel Prize in Chemistry. The copper-catalysed alkyne azide cycloaddition reaction (CuAAC) has become the most common method to prepare 1,2,3-triazoles and an extremely popular approach for uniting different molecular fragments.[140,141,143,144] The CuAAC reaction is extremely robust and results in exclusive formation of 4-substituted 1,2,3-triazoles from alkynes and azides (**Scheme 1-41**).[145,146]



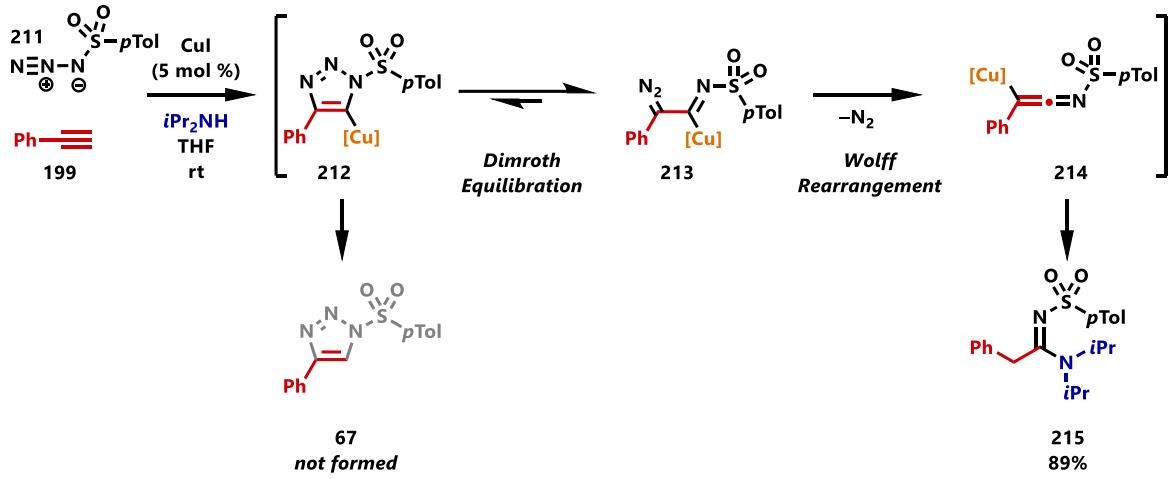
Scheme 1-41: Regiospecific formation of 1,2,3-triazoles catalysed by copper.

The mechanism of CuAAC has been the subject of intense study and is still debated.[59] It is generally accepted to proceed through stepwise formation of the 6-membered metallocycle **208** which contracts to the Cu-triazoyl species **209** (**Scheme 1-42**).[59,147–152] Protonation of the Cu-triazoyl species **209** generates the product triazole **210**.



Scheme 1-42: Proposed mechanism of the CuAAC between a terminal alkyne and azide.

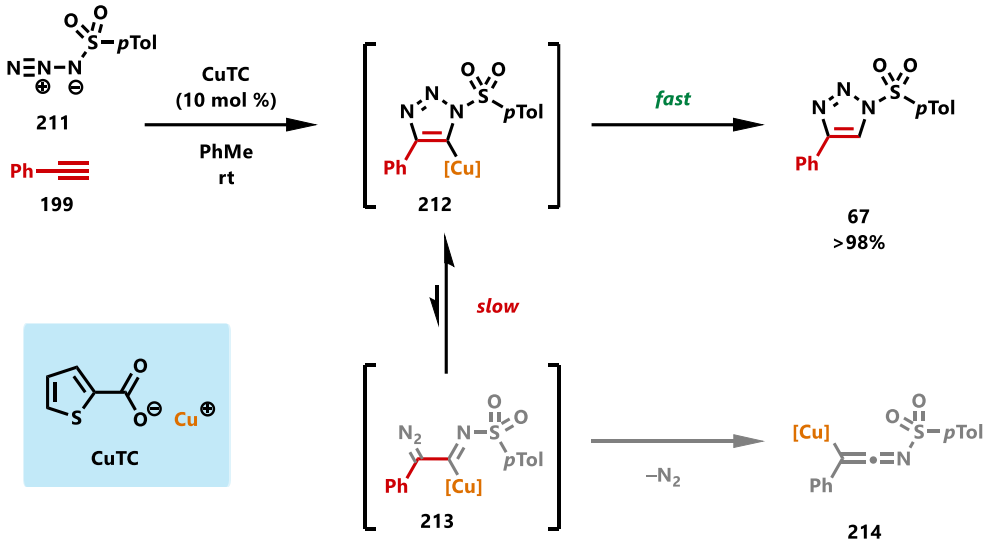
Although the CuAAC reaction is highly versatile, when a sulfonyl azide **211** was used, the desired 1-ST was not formed under standard conditions (CuI catalyst, **Scheme 1-43**).[153,154] The highly electron-withdrawing sulfonyl group facilitated Dimroth equilibration of the Cu-triazoyl intermediate **212**. Subsequent denitrogenation and Wolff rearrangement of the α-diazoimine **213** formed the keteneimine **214**, which was attacked by diisopropylamine to form the unexpected *N*-sulfonyl amidine **215** in 89% yield. While not a suitable method to prepare 1-STs, this degradation pathway has been utilised in three-component reactions of alkynes, sulfonyl azides and amines to prepare a range of synthetically useful amidine products.[153,155,156]



Scheme 1-43: CuAAC with sulfonyl azides results in decomposition to amidines under normal conditions.

In order to favour formation of 1-ST **67**, proteolysis of the Cu-triazole intermediate **212** must occur more readily than Dimroth equilibration and denitrogenation. This can be achieved by carrying out the CuAAC at 0 °C using CuI catalyst and 2,6-lutidine in dry chloroform,[157] or by using copper(I) thiophene-2-carboxylate (CuTC) as catalyst (**Scheme 1-44**).[158] CuTC is an efficient catalyst for the formation of 4-substituted 1-STs for two reasons: firstly, the electron-rich sulfur

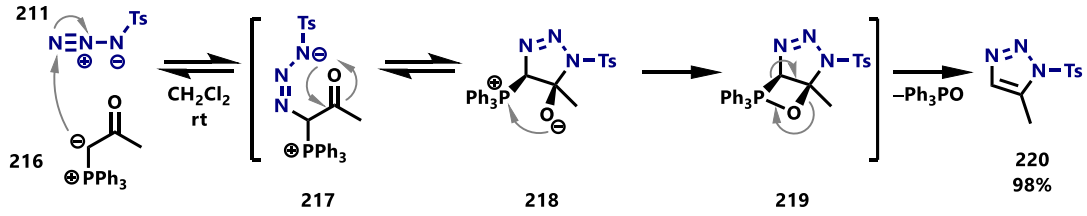
ligand is proposed to stabilise the Cu-triazole intermediate **212**, giving more time for the proteolysis to occur. Secondly, the carboxylate acts as a base to deprotonate the alkyne in the initial Cu-acetylide formation and remains ligated to copper throughout the catalytic cycle. This provides an acidic proton for the proteolysis step, which is now intramolecular and therefore fast.[158] Owing to the broad scope and readily accessible substrates, CuAAC remains the most widely used method to prepare 4-substituted 1-STs.



Scheme 1-44: Using CuTC allows for efficient and selective preparation of 4-substituted 1-STs.

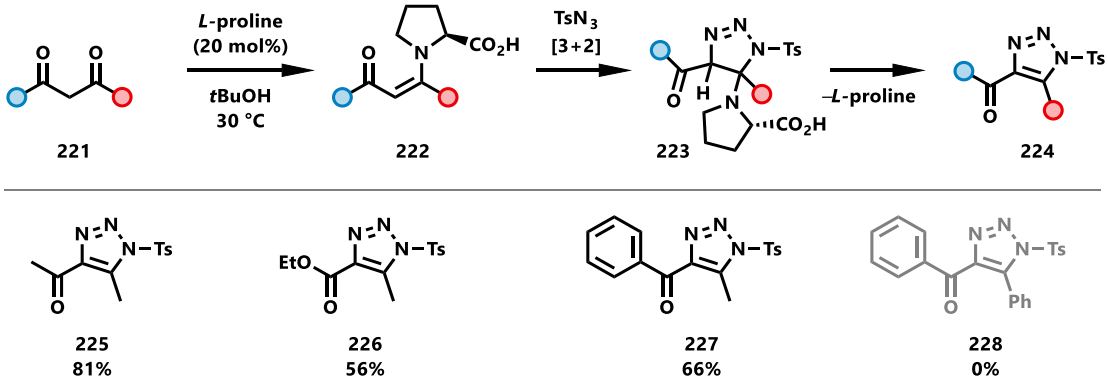
1.4.2 Preparation of 5- and 4,5-substituted 1-STs

Although there are existing catalytic methods to prepare 5- and 4,5-substituted 1,2,3-triazoles such as the ruthenium-catalysed alkyne azide cycloaddition (RuAAC),[159] these approaches are not applicable to the synthesis of 1-STs.[160] As such, the synthesis of 5- and 4,5-substituted 1-STs is more challenging and generally requires stoichiometric reactions. For example in 1966, Harvey reported the reaction between 4-methylbenzenesulfonyl azide **211** and phosphorous ylide **216** gave the 5-substituted 1-ST **220** in 98% yield under mild reaction conditions (**Scheme 1-45**).[161] The reaction proceeded through a stepwise and reversible cyclisation process in order to attain the correct geometry for formation of the oxophosphetane **219**. Elimination of triphenylphosphine oxide gave the 5-methyl 1-ST **220**. The scope of compatible substrates with this approach is limited and it suffers from poor atom economy.



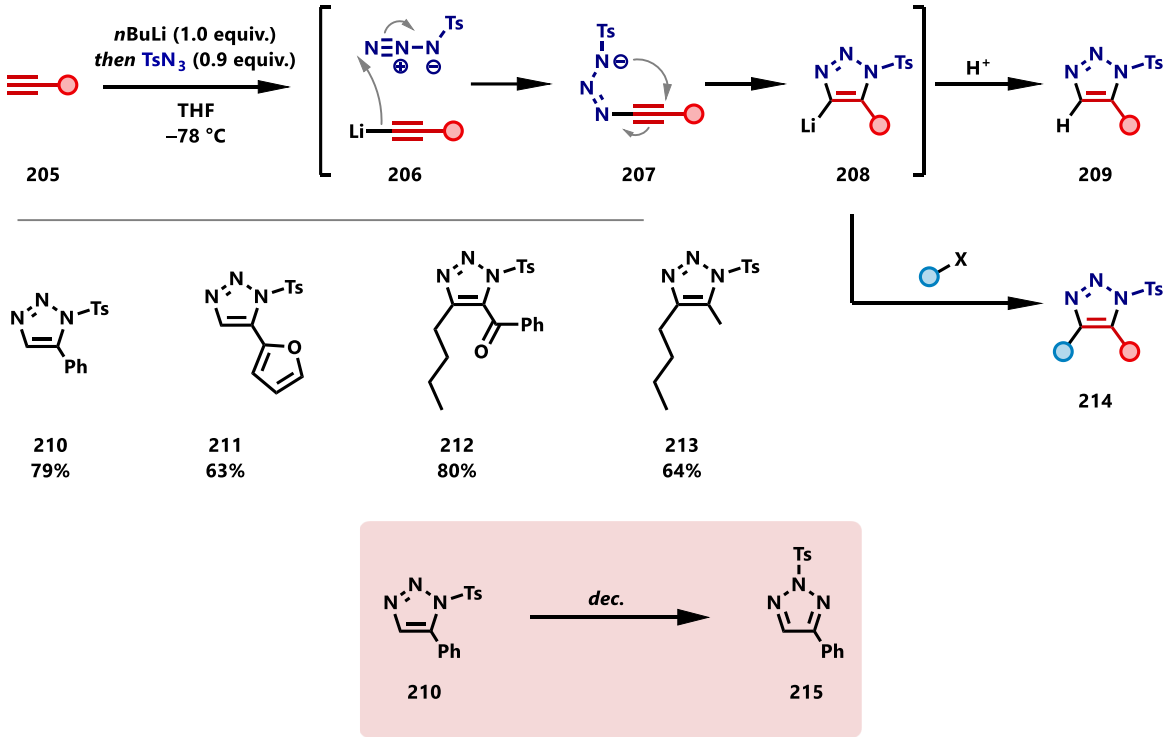
Scheme 1-45: Preparation of 5-substituted 1-STs from sulfonyl azides and phosphorous ylides

It is also possible to prepare selected 4,5-substituted 1-STs in good yields from 1,3-dicarbonyl compounds **221** using enamine cycloaddition (**Scheme 1-46**).[162] The use of 1,3-dicarbonyl compounds restricts the overall scope of accessible 1-STs using this method, and furthermore the product triazoles are limited to 4-acyl 5-methyl substitution pattern.



Scheme 1-46: Enamine-catalysed synthesis of 4,5-substituted 1-STs.

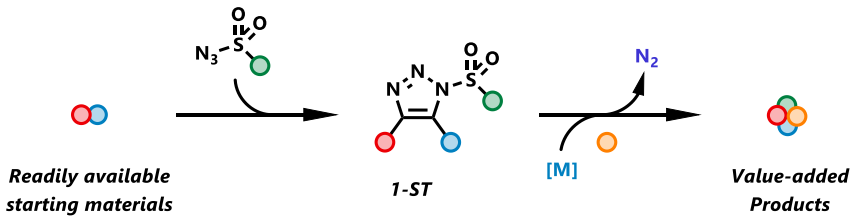
By far the most general approach to 5- and 4,5-substituted 1-STs is by addition of lithium acetylides to sulfonyl azides (**Scheme 1-47**).[160,163,164] For example, treatment of acetylene **205** with *n*BuLi generated the lithium acetylide **206**. The lithium acetylide attacked the terminal nitrogen of the tosyl azide to generate the intermediate **207**, which cyclised to generate the lithium triazoyl intermediate **208**. The lithium triazoyl intermediate **208** could either be quenched with acid to form the 5-substituted 1-ST **209** or quenched with an electrophile to generate 4,5-substituted 1-ST **214**. The reaction tolerated a range of different functional groups and proceeded with high regioselectivity when carried out at –78 °C. Although the reaction generally proceeded in good yield, the triazole products were unstable during work-up and purification because the sulfonyl group was labile and migrated to form mostly the undesired 2-ST **215** as well as other decomposition products.[160,164]



Scheme 1-47: Preparation of 5- and 4,5-substituted 1-STs from sulfonyl azides and alkynes.

1.5 Summary

The ring–chain tautomerisation of electronically biased 1,2,3-triazoles allows access to the corresponding diazoimine intermediates which generate metallocarbenes in the presence of suitable metal catalysts such as rhodium(II) carboxylates. In particular, the metallocarbenes generated from 1-sulfonyl-1,2,3-triazoles are capable of undergoing a diverse range of useful transformations including cyclopropanation, X–H bond insertion, transannular reactions, ylide formation and various rearrangements to generate molecular complexity. The use of 1-STs as carbene precursors has several advantages over their analogous diazocarbonyl compounds. These advantages include: overcoming the requirement of slow addition of diazo compound into the reaction mixture, carefully tuned reactivity of the metallocarbene that is generated and the availability of 1-STs from sulfonyl azides and alkynes. Additionally, the *N*-sulfonylimino nitrogen is able to participate in reactions which unlocks unique reactivity. The aim of the work presented in this thesis was to continue the development of new denitrogenative transformations of 1-STs, in particular towards the synthesis of heterocycles and other value-added products (**Scheme 1-48**).

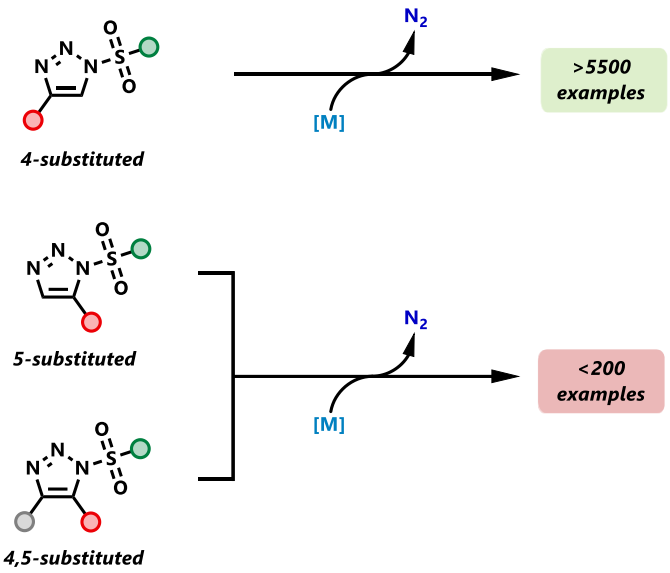


Scheme 1-48 Denitrogenative transformation of 1-STs to generate value-added products.

2 Synthesis and Reactivity of 1-STs from Cyclic Alkynes

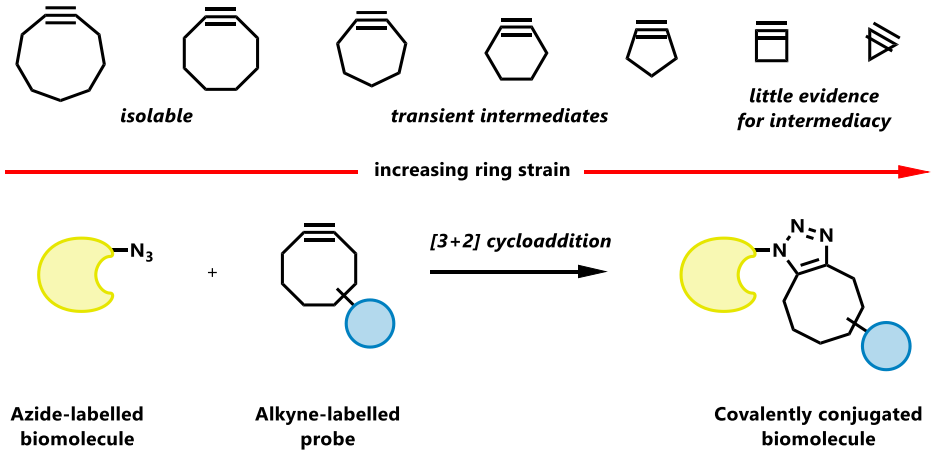
2.1 Background and Aims

In order to maximise the application of 1-ST chemical methodology, access to valuable 1-STs building blocks with all possible variation of substitution is desired. Due to the relative difficulty in accessing 5- and 4,5-substituted 1-STs, the number of reported denitrogenative transformations involving these substrates is very low when compared to 4-substituted 1-STs (**Scheme 2-01**).[165] Therefore, this is an area that required development.



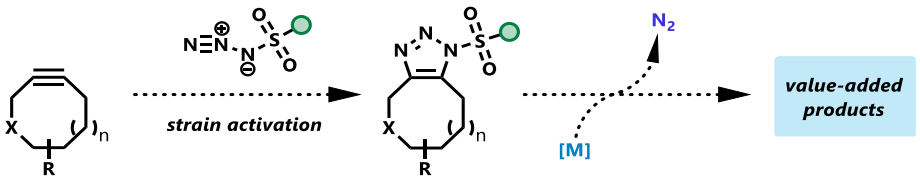
Scheme 2-01: 5- and 4,5-subistuted 1-STs are underutilised compared to 4-substituted 1-STs.[165]

The most common way to prepare 5- and 4,5-substitued 1- STs is from sulfonyl azides and terminal alkynes (*vide supra*).[160,164] One other way in which 4,5-substituted triazoles could be prepared is by exploiting the high energy of cyclic alkynes. Ideally, *sp*-hybridised atoms adopt a 180° bond angle. When constrained in a cyclic system, these alkynes are distorted from this ideal bond angle, and the relief of this ring-strain is highly enthalpically favourable. The "explosive" reaction between cyclooctyne and phenyl azide was first observed by Liu and Blomquist,[166] and the reactivity of cyclic alkynes was investigated further by Krebs and Wittig.[167] Bertozzi and co-workers realised the full potential of strained alkynes through application of the so called "strain promoted alkyne azide cycloaddition (SPAAC)" *in vivo*, and it has since become an extremely popular technique for studying biological processes (**Scheme 2-02**).[168–171] The contribution of Bertozzi to click chemistry was recently recognised by her share of the 2022 Nobel Prize in Chemistry alongside K. Barry Sharpless and Morten Meldal.[140,141,168]



Scheme 2-02: Cyclic alkynes and their application in bioconjugation

To date, the use of strain-activation in the context of 1-ST synthesis has not been explored. The aim of this project was to investigate SPAAC between cyclic alkynes and sulfonyl azides as a potential route to the underutilised 4,5-substituted 1-STs and explore the reactivity of this class of triazole (**Scheme 2-03**).

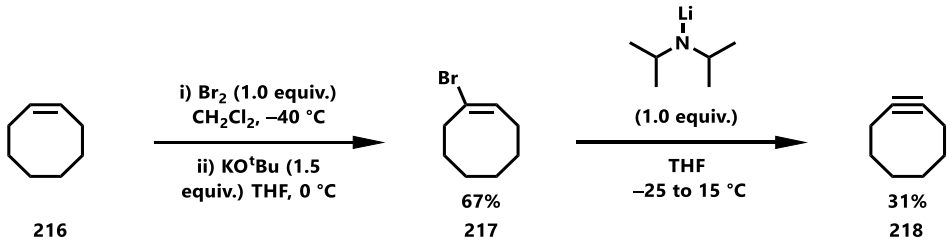


Scheme 2-03: Strain-activation as a method to prepare 1-STs.

2.2 Results

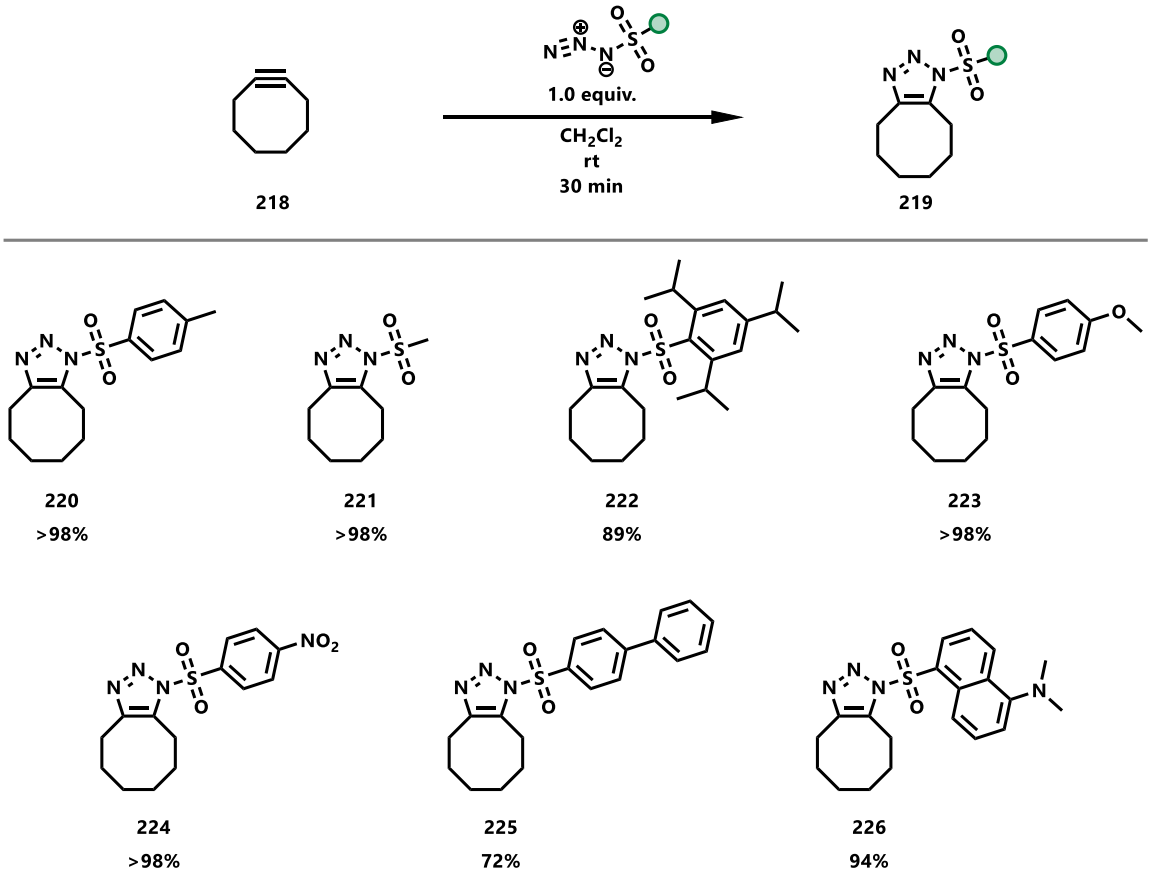
2.2.1 Synthesis and reactivity 1-sulfonylcyclooctatriazoles

To investigate the use of strained alkynes for 1-ST formation, the reaction between cyclooctyne **218** and sulfonyl azides was considered. Cyclooctyne is best prepared fresh as it decomposes over a matter of days at −20 °C under argon.[172] The preparation of cyclooctyne **218** began from *cis*-cyclooctene **216** (**Scheme 2-04**).[173] Bromination of *cis*-cyclooctene **216** followed by elimination with potassium *tert*-butoxide gave vinyl bromide **217** in 67% yield over the two steps. In order to promote the second elimination, a stronger base was required: treatment of vinyl bromide **217** with lithium diisopropylamide delivered cyclooctyne **218** in 31% yield after careful distillation.[174] Stepwise elimination is required because using an excess of lithium diisopropylamide to carry out the double elimination in one-pot is known to result in complex mixtures and very poor yield.



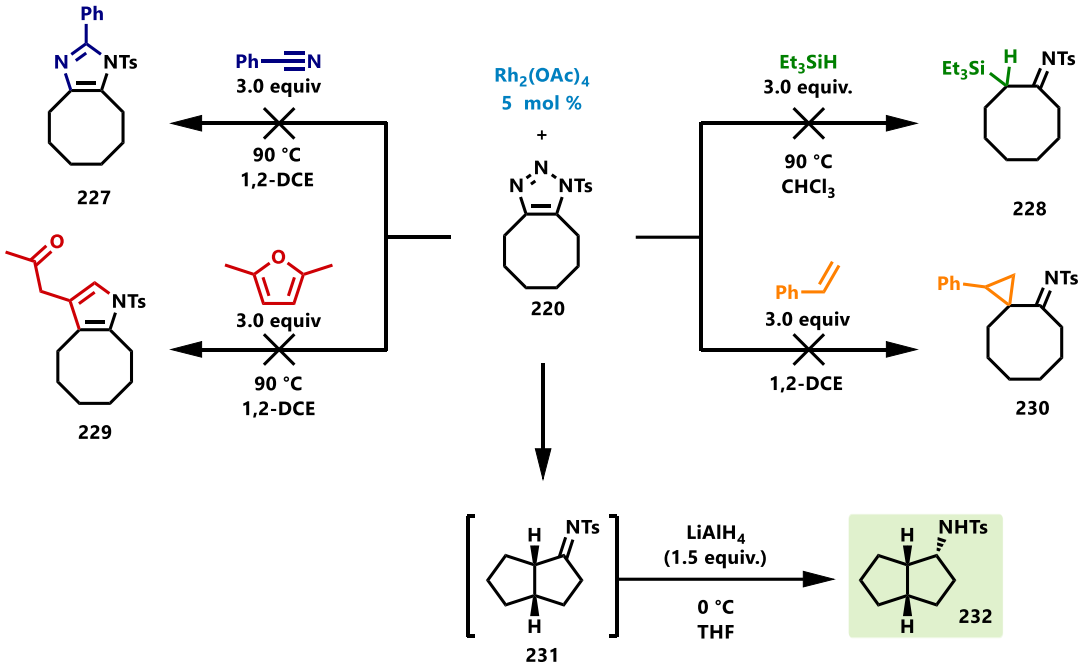
Scheme 2-04: Cyclooctyne was prepared in 3 steps from *cis*-cyclooctene

A small library of 1-STs was successfully prepared by SPAAC between cyclooctyne **218** and a range of sulfonyl azides (**Scheme 2-05**). An equimolar amount of cyclooctyne and sulfonyl azide were dissolved in dichloromethane at room temperature which afforded sulfonyl triazoles in *ca.* 30 minutes. An excess of cyclooctyne could be used to ensure the reaction went to completion and streamlined the purification process as any unreacted cyclooctyne could simply be removed *in vacuo* to afford the pure cycloadduct. Each of the corresponding triazoles were obtained in excellent yields, with the *p*-methylbenzenesulfonyl **220,** methanesulfonyl **221**, *p*-methoxybenzenesulfonyl **223** and *p*-nitrobenzenesulfonyl **224** and triazoles being obtained in quantitative yields.[175] Along with the tolerance of electron-rich and electron-poor sulfonyl azides, the reaction was also compatible with a very bulky 2,4,6-triisopropylbenzenesulfonyl azide to give triazole **222**, as well as polyaromatic azides such as biphenylsulfonyl and (5-dimethylaminonaphth-1-yl)sulfonyl to give triazoles **225** and **226** in excellent yield (**Scheme 2-05**).



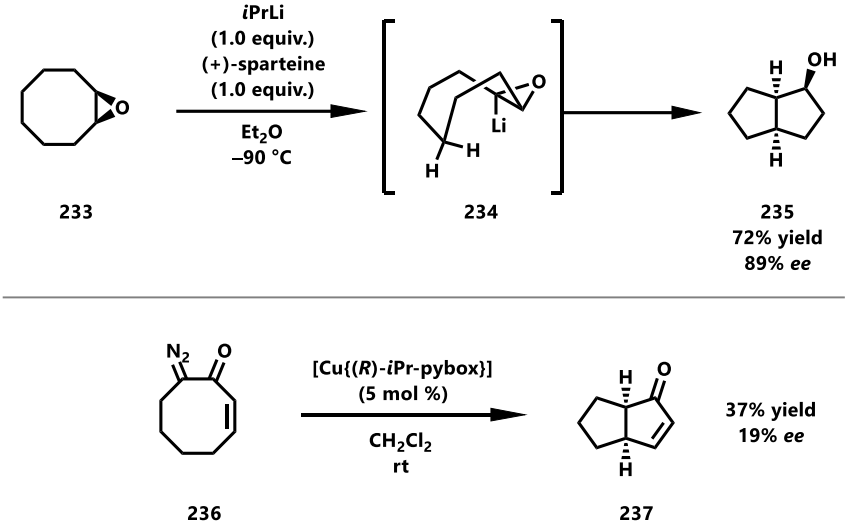
Scheme 2-05: A library of 1-STs was successfully prepared by SPAAC of sulfonyl azides and cyclooctyne.

The reactivity of this library of triazoles under denitrogenative conditions was explored[175] by treatment with rhodium(II) acetate in the presence of either triethylsilane,[176] benzonitrile,[77] styrene,[103] or 2,5-dimethylfuran[109], each of which has previously been demonstrated to undergo smooth reaction with 4-substituted 1-STs. Upon complete consumption of the starting material, ^{1}H NMR analysis of the crude reaction mixtures indicated that the same product had formed in each case. THF and lithium aluminium hydride were added in order to reduce any sulfonyl imine to the more stable sulfonyl amide. Work-up and purification followed by ^{1}H and ^{13}C NMR analysis revealed the product in each case as [3.3.0]-bicyclic compound **232** which was formed with complete diastereocontrol (**Scheme 2-06**). The relative stereochemistry in **232** was determined by comparison to a known transannular aziridine opening to prepare the same compound, whose structure was validated by crystallography.[177]



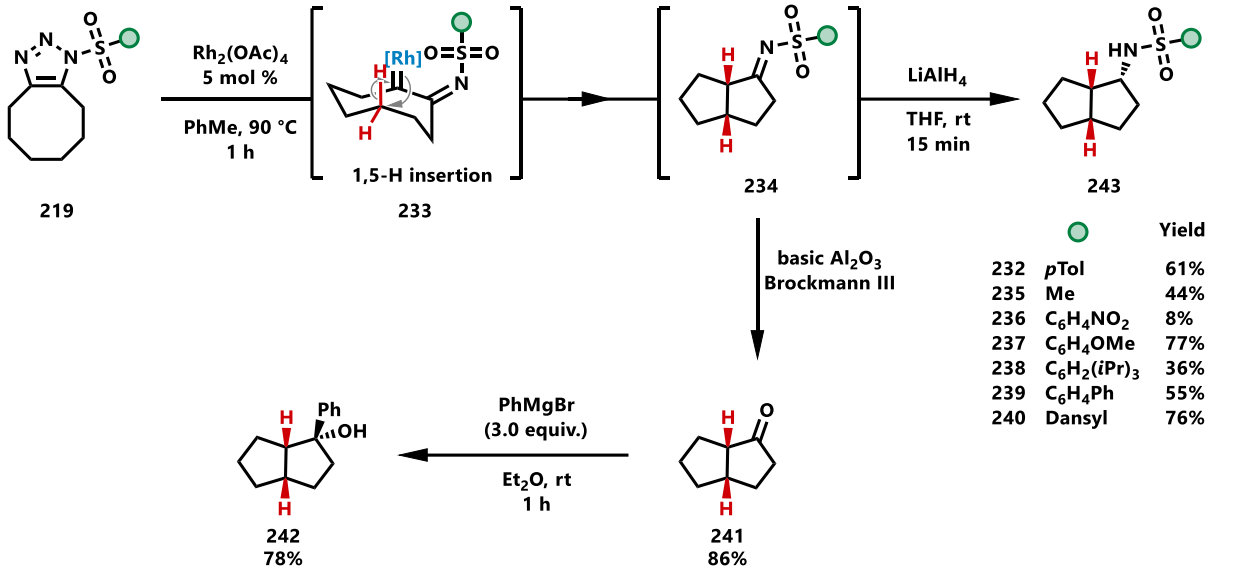
Scheme 2-06: When treated with rhodium(II) catalyst, the intramolecular transannular C–H insertion reaction occurred much faster than any other intermolecular process.[174]

Close transannular interactions in eight-membered rings are well documented.[178,179] Similar transannular bond formation in eight-membered rings has been demonstrated by deprotonation followed by electrophilic trapping,[180–184] and C−H insertion of metallocarbenes derived from α-diazocarbonyl compounds (**Scheme 2-07**)[185,186]



Scheme 2-07: Similar transannular bond-forming in eight-membered rings.[180,185]

In this case, formation of the *cis*-fused bicyclic compound **232** is believed to proceed through rhodium catalysed denitrogenation to generate metallocarbene **233**, followed by insertion of this carbene into the transannular C–H bond (**Scheme 2-08**). The different sulfonyl groups were evaluated in this process, with each giving the bicyclic product in moderate to good yield. The particularly poor yield observed for 4-nitrobenzenesulfonyl variant **236** (8%) was likely due to the incompatibility of the nitro group with the lithium aluminium hydride reduction. An alternative protocol was developed which involved hydrolysis of the intermediate sulfonyl imine to the corresponding ketone by treatment with basic alumina (Brockmann activity grade III), followed by nucleophilic addition of phenylmagnesium bromide to give tertiary alcohol **242**. Direct addition of phenylmagnesium bromide or methylmagnesium bromide to the sulfonyl imine **234** was unsuccessful.



Scheme 2-08: Transannular C–H insertion of 1-STs gave [3.3.0]-bicyclic products.

This reaction generated a complex product with three new stereocentres in good yield from a non-chiral substrate. An extensive optimisation study was carried out to see if the reaction could be performed enantioselectively. A range of different chiral rhodium(II) carboxylate catalysts in combination with various solvents, temperatures and sulfonyl groups were screened (**Table 1**). The alternative work-up procedure proved essential, as in some cases the two enantiomers of sulfonamides **243** could not be separated by chiral HPLC but could be resolved in alcohol **242**. The optimisation began with a screen of some commonly used chiral catalysts (Entries 1–4), with Rh_2(*S*-NTTL)$_4$ (23% *ee*, Entry 4) providing a modest enantioselectivity but significantly better than the other catalysts. At ambient temperatures (Entries 5 and 6), the reaction did not proceed, but changing solvent to toluene at 50 °C provided a slight improvement to the *ee* (28%, Entry 7). A screen of different solvents (Entries 10–16) revealed quite a strong solvent dependence on the enantioselectivity, with perfluorobenzene providing an improvement in *ee* (85%, Entry 15). The role of the sulfonyl group in the reaction was examined in toluene at 50 °C (Entries 18–25). Interestingly, using the electron-withdrawing *p*-nitrobenzenesulfonyl group (Entry 18) not only provided an increase in *ee* relative to toluenesulfonyl (Entry 7), but a marked increase in rate of reaction was also observed. Using the electron-donating *p*-methoxybenzenesulfonyl group gave a slightly lower *ee* of 24% (Entry 20). It was believed that using the significantly more sterically bulky 2,4,6-triisopropylbenzenesulfonyl group would help to impart enantiocontrol on the reaction but unfortunately a reduced *ee* was observed (12%, Entry 23). Combining these findings, treatment of *p*-nitrobenzenesulfonylcyclooctatriazole **224** with Rh_2(*S*-NTTL)$_4$ in C_6F_6 at 50 °C for two hours resulted in clean conversion to the bicyclic product with 94% *ee* and 78% yield (Entry 26).

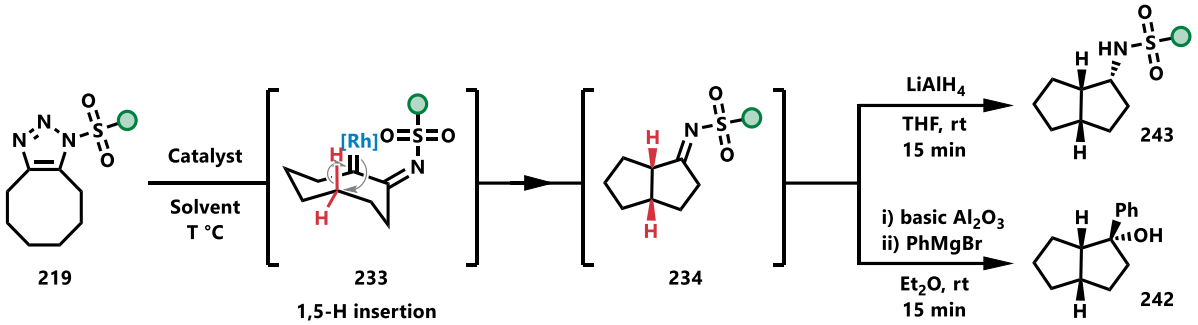


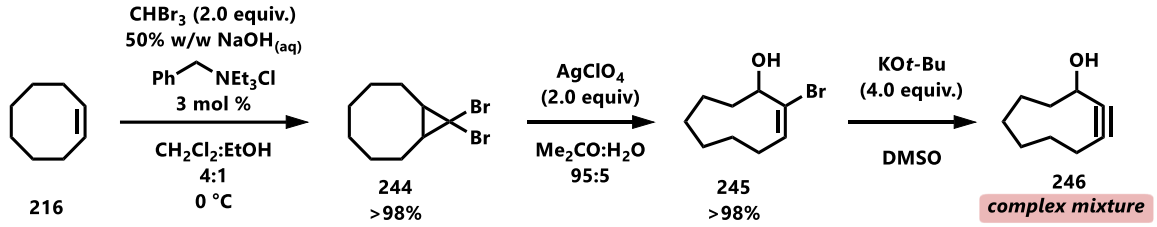
Table 1: Optimisation and *ee* data for the rhodium catalysed transannular C–H insertion reaction of triazoles **219**. All reactions carried out at 0.20 mmol scale.

Entry	●	Catalyst[a]	Solvent[b]	T[c]	Workup	Yield[d]	*ee*[e]
1	*p*Tol	$Rh_2(OAc)_4$	CH_2Cl_2	90	$LiAlH_4$	61%	0%
2	*p*Tol	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	90	$LiAlH_4$	-	8%*
3	*p*Tol	Rh_2(*S*-PTAD)$_4$	CH_2Cl_2	90	$LiAlH_4$	-	8%*
4	*p*Tol	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	90	$LiAlH_4$	29%	23%
5	*p*Tol	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	20	$LiAlH_4$	N.R.[f]	
6	*p*Tol	Rh_2(*S*-NTTL)$_4$	PhMe	20	$LiAlH_4$	N.R.[f]	
7	*p*Tol	Rh_2(*S*-NTTL)$_4$	PhMe	50	$LiAlH_4$	43%	68%
8	*p*Tol	Rh_2(*S*-NTTL)$_4$	PhMe[g]	50	$LiAlH_4$	-	69%
9	*p*Tol	Rh_2(*S*-*t*PTTL)$_4$	PhMe	50	$LiAlH_4$	-	23%
10	*p*Tol	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	50	$LiAlH_4$	36%	29%
11	*p*Tol	Rh_2(*S*-NTTL)$_4$	C_6H_6	50	$LiAlH_4$	72%	33%
12	*p*Tol	Rh_2(*S*-NTTL)$_4$	PhCl	50	$LiAlH_4$	43%	31%
13	*p*Tol	Rh_2(*S*-NTTL)$_4$	*t*BuOMe	50	$LiAlH_4$	-	46%
14	*p*Tol	Rh_2(*S*-NTTL)$_4$	cyclohexane	50	$LiAlH_4$	-	71%
15	*p*Tol	Rh_2(*S*-NTTL)$_4$	C_6F_6	50	$LiAlH_4$	72%	93%
16	*p*Tol	Rh_2(*S*-NTTL)$_4$	nC_7F_{17}	50	$LiAlH_4$	insoluble[i]	
18	$pNO_2C_6H_4$	Rh_2(*S*-NTTL)$_4$	PhMe	50	$LiAlH_4$	-	58%
19	$pNO_2C_6H_4$	Rh_2(*S*-*t*PTTL)$_4$	PhMe	50	$LiAlH_4$	-	47%
20	$pMeOC_6H_4$	Rh_2(*S*-NTTL)$_4$	PhMe	50	$LiAlH_4$	36%	24%
21	$pPhC_6H_4$	Rh_2(*S*-NTTL)$_4$	PhMe	50	$LiAlH_4$	53%	35%
22	Me	Rh_2(*S*-NTTL)$_4$	PhMe	50	Hydrolysis/Grignard	80%	32%
23	2,4,6-(iPr)$_3C_6H_2$	Rh_2(*S*-NTTL)$_4$	PhMe	50	Hydrolysis/Grignard	64%	12%
24	Dansyl	Rh_2(*S*-NTTL)$_4$	PhMe	50	Hydrolysis/Grignard	17%	9%
25	$pNO_2C_6H_4$	Rh_2(*S*-NTTL)$_4$	PhMe	50	Hydrolysis/Grignard	57%	69%
26	$pNO_2C_6H_4$	Rh_2(*S*-NTTL)$_4$	C_6F_6	50	Hydrolysis/Grignard	**78%**	**94%**

[a] 5 mol % catalyst employed; [b] 0.02 M; [c] vial sealed with Teflon cap; [d] isolated yield after purification by column chromatography. Where no yield is reported, *ee* was determined on crude reaction mixture; [e] determined by chiral solid phase HPLC; [f] no consumption of starting material detected; [g] syringe pump addition of triazole to solution of catalyst; [i] reagents and catalyst completely insoluble. *The major enantiomer was reversed using these catalysts.

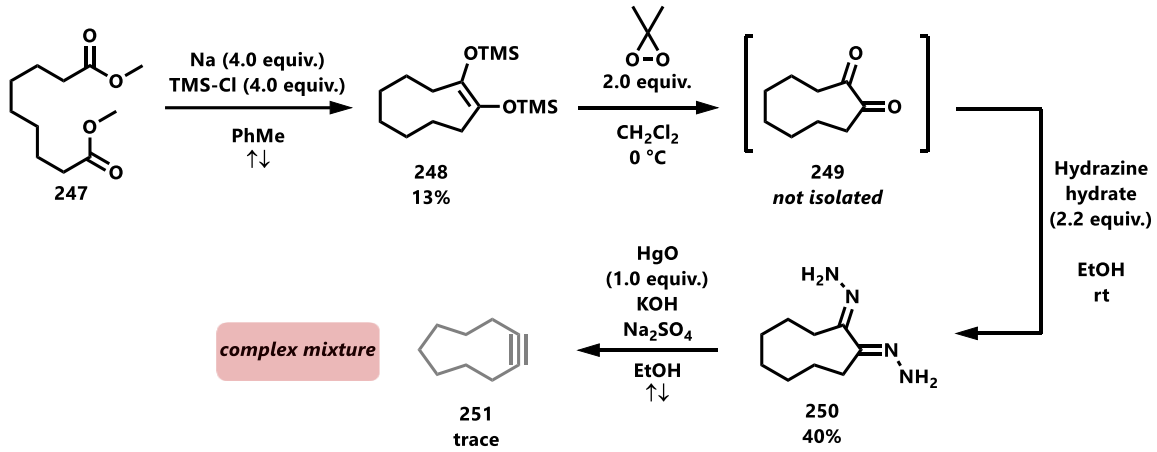
The enantioselectivity observed in this reaction is the highest reported to date in this type of transannular transformation.[180–186] With an optimised set of reaction conditions in hand, the compatibility of the transannular C–H insertion reaction was investigated with regard to 1-STs derived from different cyclic alkynes.

Firstly, alternative ring-sizes were considered. Seven-membered or smaller cyclic alkynes exist only as transient intermediates,[187] so a logical starting point was to investigate the effect of increasing the ring-size by one carbon. The attempted synthesis of cyclononyne-3-ol **246** began from *cis*-cyclooctene **216**, and employed a silver perchlorate promoted ring expansion of dibromocarbene adduct **244** to generate *trans*-2-bromocyclononen-3-ol **245** (**Scheme 2-09**).[188] It was not possible to prepare cyclononyne by the same double dehydrohalogenation approach used for cyclooctyne **218**, as the second elimination predominantly results in the formation of an allene rather than cyclic alkyne as the larger ring size is able to overcome the additional strain caused by the allene.[189,190] However, Reese and co-workers report that when the alkene **245** is treated with potassium *tert*-butoxide in DMSO at room temperature, extremely rapid elimination (*ca.* 5–10 second reaction times) of HBr occurs to give the corresponding cyclic alkyne **246** which can be isolated in good yield.[191] Unfortunately, attempts to reproduce these findings repeatedly gave an intractable mixture. Addition of *p*-toluenesulfonyl azide to the crude mixture after work up did not result in any 1-ST formation.



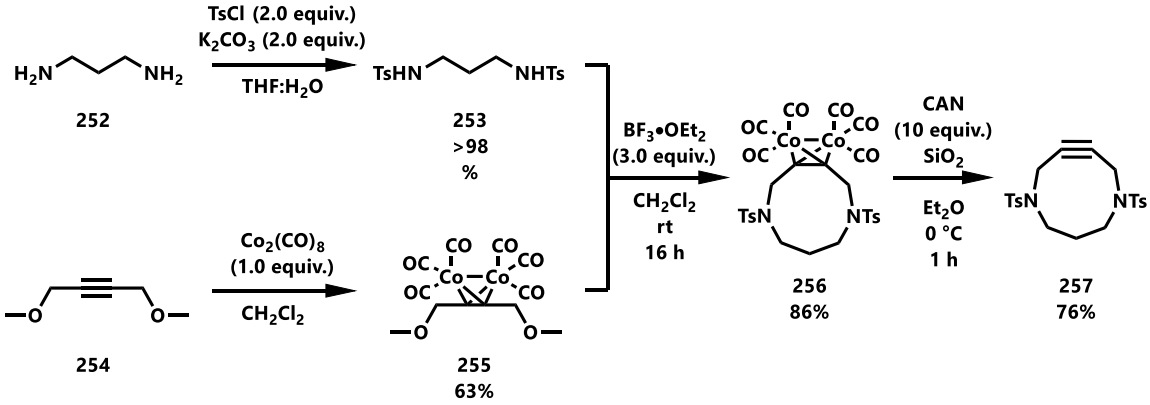
Scheme 2-09: Attempted synthesis of cyclononyne-3-ol by elimination of HBr from *trans*-2-bromocyclononen-3-ol.

An alternative route for the preparation of a cyclononyne was considered, involving base-catalysed oxidative decomposition of *bis*-hydrazone **250** (**Scheme 2-10**).[189,190] The diketone **249** was prepared by reductive coupling of dimethyl azelate **247** in the presence of TMS-chloride to give *bis*-silyl enol ether **248** in 13% yield. The electron-rich alkene **248** was oxidised using DMDO to afford diketone **249** which was immediately condensed with hydrazine hydrate to give *bis*-hydrazone **250** in 40% yield over the two steps. Treatment of *bis*-hydrazone **250** with mercury(II) oxide, ethanolic KOH and sodium sulfate afforded a very small amount (<0.01 mmol) of cyclononyne **251** as a dilute solution in benzene. Similar to the previous approach, complex mixtures were encountered throughout and a synthetically useful amount of cyclononyne could not be obtained.



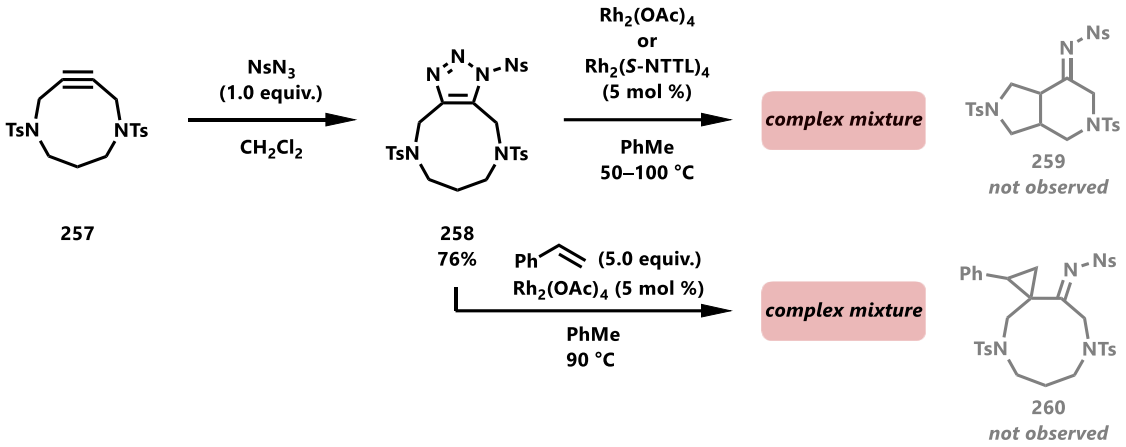
Scheme 2-10: Attempted synthesis of cyclononyne using base-catalysed oxidative decomposition of bis-hydrazone **250**.

An alternative way to access medium sized cyclic alkynes is by using a double Nicholas reaction.[192,193] Usually, this is not a good approach to cyclic alkynes as there can be complications removing the cobalt protecting group resulting in poor yield.[194] Tomooka and co-workers reported that using a *bis*-sulfonamide allowed the cobalt protecting group to be removed easily and the alkyne **257** could be purified without special care (**Scheme 2-11**).[195] The synthesis of alkyne **257** was carried out beginning by double protection of 1,3-diaminopropane **252** in quantitative yield. Alkyne **254** was treated with dicobalt octacarbonyl at room temperature to give the cobalt complex **255** in 63% yield. *Bis*-sulfonamide **253** and complex **255** were treated with an excess of Lewis acid to give the cobalt protected cyclic alkyne **256** in 86% yield after rapid purification by column chromatography. Finally, the cobalt protecting group was cleaved by treatment with ceric ammonium nitrate and silica gel to give the cyclic alkyne **257** in 76% yield.



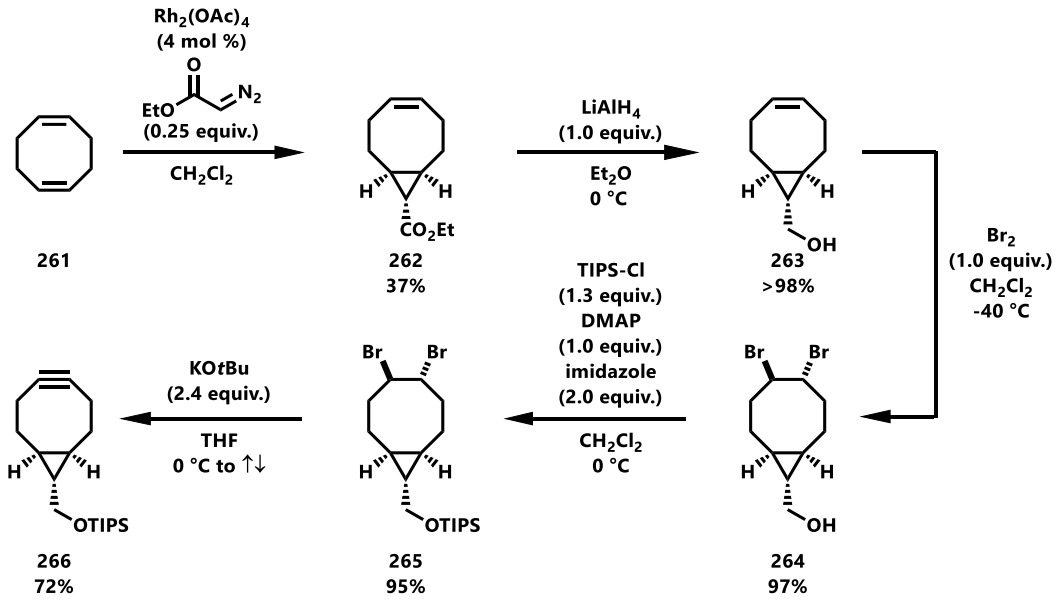
Scheme 2-11: Preparation of heteroatom-embedded cyclic alkyne by double Nicholas reaction.

The cyclic alkyne **257** was subjected to SPAAC with 4-nitrobenzenesulfonyl azide to generate 1-ST **258** in 76% yield (**Scheme 2-12**). Next, the 1-ST was treated with rhodium(II) acetate catalyst in toluene at 50 °C to promote denitrogenation and intramolecular transannular C−H insertion (**Scheme 2-12**). Unfortunately, no reactivity was observed until the temperature was raised to 100 °C. However, at this temperature a complex mixture of decomposition products was observed and there was no sign of any major product. Switching the catalyst to Rh_2(*S*-NTTL)$_4$ saw no improvement on the outcome. Similarly, attempted intermolecular reaction with an excess of styrene resulted in a very similar complex mixture of unidentified products.



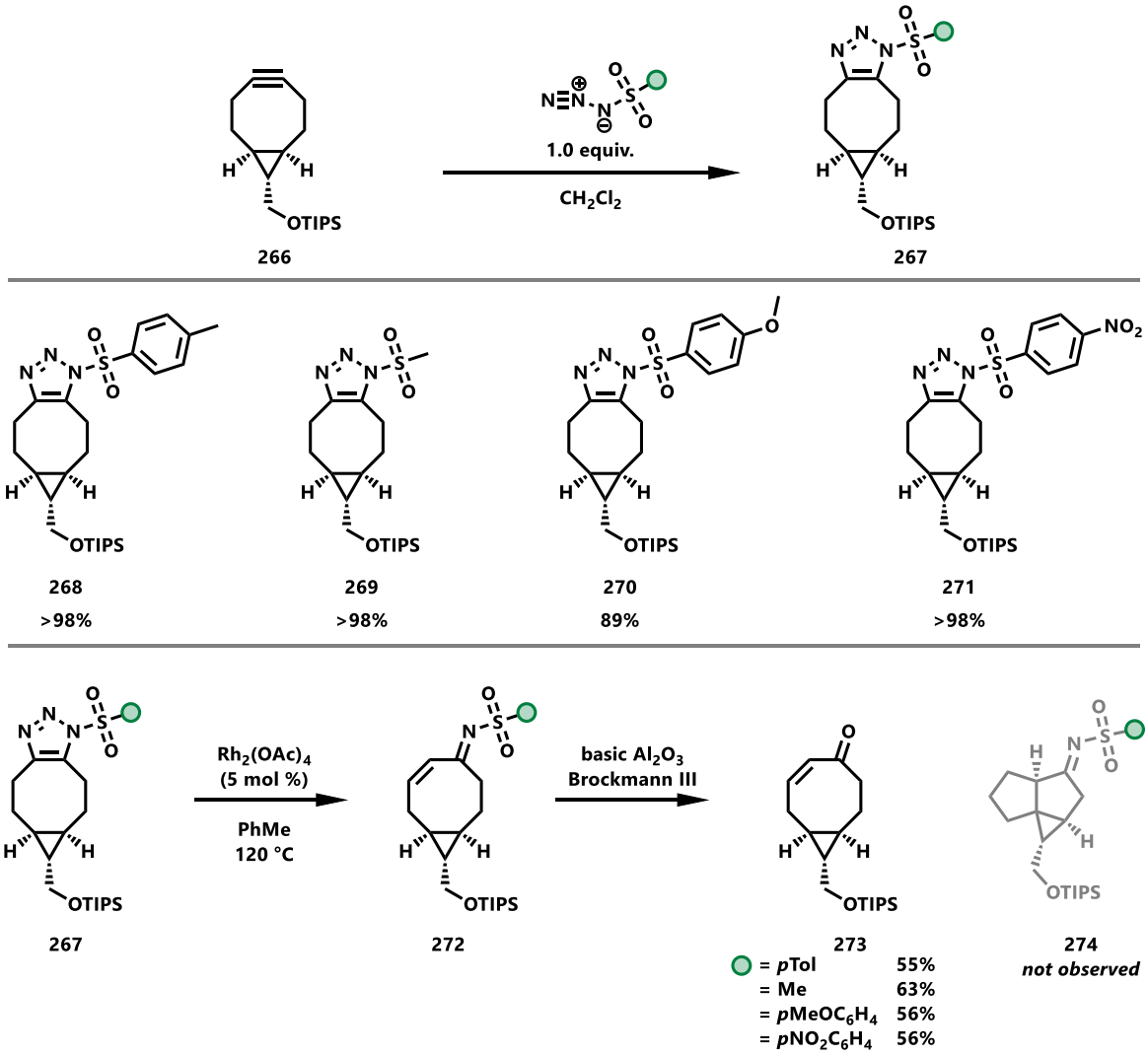
Scheme 2-12: Preparation of 1-ST **258** and attempted rhodium(II)-catalysed reactions.

Another popular class of strained alkynes are bicyclo[6.1.0]non-4-ynes (BCNs).[196] These cyclic alkynes have risen to the forefront of biological labelling owing to their relative ease of synthesis, useful functionalisation handle, and increased reactivity in SPAAC with benzyl azide relative to cyclooctyne.[196,197] The near 100-fold rate enhancement is mainly attributed to the additional three-membered ring fusion increasing the amount of strain in the molecule. Cyclic alkyne *exo*-**266** was prepared in five steps beginning from 1,5-cyclooctadiene **261** (**Scheme 2-13**).[196] Rhodium(II) catalysed cyclopropanation of *cis*-cyclooctadiene **261** gave *exo*-ester **262** in 37% yield, alongside the undesired *exo*-ester in 39% yield (not shown) which were separated by column chromatography. Reduction of ester **262** with lithium aluminium hydride gave alcohol **263** in quantitative yield. Bromination of the double bond using molecular bromine gave alcohol **264** in 97% yield, followed by installation of a TIPS protecting group to give compound **265** in 95% yield after purification over silica gel. Finally, elimination of two equivalents of HBr from **265** by treatment with an excess of potassium *tert*-butoxide first at 0 °C then under reflux gave the cyclic alkyne *exo*-**266** in 72% yield. The cyclic alkyne **266** was stable to column chromatography over silica, unlike cyclooctyne which had to be distilled. It was necessary to protect the alcohol as a silyl ether, as free alcohols are generally not compatible with 1-STs owing to the potential lability of the *N*-sulfonyl group. TIPS was selected as a suitable protecting group owing to its relative base stability compared to other silyl ethers.[198,199]



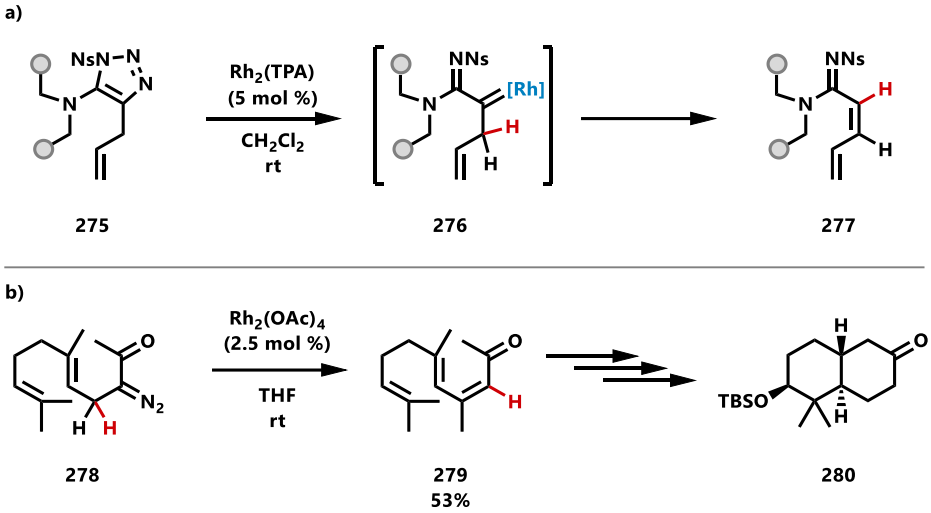
Scheme 2-13: Preparation of *exo*-**266** from 1,5-cyclooctadiene

As with cyclooctyne, *exo*-**266** smoothly underwent SPAAC with a selection of different sulfonyl azides to give 1-STs **268**–**271** in quantitative yields (**Scheme 2-14**). However, under the optimised conditions for transannular C–H insertion, the BCN derived 1-STs did not undergo denitrogenation. In fact, in order to see any reactivity at all, more forcing conditions were required, namely raising the temperature to 120 °C in toluene with $Rh_2(OAc)_4$ as catalyst. Under these conditions denitrogenation occurred to generate a metallocarbene followed by 1,2-H shift to give the α,β-unsaturated intermediates **272**, which were hydrolysed *in situ* to give the corresponding enone **273** in good yield.



Scheme 2-14: SPAAC between sulfonyl azides and *exo*-BCN **266** successfully gave 1-STs. These triazoles underwent rhodium(II)-catalysed 1,2-H shift, rather than transannular C–H insertion.

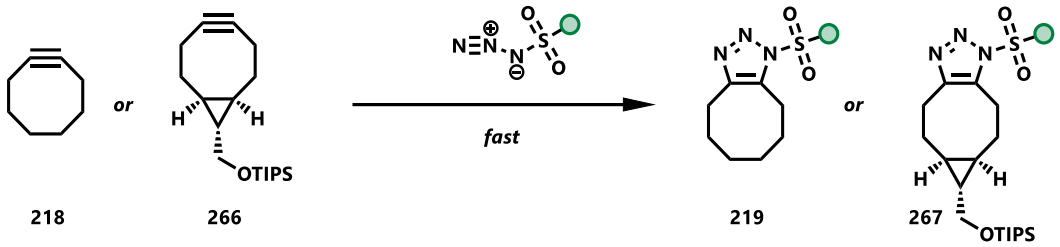
The difference in reactivity observed here was likely due to the product **274** that would result from transannular C–H insertion would be highly strained. Additionally, the additional cyclopropane ring in the substrate may alter the disposition of the transannular C–H bonds relative to the reactive carbene centre. 1,2-H shifts have previously been reported in 1-STs **275** with a β-hydride present in the metallocarbene (**Scheme 2-15a**),[121,123] but are more well documented in metallocarbenes derived from α-diazocarbonyl compounds (**Scheme 2-15b**).[200–203]



Scheme 2-15: Examples of 1,2-H shift in metallocarbenes derived from a) 1-STs b) α-diazocarbonyl compounds.[121,203]

2.2.2 Computational analysis

In the study of the reactivity of cyclooctatriazoles, it was clear that the 1,3-dipolar cycloaddition between cyclooctyne and sulfonyl azides was fast and efficient (**Scheme 2-16**). Inspired by the previous works of Houk, Bickelhaupt and van Delft in this area,[204–206] a computational study was carried out in order to give further insight into the reaction mechanism.



218 266 219 267

Scheme 2-16: SPAAC between sulfonyl azides and cyclic alkynes **218** and **266** was fast.

The groups of Houk and Bickelhaupt have described distortion-interaction transition state theory, also known as the activation-strain model to describe transition state of a reaction.[207–209] In this model, the activation energy ($\Delta E^{\ddagger}$) of a reaction is described by the energy required to distort the reagents from their ground states into their reactive conformation geometries ($\Delta E^{\ddagger}_{dist}$), which is offset by the stabilising effect of orbital interactions between the reacting components ($\Delta E^{\ddagger}_{int}$) (Equation **1**).

(1)
$$\Delta E^{\ddagger} = \Delta E^{\ddagger}_{dist} + \Delta E^{\ddagger}_{int}$$

This model is particularly suited to studying 1,3-dipolar cycloaddition reactions,[210] and the relationship between the activation energy, distortion energy, and interaction energy of the distorted dipole and dipolarophile for the 1,3-dipolar cycloaddition between an azide and acetylene is shown (**Figure 2-01**). For a concerted 1,3-dipolar cycloaddition, the transition state occurs when the orbital overlap between dipole and dipolarophile is largest, and the FMO gaps have narrowed sufficiently that the destabilising geometrical distortions are overcome by favourable stabilising interactions. To achieve this transition state geometry, significant distortion of the dipole, and a relatively small distortion of the dipolarophile are required.[205]

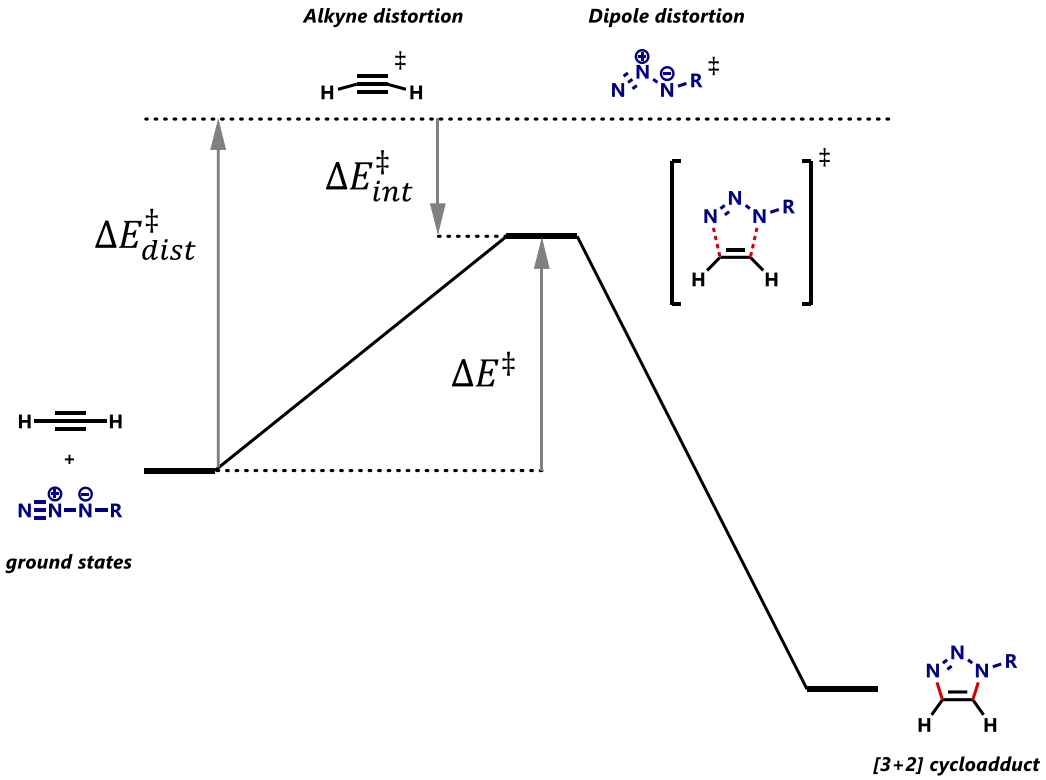


Figure 2-01: Relationship between the activation, distortion, and interaction energies for the 1,3-dipolar cycloaddition between an alkyne and azide.

Houk and others rationalise the origin of the observed rate enhancement in the "strain-promoted" cycloaddition as coming from the preorganisation of cyclooctyne towards its transition state geometry. For example, the cycloaddition reactions between phenyl azide and acetylene ("strain-free") and phenyl azide and cyclooctyne ("strain-promoted") were studied using DFT (B3LYP) (**Figure 2-02**).[204] The low activation energy for cyclooctyne ($\Delta E^{\ddagger}$ = 8.0 kcal mol^{-1}) compared to acetylene ($\Delta E^{\ddagger}$ = 16.2 kcal mol^{-1}) arises from the significantly reduced distortion energies of both cyclooctyne ($\Delta\Delta E^{\ddagger}_{dist}$ = 4.6 kcal mol^{-1}) and phenyl azide ($\Delta\Delta E^{\ddagger}_{dist}$ = 4.5 kcal mol^{-1}).

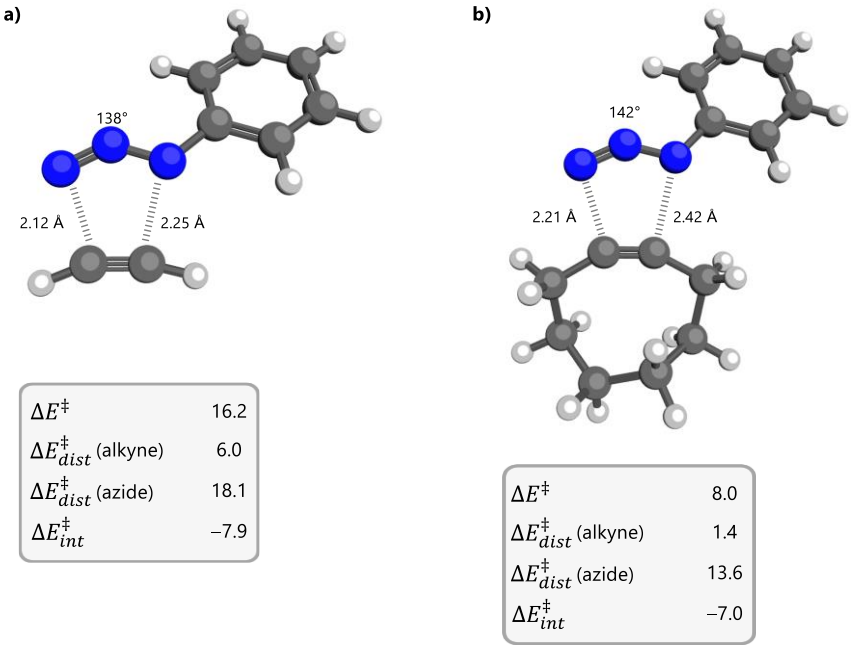


Figure 2-02: $\Delta E^{\ddagger}$, $\Delta E^{\ddagger}_{dist}$(azide), $\Delta E^{\ddagger}_{dist}$(alkyne), and $\Delta E^{\ddagger}_{int}$ for the concerted transition structures of phenyl azide cycloaddition with (a) acetylene, (b) cyclooctyne. B3LYP/6-31G(d).[204,205]

Initially, the transition states for the cycloaddition between methanesulfonyl azide **281** and cyclooctyne **218**, *exo*-**266** and acetylene **282** were considered within the framework of Houk's previous work in the area. All calculations were carried out using the open source computational chemistry package Psi4.[211] In order to perform the distortion-interaction analysis, both the transition state and ground state geometries of all components must be optimised. Importantly, cyclooctyne can exist as either a twist boat or chair conformation, with the chair conformation being preferred by approximately 3.27 kcal mol^{-1} (B3LYP/6-31G(d)) and this must be taken into consideration.[212]

This difference in energy corresponds to an approximate 200:1 Boltzmann population ratio between the two conformations, and they interconvert *via* a chair **283** ⇄ twist chair **284** ⇄ twist

boat **285** ⇄ boat **286** pathway (**Figure 2-03**). The barrier to this interconversion was calculated by Yavari and co-workers as 9.79 kcal mol^{-1} for chair **283** to twist boat **285**, and 6.52 kcal mol^{-1} for twist boat **285** to chair **283** (B3LYP/6-31g(d)//HF/6-31g(d)).[212]

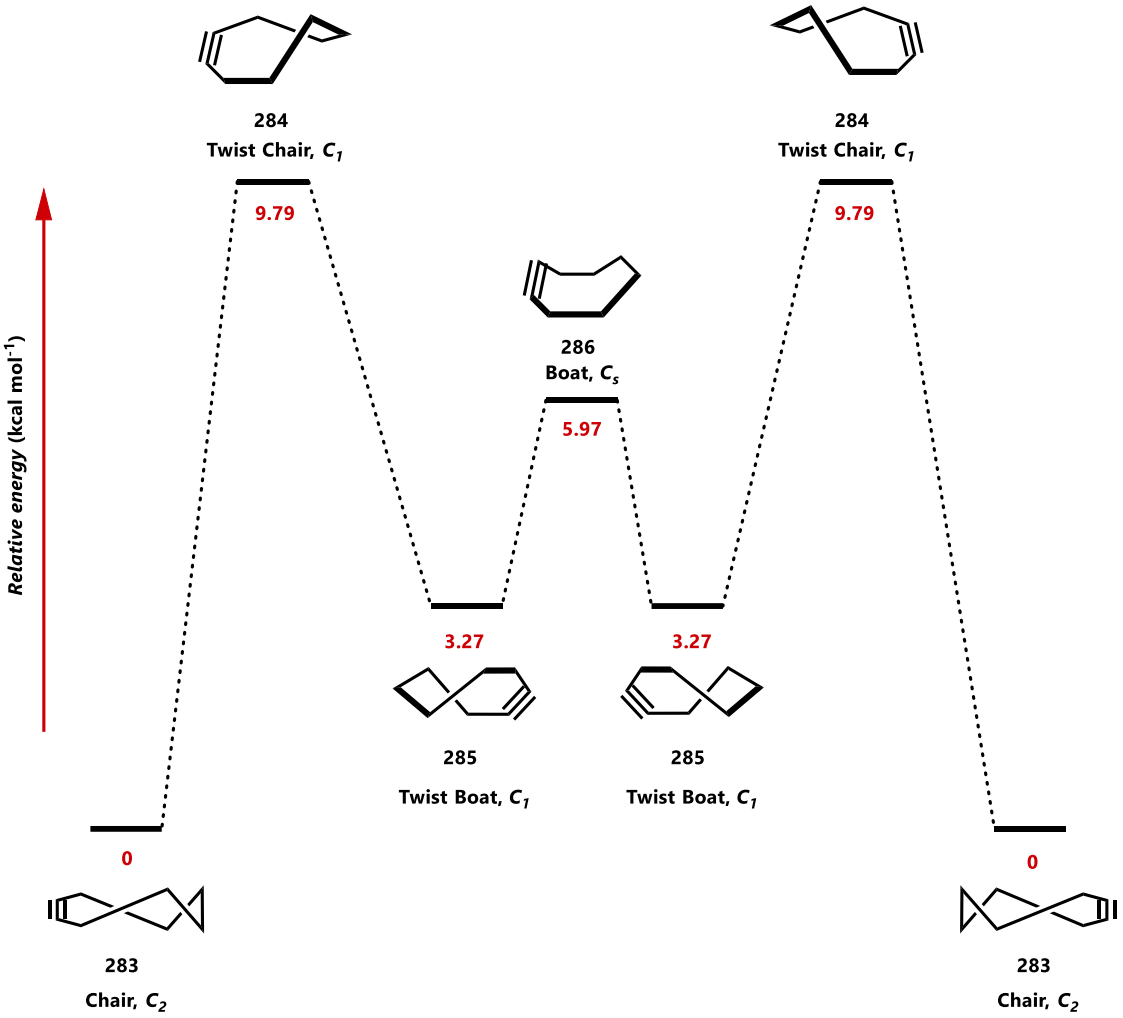
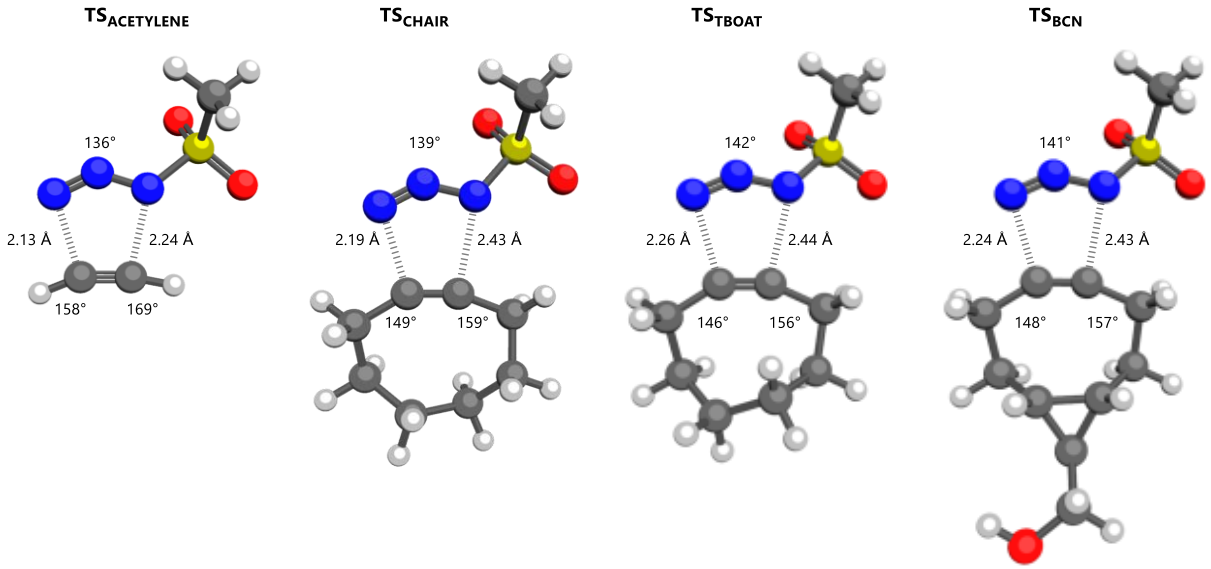


Figure 2-03: Energy profile for the interconversion of cyclooctyne conformations. All values in kcal mol^{-1} (B3LYP/6-31G(d)//HF/6-31g(d)).[212]

These two energy minima give rise to at least two potential energy pathways: cycloaddition between the chair conformation **283** with methanesulfonyl azide **281**, and the cycloaddition between twist boat **285** and methanesulfonyl azide **281**. Shown in **Figure 2-04** (*vide infra*) are the calculated transition state structures for the 1,3-dipolar cycloaddition between methanesulfonyl azide **281** and acetylene (**TS$_{ACETYLENE}$**), cyclooctyne chair (**TS$_{CHAIR}$**), cyclooctyne twist boat (**TS$_{TBOAT}$**), and *exo*-BCN **266** (**TS$_{BCN}$**) (B3LYP/6-31g(d)).



	TS$_{ACETYLENE}$	TS$_{CHAIR}$	TS$_{TBOAT}$	TS$_{BCN}$
$\Delta E^{\ddagger}$	16.1	8.4	7.0	7.2
$\Delta E^{\ddagger}_{dist}$ (alkyne)	5.4	1.7	1.2	1.2
$\Delta E^{\ddagger}_{dist}$ (azide)	21.6	17.7	15.5	16.0
$\Delta E^{\ddagger}_{int}$	–10.9	–11.0	–9.7	–10.0
$\Delta G^{\ddagger}$	28.2	20.6	19.1	19.1

Figure 2-04: Transition state structures for the cycloaddition between methanesulfonyl azide and acetylene, cyclooctyne chair, cyclooctyne twist boat and *exo*-BCN. Calculations performed at B3LYP/6-31G(d). All values given in kcal mol^{-1}.

In each of the transition states with the cyclic alkynes, the cycloadditions were concerted, with slightly shorter bond-forming distances at the unsubstituted azide terminus (2.19 Å, 2.26 Å and 2.24 Å) compared to the substituted end (2.43 Å, 2.44 Å and 2.43 Å). This was more pronounced relative to **TS$_{ACETYLENE}$** which had shorter and more synchronous C–N bond forming distances of 2.13 Å and 2.24 Å. In each transition state, the ∠N–N–N bond angle of the azide was reduced by over 35° relative to its ground state geometry, which was reflected in the corresponding distortion energies ($\Delta E^{\ddagger}_{dist}$(azide)) which were 21.6, 17.7, 15.5 and 16.0 kcal mol^{-1}. The ∠C–C–H bond angles in acetylene were distorted by 22.4° and 11.0° from their linear ground state, which was significantly more than the corresponding ∠C–C–CH$_2$ bond angles in the cyclic alkynes (<10° each). This was manifested in the nearly four-fold greater $\Delta E^{\ddagger}_{dist}$(alkyne) for acetylene (5.4 kcal mol^{-1}) compared to **TS$_{CHAIR}$** (1.7 kcal mol^{-1}), **TS$_{TBOAT}$** (1.2 kcal mol^{-1}), and **TS$_{CHAIR}$** (1.2 kcal mol^{-1}), which is the primary reason for the large rate enhancement observed. The significantly lower distortion energy of the cyclic alkynes is due to their ground-states being 'pre-distorted' towards their transition state geometries relative to acetylene, and this was also

shown in their considerably lower $\Delta G^{\ddagger}$ when compared to acetylene. The stabilising energies of interaction ($\Delta E_{int}^{\ddagger}$) between dipole and dipolarophile were comparable for each of the four transition states: **TS$_{\mathbf{ACETYLENE}}$** ($\Delta E_{int}^{\ddagger}$ = −10.9 kcal mol^{-1}), **TS$_{\mathbf{CHAIR}}$** ($\Delta E_{int}^{\ddagger}$ = −11.0 kcal mol^{-1}), **TS$_{\mathbf{TBOAT}}$** ($\Delta E_{int}^{\ddagger}$ = −9.7 kcal mol^{-1}), and **TS$_{\mathbf{BCN}}$** ($\Delta E_{int}^{\ddagger}$ = −10.0 kcal mol^{-1}), suggesting that they each have similar electrostatic, charge transfer and repulsion interactions. Overall, for the cycloaddition between acetylene and methanesulfonyl azide, the energy barrier to reaction was much greater compared to the cyclic alkynes: $\Delta E_{\text{ACETYLENE}}^{\ddagger}$ = 16.1, $\Delta E_{\text{CHAIR}}^{\ddagger}$ = 8.4, $\Delta E_{\text{TBOAT}}^{\ddagger}$ = 7.0, $\Delta E_{\text{BCN}}^{\ddagger}$ = 7.2 kcal mol^{-1}. Considering that the energy barrier for cyclooctyne to interconvert from twist boat conformation **285** to the lower energy chair conformation **283** (6.52 kcal mol^{-1}) (**Figure 2-03**) was lower than the energy required to undergo cycloaddition in twist-boat conformation ($\Delta E_{\text{TBOAT}}^{\ddagger}$ = 7.0 kcal mol^{-1}), it can be assumed that the cycloaddition between cyclooctyne and methanesulfonyl azide involves chair conformations throughout the minimum energy pathway.

The frontier molecular orbitals of the distorted transition state fragments for the 1,3-dipolar cycloaddition between cyclooctyne chair and methanesulfonyl azide (**TS$_{\mathbf{CHAIR}}$**), and *exo*-BCN and methanesulfonyl azide (**TS$_{\mathbf{BCN}}$**) were calculated (**Figure 2-05**). The orbital energies were evaluated using HF/6-311++G(2d,p) at the B3LYP/6-31(g) geometries, and the energies of the optimised ground state structures are given in parentheses. The shape of the orbitals were derived from HF/6-31g(d) calculation.[205] Examination of these energies revealed that in both cases, the gap between the alkyne HOMO (HOMO$_{\text{alkyne}}$) and azide LUMO (LUMO$_{\text{azide}}$) was significantly lower in energy than their HOMO$_{\text{azide}}$ to LUMO$_{\text{alkyne}}$ counterparts. This means that these cycloaddition reactions proceed with inverse electron-demand (IED); usually for SPAAC, the dominant orbital interactions are between the HOMO$_{\text{azide}}$ and LUMO$_{\text{alkyne}}$.[206]

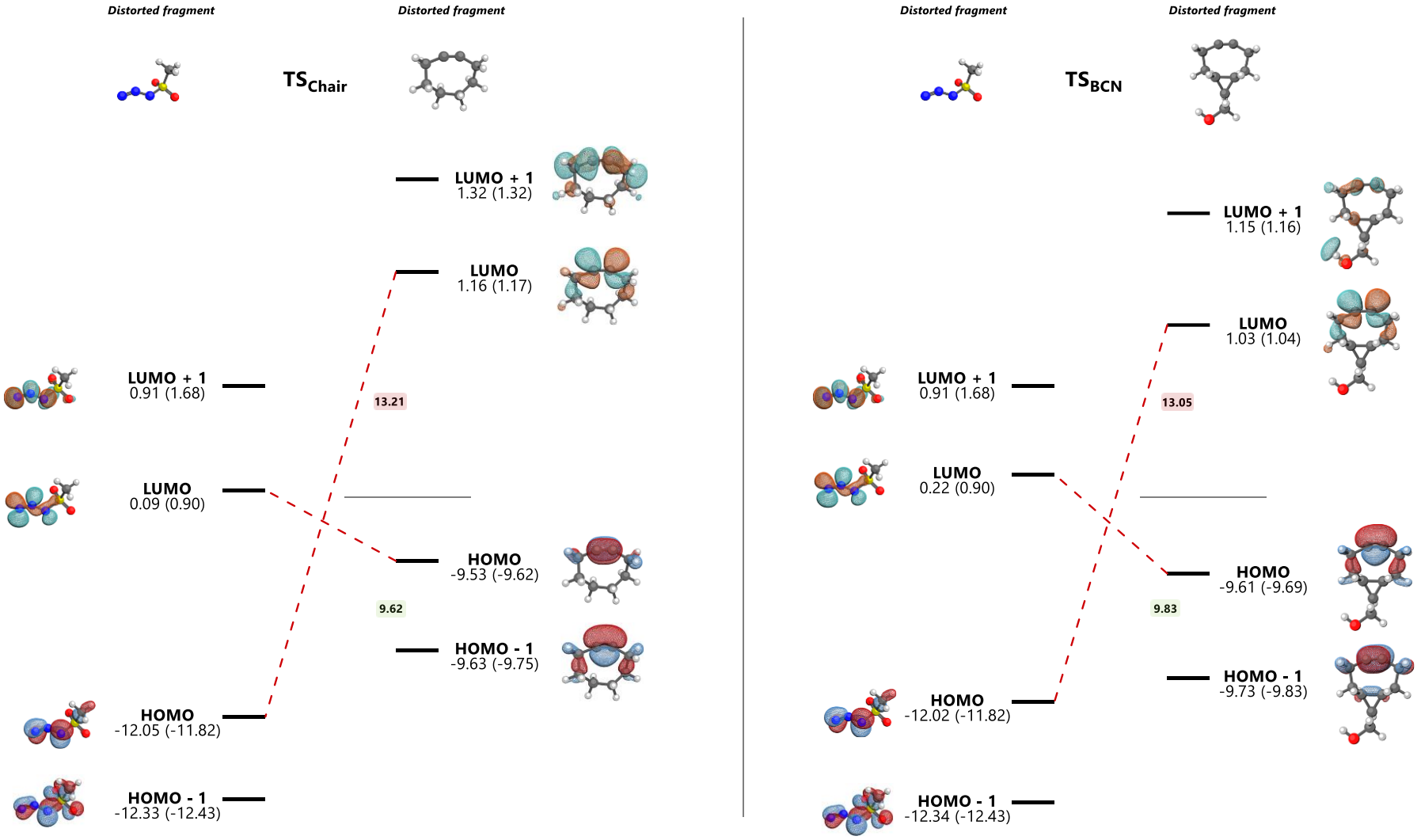


Figure 2-05: The frontier molecular orbitals of the distorted transition state fragments for the 1,3-dipolar cycloaddition between: cyclooctyne chair and methanesulfonyl azide (**TS_{CHAUR}**); *exo*-BCN and methanesulfonyl azide (**TS_{BCN}**). Orbital energies were evaluated using HF/6-311++G(2d,p) at the B3LYP/6-31(g) geometries. Orbital shapes derived from HF/6-31g(d) calculation.

2.2.3 Kinetic study

After SPAAC began to find broad application in chemical biology, it became apparent that the reaction with cyclooctyne derivatives generally suffered from poor reaction kinetics, with a large excess of reagents and long incubation times necessary.[213] Various different functionalised cyclooctynes have been developed in order to improve the reactivity without compromising stability.[214–217] The vast majority of SPAAC reactions are with simple aliphatic azides, and reaction with aryl azides generally seems to be avoided.[218–220] A possible explanation for this trend may be due *p*-azidophenylalanine having approximately sevenfold lower reactivity that the corresponding aliphatic azide with dibenzoannulated cyclooctyne (DIBAC).[220] Additionally, other studies have reported rate enhancements by introduction of electron-poor substituents on cyclooctynes.[169,214,221,222] Taken together, these observations suggest that the mechanism of SPAAC predominantly occurs through an interaction between the azide HOMO and alkyne LUMO, meaning that electron-rich azides are preferred. However, a somewhat comprehensive structure-activity relationship between aliphatic and aromatic azides and their reactivity with *endo*-BCN and DIBAC was recently carried out, with the authors disclosing a highly accelerated SPAAC between *endo*-BCN and electron-deficient aryl azides such as **287**–**290** (**Figure 2-06**).[206] The accompanying computational analysis suggested that with relatively electron-rich cyclooctynes such as *endo*-BCN, electron-poor azides can react through a $HOMO_{alkyne}$ to $LUMO_{azide}$ interaction as well, *i.e.* with inverse electron-demand. Based on these reports, it was believed that a similarly large rate enhancement may be observed in the SPAAC between electron-deficient sulfonyl azides and cyclooctyne **218** and *endo*-BCN.

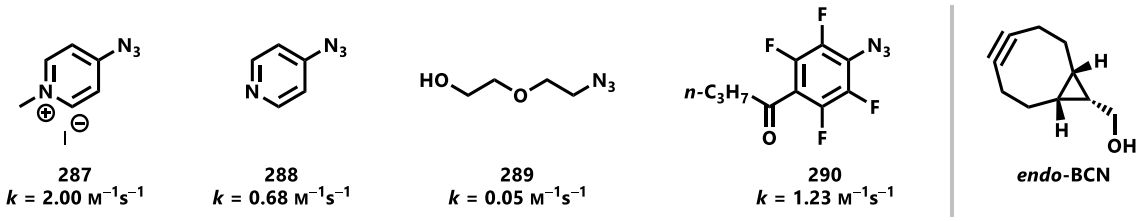


Figure 2-06: Relationship between azide structure and rate of strain-promoted cycloaddition with *endo*-BCN. Experimentally derived second order rate constants are shown.[206]

The most commonly used method to measure rate of SPAAC reactions is by NMR, where azide and alkyne are mixed in a deuterated solvent and the formation of product over time is quantified by integration of diagnostic peaks corresponding to the cycloadduct. Considering that the SPAAC between sulfonyl azides and cyclooctynes was expected to be very fast (>0.2 $M^{-1}s^{-1}$), the process of mixing reagents, inserting the sample into the magnet, shimming, *etc.* mean that most of the starting material may already have been consumed before the first measurement can be taken. One alternative to NMR is UV spectroscopy, which has been used to monitor the decay in the characteristic absorbance corresponding to the alkyne triple bond, however this is somewhat limited to reactions where there is a significant difference in UV absorption between individual substrates and product, particularly if being carried out under pseudo-first order conditions.[223,224] IR spectroscopy has emerged as perhaps the most useful tool for monitoring very fast SPAAC reactions by exploiting the characteristic azide stretching frequency (≈2100 cm^{-1}).[206] The substrate-product ratio over time can be measured by integration of this distinctive azide signal.

For studying the rate of cycloaddition between sulfonyl azides and cyclooctynes **218** and **266**, the decay in azide stretching frequency over time was measured. The second order rate constants were then determined from the integrated rate equation (**2**) (see **Appendix** for details).

(**2**) $$kt = \frac{1}{[alkyne]_0 - [azide]_0} ln \frac{[azide]_0([alkyne]_0 - [P])}{[alkyne]_0([azide]_0 - [P])}$$

Here, k = second order rate constant ($M^{-1}s^{-1}$), t = reaction time in seconds, $[azide]_0$ = initial concentration of azide (M), $[alkyne]_0$ = initial concentration of alkyne (M), and [P] = concentration of triazole product (M). From a plot of kt *vs* t, the second order rate constant is simply given by the gradient. This approach is illustrated in the cycloaddition between methanesulfonyl azide and cyclooctyne, giving a second order rate constant of 0.0207 $M^{-1}s^{-1}$ (**Figure 2-07a–c**).

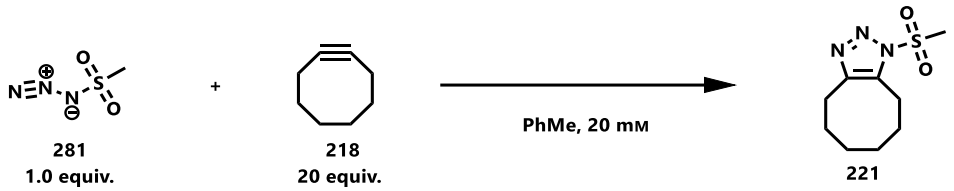


Figure 2-07a: Cycloaddition between methanesulfonyl azide and cyclooctyne.

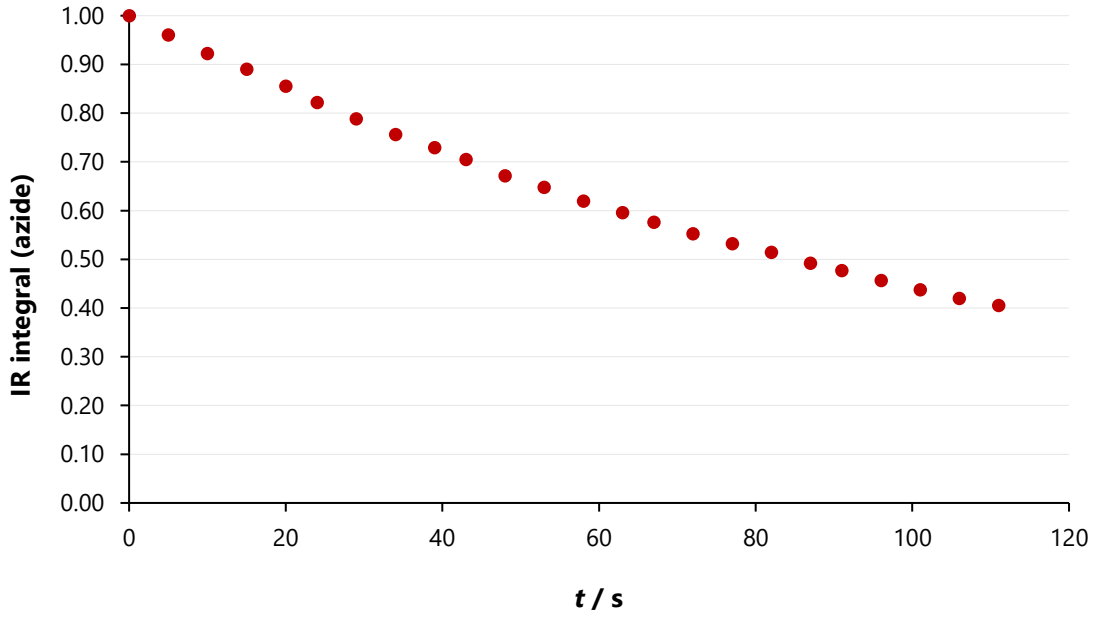


Figure 2-07b: Integration of the azide stretching frequency over time.

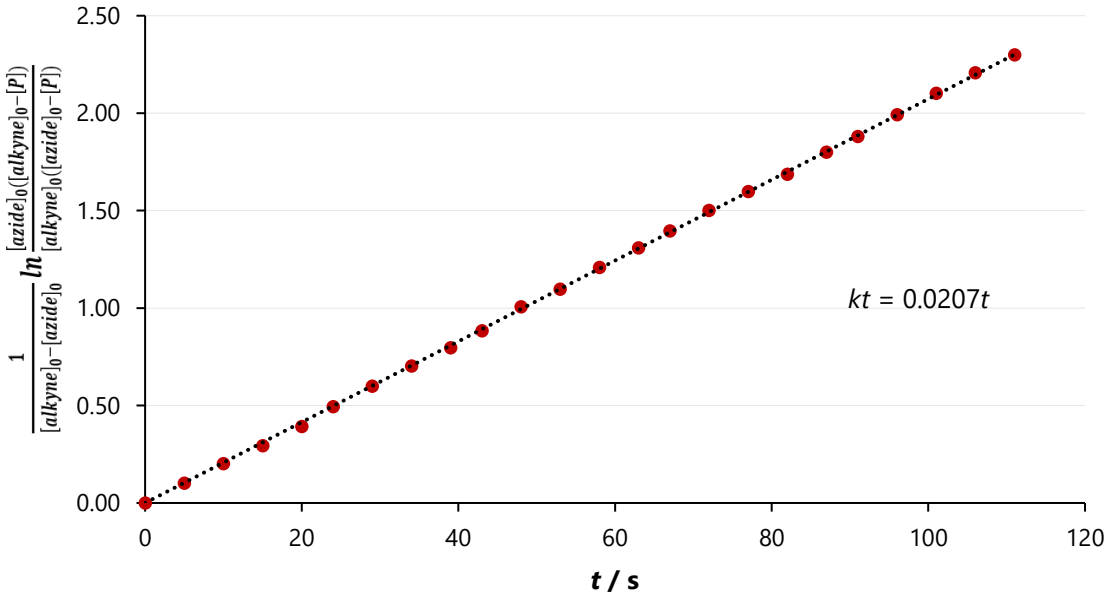
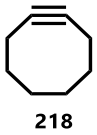


Figure 2-07c: Determination of the second order rate constant, *k*.

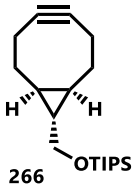
2.2.4 Rate determination

The measurements were carried out by rapidly mixing an equal volume of stock solutions of azide (40 mM in toluene) and alkyne (800 mM in toluene) followed by quickly transferring the solution to a demountable IR cell (BaF_2 window) and recording spectra at regular time intervals. Cyclooctyne **218** was freshly prepared prior to use, and a large excess was employed to minimise any experimental error that may arise due to decomposition. Each experiment was carried out *in duplo* giving very similar plots and results. The experimentally determined absolute and relative rate constants for the cycloaddition between sulfonyl azides and cyclooctyne **218** as well as *exo*-BCN **266** are shown (**Table 2**).

Table 2: Experimentally determined second order rate constants (k, $M^{-1}s^{-1}$) for the strain-promoted cycloaddition between sulfonyl azides and cyclooctyne **218** and *exo*-BCN **266**.



218



266

Entry	Azide	$k_{cyclooctyne}$			k_{rel}	k_{BCN}			k_{rel}
		i	ii	mean		i	ii	mean	
1	phenyl	0.0184	0.0153	0.0168	1.00	0.134	0.143	0.139	1.00
2	methanesulfonyl	0.0236	0.0208	0.0222	1.32	0.119	0.114	0.116	0.84
3	*p*-methylbenzenesulfonyl	0.0265	0.0245	0.0255	1.51	0.162	0.159	0.160	1.16
4	*p*-methoxybenzenesulfonyl	0.0216	0.0211	0.0213	1.27	0.141	0.148	0.145	1.04
5	*p*-nitrobenzenesulfonyl	0.0842	0.0884	0.0863	5.12	0.481	0.357	0.419	3.02
6	2,4,6-triisopropylbenzenesulfonyl	0.0134	0.0140	0.0137	0.81	-	-	-	-

With cyclooctyne, more electron poor azides generally reacted faster, with the most electron-poor *p*-nitrobenzenesulfonyl azide giving by far the fastest rate (0.0863 $M^{-1}s^{-1}$, Entry 5) which was approximately five times faster than phenyl azide (0.0168 $M^{-1}s^{-1}$, Entry 1). The next most reactive sulfonyl azide was *p*-methylbenzenesulfonyl azide (0.0255 $M^{-1}s^{-1}$, Entry 3) followed by methanesulfonyl azide (0.0222 $M^{-1}s^{-1}$, Entry 2), then *p*-methoxybenzenesulfonyl azide (0.0213 $M^{-1}s^{-1}$, Entry 4). This order of reactivity correlates with the acidities of the corresponding sulfonic acids (MsOH $pK_a = -1.92$, TsOH $pK_a = -2.8$, NsOH $pK_a = -4.0$)[225] which implies that more electron withdrawing sulfonyl azides react faster with cyclooctyne. The comparatively slow reaction between cyclooctyne and 2,4,6-triisopropylbenzenesulfonyl azide (0.0137 $M^{-1}s^{-1}$, Entry 6) may arise from the relatively electron-donating isopropyl groups raising the energy of the

$LUMO_{azide}$, but also their overall steric bulk potentially making it more difficult to achieve the orbital overlap required for 1,3-dipolar cycloaddition.

When the measurements were repeated with *exo*-BCN **266**, *p*-nitrobenzenesulfonyl azide was once again significantly faster than the other azides studied (0.419 $M^{-1}s^{-1}$, Entry 5), seeing an approximate seven-fold rate enhancement compared to cyclooctyne. The rate of cycloaddition between phenyl azide and *exo*-BCN (0.139 $M^{-1}s^{-1}$, Entry 1) measured was consistent with the value previously reported by Bickelhaupt and co-workers (0.200 $M^{-1}s^{-1}$).[206] The slightly lower measured value here can be attributed to the use of toluene in this study rather than 9:1 THF:H_2O as 1,3-dipolar cycloaddition reactions are known to generally proceed faster in more polar solvent systems.[135] A THF:H_2O solvent system was not employed in this study as aqueous conditions are generally not compatible with sulfonyl azides owing to the susceptibility of the N–S bond to hydrolysis. Comparing the values of k_{BCN} with $k_{cyclooctyne}$, the relative order of reactivity (*p*-nitrobenzenesulfonyl > *p*-methylbenzenesulfonyl > *p*-methoxybenzenesulfonyl > Phenyl) was conserved, although methanesulfonyl azide reacted slower than phenyl azide with *exo*-BCN (0.116 $M^{-1}s^{-1}$, Entry 2, and 0.139 $M^{-1}s^{-1}$, Entry 1). Phenyl azide underwent the largest rate enhancement of the azides studied (approximately eight-fold), whereas the sulfonyl azide rates were enhanced by approximately five to six times.

To accompany the IR rate study, a series of NMR competition experiments were carried out. In this approach, the cyclic alkyne (1.0 equivalent) was dissolved in toluene, and phenyl azide (20 equivalents) and a sulfonyl azide (20 equivalents) were simultaneously added. The reactions were allowed to proceed until complete consumption of the cyclic alkyne, and the ratio of the two cycloadducts was determined using ^{1}H NMR analysis of the crude reaction mixture. Integration of the signals corresponding to the triazole methylene protons allowed the product distribution to be determined which corresponded to the relative rates of SPAAC of each sulfonyl azide with respect to phenyl azide. Overall, there was a strong correlation between the relative rates of reaction measured by ^{1}H NMR competition experiments with those measured using IR spectroscopy (**Table 3**).

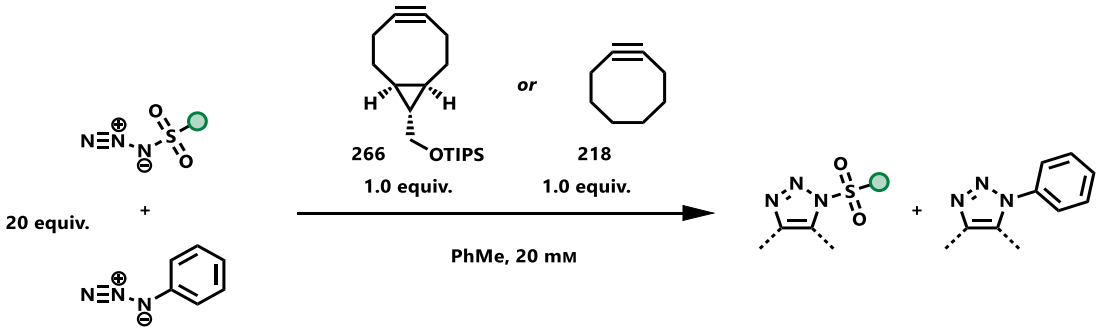


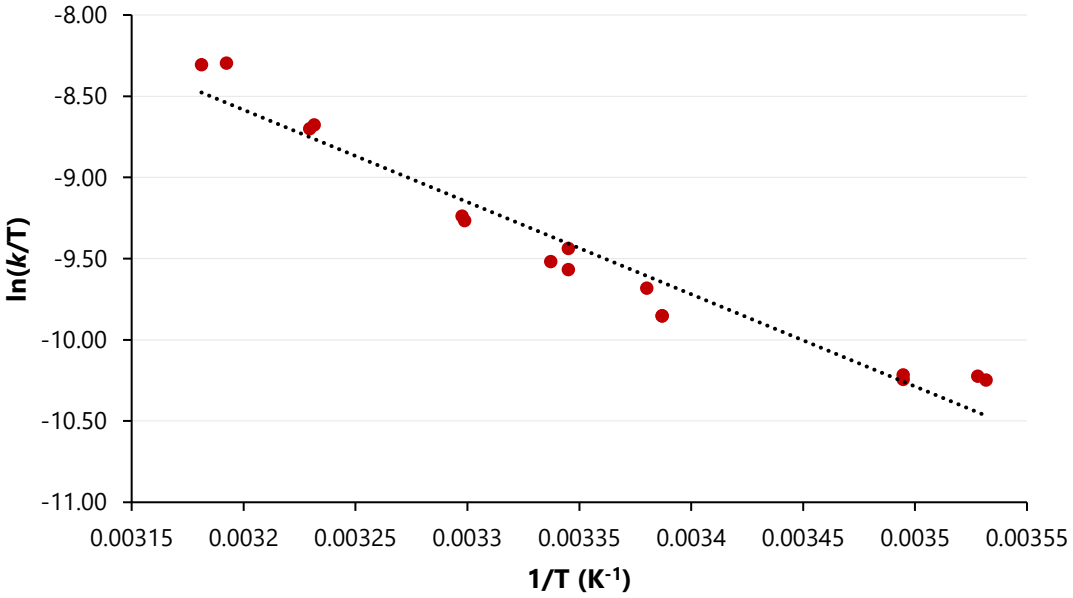
Table 3: NMR competition experiments carried out in toluene. Also shown is the experimentally derived second order rate constants ($M^{-1}s^{-1}$) for comparison.

Entry	Azide	NMR Ratio Cyclooctyne			IR	NMR Ratio *exo*-BCN			IR
		i	ii	mean	k_{rel}	i	ii	mean	k_{rel}
1	phenyl	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	methanesulfonyl	1.18	1.17	1.18	1.32	0.92	0.92	0.92	0.84
3	*p*-methylbenzenesulfonyl	1.45	1.40	1.43	1.51	1.14	1.14	1.14	1.16
4	*p*-methoxybenzenesulfonyl	1.21	1.18	1.20	1.27	1.00	1.04	1.02	1.04
5	*p*-nitrobenzenesulfonyl	5.19	3.27	4.23	5.12	3.84	3.95	3.90	3.02
6	2,4,6-triisopropylbenzenesulfonyl	0.67	0.73	0.70	0.81	-	-	-	-

With the rate of reaction of different sulfonyl azides successfully determined, the temperature dependence of the second order rate constant for the reaction of methanesulfonyl azide with cyclooctyne was investigated under pseudo-first order conditions. The thermodynamic parameters of the reaction were determined by plotting $ln\frac{k}{T}$ against $\frac{1}{T}$ (Eyring plot, **Figure 2-07**, see Appendix for details).[226]

The kinetic runs were carried out under identical conditions as previously (*i.e.* 20 mM *wrt* methanesulfonyl azide, 20-fold excess of cyclooctyne, toluene as solvent) but varying the

temperature from 10 °C to 40 °C. The experimentally determined Gibbs free energy of activation ($\Delta G^{\ddagger}$) was 19.7 kcal mol^{-1}, which was in excellent agreement with the computationally calculated (*vide supra*) value of 20.6 kcal mol^{-1}. Unsurprisingly, the reaction parameters are indicative of an associative transition state ($\Delta S^{\ddagger}$) that is large and negative, representing an increase in order. For reactions carried out at relatively low temperature (as here), the enthalpy of activation ($\Delta H^{\ddagger}$) derived from application of the Eyring equation can serve as an approximation for the activation energy. In this case, $\Delta H^{\ddagger}$ was determined as 11.3 kcal mol^{-1}, which is in reasonable agreement with the computationally derived electronic energy barrier of 8.6 kcal mol^{-1} for **TS$_{CHAIR}$**. The activation energy, E_a, was also determined by application of the Arrhenius equation (see Appendix for details) and was 11.9 kcal mol^{-1}.

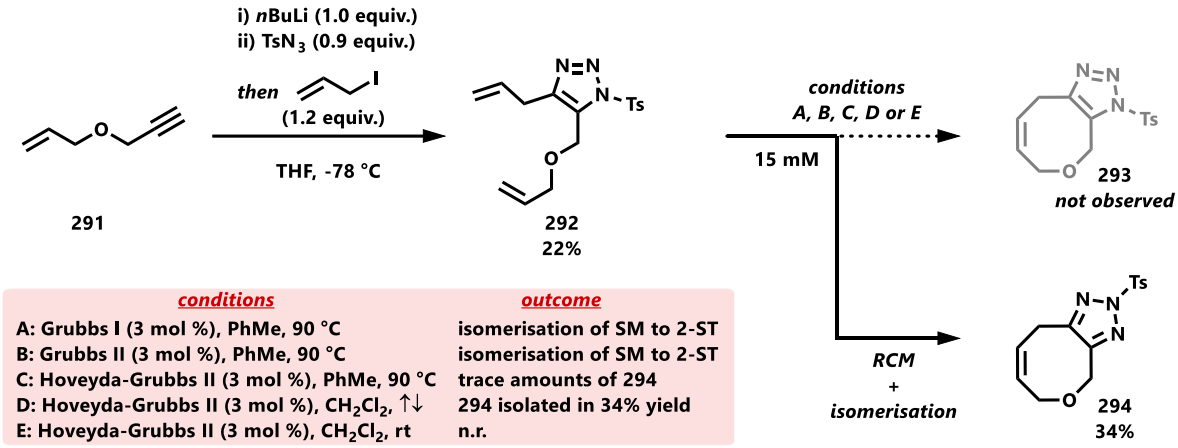


$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$ (25 °C)	E_a (Arrhenius)
11.3 kcal mol^{-1}	–118 J mol^{-1}	19.7 kcal mol^{-1}	11.9 kcal mol^{-1}

Figure 2-07: Eyring plot of the rate constant *k* for the cycloaddition of methanesulfonyl azide and cyclooctyne. Also shown are the experimentally determined activation parameters, derived from the Eyring plot (see **Appendix** for details). The gradient is given by $-\frac{\Delta H^{\ddagger}}{R}$.

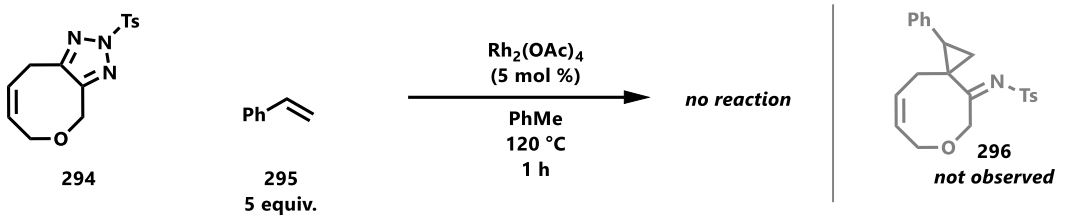
2.2.5 Alternative approaches to cyclic 1-STs

It was hypothesised that instead of preparing a cyclic alkyne and undergoing SPAAC with a sulfonyl azide, a 4,5-substituted 1-ST **292** could be prepared with two pendent terminal alkenes, which could be cyclised through ring-closing metathesis to give triazole **293** (**Scheme 2-17**). After successfully preparing 1-ST **292** in 22% yield from alkyne **291**, it was subjected to a range of different conditions typically used for ring-closing metathesis (**Scheme 2-17**).[227,228]



Scheme 2-17 Ring-closing metathesis as a potential method for preparing 4,5-substituted 1-STs.

When treated with either Grubbs 1st or 2nd generation catalyst (conditions A and B), no ring-closure was observed but the 1-ST **292** had isomerised to the corresponding 2-ST regioisomer. Upon treatment of **292** with Hoveyda-Grubbs 2nd generation catalyst, a trace amount of the cyclised product **294** was observed (conditions C). Although the ring-closing metathesis was slowly taking place, the main observation was isomerisation of the starting material **292** to the 2-ST without ring-closure, similar to conditions A and B. Finally, when dichloromethane was used with HG-II at reflux, 34% of **294** was obtained (conditions D). Distinguishing between a 1-ST and 2-ST with analytical techniques is quite challenging but when heated in the presence of a rhodium(II) catalyst the 2-ST will not denitrogenate, whereas a 1-ST will either react with an added substrate, or decompose over time. The triazole **294** was verified as the unreactive 2-ST isomer by heating with styrene **295** in the presence of rhodium(II) acetate (**Scheme 2-18**). No reaction between **294** and **295** occurred, returning completely clean starting materials.



Scheme 2-18: Triazole **294** was completely unreactive towards denitrogenative conditions, confirming it as 2-ST.

Unfortunately, it was not possible to affect ring-closing metathesis of 4,5-diallyl 1-ST **292** without concomitant isomerisation to 2-ST, and the yields for RCM were quite low. Considering these challenges, RCM was not regarded as a viable route towards 4-5-substituted cyclic 1-STs.

2.3 Summary

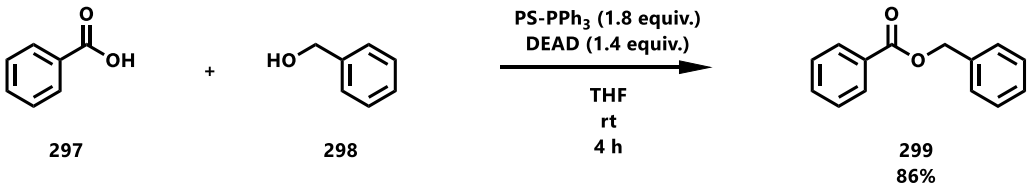
This chapter explored the use of cyclic alkynes as precursors to 1-sulfonyl-1,2,3-triazoles by exploiting the strain-promoted alkyne azide cycloaddition. Both cyclooctyne and *exo*-BCN were found to undergo rapid formation of 1-STs in excellent yield. Treatment of the triazoles derived from cyclooctyne with rhodium(II) carboxylate catalysts promoted denitrogenation followed by transannular C−H insertion to generate [3.3.0]-bicyclic compounds with good yield and excellent enantioselectivity. Transannular C−H insertion was not observed for the *exo*-BCN triazoles which instead underwent a 1,2−shift in good yield. The cycloaddition between various sulfonyl azides and these two cyclic alkynes was investigated computationally and an accompanying kinetic study was carried out. Cyclooctyne and *exo*-BCN underwent SPAAC with sulfonyl azides through an inverse electron demand mechanism which constituted a $HOMO_{alkyne}$ to $LUMO_{azide}$ dominant interaction. This interaction was demonstrated in the kinetics of the electron poor *p*-nitrobenzenesulfonyl azide which was found to undergo extremely rapid SPAAC (approximately five times faster than phenyl azide). Additionally, the activation parameters of the SPAAC between methanesulfonyl azide and cyclooctyne were determined and are in good agreement with the computationally derived values. The synthesis of cyclic 1-STs from cyclononyne, 4,8-disulfonamidocyclononyne and ring-closing metathesis strategies was found to be unsuccessful.

3 Polymer-supported 1-STs

3.1 Background and Aims

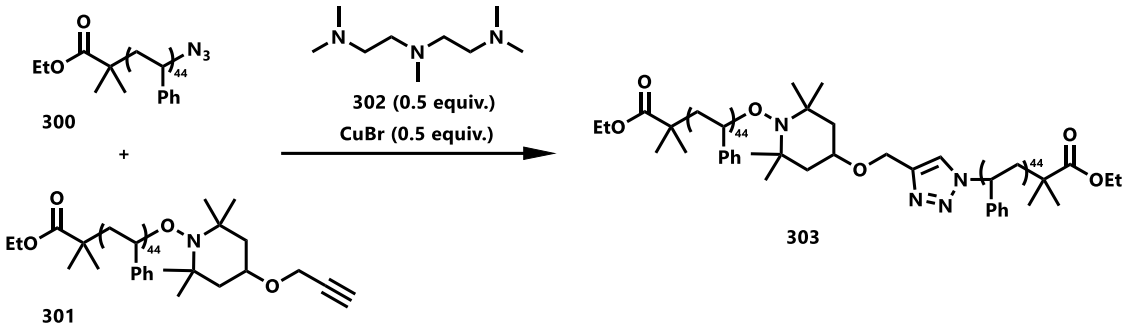
The principle of polymer-supported synthesis involves fixing a substrate or reagent to a polymeric resin; performing the desired transformation then exploiting the physical properties of the polymer to facilitate easy separation for work up and purification.[229] The use of solid-supported reagents in organic synthesis is a concept that dates back to 1946; but at the time these techniques were considered expensive and slow.[230] Merrifield and Letsinger first introduced the concept of solid-phase organic synthesis that is widely adopted today.[231,232]

There are several advantages to using solid-supported reagents in this manner, mainly: excess reagents can be used to drive the reaction to completion, and since isolation of the products is *via* simple filtration, the chemistry can be considered "clean" as byproducts and excess reagents are washed away. These features mean that solid-phase synthesis is used extensively in combinatorial chemistry.[233] There are many examples of polymer-supported reagents, from oxidising agents[234] to reducing agents,[235] diazotransfer reagents,[236] and various sequestering agents[237] to name a few. For example, polymer-supported triphenyl phosphine (PS-PPh_3) was used to in the Mitsunobu reaction to convert the carboxylic acid **297** into benzyl ester **298** in 86% yield (**Scheme 3-01**).[238,239] The excess reactants and triphenylphosphine oxide byproduct remained attached to the polymer beads allowing the product to be isolated by filtration.



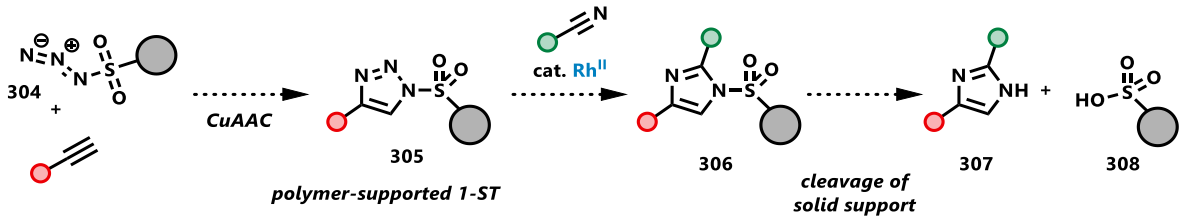
Scheme 3-01: Esterification using polymer-supported triphenyl phosphine.[238,239]

A 1,2,3-triazole moiety has been introduced into polystyrene-based polymers by copper-catalysed alkyne-azide cycloaddition.[240] A polymer with an alkyne **301** and a polymer with an azide **300** were reacted in the presence of CuBr and PMDETA **302** to give the co-polymer **303** (**Scheme 3-02**).



Scheme 3-02: Solid-phase copper-catalysed alkyne-azide cycloaddition reaction.[240]

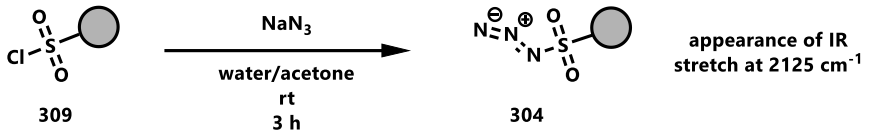
The aim of this project was to investigate 1-sulfonyl-1,2,3-triazoles as versatile polymer supported agents (**Scheme 3-03**). By using a polymer-supported sulfonyl azide **304** in a copper-catalysed click reaction with alkyne, a polymer-supported 1-ST **305** could be generated. The wealth of 1-ST methodology could be carried out in solid phase, such as transannulation with nitriles to afford polymer supported imidazoles **306** (*vide supra*).[77] Excess reagents and byproducts could be removed by filtration, and the pure product isolated from the solid support by cleavage of the labile N–S bond.[103]



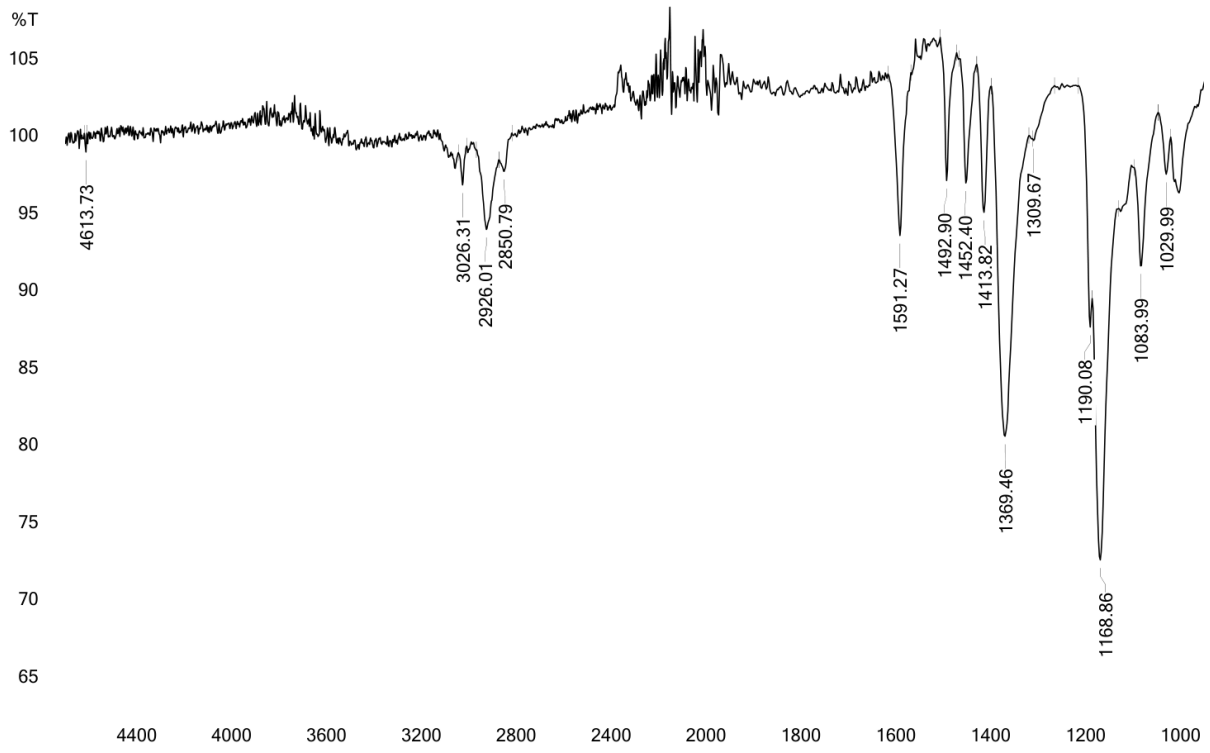
Scheme 3-03: Polymer-supported imidazole synthesis using 1-STs

3.2 Results

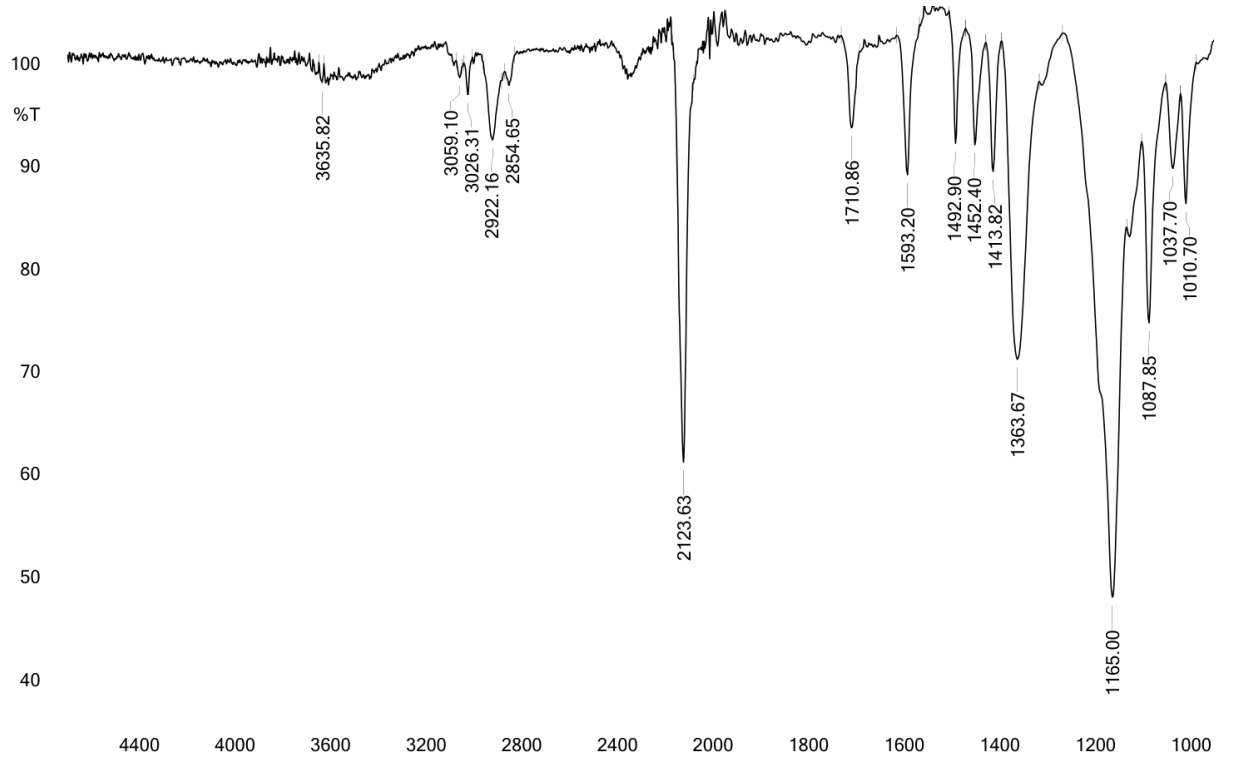
Beginning from commercially available polystyrene-supported sulfonyl chloride **309**, the sulfonyl azide **304** was prepared by simple displacement using sodium azide. A key challenge when carrying out solid-phase organic synthesis is the difficulty in obtaining accurate characterisation data, especially when compared to solution phase.[229,241] In these experiments, IR spectroscopy proved to be a powerful diagnostic tool for determining the outcome of reactions; the distinctive IR stretching frequency corresponding to the azide functional group appeared around 2124 cm^{-1} and was used to verify that transformation had been successful (**Scheme 3-04a**–**c**).



Scheme 3-04a: Preparation of polymer-supported sulfonyl azide

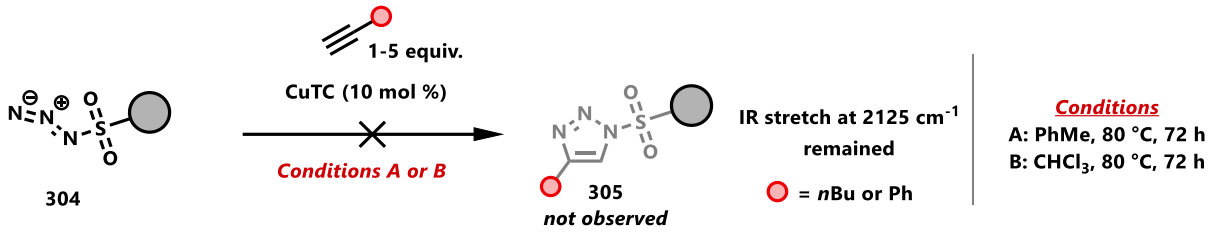


Scheme 3-04b: IR spectrum of polymer-supported sulfonyl chloride **309**.



Scheme 3-04c: IR spectrum of polymer-supported sulfonyl azide product **304**.

The next step was to carry out CuAAC using the azide **304** (**Scheme 3-05**). Unfortunately, attempts to couple either phenyl acetylene or 1-hexyne with the PS-sulfonyl azide **304** using CuTC in either toluene or chloroform were unsuccessful: the distinctive azide IR stretch remained, even after increasing the temperature to 80 °C.

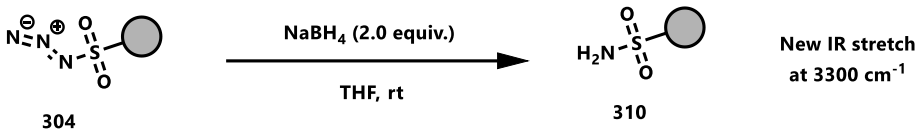


Scheme 3-05: Reactions performed on PS-sulfonyl azide

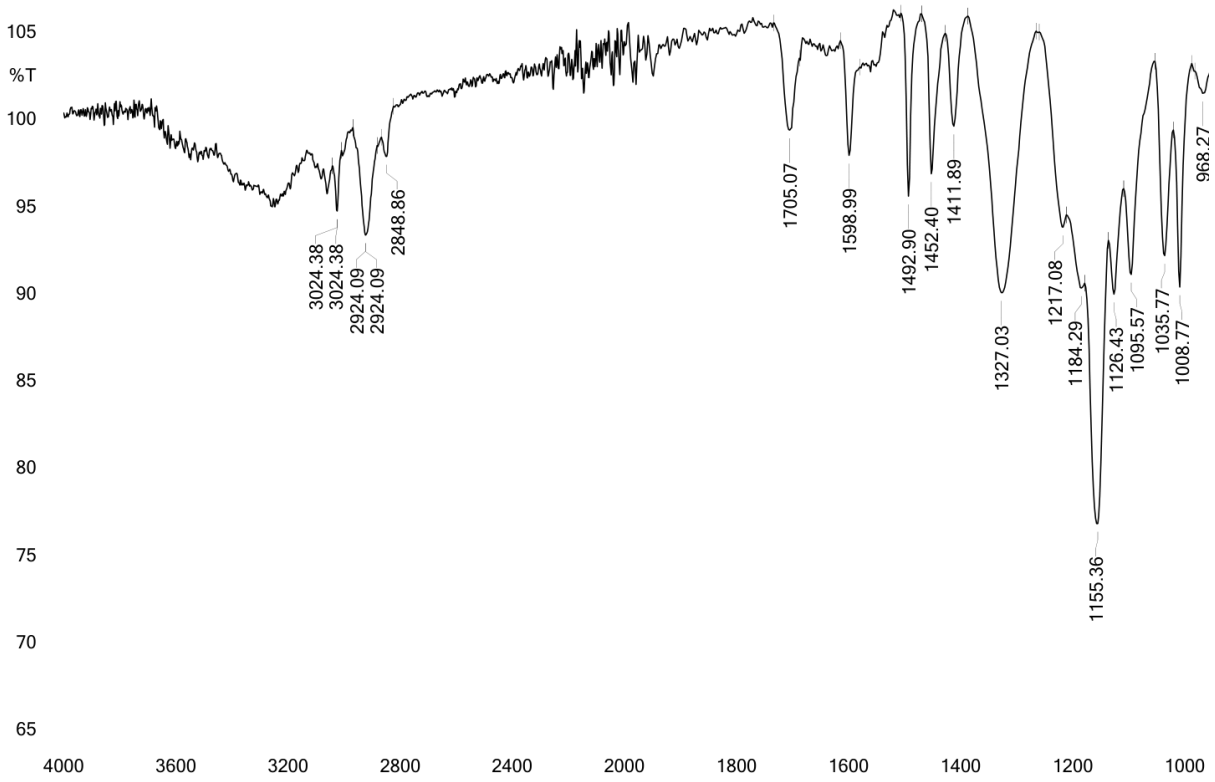
The structure of the polymer support was proprietary,[†] however it is likely that it is resembles Merrifield resin, prepared by polymerisation of 4-styrenesulfonyl chloride and styrene, meaning that the bulk of the sulfonyl azide functional groups are dispersed throughout the polymer matrix, and are therefore significantly sterically hindered.[231] The azide functional group can easily be reduced,[242] so a benchmark reaction was performed by treating the polymer-supported sulfonyl azide **304** with sodium borohydride in THF (**Scheme 3-06a**). The IR spectrum showed that the

[†] Elemental analysis was performed on all of the polymer supported compounds used in this study but was inconclusive.

azide stretching frequency was completely diminished, with a new frequency appearing at ~3300 cm^{-1} which is characteristic of amines (**Scheme 3-06b**).

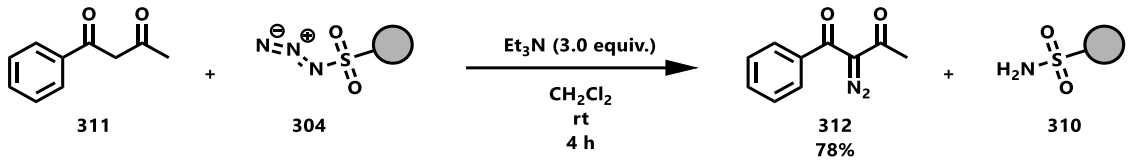


Scheme 3-06a: The polymer supported sulfonyl azide **304** was reduced using sodium borohydride.



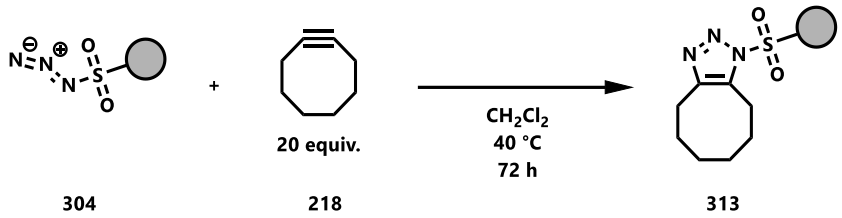
Scheme 3-06b: IR spectrum of the polymer-supported sulfonamide **310**.

Determined by these observations, the loading of the PS-sulfonyl azide **304** was experimentally measured by carrying out a diazo transfer to benzoyl acetone **311**, which is known to proceed with quantitative yield (**Scheme 3-07**).[243] Treatment of benzoyl acetone **311** with 1.0 equivalent of polymer-supported sulfonyl azide **304** afforded the diazo compound **312** in 78% yield. The loading of polymer-supported sulfonyl azide **304** was therefore calculated to be 1.19 mmol g^{-1}.



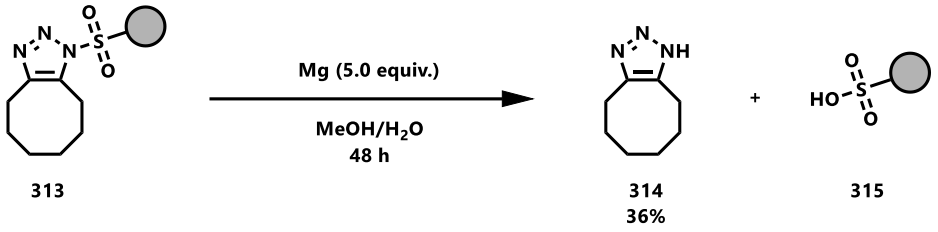
Scheme 3-07: The loading of polymer-supported sulfonyl azide was calculated by diazo transfer to benzoyl acetone.

Another way to prepare 1-STs is by copper-free strain-promoted alkyne-azide cycloaddition (see **Section 2**). Reaction of PS-sulfonyl azide **304** with a very large excess of highly strained, highly reactive cyclooctyne **218** at 40 °C over 72 hours gave the PS-sulfonyl triazole **313** (**Scheme 3-08**).



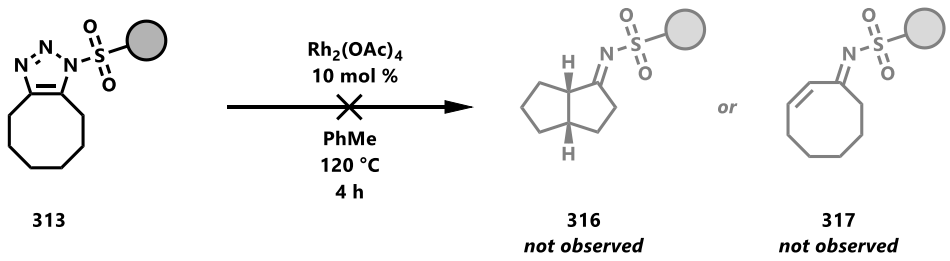
Scheme 3-08: Reaction between PS-sulfonyl azide **304** and cyclooctyne gave 1-ST **313**.

Sulfonyl groups can be readily cleaved from 1-STs using magnesium and methanol.[157] In order to verify that the 1-ST **313** had been made, it was successfully cleaved from the solid support by treatment with an excess of magnesium in methanol/water over 48 hours (**Scheme 3-09**). After filtration, free triazole **314** was obtained in 36% yield and was characterised by ^{1}H NMR spectroscopy. The low yield suggested that this process was hindered by the steric bulk of the polymer, as this is a usually a very high yielding process for traditional 1-STs.



Scheme 3-09: Cleavage of cyclooctatriazole **314** from the polymer support.

As a polymer supported 1-ST **313** had successfully been prepared, it was subjected to denitrogenative conditions to see if any reaction took place (**Scheme 3-10**). 1-Sulfonylcyclooctatriazoles such as **313** undergo rhodium(II)-catalysed 1,5-C−H insertion to generate bicyclic compounds **316**, or a 1,2-H shift to give unsaturated compounds **317** (See **Section 2**). Unfortunately, in the case of polymer-supported 1-ST **313** there was no observable reaction when treated with $Rh_2(OAc)_4$ in toluene at 120 °C and no products were isolated after applying the same cleavage using magnesium and methanol/water.



Scheme 3-10: No reaction occurred when 1-ST **313** was treated under denitrogenative conditions.

3.3 Summary

The synthesis and reactivity of polymer supported 1-STs has been investigated. Although the polymer-supported sulfonyl azide was successfully prepared, conversion of the sulfonyl azide to a polymer supported 1-ST proved very challenging. The only successful cycloaddition was with extremely reactive cyclooctyne at elevated temperatures. The 1-ST that was prepared did not undergo any reaction under denitrogenative conditions and using 1-STs as polymer supported agents was therefore deemed unfeasible using this approach.

4 Investigating the Reactivity and Selectivity of 4-Acyl 1-STs

4.1 Background and Aims

To date, the majority of 1-STs employed in rhodium(II)-catalysed transformations fall into the category of donor/acceptor carbenoids (**Figure 4-01**).[79] The "push-pull" nature of these substrates allows exquisite selectivities to be achieved while also maintaining reactivity. In contrast, the chemistry of acceptor/acceptor carbenoids derived from 1-STs is an underdeveloped area of research.[244–248] Installation of an electron withdrawing group at the 4-position of a 1-sulfonyl-1,2,3-triazole facilitates ring-chain tautomerisation, and treatment with a rhodium(II) carboxylate catalyst generates an extremely electrophilic metallocarbene.[244–248]

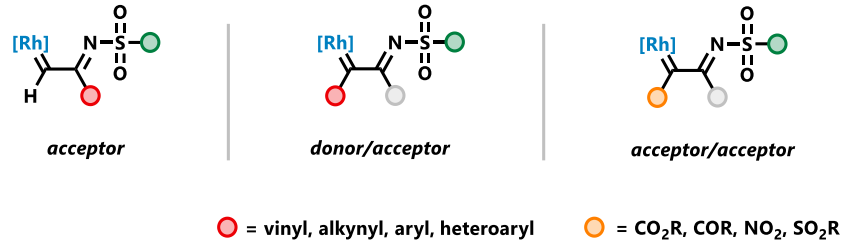
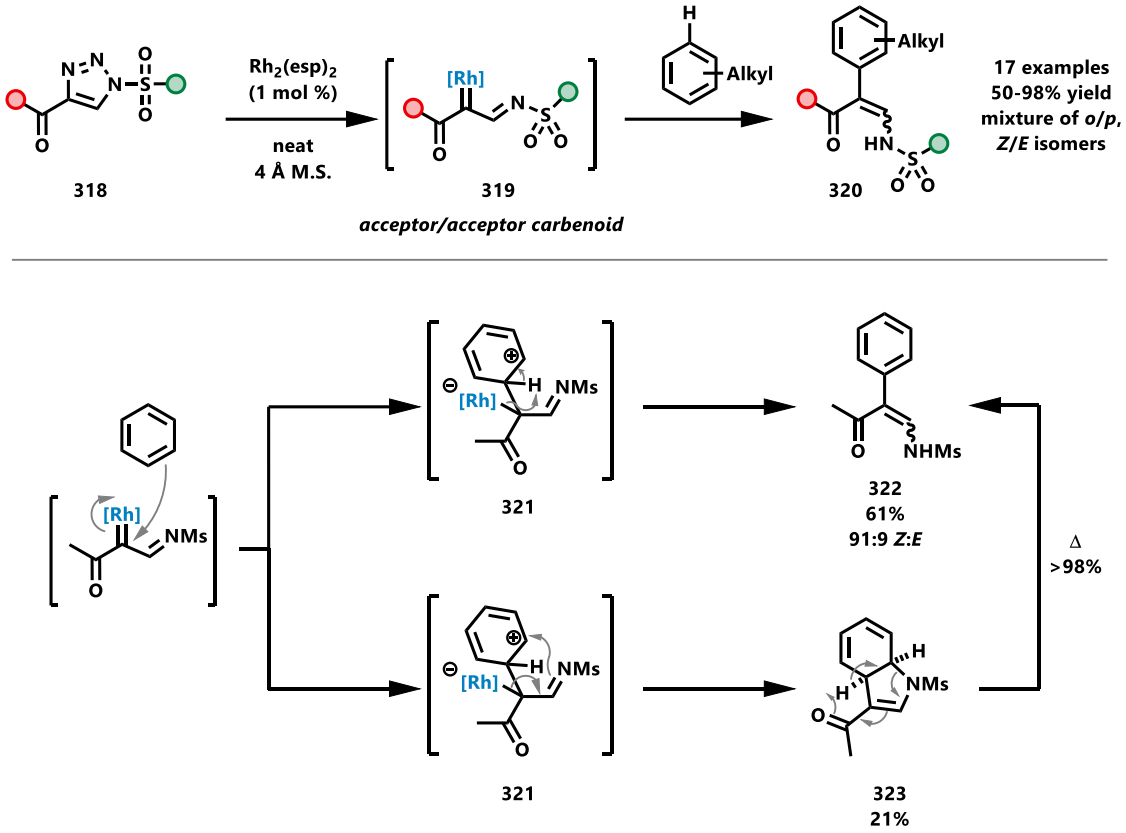


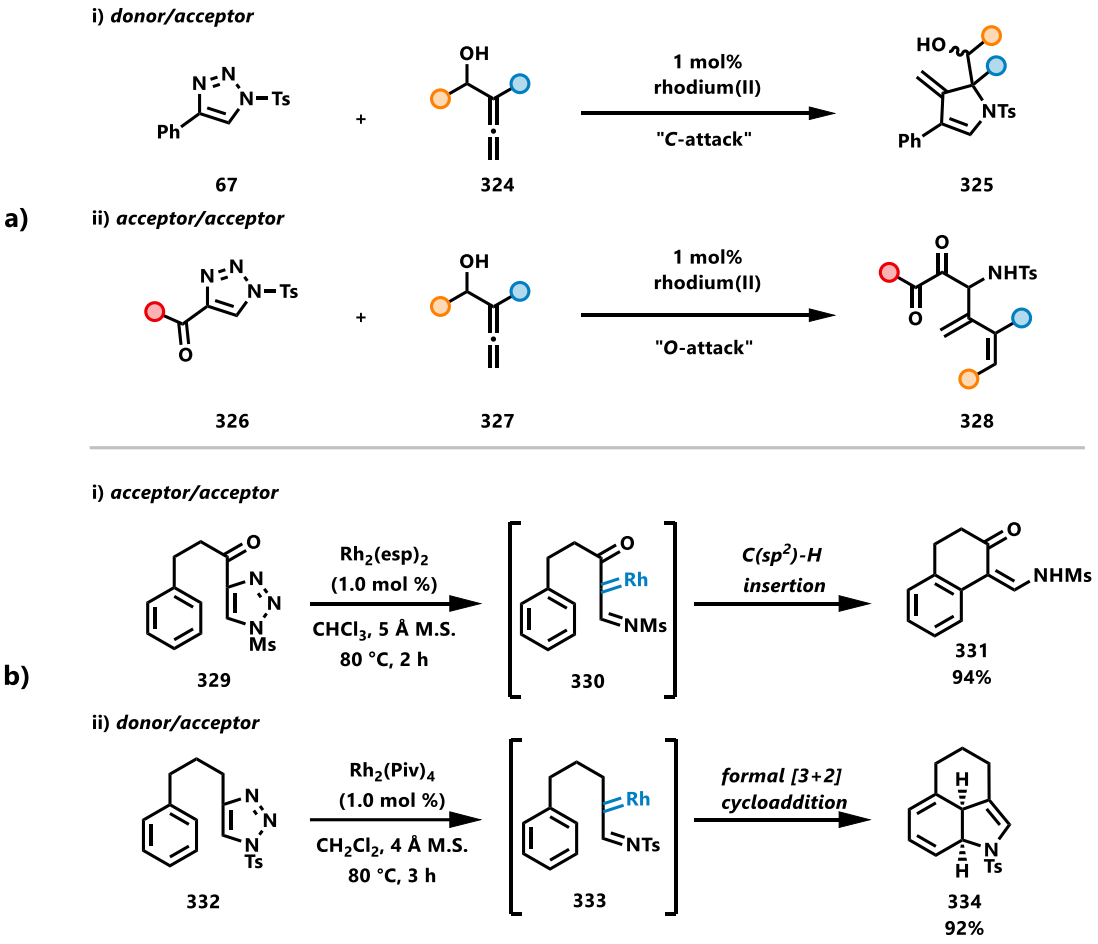
Figure 4-01: Classification of metallocarbenes derived from 1-STs.

The reactivity of 4-acyl substituted 1-STs was recently unveiled by Murakami and co-workers in their investigation of aromatic C–H functionalisation (**Scheme 4-01**).[244] The acceptor/acceptor carbenoids generated **319** underwent selective insertion into aromatic C(sp^2)–H bonds in the presence of C(sp^3)–H bonds to generate *N*-sulfonylenaminones **320** with good yields, with a mix of *ortho* and *para* regioisomers as well as *Z*/*E* alkene isomers (**Scheme 4-01**). The carbenoids **319** were extremely electron poor and attacked by the π-electrons of the aromatic system in a Friedel-Crafts type mechanism to generate intermediate **321**. Hydrogen abstraction of the metallocarbene generated *N*-sulfonylenaminone **322** in 61% yield. The intermediate **321** could also cyclise and gave dihydroindole **323** in 21% yield, which could be converted to the *N*-sulfonylenaminone **322** by heating. Notably, conventional 4-aryl substituted 1-STs did not demonstrate this reactivity.



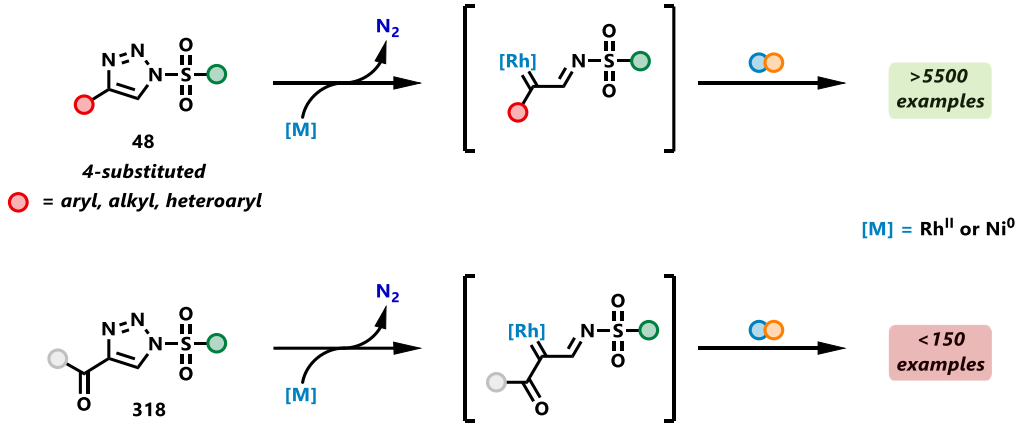
Scheme 4-01: Selective insertion into aromatic C(sp^2)-H insertion using acceptor/acceptor carbenes derived from 4-acyl 1-STs.[244]

The difference in reactivity between acceptor/acceptor and donor/acceptor carbenoids derived from 1-STs was exemplified by Delgado-Martinez and co-workers – chemoselectivity (*O*- versus *C*-attack) could be tuned in the rhodium(II)-catalysed reaction between 1-STs and allenols when switching the 4-aryl substituent with a 4-acyl substituent (**Scheme 4-02a**).[246,249] Additionally, two triazoles of similar skeleton **67** and **326**, differing only in the inclusion of a 4-acyl substituent, underwent either C(sp^2)–H insertion or [3+2] cycloaddition respectively (**Scheme 4-02b**).[244]



Scheme 4-02: Chemoselectivity switching in the rhodium(II) catalysed reactions of 4-substituted 1-STs.[244,246,249]

To date, there are a limited number of reports detailing the special selectivity of 4-acyl-triazoles.[165,244–248] The aim of the work in this chapter was to further explore the reactivity of this class of triazole (**Scheme 4-03**).

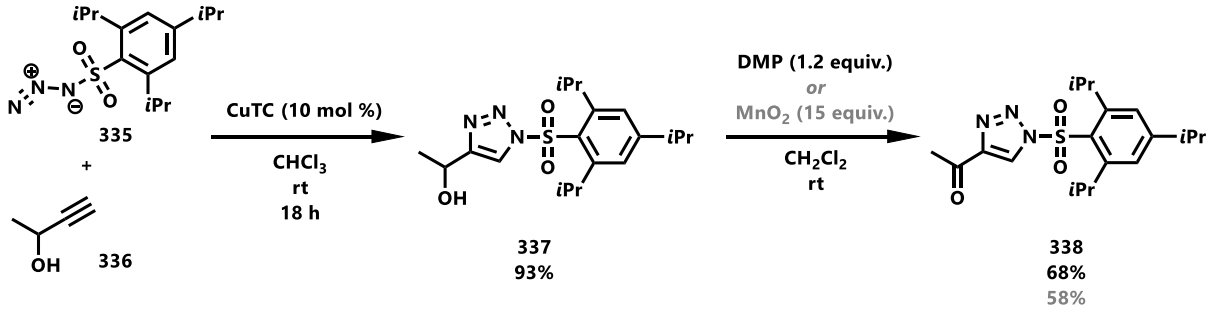


Scheme 4-03: Acceptor/acceptor 1-STs **318** are an emerging class of triazole that have relatively few existing reports compared to donor/acceptor 1-STs **48**.[165]

4.2 Results

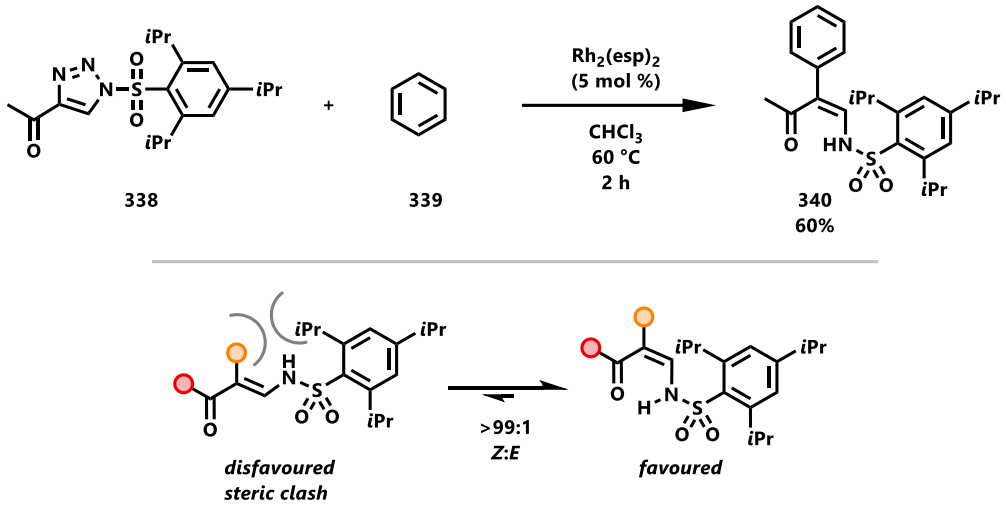
4.2.1 Initial findings

The starting point of this investigation was to prepare a suitable 1-ST. In the existing examples of 4-acyl 1-ST reactions, there is often a problem of *Z*/*E*-alkene isomerism in the products (*e.g.* **Scheme 4-01** and **Scheme 4-02a**). It was envisioned that using a large sulfonyl group in such cases would improve the selectivity by disfavouring the *E*-isomer due to unfavourable steric interactions, as well as promoting a hydrogen bonding interaction between the N–H and C=O. Preparation of the 1-ST **337** was achieved by CuAAC between triisopropylbenzenesulfonyl azide **335** and 3-butyn-2-ol **336** in 93% yield. Oxidation of **337** was carried out using either Dess-Martin Periodinane (68% yield) or manganese(IV) oxide (58% yield) and after column chromatography gave 4-acyl 1-ST **338** (**Scheme 4-04**). Oxidation using Dess-Martin Periodinane was the preferred option because the yield was higher and the reaction was faster (1 hour *vs.* 24 hours).



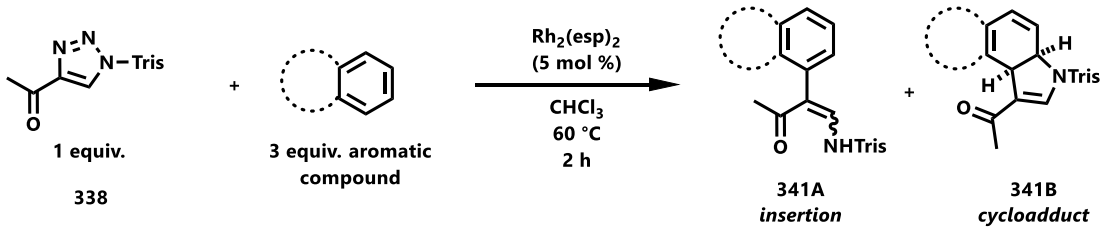
Scheme 4-04: Synthesis of 4-acyl 1-ST **338** by CuAAC and oxidation.

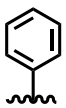
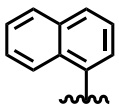
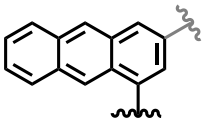
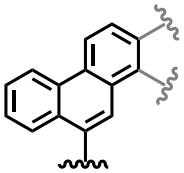
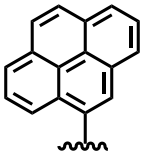
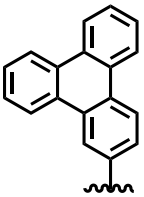
After successfully preparing triazole **338**, it was first treated with benzene under the conditions for C(sp^2)-H insertion developed by Murakami and co-workers (**Scheme 4-05**). The product of C−H insertion **340** was obtained in a comparable 60% yield but with complete *Z* selectivity whereas Murakami and co-workers reported a 91:9 *Z:E* ratio when using 4-phenyl-1-mesyl-1,2,3-triazole (**Scheme 4-01**).[244] Therefore, the selectivity of the reaction had been enhanced.



Scheme 4-05: Using the bulky trisyl sulfonyl group improved selectivity

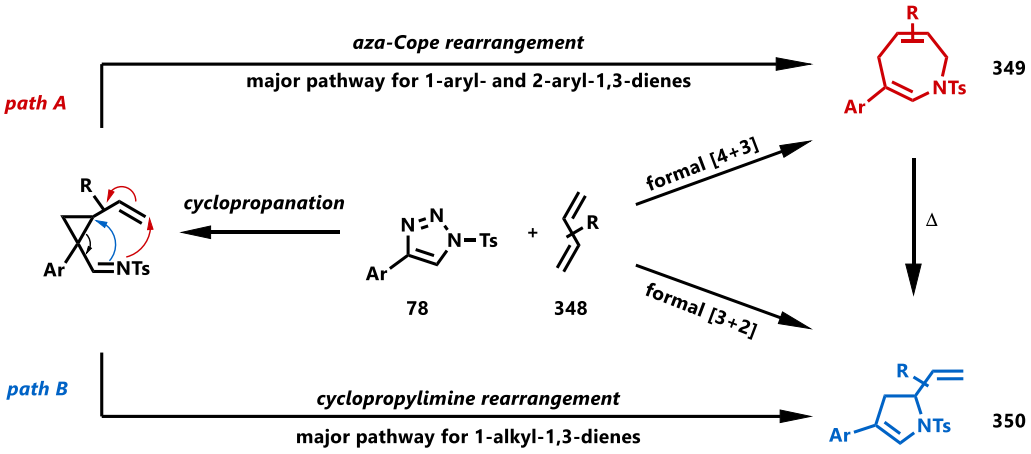
The effect of the bulky sulfonyl group on the selectivity of C−H insertion reactions with polyaromatic systems was investigated to see if it could help to control regioselectivity problems encountered by Murakami and co-workers, *i.e.* selectively functionalise one C–H bond (**Scheme 4-06**).[244] Unfortunately, although the 1-ST **338** successfully underwent C−H insertion with each of naphthalene **343**, anthracene **344**, phenanthrene **345**, pyrene **346** and triphenylene **347**, the regioselectivities were poor and resulted in several inseparable regioisomers. Additionally, in the case of naphthalene **343** and anthracene **344**, there was formation of the undesired dihydropyrroles **341B** arising from formal [3+2] cycloaddition rather than C−H insertion. Although the bulky sulfonyl group was effective at controlling the *Z/E* isomerism, it seemed to have little effect on the regioselectivity of reaction. Different catalysts including $Rh_2(OAc)_4$ and $Rh_2(TPA)_4$, as well as solvents such as dichloromethane and hexane were assessed but unfortunately no improvement was seen over the conditions originally reported by Murakami and co-workers.[244]



Entry	1	2	3	4	5	6
						
	benzene 342	naphthalene 343	anthracene 344	phenanthrene 345	pyrene 346	triphenylene 347
	A: 60%	A: 41%	A: 19% (68:32 regioismers)	A: 52% (several regioismers)	A: 53%	A: 38%
	B: 0%	B: 17%	B: 16%	B: 0%	B: 0%	B: 0%

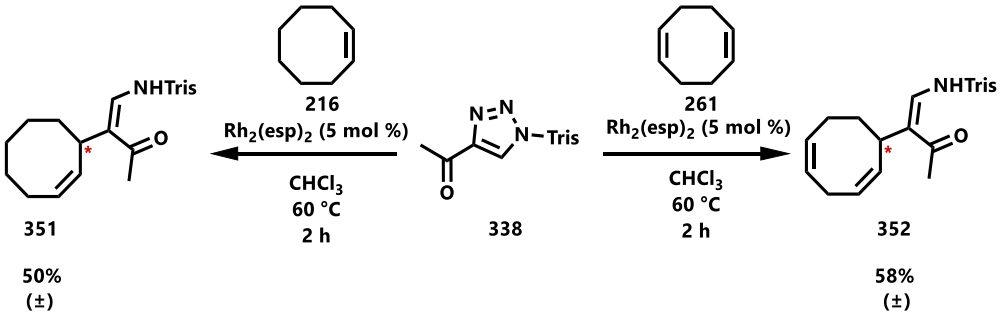
Scheme 4-06: A range of different polycyclic aromatic systems were functionalised.

Next, the reactivity of 4-acyl substituted 1-STs with alkene π-bonds was investigated. As previously described (see **Section 1.3.2**), 1-STs most commonly react with the π-bonds of an alkene by either cyclopropanation or transannulation. Rhodium(II)-catalysed cyclopropanation of alkenes with donor/acceptor carbenes derived from 1-STs was first outlined by Fokin and co-workers and has proven to be an excellent method for the synthesis of cyclopropanes with one or more stereogenic centres.[103] Since then, Tang and co-workers described an interesting cyclopropanation of 1,3-dienes, which was followed by either an aza-Cope rearrangement leading to azepines **349** (path A) or a cyclopropylimine rearrangement leading to pyrroles **350** (path B) (**Scheme 4-07**).[250] Which of the two pathways was favoured was determined by the nature of the substrates: path A was favoured by 1-aryl and 2-aryl-1,3-dienes whereas path B was favoured by 1-alkyl-1,3-dienes.



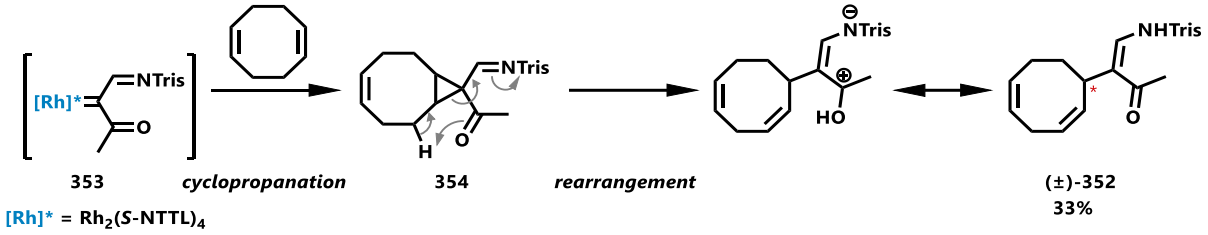
Scheme 4-07: Functionalisation of 1,3-dienes with 1-STs.[250]

Reaction of triazole **338** with cyclooctene **216** or 1,5-cyclooctadiene **261** under standard denitrogenative conditions gave similar molecules that appeared to be the products of net C–H functionalisation (**Scheme 4-08**).



Scheme 4-08: Reaction between 4-acyl 1-ST **338** and cyclic alkenes. 0.20 mmol scale, sealed tube, 0.2 M. 2.0 equiv. alkene.

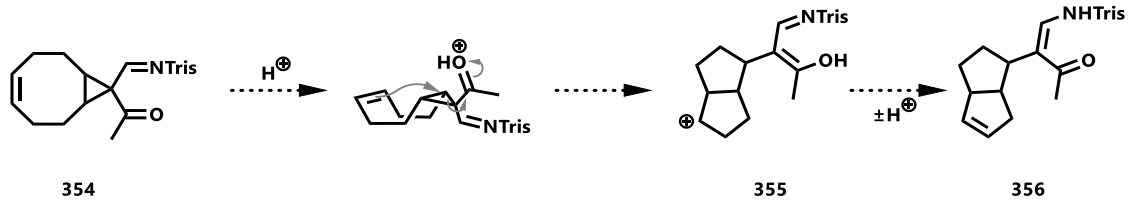
This represented an interesting transformation and generated a new stereocentre, with the products **351** and **352** having a useful enaminone handle for further functionalisation. The same reaction was carried out with 1,5-cyclooctadiene **261** using Rh_2(*S*-NTTL)$_4$ but the product was obtained in a lower yield of 33% (**Scheme 4-09**). Despite using a chiral rhodium(II) carboxylate HPLC analysis revealed the product to be a racemic mixture. The product **352** was most likely generated *via* a stepwise process involving concerted cyclopropanation to generate **354**, followed by rearrangement/elimination and relief of cyclopropane ring strain. The cyclopropane **354** is a *meso*-compound which would make control with a chiral rhodium catalyst difficult.



Scheme 4-09: Reaction using a chiral rhodium(II) catalyst resulted in a racemic product.

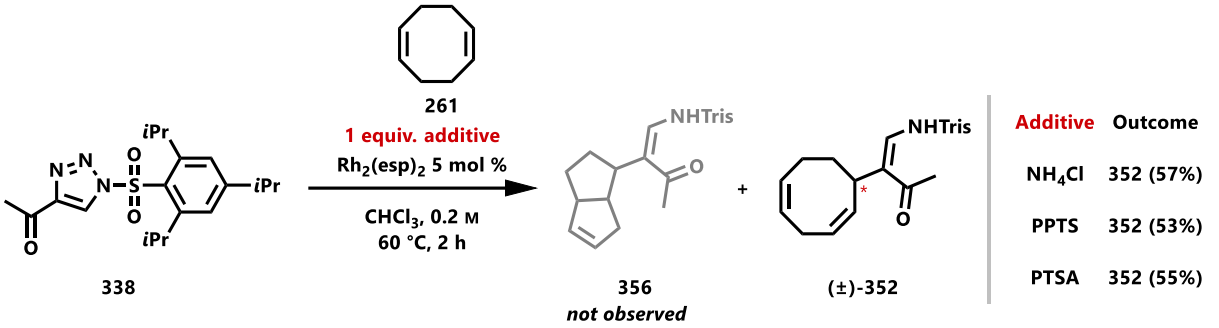
The high temperature of the reaction may have caused the elimination/rearrangement to occur spontaneously, so the reaction was carried out at reduced temperature to try and observe the intermediate cyclopropane **354**. Below 40 °C the reaction did not proceed, but at this temperature the product **352** was observed in a 28% yield by internal standard ^{1}H NMR analysis. Unfortunately, there was no trace of the intermediate cyclopropane **354**.

It was proposed that the disposition of the cyclopropane ring relative to transannular π-system may allow for a transannular bond-forming process to be promoted (**Scheme 4-10**), resulting in a [3.3.0] bicyclic system in a similar manner to that observed in the reactivity of 1-sulfonylcyclooctatriazoles (see **Section 2**).



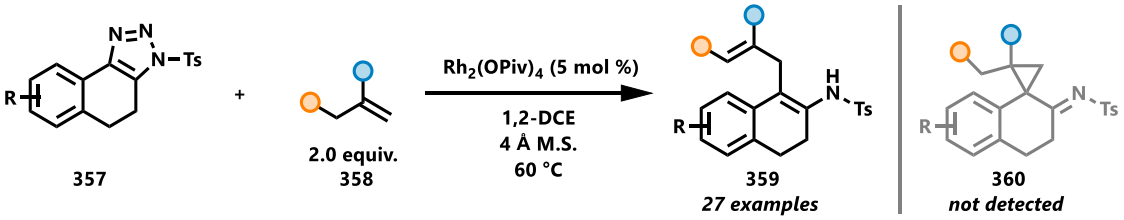
Scheme 4-10: Proposed transannular attack of alkene π-bonds, promoted by addition of weak acid

A range of acid additives were added in attempt to promote this transformation, including ammonium chloride, *p*-toluenesulfonic acid and pyridinium *p*-toluenesulfonate (**Scheme 4-11**). Unfortunately, these additives had no effect on the outcome of the reaction and there was no trace of the [3.3.0] bicycle **356**.



Scheme 4-11: Weak acid additives did not have any noticeable effect on the outcome of the reaction. 2.0 equiv. **261**. 0.20 mmol scale, sealed tube.

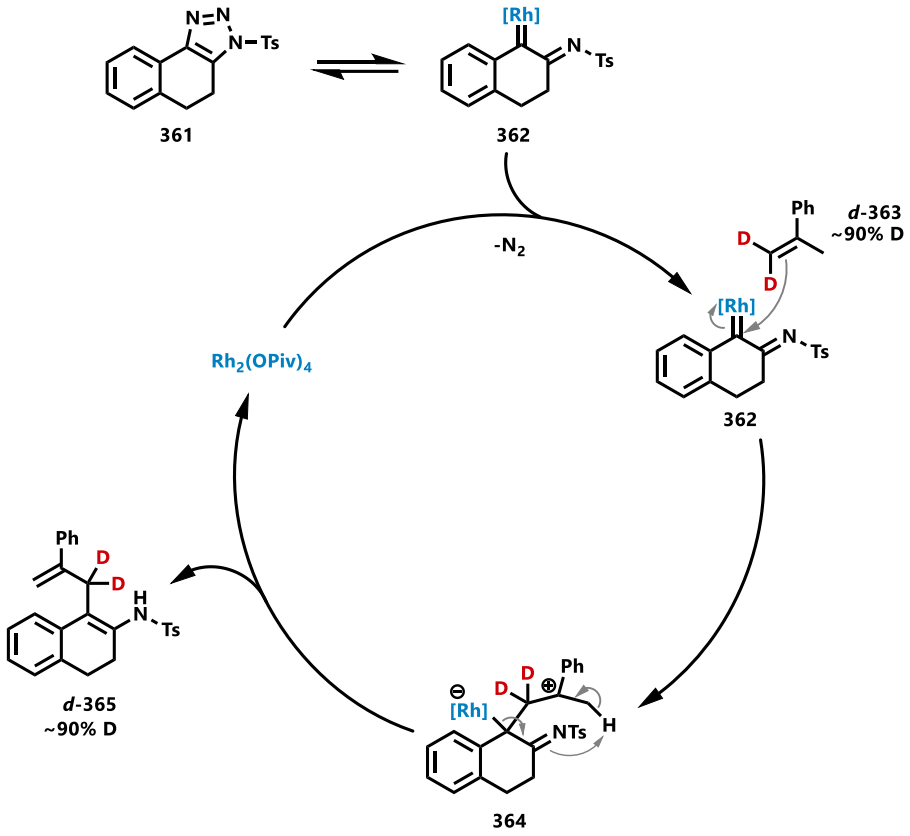
A recent report by Zhu and co-workers described a formal allylation of donor/acceptor azavinyl carbenes derived from 1-STs.[251] In this report, dihydronaphthosulfonyltriazoles **357** underwent a similar reaction with terminal alkenes catalysed by rhodium(II) (**Scheme 4-12**).



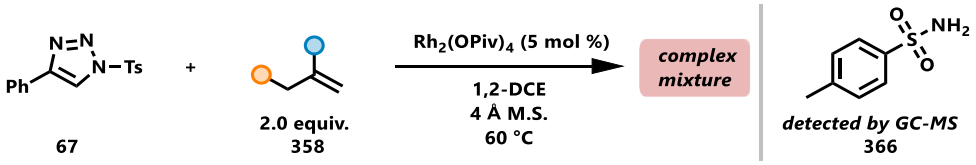
Scheme 4-12: Formal allylation of donor/acceptor azavinyl carbenes derived from fused 1-STs. 0.30 mmol scale, sealed tube, 0.1 M.[251]

Zhu and co-workers carried out a series of control experiments in order to determine the reaction mechanism. The reaction was carried out with a deuterated substrate **363**, and the product **365** was formed with no noticeable deuterium scrambling. If it proceeded *via* cyclopropanation followed by elimination, deuterium incorporation in the product **365** would be reduced. A plausible mechanism was proposed, and it is believed a similar mechanism is operative in the reaction of 4-acyl 1-ST **338** and cyclic alkenes **216** and **261**. The mechanism involved nucleophilic attack of the π-system of the alkene into the electrophilic rhodium carbene **362** which generated intermediate **364** (**Scheme 4-13a**). This charged intermediate then underwent an intramolecular proton transfer to furnish the product **365** and regenerate the rhodium catalyst. The *cis*-orientation of the C=N bond facilitated cleavage of the C(sp^3)-H bond. The need for the cyclic

triazole substrate was highlighted by the complex mixtures which were observed when acyclic 1-STs were used (**Scheme 4-13b**).

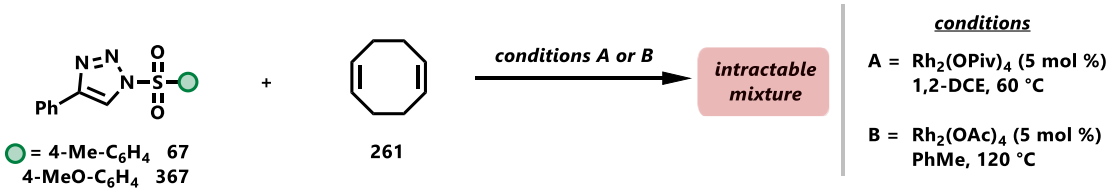


Scheme 4-13a: Proposed mechanism of the formal allylation of dihydronaphthosulfonyltriazoles.[251]



Scheme 4-13b: When non-fused 1-STs were used, complex mixtures were observed with no trace of the allylation product. 0.1 M.[251]

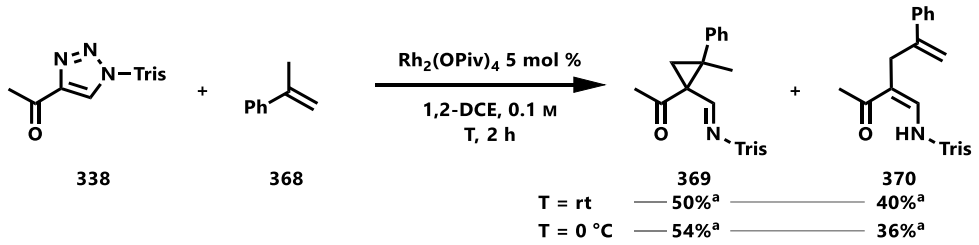
The use of acyclic triazoles **67** and **367** in the reaction with *cis*-cyclooctadiene **261** was investigated, under both the conditions described earlier (**A**) as well as the well-known cyclopropanation reaction conditions (**B**) developed by Fokin and co-workers (**Scheme 4-14**).[103] In both cases, an intractable mixture was observed.



Scheme 4-14: Reaction of **261** with triazoles without the 4-acyl substituent gave complex mixtures. 0.2 M.

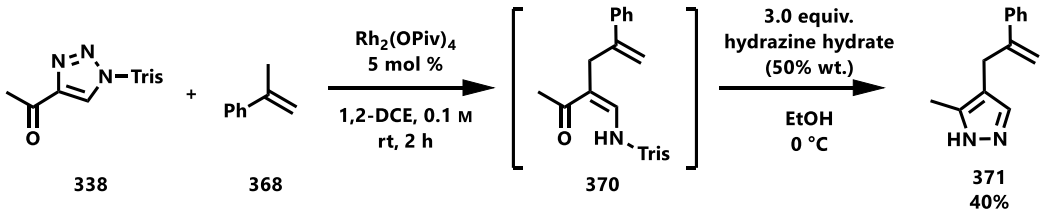
These results were encouraging because they demonstrated the need for the 4-acyl substituent in observing the desired reactivity. One of the limitations of the report by Zhu and co-workers is the need for a fused cyclic 1-ST as the substrate.[251] Using a 4-acyl substituted 1-ST could potentially overcome this limitation and allow access to a broader scope of substrates.

4-Acyl triazole **338** was reacted with α-methyl styrene **368** under the conditions developed by Zhu and co-workers in order to compare the reactivity of the 4-acyl 1-ST with the fused dihydronaphthosulfonyltriazoles (**Scheme 4-15**). Gratifyingly, the allylation product **370** was observed in a 40% yield by NMR. Unfortunately, this constituted the minor product as a 50% yield of the cyclopropanation product **369** was also observed. The reaction was repeated at 0 °C with no marked improvement on the ratio of products **369** and **370**.



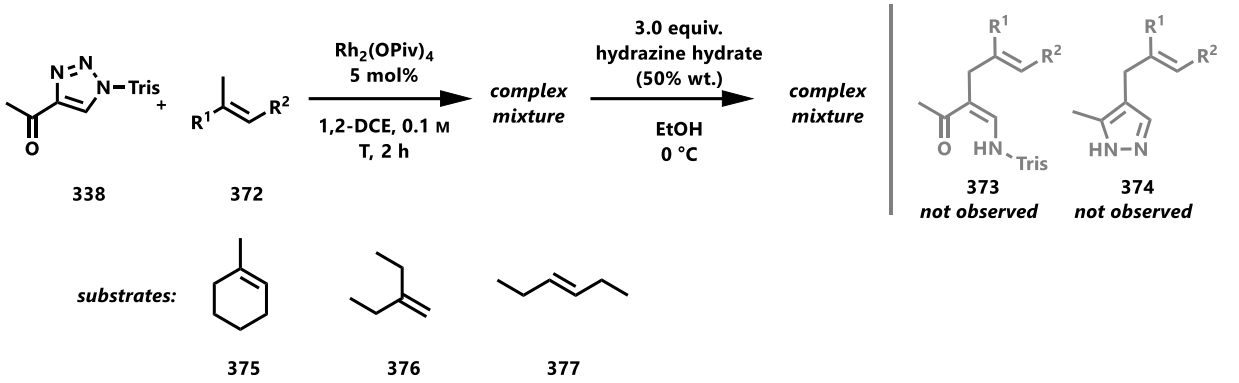
Scheme 4-15: Reaction of 4-acyl 1-ST with a-methyl styrene. [a]yield determined by ^{1}H NMR analysis of the crude reaction mixture.

Additionally, difficulties were encountered when trying to isolate the allylation product **370** by column chromatography. The enaminone functionality in **370** is a useful handle for further derivatisation, and pyrazole **371** was isolated in 40% yield by column chromatography after treatment of the crude reaction mixture with hydrazine hydrate in ethanol (**Scheme 4-16**).



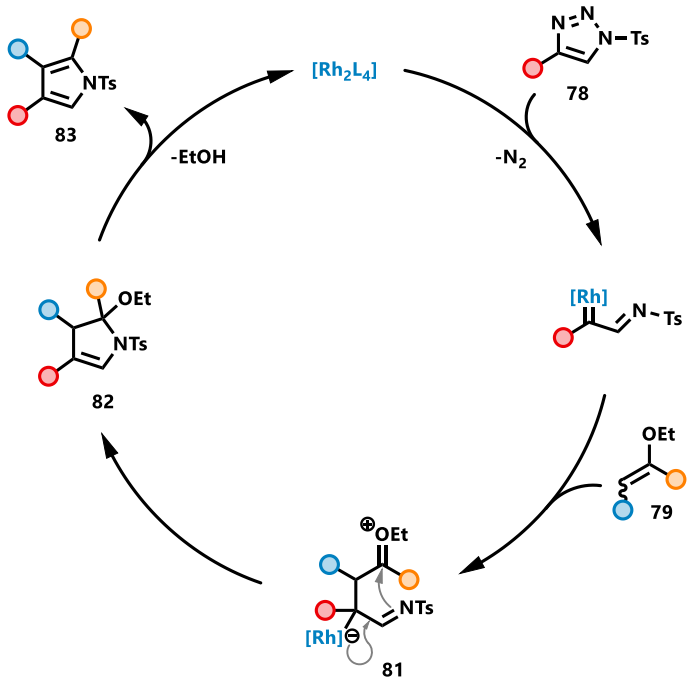
Scheme 4-16: The pyrazole **371** could be isolated by treatment of crude **370** with hydrazine hydrate.

A series of other alkenes **375**–**377** were screened under the same reaction conditions (**Scheme 4-17**). Sadly, in each case a complex crude mixture was observed even prior to the addition of hydrazine hydrate, and no identifiable downstream products from either cyclopropanation or allylation were observed.



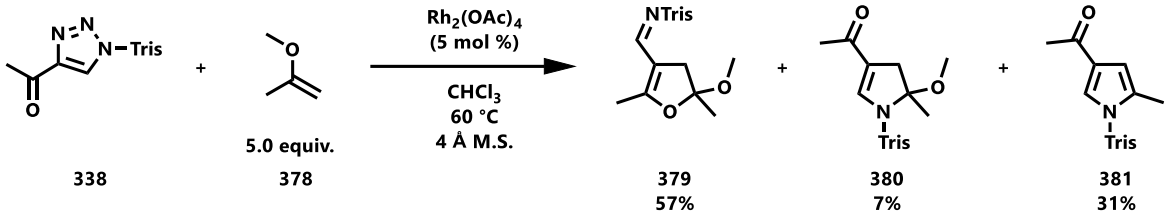
Scheme 4-17: Reaction of triazole **338** with more challenging substrates gave complex mixtures.

It was clear that the heightened reactivity of the acceptor/acceptor carbenoid generated from **338** was giving rise to selectivity issues with these more challenging substrates. Additionally, there was the issue of cyclopropanation still being the major outcome in the successful reaction with α-methyl styrene (**Scheme 4-15**). It was anticipated that pairing the electronics of the alkene substrate with the 1-ST would improve selectivity. The acceptor/acceptor carbenoid generated from **338** is very electron poor, and so an electron rich alkene such as an enol ether would make a suitable reaction partner and hopefully improve selectivity. Reactions of 4-aryl 1-STs with electron-rich alkenes such as enol ethers and silyl ketene acetals are well documented, with reports from Lee,[108] Tang,[252] and Li (see **Section 1.3.2**).[253] Rather than cyclopropanation or allylation, when enol ether substrates are used a formal [3+2] cycloaddition typically takes place to generate pyrroles **83** after elimination of ethanol (**Scheme 4-18**).



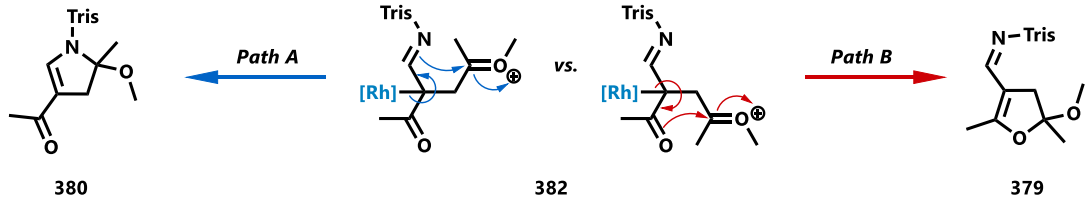
Scheme 4-18: Mechanism of pyrrole formation by rhodium(II) catalysed transannulation of 1-STs and enol ethers.[252]

2-Methoxypropene **378** was selected as electron rich alkene due to its simplicity and ready availability. Triazole **338** was treated with a catalytic amount rhodium(II) acetate and an excess of 2-methoxypropene in chloroform at 60 °C (**Scheme 4-19**). The triazole **338** was converted almost quantitatively into a mixture of three different products: a dihydropyrrole **380**, a pyrrole **381** and a dihydrofuran **379**. The pyrrole **381** and dihydropyrrole **380** were formed in 31 and 7% yield respectively, and are consistent with the findings of Lee and co-workers.[108] However, formation of dihydrofuran **379** in 57% yield was surprising and represented a change in chemoselectivity that had not previously been observed.



Scheme 4-19: Initial reaction between 1-ST **338** and 2-methoxypropene **378** gave a mixture of products. 0.30 mmol scale, sealed tube.

The unique selectivity can be explained by examination of the reaction mechanism; all three products are most likely formed through common intermediate **382** (**Scheme 4-20**). The large steric bulk afforded by the trisyl group as well as the electronegativity of the carbonyl group combine to make the *N*-sulfonyl less nucleophilic overall, therefore cyclisation through the oxygen dominated. This kind of reactivity is yet to be reported for 1-ST chemistry and is very rarely encountered in α-diazocarbonyl compounds.[254] In fact, rhodium(II)-catalysed reaction of ethyl diazoacetate and 2-methoxypropene **378** is reported to result in cyclopropanation only.[255]

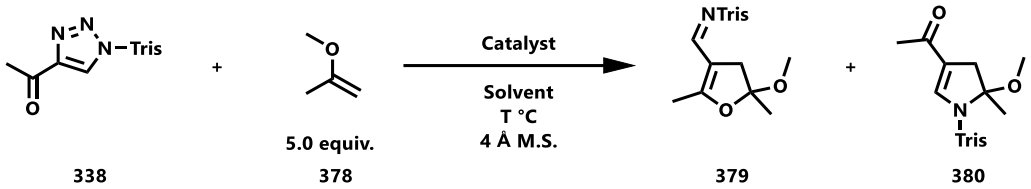


Scheme 4-20: Formation of pyrrole **381**, dihydropyrrole **380** and dihydrofuran **379** likely occur through a common intermediate.

When carrying out characterisation of these compounds, dihydrofuran **379** and dihydropyrrole **380** were both inadvertently being converted to pyrrole **381** in a matter of hours, resulting in contaminated NMR spectra. This was due to the acidity[256] of *d*-chloroform which catalysed the interconversion of these products. The acid sensitivity of these compounds was proven when dihydropyrrole **380** and dihydrofuran **379** were independently treated with 1M HCl in diethyl ether, resulting in quantitative conversion to pyrrole **381** in both cases. Therefore, alternative NMR solvents were used for subsequent studies.

4.2.2 Reaction development

The formation of dihydrofuran **379** as the major product was encouraging so a range of catalysts, solvents and temperatures were investigated to improve the selectivity for and yield of dihydrofuran **379** (**Table 4**). Since the dihydropyrrole **380** and dihydrofuran **379** were shown to be unstable to acidic conditions, protic solvents were avoided, NMR characterisation was carried out in d_6-acetone, and great care was taken to exclude moisture from the reaction. The adverse effect of using mildly acidic chloroform became immediately clear when switching to dichloromethane (Entry 2); the overall yield was increased to 81% and the dihydrofuran was formed with an approximate 9.1:1 ratio which was a large improvement over chloroform (Entry 1, 57% yield, 1.5:1 ratio). Of the rhodium(II) catalysts screened, the bulkier catalysts Rh_2(*S*-*t*PTTL)$_4$ (Entry 3, 38%) and Rh_2(TPA)$_4$ (Entry 4, 49%) gave moderate yields with no improvement in the selectivity of **379**. Bidentate Rh_2(esp)$_2$ gave an excellent overall yield of 98% (Entry 5) with an approximate 8.7:1 ratio of **379** to **380**, and Rh_2(OPiv)$_4$ gave a very similar outcome (98% yield, 8.8:1 ratio, Entry 6) and was chosen as the optimal catalyst due to cost. A screen of polar and non-polar aprotic solvents was carried out (Entries 7–12), most of which gave lower yields and selectivities than dichloromethane (Entries 7–10). When 2-methoxypropene **378** was used as the solvent, the selectivity was poor (91% yield, 2.8:1 ratio, Entry 11). 1,2-Dichloroethane gave a slightly improved selectivity over dichloromethane but the overall yield was lower (88% yield, 10:1 ratio, Entry 12). With dichloromethane being the optimal solvent, the reaction was carried out at several different temperatures. Lowering the temperature to 40 °C improved the selectivity to 13:1 without negatively effecting the overall yield (98%, Entry 13). Carrying out the reaction at room temperature gave a lower yield of 90% but did not improve selectivity (8.0:1, Entry 14). Cooling the reaction to 0 °C with an ice bath gave an excellent selectivity of 20:1 but the yield was decreased to 62% (Entry 15). Interestingly, despite the improved selectivity, the reaction appeared to generate several unidentifiable byproducts being formed which contributed to the lower yield (by ^{1}H NMR analysis). Consequently, rhodium(II) pivalate and dichloromethane at 40 °C were chosen as the optimum reaction conditions for formation of dihydrofuran **379** from 1-ST **338** and enol ether **378**. Use of basic additives into the rhodium-catalysed step did not effect the product distribution or yield.[268]



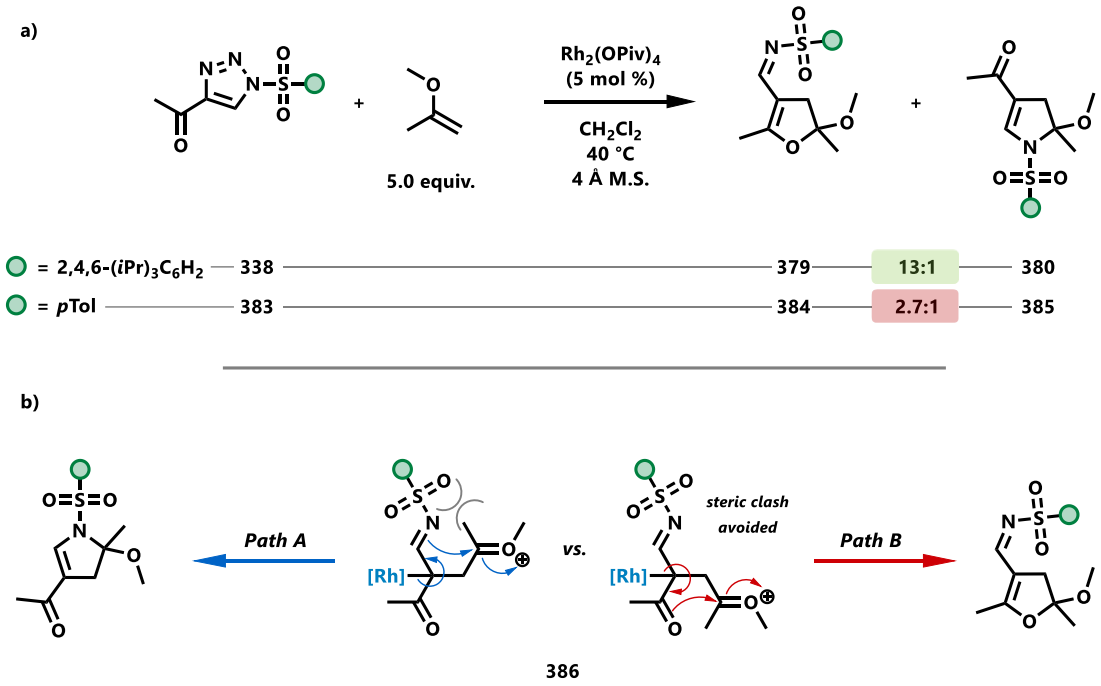
338 **378** **379** **380**

Table 4: Optimisation data for the rhodium catalysed transannulation of methyl vinyl with triazole **338**. All reactions carried out at 0.20 mmol scale.

Entry	Catalyst[a]	Solvent[b]	T/°C[c]	Total Yield[d]	Yield 379	Yield 380	Ratio
1	$Rh_2(OAc)_4$	$CHCl_3$	60	95%	57%(31%)[e]	7%	1.0:1
2	$Rh_2(OAc)_4$	CH_2Cl_2	60	81%	73%	8%	9.1:1
3	$Rh_2(S\text{-}t\text{PTTL})_4$	CH_2Cl_2	60	38%	33%	5%	6.6:1
4	$Rh_2(TPA)_4$	CH_2Cl_2	60	49%	43%	6%	7.2:1
5	$Rh_2(esp)_2$	CH_2Cl_2	60	97%	87%	10%	8.7:1
6	$Rh_2(OPiv)_4$	CH_2Cl_2	60	98%	88%	10%	8.8:1
7	$Rh_2(OPiv)_4$	cyclohexane	60	76%	59%	17%	3.5:1
8	$Rh_2(OPiv)_4$	Butanone	60	22%	19%	3%	6.3:1
9	$Rh_2(OPiv)_4$	TBME	60	19%	16%	3%	5.3:1
10	$Rh_2(OPiv)_4$	Dimethyl carbonate	60	54%	49%	5%	9.8:1
11	$Rh_2(OPiv)_4$	2-methoxypropene	60	91%	67%	24%	2.8:1
12	$Rh_2(OPiv)_4$	1,2-DCE	60	88%	80%	8%	10:1
13	$Rh_2(OPiv)_4$	CH_2Cl_2	40	**98%**	**91%**	**7%**	**13:1**
14	$Rh_2(OPiv)_4$	CH_2Cl_2	rt	90%	80%	10%	8.0:1
15	$Rh_2(OPiv)_4$	CH_2Cl_2	0	62%	59%	3%	20:1

[a] 5 mol % catalyst employed; [b] 0.02 M; [c] vial sealed with Teflon cap; [d] yields were determined by ^{1}H NMR analysis using internal standard. [e]Yield of pyrrole **381**.

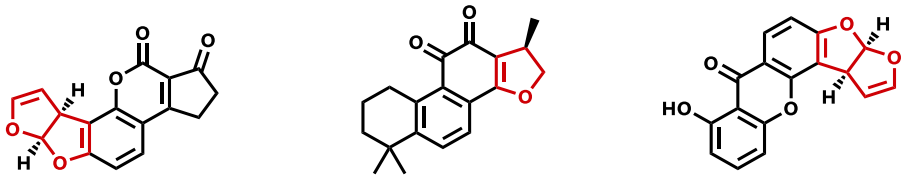
The importance of the triisopropylbenzenesulfonyl group had previously been demonstrated in terms of *Z*:*E* selectivity in π-bond functionalisation (**Scheme 4-05**). Here, it was also important in the selectivity of dihydrofuran **379** over dihydropyrrole **380**. When the same transannulation reaction with **378** under the optimised conditions was performed but using a *p*-toluenesulfonyl triazole variant **383** the crude ratio of dihydrofuran **384**:dihydropyrrole **385** was 2.7:1 (**Scheme 4-21a**), which was significantly worse than when the trisyl group was used (13:1). This selectivity enhancement can be explained by considering the intermediate **386** (**Scheme 4-21b**). The steric clash in path A is exaggerated when the sterically bulky trisyl group is used, which means that cyclisation through the nitrogen to make dihydropyrrole **380** was disfavoured relative to tosyl.



Scheme 4-21: Selectivity was significantly reduced when using the less bulky tosyl triazole **383**. 0.30 mmol scale, sealed tube.

4.2.3 Preparation of oxygen-containing heterocycles

Methods of preparing oxygen heterocycles from 1-STs are limited, primarily due to the relative nucleophilicity of the nitrogen of the sulfonylimine; nearly all transannulation reactions involving 1-STs involve cyclisation to form a nitrogen-containing heterocycle. In the reaction of 1-ST **338** and vinyl ether **378**, this constraint was lifted to favour the formation of an oxygen heterocycle instead. The dihydrofuran motif that was formed is commonly found in pharmaceutical drugs and natural products such as aflatoxin B1 **387**,[257] cryptotanshinone[258] **388** and sterigmatocystin[259] **389** (**Figure 4-02**). Furan derivatives are another important class of heterocyclic compound with important biological properties.[260] Some examples include the natural products norpinguisone **390**,[261] pyrrenocine A **391**,[262] and pukalide **392** (**Figure 4-03**).[263] The reaction between enol ethers **393** and 4-acyl substituted 1-STs **318** could also represent a viable route to furans **395** by treating the dihydrofuran intermediates **394** with reagents that would result in aromatisation (**Scheme 4-22**).



387

Aflatoxin B1
Isolated from
Aspergillus flavus

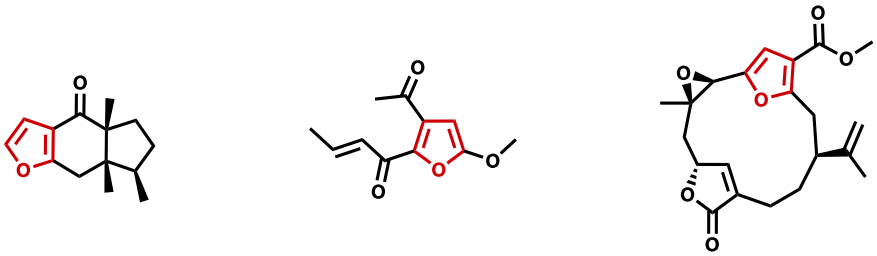
388

±-Cryptotanshinone
Isolated from
Salvia miltiorrhiza

389

Sterigmatocystin
Isolated from
Aspergillus nidulins

Figure 4-02: Several biologically active compounds feature dihydrofuran motifs.



390

Norpinguisone
Isolated from
Porella renicosa

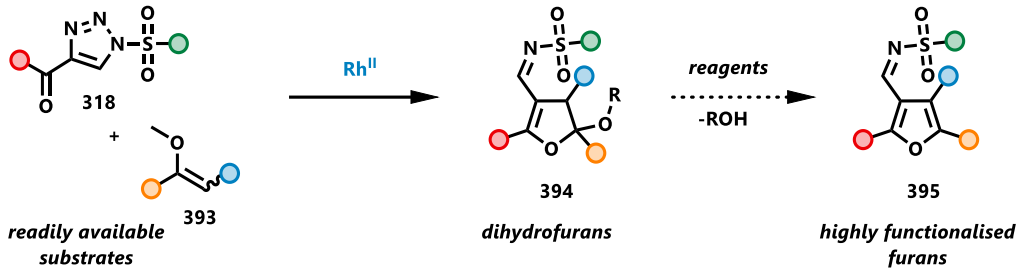
391

Pyrrenocine A
Isolated from
Aus pyrenochaeta

392

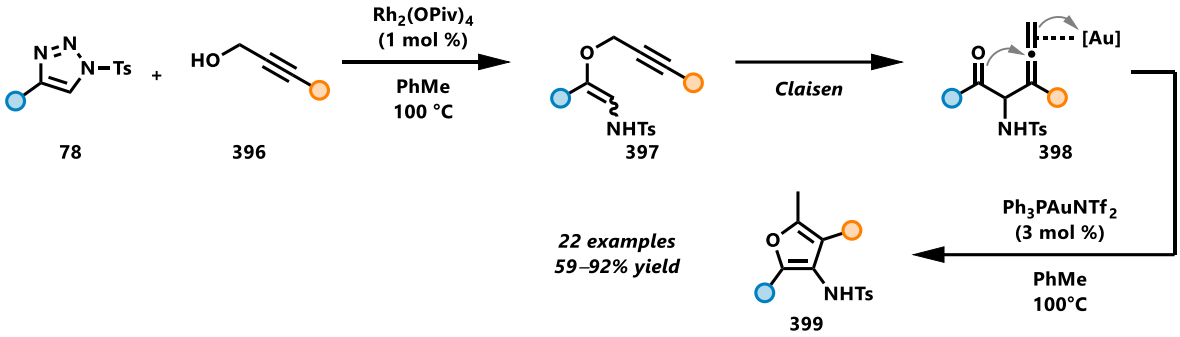
Pukalide
Isolated from
Lophogorgia alba

Figure 4-03: Furan moieties are also found in biologically active compounds.



Scheme 4-22: Rhodium(II)-catalysed reaction between 4-acyl 1-STs and enol ethers could provide a viable route to highly functionalised furans.

Although the synthesis of benzofurans from using 1-ST methodology is well documented,[113,264–266] reports of using 1-STs to prepare non-fused furans are far more scarce, with only a single example: tandem O–H insertion, propargyl-Claisen rearrangement and gold(I)-catalysed intramolecular cyclisation gave non-fused 3-azafurans **399** (**Scheme 4-23**).[267]



Scheme 4-23: Facile synthesis of 3-azafurans through tandem reaction of 1-STs with propargyl alcohols.[267]

A selection of acids, bases, Lewis acids, oxidising agents and dehydrating agents were screened in order to try and convert dihydrofuran **379** into furan **400** (**Table 5**). Dichloromethane was used as the solvent for all of the different conditions. Surprisingly, this proved to be a challenging transformation; in nearly all cases, quantitative conversion to pyrrole **381** was observed, with the exceptions being DBU (Entry 5) and basic alumina (Entry 10) which returned complex reaction mixtures. The formation of a pyrrole from dihydrofuran **379** is somewhat surprising as it was expected that certain acidic reagents may catalyse aromatisation to a furan by elimination of methanol. Addition of different Grignard and hydride reagents to the sulfonyl imine was unsuccessful.[268]

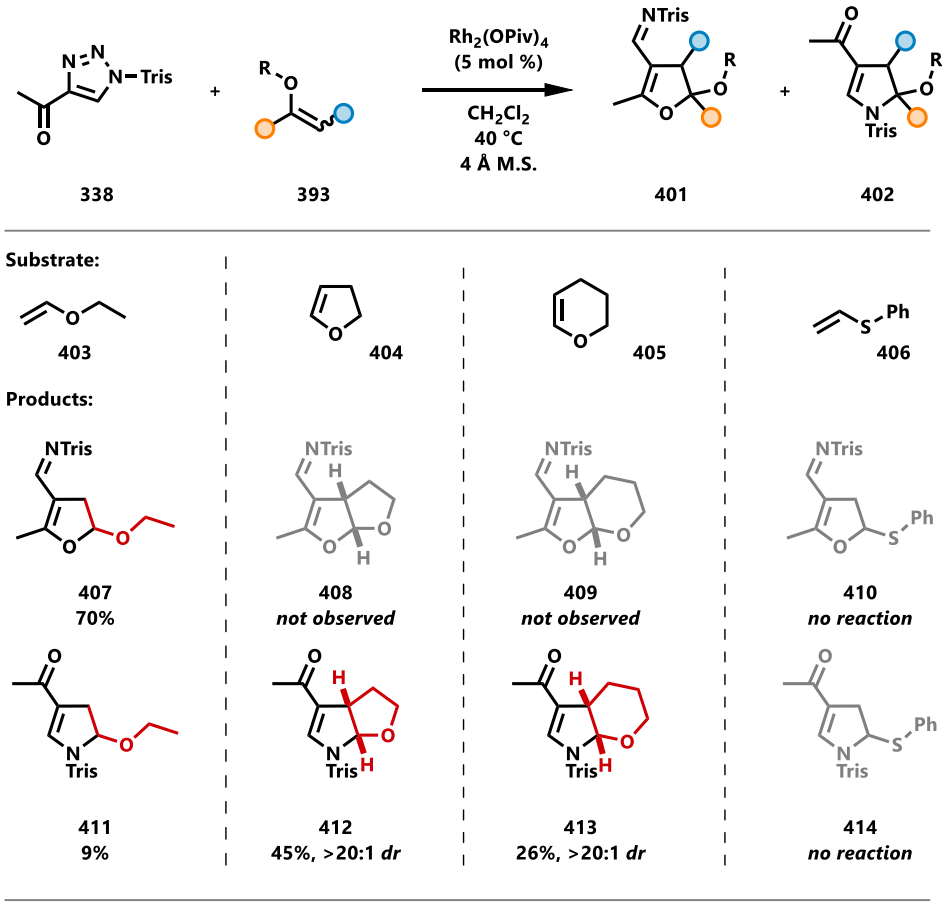
379 **400** **381**

Table 5: Reagents screened for the conversion of dihydrofuran **379** into furan **400**. All reactions carried out on 0.035 mmol scale, sealed tube.

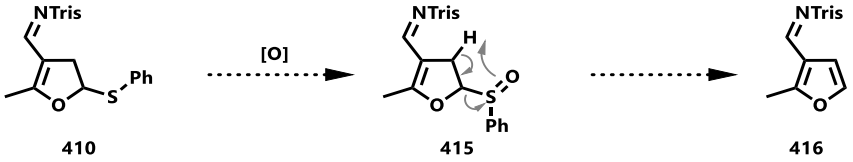
Entry	Reagent (1.5 equiv.)	Yield 400[a]	Yield 381[a]	Comment
1	HCl in dioxane	-	>98%	-
2	*p*TSA	-	>98%	-
3	TMSOTf/HMDS	-	>98%	-
4	BF_3•OEt_2	-	>98%	-
5	DBU	-	-	Complex mixture
6	DDQ	0%	0%	No reaction
7	MnO_2	0%	0%	No reaction
8	$[NO]^+[BF_4]^-$	-	>98%	-
9	$P(O)Cl_3$	-	>98%	-
10	Basic alumina (Brockmann III)	-	-	Complex mixture

[a] Determined by ^{1}H NMR analysis of crude reaction mixtures.

A brief screen of compatible substrates for the rhodium catalysed step was carried out to evaluate the generality of this process (**Scheme 4-24a**). With ethyl vinyl ether **403**, the selectivity dropped to approximately 7.8:1 and gave an overall yield of 79%. Reaction with 2,3-dihydrofuran **404** gave a 45% yield of fused dihydropyrrole **412**, but unfortunately the desired dihydrofuran **408** was not observed. Dihydrofuran **408** is an acetal and is therefore acid sensitive, which probably caused it to isomerise to the dihydropyrrole **412** readily. A similar outcome was observed for 2,3-dhydropyran **405**, albeit the yield was lower. Phenyl vinyl sulfide **406** was also used, with the aim of exploiting the sulfur in the product **410** for pericyclic *syn*-elimination (**Scheme 4-24b**). Unfortunately, this was an unreactive substrate, likely due to the nucleophilic sulfur inhibiting the rhodium catalyst.



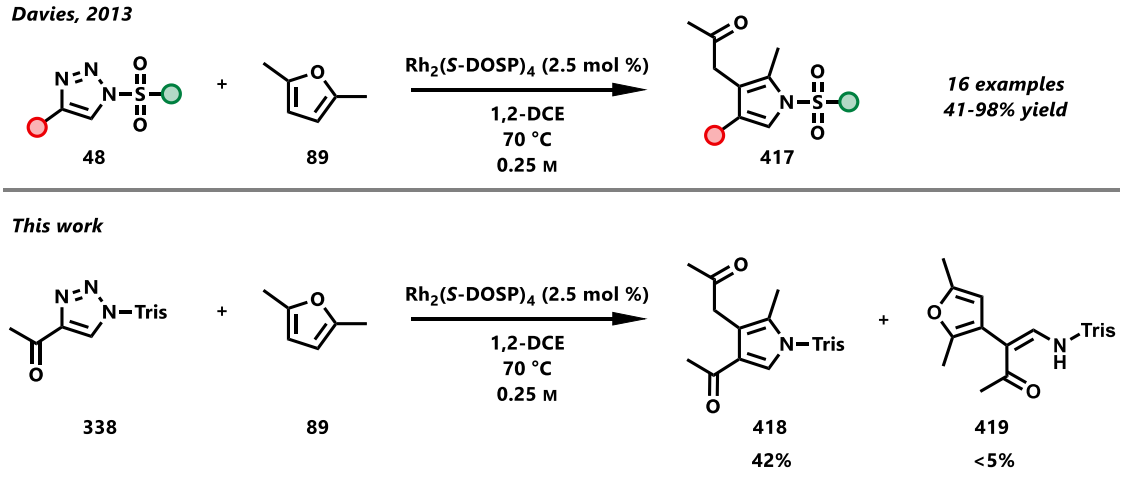
Scheme 4-24a: Rhodium(II)-catalysed reaction of 1-ST with enol ethers.



Scheme 4-24b: Potential route to furan **416** by oxidation-elimination.

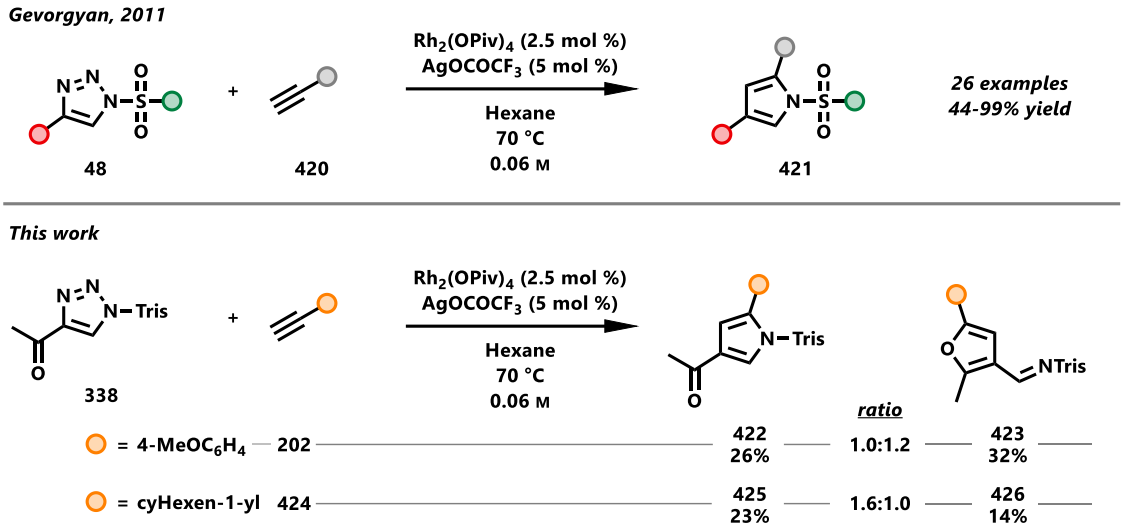
4.2.4 Controlling selectivity of other reactions

With the challenges faced in trying to aromatise dihydrofuran **379** to furan **400**, and with the somewhat poor scope of successful substrates, the use of acyl 1-STs to prepare other oxygen containing heterocycles was investigated. If the cyclisation through oxygen process is general, this would provide a useful route towards oxygen-containing heterocycles. A series of test reactions were conducted using 1-ST **338**, namely: [3+2] annulation and ring opening with furans to generate pyrroles,[109] transannulation with terminal alkynes to generate pyrroles,[269] and transannulation with nitriles to generate imidazoles.[77] These reactions were carried out using the reaction conditions from the original reports. In the case of the reaction between 4-acyl 1-ST **338** and 2,5-dimethyl furan **89**, "normal" reactivity dominated, with pyrrole **418** being isolated in 42% yield and only trace amounts of furan **419** being observed by ^{1}H NMR analysis of the crude reaction mixture (**Scheme 4-25**).



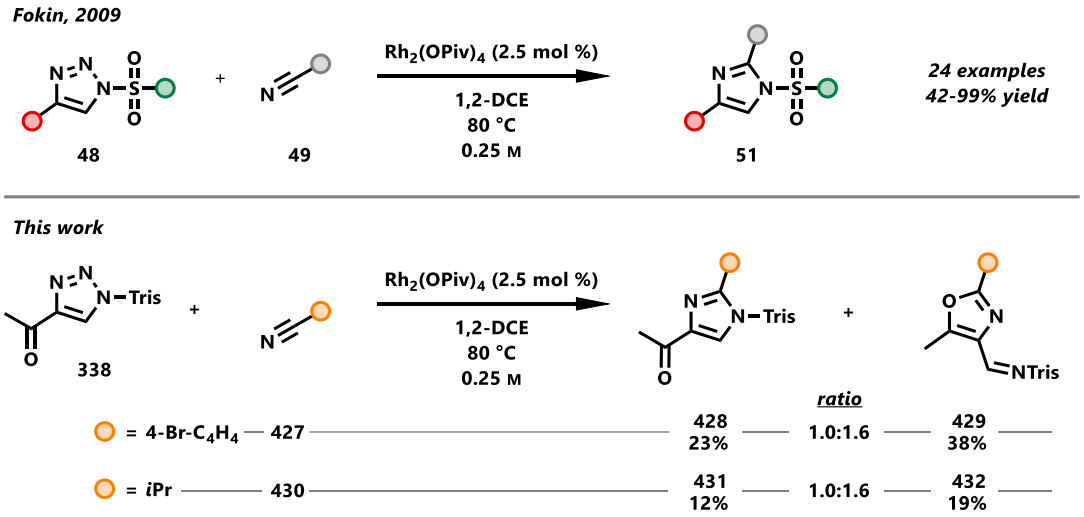
Scheme 4-25: Reaction of 1-STs with furans. 0.30 mmol scale, sealed tube.

In the reaction with terminal alkynes **202** and **424**, more encouraging outcomes were observed: with aromatic alkyne **202**, pyrrole **422** was isolated in 26% yield alongside the desired furan **423** in a moderate 32% isolated yield. Alkenyl alkyne **424** gave pyrrole **425** in a 23% yield alongside furan **426** in a 14% yield (**Scheme 4-26**). Although the ratio of products was not as good as with enol ethers, the presence of furans **423** and **426** was a promising sign.



Scheme 4-26: Transannulation of 1-STs with terminal alkynes. 0.30 mmol scale, sealed tube.

The reaction with nitriles also gave encouraging results: aromatic nitrile **427** gave imidazole **428** in 23% yield alongside the desired oxazole **429** in a 38% yield. Aliphatic nitrile **430** gave imidazole **431** in 12% yield and oxazole **432** in 19% yield (**Scheme 4-27**).



Scheme 4-27: Transannulation of 1-STs with nitriles. 0.30 mmol scale, sealed tube.

The unprecedented reactivity of 1-ST **338** with terminal alkynes and nitriles prompted further investigation. Although the nitrogen-cyclised products were still formed, and in some cases were still the major products, the presence of significant amounts of furans **423** and **426**, as well as oxazoles **429** and **432** was inspiring, especially considering that these reactions were not yet optimised for 4-acyl 1-STs.

In order to improve the selectivity towards oxazole **429**, a range of different solvents, catalysts and temperatures were screened in the reaction between 4-acyl 1-ST **338** and 4-bromobenzonitrile **427** (**Table 6**). $Rh_2(OAc)_4$ gave a moderate overall yield of 44%, with a 1.9:1.0 ratio of oxazole **429** to imidazole **428** (Entry 1). Switching to $Rh_2(OPiv)_4$ increased the overall yield to 58% but the ratio of products dropped to 1.5:1.0 (Entry 2). The effect of diluting the reaction concentration to 0.025 M was investigated but had no effect on the product distribution but the yield dropped to 40% (Entry 3). Using $Rh_2(esp)_2$ increased the overall yield to 67%, with a 44% yield of oxazole **429** (Entry 4), whereas no reaction occurred with $Rh_2(TFA)_4$ (Entry 5). Using $Rh_2(TPA)_4$ gave a lower yield (39%) and the product ratio was not improved by the bulky catalyst (Entry 6). However, using the similarly bulky $Rh_2(S\text{-}t\text{PTTL})_4$ gave an overall yield of 55% and the ratio of products improved to 2.2:1.0 (Entry 7). Next, a series of solvents were considered. Akin to the reaction with enol ethers, aromatic hydrocarbon solvents were not considered as undesirable C−H insertion to the solvent was likely to occur. Different chlorinated solvents gave similar outcomes and product distributions (Entries 7–9). Hexafluorobenzene gave an improved product ratio of 4.5:1.0, although the yield decreased to 44% (Entry 10). No reaction was observed with dimethyl carbonate even at elevated temperatures (Entry 11). Finally, cyclohexane gave a good overall yield of 63% and product ratio of 2.7:1.0 (Entry 12). Although the product distribution was not as good as hexafluorobenzene, the higher overall yield meant that the amount of oxazole was greater with cyclohexane (46%) compared to hexafluorobenzene (36%). Overall, $Rh_2(S\text{-}t\text{PTTL})_4$ catalyst with cyclohexane as solvent at 40 °C were selected as the optimal conditions.

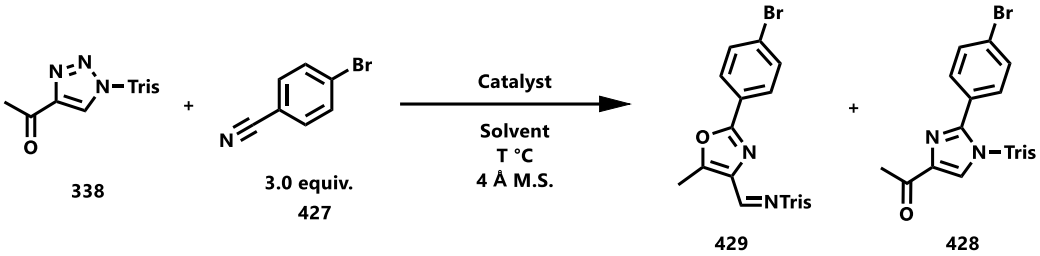


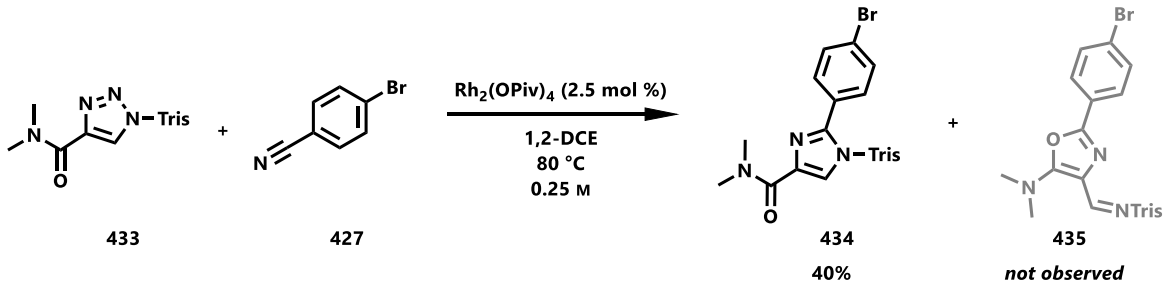
Table 6: Optimisation data for the rhodium catalysed transannulation of 4-bromobenzonitrile **427** with triazole **338**. All reactions carried out at 0.15 mmol scale.

Entry	Catalyst[a]	Solvent[b]	T/°C[c]	Total Yield[d]	Yield 429	Yield 428	Ratio
1	$Rh_2(OAc)_4$	1,2-DCE	40	44%	29%	15%	1.9:1.0
2	$Rh_2(OPiv)_4$	1,2-DCE	40	58%	35%	23%	1.5:1.0
3	$Rh_2(OPiv)_4$[e]	1,2-DCE	40	40%	24%	16%	1.5:1.0
4	$Rh_2(esp)_2$	1,2-DCE	40	67%	44%	23%	1.9:1.0
5	$Rh_2(TFA)_4$	1,2-DCE	40	n.r.	-	-	-
6	$Rh_2(TPA)_4$	1,2-DCE	40	39%	24%	15%	1.6:1.0
7	Rh_2(*S*-*t*PTTL)$_4$	1,2-DCE	40	55%	38%	17%	2.2:1.0
8	Rh_2(*S*-*t*PTTL)$_4$	$CHCl_3$	40	49%	35%	14%	2.5:1.0
9	Rh_2(*S*-*t*PTTL)$_4$	CH_2Cl_2	40	44%	32%	12%	2.7:1.0
10	Rh_2(*S*-*t*PTTL)$_4$	C_6F_6	40	44%	36%	8%	4.5:1.0
11	Rh_2(*S*-*t*PTTL)$_4$	Dimethyl carbonate	100	n.r.	-	-	-
12	Rh_2(*S*-*t*PTTL)$_4$	Cyclohexane	40	**63%**	**46%**	**17%**	**2.7:1.0**

[a] 5 mol % catalyst employed; [b] 0.05 M; [c] vial sealed with Teflon cap; [d] yields were determined by ^{1}H NMR analysis using internal standard. [e] 0.025 M **338**.

4.2.5 Controlling selectivity by tuning electronics

Although the reaction conditions had been optimised, the yield of oxazole **429** was still quite low and the product ratio was unsatisfactory. Since the unique selectivity had been attributed to a combination of the bulky trisyl group as well as the electronegativity of the carbonyl group making the intermediate sulfonyl imine nitrogen less nucleophilic, two main avenues were explored to further improve selectivity. First, the electronics of the acyl group were tuned to increase its nucleophilicity relative to the nitrogen. Amides, and to a certain extent esters, exhibit two main resonance forms through lone pair donation of nitrogen and oxygen respectively into the $\pi^*_{C=O}$ orbital. For amides in particular, this makes the oxygen nucleophilic and this type of reactivity is showcased in the formation of the Vilsmeier reagent.[270] An amide analogue of 1-ST **433** was prepared using CuAAC, and was allowed to react with 4-bromobenzonitrile **427** under the same conditions as previously (**Scheme 4-28**). Disappointingly, the furan **435** was not observed, although the imidazole **434** was isolated in 40% yield.

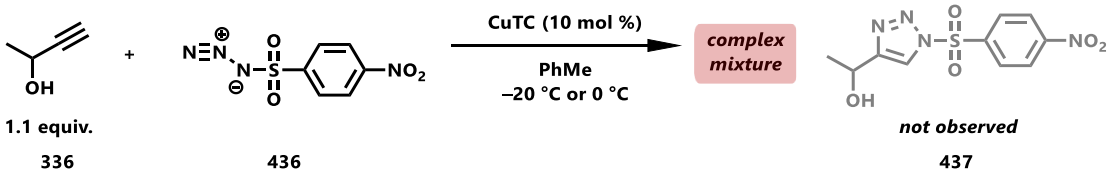


Scheme 4-28: A 4-amido 1-ST **433** was prepared and reacted with 4-bromobenzonitrile **427** under the conditions developed by Fokin and co-workers. 0.20 mmol scale, sealed tube.

A possible explanation for the complete selectivity for imidazole **434** seen with amide **433** relates to the aforementioned resonance stabilisation. The nitrogen lone pair to $\pi^*_{C=O}$ orbital interaction also makes the amide functional group overall less electron-withdrawing than a ketone carbonyl group. This means that, in terms of electronic effects, the intermediate sulfonylimino nitrogen is relatively more electron rich (and therefore more nucleophilic) in the amido 1-ST **433** than in the acyl 1-ST **338**. That this interaction completely shuts down the oxygen cyclisation route prompted an investigation into different sulfonyl groups as a way of tuning the electronic characteristics of the nitrogen.

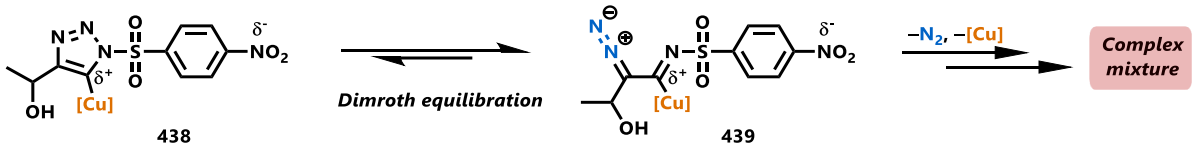
Careful tuning of the electronic character of the sulfonyl group has previously been shown by Boyer and Martin to be key in controlling selectivity in the synthesis of *Z*-α,β-unsaturated amidines.[121] In this work, using an electron-poor sulfonyl group (4-nitrobenzenesulfonyl), in combination with large rhodium(II) carboxylate ligands, resulted in exclusive *Z*-selectivity and excellent yields by supressing side reactions (see **Section 1.3.6**). A similar approach was applied to the reaction of 4-acyl 1-STs with nitriles; using an electron-poor sulfonyl group would make the intermediate sulfonylimino nitrogen more electron-poor and therefore less nucleophilic, thereby favouring cyclisation through oxygen to generate oxazoles.

3-Butyn-2-ol **336** and 4-nitrobenzenesulfonyl azide **436** were dissolved in toluene at 0 °C in the presence of 10 mol % of CuTC (**Scheme 4-29**). After 1 h, TLC analysis of the reaction mixture showed complete consumption of the azide but there were many different entities present in the reaction. Analysis by ^{1}H NMR revealed a complex mixture of products, with the product triazole not being present (identifiable by its characteristic triazole C5 proton). It seemed that if the triazole **437** or intermediate copper triazoyl species had formed, it had denitrogenated very rapidly – this was supported an audible fizz of escaping gas when the reaction vial was opened. The reaction was repeated at lower temperatures: at −20 °C the same outcome as at 0 °C was observed and no reaction occurred below this temperature.



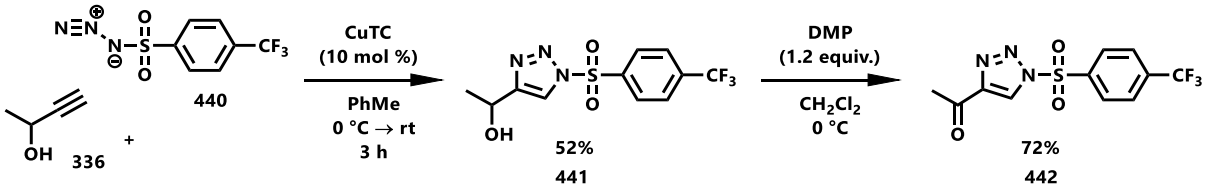
Scheme 4-29: Copper catalysed click reaction between 3-butyn-2-ol and 4-nitrobenzenesulfonyl azide.

Using electron-poor azides (such as sulfonyl azides) in CuAAC is known to result in complications (see **Section 1.4**). The Cu-triazole intermediate **438** formed during CuAAC is able to undergo Dimroth equilibration which is facilitated by the electron-withdrawing sulfonyl group.[158] In this case, the very electron withdrawing 4-nitrobenzenesulfonyl group means that the Cu-triazole intermediate **438** was extremely susceptible to Dimroth equilibration and subsequent denitrogenation, which was likely leading to the complex mixtures observed (**Scheme 4-30**).



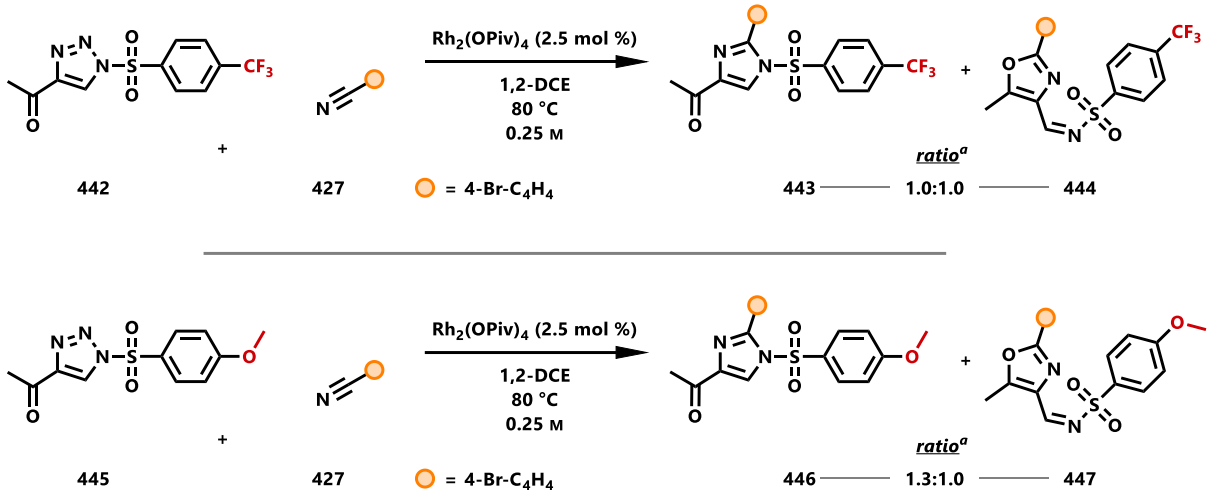
Scheme 4-30: Electron poor Cu-triazoles such as **438** are very prone to Dimroth equilibration followed by denitrogenation.

The 4-nitrobenzenesulfonyl azide is extremely electron poor compared to other sulfonyl azides such as 4-toluenensulfonyl azide, and this was exemplified in their relative rates of strain-promoted cycloaddition with cyclooctyne and BCN (see **Section 2.2.4**). With the difficulties of using 4-nitrobenzenesulfonyl azide to prepare 1-ST **437**, a slightly less electron-withdrawing 4-trifluoromethanesulfonyl azide was used instead. Ideally, it would still improve the selectivity in the reaction with nitriles but be able to overcome the difficulties in the CuAAC reaction. CuAAC between 3-butyn-2-ol **336** and azide **440**, followed by oxidation with a small excess of DMP delivered 4-acyl 1-ST **442** in 37% yield over two steps (**Scheme 4-31**).



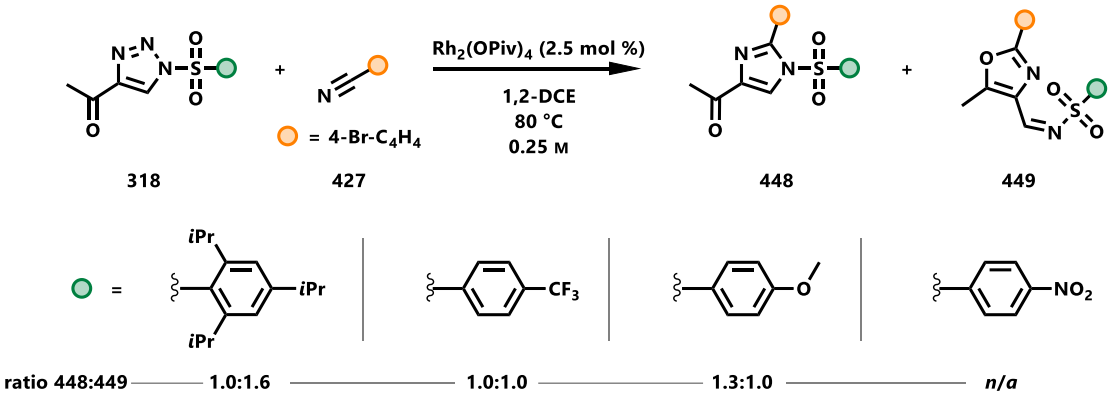
Scheme 4-31: 1-(4-Trifluoromethanesulfonyl) triazole was prepared by CuAAC followed by oxidation.

Triazole **442** was allowed to react with 4-bromobenzonitrile **427** under the denitrogenative conditions developed by Fokin and gave imidazole **443** as well as oxazole **444** in an approximate 1.0:1.0 ratio (**Scheme 4-32**). Additionally, a 1-(4-methoxybenzenesulfonyl) variant **445** was prepared, to investigate if an electron donating sulfonyl group would influence the distribution of products. Under the same denitrogenation conditions, **445** gave an approximate ratio of 1.3:1.0 in favour of imidazole **446**.



Scheme 4-32: Reaction of 4-bromobenzonitrile with electron-withdrawing and electron-donating sulfonyl triazole analogues **442** and **445**. [a]Determined by ^{1}H analysis of the crude reaction mixtures. 0.30 mmol scale, sealed tube.

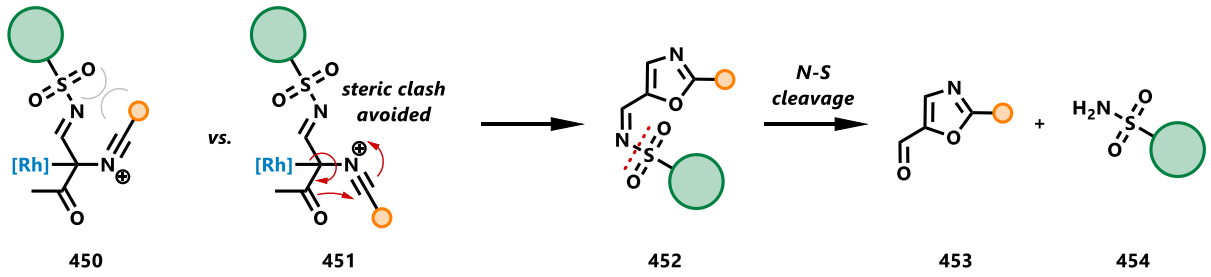
In summary, using an electron-donating sulfonyl group (4-methoxybenzenesulfonyl) slightly favoured imidazole **448**, and using an electron-poor sulfonyl group (4-trifluoromethanesulfonyl) gave less imidazole product, which was expected. However, it was clear that the effect of tuning the electronic characteristics of the system was only slight when compared to the size of the sulfonyl group – the best product distribution was obtained using the large 2,4,6-triisopropylbenzenesulfonyl group.



Scheme 4-33: Summary of sulfonyl substituent effect on the distribution of products **448** and **449**. Reactions carried out on 0.20 mmol scale. Product ratios determined by ^{1}H NMR analysis of crude reaction mixtures.

4.2.6 Controlling selectivity by enhancing sterics

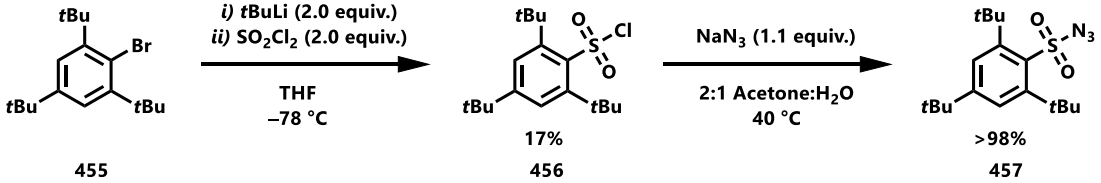
Given the importance of size of the sulfonyl group in the chemoselectivity of these transformation, it was envisaged that a larger group than triisopropylbenzenesulfonyl would lead to increased selectivity (**Scheme 4-34**).



Scheme 4-34: Concept of using bulky sulfonyl groups to direct rhodium(II)-catalysed transannulation with nitriles.

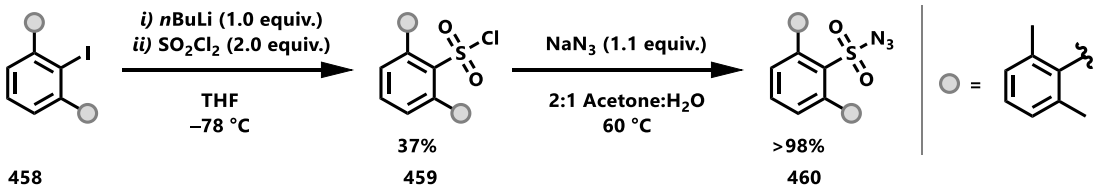
A useful and general representation of the steric bulk of a group is its A-value.[271] A-values correspond to the difference in Gibbs free energy (ΔG) of having a substituent at either the equatorial or axial position of a cyclohexane ring. Higher A-values correspond to greater steric bulk: for example, the A-value of a CH_3 group is approximately 1.7 kcal mol^{-1}, whereas Ph has an A-value of 3.0 kcal mol^{-1}. Replacing one or more of the *i*Pr groups (A-value = 2.15 kcal mol^{-1}) in the 2,4,6-triisopropylbenzenesulfonyl group with something with a larger A-value, such as *tert*butyl (A-value = 4.9 kcal mol^{-1}), would increase the steric bulk and hopefully inhibit the nucleophilicity of sulfonyl imino nitrogen in **451**, leading to a more desirable product distribution.[272]

A bulky 2,4,6-tri-*tert*-butylbenzenesulfonyl azide **457** was prepared in two steps from commercially available bromide **455** (**Scheme 4-35**). Lithium-halogen exchange of bromide **455**, followed by quenching with freshly distilled sulfuryl chloride gave sulfonyl chloride in 17% yield after column chromatography. Quantitative displacement with sodium azide afforded the sulfonyl azide **457**, although this had to be carried out at elevated temperature which is unusual for preparing sulfonyl azides,[273] presumably due to the increased steric bulk (40 °C vs ambient temperature).



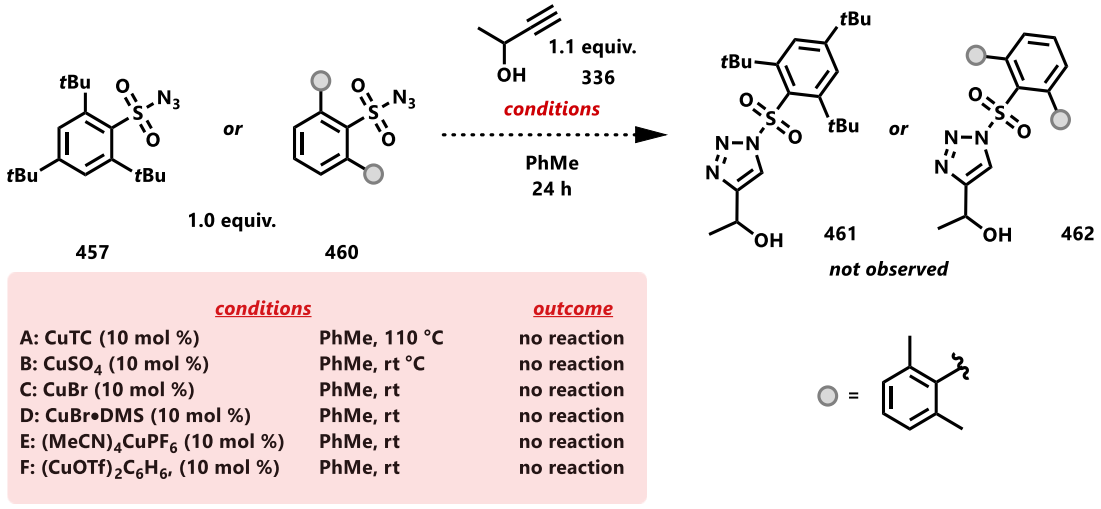
Scheme 4-35: Preparation of 2,4,6-tritertbutylbenzenesulfonyl azide.

It was also proposed that a 2,6-(diaryl)benzenesulfonyl azide **460** would give even more steric encumbrance to the sulfonyl imino nitrogen so this was prepared alongside **457**. In this case, even higher temperature required for the displacement (60 °C, **Scheme 4-36**). 2,6-(Diaryl)phenyl groups have been described as "super bulky", and are widely used to stabilise compounds of reactive main group elements.[274]



Scheme 4-36: Preparation of "super bulky" sulfonyl azide **460**.

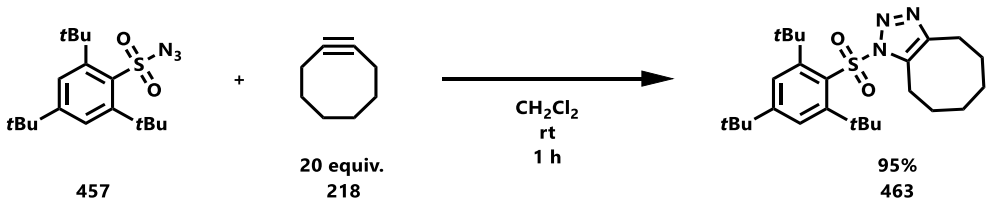
The two larger sulfonyl azides were each reacted with 3-butyn-2-ol **336** under typical CuAAC conditions for sulfonyl azides and alkynes (**Scheme 4-37**, conditions A).[158] Unfortunately, even when the temperature was increased to reflux in toluene, no reaction was observed with either of the two azides. This was not too surprising for 2,6-(diaryl)benzenesulfonyl azide **460** because it is particularly bulky and a similar azide was reported as an extremely challenging substrate, even for conventional CuAAC reaction with highly reactive copper species.[275] Some more reactive copper complexes were also screened (**Scheme 4-37**, conditions B–F), disappointingly however, there was still no reaction with either of the azides.



conditions		outcome
A: CuTC (10 mol %)	PhMe, 110 °C	no reaction
B: $CuSO_4$ (10 mol %)	PhMe, rt °C	no reaction
C: CuBr (10 mol %)	PhMe, rt	no reaction
D: CuBr•DMS (10 mol %)	PhMe, rt	no reaction
E: $(MeCN)_4CuPF_6$ (10 mol %)	PhMe, rt	no reaction
F: $(CuOTf)_2C_6H_6$, (10 mol %)	PhMe, rt	no reaction

Scheme 4-37: Attempted CuAAC between bulky sulfonyl azides and 3-butyn-2-ol. Reactions carried out on 0.10 mmol scale.

With an interest in the strain-promoted alkyne azide cycloaddition between sulfonyl azides and cyclic alkynes (see **Section 2**), azide **457** was treated with an excess of cyclooctyne in dichloromethane at room temperature (**Scheme 4-38**). Gratifyingly, triazole **463** was isolated in near quantitative yield after column chromatography.

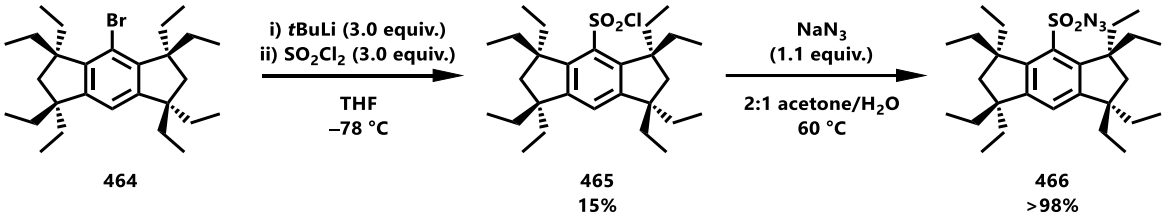


Scheme 4-38: Successful strain-promoted cycloaddition between cyclooctyne **218** and bulky sulfonyl azide **457**.

That the bulky azide **457** reacted with cyclooctyne at ambient temperatures is testament to the "explosive" reactivity of cyclic alkynes.[166] These sulfonyl azides **457**, **460** are significantly more sterically hindered when compared to 2,4,6-triisopropylbenzenesulfonyl azide, which was by

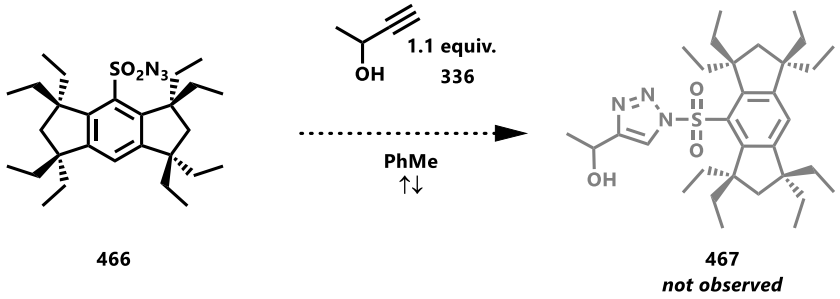
design to try and shut down the undesired *N*-cyclisation. Although there are sulfonyl azides that have intermediate steric bulk, these would be more challenging to prepare.

Another set of compounds that have been demonstrated to have significant steric bulk are the Eind ligand.[276] This ligand was recently developed for the stabilisation and isolation of main group element compounds.[276] The carbocyclic aromatic substituents are exceptionally rigid, projecting the ethyl groups outwards.[276] It was hoped that an Eind-sulfonyl azide **466** would provide the necessary steric bulk without hindering the CuAAC reaction. The corresponding sulfonyl azide **466** was prepared in two steps from the commercially available bromide **464**, employing a similar strategy to preparation of the other bulky azides (**Scheme 4-39**).



Scheme 4-39: Preparation of "Eind-SO_2N_3"

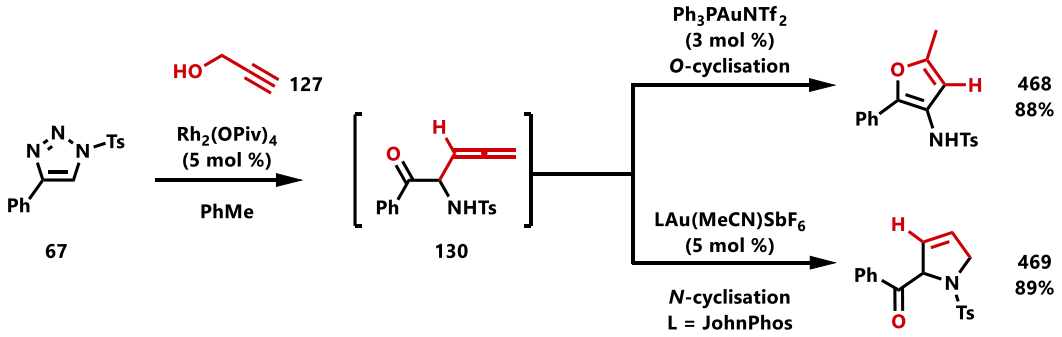
Eind-SO_2N_3 **466** was added to a solution of 3-butyn-2-ol **336** and CuTC catalyst in PhMe (**Scheme 4-40**). Unfortunately, no reaction occurred at room temperature. The reaction temperature was raised to 110 °C, but once again there was no reaction taking place, similar to the other bulky sulfonyl azides. These difficulties in carrying out CuAAC with sterically hindered sulfonyl azides were also encountered in the preparation of polymer-supported 1-STs (**Section 3**).



Scheme 4-40: Attempted CuAAC reaction using Eind-SO_2N_3.

4.2.7 Controlling selectivity by using additives

The selectivity in the reaction between 4-acyl 1-STs and nitriles proved to be difficult to control. The influence of the stereoelectronics was investigated without noticeable improvement in the selectivity or yield. Another way to control selectivity is by use of additives to coordinate functional groups in a certain way. This strategy has been employed in the rhodium(II)-catalysed reaction between 1-ST **67** and propargyl alcohol **127** (**Scheme 4-41**).[267] O–H bond insertion followed by Claisen rearrangement generated the key intermediate allene **130**. When $Ph_3PAuNTf_2$ was added, a 3-aminofuran **468** was formed by cyclisation through oxygen. This was in direct contrast to the dihydropyrrole **469** product that arose from cyclisation through nitrogen when a different gold additive was used (JohnPhosAu(MeCN)SbF_6).[277] Although the exact reason for the different gold additives giving different products was not clear, gold-catalysed nucleophilic additions to allenes are known to be sensitive to the exact nature of both substrate and catalyst.[278]



Scheme 4-41: Addition of different gold additives resulted in different products.[267]

Inspired by this report, a range of different gold additives were screened for their effect on the reaction outcome (**Table 7**). Additionally, a selection of silver additives were screened because silver is also known to activate triple bonds.[279] Of the silver additives that were screened, there was no major impact on either the yield nor distribution of products (Entries 2–5). A similar outcome was observed for Ph_3PAuCl and IMesAuCl (Entries 6 and 7): both gave an overall yield of 55% and a product distribution of 2.4:1.0 and 2.2:1.0. However, when $Ph_3PAuNTf_2$ was used, the overall yield was 40% but the selectivity was >99:1 in favour of the oxazole **429** (Entry 8).

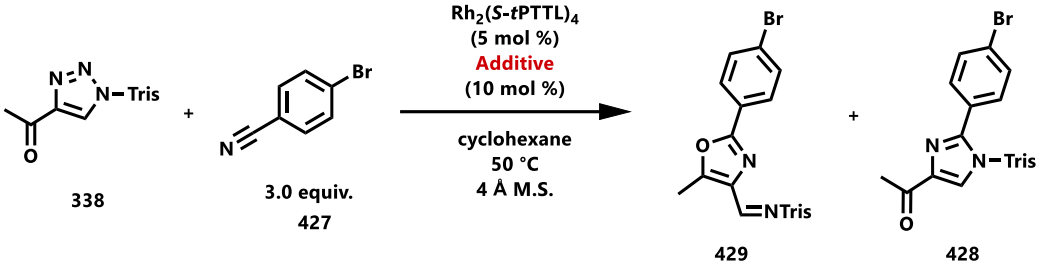
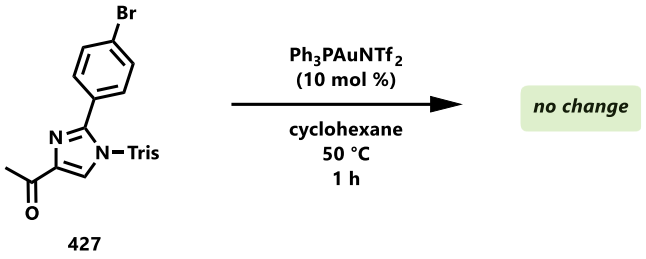


Table 7: Optimisation data for the rhodium catalysed transannulation of 4-bromobenzonitrile **427** with triazole **338**. All reactions carried out at 0.15 mmol scale, 0.05 M, vial sealed with Teflon cap.

Entry	Additive[a]	Total Yield[b]	Yield 429	Yield 428	Ratio
1	none	63%	46%	17%	2.7:1.0
2	$AgBF_4$	47%	35%	12%	2.9:1.0
3	$AgSbF_6$	40%	29%	11%	2.6:1.0
4	AgOTf	55%	40%	15%	2.7:1.0
5	AgTFA	44%	31%	13%	2.4:1.0
6	Ph_3PAuCl	55%	39%	16%	2.4:1.0
7	IMesAuCl	55%	31%	14%	2.2:1.0
8	$Ph_3PAuNTf_2$	40%	40%	<1%	>99:1.0

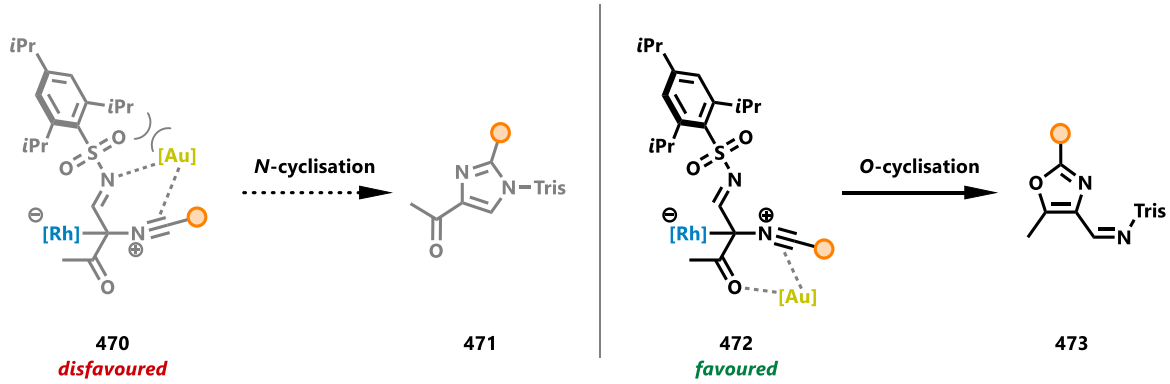
[a] 10 mol % additive employed; [b] yields were determined by ^{1}H NMR analysis using internal standard.

In order to verify that the gold additive was not selectively degrading the imidazole product **428**, a control experiment was carried out: imidazole **428** was dissolved in cyclohexane and $Ph_3PAuNTf_2$ was added (**Scheme 4-42**). The mixture was heated for 1 h and the amount of imidazole **428** in the reaction remained the same by ^{1}H NMR analysis of the reaction mixture using internal standard.



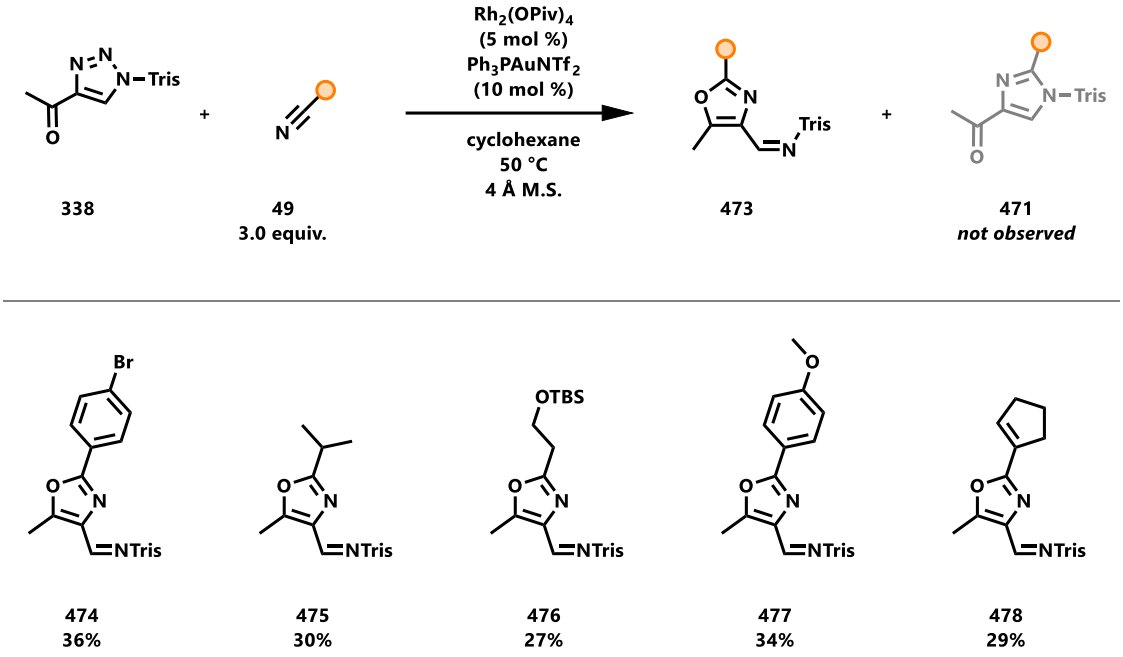
Scheme 4-42: The imidazole **428** was not being selectively destroyed by the gold additive.

This same gold catalyst was employed by Miura and co-workers to promote oxygen cyclisation in the preparation of 3-azafuran **468** (**Scheme 4-41**).[277] In the reaction between 1-ST **338** and nitrile **427**, the selectivity enhancement was proposed to arise from simultaneous coordination of the gold complex to the oxygen and C≡N triple bond (**Scheme 4-43**). This locked the intermediate into a conformation **472** which promoted oxygen cyclisation to oxazole **473**. The lack of *N*-cyclisation was once again attributed to the size of the trisyl group making coordination of the *N*-sulfonyl group to the gold complex disfavoured.



Scheme 4-43: The role of $Ph_3PAuNTf_2$ in enhancing selectivity.

With a method to selectively prepare oxazole **473** over the imidazole **471**, a range of different nitriles were subjected to the optimised reaction conditions (**Scheme 4-44**). The compatible substrates ranged from electron-poor aromatic, electron-rich aromatic, aliphatic and alkenyl nitriles with a similar yield in each case.



Scheme 4-44: Versatility of nitriles in the rhodium(II)-catalysed transannulation with 1-ST **338**. 0.30 mmol scale, 0.05 M, vial sealed with Teflon cap.

4.3 Summary

The reactivity of acceptor/acceptor carbenoids generated from 4-acyl substituted 1-STs has been investigated. Using a large sulfonyl group allowed for complete (*Z*)-alkene selectivity in the insertion into aromatic C(sp^2)–H bonds. Functionalisation of polycyclic aromatic systems using this methodology was investigated but the regioselectivity was difficult to control. Functionalisation of alkene π-bonds using the 4-acyl 1-STs was also investigated and similar problems with regioselectivity were encountered. When electron-rich alkenes such as enol ethers were used, an interesting change in chemoselectivity was observed which allowed access to dihydrofurans by cyclisation through the acyl group instead of the intermediate sulfonyl imino nitrogen. The switch in chemoselectivity was explained by the large sulfonyl group adding steric protection to the intermediate sulfonyl imino nitrogen.

The change in chemoselectivity was also observed in the transannulation reaction with alkynes to give furans, and nitriles to give oxazoles. Although the yield was disappointingly low in each case, the change in chemoselectivity represented by these examples showed the potential for this methodology. The low yields are the result of complex reaction profiles likely arising from the high reactivity of the 4-acyl 1-STs. Further investigation is required to improve the yield and expand the compatible substrates so that more oxygen heterocycles can be accessed.

5 Modular Synthesis of Highly Functionalised Pyrroles

5.1 Background and Aims

5.1.1 Pyrroles as important targets

Pyrroles are ubiquitous five-membered nitrogen heterocycles that display a diverse range of valuable properties, which means they are core components in a wide variety of natural products,[280–282] pharmaceutical drugs[283,284] and functional materials (**Figure 5-01**).[285–287]

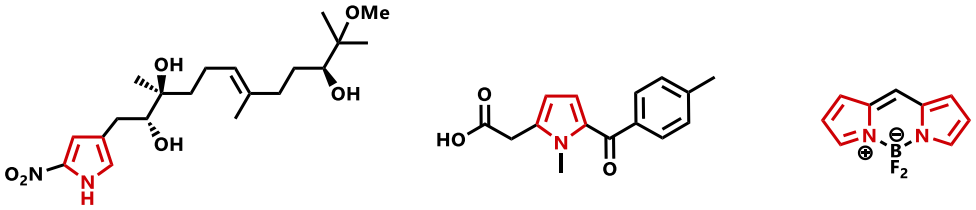
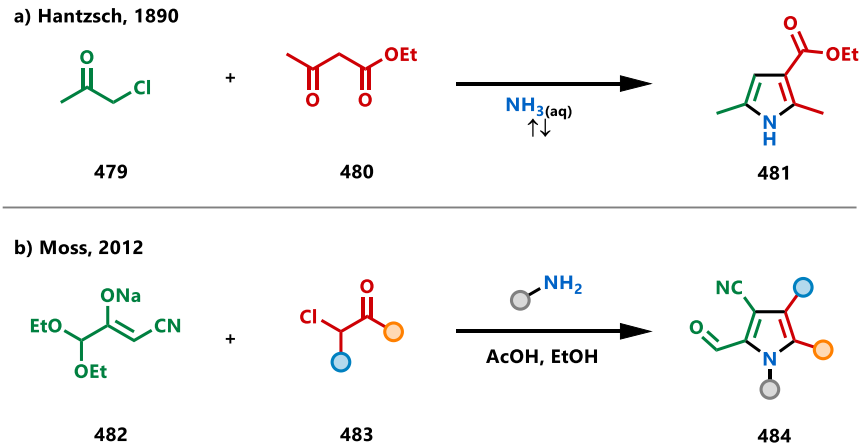


Figure 5-01: Pyrroles are an important chemical scaffold.

As a result of their broad functionality, pyrroles have been the subject of intense research interest spanning the history of organic chemistry.[288–292] For example, the reaction between chloroacetone **479** and ethyl acetoacetate **480** in concentrated ammonia under reflux to generate pyrrole **481** was first published by Hantzsch in 1890 (**Scheme 5-01a**).[291] The Hantzsch synthesis is still used today and has been adapted to preparing specific pyrrole subclasses that are difficult to reach by other means, for example pyrroles containing an aldehyde substituent at the 2-position (**Scheme 5-01b**).[293]



Scheme 5-01: Hantzsch pyrrole synthesis.[291,293]

An important sub-class of pyrroles are those with 3-aza substitution, with examples including DNA minor groove binders netropsin **485** and distamycin A **486** as well as natural products such as geranylpyrrol **487** and endostemonine D **488** (**Figure 5-02**).[294–297]

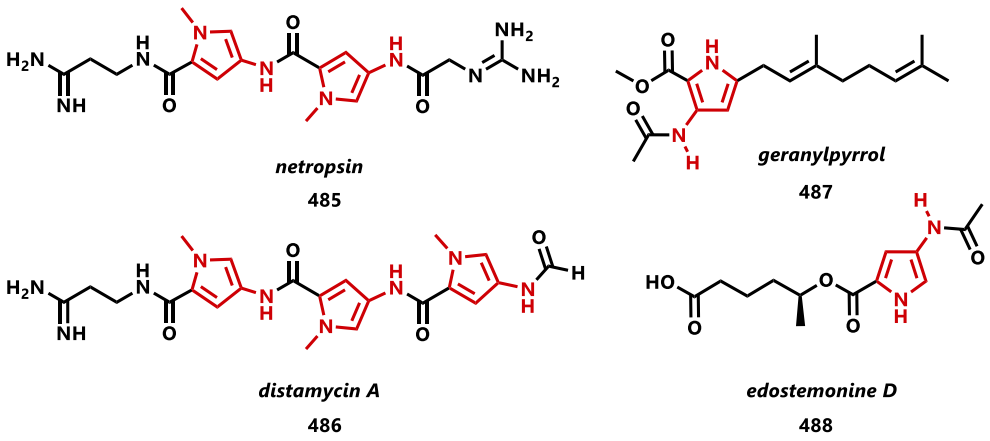
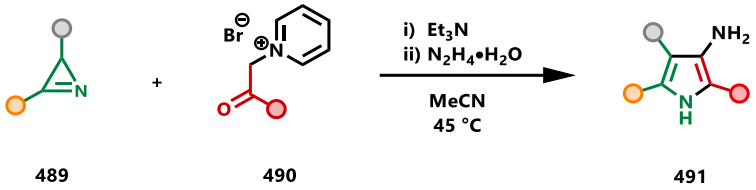


Figure 5-02: Selected biologically active 3-azapyrroles.

Despite the wealth of research on pyrrole synthesis, there are relatively few efficient preparative methods for the synthesis of functionalised 3-azapyrroles as the 3-aza substituent is difficult to accommodate using existing methods.[298–300] A recent report involves reaction between 2*H*-azirines **489** and pyridinium salts **490** in the presence of triethylamine, followed by addition of an excess of hydrazine hydrate to furnish functionalised 3-azapyrroles **491** (**Scheme 5-02**).[301]

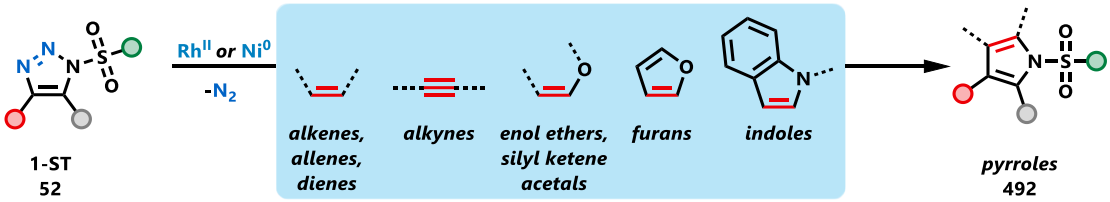


Scheme 5-02: Preparation of 3-azapyrroles by the reaction of pyridinium ylides with 2*H*-azirines.[301]

Ideally, new synthetic methodologies should be simple to carry out, begin from cheap and readily available starting materials, have wide functional group tolerance, as well as have a high atom efficiency.

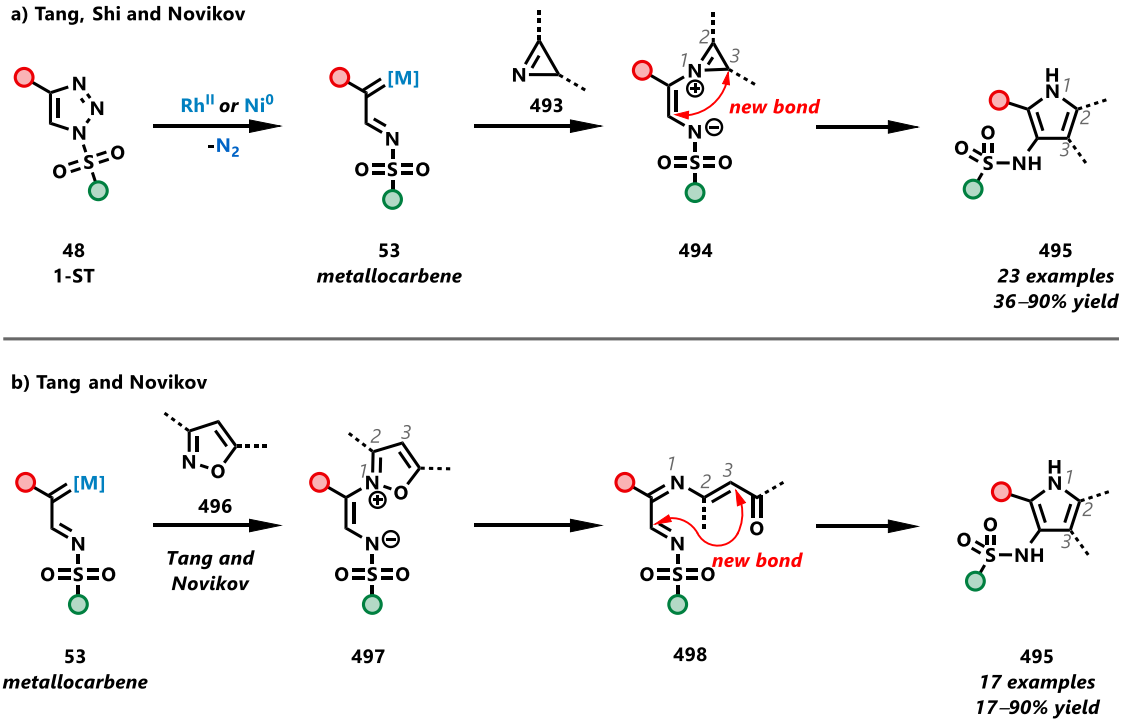
5.1.2 Existing approaches to 3-azapyrroles using 1-STs

The ready availability of sulfonyl azides and alkynes paired with the versatile reactivity of 1-STs means that many different approaches to preparing pyrroles have been developed across a wide variety of substrates including, but not limited to, alkenes,[92,249,250,302–306] alkynes,[75,110,307] enol ethers,[108,252,253,308–312] furans[109] and indoles[313–316] (**Scheme 5-03**).



Scheme 5-03: Existing approaches to pyrrole synthesis using 1-STs.

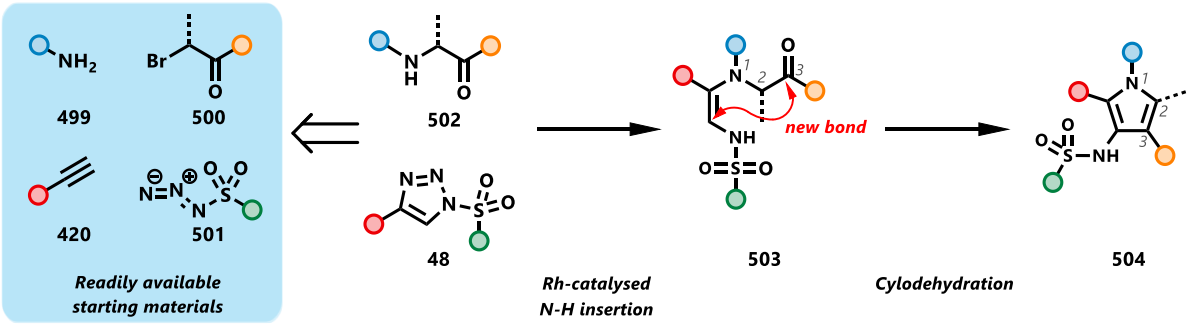
However, in the vast majority of cases, the mechanism necessitates that the nitrogen atom remaining after metal-catalysed denitrogenation of the 1-ST **52** is the nitrogen that forms the heteroatom component of the resulting heterocycle **492**. However, with certain nitrogen-containing substrates, it is possible for the triazole nitrogen to become a 3-aza substituent of the pyrrole (**Scheme 5-04**).



Scheme 5-04: Examples of 3-azapyrrole synthesis from 1-STs.[317–321]

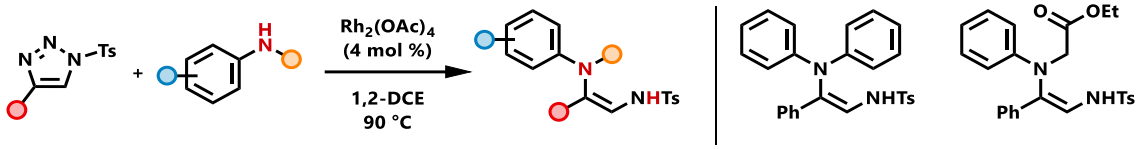
In the reaction with 2*H*-azirines **493**, 1-STs **48** underwent denitrogenation to generate an azavinyl carbene **53** (**Scheme 5-04a**).[317–320] The electron-deficient carbene was then attacked by the nitrogen lone pair of azirines **493** to generate the intermediate zwitterion **494**. Ring-expansion followed by aromatisation gave 3-azapyrroles **495** in good yield. Similarly, the nitrogen lone pair of isoxazoles **496** reacted with the electron deficient metallocarbene **53** to generate zwitterionic intermediate **497** (**Scheme 5-04b**).[321] Ring opening of the isoxazole generated 1,4-diazahexatriene intermediate **498** which was observed by NMR.[322] Cyclisation of the intermediate **498** resulted in 3-azapyrroles **495**. These reactions are unusual because the azavinylcarbene **53** behaved as a 2*C* synthon as opposed to a 1,3-ylidic synthon which is more commonly encountered in heterocycle synthesis using 1-STs.

The aim of this project was to develop a complementary approach to 3-azapyrrole synthesis from readily available starting materials. The α-aminoketones **502** were recognised as being the hydrated equivalents of 2*H*-azirines **493** and could easily be prepared by S_N2 reaction between commercially available anilines **499** and α-bromoketones **500** (**Scheme 5-05**). N–H bond insertion of 1-STs **48** into the α-aminoketones **502** would result in 1,2-diaminoalkenes **503**, which could undergo cyclodehydration to generate 3-azapyrroles **504** (**Scheme 5-05**). By careful choice of accessible starting materials, the substitution pattern of 3-azapyrroles **504** would be fully customisable maximising the range of value-added products that could be accessed.



Scheme 5-05: Proposed synthesis of 3-azapyrroles by N–H bond insertion and cyclodehydration from readily available starting materials.

This method would build upon existing work by Shang and co-workers in the area of N–H insertion of 1-STs into α-aminoketones (**Scheme 5-06**).[117] It was reported that the 1-STs **78** underwent N–H bond insertion with *N*-aryl amines **505** catalysed by $Rh_2(OAc)_4$ to afford a selection of substituted enamines **506** (**Scheme 5-06**).[117]



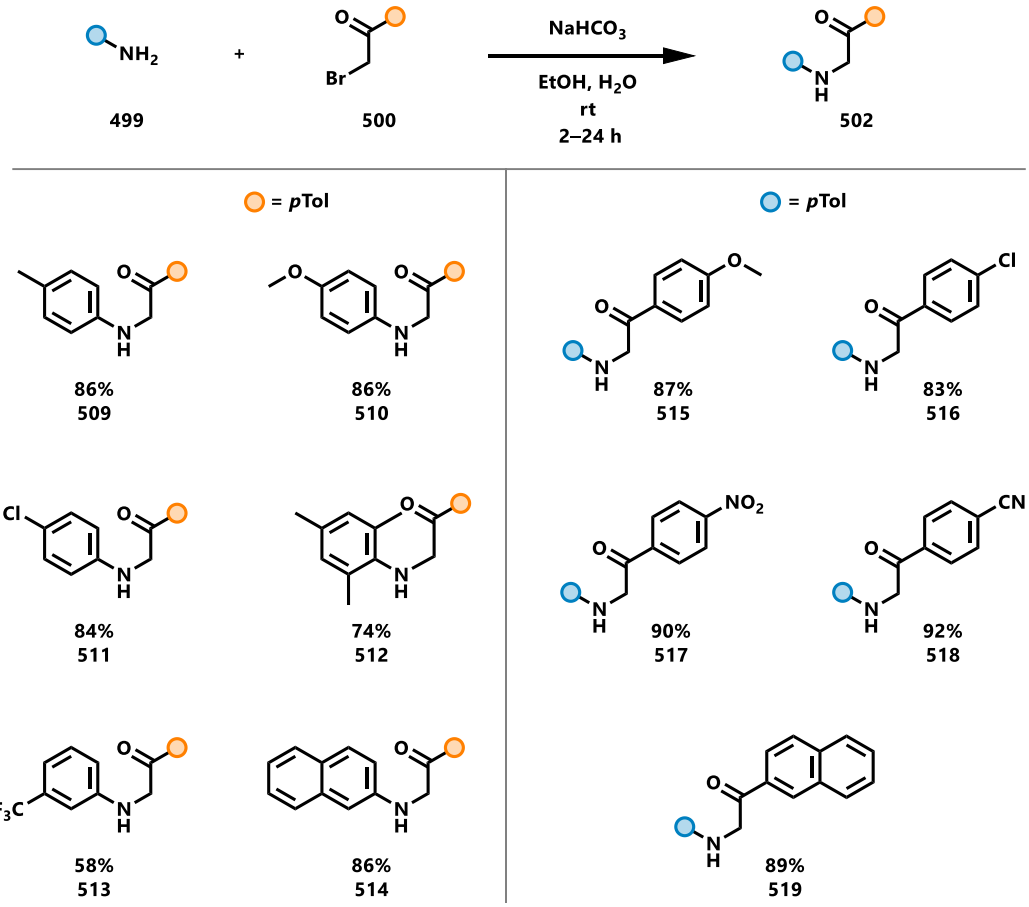
78 **505** **506** **507** 85% **508** 83%

Scheme 5-06: Synthesis of substituted enamines by rhodium-catalysed N–H insertion.[117]

5.2 Results

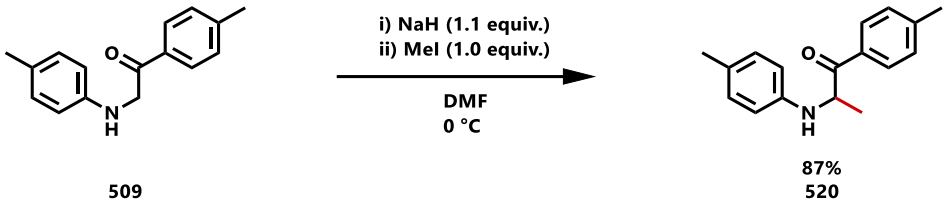
5.2.1 Synthesis of substrates

A library of α-aminoketones **502** was readily prepared from commercially available α-bromoketones **500** and anilines **499**. Simply mixing equimolar amounts of each in the presence of sodium hydrogen carbonate afforded α-aminoketones **502** in excellent yield, which were easily purified by recrystallisation (**Scheme 5-07**).



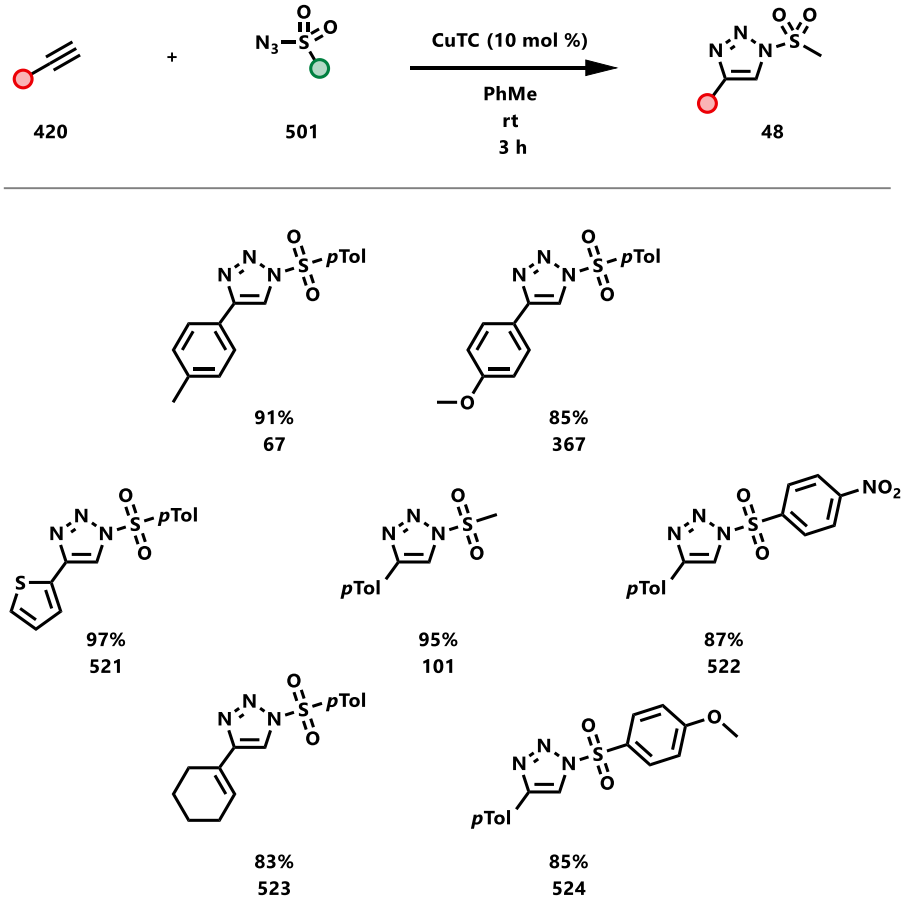
Scheme 5-07: Preparation of α-aminoketones.

The acidity of the α-position of the ketones **500** could be used to introduce additional substitution. For example, α-aminoketone **509** was treated with sodium hydride, and the resulting enolate quenched by methyl iodide to afford methyl substituted α-aminoketone **520** in excellent yield (**Scheme 5-08**).



Scheme 5-08: Additional substitution was introduced by simple alkylation.

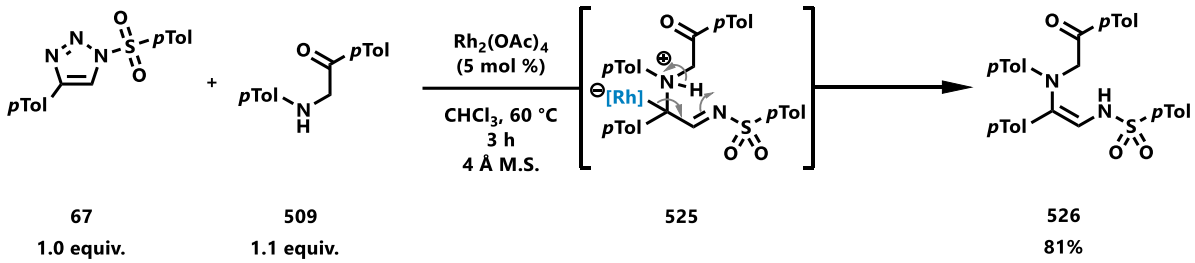
Sulfonyl azides **501** and alkynes **420** are readily available so assembly of a library of 1-STs **48** using CuAAC was trivial (**Scheme 5-09**).[323] Mixing electron rich, electron poor, alkenyl and heteroaromatic substituents was tolerated and the 1-STs were all formed in excellent yield after purification by column chromatography.



Scheme 5-09: 1-STs were prepared by CuAAC between sulfonyl azides and alkynes.

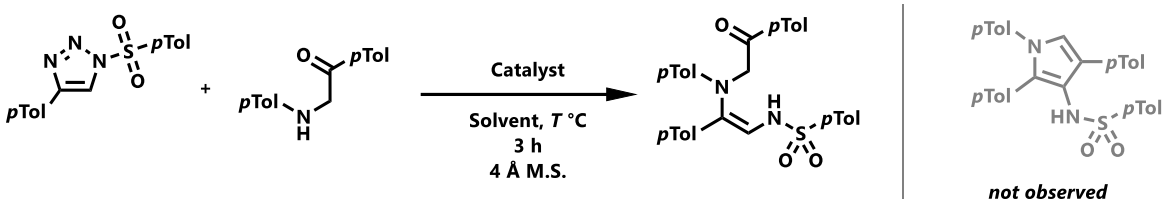
5.2.2 Reaction development

To explore the proposed reaction sequence, 4-tolyl-1-(4-methyl)benzenesulfonyl triazole **67** and a small excess of α-aminoketone **509** were treated with a catalytic amount of rhodium(II) acetate in chloroform at 60 °C, which are typical conditions for denitrogenation of 1-STs (**Scheme 5-10**). The 1,2-diaminoalkene **526** was formed in 81% yield through formation of ylide intermediate **525**.



Scheme 5-10: Rhodium(II)-catalysed N−H bond insertion gave 1,2-diaminoalkene **526**.

The reaction conditions were then optimised to maximise the efficiency of the N−H bond insertion. The reaction was repeated with a range of rhodium(II) catalysts combined with different solvents and temperatures (**Table 8**). Of the catalysts screened, $Rh_2(OAc)_4$ gave the highest yield of 1,2-diaminoalkene (81%, Entry 1). No reaction was observed when the sterically encumbered catalysts $Rh_2(TPA)_4$ and $Rh_2(S\text{-}t\text{PTTL})_4$ were used (Entries 4 and 5). Changing solvent from chloroform to 1,2-dichloroethane improved the yield of alkene **526** to 87% (Entry 6), but the highest yield was observed with toluene (93%, Entry 8). Finally, a range of temperatures were considered (Entries 9–12). Increasing the temperature to 80 °C provided a small improvement in yield (94%, Entry 9). However, carrying out the reaction at higher temperatures than this eroded the yield (Entries 10 and 11), and no reaction was observed at temperatures below 60 °C (Entry 12). It was hoped that the mild Lewis acidity the rhodium(II) carboxylate catalysts may promote spontaneous cyclodehydration of **526** to the corresponding pyrrole **527**, although this was not observed at this stage.



67 **509** **526** **527**

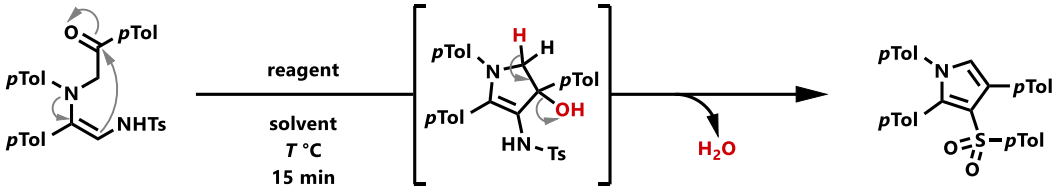
1.0 equiv. **1.1 equiv.**

Table 8: Optimisation data for the rhodium catalysed N–H insertion reaction of triazole **67**. All reactions carried out at 0.20 mmol scale.

Entry	Catalyst[a]	Solvent[b]	*T* (°C)[c]	Yield[d]
1	$Rh_2(OAc)_4$	$CHCl_3$	60	81%
2	$Rh_2(esp)_2$	$CHCl_3$	60	70%
3	$Rh_2(octanoate)_4$	$CHCl_3$	60	38%
4	$Rh_2(TPA)_4$	$CHCl_3$	60	n. r.
5	$Rh_2(S\text{-}t\text{PTTL})_4$	$CHCl_3$	60	n. r.
6	$Rh_2(OAc)_4$	1,2-DCE	60	87%
7	$Rh_2(OAc)_4$	CH_2Cl_2	60	91%
8	$Rh_2(OAc)_4$	PhMe	60	93%
9	$Rh_2(OAc)_4$	PhMe	80	94%
10	$Rh_2(OAc)_4$	PhMe	100	85%
11	$Rh_2(OAc)_4$	PhMe	120	58%
12	$Rh_2(OAc)_4$	PhMe	40	n. r.

[a] 5 mol % catalyst employed; [b] 0.03 M; [c] vial sealed with Teflon cap; [d] yield determined by ^{1}H NMR analysis of crude reaction mixtures using internal standard.

As the cyclodehydration of 1,2-diaminoalkene **526** did not spontaneously occur, a selection of dehydrating agents and Lewis acids were evaluated to promote this transformation (**Table 9**). Unfortunately, TMSOTf, *p*-toluenesulfonic acid, phosphoryl chloride and acetic acid resulted in decomposition of the 1,2-diaminoalkene with minimal formation of the desired pyrrole **527** (Entries 1–4). However, when treated with a boron trifluoride diethyl etherate (0.5 equivalents) in dichloromethane at 80 °C, the desired pyrrole was obtained in 49% yield in just 15 minutes and the reaction profile was cleaner (Entry 5). Increasing the equivalents of Lewis acid from substoichiometric to an equimolar amount gave an increase in yield to 66% (Entry 6). The yield was further increased by employing a three-fold excess of Lewis acid albeit with diminishing returns (72%, Entry 7). Next, a series of different solvents were considered: 1,2-dichloroethane, toluene and acetonitrile, although these resulted in poorer yield and more complex reaction mixtures by crude ^{1}H NMR analysis (Entries 8–10). With dichloromethane established as the best solvent, the reaction was carried out at lower temperatures, although these conditions resulted in increased reactions times alongside formation of unidentified side products (Entries 11 and 12).



526 *Cyclodehydration* 527

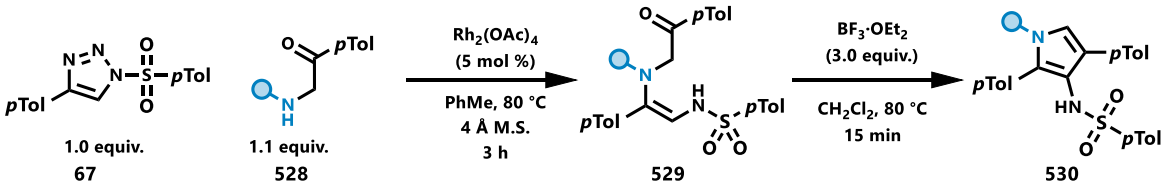
Table 9: Optimisation data for the cyclodehydration of 1,2-diaminoalkene **526**. All reactions carried out at 0.20 mmol scale.

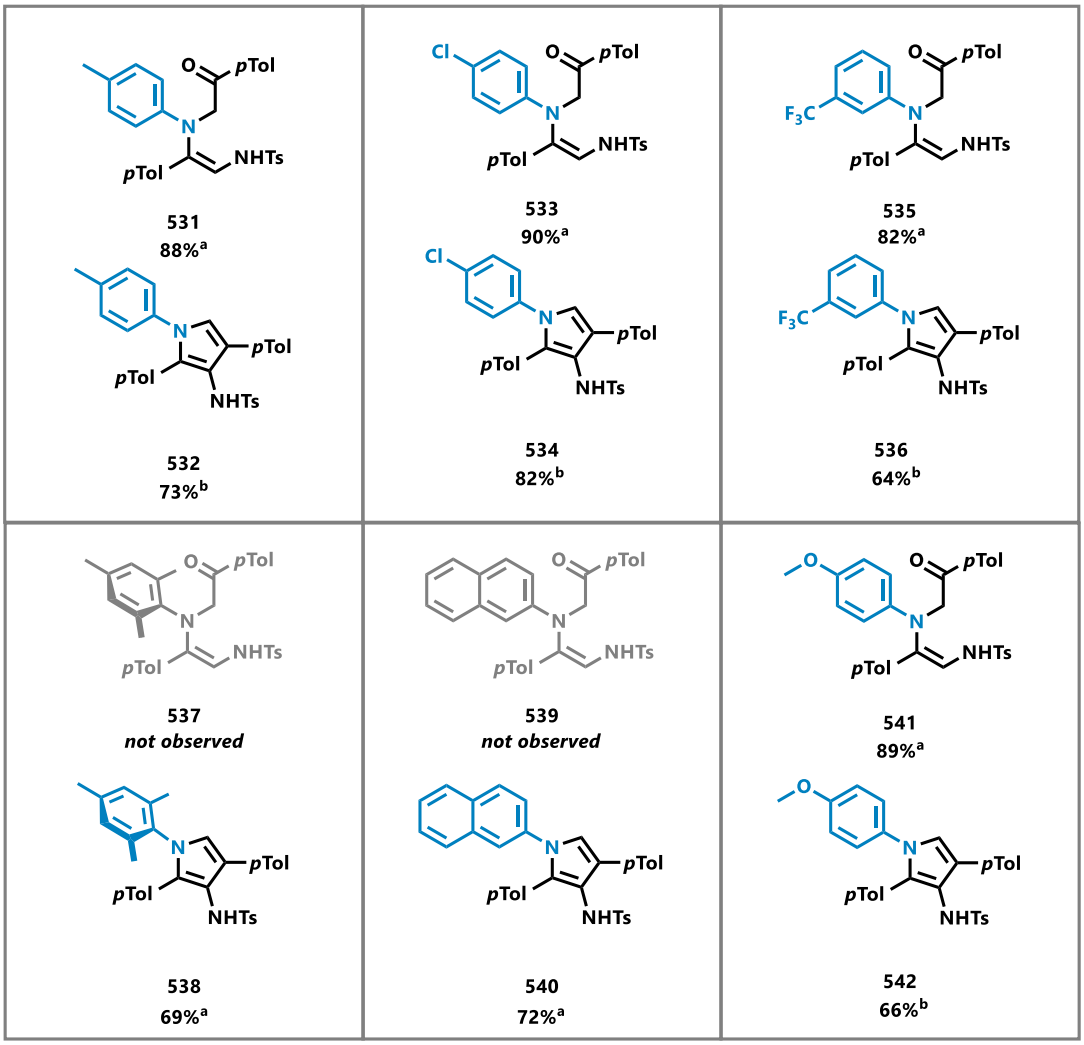
Entry	Reagent (equiv.)	Solvent[a]	*T* (°C)[b]	Yield[c]
1	TMSOTf	PhMe	rt	decomp.
2	*p*-Toluenesulfonic acid	PhMe	rt	decomp.
3	$P(O)Cl_3$	PhMe	rt	decomp.
4	Acetic acid	PhMe	rt	decomp.
5	BF_3•OEt_2 (0.5)	CH_2Cl_2	80	49%
6	BF_3•OEt_2 (1.0)	CH_2Cl_2	80	66%
7	BF_3•OEt_2 (3.0)	CH_2Cl_2	80	72%
8	BF_3•OEt_2 (3.0)	1,2-DCE	80	65%
9	BF_3•OEt_2 (3.0)	PhMe	80	19%
10	BF_3•OEt_2 (3.0)	MeCN	80	38%
11	BF_3•OEt_2 (3.0)	CH_2Cl_2	60	32%
12	BF_3•OEt_2 (3.0)	CH_2Cl_2	40	32%

[a] 0.03 M; [b] vial sealed with Teflon cap; [c] yield determined by ^{1}H NMR analysis of crude reaction mixtures using internal standard.

5.2.3 Reaction scope

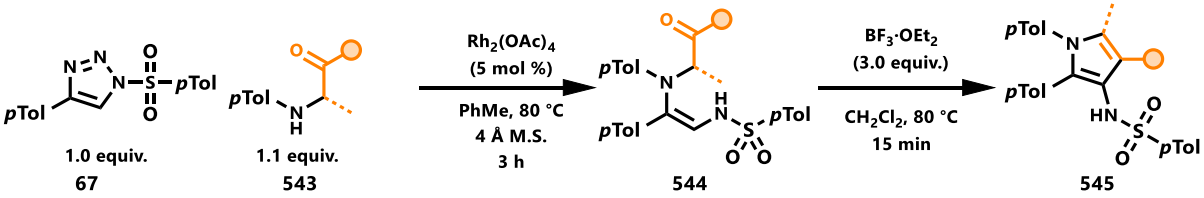
Once the conditions were established for efficient preparation of 3-azapyrrole **527** from 1-ST **67** and α-aminoketone **509**, the range of compatible substituents was explored. Firstly, the *N*-aryl substituent on the α-aminoketones **528** was varied (**Scheme 5-11**). Both the N−H bond insertion and cyclodehydration steps tolerated a range of electron withdrawing and electron donating substituents, and good yield was seen throughout. Interestingly, when the bulky mesityl derivative was used, none of the 1,2-diaminoalkene **537** was observed but the pyrrole **538** was isolated in 69% yield directly from the rhodium(II)-catalysed reaction without needing to treat with Lewis acid in a separate step. The direct formation of pyrrole **538** could be due to the increased steric bulk of the mesityl group raising the energy of unreactive conformations and bringing the reacting centres into closer proximity (Thorpe-Ingold-type effect).[324] It may also arise from the electronic effect of plane-twisting of the mesityl group, which places it out of conjugation with the alkene system which subsequently becomes slightly more electron rich. A similar outcome was observed when a naphthyl derivative was used: 1,2-diaminoalkene **539** was not observed and pyrrole **540** was isolated in 72% yield directly from the rhodium(II)-catalysed step.

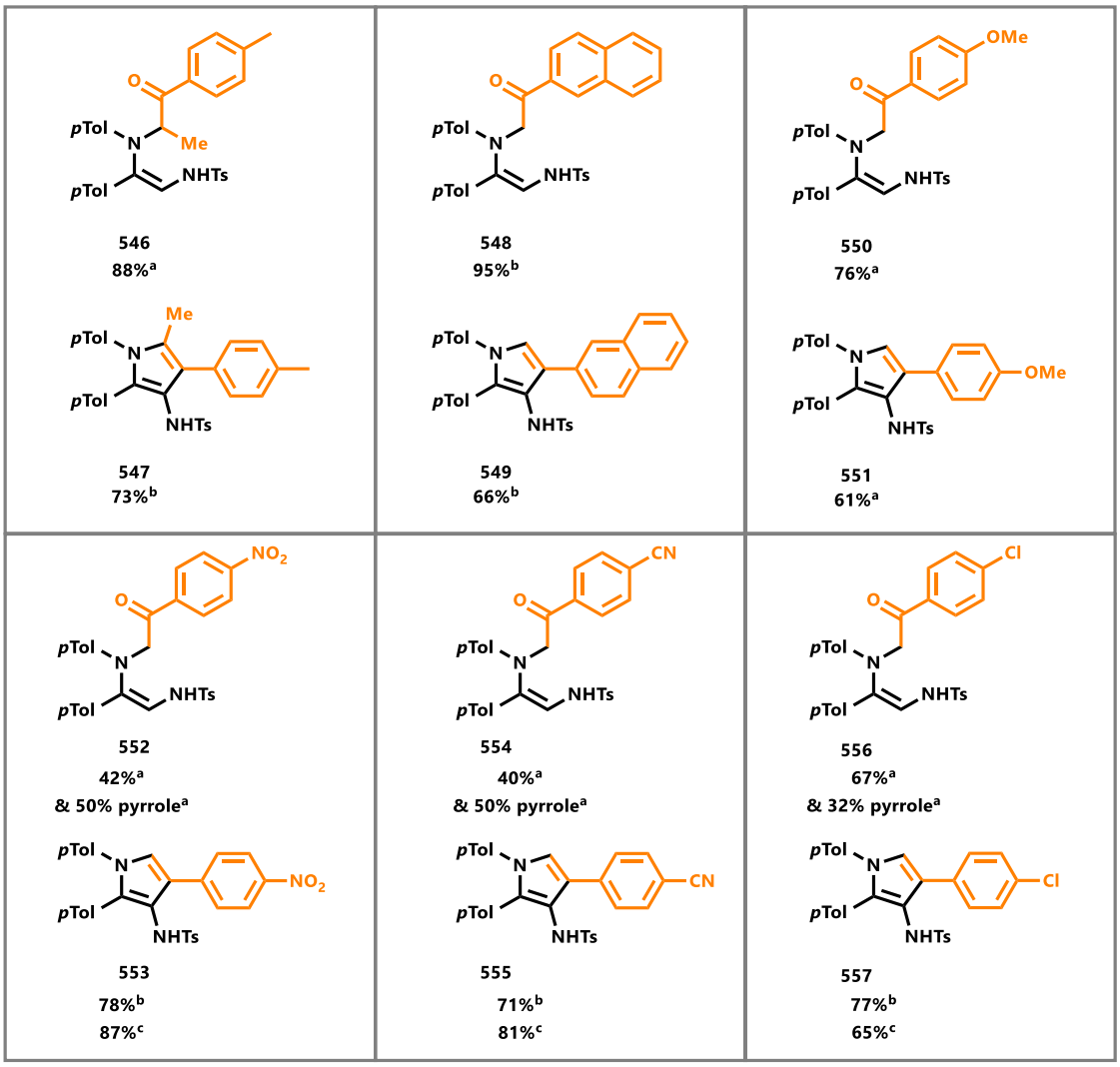




Scheme 5-11: Versatility of arylamine substituents in pyrrole synthesis from 1-STs. [a]Isolated yield after rhodium(II)-catalysed N–H insertion. [b]Isolated yield after cyclodehydration promoted by BF_3•OEt_2.

Next, variation of the α-substituent on the ketones **543** was examined, which leads to the substitution at the 4- and 5-positions of the pyrrole (**Scheme 5-12**). Additional α-substitution of the ketone was tolerated with both reactions, giving N−H insertion product **546** in 88% yield, and fully substituted pyrrole **547** in 73% yield after treatment with BF_3•OEt_2. With more conjugated and electron rich substituents, good yields were obtained over the two operations. Interestingly, when more electron withdrawing functional groups such as NO_2, CN, and Cl were used on the ketone substituent, N−H insertion products **552**, **554** and **556** were obtained alongside pyrroles **553**, **555** and **557** in almost quantitative combined yield in the rhodium(II)-catalysed step. The 1,2-diaminoalkenes were readily separated from the pyrroles and smoothly converted to the corresponding pyrroles after treatment with Lewis acid. Alternatively, the reaction time of the rhodium(II)-catalysed reaction could be extended to 16 h to allow complete formation of pyrroles **553**, **555** and **557** directly in 87%, 81% and 65% yield respectively. The spontaneous formation of cyclodehydration in these substrates was attributed to the more electron-withdrawing substituents activating the carbonyl towards nucleophilic attack. This was consistent with the more electron-withdrawing NO_2 and CN giving rise to more pyrrole product that the Cl substituent under the same conditions.

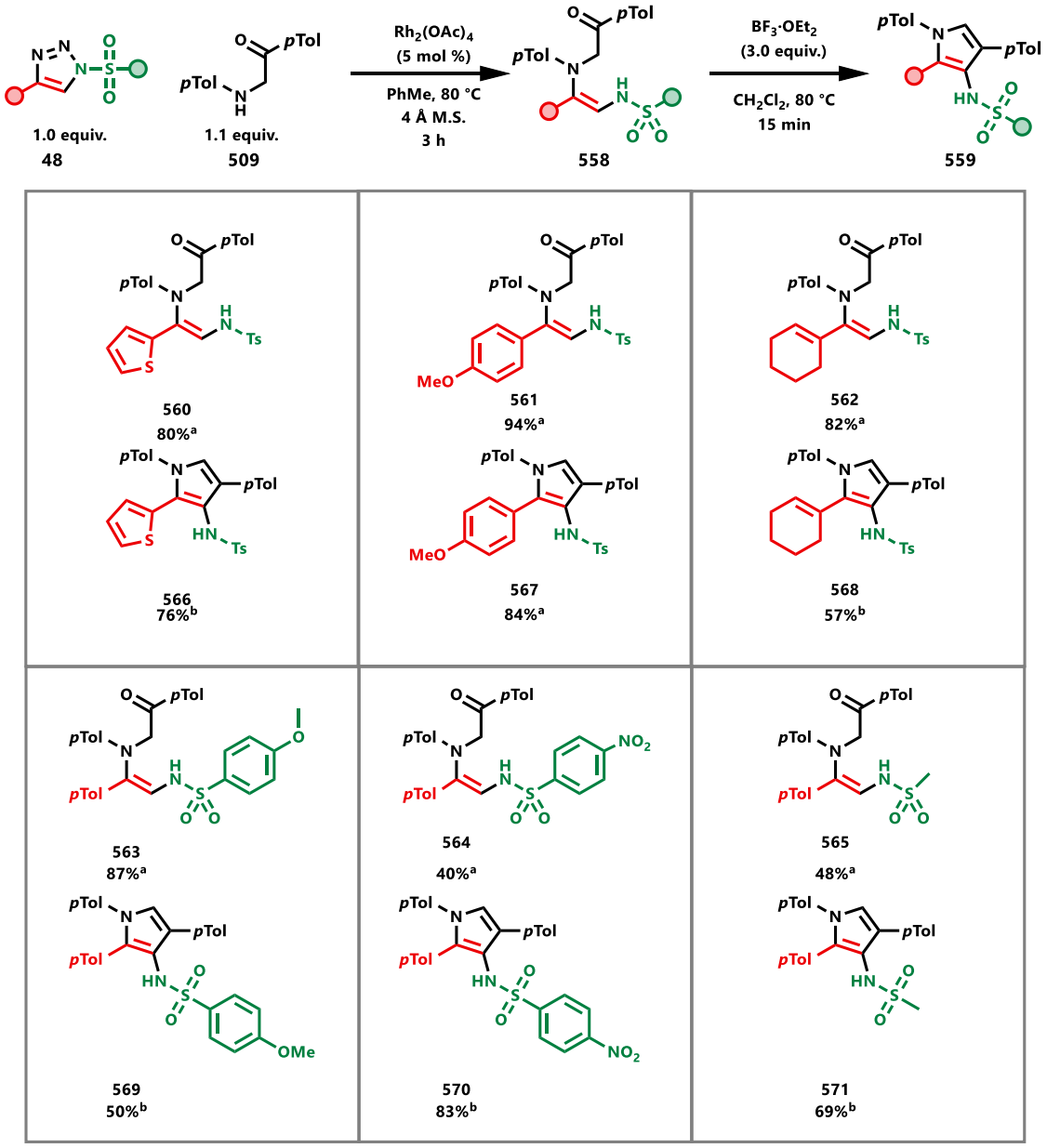




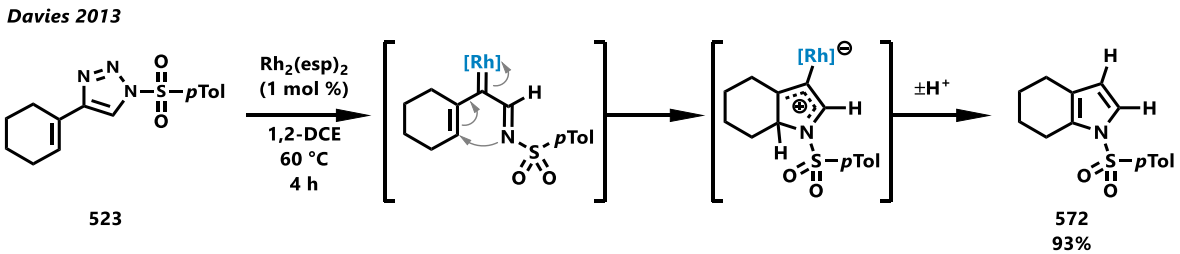
Scheme 5-12: Versatility of ketone substituents in pyrrole synthesis from 1-STs. [a]Isolated yield after rhodium(II)-catalysed N–H insertion. [b]Isolated yield after cyclodehydration promoted by BF_3•OEt_2. [c]Isolated yield with 16 h reaction time.

Finally, the range of compatible 1-STs was examined, allowing access to different substation at the 2- and 3-positions of the pyrrole (**Scheme 5-13**). A mix of heteroaromatic, electron-rich aromatic and alkenyl substituents all gave N−H insertion products **560**–**565** in excellent yield. The 1,2-diaminoalkenes **560**–**565** were readily converted to the corresponding pyrroles **566**–**570** in good yield. The formation of alkenyl N−H insertion product **562** was notable as 4-alkenyl 1-STs such as **523** are known to undergo intramolecular rearrangement to form a different class of pyrrole (**Scheme 5-14**).[325] The 2,3-fused pyrrole product **572** was not observed in the N−H insertion reaction during this study, suggesting that the N−H insertion proceeded more readily than the intramolecular rearrangement.

Next, a series of different sulfonyl groups were examined, ranging from electron-donating *p*-methoxybenzenesulfonyl, electron-poor *p*-nitrobenzenesulfonyl, and methanesulfonyl. It was generally found that increasing the electron-density on the sulfonyl group gave better yield for N−H insertion: using a relatively electron-rich *p*-methoxybenzenesulfonyl group gave N−H insertion product **563** in excellent yield (87%), which was in contrast with the electron-poor *p*-nitrobenzenesulfonyl **564** (40%) and methanesulfonyl **565** (48%). The opposite trend was observed for the pyrrole formation: electron-rich alkene **563** gave a moderate 50% yield of pyrrole **569**, whereas **564** and **565** gave the corresponding pyrroles **570** and **571** in 83% and 69% yield respectively.



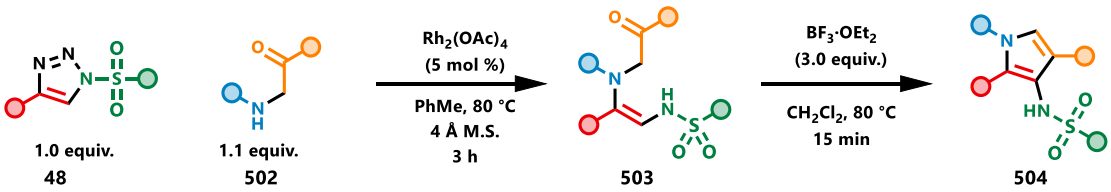
Scheme 5-13: Scope of 1-ST substituents in pyrrole synthesis. [a]Isolated yield after rhodium(II)-catalysed N–H insertion. [b]Isolated yield after cyclodehydration promoted by BF_3•OEt_2.

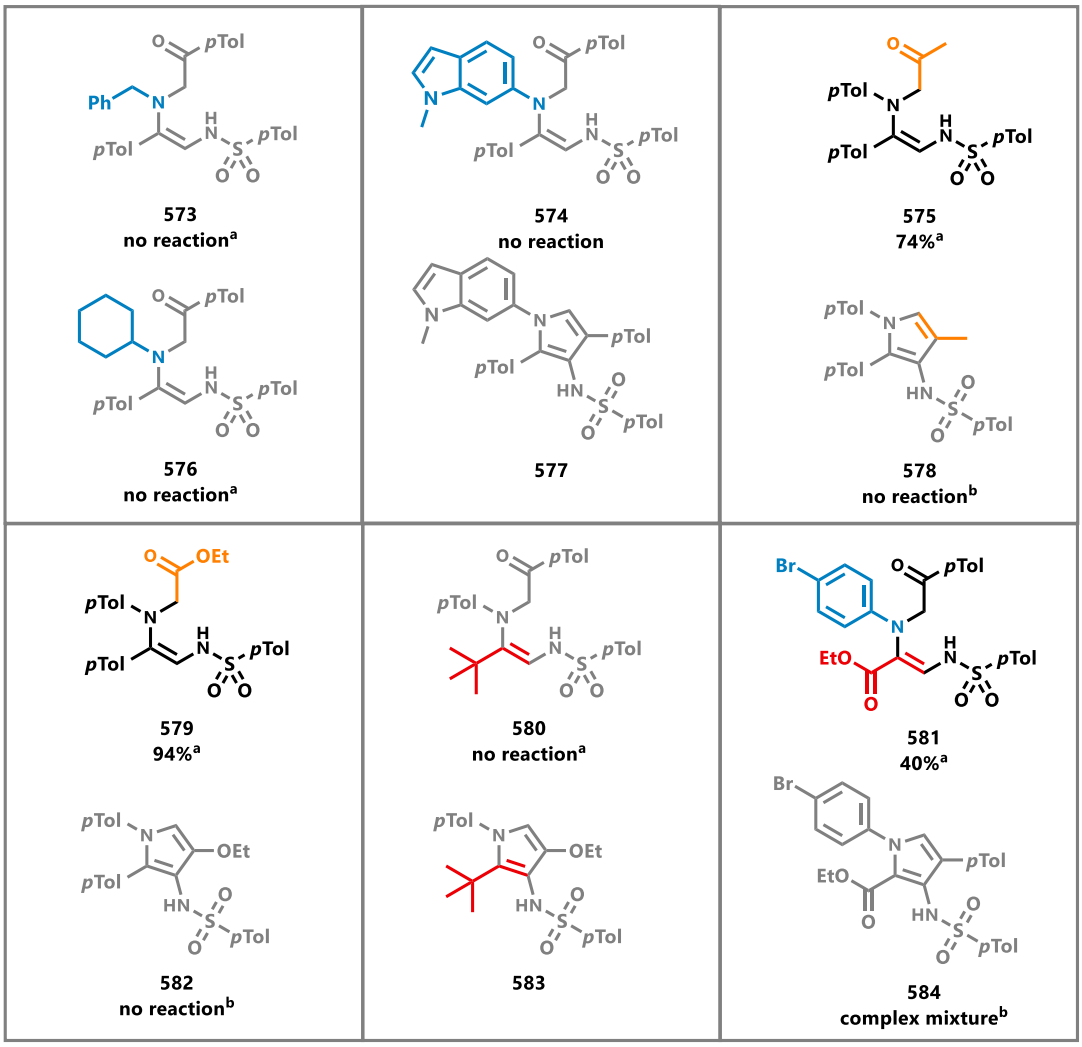


Scheme 5-14: Formation of 2,3-fused pyrrole by a 4π-electrocyclisation.[325]

5.2.4 Unsuccessful substrates

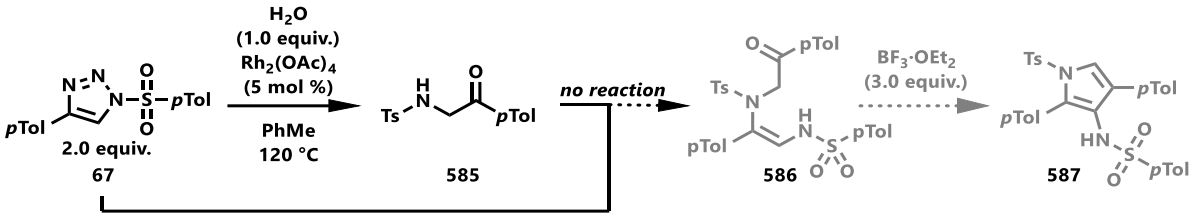
Although the range in compatible substrates was overall broad, there were some notable functional groups that were not tolerated (**Scheme 5-15**). Aliphatic amines such as benzylamine and cyclohexylamine were not suitable; preparation of the corresponding α-aminoketones was challenging due to the increased nucleophilicity of the amine resulting in decomposition. When subjected to the rhodium(II)-catalysed N−H insertion conditions, these amines did not react to give the desired 1,2-diamines **573** and **576** likely for the same reason of increased nucleophilicity of the amine portion inhibiting the rhodium catalyst. Rhodium(II)-catalysed reaction with an indole derivative was also unsuccessful, returning starting material with no observation of N−H insertion product **574**. A methyl ketone variant smoothly underwent N−H insertion to give 1,2-diaminoalkene **575**, however this did not react under the cyclodehydration conditions. The switch from an aryl to a methyl substituent reduced the electrophilicity of the carbonyl, thereby increasing the barrier to cyclodehydration to pyrrole **578**. A similar explanation can be assumed for the ester variant, which underwent N−H insertion to give 1,2-diaminoalkene **579** in 94% yield but no further reaction occurred when treated with BF_3•OEt_2. In terms of the 1-ST portion, a 4-*tert*butyl 1-ST did not undergo N−H insertion to give 1,2-diaminoalkene **580**. The bulky *tert*butyl group is adjacent to the reacting metallocarbene centre and was therefore too hindered. When the substituent at the 4-position was an ester, the 1-ST gave the product of N−H insertion **581** in 40% yield, but when treated with BF_3•OEt_2, a complex mixture was observed.





Scheme 5-15: Unsuccessful substrates in pyrrole synthesis. [a]Isolated yield after rhodium(II)-catalysed N–H insertion. [b]After treatment under optimised cyclodehydration conditions.

It is established that in the presence of water, 1-STs undergo rhodium(II)-catalysed denitrogenative hydration to give α-sulfonylaminoketones.[326] It was reasoned that using 2 equivalents of 1-ST **67** relative to water, α-sulfonylaminoketone **585** would be generated. The ketone **585** would then undergo the N−H insertion and cyclodehydration procedure with the remaining equivalent of 1-ST **67** (**Scheme 5-16**). Unfortunately, although the ketone **585** was successfully generated, it did not undergo any reaction with the 1-ST **67** even at 120 °C. The ketone **585** was isolated and subjected to the optimised reaction conditions with 1-ST **67** but again no reaction occurred. The lack of reactivity was likely because the sulfonylamine is very electron-poor and therefore could not form the aza-ylide with the metallocarbene generated from the 1-ST **67**.

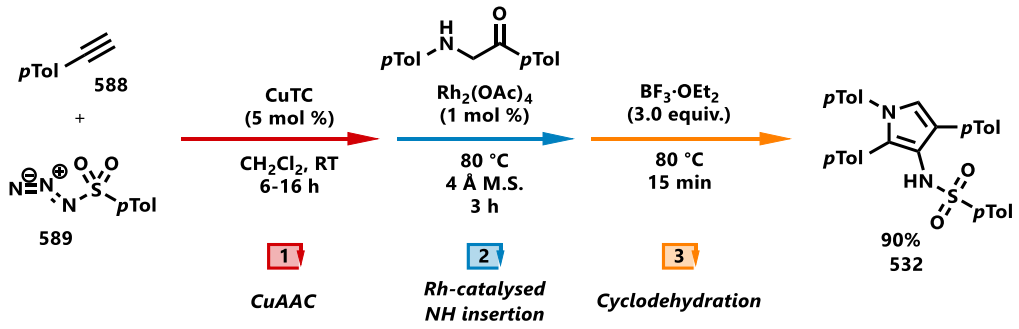


Scheme 5-16: *In-situ* generation of α-tosylaminoketone **586** and attempted N−H insertion-cyclodehydration cascade. 0.30 mmol scale, sealed tube.

5.2.5 One pot protocol

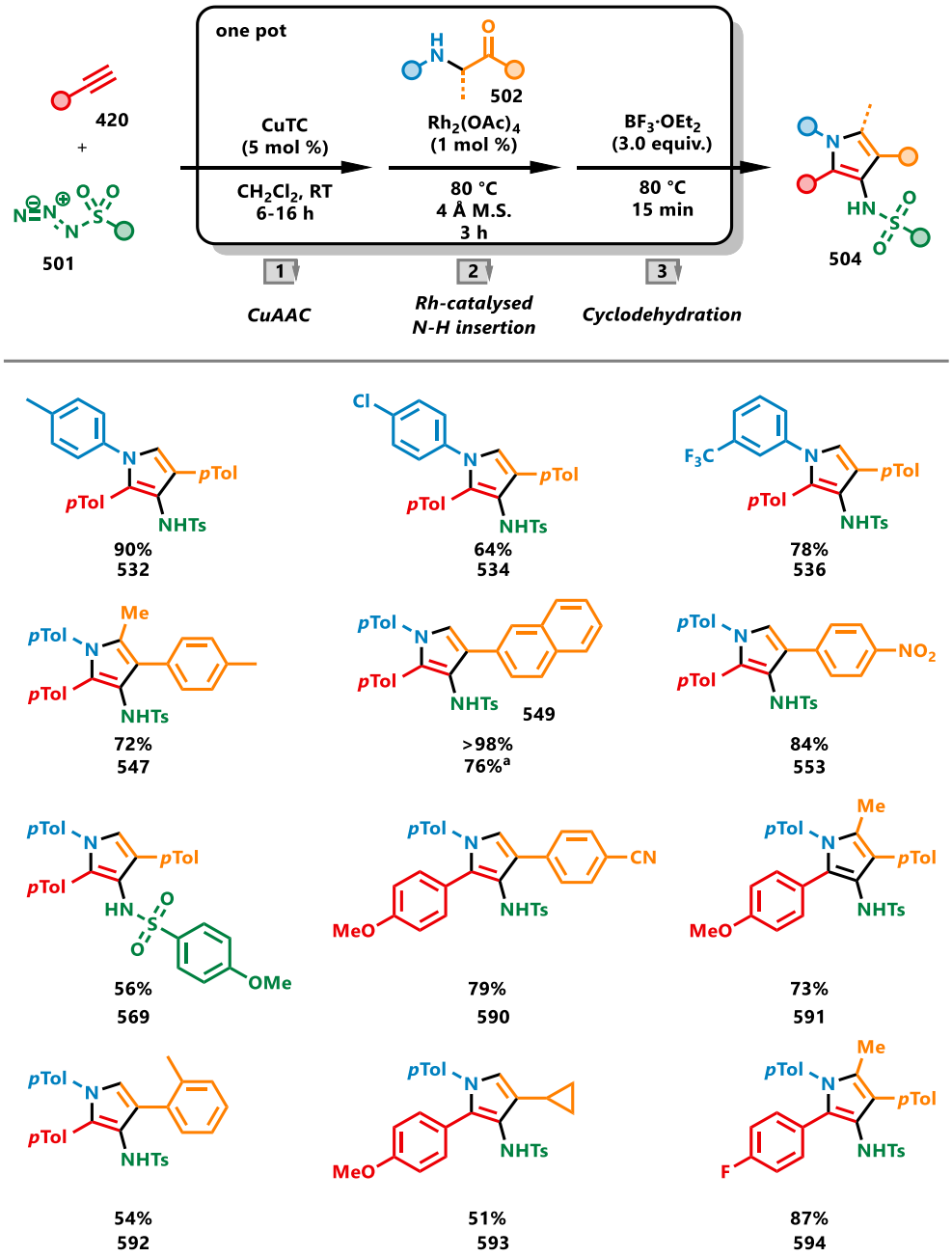
One way to not only improve the efficiency of a reaction sequence but potentially simplify the process is by telescoping multiple operations into a one-pot or domino sequence.[327–330] The versatility of CuAAC and orthogonal reactivity of rhodium(II)-catalysed denitrogenation has been exploited since the seminal works in the area.[99,325,331] Consequently, combining the CuAAC, N–H insertion and cyclodehydration reactions into a single pot was investigated.

Although the range of compatible solvents with CuAAC is broad, the cyclodehydration performed significantly better with dichloromethane than the other solvents so was the most suitable for the full reaction sequence (**Table 9**). The concentration for the one pot protocol was chosen to reflect the most concentration-sensitive rhodium(II)-catalysed step (0.03 M). Treatment of *p*-tolyl acetylene **587** with CuTC and *p*-toluenesulfonyl azide **588** in dichloromethane gave spot to spot conversion to the 1-ST by TLC analysis (**Scheme 5-17**). The 1,2-diaminoketone **509** and $Rh_2(OAc)_4$ were added directly to the reaction mixture and the vial was heated at 80 °C for 3 h, before addition of BF_3•OEt_2 and stirring for a further 15 minutes. After standard aqueous work-up and filtration through a short pad of silica, the pyrrole **532** was obtained in an excellent yield (90% over three steps). The yield obtained was considerably improved over the stepwise process (58%) and represented a clear improvement in the efficiency of the reaction sequence. Additionally, the catalyst loading for both the CuAAC and rhodium(II)-catalysed steps were lowered to 5 mol % and 1 mol % respectively without detrimental effect on the outcome of the reaction.



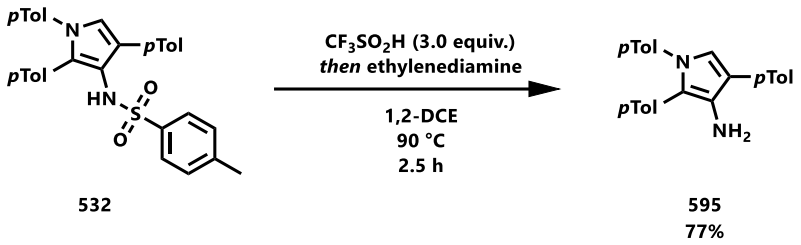
Scheme 5-17: Preparation of pyrrole **532** in one-pot beginning from alkyne **587** and azide **588**. 0.30 mmol scale, sealed tube. 0.03 M.

This validated the one-pot process as an efficient route to pyrroles **504**, and this was extended to a range of different alkynes **420**, sulfonyl azides **501** and α-aminoketones **502** to generate a library of functionalised 3-azapyrroles **504** (**Scheme 5-18**). Overall, the process was found to be extremely efficient and delivered 3-azapyrroles in excellent yield with significant improvement over the stepwise equivalents. Additionally, the process was amenable to scale up, with pyrrole **549** being obtained in 76% yield on gram scale, albeit switching to 1,2-dichloroethane as solvent under reflux instead of dichloromethane in a sealed vial.



Scheme 5-18: Three-step, one-pot synthesis of 3-azapyrroles from sulfonyl azides and alkynes. Isolated yield. [a]4.61 mmol scale, 1,2-DCE as solvent, isolated yield.

Finally, cleavage of the sulfonyl group was investigated as a means of accessing a useful functional handle for further derivatisation. Arylsulfonamides are notoriously difficult to cleave, and 3-azapyrrole **532** proved resistant to a range of reagents including refluxing samarium(II) iodide in THF-DMPU,[332] magnesium reduction,[333] refluxing iodotrimethylsilane,[334] and basic alumina (Brockmann activity grade III).[101] Fortunately, treatment with triflic acid at 90 °C followed by work-up with ethylene diamine gave the detosylated pyrrole **595** in 77% yield (**Scheme 5-19**).[335]



532 **595** **77%**

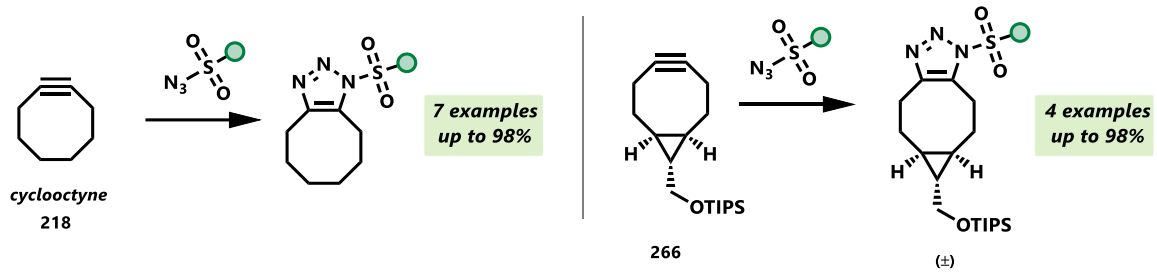
Scheme 5-19: Refluxing triflic acid was an efficient method to detosylate pyrrole **532**.

5.3 Summary

A simple procedure has been developed which begins from readily available starting materials and delivers 3-azapyrroles in short order. Rhodium(II)-catalysed N−H bond insertion of 1-STs into α-aminoketones gave 1,2-diaminoalkenes in excellent yield, which were smoothly cyclised to 3-azapyrroles when treated with boron trifluoride diethyl etherate. When bulky arylamine or electron-poor ketone substituents were used, the cyclodehydration to the corresponding 3-azapyrroles occurred spontaneously. The 1-STs were accessed by employing CuAAC, and the α-aminoketones were afforded in a single step from commercial starting materials. The CuAAC, N−H insertion and cyclodehydration steps could be combined into a one pot protocol beginning from sulfonyl azides, alkynes, and α-aminoketones. The availability of individual substrates means that this method is highly modular, allowing each of the five positions of the final heterocycle to be customised based on careful choice of starting materials.

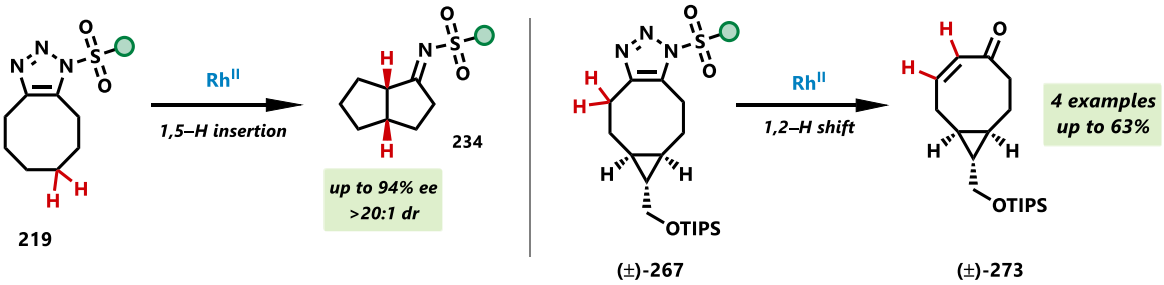
6 Conclusions

Owing to their versatile reactivity and relative ease of preparation, the metal-catalysed denitrogenative transformation of 1-STs is a burgeoning area of research. One of the main limitations in the field is the over-reliance on the 4-substituted 1-ST scaffold – these triazoles are prepared by the CuAAC reaction, whereas more substituted 1-STs are more challenging to make and are therefore less well studied. One of the aims of the work presented in this thesis was to investigate the SPAAC reaction as a new method of preparing substituted 1-STs. The strained cyclic alkynes cyclooctyne **218** and *exo*-BCN **266** were successfully prepared and underwent rapid cycloaddition with sulfonyl azides to generate 1-sulfonylcyclooctatriazoles (**Scheme 6-01**).



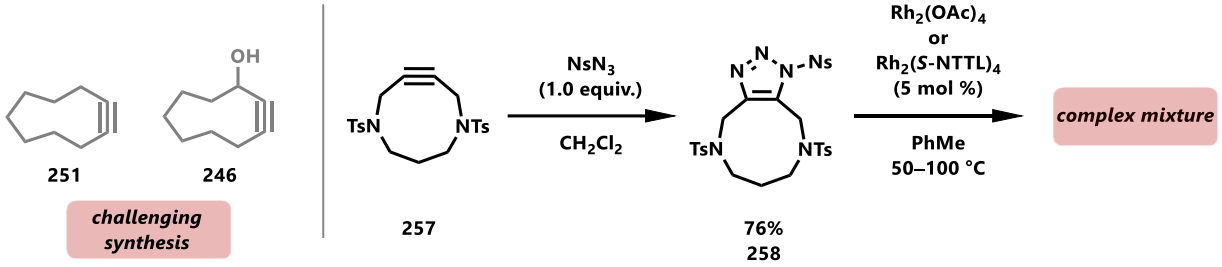
Scheme 6-01

Upon treatment with rhodium(II) catalysts, the cyclooctyne-derived triazoles underwent an interesting transannular C–H insertion reaction to afford the [3.3.0]-bicyclic compounds **234** (**Scheme 6-02**). This transformation could be carried out enantioselectively by using a chiral rhodium(II) catalyst and the conditions for this process were optimised such that the product **234** could be obtained in 94% *ee*. For the triazoles derived from *exo*-BCN **267**, transannular C–H insertion was not observed. Instead, a 1,2-H shift occurred which afforded enone **273** in good yields after removal of the sulfonyl group. The difference in reactivity was explained by the product potentially arising from transannular C–H insertion being highly strained and unfavourable to form, as well as the cyclopropane ring altering the disposition of the 1,5-C–H bonds.



Scheme 6-02

As well as eight-membered cyclic alkynes, the preparation of different sized cyclic alkynes was considered (**Scheme 6-03**). Seven-membered and below cyclic alkynes exist only as transient intermediates and are difficult to prepare. Instead, increasing the ring size to a nine-membered cyclic alkyne was investigated. The synthesis of cyclononyne **251**, cyclononyne-3-ol **246** and a heteroatom-embedded cyclic alkyne **257** were investigated. Significant challenges were encountered during the synthesis of the cyclononynes **251** and **246** which predominantly resulted in complex mixtures throughout. However, the cyclic alkyne **257** was successfully prepared and underwent smooth SPAAC to give the 1-ST **258**. Unfortunately, this triazole did not undergo selective reaction under rhodium(II)-catalysed conditions, returning only complex mixtures. Additionally, ring-closing metathesis approaches to alternative ring sizes in cyclic sulfonyl triazoles were investigated but not successful as the metathesis conditions seemed to promote isomerisation of the triazole starting material and product into their unreactive 2-ST regioisomers.

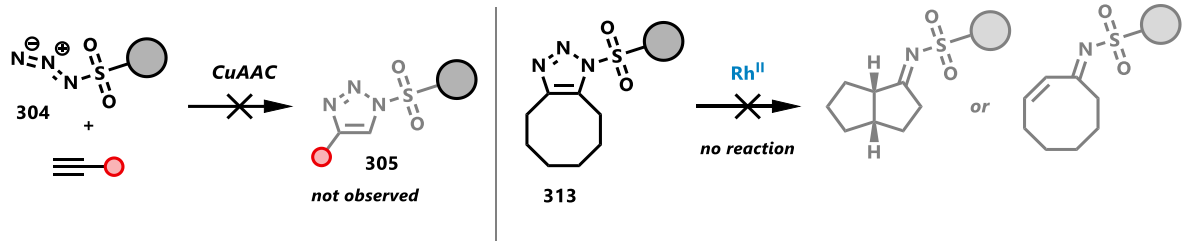


Scheme 6-03

After evaluating SPAAC as a method to prepare 1-STs, the cycloaddition between various sulfonyl azides and cyclooctyne **218** as well as *exo*-BCN **266** was investigated computationally and using a combination of NMR competition experiments and IR spectroscopy. Cyclooctyne **218** and *exo*-BCN **266** underwent SPAAC with sulfonyl azides through an inverse electron demand mechanism which constituted a $HOMO_{alkyne}$ to $LUMO_{azide}$ dominant interaction. This interaction was demonstrated in the kinetics of the electron poor *p*-nitrobenzenesulfonyl azide which was found to undergo extremely rapid SPAAC with cyclooctyne (0.083 $M^{-1}s^{-1}$, approximately five times faster than phenyl azide).

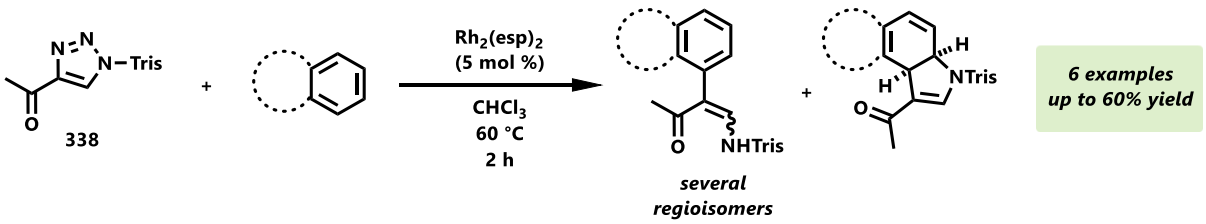
Separately, the use of a polymer-supported sulfonyl azide was investigated in 1-ST preparation (**Scheme 6-04**). Using a polymer-supported 1-ST would allow excess reagents and byproducts to be removed by filtration and the pure product isolated from the solid support by cleavage of the labile N–S bond. A polystyrene-supported sulfonyl azide was successfully prepared but CuAAC with terminal alkynes was very challenging owing to the bulkiness of the polymer matrix. This was overcome by exploiting the reactivity of cyclooctyne **218** at elevated temperatures which gave

the polymer-supported 1-ST **313**. Unfortunately, the 1-ST **313** did not undergo any denitrogenative transformation and the potential of a polymer-supported 1-ST yet remains untapped.



Scheme 6-04

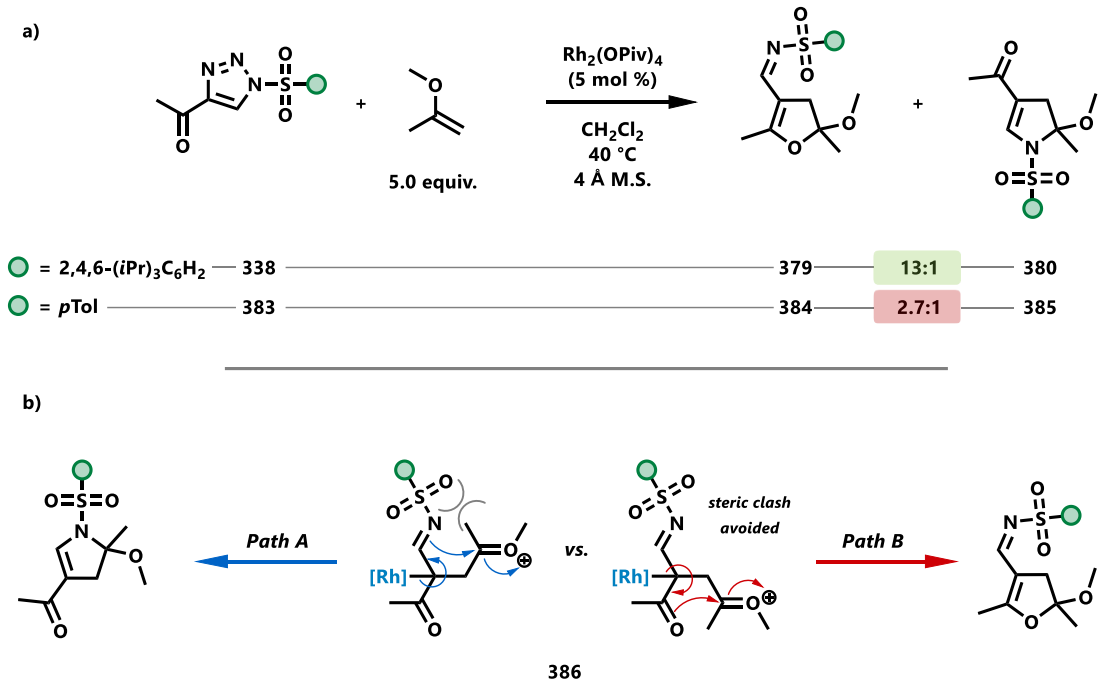
Another area of 1-ST methodology that remained underexplored was the reactivity of triazoles with an electron-withdrawing substituent such as an acyl group at the 4-position. In combination with the 1-sulfonyl group, this results in an extremely electrophilic acceptor/acceptor metallocarbene when treated with rhodium(II) catalysts. There are a limited number of reports detailing the special reactivity of this type of triazole and so work was carried out to investigate these further. The heightened electrophilicity of metallocarbenes from 4-acyl 1-ST **338** meant that it was capable of undergoing insertion into aromatic C(sp^2)–H bonds in a Friedel-Crafts type mechanism (**Scheme 6-05**). Functionalisation of polycyclic aromatic systems was investigated but the regioselectivity proved to be difficult to control, resulting in inseparable mixtures of regioisomers.



Scheme 6-05

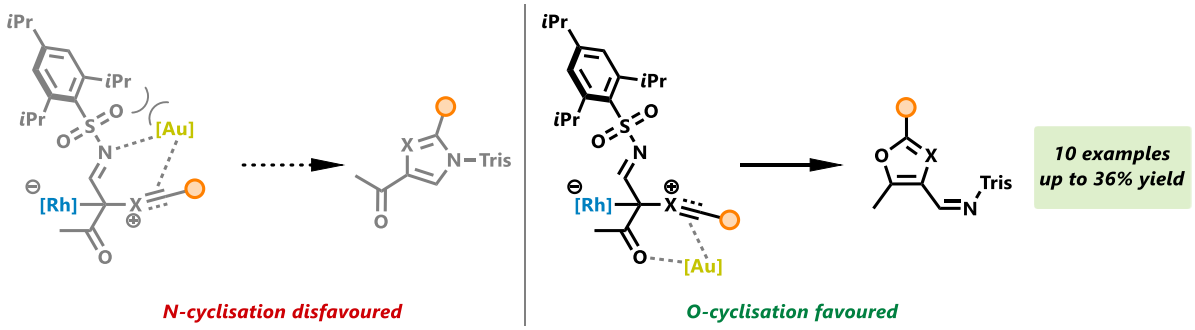
Functionalisation of alkene π-bonds was also investigated and similar problems with regioselectivity were encountered even when a large sulfonyl group was installed. However, when electron-rich alkenes such as enol ethers were used, an interesting change in chemoselectivity was observed that gave rise to dihydrofuran motifs by cyclisation through the acyl group rather than the N-sulfonyl group (**Scheme 6-06**). The reaction conditions for this process were optimised for the reaction between 1-ST **338** and 2-methoxypropene and by comparing with 4-toluenesulfonyl, the size of the 2,4,6-triisopropylbenzenesulfonyl group was crucial for

selectivity. Unfortunately, the scope of compatible substrates for preparing dihydrofurans was limited and conversion of the dihydrofuran to the more stable furan was surprisingly challenging.



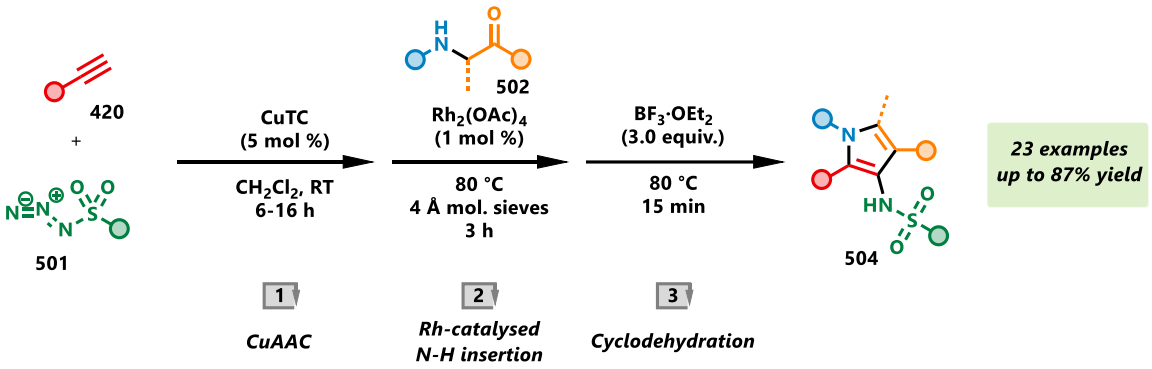
Scheme 6-06

This mode of reactivity was unprecedented for 1-STs and was extended to the preparation of other oxygen heterocycles including furans and oxazoles (**Scheme 6-07**). In the reaction with nitriles to generate oxazoles, control over the chemoselectivity was examined by careful tuning of the stereoelectronics of both the sulfonyl group and substituent at the 4-position. Using a large sulfonyl group in combination with $Ph_3PAuNTf_2$ as an additive was important for controlling the selectivity in the transannular reaction with nitriles to afford oxazoles. Although the yield was disappointingly low in each case, the change in chemoselectivity represented by these examples showed the potential for this methodology.



Scheme 6-07

As well as oxygen-containing heterocycles, the synthesis of 3-azapyrroles was investigated using acceptor/acceptor 1-STs. The 3-azapyrrole scaffold makes up the core of several biologically active compounds but there are few existing synthetic approaches. A general three step sequence was developed and optimised which consisted of CuAAC between sulfonyl azides and terminal alkynes, rhodium(II)-catalysed N–H bond insertion and Lewis acid promoted cyclodehydration (**Scheme 6-08**). Although the method tolerated electron-rich, electron-poor and sterically encumbered substrates, an *N*-aryl substituent was required in the α-aminoketone substrates to allow successful N–H insertion to take place. The key advantages of this approach are the ready availability of individual substrates, as well as the capacity to combine the three steps into a single pot which made it a highly efficient and modular way to make these privileged heterocycles.



Scheme 6-08

7 Experimental

CAUTION

NITROGEN-RICH COMPOUNDS SUCH AS AZIDES AND TRIAZOLES CAN DECOMPOSE VIOLENTLY WITH THE LOSS OF NITROGEN GAS. ALTHOUGH NO PROBLEMS WERE ENCOUNTERED IN THE COURSE OF THIS STUDY, APPROPRIATE CAUTIONS SHOULD BE TAKEN.

7.1 General Considerations

NMR spectra were recorded on 400 and 500 MHz Bruker spectrometers. Chemical shifts are given in ppm and the spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. ^{13}C NMR spectra were collected with complete proton decoupling and assignments were made using COSY, HSQC, HMBC and NOESY experiments. Samples were melted directly from the procedures described. High-resolution mass spectra were obtained on Agilent 6546 LC/Q-TOF and Bruker microTOFq instruments by Analytical Services at the University of Glasgow School of Chemistry. IR spectra were recorded using spectrometers fitted with an ATR device. CH_2Cl_2, THF, Et_2O and PhMe were purified on a PureSolv PM500 and other reagents were used as received from commercial suppliers. Elemental analysis was carried out using an Exeter CE-440 Elemental Analyser.

Reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F254 aluminium-foil baked plates. Compounds were visualized by UV light at 254 nm or by staining with potassium permanganate.

Column chromatography was performed manually using Fluorochem Silica Gel 60A 40-63au, or automatically using a Teledyne ISCO CombiFlash Rf+ System using Redisep Rf silica cartridges, eluting with solvents as supplied under a positive pressure of compressed air.

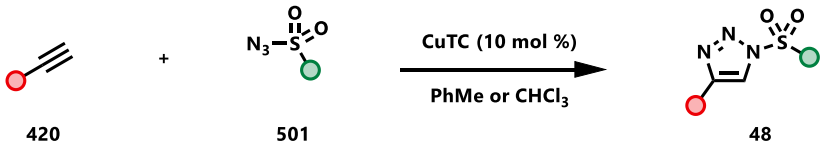
Enantiomeric excess was determined by integration of HPLC traces using chiral stationary phase Daicel Chiralpak AD-H column (0.46 ⌀ × 25 cm) using a Shimadzu Prominence System (LC20AD) with Oven (CTO20AC, 25 °C) and diode array detector (SPDM20A).

The following sulfonyl azides: 4-methylbenzenesulfonyl azide, 4-nitrobenzenesulfonyl azide, 4-methoxybenzenesulfonyl azide, methanesulfonyl azide and 2,4,6-triisopropylbenzenesulfonyl azide were prepared collectively by all members of the Boyer Research Group and involved displacement of commercial sulfonyl chlorides with sodium azide according to the protocol outlined by Curphey.[273]

7.2 Experimental Protocols and Compound Data

7.2.1 Preparation of 4-substituted 1-STs

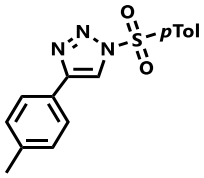
General Procedure 1: Preparation of 1-STs by CuAAC



420 501 48

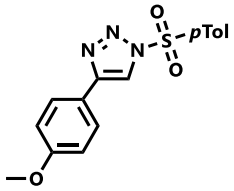
Copper(I) thiophene-2-carboxylate (10 mol %) and the requisite alkyne **420** (1.1 equiv.) were dissolved in PhMe or $CHCl_3$ (0.1 M) and cooled to 0 °C (ice bath). After 10 min, the sulfonyl azide **501** (1.0 equiv.) was added in one portion and the reaction mixture was allowed to reach ambient temperature. When the reaction was complete (TLC, 1−3 h), the mixture was diluted with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 10 mL $mmol^{-1}$). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, rapid gradient of 10−30% ethyl acetate in petroleum ether) to give the 1-ST.

67 4-(4-Tolyl)-1-tosyl-1,2,3-triazole



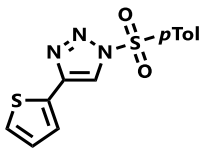
4-Ethynyltoluene (547 µL, 4.51 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (809 mg, 4.10 mmol, 1.0 equiv.) were treated with CuTC (69 mg, 0.36 mmol, 9 mol %) in PhMe (40 mL) according to General Procedure 1 to give the title compound **67** (1.17 g, 91%) as a white solid.; m.pt. 127 °C dec. (Lit. 158–159 °C)[336]; ν_{max}(film) 3150, 2940, 1593, 1497, 1392, 1328, 1194, 1179, 1103 and 1089 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.26 (1 H, s, triazole CH), 8.02 (2 H, d, J = 8.4 Hz, Ar), 7.71 (2 H, d, J = 8.4 Hz, Ar), 7.39 (2 H, d, J = 7.8 Hz, Ar), 7.23 (2 H, d, J = 7.8 Hz, Ar), 2.45 (3 H, s, CH_3) and 2.38 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 147.4 (Ar), 147.3 (triazole C4), 139.1 (Ar), 133.2 (Ar), 130.4 (2 × ArH), 129.7 (2 × ArH), 128.7 (2 × ArH), 126.0 (Ar), 126.0 (2 × ArH), 118.5 (triazole C5), 21.8 (CH_3) and 21.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{15}N_3NaO_2S^+$ 336.0777; Found 336.0767. Recorded data consistent with previous values.[336]

367 4-(4-Methoxyphenyl)-1-tosyl-1,2,3-triazole



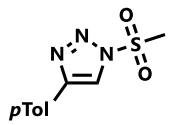
1-Ethynyl-4-methoxybenzene (535 µL, 4.18 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (740 mg, 3.80 mmol, 1.0 equiv.) were treated with CuTC (71 mg, 0.37 mmol, 10 mol %) in PhMe (40 mL) according to General Procedure 1 to give the title compound **367** (1.05 g, 85%) as a white solid.; m.pt. 96 °C dec. (Lit. 100–101 °C)[337]; ν_{max}(film) 3144, 2932, 2839, 1616, 1593, 1497, 1393, 1331, 1288, 1250, 1177 and 1088 cm^{-1}; ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.22 (1 H, s, triazole CH), 8.01 (2 H, d, *J* = 8.5 Hz, Ar), 7.74 (2 H, d, *J* = 8.9 Hz, Ar), 7.37 (2 H, d, *J* = 8.5 Hz, Ar), 6.95 (2 H, d, *J* = 8.9 Hz, Ar), 3.83 (3 H, s, OCH_3) and 2.43 (3 H, s, CH_3); $^{13}C\{^{1}H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 160.2 (Ar), 147.3 (Ar), 147.2 (triazole C4), 133.1 (Ar), 130.4 (2 × ArH), 128.6 (2 × ArH), 127.4 (2 × ArH), 121.4 (Ar), 117.9 (triazole C5), 114.4 (2 × ArH), 55.3 (OCH_3) and 21.8 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{16}N_3O_3S^+$ 330.0907; Found 330.0909. Recorded data consistent with previous values.[337]

521 4-(Thiophen-2-yl)-1-tosyl-1,2,3-triazole



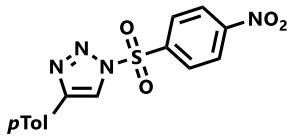
2-Ethynylthiophene (438 µL, 4.62 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (828 mg, 4.20 mmol, 1.0 equiv.) were treated with CuTC (80 mg, 0.42 mmol, 10 mol %) in PhMe (42 mL) according to General Procedure 1 to give the title compound **521** (1.24 g, 97%) as a white solid.; m.pt. 87 °C dec. (Lit. 140–141 °C)[338]; ν_{max}(film) 3136, 2924, 1593, 1497, 1393, 1346, 1292, 1196, 1177, 1092 and 1018 cm^{-1}; ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.20 (1 H, s, triazole CH), 8.02 (2 H, d, J = 8.5 Hz, Ar), 7.44 (1 H, dd, J = 3.6, 1.2 Hz, thiophene CH), 7.39 (2 H, d, J = 8.5 Hz, Ar), 7.34 (1 H, dd, J = 5.1, 1.2 Hz, thiophene CH), 7.08 (1 H, dd, J = 5.1, 3.6 Hz, thiophene CH) and 2.45 (3 H, s, CH_3); $^{13}C\{^{1}H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 147.4 (triazole C4), 142.5 (thiophene C2), 133.0 (Ar), 130.8 (Ar), 130.5 (2 × ArH), 128.7 (2 × ArH), 127.8 (thiophene CH), 126.3 (thiophene CH), 125.6 (thiophene CH), 118.1 (triazole C5) and 21.8 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{11}N_3NaO_2S_2^+$ 328.0185; Found 328.0184. Recorded data consistent with previous values.[338]

101 1-Methanesulfonyl-4-(4-tolyl)-1,2,3-triazole



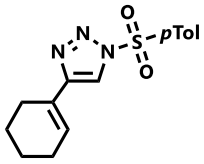
4-Ethynyltoluene (558 µL, 4.40 mmol, 1.1 equiv.) and methanesulfonyl azide (484 mg, 4.00 mmol, 1.0 equiv.) were treated with CuTC (76 mg, 0.40 mmol, 10 mol %) in PhMe (40 mL) according to General Procedure 1 to give the title compound **101** (898 mg, 95%) as a white solid.; m.pt. 95 °C dec. (Lit. 120–122 °C dec.)[112]; ν_{max}(film) 3140, 3028, 2924, 1624, 1497, 1381, 1331, 1231, 1184, 1161 and 1038 cm^{-1}; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.26 (1 H, s, triazole CH), 7.76 (2 H, d, J = 8.0 Hz, Ar), 7.28 (2 H, d, J = 8.0 Hz, Ar), 3.56 (3 H, s, CH_3) and 2.41 (3 H, s, CH_3); $^{13}C\{^{1}H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 147.6 (triazole C4), 139.4 (Ar), 129.8 (2 × ArH), 126.1 (2 × ArH), 125.8 (Ar), 118.4 (triazole C5), 42.7 (CH_3) and 21.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{12}N_3O_2S^+$ 238.0645; Found 238.0646. Recorded data consistent with previous values.[112]

522 1-(4-Nitrobenzenesulfonyl)-4-(4-tolyl)-1,2,3-triazole



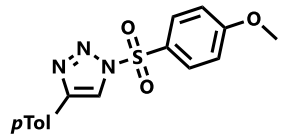
4-Ethynyltoluene (558 µL, 4.40 mmol, 1.1 equiv.) and 4-nitrobenzenesulfonyl azide (913 mg, 4.00 mmol, 1.0 equiv.) were treated with CuTC (76 mg, 0.40 mmol, 10 mol %) in PhMe (40 mL) according to General Procedure 1 to give the title compound **522** (1.20 g, 87%) as a white solid.; m.pt. 106 °C dec.; ν_{max}(film) 3140, 3109, 1609, 1532, 1408, 1397, 1346, 1316, 1188 and 1103 cm^{-1}; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.44 (2 H, d, *J* = 9.0 Hz, Ar), 8.36 (2 H, d, *J* = 9.0 Hz, Ar), 8.30 (1 H, s, triazole CH), 7.71 (2 H, d, *J* = 8.2 Hz, Ar), 7.25 (2 H, d, *J* = 8.2 Hz, Ar) and 2.39 (3 H, s, CH_3); $^{13}C\{^{1}H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 151.6 (Ar), 148.0 (triazole C4), 141.6 (Ar), 139.6 (Ar), 130.1 (2 × ArH), 129.8 (2 × ArH), 126.1 (2 × ArH), 125.4 (Ar), 125.0 (2 × ArH), 118.6 (triazole C5) and 21.4 (CH_3); HRMS (ESI-TOF) *m/z*: [M(hydrolysed triazole)+H]$^+$ Calcd for $C_9H_{10}N_3^+$ 160.0869; Found 160.0875.

523 4-(Cyclohexen-1-yl)-1-tosyl-1,2,3-triazole



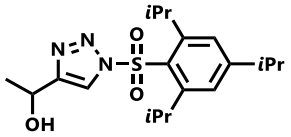
1-Ethynylcyclohex-1-ene (485 µL, 4.18 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (740 mg, 3.80 mmol, 1.0 equiv.) were treated with CuTC (71 mg, 0.37 mmol, 10 mol %) in PhMe (40 mL) according to General Procedure 1 to give the title compound **523** (950 mg, 83%) as a white solid.; m.pt. 100 °C dec. (Lit. 102–103 °C)[336]; ν_{max}(film) 3148, 2928, 2859, 1593, 1389, 1335, 1316, 1177 and 1092 cm^{-1}; ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.97 (2 H, d, J = 8.5 Hz, Ar), 7.88 (1 H, s, triazole CH), 7.36 (2 H, d, J = 8.5 Hz, Ar), 6.66 (1 H, tt, J = 3.9, 1.8 Hz, =CH), 2.43 (3 H, s, CH_3), 2.34–2.27 (2 H, m, CH_2), 2.22–2.15 (2 H, m, CH_2), 1.78–1.71 (2 H, m, CH_2) and 1.70–1.61 (2 H, m, CH_2); $^{13}C\{^{1}H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 148.9 (triazole C4), 147.0 (Ar), 133.3 (Ar), 130.3 (2 × ArH), 128.5 (2 × ArH), 127.7 (=CH), 125.8 (=C), 117.3 (triazole C5), 26.2 (CH_2), 25.3 (CH_2), 22.2 (CH_2), 22.0 (CH_2) and 21.8 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{18}N_3O_2S^+$ 304.1114; Found 304.1113. Recorded data consistent with previous values.[336]

524 1-(4-Methoxylphenylsulfonyl)-4-(4-tolyl)-1,2,3-triazole



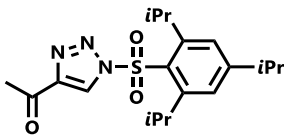
4-Ethynyltoluene (279 µL, 2.20 mmol, 1.1 equiv.) and 4-methoxybenzenesulfonyl azide (426 mg, 2.00 mmol, 1.0 equiv.) were treated with CuTC (38 mg, 0.20 mmol, 10 mol %) in PhMe (20 mL) according to General Procedure 1 to give the title compound **524** (372 mg, 56%) as a white solid.; m.pt. 102 °C dec.; ν_{max}(film) 2940, 2923, 1593, 1577, 1497, 1391, 1327, 1233, 1168, 1103 and 1090 cm^{-1}; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.26 (1 H, s, triazole CH), 8.08 (2 H, d, *J* = 9.1 Hz, Ar), 7.71 (2 H, d, *J* = 8.1 Hz, Ar), 7.24 (2 H, d, *J* = 8.1 Hz, Ar), 7.03 (2 H, d, *J* = 9.1 Hz, Ar), 3.89 (3 H, s, OCH_3) and 2.38 (3 H, s, CH_3); $^{13}C\{^{1}H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 12707.0 (Ar), 165.3 (Ar), 147.4 (triazole C4), 139.1 (Ar), 131.2 (2 × ArH), 129.7 (2 × ArH), 127.9 (Ar), 126.0 (2 × ArH), 118.4 (triazole C5), 115.1 (2 × ArH), 55.9 (OCH_3) and 21.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{15}N_3NaO_3S^+$ 352.0726; Found 352.0719.

337 1-(*N*-(2,4,6-Triisopropylbenzenesulfonyl))-1,2,3-triazol-4-yl)-ethanol



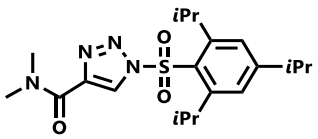
3-Butyn-2-ol (570 µL, 7.25 mmol, 1.1 equiv.) and 2,4,6-triisopropylbenzenesulfonyl azide (2.05 g, 6.63 mmol, 1.0 equiv.) were treated with CuTC (126 mg, 0.63 mmol, 10 mol %) in $CHCl_3$ (66 mL) according to General Procedure 1 to give the title compound **337** (2.35 g, 93%) as a white solid. ν_{max}(film) 3402, 2963, 2932, 2872, 1599, 1557, 1464, 1429, 1385, 1364, 1298, 1267, 1184 and 1105 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.11 (1 H, s, triazole C5), 7.23 (2 H, s, Ar), 5.11 (1 H, q, J = 6.5 Hz, CH), 4.13 (2 H, sept., J = 6.8 Hz, *i*PrCH), 2.92 (1 H, sept., J = 7.0 Hz, *i*PrCH), 1.60 (3 H, d, J = 6.6 Hz, CH_3), 1.26 (6 H, dd, J = 7.0, 3.9 Hz, 2 × *i*PrCH$_3$) and 1.20 (12 H, dd, J = 6.8, 2.8 Hz, 4 × *i*PrCH$_3$); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 156.3 (triazole C4), 152.9 (2 × ArH), 151.6 (Ar), 128.8 (Ar), 124.7 (2 × ArH), 119.1 (triazole C5), 63.1 (C–OH), 34.4 (*i*PrCH), 30.0 (2 × *i*PrCH), 24.5 (4 × *i*PrCH$_3$), 23.4 (2 × *i*PrCH$_3$) and 23.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{19}H_{29}N_3NaO_3S^+$ 402.1822; Found 402.1811. This compound decomposed readily and was used immediately in the next step.

338 4-Acetyl-1-(2,4,6-triisopropylbenzenesulfonyl)-1,2,3-triazole



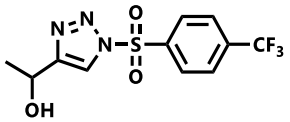
Alcohol **338** (4.99 g, 13.2 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (130 mL) and cooled to 0 °C (ice bath). Dess-Martin periodinane (6.67 g, 15.8 mmol, 1.2 equiv.) was added in one portion and the reaction mixture stirred for 1 h at this temperature. Saturated aqueous $Na_2S_2O_3$ (100 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, rapid gradient 5−25% ethyl acetate in petroleum ether) to afford the title compound as a white solid. m.pt. 115–117 °C; ν_{max}(film) 2963, 2874, 1697, 1599, 1528, 1429, 1389, 1364, 1354, 1196 and 1001 cm^{-1}; ^1H NMR (500 MHz, 25.1 °C, $CDCl_3$) δ 8.65 (1 H, s, triazole C5), 7.25 (2 H, s, Ar), 4.10 (2 H, sept., J = 6.7 Hz, *i*PrCH), 2.94 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.70 (3 H, s, CH_3), 1.26 (6 H, d, J = 6.9 Hz, 2 × *i*PrCH$_3$) and 1.22 (12 H, d, J = 6.7 Hz, 3 × *i*PrCH$_3$); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 192.0 (C=O), 156.9 (triazole C4), 153.3 (Ar), 128.1 (3 × Ar), 124.9 (2 × ArH), 124.3 (triazole C5), 34.4 (*i*PrCH), 30.2 (2 × *i*PrCH), 27.5 (CH_3), 24.5 (4 × *i*PrCH$_3$) and 23.4 (2 × *i*PrCH$_3$); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{19}H_{27}N_3NaO_3S^+$ 400.1665; Found 400.1658.

433 1-(2,4,6-Triisopropylbenzenesulfonyl)-*N,N*-dimethyl-1,2,3-triazole-4-carboxamide



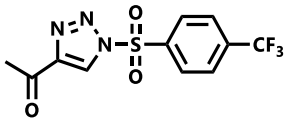
N,N-Dimethylpropynamide (350 mg, 3.55 mmol, 1.1 equiv.) and 2,4,6-triisopropylbenzenesulfonyl azide (1.00 g, 3.23 mmol, 1.0 equiv.) were treated with CuTC (62 mg, 0.36 mmol, 10 mol %) in $CHCl_3$ (35 mL) according to General Procedure 1 to give the title compound **433** (250 mg, 19%) as a white solid. m.pt. 132–135 °C dec.; ν_{max}(film) 3100, 1634, 1598, 1548, 1430, 1393, 1355, 1260 and 1190 cm^{-1}; ^1H NMR (400 MHz, 21.0 °C, $CDCl_3$) δ 8.64 (1 H, s, Ar), 7.24 (2 H, s, Ar), 4.10 (2 H, sept., J = 6.7 Hz, *i*PrCH), 3.48 (3 H, s, NCH_3), 3.13 (3 H, s, NCH_3), 2.93 (1 H, sept., J = 6.9 Hz, *i*PrCH), 1.26 (6 H, d, J = 6.9 Hz, *i*PrCH_3) and 1.21 (12 H, d, J = 6.8 Hz, *i*PrCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 21.7 °C, $CDCl_3$) δ 160.2 (C=O), 156.7 (Ar), 153.1 (2 × Ar), 143.7 (Ar), 128.3 (Ar), 126.9 (ArH), 124.8 (2 × ArH), 38.7 (NCH_3), 36.4 (NCH_3), 34.4 (*i*PrCH), 30.0 (2 × *i*PrCH), 24.5 (4 × *i*PrCH_3) and 23.4 (2 × *i*PrCH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{30}N_4NaO_3S^+$ 429.1931; Found 429.1924.

441 1-(*N*-(4-Trifluoromethanebenzenesulfonyl)-1,2,3-triazol-4-yl)-ethanol



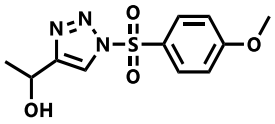
3-Butyn-2-ol (520 µL, 6.60 mmol, 1.1 equiv.) and 4-trifluoromethanebenzenesulfonyl azide (1.51 g, 6.00 mmol, 1.0 equiv.) were treated with CuTC (114 mg, 0.60 mmol, 10 mol %) in PhMe (60 mL) according to General Procedure 1 to give the title compound **441** (1.00 g, 52%) as a yellow waxy solid; ^{1}H NMR (400 MHz, 21.5 °C, $CDCl_3$) δ 8.27 (2 H, d, J = 8.3 Hz, ArH), 8.08 (1 H, app. d, J = 0.9 Hz, triazole C5), 7.88 (2 H, app. dt, J = 8.3, 0.7 Hz, ArH), 5.09 (1 H, app. qd, J = 6.6, 0.9 Hz, CH) and 1.60 (3 H, d, J = 6.6 Hz, CH_3); ^{13}C{^{1}H} NMR (101 MHz, 21.8 °C, $CDCl_3$) δ 152.2 (Ar), 139.6 (triazole C4), 137.1 (q, J = 33.7 Hz, Ar), 129.3 (2 × ArH), 127.0 (q, J = 3.6 Hz, 2 × ArH), 122.7 (q, J = 273.4 Hz, CF_3), 120.3 (triazole C5), 63.0 (C–OH) and 23.1 (CH_3). This compound decomposed readily and was used immediately in the next step.

442 4-Acetyl-1-(4-trifluoromethanebenzenesulfonyl)-1,2,3-triazole



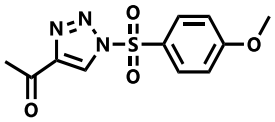
Alcohol **441** (1.00 g, 3.11 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (31 mL) and cooled to 0 °C (ice bath). Dess-Martin periodinane (1.71 g, 4.04 mmol, 1.3 equiv.) was added in one portion and the reaction mixture stirred for 1 h at this temperature. Saturated aqueous $Na_2S_2O_3$ (30 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, rapid gradient 5−25% ethyl acetate in petroleum ether) to afford the title compound **442** (756 mg, 72%) as a yellow oil. ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.65 (1 H, br s, triazole C5), 8.29 (2 H, br d, J = 8.2 Hz, ArH), 7.89 (2 H, d, J = 8.2 Hz, ArH) and 2.66 (3 H, s, CH_3); ^{13}C{^{1}H} NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 191.4 (C=O), 146.9 (triazole C4), 139.0 (q, J = 1.4 Hz, Ar), 137.5 (q, J = 31.0 Hz, Ar), 129.6 (2 × ArH), 127.2 (2 × ArH), 125.6 (triazole C5), 122.6 (q, J = 273.0 Hz, CF_3) and 27.5 (CH_3). Complete characterisation of this compound was not possible due to rapid decomposition.

445b 1-(*N*-(4-Methoxybenzenesulfonyl)-1,2,3-triazol-4-yl)-ethanol



3-Butyn-2-ol (208 µL, 2.60 mmol, 1.1 equiv.) and 4-methoxybenzenesulfonyl azide (554 mg, 2.36 mmol, 1.0 equiv.) were treated with CuTC (50 mg, 0.24 mmol, 10 mol %) in PhMe (26 mL) according to General Procedure 1 to give the title compound **445b** (576 mg, 75%) as a yellow waxy solid; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.05 (2 H, d, J = 9.0 Hz, Ar), 8.04 (1 H, s, triazole C5), 7.03 (2 H, d, J = 9.0 Hz, Ar), 5.07 (1 H, q, J = 6.5 Hz, CH), 3.89 (3 H, s, O–CH_3) and 1.58 (3 H, d, J = 6.5 Hz, CH_3); ^{13}C{^{1}H} NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 165.4 (Ar), 151.7 (triazole C4), 131.3 (2 × ArH), 126.9 (Ar), 119.9 (triazole C5), 115.1 (2 × ArH), 63.0 (C–OH), 55.9 (OCH_3) and 23.0 (CH_3). This compound decomposed readily and was used immediately in the next step.

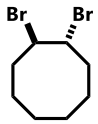
445 4-Acetyl-1-(4-methoxybenzenesulfonyl)-1,2,3-triazole



Alcohol **445b** (500 mg, 1.55 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (16 mL) and cooled to 0 °C (ice bath). Dess-Martin periodinane (770 mg, 1.86 mmol, 1.2 equiv.) was added in one portion and the reaction mixture stirred for 1 h at this temperature. Saturated aqueous $Na_2S_2O_3$ (20 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, rapid gradient 5−25% ethyl acetate in petroleum ether) to afford the title compound **445** (421 mg, 67%) as a yellow oil. ν_{max}(film) 3134, 2926, 1695, 1593, 1576, 1530, 1499, 1396, 1356, 1319, 1271, 1198, 1169, 1092 and 1005 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.58 (1 H, s, triazole C5), 8.07 (2 H, d, J = 9.1 Hz, Ar), 7.06 (2 H, d, J = 9.1 Hz, Ar), 3.90 (3 H, s, O–CH_3) and 2.67 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 191.9 (C=O), 165.8 (Ar C4), 146.6 (triazole C4), 131.6 (2 × ArH), 126.1 (Ar C1), 125.0 (triazole C5), 115.3 (2 × ArH), 56.0 (O–CH_3) and 27.5 (CH_3); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{11}H_{11}N_3NaO_4S^+$ 304.0362; Found 304.0360.

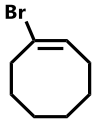
7.2.2 Preparation of cyclic alkynes

216-Br 1,2-Dibromocyclooctane



cis-Cyclooctene (50.8 mL, 390 mmol, 1.0 equiv.) was dissolved in dichloromethane (200 mL) and cooled to −40 °C (acetone, dry ice). A solution of bromine (20.0 mL, 390 mmol, 1.0 equiv.) in dichloromethane (40 mL) was added drop-wise until a persistent yellow colour was observed. The reaction was quenched by the addition of saturated aqueous sodium thiosulfate (80 mL) and the aqueous phase extracted with dichloromethane (3 × 80 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound (97.2 g, 92%) as a colourless oil. The crude product was used without further purification.; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 4.61–4.56 (2 H, m, CH), 2.45–2.38 (2 H, m, CH_2), 2.13–2.06 (2 H, m, CH_2), 1.90–1.81 (2 H, m, CH_2), 1.72–1.65 (2 H, m, CH_2), 1.64–1.55 (2 H, m, CH_2) and 1.51–1.41 (2 H, m, CH_2). Recorded data consistent with previous values.[173]

217 (*E*)-1-Bromocyclooctene



In a flame-dried flask under an atmosphere of argon, KO*t*Bu (59.5 g, 531 mmol, 1.5 equiv.) was suspended in THF (200 mL) and the suspension was cooled to 0 °C (ice bath). A solution of 1,2-dibromocyclooctane **216-Br** (95.2 g, 353 mmol, 1.0 equiv.) in THF (40 mL) was added dropwise over 30 min. Then the reaction mixture was stirred at ambient temperature for 1 h and the reaction was quenched by the addition of ice-cold saturated aqueous ammonium chloride (160 mL). The THF was removed *in vacuo* and the aqueous phase extracted with dichloromethane (3 × 80 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by Kugelrohr bulb to bulb distillation (110 °C, 15.0 mbar) to afford the title compound (48.6 g, 73%) as an orange oil. ; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 6.03 (1 H, t, J = 8.5 Hz, =CH), 2.64–2.59 (2 H, m, CH_2), 2.12–2.07 (2 H, m, CH_2), 1.66–1.61 (2 H, m, CH_2) and 1.58–1.47 (6 H, m, CH_2); ^{13}C{^{1}H} NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 131.7 (=CH), 124.8 (=C), 35.1 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 27.5 (CH_2), 26.4 (CH_2) and 25.5 (CH_2). Recorded data consistent with previous values.[173]

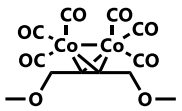
218 Cyclooctyne

In a flame-dried flask under an atmosphere of argon, a solution of diisopropylamine (26.8 mL, 191 mmol, 1.0 equiv.) in THF (90 mL) was cooled to −25 °C (dry ice, acetone) and *n*BuLi (2.5 m solution in hexanes, 76.4 mL, 191 mmol, 1.0 equiv.) was added drop-wise. 1-Bromocyclooct-1-ene **217** (36.1 g, 191 mmol, 1.0 equiv.) was added in one portion and a dark orange colour was immediately observed. The reaction was allowed to warm up to 15 °C over 45 min and stirred at this temperature for a further 3 h by which point the reaction mixture had turned pale yellow. The reaction was quenched by the addition of ice-cold HCl (2 m aq., 95.0 mL) and the aqueous phase was extracted with pentane (5 × 20 mL). The combined organic layers were washed with water and brine; dried ($MgSO_4$), filtered and carefully concentrated *in vacuo* (0 °C, ice bath, ~100 mbar). The residue was purified by distillation (Vigreux column) to afford the title compound (6.31 g, 31%) as a colourless oil. ; b.pt. 56 °C, 18 mbar; ν_{max}(film) 2928 and 1034 cm^{-1}; ^{1}H NMR (500 MHz, −3.3 °C, $CDCl_3$) δ 2.19–2.14 (4 H, m, 2 × CH_2), 1.89–1.83 (4 H, m, 2 × CH_2) and 1.65–1.60 (4 H, m, 2 × CH_2); $^{13}C\{^{1}H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 94.7 (2 × C≡C), 34.7 (2 × CH_2), 29.8 (2 × CH_2) and 21.0 (2 × CH_2). Recorded data consistent with previous values.[173]

252 *N,N'*-Ditoluenesulfonyl-1,3-diaminopropane

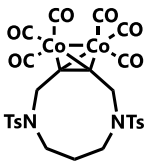
1,3-Diaminopropane (4.20 mL, 50.0 mmol, 1.0 equiv.) and K_2CO_3 (13.8 g, 100 mmol, 2.0 equiv.) were dissolved in water (85 mL). Tosyl chloride (19.1 g, 100 mmol, 2.0 equiv.) was dissolved in THF (85 mL), added dropwise over 4 h and the mixture was stirred at ambient temperature for 16 h. The reaction was cooled to 0 °C (ice bath) and water (40 mL) was added. The solid was filtered and washed with cold ethanol (40 mL × 3) to give the title compound as a white solid (19.0 g, >98%). ^{1}H NMR (400 MHz, 27.0 °C, $CDCl_3$) δ 7.73 (4 H, d, J = 8.3 Hz, 2 × TsAr), 7.31 (4 H, d, J = 8.3 Hz, 2 × TsAr), 4.80 (2 H, t, J = 6.7 Hz, 2 × NH), 3.03 (4 H, q, J = 6.5 Hz, 2 × CH_2), 2.43 (6 H, s, 2 × CH_3) and 1.72–1.62 (2 H, m, CH_2); ^{13}C{^{1}H} NMR (101 MHz, 27.0 °C, $CDCl_3$) δ 143.6 (2 × Ar), 136.8 (2 × Ar), 129.8 (4 × ArH), 127.0 (4 × ArH), 39.7 (2 × CH_2), 30.0 (CH_2) and 21.5 (2 × CH_3). Recorded data consistent with previous values.[339]

255



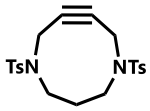
In a flame-dried flask under an atmosphere of argon, 1,3-dimethoxy-2-butyne (1.00 mL, 8.27 mmol, 1.0 equiv.) and CH_2Cl_2 (30 mL) were added. $Co_2(CO)_8$ (3.46 g, 9.10 mmol, 1.10 equiv.) was added in one portion and the reaction was stirred at ambient temperature for 2 h. The solvent was removed *in vacuo* and the crude residue purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as a dark red solid (2.08 g, 63%). ^{1}H NMR (400 MHz, 24.5 °C, $CDCl_3$) δ 4.61 (4 H, s, 2 × CH_2) and 3.50 (6 H, s, 2 × CH_3). Recorded data consistent with previous values.[339]

256



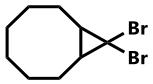
In a flame-dried flask under an atmosphere of argon, compounds **252** (500 mg, 1.25 mmol, 1.0 equiv.), **255** (478 mg, 1.25 mmol, 1.0 equiv.), and CH_2Cl_2 (100 mL) were added. Boron trifluoride diethyl etherate (462 µL, 3.75 mmol, 3.0 equiv.) was added dropwise at ambient temperature and the reaction stirred for 30 min. Saturated aqueous $NaHCO_3$ (30 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was rapidly purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as a dark red solid (658 mg, 73%).; ^{1}H NMR (400 MHz, 24.8 °C, $CDCl_3$) δ 7.72 (4 H, d, J = 8.3 Hz, 2 × TsAr), 7.37 (4 H, d, J = 8.3 Hz, 2 × TsAr), 4.57 (4 H, s, 2 × CH_2), 3.35 (4 H, t, J = 6.0 Hz, 2 × CH_2), 2.46 (6 H, s, 2 × CH_3) and 2.21 (2 H, p, J = 6.0 Hz, CH_2); ^{13}C{^{1}H} NMR (101 MHz, 24.6 °C, $CDCl_3$) δ 198.7 (6 × C=O), 143.9 (2 × Ar), 134.7 (2 × Ar), 130.0 (4 × ArH), 127.3 (4 × ArH), 90.8 (2 × C–Co), 55.2 (2 × CH_2), 47.9 (2 × CH_2), 29.8 (CH_2) and 21.5 (2 × CH_3). Recorded data consistent with previous values.[339]

257 *N*,*N*'-Bis-(*p*-toluenesulfonyl)-4,8-diazacyclononyne



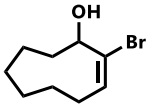
In a flame-dried flask under an atmosphere of argon, compound **256** (500 mg, 0.696 mmol, 1.0 equiv.) was dissolved in Et_2O (40 mL) and cooled to 0 °C (ice bath). Silica gel (7.00 g) was added followed by ceric ammonium nitrate (3.81 g, 6.96 mmol, 10.0 equiv.) in one portion. The reaction was allowed to warm to ambient temperature overnight and filtered, washing the filter cake with Et_2O (3 × 5 mL). The filtrate was concentrated *in vacuo* and the residue purified by flash column chromatography (SiO_2, 5% EtOAc in petroleum ether) to give the title compound as a colourless oil (230 mg, 76%).; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.65 (4 H, d, J = 8.2 Hz, 4 × TsAr), 7.33 (4 H, d, J = 8.2 Hz, 4 × TsAr), 3.78 (4 H, s, 2 × CH_2), 3.29–3.23 (4 H, m, 2 × CH_2), 2.44 (6 H, s, 2 × CH_3) and 2.11 (2 H, dtt, J = 7.8, 4.6, 2.7 Hz, CH_2); ^{13}C{^{1}H} NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 144.0 (2 × Ar), 134.0 (2 × Ar), 130.0 (2 × ArH), 129.9 (2 × ArH), 127.5 (2 × ArH), 127.3 (2 × ArH), 88.2 (2 × C≡C), 44.8 (2 × CH_2), 41.2 (2 × CH_2), 33.0 (CH_2) and 21.6 (2 × CH_3). Recorded data consistent with previous values.[339]

244 9,9-Dibromobicyclo[6.1.0]nonane



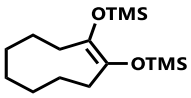
cis-Cyclooctene (10.2 mL, 80.0 mmol, 1.0 equiv.), bromoform (14.0 mL, 160 mmol, 2.0 equiv.) and triethylbenzylammonium chloride (600 mg, 2.63 mmol, 3 mol %) were dissolved in ethanol (4.0 mL) and CH_2Cl_2 (16.0 mL) and cooled to 0 °C (ice bath). An aqueous solution of NaOH (50 wt.%, 40.0 mL) was added dropwise and the reaction stirred for 16 h. Water (50.0 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 50.0 mL). The combined organic layer was acidified with aqueous HCl (1 m, 50.0 mL), washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound as a dark brown oil (22.5 g, >98%). ν_{max}(film) 2921, 2852, 1465, 1445, 1362, 1163, 1059 and 1021 cm^{-1}; ^1H NMR (400 MHz, 27.0 °C, $CDCl_3$) δ 2.98–2.12 (2 H, m, CH_2), 1.67–1.30 (10 H, m, CH_2 + cyclopropane CH) and 1.24–1.09 (2 H, m, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, 27.0 °C, $CDCl_3$) δ 37.1 (cyclopropane), 33.3 (2 × cyclopropane CH), 27.9 (2 × CH_2), 26.4 (2 × CH_2) and 25.4 (2 × CH_2). Recorded data consistent with previous values.[340]

245 (*E*)-2-Bromocyclonon-2-en-1-ol



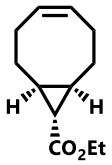
Silver perchlorate (20.0 g, 96.5 mmol, 2.0 equiv.) was dissolved in acetone (95.0 mL) and water (5.0 mL). 9,9-Dibromobicyclo[6.1.0]nonane (13.6 g, 48.2 mmol, 1.0 equiv.) was added in one portion and the reaction stirred in the dark for 1 h. The liquid was decanted and the residue triturated with EtOAc (3 × 100 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound as a pale-yellow oil (9.17 g, 87%). ν_{max}(film) 3356, 2926, 2857, 1643, 1452, 1392, 1262, 1164, 1110 and 1041 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 6.02 (1 H, dd, J = 10.4, 5.4 Hz, =CH), 4.01 (1 H, ddd, J = 11.5, 7.5, 4.5 Hz, CH) and 2.27–2.17 (12 H, m, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, 27.0 °C, $CDCl_3$) δ 127.8 (=CH), 77.0 (CH), 75.5 (=C), 35.7 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 26.5 (CH_2), 24.6 (CH_2) and 22.7 (CH_2); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_9H_{15}BrNaO^+$ 241.0198; Found 241.0195. Recorded data consistent with previous values.[341]

248 (*Z*)-1,2-Bis((trimethylsilyl)oxy)cyclononene



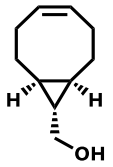
In a flame-dried flask under an atmosphere of argon, PhMe (400 mL) was degassed for 1 h. Sodium cubes (12.0 g, 520 mmol, 4.7 equiv.) were added and the mixture heated to reflux for 2 h. Dimethyl azelate (23.9 g, 111 mmol, 1.0 equiv.) and trimethylsilyl chloride (56.1 mL, 442 mmol, 4.0 equiv.) were dissolved in PhMe (40.0 mL) and added *via* dropping funnel over 2 h. After 16 h, the reaction was cooled to room temperature and the liquid decanted. The mixture was filtered through celite and the filtrate concentrated *in vacuo*. The residue was purified by distillation (Vigreux column) to afford the title compound (4.29 g, 13%) as a colourless oil. ; b.pt. 92 °C, 0.1 mbar (Lit. 90–91, 0.1 mbar)[342]; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 2.19–2.15 (4 H, m, CH_2), 1.58–1.54 (4 H, m, CH_2), 1.52–1.48 (4 H, m, CH_2), 1.46–1.44 (1 H, m, CH_2), 1.32–1.28 (1 H, m, CH_2) and 0.18 (18 H, s, CH_3); $^{13}C\{^{1}H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 134.0 (2 × =C), 30.5 (2 × CH_2), 25.8 (CH_2), 25.0 (2 × CH_2), 24.7 (2 × CH_2) and 1.13 (6 × CH_3). Recorded data consistent with previous values.[342]

262 Ethyl (1*R,8*S**,9*r**,*Z*)-bicyclo[6.1.0]non-4-ene-9-carboxylate**



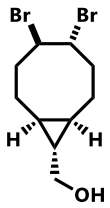
In a flame-dried flask under an atmosphere of argon, cyclooctadiene (55.4 mL, 452 mmol, 8.0 equiv.) and $Rh_2(OAc)_4$ (1.00 g, 2.26 mmol, 4 mol %) were dissolved in dichloromethane (40 mL). A solution of ethyl diazoacetate (85 wt% in dichloromethane, 7.58 g, 56.5 mmol, 1.0 equiv.) in dichloromethane (20 mL) was added drop-wise over 6 h. The reaction mixture was concentrated *in vacuo* and filtered through a short pad of silica (eluting with hexane followed by 20% EtOAc in hexane). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, gradient from 1 to 3% EtOAc in petroleum ether) to give the (1*R**,8*S**,9*s**,*Z*)-diastereomer (3.74 g, 34%) as a colourless oil (data not presented) followed by the (1*R**,8*S**,9*r**,*Z*)-diastereomer **262** (4.08 g, 37%) as a colourless oil.; ν_{max}(film) 2980, 2933, 1721, 1443, 1368, 1339, 1307, 1265, 1227, 1206, 1184, 1153, 1096, 1053 and 1013 cm^{-1}; ^1H NMR (400 MHz, 24.9 °C, $CDCl_3$) δ 5.68–5.59 (2.0 H, m, =CH), 4.10 (2 H, q, J = 7.1 Hz, Et CH_2), 2.35–2.25 (2 H, m, CH_2), 2.24–2.15 (2 H, m, CH_2), 2.13–2.04 (2 H, m, CH_2), 1.60–1.52 (2 H, m, cyclopropane CH), 1.53–1.42 (2 H, m, CH_2), 1.25 (3 H, t, J = 7.1 Hz, Et CH_3) and 1.18 (1 H, t, J = 4.5 Hz, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 24.9 °C, $CDCl_3$) δ 174.4 (C=O), 129.9 (2 × =CH), 60.2 (Et CH_2), 28.3 (2 × CH_2), 27.9 (cyclopropane CH), 27.7 (2 × cyclopropane CH), 26.6 (2 × CH_2) and 14.3 (Et CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{12}H_{18}NaO_2^+$ 217.1199; Found 217.1200. Recorded data consistent with previous values.[196]

263 (1*R,8*S**,9*r**,*Z*)-Bicyclo[6.1.0]non-4-en-9-ylmethanol**



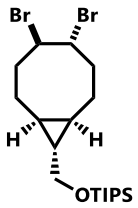
In a flame-dried flask under an atmosphere of argon, $LiAlH_4$ (1.48 g, 38.9 mmol, 1.0 equiv.) was suspended in diethyl ether (200 mL) and cooled to 0 °C (ice bath). A solution of ester **262** (7.64 g, 38.9 mmol, 1.0 equiv.) in diethyl ether (20 mL) was added drop-wise over 10 min. The reaction mixture was stirred for 15 min and then the reaction was quenched by the addition of water (1.5 mL), 1 m aqueous NaOH (1.5 mL) and water (4.5 mL). $MgSO_4$ was added and the reaction allowed to stir for 15 min before being filtrated and concentrated *in vacuo* to afford the title compound (5.92 g, >98%) as a colourless oil. The crude product was used without further purification.; ν_{max}(film) 3304, 2992, 2913, 2859, 1460, 1429, 1238, 1123, 1096 and 1026 cm^{-1}; ^1H NMR (400 MHz, 24.9 °C, $CDCl_3$) δ 5.99–5.68 (2 H, m, =CH), 3.47 (2 H, d, J = 7.0 Hz, CH_2OH), 2.34–2.24 (2 H, m, CH_2), 2.21–2.12 (2 H, m, CH_2), 2.11–2.02 (2 H, m, CH_2), 1.48–1.34 (2 H, m, CH_2), 1.28 (1 H, br s, OH), 0.83–0.73 (2 H, m, cyclopropane CH) and 0.69–0.63 (1 H, m, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 24.9 °C, $CDCl_3$) δ 130.2 (2 × =CH), 67.3 (CH_2OH), 29.0 (2 × CH_2), 28.9 (cyclopropane CH), 27.1 (2 × CH_2) and 22.1 (2 × cyclopropane CH); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{10}H_{16}NaO^+$ 175.1093; Found 175.1098. Recorded data consistent with previous values.[196]

264 (1*R,8*S**,9*r**)-4,5-Dibromobicyclo[6.1.0]non-9-ylmethanol**



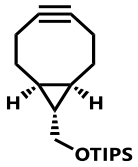
A solution of alkene **263** (5.92 g, 38.0 mmol, 1.0 equiv.) in dichloromethane (200 mL) was cooled to −40 °C. A solution of bromine (1.95 mL, 38.0 mmol, 1.0 equiv.) in dichloromethane (4 mL) was added drop-wise until a yellow colour persisted. The reaction was quenched by the addition of saturated aqueous sodium thiosulfate (8.0 mL) and the aqueous phase extracted with dichloromethane (3 × 8.0 mL). The combined organic layers were dried ($MgSO_4$) filtered and concentrated *in vacuo* to give the title compound (11.5 g, 97%) as a colourless oil. The crude product was used without further purification.; ν_{max}(film) 3337, 2990, 2920, 2862, 1466, 1427, 1381, 1258, 1184, 1099, 1080 and 1026 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 4.87–4.76 (2 H, m, CHBr), 3.45 (2 H, dd, J = 7.1, 1.2 Hz, CH_2), 2.66–2.57 (1 H, m, CH_2), 2.56–2.50 (1 H, m, CH_2), 2.24–2.14 (1 H, m, CH_2), 2.06–1.95 (3 H, m, CH_2), 1.43–1.26 (2 H, m, CH_2), 0.90–0.76 (2 H, m, cyclopropane CH) and 0.65–0.57 (1 H, m, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 66.6 (CH_2OH), 56.2 (CHBr), 53.2 (CHBr), 34.9 (CH_2), 34.8 (CH_2), 28.2 (cyclopropane CH), 24.4 (CH_2), 23.6 (CH_2), 22.5 (cyclopropane CH) and 19.8 (cyclopropane CH). Recorded data consistent with previous values.[196]

265 (1*R,8*S**,9*r**)-4,5-Dibromobicyclo[6.1.0]non-9-ylmethoxytriisopropylsilane**



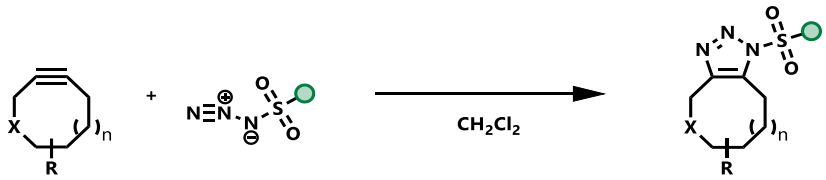
Alcohol **264** (3.00 g, 9.61 mmol, 1.0 equiv.), imidazole (1.31 g, 19.2 mmol, 2.0 equiv.) and *N*,*N*-dimethyl-4-aminopyridine (1.17 g, 9.61 mmol, 1.0 equiv.) were dissolved in dichloromethane (40 mL) and cooled to 0 °C (ice bath). Triisopropylsilylchloride (2.69 mL, 12.58 mmol, 1.3 equiv.) was added drop-wise and the reaction allowed to warm to ambient temperature overnight. Saturated aqueous sodium bicarbonate (20 mL) was added and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient from 2 to 10% EtOAc in petroleum ether) to afford the title compound (4.29 g, 95%) as a colourless oil. ν_{max}(film) 2940, 2862, 1462, 1427, 1381, 1246, 1192, 1103 and 1065 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 4.85–4.76 (2 H, m, CHBr), 3.66–3.59 (2 H, m, CH_2OTIPS), 2.71–2.63 (1 H, m, CH_2), 2.62–2.55 (1 H, m, CH_2), 2.29–2.19 (2 H, m, CH_2), 2.12–2.00 (2 H, m, CH_2), 1.49–1.29 (2 H, m, CH_2), 1.09–1.01 (21 H, m, 3 × *i*Pr), 0.96–0.81 (2 H, m, 2 × cyclopropane CH) and 0.58 (1 H, td, J = 6.1, 4.6 Hz, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 66.1 (CH_2OH), 56.6 (CHBr), 53.5 (CHBr), 35.1 (2 × CH_2), 28.2 (cyclopropane CH), 24.5 (CH_2), 23.8 (CH_2), 22.0 (cyclopropane CH), 19.2 (cyclopropane CH), 18.0 (6 × *i*Pr) and 12.1 (3 × *i*Pr).

266 (1*R,8*S**,9*r**)-Bicyclo[6.1.0]non-4-yn-9-ylmethoxytriisopropylsilane**



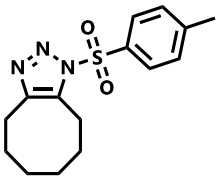
In a flame-dried flask under an atmosphere of argon, a solution of dibromobicycle **265** (4.00 g, 8.54 mmol, 1.0 equiv.) in THF (100 mL) was cooled to 0 °C (ice bath). KO*t*Bu (2.30 g, 20.5 mmol, 2.4 equiv.) was added in one portion and the reaction vigorously stirred for 1 h. The reaction was heated under reflux for a further 2 h before being cooled to ambient temperature. The reaction was quenched by the addition of saturated aqueous ammonium chloride ¬(50 mL). THF was removed *in vacuo* and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient from 2 to 10% EtOAc in petroleum ether) to give the title compound (1.89 g, 72%) as a yellow oil.; ν_{max}(film) 2940, 2864, 1462, 1445, 1383, 1248, 1134, 1098, 1067 and 1013 cm^{-1}; ^1H NMR (400 MHz, 27.0 °C, $CDCl_3$) δ 3.65 (2 H, d, J = 6.0 Hz, CH_2OTIPS), 2.43–2.36 (2 H, m, CH_2), 2.33–2.23 (2 H, m, CH_2), 2.17–2.09 (2 H, m, CH_2), 1.44–1.31 (2 H, m, CH_2), 1.07–1.04 (21 H, m, 3 × *i*Pr), 0.74–0.66 (2 H, m, cyclopropane CH) and 0.62–0.55 (1 H, m, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 27.0 °C, $CDCl_3$) δ 98.9 (2 × C≡C), 66.6 (CH_2OTIPS), 33.6 (2 × CH_2), 27.5 (cyclopropane CH), 22.1 (2 × cyclopropane CH), 21.6 (2 × CH_2), 18.0 (6 × *i*Pr) and 12.1 (3 × *i*Pr); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{34}NaOSi^+$ 329.2271; Found 329.2263.

General Procedure 2: Preparation of 1-STs by SPAAC



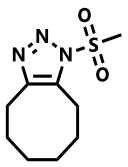
Cyclic alkyne (1.0 equiv.) was dissolved in CH_2Cl_2 (0.4 m in a flame-dried vial under an atmosphere of argon). Sulfonyl azide (1.0 equiv.) was added in one portion and the reaction stirred for 20 min. The reaction mixture was concentrated *in vacuo* to afford the triazole. Where required, purification was by flash column chromatography (SiO_2, gradient of 10−30% EtOAc in petroleum ether).

220 1-(4-Tolyl)sulfonyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



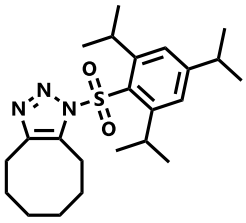
Cyclooctyne **218** (988 mg, 9.10 mmol, 1.7 equiv.) and 4-toluenesulfonyl azide (1.03 g, 5.20 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (5.0 mL) according to General Procedure 2 to give the title compound **220** (1.56 g, 98%) as a white solid. m.pt. 159–161 °C; ν_{max}(film) 2928, 2857, 1387, 1302, 1221, 1194 and 1090 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.93 (2 H, d, J = 8.5 Hz, ArH), 7.36 (2 H, d, J = 8.5 Hz, ArH), 3.07–3.03 (2 H, m, α–CH_2), 2.86–2.81 (2 H, m, α′–CH_2), 2.44 (3 H, s, CH_3), 1.84–1.78 (2 H, m, β–CH_2), 1.72–1.67 (2 H, m, β′–CH_2) and 1.44–1.36 (4 H, m, γ–CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 146.6 (Ar), 146.0 (triazole), 135.3 (triazole), 134.2 (Ar), 130.3 (2 × ArH), 128.3 (2 × ArH), 28.8 (β′–CH_2), 27.0 (β–CH_2), 25.7 (γ′–CH_2), 24.9 (γ–CH_2), 24.6 (α′–CH_2), 21.9 (α–CH_2) and 21.8 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{19}N_3NaO_2S^+$ 328.1090; Found 328.1090.

221 1-Methanesulfonyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



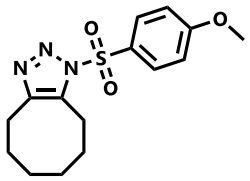
Cyclooctyne **218** (324 mg, 3.00 mmol, 0.94 equiv.) and methanesulfonyl azide (386 mg, 3.00 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (7.5 mL) according to General Procedure 2 to give the title compound **221** (725 mg, >98%) as a white solid. m.pt. 50–52 °C; ν_{max}(film) cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 3.52 (3 H, s, CH_3), 3.11–3.07 (2 H, m, α–CH_2), 2.94–2.89 (2 H, m, α′–CH_2), 1.89–1.83 (2 H, m, β–CH_2), 1.79–1.73 (2 H, m, β′–CH_2) and 1.52–1.40 (4 H, m, γ–CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 146.0 (triazole), 135.7 (triazole), 42.9 (CH_3), 28.8 (β′–CH_2), 26.9 (β–CH_2), 25.7 (α′–CH_2), 24.9 (α–CH_2), 24.6 (γ′–CH_2) and 21.7 (γ–CH_2); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_9H_{15}N_3NaO_2S^+$ 252.0777; Found 252.0769.

222 1-(2,4,6-Triisopropylbenzene)sulfonyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



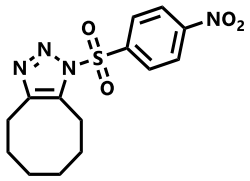
Cyclooctyne **218** (216 mg, 2.00 mmol, 1.0 equiv.) and 2,4,6-triisopropylbenzenesulfonyl azide (619 mg, 2.00 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (5.0 mL) according to General Procedure 2 to give the title compound **222** (743 mg, 89%) as a white solid. m.pt. 89–92 °C; ν_{max}(film) cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.22 (2 H, s, ArH), 4.02 (2 H, sept., J = 6.7 Hz, *i*Pr), 3.07–3.03 (2 H, m, α–CH_2), 2.94 (1 H, sept., J = 6.9 Hz, *i*Pr), 2.90–2.86 (2 H, m, α′–CH_2), 1.76–1.70 (4 H, m, β–CH_2), 1.49–1.39 (4 H, m, γ–CH_2), 1.26 (6 H, d, J = 6.9 Hz, *i*Pr) and 1.18 (12 H, d, J = 6.9 Hz, *i*Pr); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 155.9 (Ar), 152.7 (2 × Ar), 145.8 (triazole), 134.5 (triazole), 129.8 (Ar), 124.3 (2 × ArH), 34.4 (*i*Pr), 29.8 (2 × *i*Pr), 28.7 (β′–CH_2), 26.5 (β–CH_2), 25.7 (α–CH_2), 25.0 (α′–CH_2), 24.6 (γ′–CH_2), 24.4 (4 × *i*Pr), 23.4 (2 × *i*Pr) and 21.7 (γ–CH_2); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{35}N_3NaO_2S^+$ 440.2342; Found 440.2332. Recorded data consistent with previous values.[181]

223 1-(4-Methoxybenzene)sulfonyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



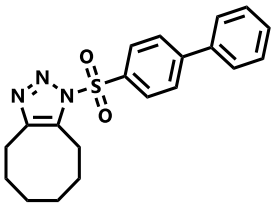
Cyclooctyne **218** (324 mg, 3.00 mmol, 1.0 equiv.) and 4-methoxybenzenesulfonyl azide (640 mg, 3.00 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (7.5 mL) according to General Procedure 2 to give the title compound **223** (961 mg, >98%) as a white solid. m.pt. 113–114 °C; ν_{max}(film) 2928, 2855, 1593, 1576, 1537, 1497, 1458, 1443, 1418, 1385, 1315, 1302, 1265, 1233, 1219, 1196, 1163, 1115, 1090 and 1018 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.99 (2 H, d, J = 9.0 Hz, Ar), 7.01 (2 H, d, J = 9.0 Hz, Ar), 3.88 (3 H, s, CH_3), 3.06 (2 H, br t, J = 6.3 Hz, α–CH_2), 2.84 (2 H, br t, J = 6.4 Hz, α′–CH_2), 1.84–1.78 (2 H, m, β–CH_2), 1.72–1.66 (2 H, m, β′–CH_2) and 1.44–1.35 (4 H, m, γ–CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 164.9 (Ar), 145.9 (triazole), 135.2 (triazole), 130.8 (2 × Ar), 128.2 (Ar), 114.9 (2 × Ar), 55.9 (OMe), 28.8 (β′–CH_2), 27.0 (β–CH_2), 25.7 (γ′–CH_2), 24.9 (γ–CH_2), 24.6 (α′–CH_2) and 21.9 (α–CH_2); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{15}H_{19}N_3NaO_3S^+$ 344.1039; Found 344.1039.

224 1-(4-Nitrobenzene)sulfonyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



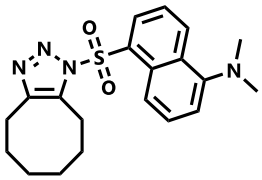
Cyclooctyne **218** (324 mg, 3.00 mmol, 1.0 equiv.) and 4-nitrobenzenesulfonyl azide (685 mg, 3.00 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (7.5 mL) according to General Procedure 2 to give the title compound **224** (1.00 g, >98%) as a white solid. m.pt. 121–122 °C; ν_{max}(film) 3107, 2930, 2857, 1607, 1574, 1533, 1443, 1393, 1348, 1304, 1233, 1219, 1192, 1173, 1107, 1086 and 1009 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.41 (2 H, d, J = 8.9 Hz, ArH), 8.27 (2 H, d, J = 8.9 Hz, ArH), 3.10–3.05 (2 H, m, α–CH_2), 2.87–2.83 (2 H, m, α′–CH_2), 1.88–1.82 (2 H, m, β–CH_2), 1.75–1.68 (2 H, m, β′–CH_2) and 1.46–1.37 (4 H, m, γ–CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 151.4 (Ar), 146.4 (triazole), 142.5 (Ar), 136.0 (triazole), 129.8 (2 × ArH), 124.8 (2 × ArH), 28.7 (β′–CH_2), 27.1 (β–CH_2), 25.6 (α′–CH_2), 24.9 (α–CH_2), 24.6 (γ′–CH_2) and 22.0 (γ–CH_2); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{16}N_4NaO_4S^+$ 359.0784; Found 359.0775.

225 1-(4-Biphenyl)sulfonyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



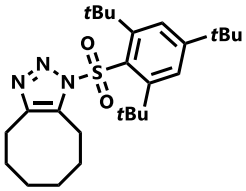
Cyclooctyne **218** (324 mg, 3.00 mmol, 1.0 equiv.) and 4-phenylbenzenesulfonyl azide (779 mg, 3.00 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (7.5 mL) according to General Procedure 2 to give the title compound **225** (798 mg, 72%) as a white solid. m.pt. 109–113 °C; ν_{max}(film) 3067, 2928, 2857, 1732, 1591, 1564, 1479, 1458, 1389, 1339, 1302, 1233, 1219, 1171, 1090 and 1007 cm^{-1}; ^1H NMR (500 MHz, 25.1 °C, $CDCl_3$) δ 8.12 (2 H, d, J = 8.6 Hz, ArH), 7.76 (2 H, d, J = 8.6 Hz, ArH), 7.60–7.56 (2 H, m, ArH), 7.51–7.41 (3 H, m, ArH), 3.10 (2 H, br t, J = 6.3 Hz, α–CH_2), 2.86 (2 H, br t, J = 6.4 Hz, α′–CH_2), 1.87–1.81 (2 H, m, β–CH_2), 1.75–1.68 (2 H, m, β′–CH_2) and 1.46–1.37 (4 H, m, γ–CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 148.2 (Ar), 146.1 (triazole), 138.5 (Ar), 135.5 (Ar), 135.5 (triazole), 129.2 (2 × ArH), 129.1 (Ar), 128.8 (2 × ArH), 128.2 (2 × ArH), 127.4 (2 × ArH), 28.8 (β′–CH_2), 27.1 (β–CH_2), 25.7 (γ′–CH_2), 25.0 (γ–CH_2), 24.6 (α′–CH_2) and 22.0 (α–CH_2); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{21}N_3NaO_2S^+$ 390.1247; Found 390.1235.

226 1-(5-Dimethylaminonaphth-1-yl)sulfonyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



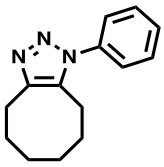
Cyclooctyne **218** (324 mg, 3.00 mmol, 1.0 equiv.) and 4-biphenylsulfonyl azide (829 mg, 3.00 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (7.5 mL) according to General Procedure 2 to give the title compound **226** (1.08 g, 94%) as a yellow solid. m.pt. 116–118 °C; ν_{max}(film) 2928, 2857, 2791, 1612, 1568, 1504, 1477, 1454, 1381, 1354, 1304, 1234, 1202, 1186, 1171, 1153, 1142, 1094, 1074 and 1061 cm^{-1}; ^1H NMR (500 MHz, 25.1 °C, $CDCl_3$) δ 8.68 (1 H, dt, J = 8.5, 1.0 Hz, Dansyl Ar), 8.51 (1 H, dd, J = 7.5, 1.3 Hz, Dansyl Ar), 8.40 (1 H, d, J = 8.7 Hz, Dansyl Ar), 7.61 (1 H, dd, J = 8.5, 7.5 Hz, Dansyl Ar), 7.55 (1 H, dd, J = 8.7, 7.6 Hz, Dansyl Ar), 7.17 (1 H, dd, J = 7.6, 1.0 Hz, Dansyl Ar), 2.95 (2 H, br t, J = 6.3 Hz, α–CH_2), 2.85 (6 H, s, NMe_2), 2.80 (2 H, br t, J = 6.4 Hz, α′–CH_2), 1.70–1.62 (4 H, m, β–CH_2) and 1.37–1.30 (4 H, m, γ–CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 152.0 (Dansyl Ar), 146.0 (triazole), 135.0 (triazole), 133.5 (Dansyl Ar), 132.1 (Dansyl Ar), 131.3 (Dansyl Ar), 129.8 (Dansyl Ar), 129.8 (Dansyl Ar), 129.6 (Dansyl Ar), 122.9 (Dansyl Ar), 118.3 (Dansyl Ar), 116.0 (Dansyl Ar), 45.4 (2 × CH_3), 28.5 (β′–CH_2), 26.6 (β–CH_2), 25.6 (γ′–CH_2), 24.9 (γ–CH_2), 24.5 (α′–CH_2) and 22.0 (α–CH_2); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{20}H_{24}N_4NaO_2S^+$ 407.1512; Found 407.1512.

463 1-(2,4,6-Tritertbutylbenzene)sulfonyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



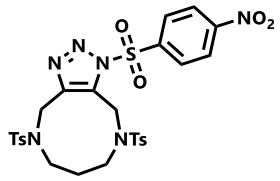
Cyclooctyne **218** (216 mg, 2.00 mmol, 20.0 equiv.) and 2,4,6-tri*tert*butylbenzenesulfonyl azide (35.0 mg, 0.10 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (1.0 mL) according to General Procedure 2 to give the title compound **463** (45.0 mg, >98%) as a white solid. ν_{max}(film) 2928, 1587, 1459, 1364, 1347, 1185 and 1023 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.54 (2 H, s, Ar), 2.91–2.85 (2 H, m, CH_2), 2.50–2.43 (2 H, m, CH_2), 1.82–1.69 (4 H, m, 2 × CH_2), 1.44–1.40 (4 H, m, CH_2), 1.40 (18 H, s, 6 × CH_3) and 1.33 (9 H, s, 3 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 157.0 (2 × Ar), 155.2 (Ar), 145.8 (triazole C5), 135.4 (triazole C4), 133.1 (Ar), 126.7 (2 × ArH), 41.0 (2 × *t*Bu), 35.1 (*t*Bu), 33.2 (6 × CH_3), 30.9 (3 × CH_3), 28.2 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 24.6 (CH_2), 24.4 (CH_2) and 21.3 (CH_2). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{41}N_3NaO_2S^+$ 482.2812; Found 482.2811

218-Ph 1-Phenyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



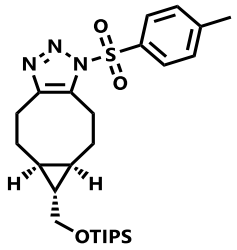
Cyclooctyne **218** (324 mg, 3.00 mmol, 1.0 equiv.) and phenyl azide (357 mg, 3.00 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (7.5 mL) according to General Procedure 2 to give the title compound **218-Ph** (670 mg, >98%) as a white solid.; ν_{max}(film) 2928, 2855, 1597, 1505, 1454, 1242, 1103 and 1003 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.55–7.48 (3 H, m, ArH), 7.44–7.41 (2 H, m, ArH), 2.99–2.95 (2 H, m, CH_2), 2.77–2.73 (2 H, m, CH_2), 1.86–1.72 (4 H, m, 2 × CH_2) and 1.58–1.49 (4 H, m, 2 × CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 145.1 (triazole), 136.7 (triazole), 134.0 (Ar), 129.4 (2 × ArH), 129.3 (ArH), 125.3 (2 × ArH), 28.2 (CH_2), 27.5 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 24.5 (CH_2) and 22.0 (CH_2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{18}N_3^+$ 228.1495; Found 228.1498. Recorded data consistent with previous values.[343]

258



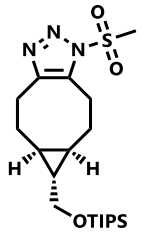
Cyclic alkyne **257** (213 mg, 0.492 mmol, 1.0 equiv.) and 4-nitrobenzenesulfonyl azide (124 mg, 0.542 mmol, 1.1 equiv.) were mixed in CH_2Cl_2 (5.0 mL) according to General Procedure 2 to give the title compound **258** (45.0 mg, >98%) as a white waxy solid.; ^{1}H NMR (500 MHz, 24.9 °C, $CDCl_3$) δ 8.42 (4 H, app. s, 2 × NsAr), 7.79 (2 H, d, *J* = 8.3 Hz, TsAr), 7.69 (2 H, d, *J* = 8.3 Hz, TsAr), 7.42 (2 H, d, *J* = 8.0 Hz, TsAr), 7.34 (2 H, d, *J* = 8.0 Hz, TsAr), 4.85 (2 H, s, CH_2), 4.46 (2 H, s, CH_2), 3.30 (2 H, t, *J* = 5.6 Hz, CH_2), 3.19 (2 H, t, *J* = 5.2 Hz, CH_2), 2.49 (3 H, s, CH_3), 2.44 (3 H, s, CH_3) and 2.08 (2 H, tt, *J* = 5.6, 5.2 Hz, CH_2); ^{13}C{^{1}H} NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 151.5 (NsAr), 144.7 (Triazole C5), 144.2 (TsAr), 143.6 (TsAr), 142.0 (NsAr), 135.0 (TsAr), 133.7 (TsAr), 133.5 (Triazole C4), 130.6 (2 × NsArH), 130.2 (2 × TsArH), 129.9 (2 × TsArH), 127.6 (4 × TsArH), 124.6 (2 × NsArH), 50.1 (CH_2), 49.8 (CH_2), 46.2 (CH_2), 44.2 (CH_2), 30.1 (CH_2), 21.6 (CH_3) and 21.6 (CH_3).

268 (5a*S,6*S**,6a*R**)-1-(4-Tolyl)sulfonyl-6-triisopropylsilyloxymethyl-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6]cycloocta[1,2-*d*][1,2,3]triazole**



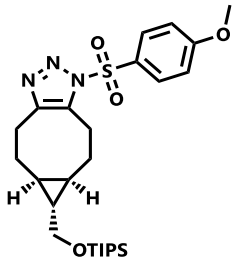
(1*R**,8*S**,9*r**)-Bicyclo[6.1.0]non-4-yn-9-ylmethoxytriisopropylsilane **266** (50 mg, 0.16 mmol, 1.0 equiv.) and 4-toluenesulfonyl azide (32 mg, 0.16 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (410 µL) according to General Procedure 2 to give the title compound **268** (81 mg, >98%) as a colourless oil. ν_{max}(film) 2941, 2864, 1595, 1462, 1389, 1196, 1177, 1092, 1065 and 1013 cm^{-1}; ^1H NMR (400 MHz, 25.5 °C, $CDCl_3$) δ 7.92 (2 H, d, *J* = 8.2 Hz, Ts Ar), 7.36 (2 H, d, *J* = 8.2 Hz, Ts Ar), 3.59 (1 H, dd, *J* = 10.5, 5.5 Hz, CH_AOTIPS), 3.53 (1 H, dd, *J* = 10.5, 5.7 Hz, CH_BOTIPS), 3.30 (1 H, dd, *J* = 7.2, 3.7 Hz, CH_A), 3.03–2.92 (2 H, m, CH_2), 2.85 (1 H, ddd, *J* = 15.8, 9.2, 4.2 Hz, CH_B), 2.44 (3 H, s, CH_3), 2.43–2.27 (2 H, m, CH_2), 1.48–1.30 (2 H, m, CH_2), 1.10–0.98 (21 H, m, 3 × *i*Pr) and 0.77–0.59 (3 H, m, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 24.8 °C, $CDCl_3$) δ 146.6 (Ts Ar), 146.2 (triazole), 135.8 (triazole), 134.2 (Ts Ar), 130.3 (2 × Ts Ar), 128.4 (2 × Ts Ar), 65.9 (CH_2OTIPS), 28.2 (cyclopropane CH), 27.3 (CH_2), 26.8 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 21.8 (CH_3), 21.4 (cyclopropane CH), 20.7 (cyclopropane CH), 18.0 (6 × *i*Pr) and 12.0 (3 × *i*Pr); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{41}N_3NaO_3SSi^+$ 526.2530; Found 526.2526.

269 (5a*S,6*S**,6a*R**)-1-Methanesulfonyl-6-triisopropylsilyloxymethyl-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6]cycloocta[1,2-*d*][1,2,3]triazole**



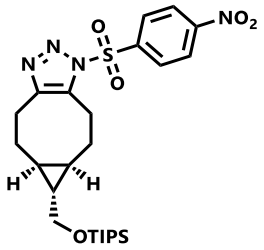
(1*R**,8*S**,9*r**)-Bicyclo[6.1.0]non-4-yn-9-ylmethoxytriisopropylsilane **266** (50 mg, 0.16 mmol, 1.0 equiv.) and methanesulfonyl azide (20 mg, 0.16 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (410 µL) according to General Procedure 2 to give the title compound **269** (69 mg, >98%) as a colourless oil. ν_{max}(film) 2941, 2864, 1566, 1464, 1379, 1193, 1179, 1131, 1103, 1066 and 1015 cm^{-1}; ^1H NMR (400 MHz, 20.7 °C, $CDCl_3$) δ 3.65–3.56 (2 H, m, CH_2OTIPS), 3.55 (3 H, s, CH_3), 3.32 (1 H, ddd, *J* = 16.7, 7.1, 3.6 Hz, CH_2), 3.08–2.99 (2 H, m, CH_2), 2.92 (1 H, ddd, *J* = 15.9, 9.2, 4.2 Hz, CH_2), 2.50–2.41 (1 H, m, CH_2), 2.40–2.32 (1 H, m, CH_2), 1.56–1.42 (2 H, m, CH_2), 1.08–1.01 (21 H, m, 3 × *i*Pr), 0.81–0.74 (2 H, m, cyclopropane CH) and 0.71–0.64 (1 H, m, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 21.4 °C, $CDCl_3$) δ 146.1 (triazole), 136.0 (triazole), 65.9 (CH_2OTIPS), 42.9 (CH_3), 28.1 (cyclopropane CH), 27.2 (CH_2), 26.6 (CH_2), 25.1 (CH_2), 22.8 (CH_2), 21.3 (cyclopropane CH), 20.6 (cyclopropane CH), 18.0 (6 × *i*Pr) and 12.0 (3 × *i*Pr); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{37}N_3NaO_3SSi^+$ 450.2217; Found 450.2206.

270 (5a*S,6*S**,6a*R**)-1-(4-Methoxybenzene)sulfonyl-6-triisopropylsilyloxymethyl-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6]cycloocta[1,2-*d*][1,2,3]triazole**



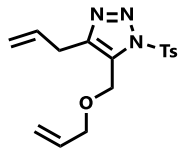
(1*R**,8*S**,9*r**)-Bicyclo[6.1.0]non-4-yn-9-ylmethoxytriisopropylsilane **266** (50 mg, 0.16 mmol, 1.0 equiv.) and 4-methoxybenzenesulfonyl azide (35 mg, 0.16 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (410 µL) according to General Procedure 2 to give the title compound **270** (84 mg, >98%) as a colourless oil. ν_{max}(film) 2941, 2864, 1593, 1578, 1499, 1462, 1389, 1315, 1267, 1198, 1169, 1094, 1065 and 1020 cm^{-1}; ^1H NMR (400 MHz, 20.8 °C, $CDCl_3$) δ 7.98 (2 H, d, *J* = 9.0 Hz, Ar), 7.01 (2 H, d, *J* = 9.0 Hz, Ar), 3.80 (3 H, s, OMe), 3.59 (1 H, dd, *J* = 10.5, 5.6 Hz, CH_AOTIPS), 3.53 (1 H, dd, *J* = 10.5, 5.9 Hz, CH_BOTIPS), 3.29 (1 H, ddd, *J* = 16.5, 7.2, 3.6 Hz, CH_A), 3.03–2.92 (2 H, m, CH_2), 2.84 (1 H, ddd, *J* = 15.9, 9.2, 4.1 Hz, CH_B), 2.46–2.36 (1 H, m, CH_2), 2.37–2.36 (1 H, m, CH_2), 1.47–1.30 (2 H, m, CH_2), 1.09–0.98 (21 H, m, 3 × *i*Pr) and 0.77–0.59 (3 H, m, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 21.4 °C, $CDCl_3$) δ 164.9 (Ar), 146.2 (triazole), 135.6 (triazole), 130.9 (2 × Ar), 128.1 (Ar), 114.9 (2 × Ar), 65.9 (CH_2OTIPS), 55.9 (OMe), 28.2 (cyclopropane CH), 27.3 (CH_2), 26.8 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 21.4 (cyclopropane CH), 20.8 (cyclopropane CH), 18.0 (6 × *i*Pr) and 12.0 (3 × *i*Pr); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{41}N_3NaO_4SSi^+$ 542.2479; Found 542.2470.

271 (5a*S,6*S**,6a*R**)-1-(4-Nitrobenzene)sulfonyl-6-triisopropylsilyloxymethyl-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6]cycloocta[1,2-*d*][1,2,3]triazole**



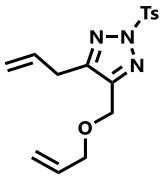
(1*R**,8*S**,9*r**)-Bicyclo[6.1.0]non-4-yn-9-ylmethoxytriisopropylsilane **266** (50 mg, 0.16 mmol, 1.0 equiv.) and 4-nitrobenzenesulfonyl azide (37 mg, 0.16 mmol, 1.0 equiv.) were mixed in CH_2Cl_2 (410 µL) according to General Procedure 2 to give the title compound **271** (84 mg, 96%) as a white waxy solid. m.pt. 136 °C dec.; ν_{max}(film) 3107, 2941, 2864, 1609, 1537, 1464, 1406, 1396, 1349, 1315, 1198, 1184, 1090, 1067 and 1013 cm^{-1}; ^1H NMR (400 MHz, 27.0 °C, $CDCl_3$) δ 8.41 (2 H, d, *J* = 9.1 Hz, Ns Ar), 8.26 (2 H, d, *J* = 9.1 Hz, Ns Ar), 3.62 (1 H, dd, *J* = 10.6, 5.5 Hz, CH_AOTIPS), 3.55 (1 H, dd, *J* = 10.6, 5.8 Hz, CH_BOTIPS), 3.30 (1 H, ddd, *J* = 16.7, 7.1, 3.7 Hz, CH_A), 3.07–2.94 (2 H, m, CH_2), 2.93–2.82 (1 H, m, CH_B), 2.50–2.40 (1 H, m, CH_2), 2.39–2.28 (1 H, m, CH_2), 1.52–1.37 (2 H, m, CH_2), 1.07–0.98 (21 H, m, 3 × *i*Pr) and 0.79–0.61 (3 H, m, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 27.0 °C, $CDCl_3$) δ 151.4 (Ns Ar), 146.5 (triazole), 142.5 (Ns Ar), 136.4 (triazole), 129.9 (2 × Ns Ar), 124.8 (2 × Ns Ar), 65.7 (CH_2OTIPS), 28.2 (cyclopropane CH), 27.1 (CH_2), 26.7 (CH_2), 25.1 (CH_2), 22.9 (CH_2), 21.2 (cyclopropane CH), 20.5 (cyclopropane CH), 18.0 (6 × *i*Pr) and 12.0 (3 × *i*Pr); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{38}N_4NaO_5SSi^+$ 557.2224; Found 557.2204.

292 4-Allyl-5-((allyloxy)methyl)-1-tosyl-1,2,3-triazole



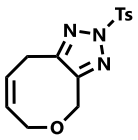
In a flame-dried flask under an atmosphere of argon, allyl propargyl ether (1.00 g, 10.4 mmol, 1.0 equiv.) was dissolved in THF (50 mL) and cooled to −78 °C (dry ice, acetone). *n*BuLi (2.5 m solution in hexanes, 4.16 mL, 10.4 mmol, 1.0 equiv.) was added dropwise and the reaction stirred for 15 min. Tosyl azide (1.45 mL, 9.36 mmol, 0.9 equiv.) was added in one portion and the reaction stirred for 45 min at −78 °C. Allyl iodide (1.14 mL, 12.5 mmol, 1.2 equiv.) was added dropwise and the reaction stirred for 1 h. Saturated aqueous ammonium chloride (20 mL) was added and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, rapid gradient of 10−30% ethyl acetate in petroleum ether) to give the title compound as a yellow oil (800 mg, 26%). ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.03 (2 H, d, J = 8.5 Hz, Ar), 7.32 (2 H, d, J = 8.5 Hz, Ar), 5.97–5.85 (2 H, m, 2 × =CH), 5.32–5.23 (2 H, m, $=CH_2$), 5.11–5.04 (2 H, m, $=CH_2$), 4.74 (2 H, s, CH_2), 3.99 (2 H, dt, J = 5.7, 1.2 Hz, CH_2), 3.48 (2 H, dt, J = 6.4, 1.5 Hz, CH_2) and 2.43 (3 H, s, CH_3); ^{13}C{^{1}H} NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 146.8 (Ar), 145.2 (triazole C4), 134.1 (=CH), 133.8 (Ar), 133.8 (=CH), 131.6 (triazole C5), 130.0 (2 × ArH), 129.0 (2 × ArH), 118.0 ($=CH_2$), 117.0 ($=CH_2$), 71.8 (CH_2), 59.0 (CH_2), 29.4 (CH_2) and 21.8 (CH_3).

292-iso 4-Allyl-5-((allyloxy)methyl)-2-tosyl-1,2,3-triazole



^{1}H NMR (400 MHz, 21.0 °C, $CDCl_3$) δ 7.94 (2 H, d, J = 8.5 Hz, Ar), 7.33 (2 H, d, J = 8.5 Hz, Ar), 5.96–5.79 (2 H, m, 2 × =CH), 5.28–5.14 (2 H, m, $=CH_2$), 5.11–5.02 (2 H, m, $=CH_2$), 4.55 (2 H, s, CH_2), 3.93 (2 H, dt, J = 5.7, 1.3 Hz, CH_2), 3.51 (2 H, dd, J = 6.5, 1.5 Hz, CH_2) and 2.42 (3 H, s, CH_3); ^{13}C{^{1}H} NMR (101 MHz, 20.4 °C, $CDCl_3$) δ 150.2 (triazole C4), 147.8 (Ar), 146.5 (triazole C5), 133.7 (=CH), 133.1 (Ar), 132.8 (=CH), 130.1 (2 × ArH), 128.6 (2 × ArH), 118.0 ($=CH_2$), 117.5 ($=CH_2$), 71.6 (CH_2), 62.6 (CH_2), 29.6 (CH_2) and 21.8 (CH_3).

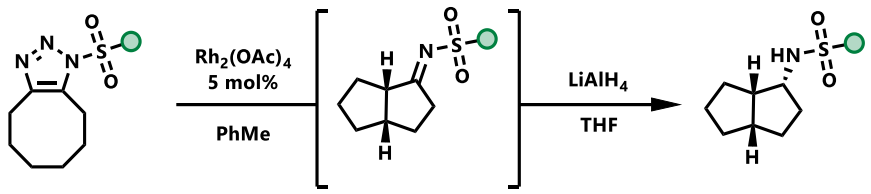
294 2-Tosyl-2,4,6,9-tetrahydrooxocino[3,4-*d*][1,2,3]triazole



In a flame-dried flask under an atmosphere of argon, triazole **292** (550 mg, 1.65 mmol, 1.0 equiv.) was dissolved in PhMe (110 mL). The solution was sparged with argon for 1 h and Hoveyda-Grubbs II catalyst (31 mg, 0.05 mmol, 3 mol %) was added. The mixture was heated to reflux for 16 h and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient of 5−25% ethyl acetate in petroleum ether) to afford the title compound as a yellow oil (172 mg, 34%). ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.93 (2 H, d, J = 8.4 Hz, Ar), 7.34 (2 H, d, J = 8.4 Hz, Ar), 5.86 (1 H, dtt, J = 11.3, 7.7, 1.8 Hz, =CH), 5.63 (1 H, dtt, J = 11.3, 7.5, 1.0 Hz, =CH), 4.78 (2 H, s, CH_2), 4.34 (2 H, dd, J = 7.5, 1.8 Hz, CH_2), 3.61 (2 H, dd, J = 7.7, 1.0 Hz, CH_2) and 2.43 (3 H, s, CH_3); ^{13}C{^{1}H} NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 150.8 (triazole C5), 149.9 (triazole C4), 146.4 (Ar), 133.2 (Ar), 130.1 (2 × ArH), 129.4 (=CH), 128.6 (2 × ArH), 126.4 (=CH), 70.8 (CH_2), 65.9 (CH_2), 24.5 (CH_2) and 21.8 (CH_3).

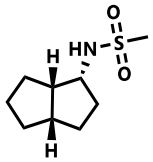
7.2.3 Preparation of [3.3.0]-bicyclic compounds

General Procedure 3: Rhodium(II)-catalysed transannular C–H insertion



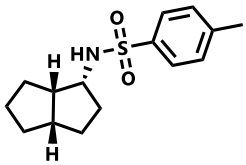
Sulfonyl triazole (1.0 equiv.) was dissolved in PhMe (0.04 M) in a flame dried vial under an atmosphere of argon. $Rh_2(OAc)_4$ (5 mol %) was added and the vial sealed with a Teflon cap and heated to 50 °C (aluminium block) until complete conversion of starting material was observed by TLC(0.5–2 h). The reaction mixture was cooled to ambient temperature and diluted with THF (0.5 reaction volumes). $LiAlH_4$ (1.5 equiv.) was added in one portion and the reaction stirred at this temperature for 15 min. The reaction was quenched by consecutive addition of water, 1 m aqueous NaOH, a further portion of water and stirred for 5 min. Anhydrous $MgSO_4$ was added and the reaction mixture filtered, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient 5–30% EtOAc in petroleum ether) to afford the sulfonamide product.

235 (1*R,3a*S**,6a*S**)-1-Methanesulfonylaminooctahydropentalene**



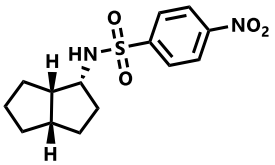
Triazole **221** (46 mg, 0.20 mmol, 1.0 equiv.) was treated was treated according to General Procedure 3 with $Rh_2(OAc)_4$ (4 mg, 0.01 mmol, 5.0 mol %) in PhMe (10 mL) at 50 °C then $LiAlH_4$ (15 mg, 0.40 mmol, 2.0 equiv.) and THF (5.0 mL) to give the title compound **235** (18 mg, 44%) as a colourless wax. m.pt. 64–67 °C; ν_{max}(film) 3275, 2945, 2864, 1454, 1414, 1312, 1153, 1132 and 1086 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 4.28 (1 H, d, J = 8.3 Hz, NH), 3.73–3.61 (1 H, m, CH), 2.91 (3 H, s, CH_3), 2.56–2.46 (1 H, m, CH), 2.44–2.34 (1 H, m, CH), 1.95–1.85 (1 H, m, CH_2), 1.85–1.78 (1 H, m, CH_2), 1.68–1.54 (2 H, m, CH_2), 1.44–1.15 (5 H, m, CH_2) and 1.11–1.00 (1 H, m, CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 57.3 (CH), 45.9 (CH), 41.4 (CH), 41.4 (Ms CH_3), 35.6 (CH_2), 31.0 (CH_2), 29.5 (CH_2), 28.2 (CH_2) and 27.4 (CH_2); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_9H_{17}NNaO_2S^+$ 226.0872; Found 226.0872.

232 (1*R,3a*S**,6a*S**)-1-(4-Tolyl)sulfonylaminooctahydropentalene**



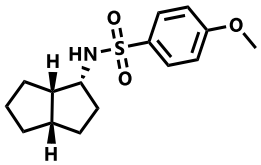
Triazole **220** (61 mg, 0.20 mmol, 1.0 equiv.) was treated was treated according to General Procedure 3 with $Rh_2(OAc)_4$ (4 mg, 0.01 mmol, 5.0 mol %) in PhMe (10 mL) at 50 °C then $LiAlH_4$ (15 mg, 0.40 mmol, 2.0 equiv.) and THF (5.0 mL) to give the title compound **232** (34 mg, 61%) as a colourless oil. ν_{max}(film) 3277, 2943, 2862, 1599, 1537, 1495, 1452, 1319, 1306, 1288, 1157 and 1094 cm^{-1}; ^1H NMR (400 MHz, 24.9 °C, $CDCl_3$) δ 7.77 (2 H, d, *J* = 7.9 Hz, ArH), 7.29 (2 H, d, *J* = 7.9 Hz, ArH), 4.52 (1 H, d, *J* = 8.2 Hz, NH), 3.59–3.50 (1 H, m, CH), 2.43 (3 H, s, CH_3), 2.37–2.28 (2 H, m, CH), 1.90–1.82 (1 H, m, CH_2), 1.66–1.39 (4 H, m, CH_2), 1.31–1.14 (4 H, m, CH_2) and 1.08–1.00 (1 H, m, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 143.2 (Ar), 138.0 (Ar), 129.6 (2 × ArH), 127.1 (2 × ArH), 57.1 (CH), 45.5 (CH), 41.3 (CH), 35.5 (CH_2), 30.6 (CH_2), 29.4 (CH_2), 28.1 (CH_2), 27.3 (CH_2) and 21.5 (CH_2); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{21}NNaO_2S^+$ 302.1185; Found 302.1180.

236 (1*R,3a*S**,6a*S**)-1-(4-Nitrobenzene)sulfonylaminooctahydropentalene**



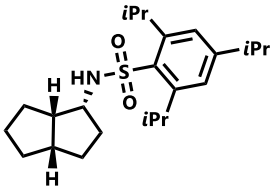
Triazole **224** (67 mg, 0.20 mmol, 1.0 equiv.) was treated was treated according to General Procedure 3 with $Rh_2(OAc)_4$ (4 mg, 0.01 mmol, 5.0 mol %) in PhMe (10 mL) at 50 °C then $LiAlH_4$ (15 mg, 0.40 mmol, 2.0 equiv.) and THF (5.0 mL) to give the title compound **236** (5 mg, 8%) as a yellow oil. ν_{max}(film) 3277, 2947, 2866, 1607, 1530, 1452, 1437, 1348, 1312, 1163 and 1094 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.29 (2 H, d, *J* = 8.9 Hz, Ns Ar), 8.01 (2 H, d, *J* = 8.9 Hz, Ns Ar), 4.64 (1 H, d, *J* = 8.4 Hz, NH), 3.61–3.52 (1 H, m, CH), 2.36–2.24 (2 H, m, CH), 1.87–1.78 (1 H, m, CH_2), 1.64–1.58 (1 H, m, CH_2), 1.56–1.46 (2 H, m, CH_2), 1.41–1.33 (1 H, m, CH_2), 1.33–1.12 (3 H, m, CH_2) and 1.10–0.96 (2 H, m, CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 150.0 (Ns Ar), 147.0 (Ns Ar), 128.3 (2 × Ns Ar), 124.4 (2 × Ns Ar), 57.4 (CH), 45.6 (CH), 41.3 (CH), 35.5 (CH_2), 30.7 (CH_2), 29.3 (CH_2), 28.1 (CH_2) and 27.3 (CH_2); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{14}H_{18}N_2NaO_4S^+$ 333.0879; Found 333.0879.

237 (1*R,3a*S**,6a*S**)-1-(4-Methoxybenzene)sulfonylaminooctahydropentalene**



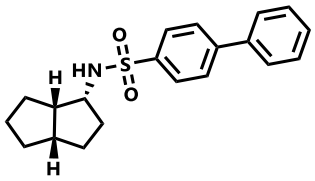
Triazole **223** (64 mg, 0.20 mmol, 1.0 equiv.) was treated was treated according to General Procedure 3 with $Rh_2(OAc)_4$ (4 mg, 0.01 mmol, 5.0 mol %) in PhMe (10 mL) at 50 °C then $LiAlH_4$ (15 mg, 0.40 mmol, 2.0 equiv.) and THF (5.0 mL) to give the title compound **237** (45 mg, 77%) as a colourless oil. ν_{max}(film) 3257, 2945, 2864, 1597, 1580, 1499, 1441, 1302, 1258, 1180, 1153, 1096 and 1026 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.82 (2 H, d, J = 8.9 Hz, ArH), 6.96 (2 H, d, J = 8.9 Hz, ArH), 4.52 (1 H, d, J = 8.3 Hz, NH), 3.87 (3 H, s, CH_3), 3.57–3.47 (1 H, m, CH), 2.38–2.27 (2 H, m, 2 × CH), 1.90–1.82 (1 H, m, CH_2), 1.65–1.59 (1 H, m, CH_2), 1.59–1.48 (2 H, m, CH_2), 1.47–1.40 (1 H, m, CH_2), 1.58–1.11 (4 H, m, CH_2) and 1.08–1.00 (1 H, m, CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 162.7 (Ar), 132.6 (Ar), 129.2 (2 × ArH), 114.1 (2 × Ar), 57.1 (CH), 55.6 (CH), 45.5 (CH_3), 41.3 (CH), 35.5 (CH_2), 30.6 (CH_2), 29.4 (CH_2), 28.1 (CH_2) and 27.3 (CH_2); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{15}H_{21}NNaO_3S^+$ 318.1134; Found 318.1134.

238 (1*R,3a*S**,6a*S**)-1-(2,4,6-Triisopropylbenzene)sulfonylaminooctahydropentalene**



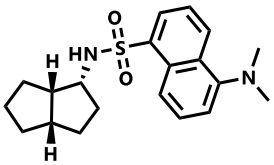
Triazole **222** (84 mg, 0.20 mmol, 1.0 equiv.) was treated was treated according to General Procedure 3 with $Rh_2(OAc)_4$ (4 mg, 0.01 mmol, 5.0 mol %) in PhMe (10 mL) at 50 °C then $LiAlH_4$ (15 mg, 0.40 mmol, 2.0 equiv.) and THF (5.0 mL) to give the title compound **238** (28 mg, 36%) as a colourless oil. ν_{max}(film) 3271, 2953, 2866, 1601, 1462, 1425, 1383, 1362, 1317, 1152, 1084 and 1041 cm^{-1}; ^1H NMR (500 MHz, 24.9 °C, $CDCl_3$) δ 7.15 (2 H, s, ArH), 4.36 (1 H, d, *J* = 8.1 Hz, NH), 4.18 (2 H, sept., *J* = 6.7 Hz, *i*Pr), 3.60–3.50 (1 H, m, CH), 2.88 (1 H, sept., *J* = 6.7 Hz, *i*Pr), 2.53–2.45 (1 H, m, CH), 2.42–2.32 (1 H, m, CH), 1.94–1.86 (1 H, m, CH_2), 1.68–1.49 (4 H, m, CH_2), 1.36–1.30 (2 H, m, CH_2), 1.27 (6 H, d, *J* = 6.7 Hz, 2 × *i*Pr), 1.25 (12 H, d, *J* = 6.7 Hz, 4 × *i*Pr) and 1.11–1.03 (3 H, m, CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 152.5 (Ar), 150.2 (2 × Ar), 133.1 (Ar), 123.7 (2 × ArH), 56.7 (CH), 46.1 (CH), 41.1 (CH), 35.6 (CH_2), 34.1 (*i*Pr), 30.6 (CH_2), 29.6 (2 × *i*Pr), 29.5 (CH_2), 28.2 (CH_2), 27.4 (CH_2), 24.9 (2 × *i*Pr), 24.8 (2 × *i*Pr) and 23.6 (2 × *i*Pr); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{37}NNaO_2S^+$ 414.2437; Found 414.2425.

239 (1*R,3a*S**,6a*S**)-1-(4-Biphenyl)sulfonylaminooctahydropentalene**



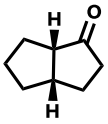
Triazole **225** (74 mg, 0.20 mmol, 1.0 equiv.) was treated was treated according to General Procedure 3 with $Rh_2(OAc)_4$ (4 mg, 0.01 mmol, 5.0 mol %) in PhMe (10 mL) at 50 °C then $LiAlH_4$ (15 mg, 0.40 mmol, 2.0 equiv.) and THF (5.0 mL) to give the title compound **239** (38 mg, 55%) as a colourless wax. m.pt. 146–149 °C; ν_{max}(film) 3277, 2947, 2864, 1595, 1481, 1450, 1321, 1159 and 1098 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.95 (2 H, d, *J* = 8.4 Hz, ArH), 7.65–7.60 (2 H, m, ArH), 7.51–7.46 (2 H, m, ArH), 7.42 (2 H, d, *J* = 8.4 Hz, ArH), 7.43–7.39 (1 H, m, ArH), 4.57 (1 H, d, *J* = 8.3 Hz, NH), 3.65–3.58 (1 H, m, CH), 2.41–2.31 (2 H, m, 2 × CH), 1.92–1.85 (1 H, m, CH_2), 1.72–1.65 (1 H, m, CH_2), 1.62–1.44 (3 H, m, CH_2), 1.38–1.14 (4 H, m, CH_2) and 1.11–0.98 (1 H, m, CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 145.4 (Ar), 139.5 (Ar), 139.3 (Ar), 129.0 (2 × ArH), 128.4 (Ar), 127.6 (2 × ArH), 127.6 (2 × ArH), 127.3 (2 × ArH), 57.2 (CH), 45.6 (CH), 41.3 (CH), 35.5 (CH_2), 30.7 (CH_2), 29.4 (CH_2), 28.1 (CH_2) and 27.3 (CH_2); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{23}NNaO_2S^+$ 364.1342; Found 364.1342.

240 (1*R,3a*S**,6a*S**)-1-(5-Dimethylaminonaphth-1-yl)sulfonylaminooctahydropentalene**



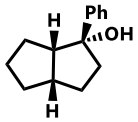
Triazole **226** (77 mg, 0.20 mmol, 1.0 equiv.) was treated was treated according to General Procedure 3 with $Rh_2(OAc)_4$ (4 mg, 0.01 mmol, 5.0 mol %) in PhMe (10 mL) at 50 °C then $LiAlH_4$ (15 mg, 0.40 mmol, 2.0 equiv.) and THF (5.0 mL) to give the title compound **240** (54 mg, 76%) as a yellow oil. ν_{max}(film) 3288, 2943, 2864, 2787, 1612, 1587, 1576, 1504, 1452, 1406, 1310, 1233, 1202, 1159, 1144, 1072 and 1063 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.53 (1 H, d, J = 8.5 Hz, Dansyl Ar), 8.32–8.24 (2 H, m, Dansyl Ar), 7.56 (1 H, dd, J = 8.6, 7.5 Hz, Dansyl Ar), 7.52 (1 H, dd, J = 8.5, 7.3 Hz, Dansyl Ar), 7.18 (1 H, d, J = 7.5 Hz, Dansyl Ar), 4.68 (1 H, d, J = 8.3 Hz, NH), 3.55–3.47 (1 H, m, CH), 2.89 (6 H, s, CH_3), 2.31–2.23 (1 H, m, CH), 2.22–2.13 (1 H, m, CH), 1.84–1.75 (1 H, m, CH_2), 1.54–1.41 (4 H, m, CH_2), 1.30–1.04 (4 H, m, CH_2) and 1.02–0.96 (1 H, m, CH_2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 152.0 (Dansyl Ar), 135.6 (Dansyl Ar), 130.3 (Dansyl Ar), 129.8 (Dansyl Ar), 129.7 (Dansyl Ar), 129.4 (Dansyl Ar), 128.2 (Dansyl Ar), 123.2 (Dansyl Ar), 118.8 (Dansyl Ar), 115.1 (Dansyl Ar), 57.3 (CH), 45.5 (2 × CH_3), 45.4 (CH), 41.1 (CH), 35.5 (CH_2), 30.5 (CH_2), 29.3 (CH_2), 27.9 (CH_2) and 27.2 (CH_2); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{20}H_{26}N_2NaO_2S^+$ 381.1607; Found 381.1601.

241 (*S*,*S*)-Hexahydropentalen-1-one



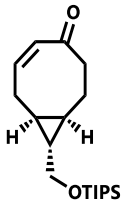
In a flame-dried flask under an atmosphere of argon, triazole **224** (750 mg, 2.23 mmol, 1.0 equiv.) was dissolved in C_6F_6 (55.8 mL). Rh_2(*S*-NTTL)$_4$ (162 mg, 0.113 mmol, 5 mol %) was added and the reaction heated to 50 °C (oil bath) for 1 h. The reaction was cooled to ambient temperature and basic alumina (22.3 g, pH 9.5, Brockmann activity III, *i.e.* 6 wt % H_2O) was added and the mixture vigorously stirred for 15 min. Filtration through celite and concentration *in vacuo* afforded a residue that was purified by flash column chromatography (silica, gradient from 2–10% ethyl acetate in petrol) to give the title compound (238 mg, 1.92 mmol, 86%) as a volatile colourless oil. $\alpha_D^{23.5}$ +159.4 (c 1.1, EtOH), Lit. $\alpha_D^{23.0}$ +116.0 (c 1.3, EtOH); ν_{max}(film) 2951, 2870, 1732, 1458, 1412, 1269, 1161, 1134 and 1103 cm^{-1}; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 2.81–2.73 (1 H, m, CH), 2.54 (1 H, td, *J* = 9.4, 4.4 Hz, CH), 2.29–2.24 (2 H, m, CH_2), 2.16–2.07 (1 H, m, CH_2), 1.90–1.76 (3 H, m, CH_2), 1.64–1.49 (3 H, m, CH_2) and 1.45–1.38 (1 H, m, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 223.5 (C=O), 52.0 (CH), 40.9 (CH), 37.9 (CH_2), 33.4 (CH_2), 29.8 (CH_2), 26.3 (CH_2) and 26.1 (CH_2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_8H_{13}O^+$ 125.0961; Found 125.0961. Recorded data consistent with previous values.[344]

242 (1*R*,3a*S,6a*S**)-1-Hydroxy-1-phenyloctahydropentalene**



In a flame-dried flask under an atmosphere of argon, triazole **224** (168 mg, 0.500 mmol, 1.0 equiv.) was dissolved in C_6F_6 (25.0 mL). Rh_2(*S*-NTTL)$_4$ (72 mg, 0.05 mmol, 5 mol %) was added and the reaction heated to 50 °C (oil bath) for 1 h. The reaction was cooled to ambient temperature and basic alumina (2.5 g, pH 9.5, Brockmann activity III, *i.e.* 6 wt % H_2O) was added and the mixture vigorously stirred for 30 min and filtered through a short pad of Celite, cooled to 0 °C and diluted with diethyl ether (12.5 mL). PhMgBr (3 M solution in diethyl ether, 0.5 mL, 1.5 mmol, 3.0 equiv.) was added drop-wise and the reaction allowed to warm to rt overnight (ca. 16 h). The reaction was quenched by the addition of saturated aqueous ammonium chloride (30.0 mL) and the aqueous phase extracted with diethyl ether (3 × 40 mL). The combined organics were washed with brine, dried $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, gel, 5–30% ethyl acetate in petrol) to afford the title compound (79.0 mg, 78%) as a colourless oil. $\alpha_D^{22.6}$ +56.7 (c 1.0, $CHCl_3$); ν_{max}(film) 3458, 2943, 2862, 2361, 2332, 1493, 1445, 1300, 1233, 1132, 1057 and 1034 cm^{-1}; ^{1}H NMR (400 MHz, 25.6 °C, $CDCl_3$) δ 7.52–7.47 (2 H, m, ArH), 7.37–7.32 (2 H, m, ArH), 7.25–7.21 (1 H, m, ArH), 2.76–2.58 (2 H, m, 2 × CH), 2.14–1.90 (3 H, m, CH_2), 1.86–1.68 (3 H, m, CH_2), 1.64–1.48 (3 H, m, CH_2) and 1.47–1.38 (1 H, m, CH_2); ^{13}C{^{1}H} NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 147.7 (Ar), 128.2 (2 × ArH), 126.7 (ArH), 125.2 (2 × ArH), 83.1 (C–OH), 54.5 (CH), 44.6 (CH), 43.6 (CH_2), 34.0 (CH_2), 30.9 (CH_2), 28.0 (CH_2) and 26.5 (CH_2); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{14}H_{18}NaO^+$ 225.1250; Found 225.1254.

273 (1*R,8*S**,9*r**)-5-Oxo-bicyclo[6.1.0]non-3-en-9-ylmethoxytriisopropylsilane**



In a flame-dried vial under an atmosphere of argon, triazole **267** (0.40 mmol, 1.0 equiv.) was dissolved in PhMe (20.0 mL). $Rh_2(OAc)_4$ (9 mg, 0.02 mmol, 5 mol %) was added and the vial sealed with a Teflon cap. The reaction was heated to 120 °C (aluminium block) for 15 min after which time the reaction was cooled to ambient temperature. Basic alumina (4.20 g, pH 9.5, Brockmann activity III, *i.e.* 6 wt % H_2O) was added and the mixture vigorously stirred for 15 min. Filtration through Celite and concentration *in vacuo* afforded a residue that was purified by flash column chromatography (silica gel, gradient from 5 to 30% ethyl acetate in petrol) to afford the title compound as a colourless oil.; ν_{max}(film) 2941, 2891, 2864, 1686, 1462, 1427, 1383, 1248, 1105, 1083, 1065 and 1013 cm^{-1}; ^1H NMR (400 MHz, 27.0 °C, $CDCl_3$) δ 5.99 (1 H, ddd, *J* = 12.9, 7.1, 4.1 Hz, =CH), 5.83 (1 H, dd, *J* = 12.9, 2.9 Hz, =CH), 9.95–0.88 (1 H, m, cyclopropane CH), 3.64–3.48 (2 H, m, CH_2OTIPS), 2.80–2.65 (2 H, m, CH_2), 2.54 (1 H, ddd, *J* = 13.5, 11.4, 5.3 Hz, CH_2), 2.19–2.11 (1 H, m, CH_2), 1.93 (1 H, dddd, *J* = 17.8, 10.6, 4.1, 3.0 Hz, CH_2), 1.63 (1 H, dddd, *J* = 14.4, 11.5, 10.2, 5.2 Hz, CH_2), 1.11–0.96 (21 H, m, 3 × *i*Pr) and 0.87–0.75 (2 H, m, cyclopropane CH); $^{13}C\{^1H\}$ NMR (101 MHz, 27.0 °C, $CDCl_3$) δ 209.2 (C=O), 135.5 (=CH), 130.3 (=CH), 65.7 (CH_2OTIPS), 45.3 (CH_2), 30.3 (CH_2), 29.1 (cyclopropane CH), 22.6 (CH_2), 20.9 (cyclopropane CH), 20.0 (cyclopropane CH), 17.9 (6 × *i*Pr) and 12.0 (3 × *i*Pr); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{34}NaO_2Si^+$ 345.2220; Found 345.2221.

Triazole **269** (128 mg) gave enone **273** (61 mg) in 63% yield.

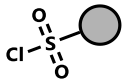
Triazole **268** (151 mg) gave enone **273** (53 mg) in 55% yield.

Triazole **270** (160 mg) gave enone **273** (54 mg) in 56% yield.

Triazole **271** (156 mg) gave enone **273** (54 mg) in 56% yield.

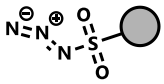
7.2.4 Polymer-supported and related compounds

309 Polymer-supported sulfonyl chloride



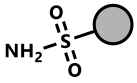
Used as provided from Sigma-Aldrich, Inc. ν_{max}(solid) 3026, 2926, 2851, 1591, 1493, 1452, 1414, 1369, 1169, 1084 and 1030 cm^{-1}; Elemental analysis: C (71.8%), H (6.0%), others (22.2%).

304 Polymer-supported sulfonyl azide



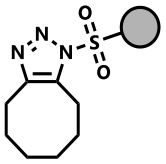
Polymer-supported sulfonyl chloride (300 mg, 0.600 mmol) was swollen in water (200 µL) and acetone (660 µL) for 30 min. Sodium azide (117 mg, 1.80 mmol) was added in one portion and the reaction stirred by rotation for 48 h. The solid was filtered and washed with water and acetone, affording the polymer supported sulfonyl azide. The loading of the sulfonyl azide was then experimentally determined to be 1.194 $mmolg^{-1}$ by repetition of a literature reaction involving diazo transfer to benzoylacetone. ν_{max}(solid) 3026, 2922, 2855, 2124, 1593, 1493, 1452, 1414, 1364, 1165, 1088, 1038 and 1011 cm^{-1}; Elemental analysis: C (69.7%), H (6.1%), N (6.2%), others (18.0%).

310 Polymer-supported sulfonamide



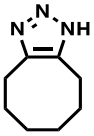
n a flame-dried flask under an atmosphere of argon, commercially available polymer-supported sulfonyl azide (100 mg, 1.50 mmol) was suspended in THF (1.5 mL). NaBH4 (34.0 mg, 0.900 mmol) was added in one portion and the reaction stirred by rotation at room temperature for 18 h. The reaction was quenched by addition of water (1.50 mL), filtered and the solid was washed with water and acetone to afford the polymer-supported sulfonamide. ν_{max}(solid) 3251, 3024, 2924, 1599, 1493, 1452, 1412, 1327, 1217, 1185, 1155, 1126, 1096, 1036 and 1009 cm^{-1}; Elemental analysis: C (70.3%), H (6.8%), N (4.5%), others (18.4%).

313 Polymer-supported 1-sulfonyl-4,5,6,7,8,9-hexahydrocycloocta[*d*][1,2,3]triazole



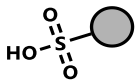
In a flame-dried flask under an atmosphere of argon, polymer-supported sulfonyl azide (100 mg, 0.119 mmol) was swollen in toluene (10 mL) for 30 min. Cyclooctyne (257 mg, 2.38 mmol) was added as a solution in toluene (1.00 mL) and the vessel was sealed with a Teflon cap and stirred at 40 °C for 72 h. The solid was filtered and washed with water and acetone, affording the polymer-supported sulfonyl triazole. ν_{max}(solid) 3026, 2926, 2855, 1597, 1493, 1452, 1412, 1362, 1219, 1167, 1125, 1090, 1034 and 1007 cm^{-1}; Elemental analysis: C (73.6%), H (6.5%), N (1.9%), others (18.0%).

314 4,5,6,7,8,9-Hexahydrocycloocta[*d*][1,2,3]triazole



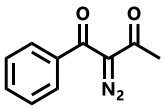
Polymer-supported triazole **313** (100 mg, 0.239 mmol) was suspended in methanol (10 mL). Magnesium turnings (24.0 mg, 1.50 mmol) were added and the reaction was stirred at ambient temperature for 48 h. Saturated aqueous NH_4Cl (5.0 mL) was added and the mixture filtered. The aqueous phase was extracted with CH_2Cl_2 (3 × 2.0 mL) and the combined organics were concentrated in vacuo to give the title compound as a white, gummy solid (13.1 mg, 36%). ν_{max}(film) 3136, 3045, 2930, 2853, 1458, 1441, 1192, 1155 cm^{-1}; ^{1}H NMR (400 MHz, 26.9 °C, $CDCl_3$) δ 12.07 (1 H, br s, NH), 2.91–2.84 (4 H, m, CH_2), 1.84–1.72 (4 H, m, CH_2), 1.51–1.45 (4 H, m, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, 27.0 °C, $CDCl_3$) δ 144.7 (2 × triazole C), 28.3 (2 × CH_2), 25.4 (2 × CH_2), 23.5 (2 × CH_2). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_8H_{13}N_3Na^+$ 174.1002; Found 174.1002.

308 Polymer-supported sulfonic acid



Polymer-supported triazole **313** (100 mg, 0.239 mmol) was suspended in methanol (10 mL). Magnesium turnings (24.0 mg, 1.50 mmol) were added and the reaction was stirred at ambient temperature for 48 h. Saturated aqueous NH_4Cl (5.0 mL) was added and the mixture filtered. The solid was washed with water and acetone (3 × 10 mL), affording the polymer-supported sulfonic acid (56 mg, 28%). ν_{max}(solid) 3121, 3026, 2924, 2851, 2810, 1599, 1493, 1443, 1400, 1165, 1125, 1034 and 1007 cm^{-1}; Elemental analysis: C (69.7%), H (6.9%), N (4.5%), others (18.9%).

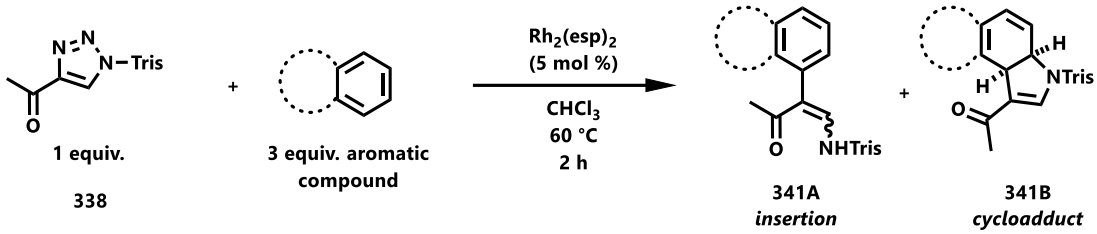
312 2-Diazo-1-phenylbutane-1,3-dione



In a flame-dried flask under an atmosphere of argon, polymer-supported sulfonyl azide **304** (500 mg) was swollen in CH_2Cl_2 (7.50 mL) for 30 min. Benzoyl acetone (122 mg, 0.750 mmol, 1.0 equiv.) and Et_3N (314 µL, 2.25 mmol, 3.0 equiv.) were added in one portion as a solution in CH_2Cl_2 (7.50 mL). The reaction was stirred at ambient temperature for 4 h, filtered and the solid washed with CH_2Cl_2 (3 × 15.0 mL). The filtrate was concentrated *in vacuo* to afford the title compound as a yellow oil (109 mg, 78%). ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.65–7.62 (2 H, m, Ar), 7.59–7.57 (1 H, m, Ar), 7.52–7.46 (2 H, m, Ar) and 2.58 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 190.8 (C=O), 185.1 (C=O), 137.3 (Ar), 132.7 (ArH), 128.9 (2 × ArH), 127.3 (2 × ArH), 83.7 (C=N) and 29.2 (CH_3). Recorded data consistent with previous values.[243]

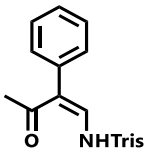
7.2.5 Insertion of 1-STs into aromatic C(sp^2)–H bonds

General Procedure 4: Rhodium(II)-catalysed reaction of 4-acyl 1-STs with aromatic compounds



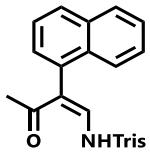
Under an atmosphere of argon, $Rh_2(esp)_2$ (5 mol %) was added to a solution of 1-ST **338** (1.0 equiv.) and aromatic compound (3.0 equiv.) in $CHCl_3$ (0.40 M) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 60 °C (heating block) until complete (TLC, 2–4 h). The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5–40% EtOAc in petroleum ether) to give the products **341A** and **341B**.

342A 2,4,6-Triisopropyl-*N*-(3-oxo-2-phenylbuten-1-yl)benzenesulfonamide



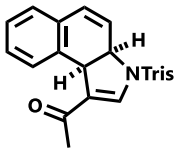
Triazole **338** (750 mg, 2.00 mmol, 1.0 equiv.) and benzene (535 µL, 6.00 mmol, 3.0 equiv.) were treated with $Rh_2(esp)_2$ (38 mg, 0.05 mmol, 2.5 mol %) in $CHCl_3$ (5 mL) according to General Procedure 4 to give the title compound as a colourless oil (544 mg, 64%). ν_{max}(film) 2961, 2930, 2870, 1647, 1599, 1568, 1495, 1462, 1425, 1377, 1341, 1315, 1249, 1150, 1105, 1072 and 1038 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 12.20 (1 H, d, J = 10.4 Hz, NH), 7.39–7.30 (3 H, m, Ph), 7.19 (2 H, s, Ar), 7.21–7.17 (2 H, m, Ph), 7.08 (1 H, d, J = 10.4 Hz, =CH), 4.10 (2 H, sept., J = 6.7 Hz, *i*PrCH × 2), 2.91 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.08 (3 H, s, CH_3), 1.29 (12 H, d, J = 6.7 Hz, *i*PrCH_3 × 4) and 1.26 (6 H, d, J = 6.9 Hz, *i*PrCH_3 × 2); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 201.0 (C=O), 153.6 (Ar), 150.0 (2 × ArH), 139.7 (=CH), 137.6 (Ar), 132.9 (Ph), 130.0 (2 × ArH), 128.6 (2 × PhH), 127.5 (PhH), 124.0 (2 × PhH), 117.4 (=C), 34.2 (*i*PrCH), 29.9 (2 × *i*PrCH), 29.6 (CH_3), 24.7 (4 × *i*PrCH_3) and 23.5 (2 × *i*PrCH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{33}NNaO_3S^+$ 450.2073; Found 450.2062.

343A 2,4,6-Triisopropyl-*N*-(3-oxo-2-naphth-1-ylbuten-1-yl)benzenesulfonamide



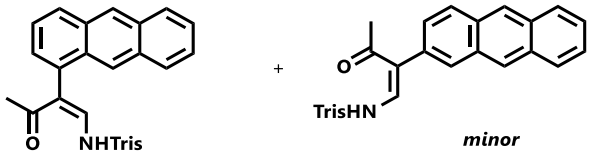
Triazole **338** (75.0 mg, 0.20 mmol, 1.0 equiv.) and naphthalene (77 mg, 0.60 mmol, 3.0 equiv.) were treated with $Rh_2(esp)_2$ (8 mg, 0.01 mmol, 5 mol %)in $CHCl_3$ (0.50 mL) according to General Procedure 4 to give the title compound as a brown oil (39 mg, 41%). ν_{max}(film) 3055, 2963, 2870, 1643 (S=O), 1566 (C=O), 1458, 1427, 1373, 1335, 1250 (S=O), 1150 (S=O), 1034 cm−1; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 12.34 (1 H, d, J = 10.5 Hz, NH), 7.93–7.81 (2 H, m, Ar H), 7.71–7.68 (1 H, m Ar H), 7.53–7.44 (3 H, m, Ar H), 7.33 (1 H, dd, J = 7.0, 1.3 Hz), 7.21 (2 H, s, Tris Ar), 7.14 (1 H, d, J = 10.5 Hz, =CH), 4.11 (2H, sept., J = 6.7 Hz, *i*PrCH), 2.92 (1 H, sept., J = 6.9 Hz, *i*PrCH), 1.86 (3 H, s, CH_3), 1.30 (6 H, d, J = 6.9 Hz, *i*PrCH_3), 1.27 (12 H, d, J = 6.7 Hz, *i*PrCH_3); ^{13}C{^{1}H} NMR (126 MHz, 22.8 °C, $CDCl_3$) δ 201.67 (C=O), 153.7 (Tris Ar), 150.1 (2 × Tris Ar), 140.16 (=CH), 134.8 (Ar), 133.7 (Ar), 133.2 (Tris Ar), 132.9 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 126.6 (Ar), 126.1 (Ar), 125.5 (Ar), 125.1 (Ar), 124.1 (2 × Tris Ar), 114.8 (C=C), 34.21 (*i*PrCH), 29.9 (2 × *i*PrCH), 24.8 (*i*PrCH_3) and 23.5 (2 × *i*PrCH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{29}H_{35}NNaO_3S^+$ 500.2230; Found 500.2220.

343B 2,4,6-Triisopropylbenzene)sulfonyl)-3a,9b-dihydrobenzo[*e*]indol-1-yl)ethan-1-one



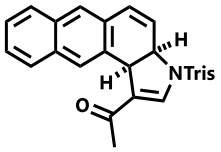
Triazole **338** (75.0 mg, 0.20 mmol, 1.0 equiv.) and naphthalene (77 mg, 0.60 mmol, 3.0 equiv.) were treated with $Rh_2(esp)_2$ (8 mg, 0.01 mmol, 5 mol %)in $CHCl_3$ (0.50 mL) according to General Procedure 4 to give the title compound as a brown semi-solid (18 mg, 19%). ν_{max}(film) 2963, 1651, 1589, 1458, 1412, 1366, 1327, 1157, 1072, 1003 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.94–7.85 (1 H, m, Ar H), 7.70 (1 H, s, =CH), 7.55–7.46 (1 H, m, Ar H), 7.39–7.30 (1 H, m, Ar H), 7.11 (2H, s, Tris Ar), 6.90–6.86 (1 H, m, Ar H), 6.31 (1 H, d, *J* = 9.7 Hz, =CH), 5.70 (1 H, dd, *J* = 9.8. 5.1 Hz, =CH), 4.93 (1 H, dd, *J* = 10.0, 5.1 Hz, bridging CH), 4.55 (1 H, d, *J* = 10.0 Hz, bridging CH), 3.91 (2 H, sept., *J* = 6.7 Hz, *i*PrCH), 2.90 (1 H, sept., *J* = 6.9 Hz, *i*PrCH), 2.39 (3 H, s, CH_3), 1.26 (6 H, d, *J* = 6.9 Hz, *i*PrCH$_3$), 1.20 (6 H, d, *J* = 6.7 Hz, *i*PrCH$_3$) and 0.96 (6 H, d, *J* = 6.7 Hz, *i*PrCH$_3$); $^{13}C\{^1H\}$ NMR (126 MHz, 22.8 °C, $CDCl_3$) δ 194.2 (C=O), 154.3 (Tris Ar), 151.1 (2 ×Tris Ar), 143.4 (=CH), 133.2 (Tris Ar), 131.3 (=CH), 131.2 (Ar), 130.6 (Ar), 129.0 (Ar), 128.8 (Ar), 128.5 (C=C), 127.1 (Ar), 126.1 (Ar), 123.9 (2 × Tris Ar), 118.3 (=CH), 62.5 (bridging CH), 42.0 (bridging CH), 34.3 (*i*PrCH), 29.6 (2 × *i*PrCH$_3$), 26.7 (CH_3), 24.7 (2 × *i*PrCH$_3$), 24.2 (2 × *i*PrCH$_3$), 23.6 (*i*PrCH$_3$) and 23.5 (*i*PrCH$_3$); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{29}H_{35}NNaO_3S^+$ 500.2230; Found 500.2219.

344A 2,4,6-Triisopropyl-*N*-(3-oxo-2-anthracen-1-ylbuten-1-yl)benzenesulfonamide and 2,4,6-Triisopropyl-*N*-(3-oxo-2-anthracen-2-ylbuten-1-yl)benzenesulfonamide



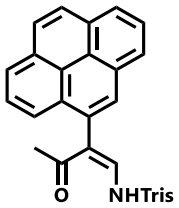
Triazole **338** (75.0 mg, 0.20 mmol, 1.0 equiv.) and anthracene (107 mg, 0.60 mmol, 3.0 equiv.) were treated with $Rh_2(esp)_2$ (8 mg, 0.01 mmol, 5 mol %)in $CHCl_3$ (0.50 mL) according to General Procedure 4 to give the isomeric compounds as an inseparable mixture of colourless oils (18 mg, 19%). ν_{max}(film) 3049, 2960, 2930, 2870, 1647, 1599, 1568, 1460, 1425, 1365, 1340, 1250, 1152 and 1038 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 12.41 (1 H, d, *J* = 10.5 Hz, NH), 12.27 (1 H, d, *J* = 10.5, NH'), 8.51–8.47 (1 H, m, Ar H), 8.45–8.41 (1 H, m, Ar H'), 8.41–8.38 (1 H, m, Ar H'), 8.25–8.21 (1 H, m, ArH), 8.06–7.98 (3 H, m, Ar H + 2 × Ar H'), 7.91–7.87 (1 H, m, Ar H), 7.82–7.79 (1 H, m, Ar H'), 7.52–7.41 (4 H, m, Ar H + 3 × Ar H'). 7.33 (1 H, dd, *J* = 6.7, 1.2 Hz, Ar H), 7.30 (1 H, dd, *J* = 8.7, 1.8 Hz, Ar H'), 7.25–7.19 (4 H, m, Tris Ar, Tris Ar', =CH, =CH'), 4.17 (4 H, sept., *J* = 6.7 Hz, iPrCH, *i*PrCH'), 2.96 (2 H, sept., *J* = 6.9 Hz, *i*PrCH, *i*PrCH'), 2.19 (3 H, s, CH_3'), 1.91 (3 H, s, CH_3) and 1.37–1.27 (36 H, m, *i*PrCH$_3$, *i*PrCH$_3$'); $^{13}C\{^1H\}$ NMR (126 MHz, 22.8 °C, $CDCl_3$, *major* isomer only) δ 202.0 (C=O), 153.7 (Tris Ar), 150.1 (2 × Tris Ar), 140.2 (=CH), 134.8 (Ar), 132.8 (Tris Ar), 131.9 (Ar), 131.9 (Ar), 131.8 (Ar), 131.7 (2 × Ar), 129.1 (Ar), 128.4 (Ar), 128.2 (Ar), 127.9 (Ar), 127.1 (Ar), 125.9 (Ar), 125.8 (Ar), 124.9 (Ar), 124.1 (2 × Tris Ar), 124.0 (Ar), 114.8 (C=C), 34.2 (*i*PrCH), 30.0 (2 × *i*PrCH), 29.1 (CH_3), 24.8 (*i*PrCH$_3$), 24.7 (2 × *i*PrCH$_3$), 24.2 (*i*PrCH$_3$), 23.5 (2 × *i*PrCH$_3$); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{33}H_{37}NNaO_3S^+$; 550.2386 Found 550.2374

344B (2,4,6-Triisopropylbenzene)sulfonyl)-3a,9b-dihydronaphtho[2,3-*e*]indol-1-yl)ethan-1-one



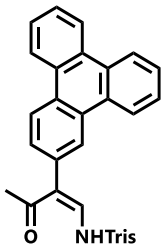
Triazole **338** (75.0 mg, 0.20 mmol, 1.0 equiv.) and anthracene (107 mg, 0.60 mmol, 3.0 equiv.) were treated with $Rh_2(esp)_2$ (8 mg, 0.01 mmol, 5 mol %)in $CHCl_3$ (0.50 mL) according to General Procedure 4 to give the compound as a white solid (17 mg, 16%). ν_{max}(film) 3055, 2959, 2928, 2870, 1651 1597, 1463, 1423, 1366, 1335, 1258, 1153, 1107, 1076, 1038 and 1003; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.82 (1 H, s, =CH), 7.70 (2 H, ddd, *J* = 14.4, 6.0, 3.3 Hz, ArH), 7.62 (1 H, d, *J* = 0.9 Hz, Ar H), 7.40–7.36 (2 H, m, Ar H), 7.34 (1 H, s, Ar H), 7.12 (2 H, s, Tris Ar), 6.46 (1 H, d, *J* = 9.8 Hz, =CH), 5.67 (1 H, dd, *J* = 9.8, 4.9 Hz, =CH), 4.99 (1 H, dd, *J* = 9.7, 4.9 Hz, bridging CH), 4.68 (1 H, dt, *J* = 9.7, 1.2 Hz, bridging CH), 4.01 (2 H, sept., *J* = 6.7 Hz, *i*PrCH), 2.92 (1 H, sept., *J* = 6.9 Hz, *i*PrCH), 2.40 (3 H, s, CH_3), 1.27 (6 H, app.. dd, *J* = 6.9, 2.4 Hz, *i*PrCH$_3$), 1.20 (6 H, d, *J* = 6.7 Hz, *i*PrCH$_3$) and 0.98 (6 H, d, *J* = 6.7 Hz, *i*PrCH3); ^{13}C{^{1}H} NMR (126 MHz, 22.8 °C, $CDCl_3$) δ 194.1 (C=O), 153.4 (Tris Ar), 151.2 (2 × Tris Ar), 143.0 (=CH), 133.6 (Tris Ar), 132.5 (Ar), 131.8 (=CH), 131.0 (Ar), 130.8 (Ar), 129.1 (C=C), 128.6 (Ar), 128.1 (Ar), 127.4 (Ar), 126.3 (Ar), 126.1 (Ar), 126.0 (Ar), 125.9 (Ar), 124.0 (2 × Tris Ar), 120.1 (=CH), 62.2 (bridging CH), 42.6 (bridging CH), 34.3 (*i*PrCH), 29.6 (2 × *i*PrCH), 26.9 (CH_3), 24.6 (2 × *i*PrCH$_3$), 24.3 (2 × *i*PrCH$_3$), 23.6 (*i*PrCH$_3$) and 23.5 (*i*PrCH$_3$); m/z (ESI) 550.2386 ([MNa]$^+$ = $C_{33}H_{37}NNaO_3S^+$ requires 550.2381).

346A 2,4,6-Triisopropyl-*N*-(3-oxo-2-pyren-1-ylbuten-1-yl)benzenesulfonamide



Triazole **338** (75.0 mg, 0.20 mmol, 1.0 equiv.) and pyrene (121 mg, 0.60 mmol, 3.0 equiv.) were treated with $Rh_2(esp)_2$ (8 mg, 0.01 mmol, 5 mol %)in $CHCl_3$ (0.50 mL) according to General Procedure 4 to give the compound as a colourless oil (106 mg, 53%). ν_{max}(film) 3042, 2961, 2928, 2870, 1645, 1599, 1566, 1460, 1425, 1364, 1337, 1298, 1248 and 1150 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 12.48 (1 H, d, J = 10.5 Hz, NH), 8.30–8.18 (3 H, m, pyrene H), 8.15–8.04 (4 H, m, pyrene H), 7.97 (1 H, d, J = 9.2 Hz, pyrene H), 7.87 (1 H, d, J = 7.8 Hz, pyrene H), 7.40 (1 H, d, J = 10.5 Hz, =CH), 7.35 (2 H, s, SO_2–Ar), 4.27 (2 H, sept., J = 6.7 Hz, *i*Pr CH × 2), 3.07 (1 H, sept., J = 7.0 Hz, *i*Pr CH), 2.02 (3 H, s, CH_3), 1.45 (12 H, d, J = 6.7 Hz, *i*Pr CH_3 × 4) and 1.41 (6 H, d, J = 7.0 Hz, *i*Pr CH_3 × 2); $^{13}C\{^1H\}$ NMR (101 MHz, 21.1 °C, $CDCl_3$) δ 201.7 (C=O), 153.8 (Ar C4), 150.1 (2 × Ar), 140.6 (=CH), 132.9 (Ar C1), 131.9 (pyrene =C), 131.3 (pyrene =C), 131.3 (pyrene =C), 130.8 (pyrene =C), 130.6 (pyrene =C), 128.8 (pyrene H), 128.2 (pyrene H), 127.8 (pyrene =C), 127.2 (pyrene =C), 126.2 (pyrene H), 125.6 (pyrene H), 125.4 (pyrene H), 124.9 (pyrene H), 124.8 (pyrene H), 124.6 (pyrene H), 124.2 (pyrene H), 124.1 (2 × ArH), 115.2 (=C), 34.2 (*i*PrCH), 30.0 (2 × *i*PrCH), 29.4 (CH_3), 24.8 (2 × *i*PrCH$_3$), 24.8 (2 × *i*PrCH$_3$) and 23.5 (2 × *i*PrCH$_3$); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{35}H_{37}NNaO_3S^+$ 574.2386; Found 574.2381.

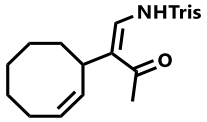
347A 2,4,6-Triisopropyl-*N*-(3-oxo-2-triphenylen-2-ylbuten-1-yl)benzenesulfonamide



Triazole **338** (75.0 mg, 0.20 mmol, 1.0 equiv.) and triphenylene (137 mg, 0.60 mmol, 3.0 equiv.) were treated with $Rh_2(esp)_2$ (8 mg, 0.01 mmol, 5 mol %) in $CHCl_3$ (0.50 mL) according to General Procedure 4 to give the compound as a colourless oil (44 mg, 38%). ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 12.32 (1 H, d, *J* = 10.5 Hz, NH), 8.70–8.57 (3 H, m, Ar), 8.46 (1 H, d, *J* = 1.8 Hz, Ar), 7.71–7.65 (6 H, m, Ar), 7.50 (1 H, dd, *J* = 8.4, 1.8 Hz, Ar), 7.28 (1 H, d, *J* = 10.5 Hz, =CH), 7.22 (2 H, s, Tris Ar), 4.15 (2 H, sept., *J* = 6.7 Hz, *i*PrCH), 2.93 (1 H, sept., *J* = 6.9 Hz, *i*PrCH), 2.18 (3 H, s, CH_3), 1.33 (12 H, d, *J* = 6.7 Hz, *i*PrCH_3), 1.28 (6 H, d, *J* = 6.9 Hz, *i*PrCH_3).

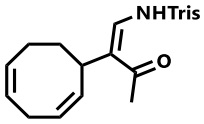
7.2.6 Reaction of 1-STs with π-bonds

351 (±)-*N*-[2-(Cyclooct-2-en-1-yl)-3-oxobut-1-en-1-yl]-2,4,6-triisopropylbenzenesulfonamide



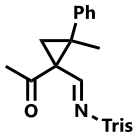
Under an atmosphere of argon, $Rh_2(esp)_2$ (4 mg, 0.01 mmol, 5 mol %) was added to a solution of 1-ST **338** (76 mg, 0.20 mmol, 1.0 equiv.) and *cis*-cyclooctene (78 µL, 0.60 mmol, 3.0 equiv.) in $CHCl_3$ (1.0 mL) in a flame-dried vial. The vial was sealed with a Teflon cap and stirred at 60 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−30% EtOAc in petroleum ether) to give the title compound as a yellow oil (45 mg, 50%). ν_{max}(film) 2959 (C–H), 2928, 2868, 1651 (C=O), 1649 (C=C), 1599 (S=O), 1570, 1460, 1423,1365, 1341, 1260 (S=O), 1152 (S=O), 1105 and 1038; ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 12.12 (1 H, d, *J* = 10.2 Hz, NH), 7.16 (2 H, s, Tris Ar), 6.99 (1 H, d, *J* = 10.2 Hz, =CH), 5.70 (1 H, dddd, *J* = 10.1, 8.7, 7.4, 1.2 Hz, =CH), 5.16 (1 H, ddd, *J* = 10.1, 9.0, 1.5 Hz, =CH), 4.09 (2 H, sept., *J* = 6.7 Hz, *i*PrCH), 3.48 (1 H, ddd, *J* = 12.2, 9.0, 3.0 Hz, CH), 2.89 (1 H, sept., *J* = 6.9 Hz, *i*PrCH), 2.20 (3H, s, CH_3), 2.26–2.09 (2 H, m, CH_2), 1.77–1.66 (2 H, m, CH_2), 1.64–1.30 (6 H, m, CH_2), 1.26 (12 H, d, *J* = 6.7 Hz, *i*PrCH$_3$) and 1.24 (6 H, d, *J* = 6.9 Hz, *i*PrCH$_3$); δ_C(126 MHz, 25.0 °C, $CDCl_3$): 202.6 (C=O), 153.3 (Tris Ar), 159.9 (2 × Tris Ar), 136.3 (=CH), 133.9 (=CH), 133.2 (Tris Ar), 130.2 (=CH), 123.9 (2 × Tris Ar), 118.3 (C=C), 36.2 (CH), 34.6 (CH_2), 34.2 (*i*PrCH), 29.8 (2 × *i*PrCH), 29.5 (CH2), 27.9 (CH_3), 26.5 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 24.7 (2 × *i*PrCH$_3$), 24.6 (2 × *i*PrCH$_3$) and 23.5 (2 × *i*PrCH$_3$); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{27}H_{41}NNaO_3S^+$ 482.2682; Found 482.2688.

352 (±)-*N*-[2-(Cycloocta-2,5-dien-1-yl)-3-oxobut-1-en-1-yl]-2,4,6-triisopropylbenzenesulfonamide



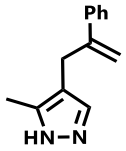
Under an atmosphere of argon, $Rh_2(esp)_2$ (11 mg, 0.015 mmol, 5 mol %) was added to a solution of 1-ST **338** (113 mg, 0.30 mmol, 1.0 equiv.) and 1,5-cyclooctadiene (110 µL, 0.90 mmol, 3.0 equiv.) in $CHCl_3$ (1.50 mL) in a flame-dried vial. The vial was sealed with a Teflon cap and stirred at 60 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−30% EtOAc in petroleum ether) to give the title compound as a yellow oil (80 mg, 58%). ν_{max}(film) 3020, 2959, 2930, 2870, 1651, 1599, 1574, 1462, 1425, 1398, 1370, 1343, 1250, 1182, 1150, 1105, 1071, 1038 and 1022 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 12.12 (1 H, d, *J* = 10.2 Hz, NH), 7.16 (2 H, s, Tris Ar), 7.00 (1 H, d, *J* = 10.2 Hz, =CH), 5.76 (1 H, dt, *J* = 10.9, 5.5 Hz, =CH), 5.69 (1 H, dt, *J* = 9.8, 4.5 Hz, =CH), 5.43 (1 H, dddt, *J* = 11.2, 9.8, 8.0, 2.1 Hz, =CH), 5.01 (1 H, ddt, *J* = 10.9, 8.9, 1.8 Hz, =CH), 4.09 (2 H, sept., *J* = 6.8 Hz, *i*Pr CH), 3.89 (1 H, ddd, *J* = 12.8, 8.9, 4.3 Hz, CH), 2.94–2.84 (3 H, m, *i*Pr CH + CH_2), 2.74–2.63 (1 H, m, CH_2A), 2.21 (3 H, s, CH_3), 2.10–2.02 (1 H, m, CH_2A), 1.49–1.43 (1 H, m, CH_2B), 1.41–1.33 (1 H, m, CH_2B), 1.27 (12 H, d, *J* = 6.8 Hz, *i*Pr CH_3) and 1.24 (6 H, d, *J* = 6.8 Hz, *i*Pr CH_3); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 202.6 (C=O), 153.3 (Tris Ar), 149.8 (2 × Tris Ar), 136.4 (=CH), 133.2 (=CH), 133.2 (Tris Ar), 130.2 (=CH), 129.1 (=CH), 127.8 (=CH), 123.9 (2 × Tris Ar), 117.5 (=C), 36.1 (CH), 34.1 (*i*Pr CH), 29.9 (CH_2), 29.8 (2 × *i*Pr CH), 27.9 (CH_3), 27.5 (CH_2), 24.7 (2 × *i*Pr CH_3), 24.7 (2 × *i*Pr CH_3), 24.1 (CH_2) and 23.5 (2 × *i*Pr CH_3); HRMS (ESI-TOF) *m/z*: $[MNa]^+$ Calcd for $C_{27}H_{39}NNaO_3S^+$ 480.2543; Found 480.2543.

369 (±)-*N*-[(1-Acetyl-2-methyl-2-phenylcyclopropyl)methylene]-2,4,6-triisopropylbenzenesulfonamide



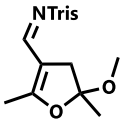
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (9 mg, 0.015 mmol, 5 mol %) was added to a solution of 1-ST **338** (113 mg, 0.30 mmol, 1.0 equiv.) and α-methylstyrene (78 µL, 0.60 mmol, 2.0 equiv.) in 1,2-DCE (1.50 mL) in a flame-dried vial at 0 °C (ice bath). The vial was sealed with a Teflon cap and stirred at this temperature for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−30% EtOAc in petroleum ether) to give the title compound as a yellow oil (75 mg, 54%). ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.81 (1 H, s, imine CH), 7.37–7.27 (5 H, m, Ph), 7.14 (2 H, s, Ar), 4.35 (2 H, sept., J = 6.9 Hz, *i*PrCH), 3.14 (1 H, d, J = 14.7 Hz, cyclopropane), 3.07 (1 H, d, J = 14.7 Hz, cyclopropane), 2.88 (1 H, sept., J = 6.8 Hz, *i*PrCH), 2.25 (3 H, s, CH_3), 1.71 (3 H, s, CH_3), 1.26 (12 H, d, J = 6.9 Hz, *i*PrCH_3) and 1.24 (6 H, d, J = 6.8 Hz, *i*PrCH_3); ^{13}C{^{1}H} NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 174.1 (C=O), 161.5 (imine CH), 152.7 (Ar), 150.4 (2 × Ar), 145.0 (Ph), 132.8 (Ar), 128.6 (2 × PhH), 127.7 (PhH), 124.2 (2 × PhH), 123.6 (2 × ArH), 42.2 (cyclopropane CH_2), 34.2 (*i*PrCH), 29.6 (2 × *i*PrCH), 29.5 (CH_3), 27.6 (cyclopropane), 24.8 (4 × *i*PrCH_3), 24.7 (2 × *i*PrCH_3), 23.6 (cyclopropane) and 13.2 (CH_3).

371 5-Methyl-4-(2-phenylallyl)pyrazole



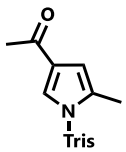
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (9 mg, 0.015 mmol, 5 mol %) was added to a solution of 1-ST **338** (113 mg, 0.30 mmol, 1.0 equiv.) and α-methylstyrene (78 µL, 0.60 mmol, 2.0 equiv.) in 1,2-DCE (1.50 µL) in a flame-dried vial. The vial was sealed with a Teflon cap and stirred at ambient temperature for 2 h. Ethanol (2.0 mL) was added and the vial cooled to 0 °C (ice bath) and hydrazine hydrate (50% wt, 57 µL, 0.90 mmol, 3.0 equiv.) was added dropwise. The mixture was stirred for 30 min, concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, gradient from 20−60% EtOAc in petroleum ether) to afford the title compound as an oily solid (25 mg, 42%). ν_{max}(film) 3144, 3059, 2924, 1623, 1597, 1493, 1443, 1312 and 1099 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.44–7.41 (2 H, m, Ph), 7.32–7.27 (3 H, m, Ph), 7.25 (1 H, s, =CH), 5.39 (1 H, d, J = 1.3 Hz, $=CH_2$), 4.97 (1 H, app. q, J = 1.5 Hz, $=CH_2$), 3.60 (2 H, app. t, J = 1.1 Hz, CH_2) and 2.22 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 146.6 (Ph), 141.9 (pyrazole C), 140.9 (C=C), 134.4 (pyrazole CH), 128.3 (2 × PhH), 127.5 (PhH), 126.0 (2 × PhH), 115.6 (pyrazole C), 113.3 ($=CH_2$), 29.7 (CH_2) and 10.6 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{15}N_2^+$ 199.1230; Found 199.1230.

379 (±)-2,4,6-Triisopropyl-*N*-((5-methoxy-2,5-dimethyl-4,5-dihydrofuran-3-yl)methylene)benzenesulfonamide



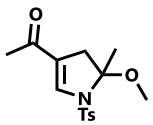
Under an atmosphere of argon, $Rh_2(OAc)_4$ (6 mg, 0.015 mmol, 5 mol %) was added to a solution of 2-methoxypropene (151 µL, 1.50 mmol, 5.0 equiv.) and triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) in 1,2-DCE (10 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 60 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−15% EtOAc in petroleum ether) to give the dihydrofuran as a white waxy solid (77 mg, 61%). ν_{max}(film) 2924, 1682, 1628, 1597, 1574, 1493, 1443, 1312 and 1099 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, Acetone-D_6) δ 8.66 (1 H, s, imine CH), 7.28 (2 H, s, Ar), 4.39 (2 H, sept., J = 6.8 Hz, *i*PrCH), 3.26 (3 H, s, OCH_3), 2.95 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.88 (1 H, d, J = 16.2 Hz, CH_2), 2.81 (3 H, s, CH_3), 2.76 (1 H, d, J = 16.2 Hz, CH_2), 1.61 (3 H, s, CH_3), 1.25 (6 H, d, J = 6.9 Hz, *i*PrCH$_3$) and 1.23 (12 H, d, J = 6.8 Hz, *i*PrCH$_3$); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, Acetone-D_6) δ 175.4 (imine), 162.3 (C=C), 153.7 (Ar), 151.1 (Ar), 134.4 (2 × Ar), 124.4 (2 × ArH), 115.3 (C(OCH_3)), 111.8 (C=C), 50.4 (OCH_3), 37.8 (CH_2), 34.9 (*i*PrCH), 30.1 (2 × *i*PrCH), 28.1 (CH_3), 25.0 (CH_3), 24.9 (4 × *i*PrCH$_3$) and 23.9 (2 × *i*PrCH$_3$); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{36}NO_4S^+$ 422.2360; Found 422.2367.

381 4-Acetyl-2-methyl-*N*-(2,4,6-triisopropylbenzenesulfonyl)pyrrole



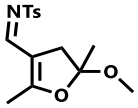
In a flame-dried vial under an atmosphere of argon, dihydrofuran **379** (40 mg, 0.095 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (4.75 mL). Boron trifluoride diethyl etherate (18 µL, 0.142 mmol, 1.5 equiv.) was added dropwise and the reaction stirred at ambient temperature for 30 min. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (SiO_2, gradient from 5−25% EtOAc in petroleum ether) to give the title compound as a yellow oil (29 mg, 78%). ν_{max}(film) 2932, 2923, 2874, 1674, 1601, 1516, 1462, 1427, 1346, 1163, 1157 and 1049 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.87 (1 H, d, J = 2.0 Hz, =CH), 7.20 (2 H, s, Ar), 6.30 (1 H, dd, J = 2.0, 1.1 Hz, =CH), 4.02 (2 H, sept., J = 6.7 Hz, *i*PrCH), 2.93 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.42 (3 H, s, CH_3), 1.92 (3 H, d, J = 1.1 Hz, CH_3), 1.26 (6 H, d, J = 6.9 Hz, *i*PrCH$_3$) and 1.12 (12 H, d, J = 6.7 Hz, *i*PrCH$_3$); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 193.1 (C=O), 155.4 (Ar), 151.4 (2 × Ar), 131.9 (=C), 130.4 (Ar), 125.7 (=C), 125.3 (=CH), 124.3 (2 × ArH), 110.6 (=CH), 34.3 (*i*PrCH), 29.6 (2 × *i*PrCH), 27.1 (CH_3), 24.3 (4 × *i*PrCH$_3$), 23.5 (2 × *i*PrCH$_3$) and 12.5 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{32}NO_3S^+$ 390.2097; Found 390.2106.

385 (±)-4-Acetyl-2-methoxy-2-methyl-1-tosyl-3,3-dihydropyrrole



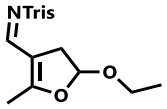
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (3 mg, 0.005 mmol, 5 mol %) was added to a solution of 2-methoxypropene (51 µL, 0.530 mmol, 5.0 equiv.) and tosyl triazole **383** (28 mg, 0.106 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 60 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−15% EtOAc in petroleum ether) to give the title compound as a yellow oil (10 mg, 30%). ^{1}H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.80 (2 H, d, J = 8.0 Hz, Ar), 7.56 (1 H, d, J = 2.2 Hz, =CH), 7.34 (2 H, d, J = 8.0 Hz, Ar), 3.00 (1 H, d, J = 17.7 Hz, CH_2), 2.79 (3 H, s, OCH_3), 2.71 (1 H, dd, J = 17.7 Hz, CH_2), 2.44 (3 H, s, CH_3), 2.26 (3 H, s, CH_3) and 1.72 (3 H, s, CH_3); ^{13}C{^{1}H} NMR (126 MHz, 22.8 °C, $CDCl_3$) δ 193.0 (C=O), 144.6 (Ar), 141.4 (=CH), 137.3 (Ar), 129.9 (2 × ArH), 127.3 (2 × ArH), 119.1 (=C), 100.4 ($C(OCH_3)$), 50.3 (OCH_3), 39.4 (CH_2), 27.5 (CH_3), 25.7 (CH_3) and 21.6 (CH_3).

384 (±)-4-Tolyl-*N*-((5-methoxy-2,5-dimethyl-4,5-dihydrofuran-3-yl)methylene)benzenesulfonamide



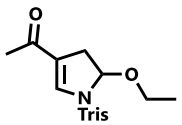
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (3 mg, 0.005 mmol, 5 mol %) was added to a solution of 2-methoxypropene (51 µL, 0.530 mmol, 5.0 equiv.) and tosyl triazole **383** (28 mg, 0.106 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 60 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−15% EtOAc in petroleum ether) to give the title compound as a yellow oil (13 mg, 40%). ν_{max}(film) 3137, 2968, 2927, 1720, 1671, 1517, 1400, 1366, 1308, 1158 and 1096 cm^{-1}; ^1H NMR (500 MHz, 22.4 °C, $CDCl_3$) δ 8.78 (1 H, s, imine CH), 7.79 (2 H, d, J = 7.9 Hz, Ar), 7.28 (2 H, d, J = 7.9 Hz, Ar), 3.26 (3 H, s, OCH_3), 2.91 (1 H, d, J = 16.2 Hz, CH_2), 2.73 (1 H, d, J = 16.2 Hz, CH_2), 2.41 (3 H, s, CH_3), 2.20 (3 H, s, CH_3) and 1.58 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (126 MHz, 22.8 °C, $CDCl_3$) δ 174.5 (imine), 162.4 (=C), 143.6 (Ar), 136.8 (Ar), 129.5 (2 × ArH), 127.4 (2 × ArH), 114.7 ($C(OCH_3)$), 111.2 (=C), 50.3 (OCH_3), 31.2 (CH_2), 24.7 (CH_3), 21.5 (CH_3) and 13.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{18}NNaO_4S^+$ 331.0849; Found 332.0923.

407 (±)-2,4,6-Triisopropyl-*N*-((5-ethoxy-2-methyl-4,5-dihydrofuran-3-yl)methylene)benzenesulfonamide



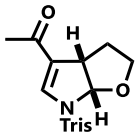
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (9 mg, 0.015 mmol, 5 mol %) was added to a solution of ethyl vinyl ether (144 μL, 1.50 mmol, 5.0 equiv.) and triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 40 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−15% EtOAc in petroleum ether) to give the title compound as a yellow oil (86 mg, 70%). ν_{max}(film) 2960, 2930, 2871, 1721, 1624, 1600, 1562, 1374, 1346, 1242, 1150 and 1108 cm^{-1}; ^1H NMR (400 MHz, 21.0 °C, $CDCl_3$) δ 8.79 (1 H, s, imine CH), 7.14 (2 H, s, Ar), 5.71 (1 H, dd, J = 7.0, 3.3 Hz, CH), 4.37 (2 H, sept., J = 6.7 Hz, *i*PrCH), 3.87 (1 H, dq, J = 9.4, 7.0 Hz, OCH_2), 3.62 (1 H, dq, J = 9.4, 7.0 Hz, OCH_2), 3.00 (1 H, dddd, J = 16.1, 7.5, 1.5, 1.0 Hz, CH_2), 2.89 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.73 (1 H, dddt, J = 16.2, 3.3, 2.5, 1.3 Hz, CH_2), 2.18 (3 H, t, J = 1.5 Hz, CH_3), 1.27–1.23 (18 H, m, *i*PrCH$_3$) and 1.21 (3 H, t, J = 7.1 Hz, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 21.6 °C, $CDCl_3$) δ 173.5 (C=N), 161.3 (=C), 152.7 (Ar), 150.4 (2 × Ar), 132.7 (Ar), 123.5 (2 × ArH), 110.9 (=C), 107.8 (CH), 65.1 (OCH_2), 34.5 (CH_2), 34.2 (*i*PrCH), 29.6 (2 × *i*PrCH), 24.7 (2 × *i*PrCH$_3$), 24.7 (2 × *i*PrCH$_3$), 23.6 (2 × *i*PrCH$_3$), 14.9 (CH_3) and 13.1 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{35}NNaO_4S^+$ 444.2179; Found 444.2177.

411 (±)-4-Acetyl-2-ethoxy-1-(triisopropylbenzenesulfonyl)-2,3-dihydropyrrole



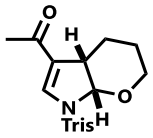
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (9 mg, 0.015 mmol, 5 mol %) was added to a solution of ethyl vinyl ether (144 μL, 1.50 mmol, 5.0 equiv.) and triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 40 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−15% EtOAc in petroleum ether) to give the title compound as an orange oil (11 mg, 9%). ν_{max}(film) 2962, 2931, 2871, 1721, 1654, 1601, 1471, 1427, 1366, 1339, 1260, 1167 and 1100 cm^{-1}; ^1H NMR (400 MHz, 21.0 °C, $CDCl_3$) δ 7.43 (1 H, dd, J = 2.1, 1.1 Hz, =CH), 7.19 (2 H, s, Ar), 5.58 (1 H, dd, J = 8.3, 2.7 Hz, CH), 4.05 (2 H, sept, J = 6.7 Hz, *i*PrCH), 3.28 (2 H, q, J = 7.0 Hz, CH_2), 2.99 (1 H, ddd, J = 17.4, 8.3, 2.3 Hz, CH_2), 2.91 (1 H, sept, J = 6.9 Hz, *i*PrCH), 2.79 (1 H, ddd, J = 17.4, 2.7, 1.1 Hz, CH_2), 2.26 (3 H, s, CH_3), 1.30–1.26 (18 H, m, *i*PrCH$_3$) and 0.85 (3 H, t, J = 7.0 Hz, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 21.7 °C, $CDCl_3$) δ 193.3 (C=O), 154.3 (Ar), 151.4 (2 × Ar), 139.4 (=CH), 131.1 (Ar), 124.2 (2 × ArH), 121.2 (=C), 90.6 (CH), 61.3 (CH_2), 35.2 (CH_2), 34.2 (*i*PrCH), 29.7 (2 × *i*PrCH), 26.0 (CH_3), 24.8 (2 × *i*PrCH$_3$), 24.7 (2 × *i*PrCH$_3$), 23.5 (2 × *i*PrCH$_3$) and 14.6 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{35}NNaO_4S^+$ 444.2179; Found 444.2177.

412 (±)-4-Acetyl-6-(2,4,6-triisopropylbenzenesulfonyl)-3,3a,6,6a-tetrahydrofuro[2,3-*b*]pyrrole



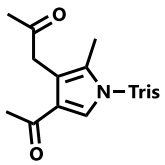
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (9 mg, 0.015 mmol, 5 mol %) was added to a solution of 2,3-dihydrofuran (113 µL, 1.50 mmol, 5.0 equiv.) and triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 40 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−15% EtOAc in petroleum ether) to give the title compound as colourless oil (57 mg, 45%). ^{1}H NMR (400 MHz, 25.0 °C, CD_2Cl_2) δ 7.51 (1 H, d, J = 1.1 Hz, =CH), 7.23 (2 H, s, Ar), 5.94 (1 H, d, J = 7.2 Hz, bridging CH), 4.07 (2 H, d, J = 6.7 Hz, *i*PrCH), 3.88 (1 H, ddd, J = 8.7, 7.1, 1.5 Hz, CH_2), 3.78 (1 H, dd, J = 8.6, 7.1 Hz, bridging CH), 3.39 (1 H, ddd, J = 11.5, 8.8, 5.6 Hz, CH_2), 2.93 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.23 (3 H, s, CH_3), 2.10–1.96 (2 H, m, CH_2), 1.26 (12 H, d, J = 6.7 Hz, *i*PrCH$_3$) and 1.23 (6 H, d, J = 6.9 Hz, *i*PrCH$_3$); ^{13}C{^{1}H} NMR (101 MHz, 25.0 °C, CD_2Cl_2) δ 193.2 (C=O), 154.9 (Ar), 152.1 (2 × Ar), 141.2 (=CH), 131.4 (Ar), 124.9 (2 × ArH), 122.8 (=C), 95.8 (bridging CH), 67.3 (CH_2), 47.9 (bridging CH), 34.8 (*i*PrCH), 31.5 (CH_2), 30.3 (2 × *i*PrCH), 26.6 (CH_3), 25.1 (2 × *i*PrCH$_3$), 25.0 (2 × *i*PrCH$_3$), 23.8 (*i*PrCH$_3$) and 23.8 (*i*PrCH$_3$).

413 (±)-4-Acetyl-6-(2,4,6-triisopropylbenzenesulfonyl)-2,3,4,4a,7,7a-hexahydropyrano[2,3-*b*]pyrrole



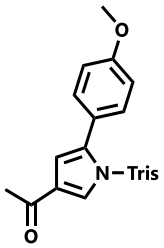
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (9 mg, 0.015 mmol, 5 mol %) was added to a solution of 3,4-dihydro-2*H*-pyran (137 µL, 1.50 mmol, 5.0 equiv.) and triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 40 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5−15% EtOAc in petroleum ether) to give the dihydropyrrole **413** as a colourless oil (33 mg, 25%).; ^{1}H NMR (400 MHz, 24.9 °C, CD_2Cl_2) δ 7.57 (1 H, d, J = 0.8 Hz, =CH), 7.22 (2 H, s, Ar), 5.65 (1 H, d, J = 7.8 Hz, bridging CH), 4.28 (2 H, sept., J = 6.7 Hz, *i*PrCH), 3.65–3.34 (1 H, m, CH_2), 3.05–2.86 (2 H, m, CH_2 + bridging CH), 2.90 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.23 (3 H, s, CH_3), 1.91–1.87 (1 H, m, CH_2), 1.73–1.63 (1 H, m, CH_2), 1.43–1.33 (2 H, m, CH_2), 1.20 (6 H, d, J = 6.9 Hz, *i*PrCH$_3$) and 1.16 (12 H, d, J = 6.7 Hz, *i*PrCH$_3$); ^{13}C{^{1}H} NMR (101 MHz, 24.9 °C, CD_2Cl_2) δ 193.5 (C=O), 157.9 (2 × Ar), 154.7 (Ar), 140.5 (=CH), 131.7 (Ar), 126.1 (=C), 124.7 (2 × ArH), 90.9 (bridging CH), 61.5 (CH_2), 38.6 (bridging CH), 34.8 (*i*PrCH), 30.2 (2 × *i*PrCH), 26.2 (CH_3), 25.2 (2 × *i*PrCH$_3$), 25.0 (2 × *i*PrCH$_3$), 23.9 (CH_2), 23.8 (2 × *i*PrCH$_3$) and 21.1 (CH_2); ν_{max}(film) 2958, 2870, 1718, 1652, 1598, 1559, 1462, 1425, 1372, 1336, 1144, 1089 and 1038 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{24}H_{36}NO_4S^+$ 434.2360; Found 434.2369.

418 4-Acetyl-2-methyl-3-(propan-2-one)-*N*-(2,4,6-triisopropylbenzenesulfonyl)pyrrole



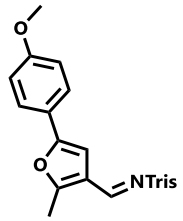
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (6 mg, 0.01 mmol, 2.5 mol %) was added to a solution of 2,5-dimethylfuran (130 µL, 1.20 mmol, 3.0 equiv.) and triazole **338** (151 mg, 0.40 mmol, 1.0 equiv.) in 1,2-DCE (1.60 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 70 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as a yellow oil (85 mg, 48%). ^{1}H NMR (400 MHz, 20.8 °C, $CDCl_3$) δ 7.74 (1 H, s, =CH), 7.19 (2 H, s, Ar), 3.95 (2 H, sept., J = 6.7 Hz, *i*PrCH), 3.57 (2 H, s, CH_2), 2.92 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.41 (3 H, s, CH_3), 2.10 (3 H, s, CH_3), 1.91 (3 H, s, CH_3), 1.26 (6 H, d, J = 6.9 Hz, *i*PrCH_3) and 1.15 (12 H, d, J = 6.7 Hz, *i*PrCH_3); ^{13}C{^{1}H} NMR (101 MHz, 21.5 °C, $CDCl_3$) δ 202.5 (C=O), 193.9 (C=O), 155.6 (Ar), 151.6 (2 × Ar), 130.3 (Ar), 126.4 (pyrrole CH), 125.2 (pyrrole), 124.7 (pyrrole), 124.5 (2 × ArH), 123.4 (pyrrole), 38.9 (CH_2), 34.3 (*i*PrCH), 29.7 (2 × *i*PrCH), 28.7 (CH_3), 27.9 (CH_3), 24.4 (4 × *i*PrCH_3), 23.4 (2 × *i*PrCH_3) and 10.6 (CH_3).

422 4-Acetyl-2-(4-methoxybenzene)-*N*-(2,4,6-triisopropylbenzenesulfonyl)pyrrole



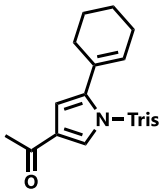
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (6 mg, 0.01 mmol, 2.5 mol %) was added to a solution of 4-ethynylanisole (78 µL, 0.60 mmol, 1.5 equiv.), triazole **338** (151 mg, 0.40 mmol, 1.0 equiv.) and silver(I) trifluoroacetate (4 mg, 0.02 mmol, 5 mol %) in hexane (6.67 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 70 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as a yellow oil (50 mg, 26%). ν_{max}(film) 2963, 2932, 2874, 1674, 1601, 1570, 1485, 1462, 1427, 1373, 1346, 1304, 1250, 1219, 1169, 1103 and 1049 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.09 (1 H, d, J = 2.0 Hz, pyrrole), 6.95 (2 H, s, Tris Ar), 6.77 (2 H, d, J = 8.8 Hz, Ar), 6.55 (2 H, d, J = 8.8 Hz, Ar), 6.43 (1 H, d, J = 2.0 Hz, pyrrole), 3.75 (3 H, s, OCH_3), 3.67 (2 H, sept., J = 6.7 Hz, *i*PrCH), 2.85 (1 H, sept., J = 6.8 Hz, *i*PrCH), 2.49 (3 H, s, CH_3), 1.23 (6 H, d, J = 6.8 Hz, *i*PrCH$_3$) and 0.97 (12 H, d, J = 6.7 Hz, *i*PrCH$_3$); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 193.2 (C=O), 159.5 (Ar), 154.9 (Tris Ar), 151.2 (2 × Tris Ar), 135.7 (pyrrole C2), 131.8 (2 × ArH), 130.8 (Tris Ar), 125.7 (pyrrole C5), 125.5 (pyrrole C4), 123.5 (2 × Tris ArH), 122.2 (Ar), 112.9 (2 × ArH), 112.7 (pyrrole C3), 55.1 (OCH_3), 34.3 (*i*PrCH), 29.4 (2 × *i*PrCH), 27.2 (CH_3), 24.3 (4 × *i*PrCH$_3$) and 23.5 (2 × *i*PrCH$_3$); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{36}NO_4S^+$ 482.2360; Found 482.2366.

423 2,4,6-Triisopropyl-*N*-[(5-(4-methoxyphenyl)-2-methylfuran-3-yl)methylene]benzenesulfonamide



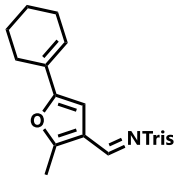
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (6 mg, 0.01 mmol, 2.5 mol %) was added to a solution of 4-ethynylanisole (78 µL, 0.60 mmol, 1.5 equiv.), triazole **338** (151 mg, 0.40 mmol, 1.0 equiv.) and silver(I) trifluoroacetate (4 mg, 0.02, 5 mol %) in hexane (6.67 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 70 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as an off-white oily solid (45 mg, 23%). ν_{max}(film) 2963, 2932, 2870, 1690, 1605, 1574, 1505, 1462, 1427, 1377, 1304, 1250, 1150, 1107, 1069 and 1030 cm^{-1}; ^1H NMR (400 MHz, 24.7 °C, $CDCl_3$) δ 8.96 (1 H, s, imine CH), 7.56 (2 H, d, J = 8.8 Hz, Ar), 7.19 (2 H, s, Tris Ar), 6.93 (2 H, d, J = 8.8 Hz, Ar), 6.78 (1 H, s, furan), 4.36 (2 H, sept., J = 6.7 Hz, *i*PrCH), 3.84 (3 H, s, OCH_3), 2.91 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.60 (3 H, s, CH_3), 1.29 (12 H, d, J = 6.7 Hz, *i*PrCH_3) and 1.26 (6 H, d, J = 6.9 Hz, *i*PrCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 24.8 °C, $CDCl_3$) δ 162.0 (furan C2), 160.4 (imine CH), 159.8 (Ar), 154.3 (furan C4), 153.3 (Tris Ar), 150.9 (2 × Tris Ar), 131.7 (Tris Ar), 125.5 (2 × ArH), 123.8 (2 × Tris ArH), 122.2 (Ar), 120.1 (furan C3), 114.3 (2 × ArH), 101.3 (furan C4), 55.4 (OCH_3), 34.2 (*i*PrCH), 29.7 (2 × *i*PrCH), 24.8 (4 × *i*PrCH_3), 23.6 (2 × *i*PrCH_3) and 12.9 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{36}NO_4S^+$ 482.2360; Found 482.2378.

425 4-Acetyl-2-(cyclohexen-1-yl)-*N*-(2,4,6-triisopropylbenzenesulfonyl)pyrrole



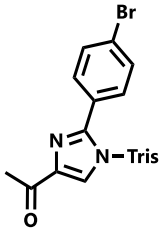
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (6 mg, 0.01 mmol, 2.5 mol %) was added to a solution of 1-ethynylcyclohexene (71 µL, 0.60 mmol, 1.5 equiv.), triazole **338** (151 mg, 0.40 mmol, 1.0 equiv.) and silver(I) trifluoroacetate (4 mg, 0.02 mmol, 5 mol %) in hexane (6.67 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 70 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as a yellow oil (58 mg, 32%). ν_{max}(film) 2963, 2931, 2874, 1674, 1601, 1570, 1485, 1462, 1427, 1373, 1346, 1304, 1250, 1219, 1169, 1103 and 1049 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.90 (1 H, d, *J* = 2.0 Hz, pyrrole C5), 7.15 (2 H, s, Tris Ar), 6.31 (1 H, d, *J* = 2.0 Hz, pyrrole C3), 5.36 (1 H, tt, *J* = 3.8, 1.8 Hz, =CH), 3.89 (2 H, sept., *J* = 6.7 Hz, *i*PrCH), 2.92 (1 H, sept., *J* = 6.9 Hz, *i*PrCH), 2.43 (3 H, s, CH_3), 1.86–1.81 (2 H, m, CH_2), 1.72–1.67 (2 H, m, CH_2), 1.45–1.35 (4 H, m, CH_2), 1.25 (6 H, d, *J* = 6.9 Hz, *i*PrCH$_3$) and 1.11 (12 H, d, *J* = 6.7 Hz, *i*PrCH$_3$); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 193.2 (C=O), 154.9 (Tris Ar), 151.3 (2 × Tris Ar), 138.5 (C=C), 132.2 (=CH), 131.7 (Tris Ar), 127.9 (C=C), 125.6 (pyrrole C4), 125.3 (pyrrole C5), 123.7 (2 × Tris ArH), 110.4 (pyrrole C3), 34.4 (*i*PrCH), 30.2 (CH_2), 29.7 (2 × *i*PrCH), 27.1 (CH_3), 25.4 (CH_2), 24.5 (4 × *i*PrCH$_3$), 23.5 (2 × *i*PrCH$_3$), 22.4 (CH_2) and 21.1 (Ch2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{38}NO_3S^+$ 456.2567; Found 456.2587.

426 2,4,6-Triisopropyl-*N*-[(5-(cyclohexen-1-yl)-2-methylfuran-3-yl)methylene]benzenesulfonamide



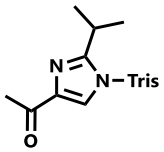
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (6 mg, 0.01 mmol, 2.5 mol %) was added to a solution of 1-ethynylcyclohexene (71 µL, 0.60 mmol, 1.5 equiv.), triazole **338** (151 mg, 0.40 mmol, 1.0 equiv.) and silver(I) trifluoroacetate (4 mg, 0.02 mmol, 5 mol %) in hexane (6.67 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 70 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as a yellow oil (25 mg, 14%). ν_{max}(film) 2963, 2932, 2870, 1690, 1605, 1574, 1505, 1462, 1427, 1377, 1304, 1250, 1150, 1107, 1069 and 1030 cm^{-1}; ν_{max}(film) 2959, 2932, 2870, 1605, 1574, 1458, 1427, 1362, 1316, 1258, 1153 and 1045 cm^{-1}; ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.90 (1 H, d, J = 0.5 Hz, imine CH), 7.18 (2 H, s, ArH), 6.41 (1 H, d, J = 0.5 Hz, furan), 6.32 (1 H, tt, J = 3.8, 1.8 Hz, =CH), 4.33 (2 H, sept., J = 6.8 Hz, *i*PrCH), 2.90 (1 H, sept., J = 7.0 Hz, *i*PrCH), 2.53 (3 H, s, CH_3), 2.24–2.15 (4 H, m, CH_2), 1.75–1.68 (2 H, m, CH_2), 1.67–1.61 (2 H, m, CH_2), 1.27 (12 H, d, J = 6.8 Hz, *i*PrCH$_3$) and 1.25 (6 H, d, J = 7.0 Hz, *i*PrCH$_3$); ^{13}C{^{1}H} NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 162.0 (furan C2), 160.4 (imine), 155.7 (furan C4), 153.2 (Tris Ar), 150.8 (2 × Tris Ar), 131.8 (Tris Ar), 126.1 (C=C), 124.5 (=CH), 123.7 (2 × Tris ArH), 119.5 (furan), 101.4 (furan CH), 34.2 (*i*PrCH), 29.7 (2 × *i*PrCH), 25.2 (CH_2), 24.8 (4 × *i*PrCH$_3$), 24.6 (CH_2), 23.6 (2 × *i*PrCH$_3$), 22.1 (CH_2), 22.0 (CH_2) and 12.8 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{38}NO_3S^+$ 456.2567; Found 456.2573.

428 4-Acetyl-2-(4-Bromophenyl)-1-(2,4,6-triisopropylbenzenesulfonyl)imidazole



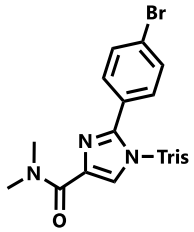
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (6 mg, 0.01 mmol, 2.5 mol %) was added to a solution of 4-bromobenzonitrile (218 mg, 1.20 mmol, 3.0 equiv.), triazole **338** (151 mg, 0.40 mmol, 1.0 equiv.) in 1,2-DCE (1.60 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 80 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as a brown solid (48 mg, 23%). ν_{max}(film) 2963, 2932, 2874, 1690, 1597, 1539, 1466, 1427, 1377, 1366, 1319, 1196, 1173, 1126, 1065 and 1003 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.24 (1 H, s, imidazole), 7.29 (2 H, d, J = 8.5 Hz, Ar), 7.05 (2 H, d, J = 8.5 Hz, Ar), 7.00 (2 H, s, Tris Ar), 3.63 (2 H, sept., J = 6.7 Hz, *i*PrCH), 2.87 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.57 (3 H, s, CH_3), 1.23 (6 H, d, J = 6.9 Hz, *i*PrCH_3) and 1.02 (12 H, d, J = 6.7 Hz, *i*PrCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 193.7 (C=O), 156.2 (Tris Ar), 151.6 (2 × Tris Ar), 146.3 (imidazole C2), 139.4 (imidazole C5), 131.2 (2 × ArH), 131.1 (2 × ArH), 129.6 (Ar), 127.7 (Ar), 124.5 (Tris Ar), 123.9 (2 × Tris ArH), 123.1 (imidazole C4), 34.4 (*i*PrCH), 29.7 (2 × *i*PrCH), 27.0 (CH_3), 24.2 (4 × *i*PrCH_3) and 23.4 (2 × *i*PrCH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{32}BrN_2O_3S^+$ 531.1312; Found 531.1308.

431 4-Acetyl-2-isopropyl-1-(2,4,6-triisopropylbenzenesulfonyl)imidazole



Under an atmosphere of argon, $Rh_2(OPiv)_4$ (6 mg, 0.01 mmol, 2.5 mol %) was added to a solution of isobutyronitrile (108 µL, 1.20 mmol, 3.0 equiv.), triazole **338** (151 mg, 0.40 mmol, 1.0 equiv.) in 1,2-DCE (1.60 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 80 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as a yellow oil (20 mg, 12%). ν_{max}(film) 2963, 2932, 2874, 1686, 1601, 1543, 1462, 1427, 1377, 1362, 1304, 1238, 1173, 1134, 1107 and 1042 cm^{-1}; ^1H NMR (400 MHz, 25.4 °C, $CDCl_3$) δ 7.87 (1 H, s, imidazole), 7.22 (2 H, s, Tris Ar), 3.95 (2 H, sept., J = 6.7 Hz, *i*PrCH), 3.00 (1 H, sept., J = 7.0 Hz, *i*PrCH), 2.94 (1 H, sept., J = 6.8 Hz, *i*PrCH), 2.51 (3 H, s, CH_3), 1.26 (6 H, d, J = 7.0 Hz, *i*PrCH_3), 1.14 (12 H, d, J = 6.7 Hz, *i*PrCH_3) and 1.08 (6 H, d, J = 6.8 Hz, *i*PrCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.2 °C, $CDCl_3$) δ 193.7 (C=O), 156.2 (Tris Ar), 154.7 (imidazole C2), 151.7 (2 × Tris Ar), 139.1 (imidazole C5), 130.2 (Tris Ar), 124.7 (2 × Tris ArH), 121.7 (imidazole C4), 34.4 (*i*PrCH), 29.7 (2 × *i*PrCH), 27.6 (*i*PrCH), 26.8 (CH_3), 24.3 (4 × *i*PrCH_3), 23.4 (2 × *i*PrCH_3) and 21.4 (2 × *i*PrCH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{35}N_2O_3S^+$ 419.2363; Found 419.2370.

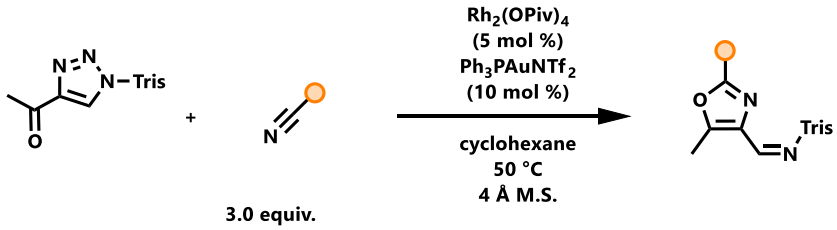
434 2-(4-Bromophenyl)-4-(*N,N*-dimethylacetamido)-1-(2,4,6-triisopropylbenzenesulfonyl)imidazole



Under an atmosphere of argon, $Rh_2(OPiv)_4$ (6 mg, 0.01 mmol, 2.5 mol %) was added to a solution of 4-bromobenzonitrile (218 mg, 1.20 mmol, 3.0 equiv.), triazole **433** (163 mg, 0.40 mmol, 1.0 equiv.) in 1,2-DCE (1.60 mL) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 80 °C (heating block) for 2 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 10−30% EtOAc in petroleum ether) to give the title compound as a brown oil (85 mg, 40%). ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.15 (1 H, s, =CH), 7.32 (2 H, d, J = 8.5 Hz, Ar), 7.12 (2 H, d, J = 8.5 Hz, Ar), 7.03 (2 H, s, Ar), 3.70 (2 H, sept., J = 6.7 Hz, *i*PrCH), 3.42 (3 H, br s, NCH_3), 3.10 (3 H, br s, NCH_3), 2.89 (1 H, sept., J = 6.9 Hz, *i*PrCH), 1.25 (6 H, d, J = 6.9 Hz, *i*PrCH$_3$) and 1.06 (12 H, d, J = 6.7 Hz, *i*PrCH$_3$); ^{13}C{^{1}H} NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 163.0 (C=O), 155.9 (Ar), 151.6 (2 × Ar), 144.8 (Ar), 136.3 (Ar), 131.3 (2 × ArH), 131.0 (2 × ArH), 130.0 (Ar), 128.1 (imidazole), 124.5 (imidazole), 124.3 (=CH), 123.8 (2 × ArH), 38.7 (NCH_3), 36.3 (NCH_3), 34.4 (*i*PrCH), 29.7 (2 × *i*PrCH), 24.2 (4 × *i*PrCH$_3$) and 23.4 (2 × *i*PrCH$_3$).

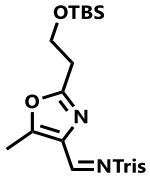
7.2.7 Preparation of oxazoles

General Procedure 5: Rhodium(II)-catalysed transannulation of 1-STs with nitriles



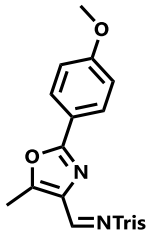
Under an atmosphere of argon, $Rh_2(OPiv)_4$ (5 mol %) was added to a solution of 1-ST **338** (1.0 equiv.), nitrile (3.0 equiv.) and $Ph_3PAuNTf_2$ (10 mol %) in cyclohexane (0.03 M) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 50 °C (heating block) until complete (TLC, 1–2 h). The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 5–25% EtOAc in petroleum ether) to give the product oxazole product.

476 2-(2-(*tert*-Butyldimethylsilyl)oxyethyl)-5-methyloxazole-4-[(*N*-2,4,6-triisopropylbenzenesulfonyl])methanimine



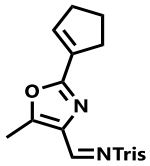
Triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) and 3-((*t*butyldimethylsilyl)oxy)propanenitrile (167 mg, 0.90 mmol, 3.0 equiv.) were treated with $Rh_2(OPiv)_4$ (8 mg, 0.015 mmol, 5 mol %) and $Ph_3PAuNTf_2$ (24 mg, 0.030 mmol, 10 mol %) in cyclohexane (6.0 mL) according to General Procedure 5 to give the compound as a colourless oil (43 mg, 27%). ν_{max}(film) 2958, 1615, 1363, 1321, 1256, 1152 and 1107 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.88 (1 H, s, imine CH), 7.18 (2 H, s, Ar), 4.23 (2 H, sept., J = 6.7 Hz, *i*PrCH), 3.97 (2 H, t, J = 6.5 Hz, CH_2), 2.95 (2 H, t, J = 6.5 Hz, CH_2), 2.90 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.64 (3 H, s, CH_3), 1.26 (6 H, d, J = 6.9 Hz, *i*PrCH_3), 1.25 (12 H, d, J = 6.7 Hz, *i*PrCH_3), 0.83 (9 H, s, 3 × CH_3) and 0.01 (6 H, s, 2 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 162.2 (imine CH), 161.0 (oxazole C2), 157.3 (oxazole C5), 153.7 (2 × Ar), 151.3 (Ar), 131.1 (oxazole C4), 130.6 (Ar), 123.9 (2 × ArH), 60.2 (CH_2), 34.3 (*i*PrCH), 31.8 (CH_2), 29.8 (2 × *i*PrCH), 25.7 (3 × CH_3), 24.7 (4 × *i*PrCH_3), 23.6 (2 × *i*PrCH_3), 18.1 (*t*Bu), 12.3 (CH_3) and −5.5 (2 × CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{46}N_2NaO_4SSi^+$ 557.2840; Found 557.2853.

477 2-(4-Methoxyphenyl)-5-methyloxazole-4-[(*N*-2,4,6-triisopropylbenzenesulfonyl])methanimine



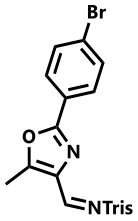
Triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) and 4-methoxbenzonitrile (120 mg, 0.90 mmol, 3.0 equiv.) were treated with $Rh_2(OPiv)_4$ (8 mg, 0.015 mmol, 5 mol %) and $Ph_3PAuNTf_2$ (24 mg, 0.030 mmol, 10 mol %) in cyclohexane (6.0 mL) according to General Procedure 5 to give the compound as a yellow oil (43 mg, 34%). ν_{max}(film) 2960, 1618, 1504, 1256 and 1152 cm^{-1}; ^1H NMR (400 MHz, 24.9 °C, $CDCl_3$) δ 8.99 (1 H, s, imine CH), 7.95 (2 H, d, J = 8.9 Hz, Ar), 7.19 (2 H, s, Ar), 6.97 (2 H, d, J = 8.9 Hz, Ar), 4.28 (2 H, sept., J = 6.7 Hz, *i*PrCH), 3.86 (3 H, s, OCH_3), 2.91 (1 H, sept., J = 7.0 Hz, *i*PrCH), 2.74 (3 H, s, CH_3), 1.28 (12 H, d, J = 6.7 Hz, *i*PrCH_3) and 1.26 (6 H, d, J = 7.0 Hz, *i*PrCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 24.9 °C, $CDCl_3$) δ 161.9 (oxazole C2), 161.2 (imine), 161.1 (Ar), 157.1 (oxazole C5), 153.7 (Tris Ar), 151.3 (2 × Tris Ar), 132.2 (oxazole C4), 130.8 (Tris Ar), 128.3 (2 × ArH), 123.9 (2 × Tris ArH), 118.8 (Ar), 114.3 (2 × ArH), 55.4 (OCH_3), 34.3 (*i*PrCH), 29.8 (2 × *i*PrCH), 24.8 (4 × *i*PrCH_3), 23.6 (2 × *i*PrCH_3) and 12.5 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{35}N_2O_4S^+$ 483.2312; Found 483.2324.

478 2-(Cyclohexen-1-yl)-5-methyloxazole-4-[(*N*-2,4,6-triisopropylbenzenesulfonyl])methanimine



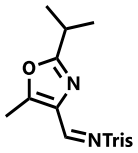
Triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) and 1-cyanocyclopentene (84 mg, 0.90 mmol, 3.0 equiv.) were treated with $Rh_2(OPiv)_4$ (8 mg, 0.015 mmol, 5 mol %) and $Ph_3PAuNTf_2$ (24 mg, 0.030 mmol, 10 mol %) in cyclohexane (6.0 mL) according to General Procedure 5 to give the compound as a colourless oil (38 mg, 29%). ν_{max}(film) 2958, 1593, 1463, 1363, 1320, 1152 and 1039 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.93 (1 H, s, imine CH), 7.17 (2 H, s, Ar), 6.64–6.59 (1 H, m, =CH), 4.23 (2 H, d, J = 6.7 Hz, *i*PrCH), 2.89 (1 H, d, J = 6.9 Hz, *i*PrCH), 2.79–2.72 (2 H, m, CH_2), 2.69 (3 H, s, CH_3), 2.61–2.54 (2 H, m, CH_2), 2.03 (2 H, app. p, J = 7.6 Hz, CH_2), 1.27 (12 H, d, J = 6.7 Hz, *i*PrCH$_3$) and 1.26 (6 H, d, J = 6.9 Hz, *i*PrCH$_3$); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 161.4 (imine CH), 159.5 (oxazole C2), 157.0 (oxazole C5), 153.7 (2 × Ar), 151.3 (Ar), 136.8 (=CH), 131.7 (oxazole C4), 130.6 (Ar), 130.3 (=C), 123.9 (2 × ArH), 34.3 (*i*PrCH), 33.7 (CH_2), 32.0 (CH_2), 29.8 (2 × *i*PrCH), 24.7 (4 × *i*PrCH$_3$), 23.6 (2 × *i*PrCH$_3$), 23.1 (CH_2) and 12.6 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{35}N_2O_3S^+$ 443.2363; Found 443.2376.

474 2-(4-Bromophenyl)-5-methyloxazole-4-[(*N*-2,4,6-triisopropylbenzenesulfonyl])methanimine



Triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) and 4-bromobenzonitrile (164 mg, 0.90 mmol, 3.0 equiv.) were treated with $Rh_2(OPiv)_4$ (8 mg, 0.015 mmol, 5 mol %) and $Ph_3PAuNTf_2$ (24 mg, 0.030 mmol, 10 mol %) in cyclohexane (6.0 mL) according to General Procedure 5 to give the compound as a yellow oil (58 mg, 36%). ν_{max}(film) 2963, 2932, 2870, 1690, 1616, 1601, 1462, 1427, 1366, 1319, 1153, 1072, 1042 and 1011 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 9.01 (1 H, s, imine CH), 7.89 (2 H, d, J = 8.6 Hz, Ar), 7.61 (2 H, d, J = 8.6 Hz, Ar), 7.19 (2 H, s, Tris Ar), 4.27 (2 H, sept., J = 6.8 Hz, *i*PrCH), 2.91 (1 H, sept., J = 6.9 Hz, *i*PrCH), 2.76 (3 H, s, CH_3), 1.28 (12 H, d, J = 6.8 Hz, *i*PrCH_3) and 1.26 (6 H, d, J = 6.9 Hz, *i*PrCH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 161.1 (imine CH), 160.2 (oxazole C2), 157.5 (oxazole C5), 153.8 (Tris Ar), 151.3 (2 × Tris Ar), 132.5 (oxazole C4), 132.2 (2 × ArH), 130.7 (Tris Ar), 128.0 (2 × ArH), 125.7 (Ar), 125.1 (Ar), 123.9 (2 × Tris ArH), 34.3 (*i*PrCH), 29.8 (2 × *i*PrCH), 24.8 (4 × *i*PrCH_3), 23.6 (2 × *i*PrCH_3) and 12.6 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{32}BrN_2O_3S^+$ 531.1312; Found 531.1316.

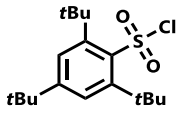
475 2-*iso*-Propyl-5-methyloxazole-4-[(*N*-2,4,6-triisopropylbenzenesulfonyl])methanimine



Triazole **338** (113 mg, 0.30 mmol, 1.0 equiv.) and of isobutyronitrile (108 µL, 0.90 mmol, 3.0 equiv.) were treated with $Rh_2(OPiv)_4$ (8 mg, 0.015 mmol, 5 mol %) and $Ph_3PAuNTf_2$ (24 mg, 0.030 mmol, 10 mol %) in cyclohexane (6.0 mL) according to General Procedure 5 to give the compound as a colourless oil (38 mg, 30%). ν_{max}(film) 2963, 2932, 2874, 1613, 1570, 1462, 1427, 1366, 1319, 1258, 1192 and 1153 cm^{-1}; ^1H NMR (400 MHz, 25.5 °C, $CDCl_3$) δ 8.91 (1 H, s, imine CH), 7.17 (2 H, s, Tris Ar), 4.25 (2 H, sept., *J* = 6.7 Hz, *i*PrCH), 3.06 (1 H, sept., *J* = 6.8 Hz, *i*PrCH), 2.90 (1 H, sept., *J* = 6.9 Hz, *i*PrCH), 2.65 (3 H, s, CH_3), 1.33 (6 H, d, *J* = 6.9 Hz, *i*PrCH$_3$), 1.26 (12 H, d, *J* = 6.7 Hz, *i*PrCH$_3$) and 1.25 (6 H, d, *J* = 6.8 Hz, *i*PrCH$_3$); $^{13}C\{^1H\}$ NMR (101 MHz, 24.9 °C, $CDCl_3$) δ 168.4 (oxazole C2), 161.3 (imine CH), 157.2 (oxazole C5), 153.6 (2 × Tris Ar), 151.3 (Tris Ar), 130.8 (Tris Ar), 130.8 (oxazole C4), 123.8 (2 × Tris ArH), 34.2 (*i*PrCH), 29.8 (2 × *i*PrCH), 28.2 (*i*PrCH), 24.7 (4 × *i*PrCH$_3$), 23.6 (2 × *i*PrCH$_3$), 20.1 (2 × *i*PrCH$_3$) and 12.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{35}N_2O_3S^+$ 419.2363; Found 419.2373.

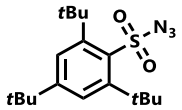
7.2.8 Preparation of sterically hindered sulfonyl azides

456 2,4,6-Tritertbutylbenzenesulfonyl chloride



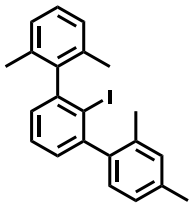
In flame-dried flask under an atmosphere of argon, 1-bromo-2,4,6-tritertbutylbenzene (3.25 g, 10.0 mmol, 1.0 equiv.) was dissolved in THF (100 mL) and cooled to −78 °C (dry ice, acetone). *t*BuLi (1.7 m solution in pentane, 11.77 mL, 20.0 mmol, 2.0 equiv.) was added drop-wise and the reaction stirred at −78 °C for 3 h. At this temperature, freshly distilled SO_2Cl_2 (1.62 mL, 20.0 mmol, 2.0 equiv.) was added drop-wise and the reaction allowed to warm to ambient temperature over 2 h. Saturated aqueous NH_4Cl (50 mL) was added and the aqueous phase extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient from 1−5% EtOAc in petroleum ether) to give the title compound as a yellow oil (260 mg, 17%). ν_{max}(film) 2963, 2870, 1586, 1462, 1432, 1400, 1358, 1234, 1173 and 1126 cm^{-1}; ^1H NMR (400 MHz, 21.6 °C, $CDCl_3$) δ 7.47 (2 H, s, ArH), 1.60 (18 H, s, 6 × CH_3) and 1.31 (9 H, s, 3 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 22.2 °C, $CDCl_3$) δ 157.1 (2 × Ar), 155.5 (Ar), 144.3 (Ar–SO_2Cl), 126.7 (2 × ArH), 41.2 (3 × *t*Bu), 33.7 (6 × CH_3) and 30.8 (3 × CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{29}ClNaO_2S^+$ 367.1469; Found 367.1467.

457 2,4,6-Tritertbutylbenzenesulfonyl azide



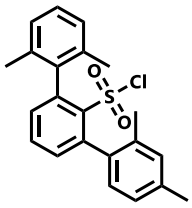
In a vial, 2,4,6-tritertbutylbenzenesulfonyl chloride **456** (227 mg, 0.658 mmol, 1.0 equiv.) was dissolved in acetone (5.0 mL) and water (5.0 mL). NaN_3 (51 mg, 0.790 mmol, 1.20 equiv.) was added, the vial sealed with a Teflon cap and heated to 40 °C for 24 h. Acetone was removed *in vacuo* and the aqueous phase extracted with EtOAc (3 × 5.0 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a red oil (179 mg, 77%). ν_{max}(film) 2963, 2913, 2870, 2122, 1589, 1462, 1362, 1246, 1204, 1165 and 1130 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.44 (2 H, s, ArH), 1.54 (18 H, s, 6 × CH_3) and 1.31 (9 H, s, 3 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 155.3 (2 × Ar), 153.8 (Ar), 149.9 (Ar–SO_2N_3), 125.7 (2 × ArH), 40.4 (3 × *t*Bu), 33.3 (6 × CH_3) and 31.6 (3 × CH_3); HRMS (ESI-TOF) *m/z*: $[M+NH_4]^+$ Calcd for $C_{18}H_{33}N_4O_2S^+$ 369.2319; Found 369.2316.

458 2,6-Di(2,6-dimethylphenyl)iodobenzene



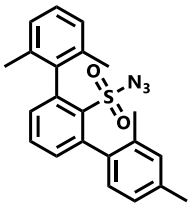
In a flame-dried flask under an atmosphere of argon was added Mg turnings (2.43 g, 100 mmol, 4.0 equiv.). A solution of 2,6-dimethylbromobenzene (13.3 mL, 100 mmol, 4.0 equiv.) in THF (100 mL) was slowly added *via* dropping funnel such that a gentle reflux was maintained. After complete addition (*ca.* 1 h) the reaction was heated to reflux for 4 h. A solution of 2,6-dichloroiodobenzene (6.82 g, 25.0 mmol, 1.0 equiv.) in THF (100 mL) was added *via* dropping funnel over 1 h. The reaction was heated to reflux for 18 h, cooled to 0 °C (ice bath) and iodine (25.38 g, 100 mmol, 4.0 equiv.) was added in one portion. The mixture was stirred vigorously for 4 h and diluted with water (50 mL). Saturated aqueous $Na_2S_2O_3$ was added until the purple colour dissipated (~100 mL) and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with water, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was triturated with pentane (3 × 100 mL) to afford the title compound as a white solid (5.41 g, 53%). ν_{max}(film) 3063, 3021, 2967, 2944, 2916, 1582, 1458, 1381, 1165, 1080 and 1003 cm^{-1}; ^1H NMR (400 MHz, 25.3 °C, $CDCl_3$) δ 7.50 (1 H, t, J = 7.5 Hz, ArH), 7.23 (2 H, dd, J = 8.3, 6.7 Hz, ArH), 7.15–7.12 (4 H, m, ArH), 7.11 (2 H, d, J = 7.5 Hz, ArH) and 2.03 (12 H, s, 4 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 24.8 °C, $CDCl_3$) δ 147.1 (2 × Ar), 144.7 (2 × Ar), 135.6 (4 × Ar), 128.9 (ArH), 127.6 (2 × ArH), 127.3 (6 × ArH), 106.7 (Ar–I) and 20.3 (4 × CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{22}I^+$ 413.0761; Found 413.0747.

459 2,6-Di(2,6-dimethylphenyl)benzenesulfonyl chloride



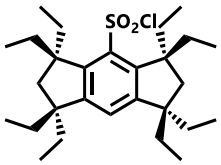
In flame-dried flask under an atmosphere of argon, iodide **458** (4.14 g, 10.0 mmol, 1.0 equiv.) was dissolved in cyclohexane (30 mL) and cooled to −78 °C (dry ice, acetone). *n*BuLi (2.5 m solution in hexanes, 4.00 mL, 10.0 mmol, 1.0 equiv.) was added drop-wise and the reaction stirred at −78 °C for 2 h. The solvent was removed *in vacuo* and the residue suspended in Et_2O (30 mL). The mixture was cooled to −78 °C (dry ice, acetone) and freshly distilled SO_2Cl_2 (0.93 mL, 11.5 mmol, 1.15 equiv.) was added drop-wise and the reaction allowed to warm to ambient temperature over 2 h. Saturated aqueous NH_4Cl (50 mL) was added and the aqueous phase extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 5% EtOAc in petroleum ether) to give the title compound as a white solid (1.41 g, 37%). ν_{max}(film) 3063, 3021, 2920, 2859, 1570, 1458, 1377, 1273 and 1180 cm^{-1}; ^1H NMR (400 MHz, 24.7 °C, $CDCl_3$) δ 7.79 (1 H, t, *J* = 7.6 Hz, ArH), 7.31 (2 H, d, *J* = 7.6 Hz, ArH), 7.24 (2 H, dd, *J* = 8.2, 6.9 Hz, ArH), 7.14 (4 H, d, *J* = 7.6 Hz, ArH) and 2.10 (12 H, s, 4 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.2 °C, $CDCl_3$) δ 142.6 (2 × Ar), 141.6 (Ar–SO_2Cl), 138.5 (2 × Ar), 135.7 (4 × Ar), 135.0 (ArH), 132.2 (2 × ArH), 128.0 (2 × ArH), 127.1 (4 × ArH) and 21.0 (4 × CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{21}ClNaO_2S^+$ 407.0843; Found 407.0852.

460 2,6-Di(2,6-dimethylphenyl)benzenesulfonyl azide



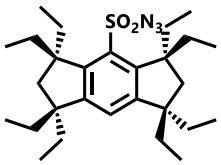
In a vial, sulfonyl chloride **459** (300 mg, 0.780 mmol, 1.0 equiv.) was dissolved in acetone (5.0 mL) and water (5.0 mL). NaN_3 (56 mg, 0.857 mmol, 1.2 equiv.) was added, the vial sealed with a Teflon cap and heated to 75 °C for 2 h. Acetone was removed *in vacuo* and the aqueous phase extracted with EtOAc (3 × 5.0 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a yellow solid (216 mg, 71%). ν_{max}(film) 3063, 3021, 2955, 2924, 2855, 2133, 1574, 1454, 1366, 1192, 1169, 1115, 1080 and 1038 cm^{-1}; ^1H NMR (400 MHz, 21.4 °C, $CDCl_3$) δ 7.75 (1 H, t, J = 7.6 Hz, ArH), 7.25 (2 H, d, J = 7.6 Hz, ArH), 7.23 (2 H, dd, J = 6.9, 6.5 Hz, ArH), 7.15 (4 H, d, J = 6.9 Hz, ArH) and 2.09 (12 H, s, 4 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 22.2 °C, $CDCl_3$) δ 142.7 (2 × Ar), 139.0 (2 × Ar), 136.6 (Ar–SO_2N3), 135.8 (4 × Ar), 134.2 (ArH), 131.7 (2 × ArH), 128.0 (2 × ArH), 127.3 (4 × ArH) and 20.8 (4 × CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{21}N_3NaO_2S^+$ 414.1247; Found 414.1251.

465 4-(Chlorosulfonyl)-1,1,3,3,5,5,7,7-octaethyl-1,2,3,5,6,7-hexahydro-*s*-indacene



4-Bromo-1,1,3,3,5,5,7,7-octaethyl-1,2,3,5,6,7-hexahydro-*s*-indacene (100 mg, 0.217 mmol, 1.0 equiv.) was dissolved in THF (2.17 mL) and cooled to −78 °C (dry ice, acetone). *t*BuLi (1.7 m solution in pentane, 383 µL, 0.434 mmol, 2.0 equiv.) was added drop-wise and the reaction stirred at −78 °C for 3 h. At this temperature, freshly distilled SO_2Cl_2 (53 µL, 0.651 mmol, 3.0 equiv.) was added drop-wise and the reaction allowed to warm to ambient temperature over 2 h. Saturated aqueous NH_4Cl (5.0 mL) was added and the aqueous phase extracted with Et_2O (3 × 5.0 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient from 1−5% EtOAc in petroleum ether) to give the title compound as a yellow oil (32 mg, 31%). ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.02 (1 H, s, ArH), 2.22–2.00 (8 H, m, 4 × CH_2), 1.99 (4 H, s, 2 × CH_2), 1.72–1.52 (8 H, m, 4 × CH_2) and 0.87–0.79 (24 H, m, 8 × CH_3); ^{13}C{^{1}H} NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 154.9 (2 × Ar), 147.3 (2 × Ar), 143.1 (Ar–SO_2Cl), 127.7 (ArH), 56.7 (2 × benzylic C), 47.4 (2 × benzylic C), 44.7 (2 × CH_2), 32.9 (4 × CH_2), 10.4 (4 × CH_2) and 9.0 (8 × CH_3); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{28}H_{44}ClO_2S^-$ 479.2756; Found 479.2756.

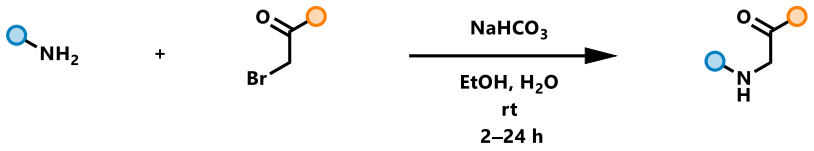
466 4-(Azidosulfonyl)-1,1,3,3,5,5,7,7-octaethyl-1,2,3,5,6,7-hexahydro-*s*-indacene



In a vial, sulfonyl chloride **465** (20 mg, 0.042 mmol, 1.0 equiv.) was dissolved in acetone (1.0 mL) and water (1.0 mL). NaN_3 (3 mg, 0.046 mmol, 1.1 equiv.) was added, the vial sealed with a Teflon cap and heated to 40 °C for 2 h. Acetone was removed *in vacuo* and the aqueous phase extracted with EtOAc (3 × 2.0 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a yellow waxy solid (18 mg, 88%). ν_{max}(film) 2962, 2120, 1458 and 1375 cm^{-1}; ^1H NMR (400 MHz, 19.5 °C, $CDCl_3$) δ 7.02 (1 H, s, ArH), 2.20–2.00 (8 H, m, 4 × CH_2), 1.99 (4 H, s, 2 × CH_2), 1.73–1.52 (8 H, m, 4 × CH_2) and 0.86–0.76 (24 H, m, 8 × CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, 20.2 °C, $CDCl_3$) δ 154.9 (2 × Ar), 147.2 (2 × Ar), 143.1 (Ar–SO_2N3), 127.6 (ArH), 56.6 (2 × benzylic C), 47.4 (2 × benzylic C), 44.7 (2 × CH_2), 32.9 (4 × CH_2), 10.4 (4 × CH_2) and 8.9 (8 × CH_2).

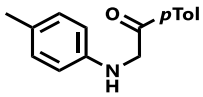
7.2.9 Preparation of α-aminoketones

General Procedure 6: Formation of α-aminoketones



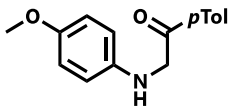
Amine (1.0 equiv.) was dissolved in a 1:1 mixture of water and ethanol (0.2 M). $NaHCO_3$ (1.0 equiv.) was added followed by the α-bromoketone (1.0 equiv.), and the reaction mixture was stirred until completion (TLC, 2−24 h). The reaction mixture was diluted with ethyl acetate, and the aqueous phase was extracted with ethyl acetate (3 × 5 mL $mmol^{-1}$). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. This product was either purified by recrystallisation from $CHCl_3$/pentane or by column chromatography (SiO_2, gradient of 10−30% EtOAc in petroleum ether).

509 1-(4-Tolyl)-2-(4-tolylamino)ethan-1-one



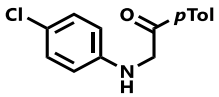
p-Toluidine (1.00 g, 9.4 mmol, 1.0 equiv.) and 2-bromo-4′-methylacetophenone (2.00 g, 9.4 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (789 mg, 9.4 mmol, 1.0 equiv.) in ethanol (30 mL) and water (30 mL) according to General Procedure 6 for 16 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **509** (1.93 g, 86%) as a yellow solid. m.pt. 130–138 °C (Lit. 130–133 °C)[345]; ν_{max}(film) 3405, 3029, 2918, 1682, 1612, 1606, 1576, 1527, 1356, 1264, 1224, 1146, 1112 and 1052 cm^{-1}; ^1H NMR (500 MHz, 22.2 °C, $CDCl_3$) δ 7.92 (2 H, d, J = 8.5 Hz, Ar), 7.31 (2 H, d, J = 7.8 Hz, Ar), 7.04 (2 H, d, J = 7.8 Hz, Ar), 6.65 (2 H, d, J = 8.5 Hz, Ar), 4.85 (1 H, br s, NH), 4.58 (2 H, s, CH_2), 2.44 (3 H, s, CH_3) and 2.26 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (126 MHz, 22.6 °C, $CDCl_3$) δ 194.9 (C=O), 144.9 (Ar), 144.8 (Ar), 132.5 (Ar), 129.8 (2 × ArH), 129.5 (2 × ArH), 127.8 (2 × ArH), 127.0 (Ar), 113.2 (2 × ArH), 50.6 (CH_2), 21.8 (CH_3) and 20.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{17}NNaO^+$ 262.1202; Found 262.1204.

510 2-(4-Methoxyphenylamino)-1-(4-tolyl)ethan-1-one



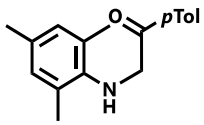
p-Anisidine (246 mg, 2.0 mmol, 1.0 equiv.) and 2-bromo-4′-methylacetophenone (426 mg, 2.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (168 mg, 2.0 mmol, 1.0 equiv.) in ethanol (5 mL) and water (5 mL) according to General Procedure 6 for 24 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **510** (454 mg, 89%) as a yellow solid. m.pt. 97–100 °C (Lit. 102–103 °C)[345]; ν_{max}(film) 3395, 3007, 2930, 2832, 1675, 1607, 1515, 1441, 1305, 1236, 1182, 1142 and 1037 cm^{-1}; ^1H NMR (400 MHz, 22.4 °C, $CDCl_3$) δ 7.91 (2 H, d, J = 8.2 Hz, Ar), 7.31 (2 H, d, J = 8.2 Hz, Ar), 6.83 (2 H, d, J = 8.9 Hz, Ar), 6.68 (2 H, d, J = 8.9 Hz, Ar), 4.55 (2 H, s, CH_2), 3.76 (3 H, s, OCH_3) and 2.44 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 23.0 °C, $CDCl_3$) δ 195.0 (C=O), 152.3 (Ar), 144.7 (Ar), 141.6 (Ar), 132.5 (Ar), 129.5 (2 × ArH), 127.8 (2 × ArH), 115.0 (2 × ArH), 114.2 (2 × ArH), 55.8 (OCH_3), 51.1 (CH_2) and 21.7 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO_2^+$ 256.1332; Found 256.1330.

511 2-(4-Chlorophenylamino)-1-(4-tolyl)ethan-1-one



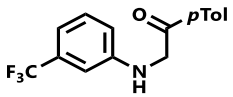
4-Chloroaniline (255 mg, 2.0 mmol, 1.0 equiv.) and 2-bromo-4′-methylacetophenone (426 mg, 2.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (168 mg, 2.0 mmol, 1.0 equiv.) in ethanol (5 mL) and water (5 mL) according to General Procedure 6 for 24 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **511** (438 mg, 84%) as a white solid. m.pt. 125 °C dec. (Lit. 167–169 °C)[346]; ν_{max}(film) 3393, 3030, 2945, 2919, 2789, 1675, 1603, 1576, 1499, 1353, 1261, 1211, 1188, 1146 and 1092 cm^{-1}; ^1H NMR (400 MHz, 22.4 °C, $CDCl_3$) δ 7.90 (2 H, d, J = 8.2 Hz, Ar), 7.31 (2 H, d, J = 8.2 Hz, Ar), 7.16 (2 H, d, J = 8.8 Hz, Ar), 6.64 (2 H, d, J = 8.8 Hz, Ar), 4.54 (2 H, s, CH_2) and 2.44 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 22.8 °C, $CDCl_3$) δ 194.2 (C=O), 145.6 (Ar), 145.0 (Ar), 132.2 (Ar), 129.6 (2 × ArH), 129.2 (2 × ArH), 127.8 (2 × ArH), 122.4 (Ar), 114.1 (2 × ArH), 50.1 (CH_2) and 21.7 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{14}ClNNaO^+$ 282.0656; Found 282.0655.

512 1-(4-Tolyl)-2-(2,4,6-trimethylphenylamino)ethan-1-one



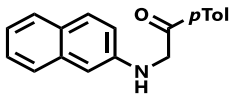
2,4,6-Trimethylaniline (271 mg, 2.0 mmol, 1.0 equiv.) and 2-bromo-4′-methylacetophenone (426 mg, 2.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (168 mg, 2.0 mmol, 1.0 equiv.) in ethanol (5 mL) and water (5 mL) according to General Procedure 6 for 16 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **512** (397 mg, 74%) as an off white solid. m.pt. 123 °C dec.; ν_{max}(film) 3028, 2974, 2924, 2870, 1686, 1609, 1524, 1285, 1180 and 1069 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.84 (2 H, d, J = 7.8 Hz, Ar), 7.27 (2 H, d, J = 7.8 Hz, Ar), 6.84 (2 H, s, Ar), 4.54 (1 H, br s, NH), 4.48 (2 H, s, CH_2), 2.42 (3 H, s, CH_3), 2.35 (6 H, s, 2 × CH_3) and 2.24 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 196.4 (C=O), 144.6 (Ar), 143.9 (Ar), 132.5 (Ar), 131.1 (Ar), 129.5 (2 × ArH), 129.4 (2 × ArH), 129.0 (2 × Ar), 127.7 (2 × ArH), 55.3 (CH_2), 21.7 (CH_3), 20.5 (CH_3) and 18.7 (2 × CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{22}NO^+$ 268.1696; Found 268.1696.

513 1-(4-Tolyl)-2-(3-trifluoromethylphenylamino)ethan-1-one



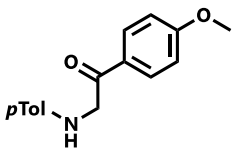
3-Trifluoromethylaniline (323 mg, 2.0 mmol, 1.0 equiv.) and 2-bromo-4′-methylacetophenone (426 mg, 2.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (168 mg, 2.0 mmol, 1.0 equiv.) in ethanol (5 mL) and water (5 mL) according to General Procedure 6 for 16 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **513** (343 mg, 58%) as a white solid. m.pt. 133–135 °C; ν_{max}(film) 3402, 2928, 2843, 1678, 1605, 1501, 1362, 1339, 1254, 1161, 1115 and 1072 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.94 (2 H, d, J = 8.2 Hz, Ar), 7.33 (2 H, d, J = 8.2 Hz, Ar), 7.32–7.29 (1 H, m, Ar), 7.01–6.96 (1 H, m, Ar), 6.90–6.84 (2 H, m, Ar), 5.22 (1 H, br s, NH), 4.60 (2 H, s, CH_2) and 2.45 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 193.9 (C=O), 147.2 (Ar), 145.1 (Ar), 132.2 (Ar), 131.7 (q, J = 31.9 Hz, ArH), 129.7 (ArH), 129.6 (2 × ArH), 127.9 (2 × ArH), 124.3 (q, J = 272.3 Hz, CF_3), 116.3 (ArH), 114.1 (q, J = 4.1 Hz, ArH), 108.7 (q, J = 4.0 Hz, ArH), 49.7 (CH_2) and 21.8 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{15}F_3NO^+$ 294.1100; Found 294.1110.

514 2-(Naphth-2-ylamino)-1-(4-tolyl)ethan-1-one



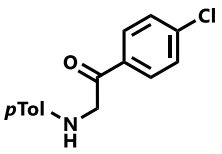
2-Naphthylamine (285 mg, 2.0 mmol, 1.0 equiv.) and 2-bromo-4′-methylacetophenone (426 mg, 2.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (202 mg, 2.4 mmol, 1.2 equiv.) in ethanol (5 mL) and water (5 mL) according to General Procedure 6 for 16 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **514** (422 mg, 77%) as a grey solid. m.pt. 120–125 °C; ν_{max}(film) 3418, 3051, 2920, 1724, 1686, 1582, 1523, 1478, 1408, 1343, 1235, 1211 and 1146 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.09–8.04 (1 H, m, naphthyl CH), 7.99 (2 H, d, *J* = 8.1 Hz, Ar), 7.84–7.79 (1 H, m, naphthyl CH), 7.54–7.46 (2 H, m, naphthyl CH), 7.38 (1 H, dd, *J* = 8.2, 7.5 Hz, naphthyl CH), 7.34 (2 H, d, *J* = 8.1 Hz, Ar), 7.29–7.26 (1 H, m, naphthyl CH), 6.61 (1 H, dd, *J* = 7.5, 1.1 Hz, naphthyl CH), 5.83 (1 H, br s, NH), 4.73 (2 H, s, CH_2) and 2.46 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 194.6 (C=O), 145.0 (naphthyl C), 142.4 (Ar), 134.4 (naphthyl C), 132.5 (naphthyl C), 129.7 (2 × ArH), 128.6 (naphthyl CH), 128.0 (2 × ArH), 126.5 (naphthyl CH), 126.0 (naphthyl CH), 124.9 (naphthyl CH), 123.4 (Ar), 120.3 (naphthyl CH), 117.7 (naphthyl CH), 104.4 (naphthyl CH), 50.2 (CH_2) and 21.8 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{18}NO^+$ 276.1383; Found 276.1389.

515 1-(4-Methoxyphenyl)-2-(4-tolylamino)ethan-1-one



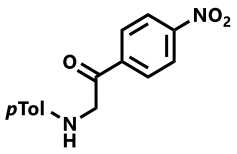
p-Toluidine (429 mg, 4.0 mmol, 1.0 equiv.) and 2-bromo-4′-methoxyacetophenone (916 mg, 4.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (336 mg, 4.0 mmol, 1.0 equiv.) in ethanol (10 mL) and water (10 mL) according to General Procedure 6 for 2 h to give the title compound **515** (888 mg, 87%) as a brown solid. m.pt. 111–114 °C; ν_{max}(film) 3402, 3001, 2920, 2843, 1674, 1601, 1512, 1424, 1358, 1315, 1258, 1177 and 1034 cm^{-1}; ^{1}H NMR (400 MHz, 22.3 °C, $CDCl_3$) δ 8.00 (2 H, d, J = 8.9 Hz, Ar), 7.04 (2 H, d, J = 8.3 Hz, Ar), 6.98 (2 H, d, J = 8.9 Hz, Ar), 6.66 (2 H, d, J = 8.3 Hz, Ar), 5.00 (1 H, br s, NH), 4.56 (2 H, s, CH_2), 3.90 (3 H, s, OCH_3) and 2.26 (3 H, s, CH_3); $^{13}C\{^{1}H\}$ NMR (101 MHz, 23.0 °C, $CDCl_3$) δ 193.6 (C=O), 164.0 (Ar), 144.9 (Ar), 130.1 (2 × ArH), 129.9 (2 × ArH), 128.0 (Ar), 127.1 (Ar), 114.0 (2 × ArH), 113.3 (2 × ArH), 55.5 (OCH_3), 50.4 (CH_2) and 20.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO_2^+$ 256.1332; Found 256.1333.

516 1-(4-Chlorophenyl)-2-(4-tolylamino)ethan-1-one



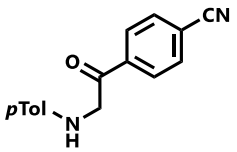
p-Toluidine (429 mg, 4.0 mmol, 1.0 equiv.) and 2-bromo-4′-chloroacetophenone (934 mg, 4.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (336 mg, 4.0 mmol, 1.0 equiv.) in ethanol (10 mL) and water (10 mL) according to General Procedure 6 for 2 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **516** (866 mg, 83%) as a yellow solid. m.pt. 127–130 °C (Lit. 150–152 °C)[346]; ν_{max}(film) 3391, 2916, 2859, 1724, 1682, 1620, 1589, 1524, 1397, 1350, 1316, 1219 and 1142 cm^{-1}; ^1H NMR (400 MHz, 22.4 °C, $CDCl_3$) δ 7.96 (2 H, d, J = 8.6 Hz, Ar), 7.49 (2 H, d, J = 8.6 Hz, Ar), 7.04 (2 H, d, J = 8.4 Hz, Ar), 6.64 (2 H, d, J = 8.4 Hz, Ar), 4.76 (1 H, br s, NH), 4.58 (2 H, s, CH_2) and 2.26 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 22.8 °C, $CDCl_3$) δ 194.2 (C=O), 144.7 (Ar), 140.3 (Ar), 133.3 (Ar), 129.9 (2 × ArH), 129.2 (2 × ArH), 129.2 (2 × ArH), 127.2 (Ar), 113.2 (2 × ArH), 50.7 (CH_2) and 20.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{15}ClNO^+$ 260.0837; Found 260.0834.

517 1-(4-Nitrophenyl)-2-(4-tolylamino)ethan-1-one



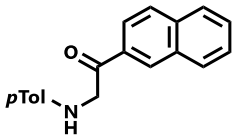
p-Toluidine (429 mg, 4.0 mmol, 1.0 equiv.) and 2-bromo-4′-nitroacetophenone (976 mg, 4.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (336 mg, 4.0 mmol, 1.0 equiv.) in ethanol (10 mL) and water (10 mL) according to General Procedure 6 for 2 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **517** (971 mg, 90%) as a red solid. m.pt. 127 °C dec. (Lit. 147–150 °C)[347]; ν_{max}(film) 3032, 2924, 2866, 1678, 1601, 1524, 1404, 1346, 1316, 1258, 1173 and 1054 cm^{-1}; ^1H NMR (400 MHz, 22.2 °C, $CDCl_3$) δ 8.37 (2 H, d, J = 8.8 Hz, Ar), 8.18 (2 H, d, J = 8.8 Hz, Ar), 7.05 (2 H, d, J = 8.4 Hz, Ar), 6.65 (2 H, d, J = 8.4 Hz, Ar), 4.74 (1 H, br s, NH), 4.66 (2 H, s, CH_2) and 2.26 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 23.0 °C, $CDCl_3$) δ 194.1 (C=O), 150.7 (Ar), 144.4 (Ar), 139.4 (Ar), 130.0 (2 × ArH), 128.9 (2 × ArH), 127.6 (Ar), 124.1 (2 × ArH), 113.2 (2 × ArH), 51.4 (CH_2) and 20.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{15}N_2O_3^+$ 271.1077; Found 271.1084.

518 1-(4-Cyanophenyl)-2-(4-tolylamino)ethan-1-one



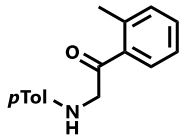
p-Toluidine (429 mg, 4.0 mmol, 1.0 equiv.) and 2-bromo-4′-cyanoacetophenone (896 mg, 4.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (336 mg, 4.0 mmol, 1.0 equiv.) in ethanol (10 mL) and water (10 mL) according to General Procedure 6 for 2 h to give the title compound **518** (921 mg, 92%) as an orange solid. m.pt. 126 °C dec.; ν_{max}(film) 3322, 2924, 2866, 2230, 1678, 1605, 1516, 1404, 1277, 1177, 1111 and 1018 cm^{-1}; ^{1}H NMR (400 MHz, 22.1 °C, $CDCl_3$) δ 8.11 (2 H, d, J = 8.5 Hz, Ar), 7.83 (2 H, d, J = 8.5 Hz, Ar), 7.04 (2 H, d, J = 8.4 Hz, Ar), 6.64 (2 H, d, J = 8.4 Hz, Ar), 4.62 (2 H, s, CH_2) and 2.26 (3 H, s, CH_3); $^{13}C\{^{1}H\}$ NMR (101 MHz, 23.0 °C, $CDCl_3$) δ 194.3 (C=O), 144.4 (Ar), 137.9 (Ar), 132.7 (2 × ArH), 129.9 (2 × ArH), 128.2 (2 × ArH), 127.5 (Ar), 117.7 (Ar), 117.1 (C≡N), 113.2 (2 × ArH), 51.2 (CH_2) and 20.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{15}N_2O^+$ 251.1179; Found 251.1178.

519 1-(Naphth-2-yl)-2-(4-tolylamino)ethan-1-one



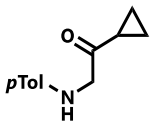
p-Toluidine (429 mg, 4.0 mmol, 1.0 equiv.) and 2-bromo-1-(naphthalen-2-yl)ethan-1-one (996 mg, 4.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (336 mg, 4.0 mmol, 1.0 equiv.) in ethanol (10 mL) and water (10 mL) according to General Procedure 6 for 2 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **519** (980 mg, 89%) as a yellow solid. m.pt. 130 °C dec.; ν_{max}(film) 3395, 2970, 2924, 2862, 1682, 1620, 1528, 1470, 1435, 1358, 1180, 1126, 1057 and 1015 cm^{-1}; ^1H NMR (400 MHz, 22.0 °C, $CDCl_3$) δ 8.55 (1 H, s, naphthyl CH), 8.07 (1 H, dd, J = 8.6, 1.8 Hz, naphthyl CH), 8.01 (1 H, dd, J = 8.0, 1.3 Hz, naphthyl CH), 7.95 (1 H, d, J = 8.6 Hz, naphthyl CH), 7.91 (1 H, d, J = 8.4 Hz, naphthyl CH), 7.64 (1 H, ddd, J = 8.2, 6.9, 1.5 Hz, naphthyl CH), 7.59 (1 H, ddd, J = 8.2, 6.9, 1.5 Hz, naphthyl CH), 7.07 (2 H, d, J = 8.6 Hz, Ar), 6.72 (2 H, d, J = 8.4 Hz, Ar), 5.05 (1 H, br s, NH), 4.76 (2 H, s, CH_2) and 2.27 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 22.7 °C, $CDCl_3$) δ 195.2 (C=O), 144.8 (naphthyl C), 135.9 (Ar), 132.5 (naphthyl C), 132.3 (naphthyl C), 129.9 (2 × ArH), 129.6 (naphthyl CH), 129.4 (naphthyl CH), 128.8 (naphthyl CH), 128.8 (naphthyl CH), 127.9 (naphthyl CH), 127.2 (Ar), 127.1 (naphthyl CH), 123.4 (naphthyl CH), 113.3 (2 × ArH), 50.9 (CH_2) and 20.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{18}NO^+$ 276.1383; Found 276.1391.

596 1-(2-Tolyl)-2-(4-tolylamino)ethan-1-one



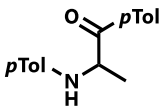
p-Toluidine (429 mg, 4.0 mmol, 1.0 equiv.) and 2-bromo-2′-methylacetophenone (852 mg, 4.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (336 mg, 4.0 mmol, 1.0 equiv.) in ethanol (10 mL) and water (10 mL) according to General Procedure 6 for 16 h and then the crude product was purified by recrystallisation ($CHCl_3$/pentane) to give the title compound **596** (421 mg, 44%) as an orange solid. m.pt. 124–127 °C; ν_{max}(film) 3387, 2924, 2851, 1690, 1620, 1524, 1454, 1346, 1319, 1292, 1257, 1219 and 1126 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.74–7.71 (1 H, m, Ar), 7.46–7.42 (1 H, m, Ar), 7.34–7.29 (2 H, m, Ar), 7.03 (2 H, d, J = 8.3 Hz, Ar), 6.62 (2 H, d, J = 8.3 Hz, Ar), 4.48 (2 H, s, CH_2), 2.55 (3 H, s, CH_3) and 2.25 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 198.8 (C=O), 144.9 (Ar), 138.9 (Ar), 135.4 (Ar), 132.3 (ArH), 132.1 (ArH), 129.9 (2 × ArH), 128.1 (ArH), 127.0 (Ar), 125.9 (ArH), 113.2 (2 × ArH), 52.6 (CH_2), 21.4 (CH_3) and 20.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO^+$ 240.1383; Found 240.1388.

597 1-Cyclopropyl-2-(4-tolylamino)ethan-1-one



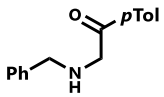
p-Toluidine (429 mg, 4.0 mmol, 1.0 equiv.) and 2-bromo-1-cyclopropylethanone (652 mg, 4.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (336 mg, 4.0 mmol, 1.0 equiv.) in ethanol (10 mL) and water (10 mL) according to General Procedure 6 for 16 h to give the title compound **597** (562 mg, 74%) as a brown solid. m.pt. 75–78 °C; ν_{max}(film) 3395, 3013, 2920, 2859, 1694, 1616, 1524, 1435, 1393, 1319, 1304, 1196, 1157 and 1069 cm^{-1}; ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.01 (2 H, d, J = 8.5 Hz, Ar), 6.54 (2 H, d, J = 8.5 Hz, Ar), 4.52 (1 H, br s, NH), 4.15 (2 H, s, CH_2), 2.24 (3 H, s, CH_3), 2.01 (1 H, tt, J = 7.8, 4.6 Hz, cyclopropane CH), 1.16–1.12 (2 H, m, cyclopropane CH_2) and 1.01–0.95 (2 H, m, cyclopropane CH_2); $^{13}C\{^{1}H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 206.5 (C=O), 144.8 (Ar), 129.8 (2 × ArH), 126.9 (Ar), 113.0 (2 × ArH), 54.5 (CH_2), 20.4 (CH_3), 18.8 (cyclopropane CH) and 11.3 (2 × cyclopropane CH_2); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{16}NO^+$ 190.1226; Found 190.1230.

520 1-(4-Tolyl)-2-(4-tolylamino)propan-1-one



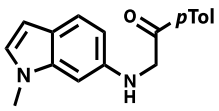
NaH (60% suspension in mineral oil, 50 mg, 1.25 mmol, 1.1 equiv.) was suspended in DMF (10 mL) and cooled to 0 °C (ice bath) and 1-(4-tolyl)-2-(4-tolylamino)ethan-1-one (338 mg, 1.14 mmol, 1.0 equiv.) was added in 3 portions. The reaction was stirred for 30 min then MeI (92 µL, 1.48 mmol, 1.3 equiv.) was added and the reaction stirred for a further 3 h. Water was added and the aqueous phase extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, gradient of 5–20% EtOAc in petrol) gave the title compound as an orange oil (250 mg, 87%).; ν_{max}(film) 3387, 2982, 2920, 1682, 1609, 1520, 1447, 1404, 1316, 1292, 1227 and 1157 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.92 (2 H, d, J = 8.3 Hz, Ar), 7.30 (2 H, d, J = 7.9 Hz, Ar), 6.98 (2 H, d, J = 7.9 Hz, Ar), 6.60 (2 H, d, J = 8.3 Hz, Ar), 5.08 (1 H, q, J = 6.9 Hz, CH), 2.43 (3 H, s, CH_3), 2.23 (3 H, s, CH_3) and 1.46 (3 H, d, J = 6.9 Hz, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 200.5 (C=O), 144.5 (Ar), 144.3 (Ar), 132.2 (Ar), 129.8 (2 × ArH), 129.5 (2 × ArH), 128.6 (2 × ArH), 127.1 (Ar), 113.7 (2 × ArH), 53.6 (CH), 21.7 (CH_3), 20.4 (CH_3) and 19.7 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{20}NO^+$ 254.1539; Found 254.1542. Recorded data consistent with previous values.[348]

598 1-(4-Tolyl)-2-(*N*-benzylamino)ethan-1-one



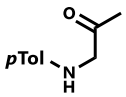
Benzylamine (506 µL, 5.00 mmol, 2.5 equiv.) was dissolved in Et_2O (4.0 mL) and cooled to −78 °C (dry ice, acetone). 2-Bromo-4′-methylacetophenone (426 mg, 2.00 mmol, 1.0 equiv.) was dissolved in Et_2O (1.0 mL) and added dropwise over 10 min. The reaction mixture was allowed to warm to ambient temperature over 3 h. H_2O (5.0 mL) was added and the aqueous phase extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was passed through a short pad of silica, eluting with Et_2O (10 mL). The filtrate was concentrated *in vacuo* to give the title compound as an orange oil (100 mg, 21%). ^{1}H NMR (400 MHz, 22.1 °C, $CDCl_3$) δ 7.82 (2 H, d, J = 8.3 Hz, Ar), 7.49–7.31 (4 H, m, Ar), 7.29–7.22 (4 H, m, Ar), 4.10 (2 H, s, CH_2), 3.89 (2 H, s, CH_2) and 2.40 (3 H, s, CH_3); ^{13}C{^{1}H} NMR (101 MHz, 23.1 °C, $CDCl_3$) δ 197.4 (C=O), 144.3 (Ar), 139.6 (Ar), 133.0 (Ar), 129.4 (2 × ArH), 128.5 (2 × ArH), 128.3 (2 × ArH), 127.8 (2 × ArH), 127.2 (ArH), 54.4 (CH_2), 53.4 (CH_2) and 21.7 (CH_3).

599 6-((4′-Methylacetophenone)amino)-*N*-methylindole



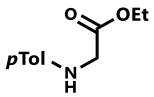
6-Amino-*N*-methylindole (200 mg, 2.0 mmol, 1.0 equiv.), 2-bromo-4′-methylacetophenone (426 mg, 2.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (168 mg, 2.0 mmol, 1.0 equiv.) in ethanol (10 mL) and water (10 mL) according to General Procedure 6 for 16 h to give the title compound **599** as a dark brown solid (421 mg, 76%). ^{1}H NMR (500 MHz, 24.9 °C, $CDCl_3$) δ 7.95 (2 H, d, J = 8.0 Hz, Ar), 7.31 (2 H, d, J = 8.0 Hz, Ar), 7.19 (1 H, d, J = 8.6 Hz, indole), 6.98 (1 H, d, J = 3.0 Hz, indole), 6.92 (1 H, d, J = 2.2 Hz, indole), 6.81 (1 H, dd, J = 8.6, 2.2 Hz, indole), 6.35 (1 H, d, J = 3.0 Hz, indole), 4.65 (2 H, s, CH_2), 3.74 (3 H, s, NCH_3) and 2.45 (3 H, s, CH_3); ^{13}C{^{1}H} NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 195.4 (C=O), 144.6 (Ar), 141.0 (indole Ar), 132.6 (indole Ar), 131.4 (indole Ar), 129.5 (2 × ArH), 129.3 (Ar), 128.9 (indole ArH), 127.9 (2 × ArH), 112.0 (indole ArH), 110.0 (indole ArH), 102.6 (indole ArH), 99.7 (indole ArH), 51.8 (CH_2), 32.9 (NCH_3) and 21.7 (CH_3).

600 1-(4-Tolylamino)propan-2-one



In a flame-dried vial under an atmosphere of argon, *p*-toluidine (1.00 g, 9.35 mmol, 1.0 equiv.), K_2CO_3 (1.55 g, 11.2 mmol, 1.2 equiv.) and KI (1.71 g, 10.28 mmol, 1.1 equiv.) were dissolved in acetone (20 mL). Chloroacetone (820 µL, 10.28 mmol, 1.1 equiv.) was added, the vial sealed with a Teflon cap and heated to 60 °C (heating block) for 16 h. The mixture was cooled to ambient temperature and filtered through celite. The filtrate was concentrated *in vacuo* and redissolved in CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The organic phase was dried ($MgSO_4$), filtered and purified by flash column chromatography (eluting with 20% EtOAc in petroleum ether) to afford the title compound **600** as an orange oil (300 mg, 20%). ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.01 (2 H, d, J = 8.5 Hz, Ar), 6.52 (2 H, d, J = 8.5 Hz, Ar), 4.43 (1 H, br s, NH), 3.99 (2 H, s, CH_2), 2.26 (3 H, s, CH_3) and 2.24 (3 H, s, CH_3); ^{13}C{^{1}H} NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 204.3 (C=O), 144.6 (Ar), 129.8 (2 × ArH), 127.1 (Ar), 112.9 (2 × ArH), 54.7 (CH_2), 27.4 (CH_3) and 20.4 (CH_3). Recorded data consistent with previous values.[349]

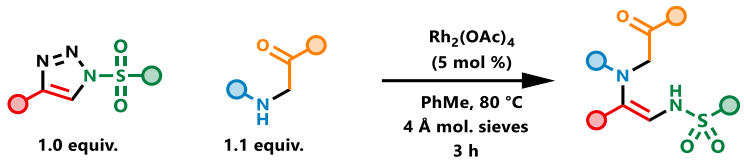
601 Ethyl (4-tolyl)glycinate



p-Toluidine (1.07 g, 10.0 mmol, 1.0 equiv.), ethyl bromoacetate (1.07 mL, 10.0 mmol, 1.0 equiv.) were treated with sodium hydrogen carbonate (168 mg, 2.0 mmol, 1.0 equiv.) in ethanol (10 mL) at 85 °C according to General Procedure 6 for 16 h to give the title compound **601** as an orange solid (1.54 g, 80%). ^{1}H NMR (500 MHz, 22.2 °C, $CDCl_3$) δ 7.01 (2 H, d, J = 8.0 Hz, Ar), 6.55 (2 H, d, J = 8.0 Hz, Ar), 4.24 (2 H, q, J = 7.1 Hz, CH_2), 4.16 (1 H, br s, NH), 3.88 (2 H, s, CH_2), 2.25 (3 H, s, CH_3) and 1.30 (3 H, t, J = 7.1 Hz, CH_3); ^{13}C{^{1}H} NMR (126 MHz, 22.4 °C, $CDCl_3$) δ 171.3 (C=O), 144.8 (Ar), 129.8 (2 × ArH), 127.4 (Ar), 113.2 (2 × ArH), 61.2 (CH_2), 46.2 (CH_2), 20.4 (CH_3) and 14.2 (CH_3). Recorded data consistent with previous values.[350]

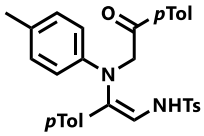
7.2.10 Preparation of 1,2-diamines

General Procedure 7: Rhodium(II)-catalysed N–H bond insertion



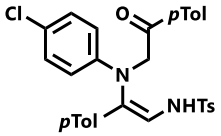
Under an atmosphere of argon, $Rh_2(OAc)_4$ (5 mol %) was added to a solution of α-aminoketone (1.1 equiv.) and triazole (1.0 equiv.) in toluene (0.03 M) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The vial was sealed with a Teflon cap and stirred at 80 °C (heating block) until complete (TLC, 2–4 h). The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, gradient from 10–30% EtOAc in petroleum ether) to give the 1,2-diamine product.

526 1-[(2-Oxo-2-(4-tolyl)ethyl)(4-tolyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene

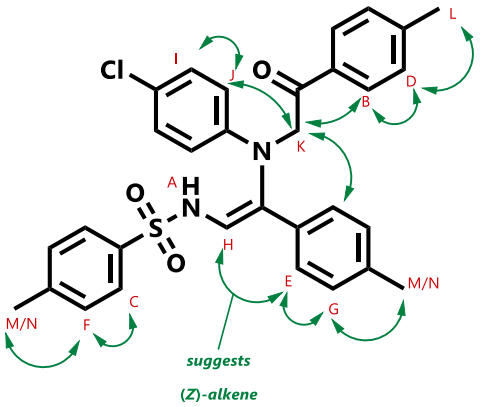


Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **509** (79 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **526** (139 mg, 88%) as a yellow solid.; m.pt. 61–69 °C; ν_{max}(film) 3250, 3032, 2924, 1690, 1609, 1512, 1408, 1339, 1161, 1092 and 1033 cm^{-1}; ^1H NMR (400 MHz, 22.4 °C, $CDCl_3$) δ 9.36 (1 H, d, J = 10.6 Hz, NH), 7.87 (2 H, d, J = 8.3 Hz, Ar), 7.65 (2 H, d, J = 8.3 Hz, Ar), 7.30 (2 H, d, J = 8.0 Hz, Ar), 7.17 (2 H, d, J = 8.3 Hz, Ar), 7.12 (2 H, d, J = 8.3 Hz, Ar), 7.10 (2 H, d, J = 8.3 Hz, Ar), 6.92 (1 H, d, J = 10.6 Hz, =CH), 6.75 (2 H, d, J = 8.6 Hz, Ar), 6.30 (2 H, d, J = 8.6 Hz, Ar), 4.66 (2 H, br s, CH_2), 2.45 (3 H, s, CH_3), 2.34 (3 H, s, CH_3), 2.33 (3 H, s, CH_3) and 2.20 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 23.2 °C, $CDCl_3$) δ 197.2 (C=O), 145.3 (Ar), 143.3 (Ar), 143.0 (Ar), 137.9 (Ar), 137.4 (Ar), 132.7 (Ar), 131.8 (Ar), 129.7 (2 × ArH), 129.6 (2 × ArH), 129.5 (2 × ArH), 129.4 (2 × ArH), 128.3 (2 × ArH), 127.1 (Ar), 126.6 (2 × ArH), 125.9 (=C), 124.9 (2 × ArH), 121.8 (=CH), 112.2 (2 × ArH), 56.5 (CH_2), 21.8 (CH_3), 21.4 (CH_3), 21.1 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{33}N_2O_3S^+$ 525.2206; Found 525.2204.

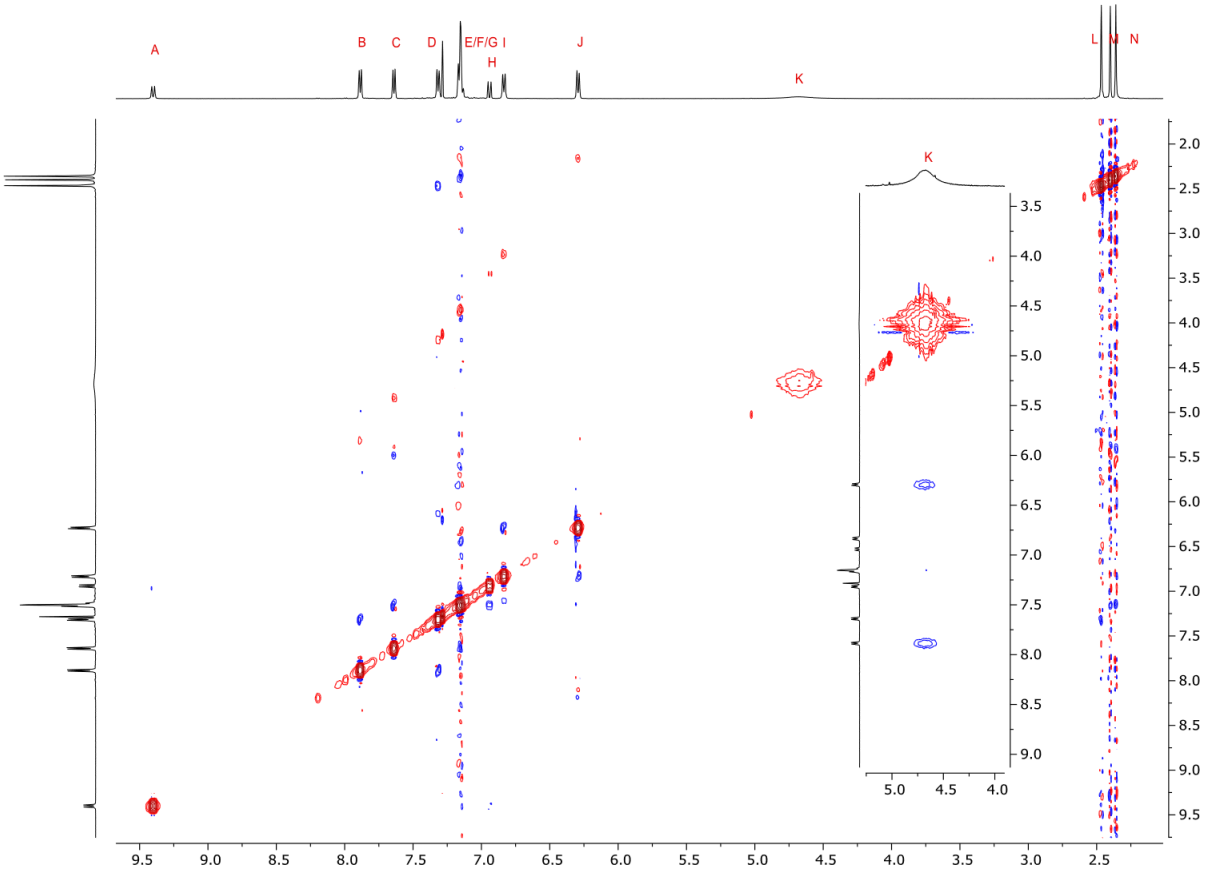
533 1-[(4-Chlorophenyl)(2-oxo-2-(4-tolyl)ethyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene



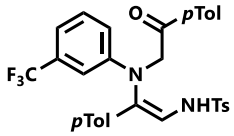
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **511** (86 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **533** (147 mg, 90%) as a yellow solid.; m.pt. 72 °C dec.; ν_{max}(film) 3264, 3063, 2924, 1686, 1605, 1493, 1404, 1339, 1289, 1161, 1092 and 1015 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 9.40 (1 H, d, *J* = 10.6 Hz, NH), 7.89 (2 H, d, *J* = 8.2 Hz, COTol), 7.64 (2 H, d, *J* = 8.3 Hz, SO_2Tol), 7.32 (2 H, d, *J* = 7.9 Hz, Tol), 7.18–7.12 (6 H, m, Ar), 6.94 (1 H, d, *J* = 10.6 Hz, =CH), 6.84 (2 H, d, *J* = 9.1 Hz, NTol), 6.30 (2 H, d, *J* = 9.1 Hz, NTol), 4.68 (2 H, br s, CH_2), 2.47 (3 H, s, CH_3), 2.40 (3 H, s, CH_3) and 2.36 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 196.8 (C=O), 145.7 (Ar), 144.5 (Ar), 143.4 (Ar), 138.1 (Ar), 137.8 (Ar), 132.2 (Ar), 131.6 (Ar), 129.7 (2 × ArH), 129.6 (2 × ArH), 129.5 (2 × ArH), 128.9 (2 × ArH), 128.4 (2 × ArH), 126.5 (2 × ArH), 125.5 (=C), 124.8 (2 × ArH), 123.0 (Ar), 122.1 (=CH), 113.5 (2 × ArH), 56.4 (OCH_3), 21.8 (CH_3), 21.5 (CH_3) and 21.1 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{30}ClN_2O_3S^+$ 545.1660; Found 545.1655.



$^{1}H\leftrightarrow{}^{1}H$ NOESY, 400 MHz, $CDCl_3$

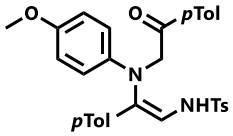


535 1-[(2-Oxo-2-(4-tolyl)ethyl)(3-trifluoromethylphenyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene

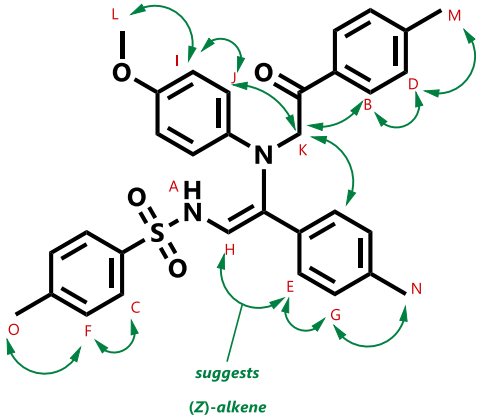


Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **513** (97 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **535** (142 mg, 82%) as a white solid.; m.pt. 110 °C dec.; ν_{max}(film) 3136, 3032, 2928, 1678, 1609, 1497, 1462, 1335, 1231, 1184, 1165 and 1123 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 9.40 (1 H, d, *J* = 10.6 Hz, NH), 7.86 (2 H, d, *J* = 8.3 Hz, Ar), 7.65 (2 H, d, *J* = 8.3 Hz, Ar), 7.31 (2 H, d, *J* = 7.9 Hz, Ar), 7.15–7.10 (6 H, m, Ar), 7.06 (1 H, dd, *J* = 8.1, 7.9 Hz, Ar), 6.97 (1 H, d, *J* = 10.6 Hz, =CH), 6.94 (1 H, d, *J* = 7.9 Hz, Ar), 6.64–6.60 (1 H, m, Ar), 6.57 (1 H, dd, *J* = 8.1, 2.6 Hz, Ar), 4.71 (2 H, br s, CH_2), 2.45 (3 H, s, CH_3), 2.34 (3 H, s, CH_3) and 2.32 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 196.6 (C=O), 146.2 (Ar), 145.8 (Ar), 143.4 (Ar), 137.8 (Ar), 137.7 (Ar), 131.8 (Ar), 131.8 (q, *J* = 33.3 Hz, Ar), 131.5 (Ar), 129.8 (ArH), 129.8 (2 × ArH), 129.7 (2 × ArH), 129.6 (2 × ArH), 128.4 (2 × ArH), 126.6 (2 × ArH), 124.7 (2 × ArH), 124.5 (=C), 122.5 (=CH), 115.5 (ArH), 114.9 (q, *J* = 4.1 Hz, ArH), 108.5 (q, *J* = 2.4 Hz, ArH), 56.5 (CH_2), 21.9 (CH_3), 21.4 (CH_3) and 21.1 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{30}F_3N_2O_3S^+$ 579.1924; Found 579.1928.

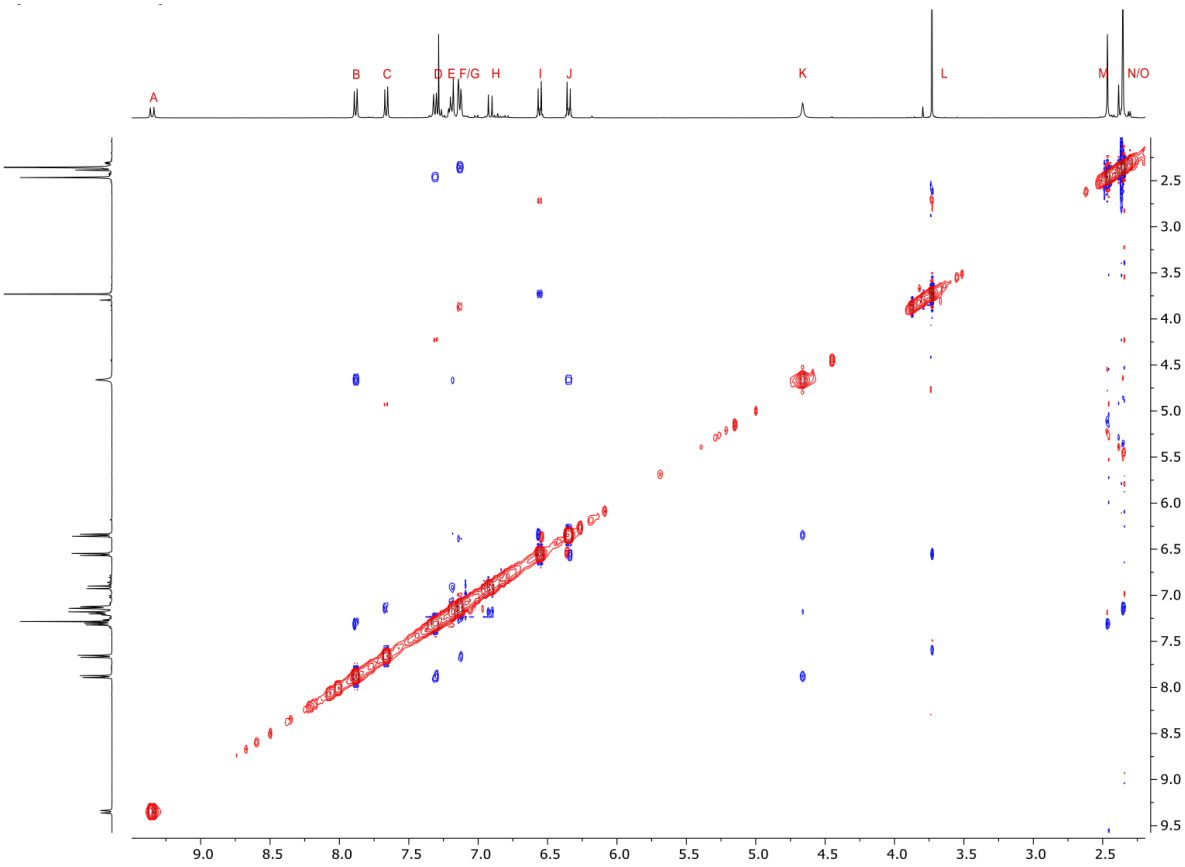
541 1-[(4-Methoxyphenyl)(2-oxo-2-(4-tolyl)ethyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene



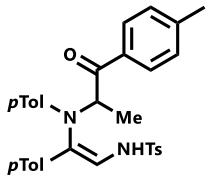
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **510** (84 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **541** (144 mg, 89%) as a yellow solid.; m.pt. 45–50 °C; ν_{max}(film) 3252, 2924, 2855, 1690, 1609, 1512, 1443, 1339, 1250, 1161, 1119 and 1034 cm^{-1}; ^1H NMR (500 MHz, 25.1 °C, $CDCl_3$) δ 9.32 (1 H, d, *J* = 10.6 Hz, NH), 7.86 (2 H, d, *J* = 8.3 Hz, COTol), 7.63 (2 H, d, *J* = 8.3 Hz, SO_2Tol), 7.28 (2 H, d, *J* = 8.0 Hz, COTol), 7.16 (2 H, d, *J* = 8.3 Hz, Tol), 7.11 (2 H, d, *J* = 8.3 Hz, SO_2Tol), 7.10 (2 H, d, *J* = 8.0 Hz, Tol), 6.88 (1 H, d, *J* = 10.6 Hz, =CH), 6.53 (2 H, d, *J* = 9.1 Hz, NC_6H_4OMe), 6.32 (2 H, d, *J* = 9.1 Hz, NC_6H_4OMe), 4.63 (2 H, br s, CH_2), 3.70 (3 H, s, OCH_3), 2.44 (3 H, s, COTol), 2.33 (3 H, s, CH_3) and 2.33 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 197.4 (C=O), 152.4 (Ar), 145.4 (Ar), 143.1 (Ar), 139.9 (Ar), 138.0 (Ar), 137.5 (Ar), 132.8 (Ar), 131.9 (Ar), 129.6 (2 × ArH), 129.6 (2 × ArH), 129.5 (2 × ArH), 128.3 (2 × ArH), 126.7 (2 × ArH), 126.2 (=C), 124.9 (2 × ArH), 121.8 (=CH), 114.7 (2 × ArH), 113.3 (2 × ArH), 56.8 (CH_2), 55.6 (OCH_3), 21.8 (CH_3), 21.5 (CH_3) and 21.1 (CH_3); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{32}H_{31}N_2O_4S^-$ 539.2010; Found 539.2017.



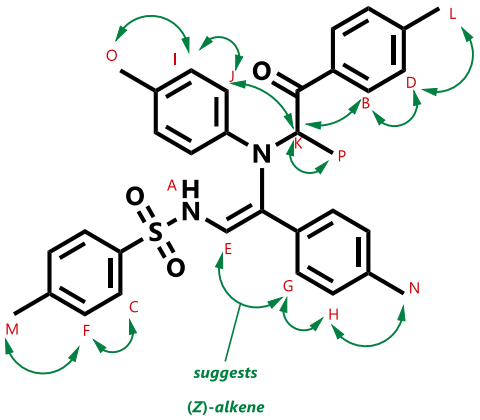
$^{1}H \leftrightarrow {}^{1}H$ NOESY, 400 MHz, $CDCl_3$



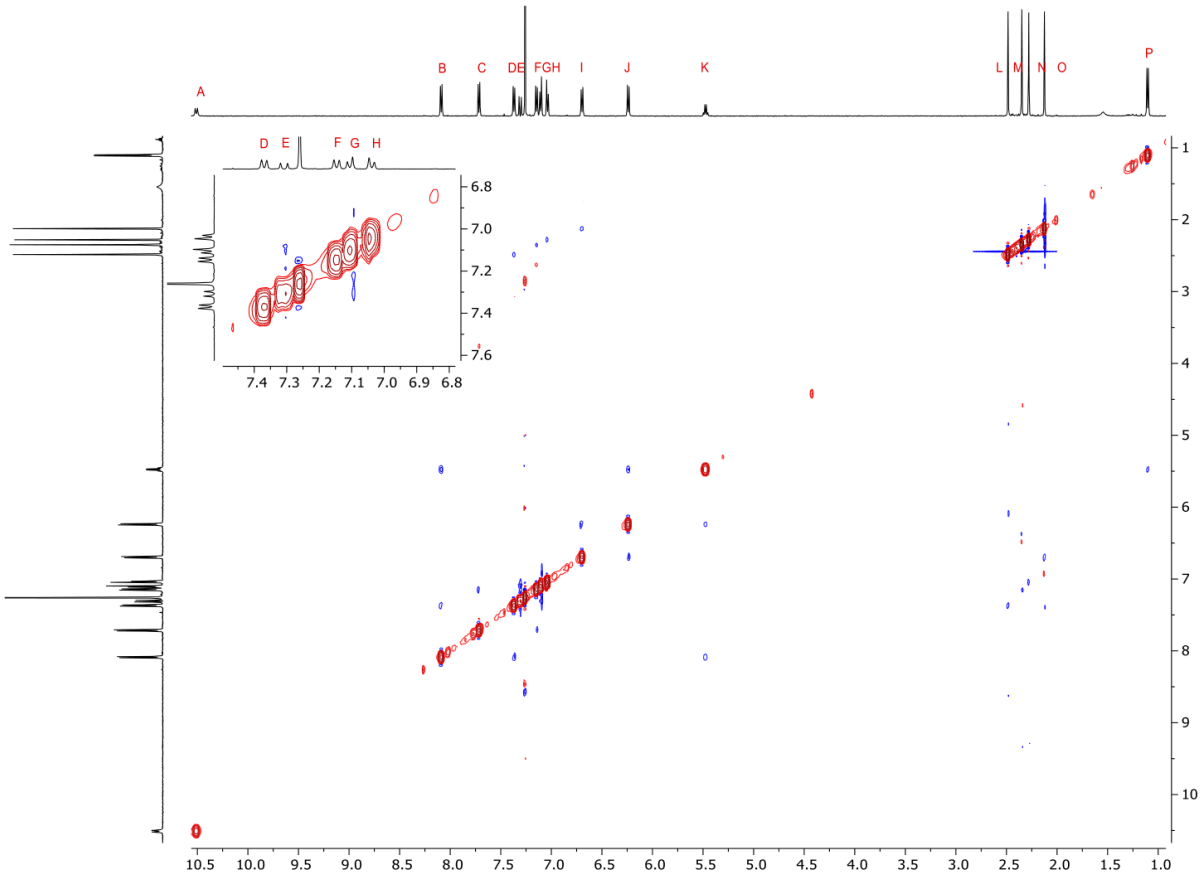
546 1-[(1-Oxo-1-(4-tolyl)prop-2-yl)(4-tolyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene



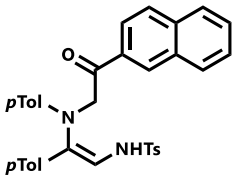
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **520** (84 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **546** (142 mg, 88%) as a yellow solid.; m.pt. 65 °C dec.; ν_{max}(film) 3094, 3028, 2924, 1674, 1605, 1512, 1451, 1412, 1343, 1289, 1235, 1157 and 1092 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 10.51 (1 H, d, *J* = 10.8 Hz, NH), 8.09 (2 H, d, *J* = 8.2 Hz, COTol), 7.72 (2 H, d, *J* = 8.3 Hz, SO_2Tol), 7.37 (2 H, d, *J* = 8.2 Hz, COTol), 7.31 (1 H, d, *J* = 10.8 Hz, =CH), 7.15 (2 H, d, *J* = 8.3 Hz, SO_2Tol), 7.11 (2 H, d, *J* = 8.1 Hz, Tol), 7.04 (2 H, d, *J* = 8.1 Hz, Tol), 6.70 (2 H, d, *J* = 8.7 Hz, NTol), 6.25 (2 H, d, *J* = 8.7 Hz, NTol), 5.48 (1 H, q, *J* = 7.4 Hz, CH), 2.49 (3 H, s, COTol), 2.35 (3 H, s, SO_2Tol), 2.28 (3 H, s, Tol), 2.13 (3 H, s, NTol) and 1.11 (3 H, d, *J* = 7.4 Hz, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 203.3 (C=O), 145.5 (Ar), 143.2 (Ar), 143.0 (Ar), 138.1 (Ar), 136.6 (Ar), 134.6 (Ar), 131.4 (Ar), 129.9 (2 × ArH), 129.7 (2 × ArH), 129.5 (2 × ArH), 129.5 (2 × ArH), 128.7 (2 × ArH), 126.9 (Ar), 126.7 (2 × ArH), 125.5 (=CH), 123.9 (2 × ArH), 121.2 (=C), 112.3 (2 × ArH), 57.7 (CH), 21.8 (CH_3), 21.5 (CH_3), 21.0 (CH_3), 20.2 (CH_3) and 16.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{33}H_{35}N_2O_3S^+$ 539.2363; Found 539.2368.



$^{1}H\leftrightarrow{}^{1}H$ NOESY, 400 MHz, $CDCl_3$

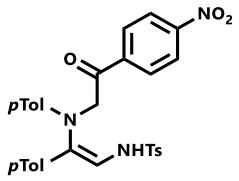


548 1-[(2-(Naphth-2-yl)-2-oxoethyl)(4-tolyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene



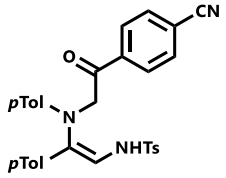
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **519** (91 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **548** (159 mg, 95%) as a yellow solid.; m.pt. 58 °C dec.; ν_{max}(film) 3240, 3032, 2920, 2862, 1678, 1597, 1512, 1339, 1161 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.4 °C, $CDCl_3$) δ 9.31 (1 H, d, *J* = 10.7 Hz, NH), 8.46 (1 H, s, naphthyl CH), 8.02 (1 H, dd, *J* = 8.6, 1.7 Hz, naphthyl CH), 7.95 (1 H, d, *J* = 7.5 Hz, naphthyl CH), 7.94 (1 H, d, *J* = 8.7 Hz, naphthyl CH), 7.91 (1 H, d, *J* = 8.0 Hz, naphthyl CH), 7.66 (2 H, d, *J* = 8.3 Hz, Ar), 7.65–7.63 (1 H, m, naphthyl CH), 7.59 (1 H, ddd, *J* = 8.1, 6.9, 1.3 Hz, naphthyl CH), 7.21 (2 H, d, *J* = 8.3 Hz, Ar), 7.13 (2 H, d, *J* = 8.1 Hz, Ar), 7.08 (2 H, d, *J* = 8.1 Hz, Ar), 6.94 (1 H, d, *J* = 10.7 Hz, =CH), 6.77 (2 H, d, *J* = 7.9 Hz, Ar), 6.34 (2 H, d, *J* = 8.7 Hz, Ar), 4.81 (2 H, br s, CH_2), 2.34 (3 H, s, CH_3), 2.26 (3 H, s, CH_3) and 2.20 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 24.8 °C, $CDCl_3$) δ 197.6 (C=O), 143.3 (Ar), 143.1 (naphthyl C), 138.0 (Ar), 137.5 (naphthyl C), 136.1 (naphthyl C), 132.8 (Ar), 132.3 (Ar), 131.7 (Ar), 130.0 (naphthyl CH), 129.7 (2 × ArH), 129.6 (2 × ArH), 129.6 (naphthyl CH), 129.4 (2 × ArH), 129.1 (naphthyl CH), 128.8 (naphthyl CH), 127.9 (naphthyl CH), 127.3 (Ar), 127.2 (naphthyl CH), 126.7 (2 × ArH), 125.9 (=C), 125.0 (2 × ArH), 123.6 (naphthyl CH), 122.0 (=CH), 112.3 (2 × ArH), 56.8 (CH_2), 21.4 (CH_3), 21.1 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{35}H_{33}N_2O_3S^+$ 561.2206; Found 561.2208.

552 1-[(2-(4-Nitrophenyl)-2-oxoethyl)(4-tolyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene



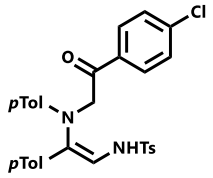
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **517** (89 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **552** (70 mg, 42%) as a pink solid. Under the reaction conditions there was also some cyclodehydration to the corresponding pyrrole **553** (80 mg, 50%).; m.pt. 115 °C dec.; ν_{max}(film) 3183, 2924, 2856, 1694, 1601, 1516, 1343, 1215, 1161, 1092 and 1042 cm^{-1}; ^1H NMR (400 MHz, 24.9 °C, $CDCl_3$) δ 8.78 (1 H, d, *J* = 10.8 Hz, NH), 8.34 (2 H, d, *J* = 8.8 Hz, Ar), 8.11 (2 H, d, *J* = 8.8 Hz, Ar), 7.64 (2 H, d, *J* = 8.4 Hz, Ar), 7.17 (2 H, d, *J* = 8.4 Hz, Ar), 7.15 (2 H, d, *J* = 8.0 Hz, Ar), 7.11 (2 H, d, *J* = 8.6 Hz, Ar), 6.88 (1 H, d, *J* = 10.8 Hz, =CH), 6.76 (2 H, d, *J* = 8.0 Hz, Ar), 6.28 (2 H, d, *J* = 8.6 Hz, Ar), 4.71 (2 H, s, CH_2), 2.37 (3 H, s, CH_3), 2.33 (3 H, s, CH_3) and 2.21 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 196.5 (C=O), 150.9 (Ar), 143.3 (Ar), 143.0 (Ar), 138.7 (Ar), 137.9 (Ar), 137.8 (Ar), 132.4 (Ar), 129.8 (2 × ArH), 129.7 (2 × ArH), 129.5 (2 × ArH), 129.3 (2 × ArH), 127.8 (Ar), 126.7 (2 × ArH), 125.4 (=C), 125.0 (2 × ArH), 124.1 (2 × ArH), 121.6 (=CH), 112.3 (2 × ArH), 57.0 (CH_2), 21.5 (CH_3), 21.1 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{30}N_3O_5S^+$ 556.1901; Found 556.1883.

554 1-[(2-(4-Cyanophenyl)-2-oxoethyl)(4-tolyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene



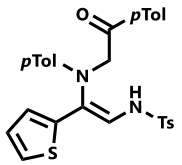
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **518** (83 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **554** (65 mg, 40%) as a yellow solid. Under the reaction conditions there was also some cyclodehydration to the corresponding pyrrole **555** (78 mg, 50%).; m.pt. 113 °C dec.; ν_{max}(film) 3245, 3028, 2924, 2856, 2230, 1690, 1601, 1512, 1404, 1370, 1339, 1219, 1161, 1092 and 1041 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.81 (1 H, d, *J* = 10.8 Hz, NH), 8.04 (2 H, d, *J* = 8.8 Hz, Ar), 7.80 (2 H, d, *J* = 8.8 Hz, Ar), 7.64 (2 H, d, *J* = 8.3 Hz, Ar), 7.16 (2 H, d, *J* = 7.9 Hz, Ar), 7.14 (2 H, d, *J* = 8.7 Hz, Ar), 7.11 (2 H, d, *J* = 8.3 Hz, Ar), 6.88 (1 H, d, *J* = 10.8 Hz, =CH), 6.75 (2 H, d, *J* = 7.9 Hz, Ar), 6.27 (2 H, d, *J* = 8.7 Hz, Ar), 4.68 (2 H, s, CH_2), 2.37 (3 H, s, CH_3), 2.33 (3 H, s, CH_3) and 2.20 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 26.0 °C, $CDCl_3$) δ 196.7 (C=O), 143.2 (Ar), 143.0 (Ar), 137.9 (Ar), 137.7 (Ar), 137.2 (Ar), 132.7 (2 × ArH), 132.4 (Ar), 129.8 (2 × ArH), 129.7 (2 × ArH), 129.5 (2 × ArH), 128.6 (2 × ArH), 127.8 (Ar), 126.7 (2 × ArH), 125.4 (=C), 125.0 (2 × ArH), 121.6 (=CH), 117.6 (Ar), 117.5 (C≡N), 112.3 (2 × ArH), 56.9 (CH_2), 21.5 (CH_3), 21.1 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{30}N_3O_3S^+$ 536.2002; Found 536.2005.

556 1-[(2-(4-Chlorophenyl)-2-oxoethyl)(4-tolyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene



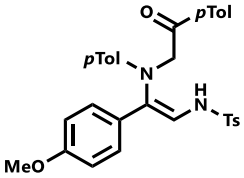
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **516** (86 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **556** (109 mg, 67%) as a yellow solid. Under the reaction conditions there was also some cyclodehydration to the corresponding pyrrole **557** (50 mg, 32%).; m.pt. 63 °C dec.; ν_{max}(film) 3175, 3028, 2920, 1686, 1589, 1512, 1400, 1370, 1339, 1223, 1161 and 1092 cm^{-1}; ^1H NMR (400 MHz, 26.0 °C, $CDCl_3$) δ 9.09 (1 H, d, *J* = 10.7 Hz, NH), 7.89 (2 H, d, *J* = 8.6 Hz, Ar), 7.63 (2 H, d, *J* = 8.3 Hz, Ar), 7.47 (2 H, d, *J* = 8.6 Hz, Ar), 7.15 (2 H, d, *J* = 8.3 Hz, Ar), 7.12 (2 H, d, *J* = 8.6 Hz, Ar), 7.10 (2 H, d, *J* = 8.6 Hz, Ar), 6.90 (1 H, d, *J* = 10.7 Hz, =CH), 6.75 (2 H, d, *J* = 8.7 Hz, Ar), 6.28 (2 H, d, *J* = 8.7 Hz, Ar), 4.64 (2 H, br s, CH_2), 2.35 (3 H, s, CH_3), 2.33 (3 H, s, CH_3) and 2.20 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 26.0 °C, $CDCl_3$) δ 196.6 (C=O), 143.2 (Ar), 143.1 (Ar), 140.9 (Ar), 137.9 (Ar), 137.6 (Ar), 132.6 (Ar), 132.6 (Ar), 129.7 (2 × ArH), 129.6 (2 × ArH), 129.6 (2 × ArH), 129.4 (2 × ArH), 129.2 (2 × ArH), 127.5 (Ar), 126.7 (2 × ArH), 125.7 (=C), 124.9 (2 × ArH), 121.8 (=C), 112.2 (2 × ArH), 56.6 (CH_2), 21.5 (CH_3), 21.1 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{30}ClN_2O_3S^+$ 545.1660; Found 545.1659.

560 1-[(2-Oxo-2-(4-tolyl)ethyl)(4-tolyl)amino]-1-(thiophen-2-yl)-2-(tosylamino)ethene



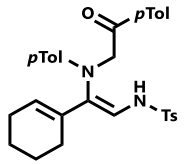
Triazole **521** (92 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **509** (79 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **560** (124 mg, 80%) as an orange solid.; m.pt. 126 °C dec.; ν_{max}(film) 3148, 3032, 2920, 1678, 1640, 1609, 1516, 1412, 1339, 1231, 1161 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 9.39 (1 H, d, J = 10.7 Hz, NH), 7.88 (2 H, d, J = 8.3 Hz, Ar), 7.64 (2 H, d, J = 8.3 Hz, Ar), 7.31 (2 H, d, J = 8.3 Hz, Ar), 7.12 (1 H, dd, J = 5.1, 1.2 Hz, thiophene CH), 7.10 (2 H, d, J = 8.3 Hz, Ar), 6.92 (1 H, dd, J = 5.1, 3.6 Hz, thiophene CH), 6.90 (1 H, d, J = 10.7 Hz, =CH), 6.84 (1 H, dd, J = 3.6, 1.2 Hz, thiophene CH), 6.77 (2 H, d, J = 8.3 Hz, Ar), 6.31 (2 H, d, J = 8.3 Hz, Ar), 4.71 (2 H, br s, CH_2), 2.45 (3 H, s, CH_3), 2.33 (3 H, s, CH_3) and 2.19 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 197.2 (C=O), 145.5 (Ar), 143.1 (Ar), 142.6 (thiophene C2), 141.0 (Ar), 137.8 (Ar), 131.8 (Ar), 129.7 (2 × ArH), 129.6 (2 × ArH), 129.4 (2 × ArH), 128.3 (2 × ArH), 127.7 (thiophene CH), 127.5 (Ar), 126.7 (2 × ArH), 123.8 (thiophene CH), 122.9 (thiophene CH), 122.0 (=CH), 121.7 (=C), 112.4 (2 × ArH), 56.5 (CH_2), 21.8 (CH_3), 21.5 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{29}N_2O_3S_2^+$ 517.1614; Found 517.1617.

561 1-(4-Methoxyphenyl)-1-[(2-oxo-2-(4-tolyl)ethyl)(4-tolyl)amino]-2-(tosylamino)ethene



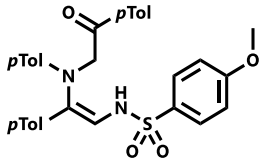
Triazole **367** (99 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **509** (79 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **561** (152 mg, 94%) as an orange solid.; m.pt. 66–70 °C; ν_{max}(film) 3275, 3032, 2924, 1682, 1601, 1574, 1512, 1424, 1339, 1250, 1161, 1119, 1092 and 1030 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 9.27 (1 H, d, J = 10.6 Hz, NH), 7.86 (2 H, d, J = 8.3 Hz, Ar), 7.64 (2 H, d, J = 8.3 Hz, Ar), 7.28 (2 H, d, J = 8.3 Hz, Ar), 7.19 (2 H, d, J = 8.8 Hz, Ar), 7.11 (2 H, d, J = 8.3 Hz, Ar), 6.82 (2 H, d, J = 8.8 Hz, Ar), 6.81 (1 H, d, J = 10.6 Hz, =CH), 6.74 (2 H, d, J = 8.6 Hz, Ar), 6.29 (2 H, d, J = 8.6 Hz, Ar), 4.63 (2 H, br s, CH_2), 3.79 (3 H, s, CH_3), 2.44 (3 H, s, CH_3), 2.34 (3 H, s, CH_3) and 2.19 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 197.2 (C=O), 159.3 (Ar), 145.3 (Ar), 143.3 (Ar), 143.0 (Ar), 138.0 (Ar), 131.9 (Ar), 129.7 (2 × ArH), 129.5 (2 × ArH), 129.4 (2 × ArH), 128.3 (2 × ArH), 128.1 (Ar), 127.2 (Ar), 126.7 (2 × ArH), 126.3 (2 × ArH), 125.8 (=C), 120.8 (=CH), 114.3 (2 × ArH), 112.3 (2 × ArH), 56.4 (CH_2), 55.4 (OCH_3), 21.8 (CH_3), 21.5 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{33}N_2O_4S^+$ 541.2156; Found 541.2148.

562 1-(Cyclohexen-1-yl)-1-[(2-oxo-2-(4-tolyl)ethyl)(4-tolyl)amino]-2-(tosylamino)ethene



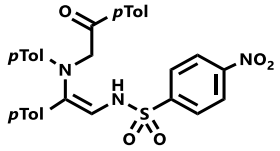
Triazole **523** (91 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **509** (79 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **562** (126 mg, 82%) as a yellow solid.; m.pt. 140 °C dec.; ν_{max}(film) 3152, 3032, 2924, 2859, 1678, 1609, 1516, 1416, 1343, 1231, 1161 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 9.41 (1 H, d, *J* = 10.7 Hz, NH), 7.90 (2 H, d, *J* = 8.2 Hz, Ar), 7.64 (2 H, d, *J* = 8.3 Hz, Ar), 7.32 (2 H, d, *J* = 8.2 Hz, Ar), 7.09 (2 H, d, *J* = 8.3 Hz, Ar), 6.79 (2 H, d, *J* = 8.6 Hz, Ar), 6.51 (1 H, d, *J* = 10.7 Hz, =CH), 6.18 (2 H, d, *J* = 8.6 Hz, Ar), 5.46 (1 H, t, *J* = 4.2 Hz, =CH), 4.62 (2 H, br s, CH_2), 2.46 (3 H, s, CH_3), 2.31 (3 H, s, CH_3), 2.19 (3 H, s, CH_3), 2.15–2.08 (2 H, m, CH_2), 2.07–2.00 (2 H, m, CH_2), 1.72–1.64 (2 H, m, CH_2) and 1.62–1.52 (2 H, m, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 197.6 (C=O), 145.3 (Ar), 143.3 (Ar), 142.9 (Ar), 137.8 (Ar), 132.0 (Ar), 129.9 (=C), 129.6 (2 × ArH), 129.5 (2 × ArH), 129.3 (2 × ArH), 128.4 (=C), 128.3 (2 × ArH), 126.6 (2 × ArH), 126.5 (Ar), 123.5 (=CH), 121.3 (=CH), 111.7 (2 × ArH), 57.2 (CH_2), 25.5 (CH_2), 24.9 (CH_2), 22.5 (CH_2), 22.2 (CH_2), 21.8 (CH_3), 21.4 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{35}N_2O_3S^+$ 515.2363; Found 515.2355.

563 2-(4-Methoxybenzenesulfonylamino)-1-[(2-oxo-2-(4-tolyl)ethyl)(4-tolyl)amino]-1-(4-tolyl)ethene



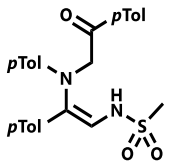
Triazole **524** (99 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **509** (79 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **563** (142 mg, 87%) as a yellow solid.; m.pt. 60–66 °C; ν_{max}(film) 3148, 3028, 2920, 1678, 1597, 1516, 1416, 1339, 1304, 1258, 1157 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 9.31 (1 H, d, *J* = 10.7 Hz, NH), 7.86 (2 H, d, *J* = 8.3 Hz, Ar), 7.69 (2 H, d, *J* = 9.0 Hz, Ar), 7.28 (2 H, d, *J* = 7.8 Hz, Ar), 7.16 (2 H, d, *J* = 8.3 Hz, Ar), 7.10 (2 H, d, *J* = 7.8 Hz, Ar), 6.90 (1 H, d, *J* = 10.7 Hz, =CH), 6.77 (2 H, d, *J* = 9.0 Hz, Ar), 6.76 (2 H, d, *J* = 8.4 Hz, Ar), 6.30 (2 H, d, *J* = 8.4 Hz, Ar), 4.65 (2 H, br s, CH_2), 3.79 (3 H, s, OCH_3), 2.44 (3 H, s, CH_3), 2.32 (3 H, s, CH_3) and 2.19 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 197.2 (C=O), 162.6 (Ar), 145.3 (Ar), 143.4 (Ar), 137.4 (Ar), 132.8 (Ar), 132.7 (Ar), 131.9 (Ar), 129.7 (2 × ArH), 129.6 (2 × ArH), 129.5 (2 × ArH), 128.8 (2 × ArH), 128.3 (2 × ArH), 127.2 (Ar), 125.8 (=C), 124.9 (2 × ArH), 122.0 (=CH), 113.9 (2 × ArH), 112.2 (2 × ArH), 56.5 (OCH_3), 55.4 (CH_3), 21.8 (CH_3), 21.1 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{33}N_2O_4S^+$ 541.2156; Found 541.2158.

564 2-(4-Nitrobenzenesulfonylamino)-1-[(2-oxo-2-(4-tolyl)ethyl)(4-tolyl)amino]-1-(4-tolyl)ethene



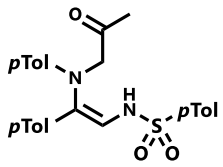
Triazole **522** (103 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **509** (79 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **564** (66 mg, 40%) as a yellow solid.; m.pt. 143 °C dec.; ν_{max}(film) 3102, 3032, 2920, 2862, 1678, 1605, 1516, 1416, 1346, 1312, 1231, 1165 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 9.77 (1 H, d, *J* = 10.2 Hz, NH), 8.12 (2 H, d, *J* = 9.0 Hz, Ar), 7.88 (2 H, d, *J* = 9.0 Hz, Ar), 7.85 (2 H, d, *J* = 8.3 Hz, Ar), 7.29 (2 H, d, *J* = 8.6 Hz, Ar), 7.18 (2 H, d, *J* = 8.3 Hz, Ar), 7.12 (2 H, d, *J* = 7.9 Hz, Ar), 6.88 (1 H, d, *J* = 10.2 Hz, =CH), 6.68 (2 H, d, *J* = 7.9 Hz, Ar), 6.26 (2 H, d, *J* = 8.6 Hz, Ar), 4.65 (2 H, br s, CH_2), 2.44 (3 H, s, CH_3), 2.34 (3 H, s, CH_3) and 2.16 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 197.9 (C=O), 149.7 (Ar), 146.6 (Ar), 145.9 (Ar), 143.7 (Ar), 138.2 (Ar), 132.1 (Ar), 131.5 (Ar), 129.7 (2 × ArH), 129.7 (2 × ArH), 129.6 (2 × ArH), 128.3 (2 × ArH), 128.0 (Ar), 127.9 (=C), 127.7 (2 × ArH), 125.2 (2 × ArH), 124.0 (2 × ArH), 120.6 (=CH), 112.5 (2 × ArH), 56.6 (CH_2), 21.8 (CH_3), 21.1 (CH_3) and 20.1 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{30}N_3O_5S^+$ 556.1901; Found 556.1903.

565 2-(Mesylamino)-1-[(2-oxo-2-(4-tolyl)ethyl)(4-tolyl)amino]-1-(4-tolyl)ethene



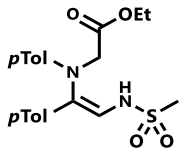
Triazole **101** (71 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **509** (79 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **565** (65 mg, 48%) as a yellow solid.; m.pt. 111–116 °C; ν_{max}(film) 2924, 1682, 1609, 1516, 1412, 1370, 1331, 1231, 1194, 1150 and 1053 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 9.18 (1 H, d, *J* = 10.4 Hz, NH), 7.91 (2 H, d, *J* = 8.2 Hz, Ar), 7.29 (2 H, d, *J* = 7.9 Hz, Ar), 7.24 (2 H, d, *J* = 8.2 Hz, Ar), 7.14 (2 H, d, *J* = 7.9 Hz, Ar), 6.98 (2 H, d, *J* = 8.5 Hz, Ar), 6.85 (1 H, d, *J* = 10.4 Hz, =CH), 6.54 (2 H, d, *J* = 8.5 Hz, Ar), 4.76 (2 H, br s, CH_2), 2.90 (3 H, s, CH_3), 2.43 (3 H, s, CH_3), 2.35 (3 H, s, CH_3) and 2.23 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 197.5 (C=O), 145.5 (Ar), 143.7 (Ar), 137.7 (Ar), 132.6 (Ar), 131.8 (Ar), 130.0 (2 × ArH), 129.7 (2 × ArH), 129.6 (2 × ArH), 128.3 (2 × ArH), 127.8 (Ar), 125.7 (=C), 125.0 (2 × ArH), 121.4 (=CH), 112.6 (2 × ArH), 56.4 (CH_2), 42.0 (CH_3), 21.8 (CH_3), 21.1 (CH_3) and 20.3 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{29}N_2O_3S^+$ 449.1893; Found 449.1901.

575 1-[(2-Methyl-2-oxoethyl)(4-tolyl)amino]-1-(4-tolyl)-2-(tosylamino)ethene



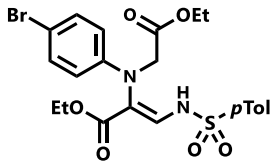
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **600** (54 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **575** as a yellow solid. ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.80 (1 H, d, *J* = 10.7 Hz, NH), 7.55 (2 H, d, *J* = 8.3 Hz, Ar), 7.11 (2 H, d, *J* = 8.3 Hz, Ar), 7.01 (4 H, app. s, Ar), 6.77 (1 H, d, *J* = 10.7 Hz, =CH), 6.68 (2 H, d, *J* = 8.8 Hz, Ar), 6.15 (2 H, d, *J* = 8.8 Hz, Ar), 3.97 (2 H, s, CH_2), 2.33 (3 H, s, CH_3), 2.23 (3 H, s, CH_3), 2.12 (3 H, s, CH_3) and 2.08 (3 H, s, CH_3); ^{13}C{^{1}H} NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 207.4 (C=O), 143.2 (Ar), 143.1 (Ar), 137.9 (Ar), 137.5 (Ar), 132.5 (Ar), 129.7 (2 × ArH), 129.6 (2 × ArH), 129.4 (2 × ArH), 127.4 (Ar), 126.7 (2 × ArH), 125.5 (=C), 124.8 (2 × ArH), 121.4 (=CH), 112.1 (2 × ArH), 60.1 (CH_2), 26.5 (CH_3), 21.5 (CH_3), 21.1 (CH_3) and 20.3 (CH_3).

579 1-[Ethyl (4-tolyl)glycinate]-1-(4-tolyl)-2-(mesylamino)ethene



Triazole **67** (71 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **601** (63 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **579** (113 mg, 94%) as a yellow solid. ν_{max}(film) 3284, 2981, 2921, 1737, 1685, 1607, 1522, 1445, 1408, 1321, 1207, 1184 and 1022 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 8.61 (1 H, d, J = 10.5 Hz, NH), 7.18 (2 H, d, J = 8.3 Hz, Ar), 7.11 (2 H, d, J = 8.3 Hz, Ar), 7.03 (2 H, d, J = 8.2 Hz, Ar), 6.85 (1 H, d, J = 10.5 Hz, =CH), 6.59 (2 H, d, J = 8.2 Hz, Ar), 4.29 (2 H, q, J = 7.1 Hz, CH_2), 4.06 (2 H, s, CH_2), 2.88 (3 H, s, CH_3), 2.33 (3 H, s, CH_3), 2.25 (3 H, s, CH_3) and 1.32 (3 H, t, J = 7.1 Hz, CH_3); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 173.1 (C=O), 143.4 (Ar), 137.7 (Ar), 132.2 (Ar), 130.1 (2 × ArH), 129.6 (2 × ArH), 128.1 (Ar), 125.8 (=C), 124.9 (2 × ArH), 120.9 (=CH), 112.5 (2 × ArH), 62.2 (CH_2), 51.8 (CH_2), 41.9 (CH_3), 21.1 (CH_3), 20.3 (CH_3) and 14.2 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{27}N_2O_4S^+$ 403.1686; Found 403.1687.

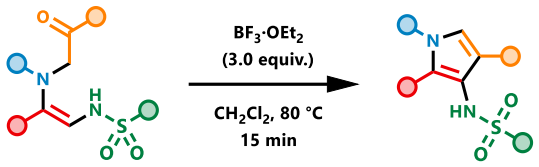
581 1-[Ethyl (4-bromophenyl)glycinate]-1-(4-ethyl acetate)-2-(mesylamino)ethene



Triazole **603** (89 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **602** (100 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 7 to give the title compound **581** as a colourless oil (100 mg, 40%). ν_{max}(film) 3152, 2980, 1711, 1675, 1635, 1594, 1491, 1364, 1348, 1215, 1197, 1162, 1088 and 1044 cm^{-1}; ^1H NMR (400 MHz, 21.9 °C, $CDCl_3$) δ 9.90 (1 H, s, NH), 7.89 (2 H, d, *J* = 8.4 Hz, Ar), 7.75 (1 H, s, =CH), 7.70 (2 H, d, *J* = 8.4 Hz, Ar), 7.32 (2 H, d, *J* = 8.1 Hz, Ar), 7.21 (2 H, d, *J* = 8.1 Hz, Ar), 7.08 (2 H, d, *J* = 9.0 Hz, Ar), 6.22 (2 H, d, *J* = 9.0 Hz, Ar), 5.12 (1 H, br s, CH_2), 4.35 (1 H, br s, CH_2), 4.20 (2 H, q, *J* = 7.1 Hz, CH_2), 2.45 (3 H, s, CH_3), 2.37 (3 H, s, CH_3) and 1.27 (3 H, t, *J* = 7.1 Hz, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 22.6 °C, $CDCl_3$) δ 197.6 (C=O), 164.9 (C=O), 145.9 (Ar), 144.5 (Ar), 144.2 (Ar), 137.7 (=CH), 137.1 (Ar), 131.9 (2 × ArH), 131.5 (Ar), 129.8 (2 × ArH), 129.7 (2 × ArH), 128.3 (2 × ArH), 126.6 (2 × ArH), 115.6 (=C), 113.8 (2 × ArH), 110.7 (Ar), 61.0 (CH_2), 57.7 (CH_2), 21.8 (CH_3), 21.5 (CH_3) and 14.4 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{27}BrN_2NaO_5S^+$ 593.0716; Found 593.0716.

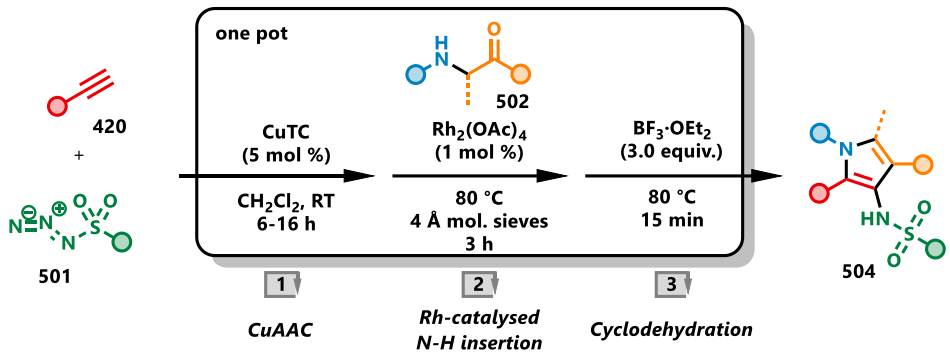
7.2.11 Preparation of pyrroles

General Procedure 8: Cyclodehydration of 1,2-diaminoalkenes



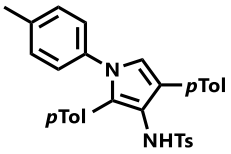
Under an atmosphere of argon, borontrifluoride diethyl etherate (3.0 equiv.) was added in one portion to a solution of 1,2-diamine (1.0 equiv.) in CH_2Cl_2 (0.03 M) in a flame-dried vial. The vial was sealed with a Teflon cap and heated at 80 °C (heating block) for 15 min. The reaction mixture was cooled to ambient temperature; saturated aqueous NaHCO3 was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL $mmol^{-1}$). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, gradient of 10−30% EtOAc in petroleum ether) gave the pyrrole product.

General Procedure 9: One-pot synthesis of pyrroles



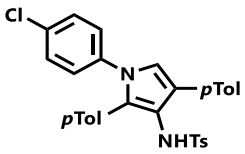
Under an atmosphere of argon, copper(I) thiophene-2-carboxylate (5 mol %) was added to a solution of alkyne **420** (1.1 equiv.) in CH_2Cl_2 (0.03 M) in a flame-dried vial containing freshly dried 4 Å molecular sieves. The mixture was cooled to 0 °C (ice bath) and stirred for 10 min. Then sulfonyl azide **501** (1.1 equiv.) was added, and the reaction mixture was allowed to reach ambient temperature. When the CuAAC reaction was complete (TLC, 6–16 h), amine **502** (1.0 equiv.) was added, followed by $Rh_2(OAc)_4$ (1 mol %), and the vial was sealed with a Teflon cap and heated to 80 °C (heating block) for 3 h. The reaction mixture was cooled to ambient temperature and boron trifluoride diethyl etherate (3.0 equiv.) was added in one portion. The vial was sealed and heated to 80 °C (heating block) for 15 min. After being cooled to ambient temperature, the reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL $mmol^{-1}$). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through a short pad of silica (eluting with CH_2Cl_2), and concentrated *in vacuo* to deliver the pyrrole **504**.

532 3-Tosylamino-1,2,4-tri(4-tolyl)pyrrole



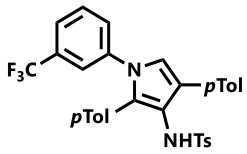
1,2-Diaminoalkene **531** (105 mg, 0.20 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (74 µL, 0.60 mmol, 3.0 equiv.) in CH_2Cl_2 (6.7 mL) according to General Procedure 8 to give the title compound **532** (74 mg, 73%) as an orange solid. 4-Ethynyltoluene (64 µL, 0.55 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (108 mg, 0.55 mmol, 1.1 equiv.) were treated with CuTC (5 mg, 0.026 mmol, 5 mol %) in CH_2Cl_2 (17 mL); followed by α-aminoketone **509** (120 mg, 0.50 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (2 mg, 0.05 mmol, 1 mol %); and finally $BF_3{\cdot}OEt_2$ (185 µL, 1.5 mmol, 3.0 equiv.) according to General Procedure 9 to give the title compound **532** (228 mg, 90%).; m.pt. 170 °C dec.; ν_{max}(film) 3268, 3028, 2920, 1562, 1516, 1389, 1327, 1157 and 1091 cm^{-1}; ^1H NMR (500 MHz, 25.0 °C, $CDCl_3$) δ 7.35 (2 H, d, *J* = 8.1 Hz, Ar), 7.25 (2 H, d, *J* = 8.0 Hz, Ar), 7.09 (2 H, d, *J* = 8.1 Hz, Ar), 7.07 (2 H, d, *J* = 8.4 Hz, Ar), 6.97 (2 H, d, *J* = 8.4 Hz, Ar), 6.94 (2 H, d, *J* = 8.1 Hz, Ar), 6.88 (1 H, s, pyrrole CH), 6.87 (2 H, d, *J* = 8.1 Hz, Ar), 6.82 (2 H, d, *J* = 8.0 Hz, Ar), 6.24 (1 H, s, NH), 2.37 (3 H, s, CH_3), 2.33 (3 H, s, CH_3), 2.32 (3 H, s, CH_3) and 2.30 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (126 MHz, 25.0 °C, $CDCl_3$) δ 142.3 (Ar), 137.4 (Ar), 137.0 (Ar), 136.7 (Ar), 136.4 (Ar), 135.5 (Ar), 131.9 (Ar), 131.0 (Ar), 129.8 (2 × ArH), 129.5 (2 × ArH), 129.0 (2 × ArH), 128.7 (2 × ArH), 128.6 (2 × ArH), 127.4 (2 × ArH), 127.2 (pyrrole), 127.0 (2 × ArH), 125.2 (2 × ArH), 123.6 (pyrrole), 119.3 (pyrrole CH), 115.3 (pyrrole), 21.3 (CH_3), 21.3 (CH_3), 21.2 (CH_3) and 21.2 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_2S^+$ 507.2101; Found 507.2100.

534 1-(4-Chlorophenyl)-2,4-di(4-tolyl)-3-tosylaminopyrrole



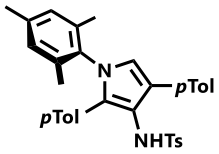
1,2-Diaminoalkene **533** (109 mg, 0.20 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (74 µL, 0.60 mmol, 3.0 equiv.) in CH_2Cl_2 (6.7 mL) according to General Procedure 8 to give the title compound **534** (86 mg, 82%) as a yellow solid. 4-Ethynyltoluene (38 µL, 0.33 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (66 mg, 0.33 mmol, 1.1 equiv.) were treated with CuTC (3 mg, 0.015 mmol, 5 mol %) in CH_2Cl_2 (10 mL); followed by α-aminoketone **511** (78 mg, 0.30 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (1 mg, 0.02 mmol, 1 mol %); and finally $BF_3{\cdot}OEt_2$ (111 µL, 0.90 mmol, 3.0 equiv.) according to General Procedure 9 to give the title compound **534** (101 mg, 64%).; m.pt. 170 °C dec.; ν_{max}(film) 3268, 3020, 2920, 1497, 1385, 1327, 1157 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.31 (2 H, d, *J* = 8.0 Hz, Ar), 7.22 (2 H, d, *J* = 8.0 Hz, Ar), 7.21 (2 H, d, *J* = 8.7 Hz, Ar), 7.07 (2 H, d, *J* = 8.0 Hz, Ar), 6.99 (2 H, d, *J* = 8.7 Hz, Ar), 6.94 (2 H, d, *J* = 7.9 Hz, Ar), 6.85 (1 H, s, pyrrole CH), 6.84 (2 H, d, *J* = 7.9 Hz, Ar), 6.81 (2 H, d, *J* = 8.0 Hz, Ar), 6.19 (1 H, s, NH), 2.35 (3 H, s, CH_3), 2.31 (3 H, s, CH_3) and 2.28 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 23.0 °C, $CDCl_3$) δ 142.4 (Ar), 138.4 (Ar), 137.1 (Ar), 137.0 (Ar), 135.8 (Ar), 132.3 (Ar), 130.7 (Ar), 129.9 (2 × ArH), 129.3 (Ar), 129.1 (2 × ArH), 129.0 (2 × ArH), 128.9 (2 × ArH), 128.7 (2 × ArH), 127.4 (2 × ArH), 127.0 (2 × ArH), 126.8 (pyrrole), 126.5 (2 × ArH), 124.2 (pyrrole), 119.1 (pyrrole CH), 115.9 (pyrrole), 21.4 (CH_3), 21.3 (CH_3) and 21.2 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{28}ClN_2O_2S^+$ 527.1555; Found 527.1562.

536 2,4-Di(4-tolyl)-3-tosyl-1-(3-trifluoromethylphenyl)aminopyrrole



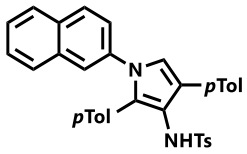
1,2-Diaminoalkene **535** (58 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **536** (36 mg, 64%) as a yellow solid. 4-Ethynyltoluene (38 µL, 0.33 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (66 mg, 0.33 mmol, 1.1 equiv.) were treated with CuTC (3 mg, 0.015 mmol, 5 mol %) in CH_2Cl_2 (10 mL); followed by α-aminoketone **513** (88 mg, 0.30 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (1 mg, 0.02 mmol, 1 mol %); and finally $BF_3{\cdot}OEt_2$ (111 µL, 0.90 mmol, 3.0 equiv.) according to General Procedure 9 to give the title compound **536** (131 mg, 78%).; m.pt. 145 °C dec.; ν_{max}(film) 3256, 2924, 1690, 1497, 1458, 1385, 1327, 1161, 1130, 1096 and 1072 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.48–7.43 (1 H, m, Ar), 7.40–7.37 (1 H, m, Ar), 7.35 (1 H, d, *J* = 7.8 Hz, Ar), 7.31 (2 H, d, *J* = 7.9 Hz, Ar), 7.23 (2 H, d, *J* = 8.2 Hz, Ar), 7.17–7.13 (1 H, m, Ar), 7.07 (2 H, d, *J* = 7.9 Hz, Ar), 6.95 (2 H, d, *J* = 8.0 Hz, Ar), 6.91 (1 H, s, pyrrole CH), 6.84 (2 H, d, *J* = 8.0 Hz, Ar), 6.82 (2 H, d, *J* = 8.2 Hz, Ar), 6.20 (1 H, s, NH), 2.35 (3 H, s, CH_3), 2.30 (3 H, s, CH_3) and 2.28 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 142.5 (Ar), 140.3 (Ar), 137.4 (Ar), 136.9 (Ar), 135.9 (Ar), 132.1 (Ar), 131.5 (q, *J* = 32.9 Hz, Ar), 130.5 (Ar), 129.9 (2 × ArH), 129.4 (ArH), 129.0 (2 × ArH), 129.0 (2 × ArH), 128.7 (2 × ArH), 128.6 (ArH), 127.5 (2 × ArH), 127.0 (2 × ArH), 126.6 (pyrrole), 124.6 (pyrrole), 123.5 (q, *J* = 272.4 Hz, CF_3), 123.2 (q, *J* = 3.8 Hz, ArH), 121.9 (q, *J* = 3.5 Hz, ArH), 118.9 (pyrrole CH), 116.4 (pyrrole), 21.4 (CH_3), 21.3 (CH_3) and 21.2 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{28}F_3N_2O_2S^+$ 561.1818; Found 561.1826.

538 2,4-Di(4-tolyl)-3-tosyl-1-(2,4,6-trimethylphenyl)aminopyrrole



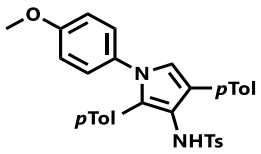
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **512** (88 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 8. During the N–H insertion, spontaneous cyclodehydration occurred to give the title compound **538** (111 mg, 69%) as a yellow wax.; ν_{max}(film) 3264, 3024, 2920, 2866, 1600, 1562, 1493, 1381, 1327 and 1161 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.35 (2 H, d, *J* = 8.0 Hz, Ar), 7.19 (2 H, d, *J* = 8.3 Hz, Ar), 7.09 (2 H, d, *J* = 8.0 Hz, Ar), 6.84 (2 H, d, *J* = 8.0 Hz, Ar), 6.81 (2 H, s, Ar), 6.80 (2 H, d, *J* = 8.3 Hz, Ar), 6.69 (2 H, d, *J* = 8.0 Hz, Ar), 6.57 (1 H, s, pyrrole CH), 6.27 (1 H, s, NH), 2.35 (3 H, s, CH_3), 2.28 (3 H, s, CH_3), 2.25 (3 H, s, CH_3), 2.24 (3 H, s, CH_3) and 1.92 (6 H, s, 2 × CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 142.5 (Ar), 137.9 (Ar), 136.5 (Ar), 136.0 (Ar), 135.7 (2 × Ar), 135.6 (Ar), 135.4 (Ar), 132.0 (Ar), 131.3 (Ar), 128.9 (2 × ArH), 128.7 (2 × ArH), 128.6 (2 × ArH), 128.5 (4 × ArH), 127.3 (pyrrole), 127.3 (2 × ArH), 127.2 (2 × ArH), 123.4 (pyrrole), 118.6 (pyrrole CH), 113.7 (pyrrole), 21.5 (CH_3), 21.2 (CH_3), 21.2 (CH_3), 21.0 (CH_3) and 17.7 (2 × CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{35}N_2O_2S^+$ 535.2414; Found 535.2423.

540 2,4-Di(4-tolyl)-1-naphth-2-yl-3-tosylaminopyrrole



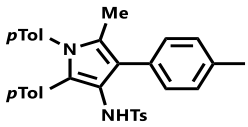
Triazole **67** (94 mg, 0.30 mmol, 1.0 equiv.) and α-aminoketone **514** (91 mg, 0.33 mmol, 1.1 equiv.) were treated with $Rh_2(OAc)_4$ (7 mg, 0.015 mmol, 5 mol %) in PhMe (10 mL) according to General Procedure 8. During the N–H insertion, spontaneous cyclodehydration occurred to give the title compound **540** (117 mg, 72%) as a yellow solid.; m.pt. 150 °C dec.; ν_{max}(film) 3268, 3048, 2920, 2866, 1597, 1508, 1412, 1323, 1157, 1092 and 1042 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.88–7.83 (1 H, m, naphthyl CH), 7.79 (1 H, d, *J* = 8.4 Hz, naphthyl CH), 7.62–7.58 (1 H, m, naphthyl CH), 7.55–7.45 (2 H, m, naphthyl CH), 7.40 (2 H, d, *J* = 8.1 Hz, Ar), 7.34 (1 H, dd, *J* = 8.3, 7.3 Hz, naphthyl CH), 7.28 (2 H, d, *J* = 8.4 Hz, Ar), 7.21 (1 H, dd, *J* = 7.3, 1.2 Hz, naphthyl CH), 7.10 (2 H, d, *J* = 7.6 Hz, Ar), 6.89 (1 H, s, pyrrole CH), 6.83 (2 H, d, *J* = 7.6 Hz, Ar), 6.73 (4 H, app. s, Ar), 6.29 (1 H, s, NH), 2.36 (3 H, s, CH_3), 2.27 (3 H, s, CH_3) and 2.16 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 142.5 (naphthyl C), 136.7 (Ar), 136.6 (Ar), 136.4 (Ar), 135.6 (Ar), 134.0 (naphthyl C), 133.8 (pyrrole), 131.0 (Ar), 130.8 (naphthyl C), 129.2 (2 × ArH), 129.0 (2 × ArH), 128.7 (2 × ArH), 128.5 (2 × ArH), 128.4 (naphthyl CH), 128.1 (naphthyl CH), 127.4 (2 × ArH), 127.2 (2 × ArH), 127.1 (Ar), 127.0 (naphthyl CH), 126.5 (naphthyl CH), 125.7 (naphthyl CH), 125.0 (naphthyl CH), 123.3 (pyrrole), 123.1 (naphthyl CH), 121.1 (pyrrole CH), 114.6 (pyrrole), 21.4 (CH_3), 21.2 (CH_3) and 21.1 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{35}H_{31}N_2O_2S^+$ 543.2101; Found 543.2109.

542 2,4-Di(4-tolyl)-1-(4-methoxyphenyl)-3-tosylaminopyrrole



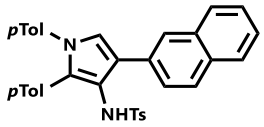
1,2-Diaminoalkene **541** (108 mg, 0.20 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (74 µL, 0.60 mmol, 3.0 equiv.) in CH_2Cl_2 (6.7 mL) according to General Procedure 8 to give the title compound **542** (69 mg, 66%) as a yellow solid.; m.pt. 158 °C dec.; ν_{max}(film) 3271, 2920, 2859, 1512, 1443, 1393, 1323, 1304, 1250, 1157, 1092 and 1034 cm^{-1}; ^1H NMR (400 MHz, 22.1 °C, $CDCl_3$) δ 7.33 (2 H, d, J = 8.0 Hz, Ar), 7.23 (2 H, d, J = 8.2 Hz, Ar), 7.06 (2 H, d, J = 8.0 Hz, Ar), 6.99 (2 H, d, J = 9.0 Hz, Ar), 6.91 (2 H, d, J = 7.8 Hz, Ar), 6.84 (2 H, d, J = 7.8 Hz, Ar), 6.83 (1 H, s, pyrrole CH), 6.80 (2 H, d, J = 8.2 Hz, Ar), 6.77 (2 H, d, J = 9.0 Hz, Ar), 6.23 (1 H, s, NH), 3.77 (3 H, s, OCH_3), 2.34 (3 H, s, CH_3), 2.29 (3 H, s, CH_3) and 2.27 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 22.9 °C, $CDCl_3$) δ 158.1 (Ar), 142.3 (Ar), 137.0 (Ar), 136.7 (Ar), 135.5 (Ar), 133.0 (Ar), 132.1 (Ar), 131.1 (Ar), 129.9 (2 × ArH), 128.9 (2 × ArH), 128.7 (2 × ArH), 128.6 (2 × ArH), 127.4 (2 × ArH), 127.2 (pyrrole), 127.0 (2 × ArH), 126.7 (2 × ArH), 123.4 (pyrrole), 119.5 (pyrrole CH), 115.0 (pyrrole), 114.0 (2 × ArH), 55.4 (OCH_3), 21.4 (CH_3), 21.3 (CH_3) and 21.2 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{30}N_2NaO_3S^+$ 545.1869; Found 545.1858.

547 5-Methyl-3-tosylamino-1,2,4-tri(4-tolyl)pyrrole



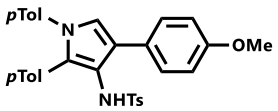
1,2-Diaminoalkene **546** (54 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **547** (38 mg, 73%) as a yellow solid. 4-Ethynyltoluene (38 µL, 0.33 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (66 mg, 0.33 mmol, 1.1 equiv.) were treated with CuTC (3 mg, 0.015 mmol, 5 mol %) in CH_2Cl_2 (10 mL); followed by α-aminoketone **520** (76 mg, 0.30 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (1 mg, 0.02 mmol, 1 mol %); and finally $BF_3{\cdot}OEt_2$ (111 µL, 0.90 mmol, 3.0 equiv.) according to General Procedure 9 to give the title compound **547** (106 mg, 68%).; m.pt. 154 °C dec.; ν_{max}(film) 3271, 3028, 2920, 2866, 1717, 1601, 1512, 1451, 1381, 1323, 1157 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.19 (2 H, d, J = 8.3 Hz, Ar), 7.14–7.06 (6 H, m, Ar), 6.98 (2 H, d, J = 8.3 Hz, Ar), 6.86–6.84 (4 H, m, Ar), 6.81 (2 H, d, J = 7.9 Hz, Ar), 6.18 (1 H, s, NH), 2.37 (3 H, s, CH_3), 2.32 (3 H, s, CH_3), 2.29 (3 H, s, CH_3), 2.25 (3 H, s, CH_3) and 2.01 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 142.0 (Ar), 137.2 (Ar), 137.2 (Ar), 136.0 (Ar), 135.9 (Ar), 135.2 (Ar), 131.4 (Ar), 131.0 (Ar), 129.8 (2 × ArH), 129.6 (2 × ArH), 129.4 (2 × ArH), 128.8 (2 × ArH), 128.6 (2 × ArH), 128.4 (2 × ArH), 128.3 (2 × ArH), 127.9 (pyrrole), 126.9 (2 × ArH), 125.9 (pyrrole), 120.6 (pyrrole), 114.6 (pyrrole), 21.4 (CH_3), 21.2 (CH_3), 21.2 (CH_3), 21.1 (CH_3) and 12.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{33}H_{33}N_2O_2S^+$ 521.2257; Found 521.2256.

549 1,2-Di(4-tolyl)-4-(naphth-2-yl)-3-tosylaminopyrrole



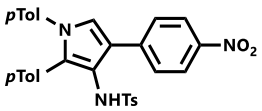
4-Ethynyltoluene (590 µL, 5.1 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (1.29 g, 6.5 mmol, 1.4 equiv.) were treated with CuTC (44 mg, 0.23 mmol, 5 mol %) in CH_2Cl_2 (170 mL); followed by α-aminoketone **519** (1.27 g, 4.6 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (20 mg, 0.046 mmol, 1 mol %); and finally $BF_3{\cdot}OEt_2$ (1.71 mL, 14 mmol, 3.0 equiv.) according to General Procedure 8 to give the title compound (1.89 g, 76%) as an orange solid.; 1,2-Diaminoalkene **548** (56 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 4 to give the title compound **549** (36 mg, 66%) as an orange solid. 4-Ethynyltoluene (38 µL, 0.33 mmol, 1.3 equiv.) and 4-toluenesulfonyl azide (66 mg, 0.33 mmol, 1.3 equiv.) were treated with CuTC (3 mg, 0.015 mmol, 5 mol %) in CH_2Cl_2 (10 mL); followed by α-aminoketone **519** (72 mg, 0.26 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (1 mg, 0.02 mmol, 1 mol %); and finally $BF_3{\cdot}OEt_2$ (111 µL, 0.90 mmol, 3.4 equiv.) according to General Procedure 9 to give the title compound **549** (142 mg, >98%).; m.pt. 160 °C dec.; ν_{max}(film) 3264, 3036, 2924, 1601, 1516, 1377, 1327, 1215, 1157 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.79–7.76 (2 H, m, Ar), 7.73–7.69 (1 H, m, Ar), 7.67 (1 H, d, J = 8.5 Hz, Ar), 7.52 (1 H, dd, J = 8.4, 1.7 Hz, Ar), 7.47–7.39 (2 H, m, Ar), 7.21 (2 H, d, J = 8.3 Hz, Ar), 7.08 (2 H, d, J = 7.9 Hz, Ar), 7.02–6.98 (6 H, m, Ar), 7.00 (1 H, s, pyrrole CH), 6.57 (2 H, d, J = 7.8 Hz, Ar), 6.27 (1 H, s, NH), 2.33 (3 H, s, CH_3), 2.32 (3 H, s, CH_3) and 1.98 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 142.5 (Ar), 137.4 (Ar), 137.0 (Ar), 136.9 (Ar), 136.6 (Ar), 133.6 (naphthyl C), 132.7 (Ar), 132.0 (naphthyl C), 131.5 (naphthyl C), 130.0 (2 × ArH), 129.5 (2 × ArH), 128.8 (2 × ArH), 128.6 (2 × ArH), 127.9 (naphthyl CH), 127.7 (naphthyl CH), 127.5 (naphthyl CH), 127.2 (naphthyl CH), 126.9 (2 × ArH), 126.3 (naphthyl CH), 125.7 (pyrrole), 125.6 (naphthyl CH), 125.3 (2 × ArH), 125.2 (naphthyl CH), 123.4 (pyrrole), 119.9 (pyrrole CH), 115.5 (pyrrole), 21.3 (CH_3), 21.1 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{35}H_{31}N_2O_2S^+$ 543.2101; Found 543.2109.

551 1,2-Di(4-tolyl)-4-(4-methoxyphenyl)-3-tosylaminopyrrole



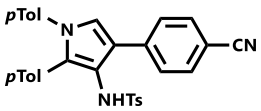
1,2-Diaminoalkene **550** (54 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **551** (32 mg, 61%) as a yellow solid.; m.pt. 160 °C dec.; ν_{max}(film) 3264, 3036, 2920, 2859, 1686, 1562, 1505, 1389, 1323, 1242, 1157, 1092 and 1022 cm^{-1}; ^1H NMR (400 MHz, 26.0 °C, $CDCl_3$) δ 7.36 (2 H, d, *J* = 8.8 Hz, Ar), 7.24 (2 H, d, *J* = 8.4 Hz, Ar), 7.04 (2 H, d, *J* = 7.9 Hz, Ar), 6.94 (2 H, d, *J* = 8.2 Hz, Ar), 6.91 (2 H, d, *J* = 8.2 Hz, Ar), 6.84 (2 H, d, *J* = 7.9 Hz, Ar), 6.83 (1 H, s, pyrrole CH), 6.82 (2 H, d, *J* = 8.4 Hz, Ar), 6.80 (2 H, d, *J* = 8.8 Hz, Ar), 6.17 (1 H, s, NH), 3.82 (3 H, s, OCH_3), 2.30 (3 H, s, CH_3), 2.29 (3 H, s, CH_3) and 2.28 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 26.0 °C, $CDCl_3$) δ 158.1 (Ar), 142.4 (Ar), 137.4 (Ar), 137.1 (Ar), 136.8 (Ar), 136.4 (Ar), 131.8 (Ar), 129.9 (2 × ArH), 129.5 (2 × ArH), 128.7 (2 × ArH), 128.7 (2 × ArH), 128.6 (2 × ArH), 127.3 (Ar), 127.1 (2 × ArH), 126.6 (pyrrole), 125.2 (2 × ArH), 123.3 (pyrrole), 119.1 (pyrrole CH), 115.3 (pyrrole), 113.7 (2 × ArH), 55.2 (OCH_3), 21.4 (CH_3), 21.3 (CH_3) and 20.9 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_3S^+$ 523.2050; Found 523.2059.

553 1,2-Di(4-tolyl)-4-(4-nitrophenyl)-3-tosylaminopyrrole



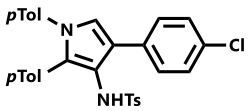
1,2-Diaminoalkene **552** (56 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **553** (42 mg, 78%) as an orange solid. 4-Ethynyltoluene (38 µL, 0.33 mmol, 1.1 equiv.) and 4-toluenesulfonyl azide (66 mg, 0.33 mmol, 1.1 equiv.) were treated with CuTC (3 mg, 0.015 mmol, 5 mol %) in CH_2Cl_2 (10 mL); followed by α-aminoketone **513** (81 mg, 0.30 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (1 mg, 0.02 mmol, 1 mol %); and finally $BF_3{\cdot}OEt_2$ (111 µL, 0.90 mmol, 3.0 equiv.) according to General Procedure 9 to give the title compound **553** (120 mg, 74%).; m.pt. 175 °C dec.; ν_{max}(film) 3264, 3036, 2924, 1597, 1562, 1393, 1335, 1219, 1161, 1151 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 8.11 (2 H, d, J = 8.9 Hz, Ar), 7.71 (2 H, d, J = 8.9 Hz, Ar), 7.23 (2 H, d, J = 8.3 Hz, Ar), 7.07 (2 H, d, J = 8.1 Hz, Ar), 7.04 (1 H, s, pyrrole CH), 6.96–6.90 (4 H, m, Ar), 6.83 (2 H, d, J = 8.3 Hz, Ar), 6.74 (2 H, d, J = 8.1 Hz, Ar), 6.32 (1 H, s, NH), 2.31 (3 H, s, CH_3), 2.30 (3 H, s, CH_3) and 2.25 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 145.6 (Ar), 143.1 (Ar), 141.4 (Ar), 137.4 (Ar), 137.2 (Ar), 136.8 (Ar), 136.5 (Ar), 132.9 (Ar), 129.7 (2 × ArH), 129.6 (2 × ArH), 128.9 (2 × ArH), 128.9 (2 × ArH), 127.4 (2 × ArH), 127.1 (2 × ArH), 126.3 (pyrrole), 125.1 (2 × ArH), 123.7 (2 × ArH), 121.3 (pyrrole), 120.8 (pyrrole CH), 115.4 (pyrrole), 21.3 (CH_3), 21.3 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{28}N_3O_4S^+$ 538.1795; Found 538.1803.

555 4-(4-Cyanophenyl)-1,2-di(4-tolyl)-3-tosylaminopyrrole



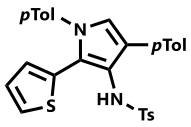
1,2-Diaminoalkene **554** (54 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **555** (37 mg, 71%) as a yellow solid.; m.pt. 165 °C dec.; ν_{max}(film) 3275, 3036, 2924, 2226, 1681, 1605, 1543, 1516, 1393, 1327, 1219, 1161 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.65 (2 H, d, *J* = 8.7 Hz, Ar), 7.52 (2 H, d, *J* = 8.7 Hz, Ar), 7.22 (2 H, d, *J* = 8.1 Hz, Ar), 7.06 (2 H, d, *J* = 7.9 Hz, Ar), 6.99 (1 H, s, pyrrole CH), 6.95–6.90 (4 H, m, Ar), 6.84 (2 H, d, *J* = 8.1 Hz, Ar), 6.74 (2 H, d, *J* = 8.1 Hz, Ar), 6.27 (1 H, s, NH), 2.31 (3 H, s, CH_3), 2.30 (3 H, s, CH_3) and 2.30 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 143.0 (Ar), 139.2 (Ar), 137.3 (Ar), 137.1 (Ar), 136.9 (Ar), 136.5 (Ar), 132.8 (Ar), 132.0 (2 × ArH), 129.7 (2 × ArH), 129.6 (2 × ArH), 128.9 (2 × ArH), 128.9 (2 × ArH), 127.5 (2 × ArH), 127.0 (2 × ArH), 126.4 (pyrrole), 125.1 (2 × ArH), 121.7 (pyrrole), 120.5 (pyrrole CH), 119.4 (pyrrole), 115.3 (C≡N), 109.0 (Ar), 21.4 (CH_3), 21.3 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{28}N_3O_2S^+$ 518.1897; Found 518.1904.

557 4-(4-Chlorophenyl)-1,2-di(4-tolyl)-3-tosylaminopyrrole



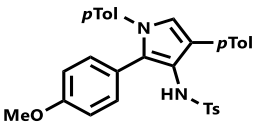
1,2-Diaminoalkene **556** (55 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **557** (41 mg, 77%) as a yellow solid.; m.pt. 160 °C dec.; ν_{max}(film) 3268, 2924, 1686, 1601, 1501, 1389, 1219, 1157, 1092 and 1018 cm^{-1}; ^1H NMR (400 MHz, 26.0 °C, $CDCl_3$) δ 7.36 (2 H, d, *J* = 8.5 Hz, Ar), 7.24 (2 H, d, *J* = 8.3 Hz, Ar), 7.18 (2 H, d, *J* = 8.5 Hz, Ar), 7.05 (2 H, d, *J* = 8.0 Hz, Ar), 6.95 (2 H, d, *J* = 8.1 Hz, Ar), 6.93 (2 H, d, *J* = 8.3 Hz, Ar), 6.88 (1 H, s, pyrrole CH), 6.85 (2 H, d, *J* = 8.1 Hz, Ar), 6.84 (2 H, d, *J* = 8.0 Hz, Ar), 6.18 (1 H, s, NH), 2.31 (6 H, s, 2 × CH_3) and 2.30 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 26.0 °C, $CDCl_3$) δ 142.8 (Ar), 137.2 (Ar), 137.1 (Ar), 136.9 (Ar), 136.7 (Ar), 132.6 (Ar), 132.4 (Ar), 131.8 (Ar), 129.9 (2 × ArH), 129.5 (2 × ArH), 128.8 (2 × ArH), 128.8 (2 × ArH), 128.6 (2 × ArH), 128.3 (2 × ArH), 127.0 (2 × ArH), 126.9 (pyrrole), 125.2 (2 × ArH), 122.4 (pyrrole), 119.6 (pyrrole CH), 115.2 (pyrrole), 21.5 (CH_3), 21.3 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{28}ClN_2O_2S^+$ 527.1555; Found 527.1559.

566 1,4-Di(4-tolyl)-2-(thiophen-2-yl)-3-tosylaminopyrrole



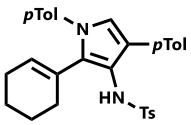
1,2-Diaminoalkene **563** (52 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **566** (38 mg, 76%) as a yellow solid.; m.pt. 187 °C dec.; ν_{max}(film) 3268, 2920, 1516, 1397, 1327, 1161 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.32 (2 H, d, *J* = 8.3 Hz, Ar), 7.24 (2 H, d, *J* = 8.1 Hz, Ar), 7.18 (1 H, dd, *J* = 5.1, 1.2 Hz, thiophene CH), 7.12 (2 H, d, *J* = 8.2 Hz, Ar), 7.05 (2 H, d, *J* = 8.2 Hz, Ar), 7.03 (2 H, d, *J* = 8.1 Hz, Ar), 6.86 (2 H, d, *J* = 8.3 Hz, Ar), 6.85 (1 H, s, pyrrole CH), 6.82 (1 H, dd, *J* = 5.1, 3.6 Hz, thiophene CH), 6.66 (1 H, dd, *J* = 3.6, 1.2 Hz, thiophene CH), 6.32 (1 H, s, NH), 2.35 (3 H, s, CH_3), 2.34 (3 H, s, CH_3) and 2.28 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 142.5 (Ar), 137.3 (Ar), 137.1 (Ar), 136.9 (Ar), 135.6 (Ar), 130.7 (Ar), 130.7 (thiophene C2), 129.5 (2 × ArH), 128.9 (2 × ArH), 128.8 (2 × ArH), 128.4 (thiophene CH), 127.3 (2 × ArH), 127.1 (2 × ArH), 126.7 (thiophene CH), 126.4 (thiophene CH), 125.7 (2 × ArH), 125.6 (pyrrole), 123.6 (pyrrole), 120.4 (pyrrole CH), 116.5 (pyrrole), 21.4 (CH_3), 21.2 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{27}N_2O_2S_2^+$ 499.1508; Found 499.1517.

567 1,4-Di(4-tolyl)-2-(4-methoxyphenyl)-3-tosylaminopyrrole



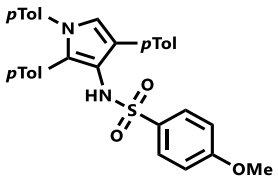
1,2-Diaminoalkene **561** (54 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **567** (44 mg, 84%) as a yellow solid.; m.pt. 75 °C dec.; ν_{max}(film) 3275, 2924, 1613, 1516, 1393, 1323, 1292, 1250, 1157, 1092 and 1038 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.31 (2 H, d, *J* = 8.1 Hz, Ar), 7.24 (2 H, d, *J* = 8.3 Hz, Ar), 7.06 (2 H, d, *J* = 8.1 Hz, Ar), 7.05 (2 H, d, *J* = 8.3 Hz, Ar), 6.94 (2 H, d, *J* = 8.4 Hz, Ar), 6.90 (2 H, d, *J* = 8.8 Hz, Ar), 6.85 (1 H, s, pyrrole CH), 6.82 (2 H, d, *J* = 8.4 Hz, Ar), 6.65 (2 H, d, *J* = 8.8 Hz, Ar), 6.15 (1 H, s, NH), 3.78 (3 H, s, OCH_3), 2.34 (3 H, s, CH_3), 2.31 (3 H, s, CH_3) and 2.27 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 158.7 (Ar), 142.4 (Ar), 137.4 (Ar), 137.1 (Ar), 136.5 (Ar), 135.5 (Ar), 131.8 (Ar), 131.3 (2 × ArH), 131.1 (Ar), 129.5 (2 × ArH), 129.0 (2 × ArH), 128.7 (2 × ArH), 127.4 (2 × ArH), 127.1 (2 × ArH), 125.3 (2 × ArH), 123.5 (pyrrole), 122.7 (pyrrole), 119.2 (pyrrole CH), 115.2 (pyrrole), 113.5 (2 × ArH), 55.1 (OCH_3), 21.4 (CH_3), 21.2 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_3S^+$ 523.2050; Found 523.2057.

568 1,4-Di(4-tolyl)-2-(cyclohexen-1-yl)-3-tosylaminopyrrole



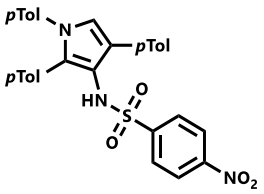
1,2-Diaminoalkene **562** (51 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **568** (28 mg, 57%) as a brown solid.; m.pt. 80 °C dec.; ν_{max}(film) 3271, 3036, 2928, 1709, 1593, 1516, 1492, 1393, 1246, 1157, 1092 and 1022 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.41 (2 H, d, *J* = 8.3 Hz, Ar), 7.22 (2 H, d, *J* = 8.5 Hz, Ar), 7.19 (2 H, d, *J* = 8.5 Hz, Ar), 7.17 (2 H, d, *J* = 8.3 Hz, Ar), 7.00 (2 H, d, *J* = 7.9 Hz, Ar), 6.97 (2 H, d, *J* = 7.9 Hz, Ar), 6.69 (1 H, s, pyrrole CH), 6.15 (1 H, s, NH), 5.80–5.76 (1 H, m, =CH), 2.37 (3 H, s, CH_3), 2.32 (3 H, s, CH_3), 2.30 (3 H, s, CH_3), 2.10–2.03 (2 H, m, CH_2), 1.57–1.52 (2 H, m, CH_2), 1.48–1.42 (2 H, m, CH_2) and 1.39–1.32 (2 H, m, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 142.6 (Ar), 138.1 (Ar), 137.2 (Ar), 136.5 (Ar), 135.2 (Ar), 134.5 (pyrrole), 131.5 (=CH), 131.2 (Ar), 129.6 (2 × ArH), 128.9 (2 × ArH), 128.8 (2 × ArH), 128.7 (=C), 127.4 (2 × ArH), 127.2 (2 × ArH), 124.0 (2 × ArH), 123.0 (pyrrole), 118.1 (pyrrole CH), 114.4 (pyrrole), 28.2 (CH_2), 25.7 (CH_2), 22.4 (CH_2), 21.5 (CH_2), 21.4 (CH_3), 21.1 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{33}N_2O_2S^+$ 497.2257; Found 497.2265.

569 3-(4-Methoxybenzenesulfonylamino)-1,2,4-tri(4-tolyl)pyrrole



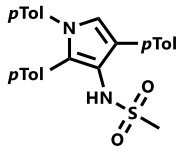
1,2-Diaminoalkene **563** (54 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **569** (26 mg, 50%) as a yellow solid. 4-Ethynyltoluene (38 µL, 0.33 mmol, 1.1 equiv.) and 4-methoxybenzenesulfonyl azide (70 mg, 0.33 mmol, 1.1 equiv.) were treated with CuTC (3 mg, 0.015 mmol, 5 mol %) in CH_2Cl_2 (10 mL); followed by α-aminoketone **509** (72 mg, 0.30 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (1 mg, 0.02 mmol, 1 mol %); and finally $BF_3{\cdot}OEt_2$ (111 µL, 0.90 mmol, 3.0 equiv.) according to General Procedure 9 to give the title compound **569** (88 mg, 56%).; m.pt. 150 °C dec.; ν_{max}(film) 3271, 3020, 2920, 1593, 1501, 1389, 1323, 1258, 1153, 1096 and 1030 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.33 (2 H, d, *J* = 8.2 Hz, Ar), 7.27 (2 H, d, *J* = 8.9 Hz, Ar), 7.06 (2 H, d, *J* = 7.7 Hz, Ar), 7.05 (2 H, d, *J* = 7.7 Hz, Ar), 6.95 (2 H, d, *J* = 8.9 Hz, Ar), 6.93 (2 H, d, *J* = 8.2 Hz, Ar), 6.87 (2 H, d, *J* = 9.1 Hz, Ar), 6.86 (1 H, s, pyrrole CH), 6.47 (2 H, d, *J* = 9.1 Hz, Ar), 6.17 (1 H, s, NH), 3.76 (3 H, s, OCH_3), 2.34 (3 H, s, CH_3), 2.31 (3 H, s, CH_3) and 2.29 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 162.3 (Ar), 137.4 (Ar), 136.7 (Ar), 136.5 (Ar), 135.5 (Ar), 131.9 (Ar), 131.6 (Ar), 131.1 (Ar), 129.9 (2 × ArH), 129.5 (2 × ArH), 129.1 (2 × ArH), 129.0 (2 × ArH), 128.8 (2 × ArH), 127.4 (2 × ArH), 127.3 (pyrrole), 125.2 (2 × ArH), 123.5 (pyrrole), 119.4 (pyrrole CH), 115.4 (pyrrole), 113.2 (2 × ArH), 55.3 (OCH_3), 21.2 (CH_3), 21.1 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_3S^+$ 523.2050; Found 523.2058.

570 3-(4-Nitrobenzenesulfonylamino)-1,2,4-tri(4-tolyl)pyrrole



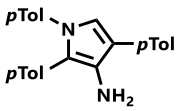
1,2-Diaminoalkene **564** (56 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **570** (45 mg, 83%) as an orange solid.; m.pt. 180 °C dec.; ν_{max}(film) 3271, 3036, 2920, 2862, 1609, 1562, 1516, 1404, 1389, 1346, 1219, 1161, 1092 and 1015 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.80 (2 H, d, *J* = 8.8 Hz, Ar), 7.53 (2 H, d, *J* = 8.8 Hz, Ar), 7.26 (2 H, d, *J* = 8.1 Hz, Ar), 7.06 (2 H, d, *J* = 7.6 Hz, Ar), 7.05 (2 H, d, *J* = 7.6 Hz, Ar), 6.94 (2 H, d, *J* = 8.3 Hz, Ar), 6.93 (2 H, d, *J* = 7.8 Hz, Ar), 6.88 (2 H, d, *J* = 8.3 Hz, Ar), 6.87 (1 H, s, pyrrole CH), 6.53 (1 H, s, NH), 2.32 (3 H, s, CH_3), 2.31 (3 H, s, CH_3) and 2.29 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 149.3 (Ar), 145.7 (Ar), 137.4 (Ar), 137.1 (Ar), 136.8 (Ar), 136.2 (Ar), 132.6 (Ar), 130.7 (Ar), 129.9 (2 × ArH), 129.6 (2 × ArH), 129.1 (2 × ArH), 128.9 (2 × ArH), 128.2 (2 × ArH), 127.4 (2 × ArH), 127.0 (pyrrole), 125.2 (2 × ArH), 123.7 (pyrrole), 123.2 (2 × ArH), 119.7 (pyrrole CH), 114.0 (pyrrole), 21.2 (CH_3), 21.0 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{28}N_3O_4S^+$ 538.1795; Found 538.1805.

570 3-Mesylamino-1,2,4-tri(4-tolyl)pyrrole



1,2-Diaminoalkene **565** (45 mg, 0.10 mmol, 1.0 equiv.) was treated with $BF_3{\cdot}OEt_2$ (37 µL, 0.30 mmol, 3.0 equiv.) in CH_2Cl_2 (3.3 mL) according to General Procedure 8 to give the title compound **570** (30 mg, 69%) as an orange solid.; m.pt. 93–94 °C; ν_{max}(film) 3268, 2924, 1562, 1516, 1393, 1319, 1219, 1153 and 1092 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.51 (2 H, d, *J* = 8.1 Hz, Ar), 7.22 (2 H, d, *J* = 7.8 Hz, Ar), 7.15 (2 H, d, *J* = 8.4 Hz, Ar), 7.10 (2 H, d, *J* = 8.1 Hz, Ar), 7.09 (2 H, d, *J* = 8.1 Hz, Ar), 7.02 (2 H, d, *J* = 8.4 Hz, Ar), 6.96 (1 H, s, pyrrole CH), 5.92 (1 H, s, NH), 2.37 (3 H, s, CH_3), 2.33 (3 H, s, CH_3), 2.32 (3 H, s, CH_3) and 2.29 (3 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 137.5 (Ar), 137.4 (Ar), 136.7 (Ar), 136.3 (Ar), 132.1 (Ar), 131.0 (Ar), 130.2 (2 × ArH), 129.6 (2 × ArH), 129.5 (2 × ArH), 129.2 (2 × ArH), 127.9 (2 × ArH), 127.5 (pyrrole), 125.3 (2 × ArH), 123.7 (pyrrole), 119.5 (pyrrole CH), 115.3 (pyrrole), 40.7 (Ms), 21.3 (CH_3), 21.2 (CH_3) and 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{27}N_2O_2S^+$ 431.1788; Found 431.1797.

595 3-Amino-1,2,4-tri(4-tolyl)pyrrole



Triflic acid (16 µL, 0.18 mmol, 3.0 equiv.) was added to a solution of pyrrole **532** (30 mg, 0.059 mmol, 1.0 equiv.) in 1,2-dichloroethane (2.0 mL) at 0 °C (ice bath). The mixture was heated at 90 °C (heating block) in a sealed vial for 2.5 h. The reaction mixture was cooled to ambient temperature and the reaction was quenched by the addition of ethylenediamine (2 drops) followed by 1 m aqueous NaOH (2.0 mL). The aqueous phase was extracted with dichloromethane (3 × 2.0 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 5% hexane in ethyl acetate) to give the title compound **595** (16 mg, 77%) as a yellow oil.; ν_{max}(film) 3402, 3322, 3028, 2920, 2859, 1613, 1586, 1562, 1516, 1454, 1389, 1258, 1242 and 1208 cm^{-1}; ^1H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ 7.52 (2 H, d, J = 8.1 Hz, Ar), 7.23 (2 H, d, J = 7.7 Hz, Ar), 7.12–7.00 (8 H, m, Ar), 6.85 (1 H, s, pyrrole CH), 3.35 (2 H, br s, NH), 2.38 (3 H, s, 2 × CH_3) and 2.32 (6 H, s, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, 25.0 °C, $CDCl_3$) δ 138.1 (Ar), 135.4 (Ar), 135.4 (Ar), 135.3 (Ar), 131.9 (pyrrole), 129.5 (2 × ArH), 129.5 (2 × ArH), 129.2 (3 × ArH & Ar), 128.9 (2 × ArH), 128.6 (pyrrole), 127.1 (2 × ArH), 124.5 (2 × ArH), 119.2 (pyrrole CH), 117.9 (Ar), 116.9 (pyrrole), 21.2 (CH_3), 21.1 (CH_3) and 20.9 (CH_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{25}N_2^+$ 353.2012; Found 353.2014.

8 Appendix

8.1 HPLC Spectra and Optimisation Data

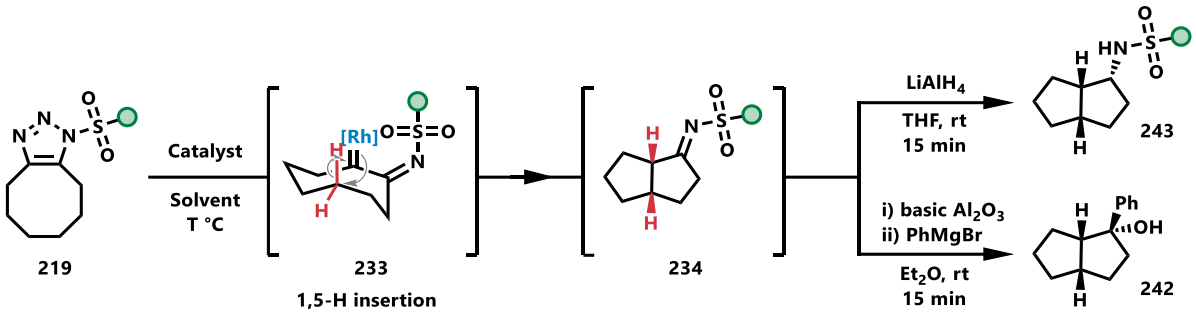


Table 1: Optimisation and *ee* data for the rhodium catalysed transannular C–H insertion reaction of triazoles **219**. All reactions carried out at 0.20 mmol scale.

Entry		Catalyst[a]	Solvent[b]	T[c]	Workup	Yield[d]	ee[e]
1	*p*Tol	$Rh_2(OAc)_4$	CH_2Cl_2	90	$LiAlH_4$	61%	0%
2	*p*Tol	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	90	$LiAlH_4$	-	−8%
3	*p*Tol	Rh_2(*S*-PTAD)$_4$	CH_2Cl_2	90	$LiAlH_4$	-	−8%
4	*p*Tol	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	90	$LiAlH_4$	29%	23%
5	*p*Tol	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	20	$LiAlH_4$	N.R.[f]	
6	*p*Tol	Rh_2(*S*-NTTL)$_4$	PhMe	20	$LiAlH_4$	N.R.[f]	
7	*p*Tol	Rh_2(*S*-NTTL)$_4$	PhMe	50	$LiAlH_4$	43%	68%
8	*p*Tol	Rh_2(*S*-NTTL)$_4$	PhMe[g]	50	$LiAlH_4$	-	69%
9	*p*Tol	Rh_2(*S*-*t*PTTL)$_4$	PhMe	50	$LiAlH_4$	-	23%
10	*p*Tol	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	50	$LiAlH_4$	36%	29%
11	*p*Tol	Rh_2(*S*-NTTL)$_4$	C_6H_6	50	$LiAlH_4$	72%	33%
12	*p*Tol	Rh_2(*S*-NTTL)$_4$	PhCl	50	$LiAlH_4$	43%	31%
13	*p*Tol	Rh_2(*S*-NTTL)$_4$	*t*BuOMe	50	$LiAlH_4$	-	46%
14	*p*Tol	Rh_2(*S*-NTTL)$_4$	cyclohexane	50	$LiAlH_4$	-	71%
15	*p*Tol	Rh_2(*S*-NTTL)$_4$	C_6F_6	50	$LiAlH_4$	72%	93%
16	*p*Tol	Rh_2(*S*-NTTL)$_4$	nC_7F_{17}	50	$LiAlH_4$	insoluble[i]	
18	$pNO_2C_6H_4$	Rh_2(*S*-NTTL)$_4$	PhMe	50	$LiAlH_4$	-	58%
19	$pNO_2C_6H_4$	Rh_2(*S*-*t*PTTL)$_4$	PhMe	50	$LiAlH_4$	-	47%
20	$pMeOC_6H_4$	Rh_2(*S*-NTTL)$_4$	PhMe	50	$LiAlH_4$	36%	24%
21	$pPhC_6H_4$	Rh_2(*S*-NTTL)$_4$	PhMe	50	$LiAlH_4$	53%	35%
22	Me	Rh_2(*S*-NTTL)$_4$	PhMe	50	Hydrolysis/Grignard	80%	32%
23	2,4,6-(iPr)$_3C_6H_2$	Rh_2(*S*-NTTL)$_4$	PhMe	50	Hydrolysis/Grignard	64%	12%
24	Dansyl	Rh_2(*S*-NTTL)$_4$	PhMe	50	Hydrolysis/Grignard	17%	9%
25	$pNO_2C_6H_4$	Rh_2(*S*-NTTL)$_4$	PhMe	50	Hydrolysis/Grignard	57%	69%
26	$pNO_2C_6H_4$	Rh_2(*S*-NTTL)$_4$	C_6F_6	50	Hydrolysis/Grignard	**78%**	**94%**

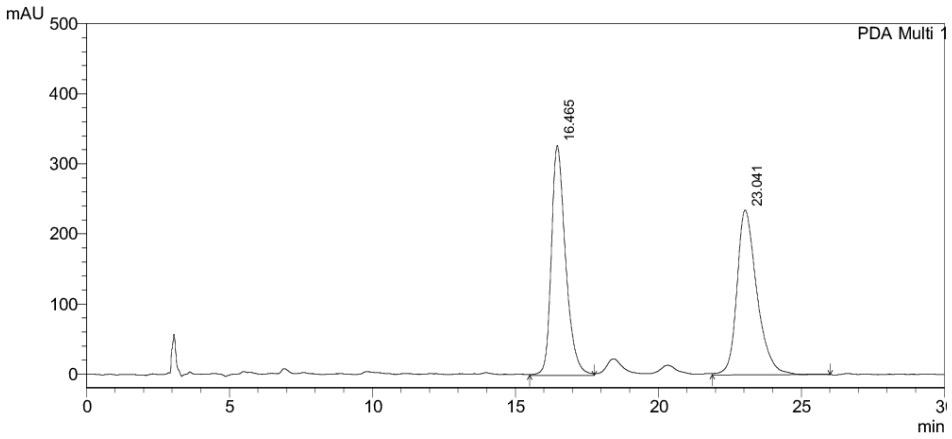
[a] 5 mol % catalyst employed; [b] 0.02 M; [c] vial sealed with Teflon cap; [d] isolated yield after purification by column chromatography. Where no yield is reported, ee was determined on crude reaction mixture; [e] determined by chiral solid phase HPLC; [f] no consumption of starting material detected; [g] syringe pump addition of triazole to solution of catalyst; [i] reagents and catalyst completely insoluble.

Entry 1 R = *p*Tol, $Rh_2(OAc)_4$, 90 °C, CH_2Cl_2, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 1nm

Peak#	Ret. Time	Height	Area	Area %
1	16.47	328290	11409010	49.944
2	23.04	235032	11434799	50.056
Total		563322	22843810	100.000

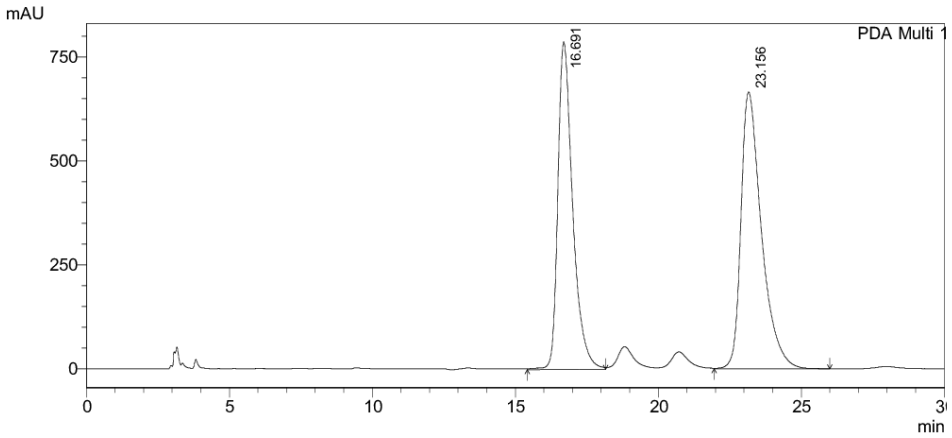


Entry 2 R = *p*Tol, $Rh_2(S\text{-DOSP})_4$, 90 °C, CH_2Cl_2, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	16.69	788109	28417142	46.030
2	23.16	666393	33318880	53.970
Total		1454502	61736021	100.000

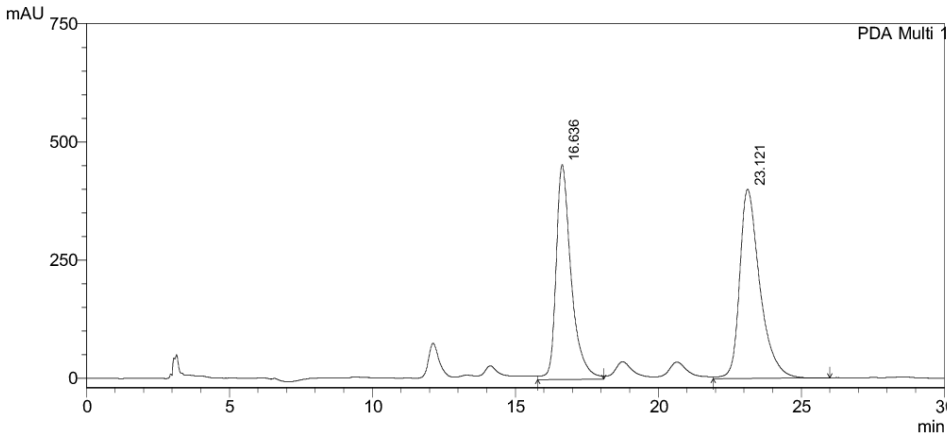


Entry 3 R = *p*Tol, Rh_2(*S*-PTAD)$_4$, 90 °C, CH_2Cl_2, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	16.64	454609	16748482	46.089
2	23.12	399983	19591168	53.911
Total		854592	36339650	100.000

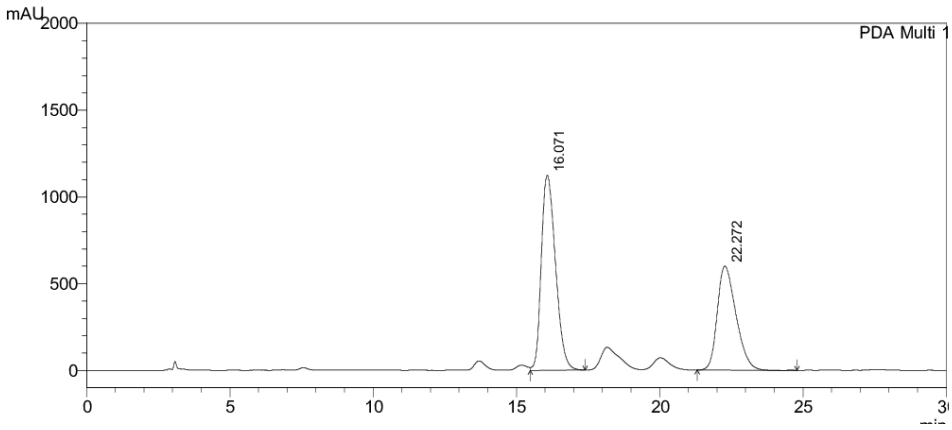


Entry 4 R = *p*Tol, Rh_2(*S*-NTTL)$_4$, 90 °C, CH_2Cl_2, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 1nm

Peak#	Ret. Time	Height	Area	Area %
1	16.07	1124451	38842213	58.805
2	22.27	600179	27209965	41.195
Total		1724630	66052177	100.000

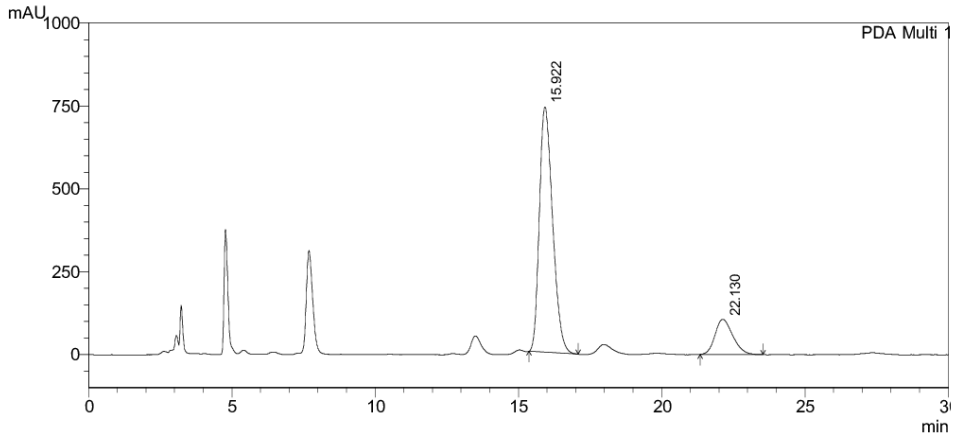


Entry 7 R = *p*Tol, Rh_2(*S*-NTTL)$_4$, 50 °C, PhMe, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 1nm

Peak#	Ret. Time	Height	Area	Area %
1	15.92	740105	23811827	83.932
2	22.13	105852	4558450	16.068
Total		845956	28370277	100.000

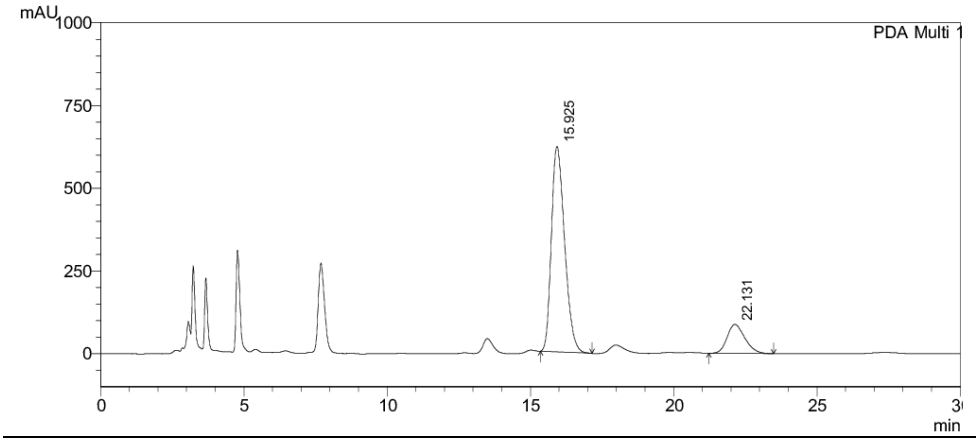


Entry 8 R = *p*Tol, Rh_2(*S*-NTTL)$_4$, 50 °C, PhMe, syringe pump, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 1nm

Peak#	Ret. Time	Height	Area	Area %
1	15.92	620753	19883161	84.265
2	22.13	87025	3712702	15.735
Total		707778	23595863	100.000

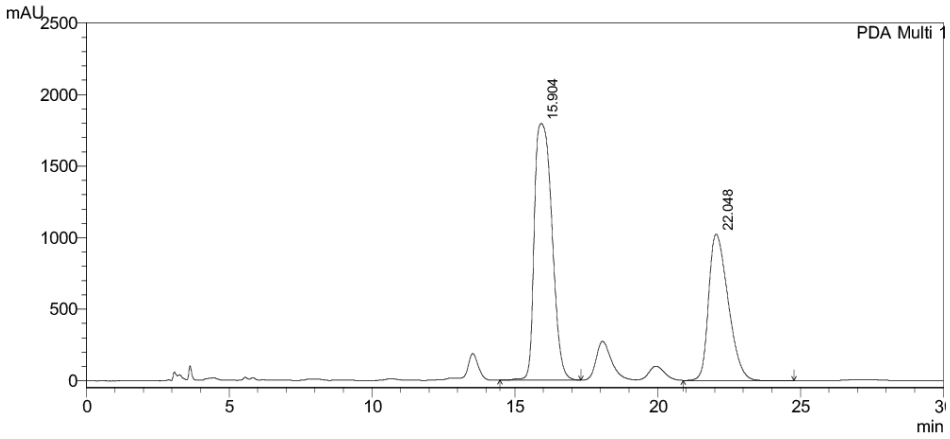


Entry 9 R = *p*Tol, Rh_2(*S*- *t*PTTL)$_4$, 50 °C, PhMe, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 1nm

Peak#	Ret. Time	Height	Area	Area %
1	15.90	1792874	76941999	61.364
2	22.05	1022704	48443898	38.636
Total		2815578	125385897	100.000

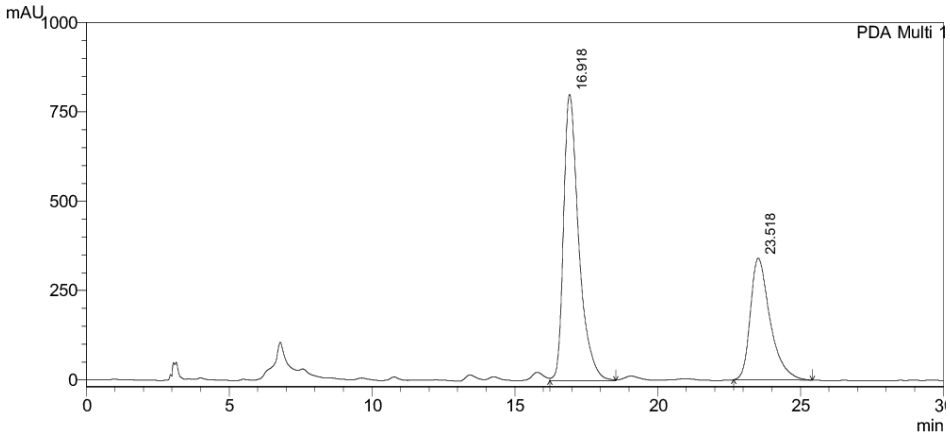


Entry 10 R = *p*Tol, Rh_2(*S*-NTTL)$_4$, 50 °C, CH_2Cl_2, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	16.92	801589	29700606	64.505
2	23.52	340451	16343243	35.495
Total		1142040	46043849	100.000

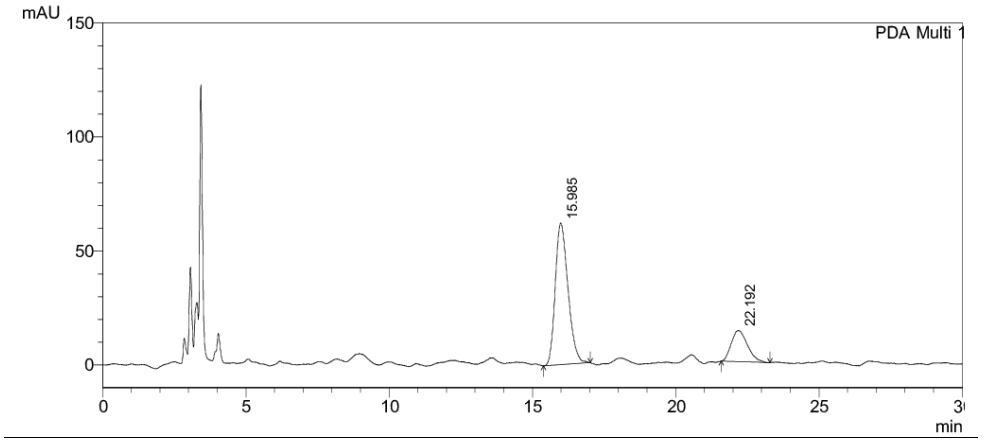


Entry 11 R = *p*Tol, Rh_2(*S*-NTTL)$_4$, 50 °C, C_6H_6, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 1nm

Peak#	Ret. Time	Height	Area	Area %
1	15.99	62129	1922935	78.178
2	22.19	13757	536742	21.822
Total		75885	2459676	100.000

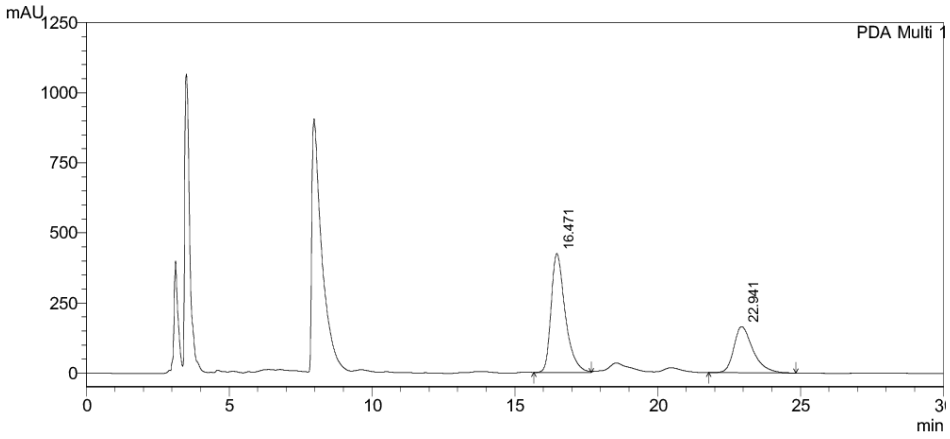


Entry 12 R = *p*Tol, Rh_2(*S*-NTTL)$_4$, 50 °C, C_6H_6, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	16.47	424241	14600490	65.499
2	22.94	165095	7690543	34.501
Total		589336	22291033	100.000

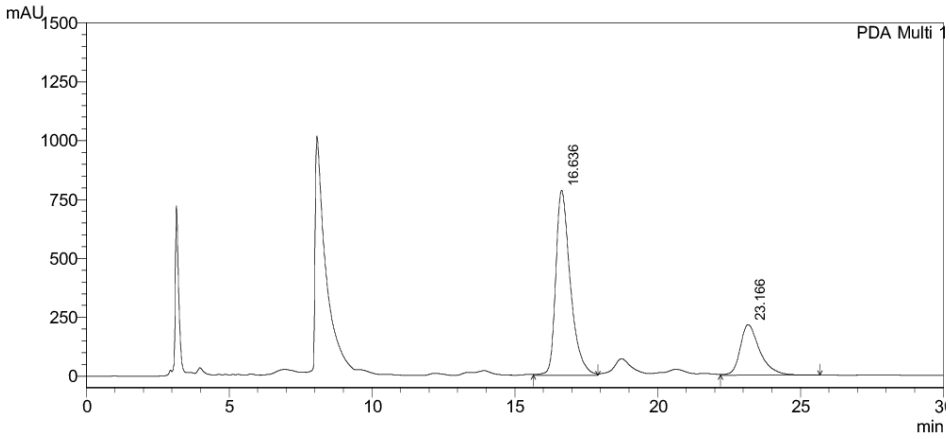


Entry 13 R = *p*Tol, Rh_2(*S*-NTTL)$_4$, 50 °C, *t*BuOMe, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	16.64	786182	27837788	73.225
2	23.17	214192	10178796	26.775
Total		1000374	38016583	100.000

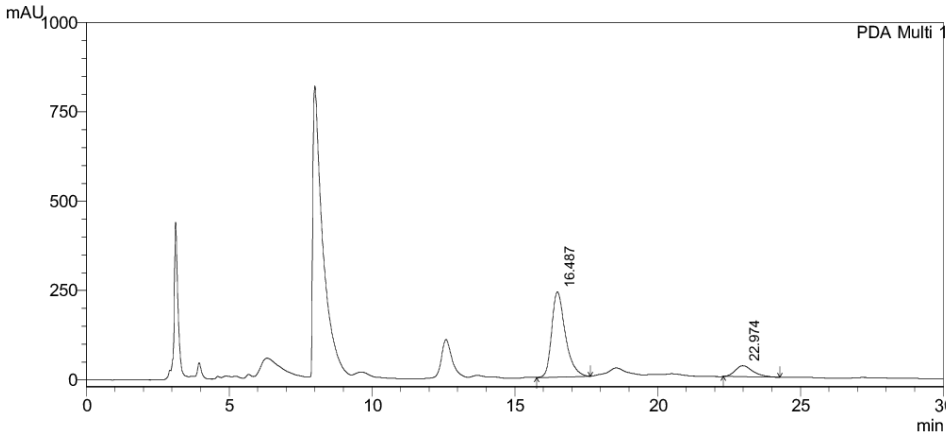


Entry 14 R = *p*Tol, Rh_2(*S*-NTTL)$_4$, 50 °C, *cy*Hex, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	16.49	239196	7946477	85.527
2	22.97	30976	1344678	14.473
Total		270171	9291155	100.000

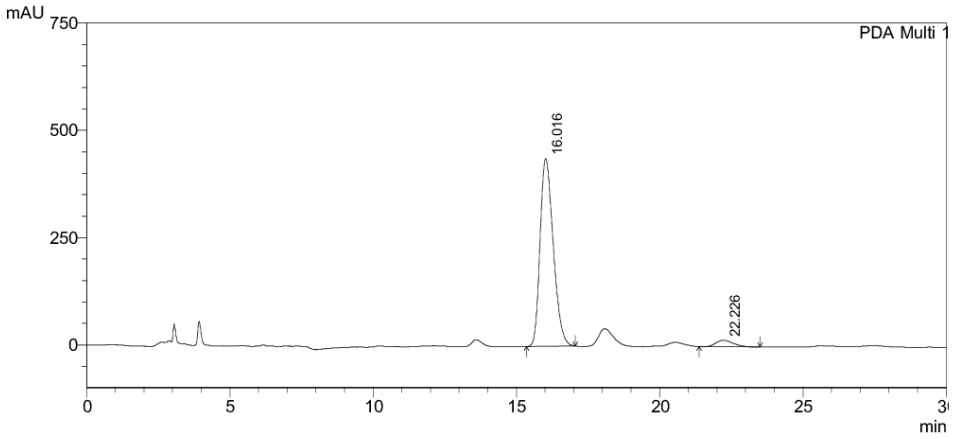


Entry 15 R = *p*Tol, Rh_2(*S*-NTTL)$_4$, 50 °C, C_6F_6, $LiAlH_4$ workup

AD-H, 7% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 1nm

Peak#	Ret. Time	Height	Area	Area %
1	16.02	436885	13975150	95.689
2	22.23	15206	629616	4.311
Total		452091	14604766	100.000

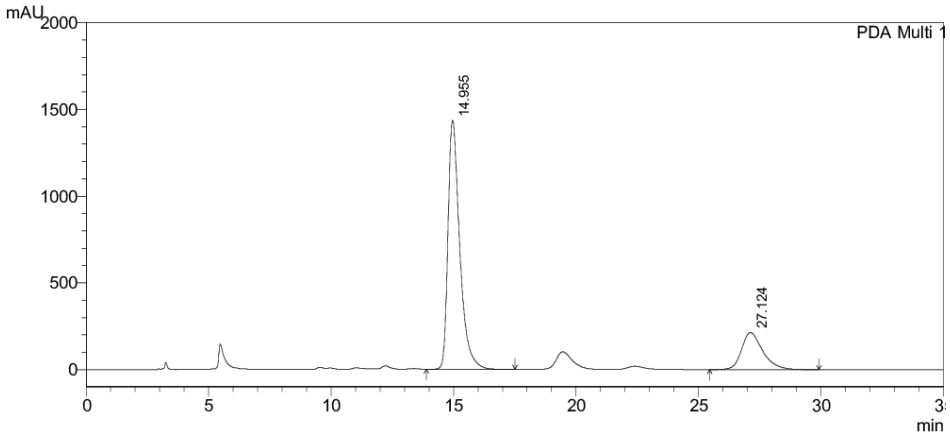


Entry 18 R = *p*$NO_2C_6H_4$, Rh_2(*S*-NTTL)$_4$, 50 °C, PhMe, $LiAlH_4$ workup

AD-H, 15% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 268nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	14.96	1436823	48007626	78.907
2	27.12	213350	12832865	21.093
Total		1650173	60840490	100.000

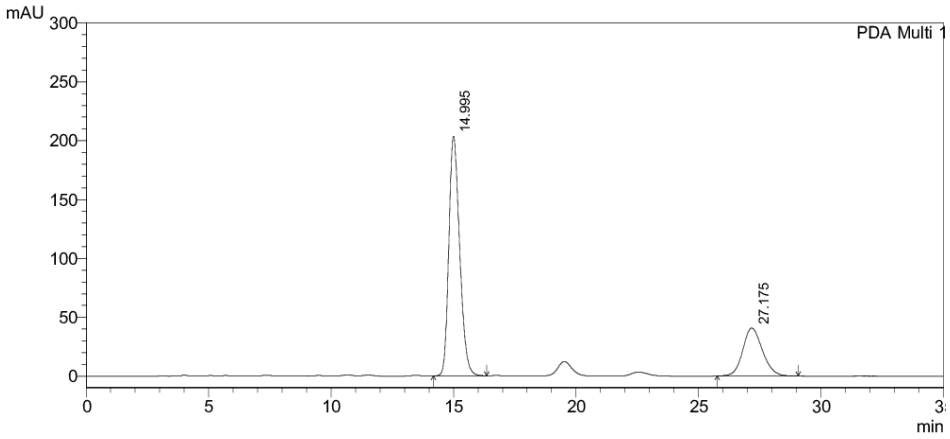


Entry 19 R = *p*$NO_2C_6H_4$, Rh_2(*S*-*t*PTTL)$_4$, 50 °C, PhMe, $LiAlH_4$ workup

AD-H, 15% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 268nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	14.99	203636	6271089	73.431
2	27.17	40759	2269075	26.569
Total		244395	8540164	100.000

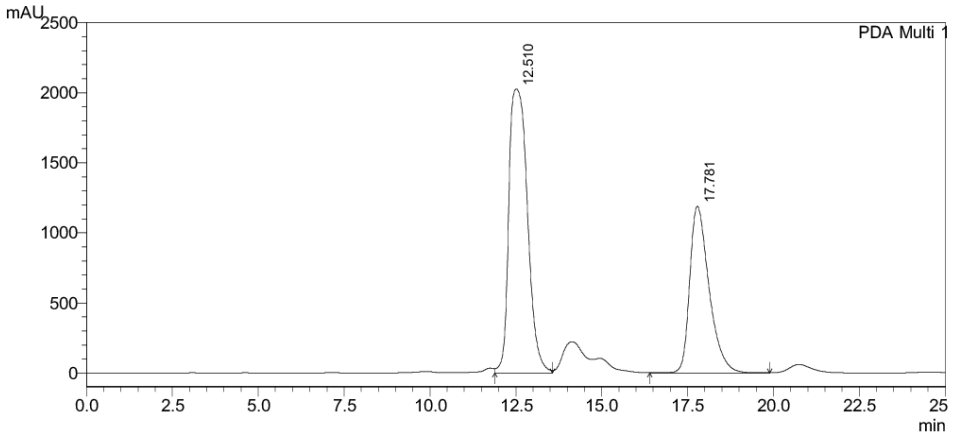


Entry 20 R = *p*$MeOC_6H_4$, Rh_2(*S*-NTTL)$_4$, 50 °C, PhMe, $LiAlH_4$ workup

AD-H, 15% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 238nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	12.51	2027105	76618292	62.133
2	17.78	1188906	46694981	37.867
Total		3216011	123313273	100.000

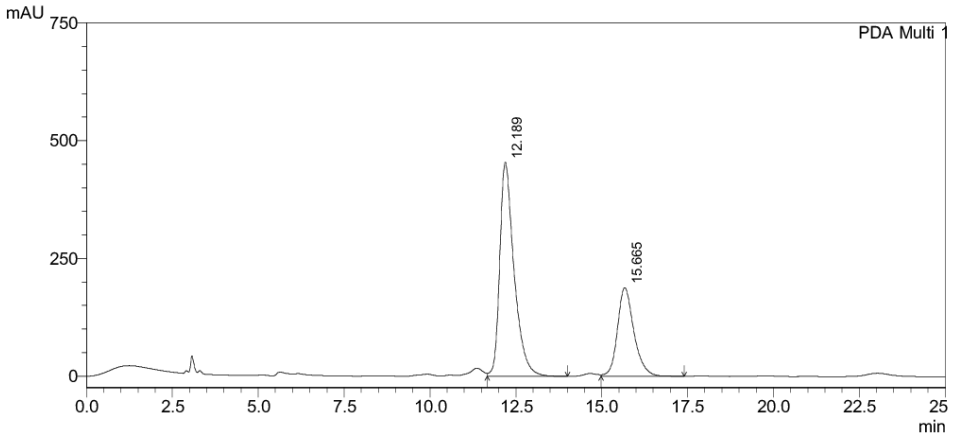


Entry 21 R = *p*PhC$_6$H$_4$, Rh$_2$(*S*-NTTL)$_4$, 50 °C, PhMe, LiAlH$_4$ workup

AD-H, 15% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 209nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	12.19	454658	13176524	67.655
2	15.67	188482	6299615	32.345
Total		643140	19476139	100.000

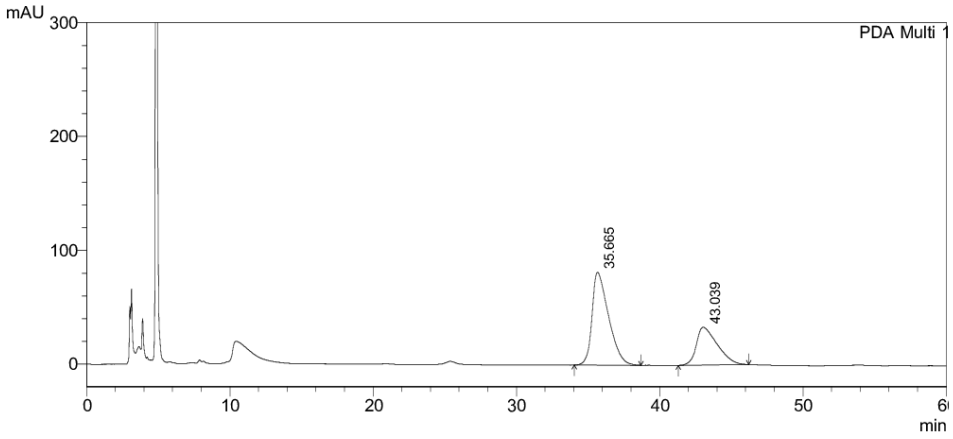


Entry 22 R = Me, Rh$_2$(*S*-NTTL)$_4$, 50 °C, PhMe, hydrolysis/Grignard workup

AD-H, 0.25% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	35.66	81513	6546925	65.913
2	43.04	33231	3385724	34.087
Total		114744	9932648	100.000

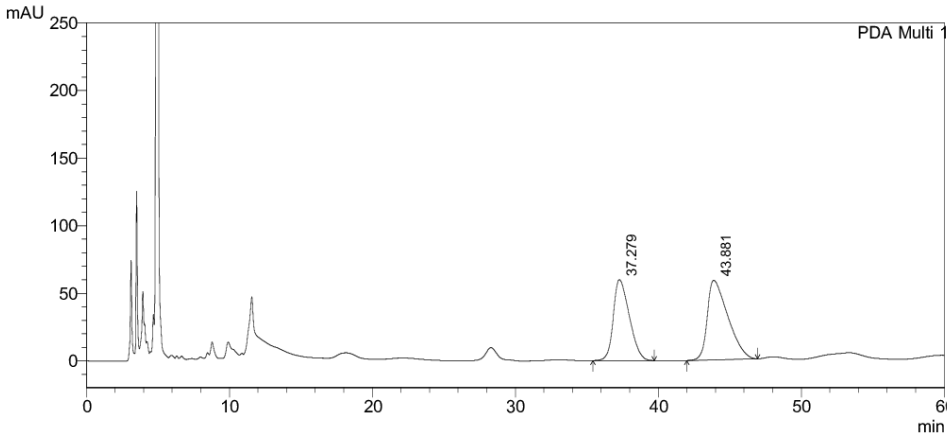


Entry 23 R = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$, Rh$_2$(*S*-NTTL)$_4$, 50 °C, PhMe, hydrolysis/Grignard workup

AD-H, 0.25% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	37.28	59780	4656926	44.181
2	43.88	58876	5883700	55.819
Total		118656	10540626	100.000

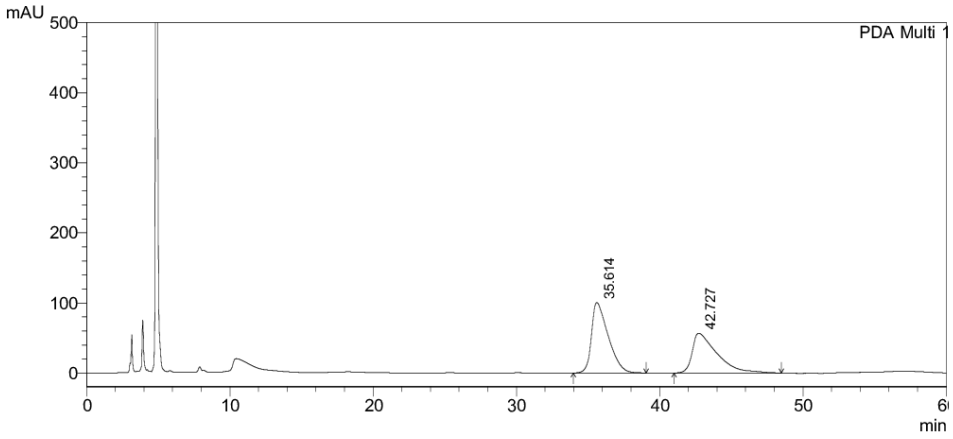


Entry 24 R = Dansyl, Rh$_2$(*S*-NTTL)$_4$, 50 °C, PhMe, hydrolysis/Grignard workup

AD-H, 0.25% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	35.61	100471	8131938	54.496
2	42.73	56826	6790281	45.504
Total		157297	14922219	100.000

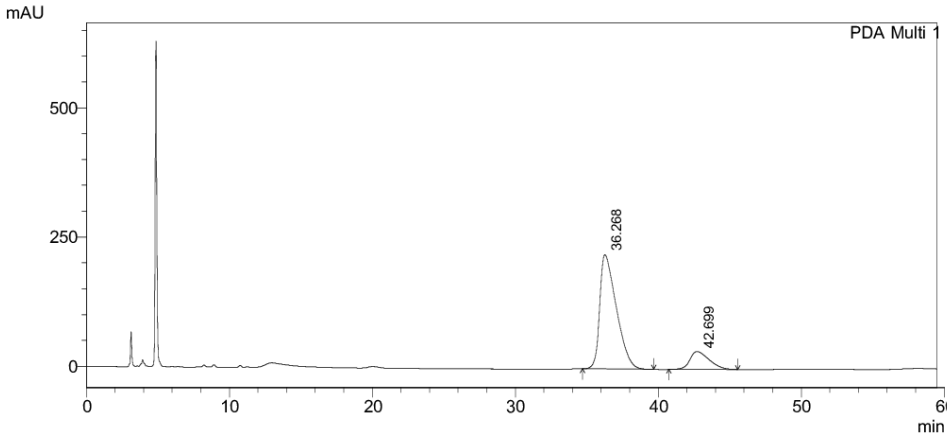


Entry 25 R = *p*$NO_2C_6H_4$, Rh_2(*S*-NTTL)$_4$, 50 °C, PhMe, hydrolysis/Grignard workup

AD-H, 0.25% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	36.27	220744	17845494	84.621
2	42.70	34549	3243124	15.379
Total		255293	21088617	100.000

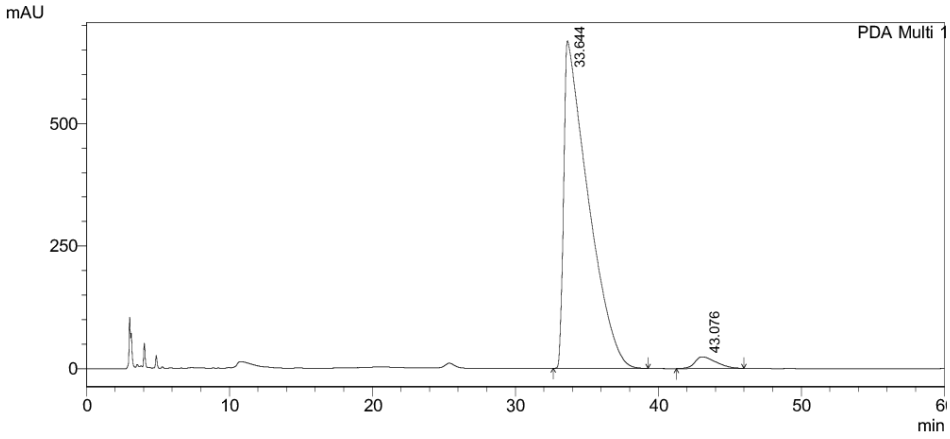


Entry 26 R = *p*$NO_2C_6H_4$, Rh_2(*S*-NTTL)$_4$, 50 °C, C_6F_6, hydrolysis/Grignard workup

AD-H, 0.25% *i*PrOH in hexane, 1 cm^3 min^{-1}

PDA Ch1 204nm 4nm

Peak#	Ret. Time	Height	Area	Area %
1	33.64	667819	79116805	97.010
2	43.08	23833	2438555	2.990
Total		691652	81555360	100.000



8.2 Optimised Structure and Thermochemical Analyses

All calculations were performed using open-source PSI4 program.[211]

Geometry optimisations and thermochemistry analysis was performed using B3LYP/6-31G(d).

Molecular orbitals were calculated using HF/6-311++G(2d,p) at B3LYP/6-31G(d) geometry.

Ground state structures were optimised and found to have zero imaginary frequencies by vibrational analysis:

- **GS1**: Methanesulfonyl azide
- **GS2**: Cyclooctyne in a chair conformation
- **GS3**: Cyclooctyne in a twist boat conformation
- **GS4**: Bicyclononyne
- **GS5**: Acetylene

Geometries were inspired by previous work by the groups of Zeng[351] and Houk.[204,205]

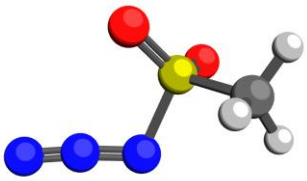
Transition structures were optimised and found to have exactly one imaginary frequency by vibrational analysis:

- **TS_{CHAIR}**: MsN3 + Cyclooctyne chair
- **TS_{TBOAT}**: MsN3 + Cyclooctyne boat
- **TS_{BCN}**: MsN3 + BCN
- **$TS_{ACETYLENE}$**: MsN3 + Acetylene

Geometries were inspired by previous work by groups of Houk[204,205] and Bickelhaupt et al.[206]

Distortion interaction analysis was performed following the work in this area by Houk et al.[204,205]

GS1



B3LYP/6-31G(D) optimised cartesian coordinates in Å

C	-1.608519319467	1.457500593759	-0.063963233043
H	-2.591326236454	1.284233387220	0.380714572510
H	-1.703330072376	1.703787214968	-1.122526158519
H	-1.066467955548	2.232920246299	0.478506732644
N	0.730021096991	0.400535623236	-0.835722057356
N	1.790949197114	0.048652886187	-0.287660921488
N	2.807257072661	-0.226759045565	0.137837070379
O	-1.393245800251	-1.114220638337	-0.699273589930
O	-0.315596877748	-0.322374532977	1.469000339776
S	-0.706036913645	-0.090337630567	0.078877676271

N1-N2 distance : 1.245 Å
N2-N3 distance : 1.136 Å
Azide N-N-N angle : 174.96°

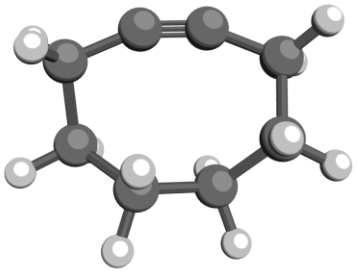
B3LYP/6-31G(D) frequency analysis

Number of imaginary frequencies: 0

E0 : -752.66557042 Ha
ZPE: -752.60487666 Ha
H : -752.59652407 Ha
S : 0.13770244 mHa/K
G : -752.63758005 Ha
evaluated at 298.15 K

HOMO-1	HOMO	LUMO	LUMO+1		
-12.434656	-11.815705	0.902765	1.685338	eV	HF/6-311++G(2D,P)

GS2



B3LYP/6-31G(D) optimised cartesian coordinates in Å

C	-1.950674577258	-0.872434863451	-0.132659300671
C	-1.854882674202	0.620417969012	0.290791614893
C	-0.698207387431	1.429617578033	-0.353182137875
C	-0.604210769791	-1.431719108537	-0.035598782290
C	0.604281019996	-1.431678020515	0.035652352377
C	0.698135403896	1.429670144360	0.353127403667
C	1.854853651130	0.620505769309	-0.290812981004
C	1.950717841297	-0.872327732409	0.132691459716
H	-2.810441636177	1.102275105372	0.042928450235
H	-2.681695085584	-1.395968343418	0.496870195418
H	-2.319706995271	-0.946365782036	-1.165443627177
H	-1.758620098866	0.666886709905	1.383247961761
H	-1.037120632674	2.472810040819	-0.389173207832
H	-0.580908227713	1.124072540978	-1.401817423593
H	0.580853087312	1.124162616689	1.401775545124
H	1.036992982379	2.472882213043	0.389074632411
H	1.758592832225	0.666931041743	-1.383271340529
H	2.319755234564	-0.946203531625	1.165477957667
H	2.681762036372	-1.395848927384	-0.496820741601
H	2.810387577134	1.102419277917	-0.042963050523

Alkyne C-C distance : 1.211 Å
Alkyne bond angles : 157.48°, 157.48°

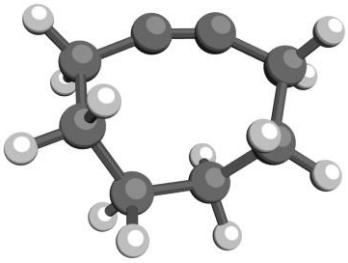
B3LYP/6-31G(D) frequency analysis

Number of imaginary frequencies: 0

E0 : -312.00018962 Ha
ZPE: -311.81936907 Ha
H : -311.81059064 Ha
S : 0.13622001 mHa/K
G : -311.85120464 Ha
evaluated at 298.15 K

HOMO-1	HOMO	LUMO	LUMO+1		
-9.745517	-9.619991	1.166634	1.320705	eV	HF/6-311++G(2D,P)

GS3



B3LYP/6-31G(D) optimised cartesian coordinates in Å

C	-2.025590917712	-0.676194969898	0.091307225017
C	-1.603076182859	0.790167385620	0.413636473282
C	-0.775376235892	-1.422796798399	-0.073982003160
C	-0.541978698868	1.357604315621	-0.570430252859
C	0.426553396729	-1.495729627069	-0.213019641813
C	0.927853462585	1.527068393118	-0.088669677215
C	1.728424888098	0.376438288651	0.571205388307
C	1.797139215932	-0.980045404047	-0.183054802379
H	-2.663262739198	-1.076961787656	0.889208913014
H	-2.623052698229	-0.701973686956	-0.830556495142
H	-2.502792684120	1.419320850035	0.398854470383
H	-1.221731633076	0.818792886505	1.441951514804
H	-0.860355522988	2.362464229806	-0.878782790481
H	-0.551809418499	0.754450948568	-1.485023758483
H	0.952913083512	2.359256126387	0.629543991025
H	1.322804823730	0.170221064232	1.569044922172
H	1.496627149088	1.880571665817	-0.961120152560
H	2.191897303748	-0.843825663348	-1.199828364908
H	2.492388649905	-1.654453420557	0.333687537985
H	2.752832484658	0.745223679162	0.724168942969

Alkyne C-C distance : 1.212 Å
Alkyne bond angles : 152.81°, 154.73°

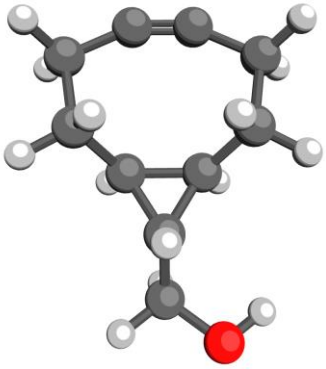
B3LYP/6-31G(D) frequency analysis

Number of imaginary frequencies: 0

E0 : -311.99515500 Ha
ZPE: -311.81408606 Ha
H : -311.80544728 Ha
S : 0.13466088 mHa/K
G : -311.84559642 Ha
evaluated at 298.15 K

HOMO-1	HOMO	LUMO	LUMO+1		
-9.773708	-9.556153	1.116538	1.299453	eV	HF/6-311++G(2D,P)

GS4



B3LYP/6-31G(D) optimised cartesian coordinates in Å

C	-1.535097805949	0.216503152613	0.780603654246
C	-1.495090093543	1.592247350513	1.512416110485
C	-0.583177128793	2.434719011952	0.735956935942
C	-0.169263588230	-0.441440948246	0.623624893310
C	0.109186941333	-1.468694381617	-0.458871679429
C	0.244048846417	2.653339920087	-0.121852450203
C	0.767282996305	0.828386259312	-1.611291291532
C	0.785648802185	-2.780881364275	-0.134939498689
C	0.872157587237	-0.163406806813	-0.458921400949
C	1.140428599355	2.290573658533	-1.221560587898
H	-2.508430457570	2.008394816913	1.578569841869
H	-2.195452973410	-0.464822382033	1.337290223612
H	-1.998249942838	0.367435601721	-0.201268965622
H	-1.140115995246	1.466284535412	2.544651523560
H	-0.667538343066	-1.554610854643	-1.219833441177
H	-0.586794161487	-3.376231200620	1.101739405570
H	-0.251051046393	0.834619363749	-2.016709540497
H	0.291822242378	-0.667666194936	1.588307389820
H	1.033395614403	2.947897589999	-2.093820310176
H	1.236828759874	-3.216391703341	-1.033506361872
H	1.428297890856	0.493937387495	-2.423986640385
H	1.601612453019	-2.605739035855	0.587565164217
H	1.892651806174	-0.241947999357	-0.078830560910
H	2.193451540313	2.347571154581	-0.913147757673
O	-0.122946256015	-3.767565082668	0.344530139492

Alkyne C-C distance : 1.212 Å
Alkyne bond angles : 154.75°, 154.81°

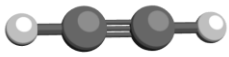
B3LYP/6-31G(D) frequency analysis

Number of imaginary frequencies: 0

E0 : -464.59664904 Ha
ZPE: -464.37720029 Ha
H : -464.36559127 Ha
S : 0.15892050 mHa/K
G : -464.41297342 Ha
evaluated at 298.15 K

HOMO-1	HOMO	LUMO	LUMO+1		
-9.829246	-9.688074	1.037652	1.160974	eV	HF/6-311++G(2D,P)

GS5



B3LYP/6-31G(D) optimised cartesian coordinates in Å

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  C  -0.000000010212  0.000000044425 -0.602484980775
  C  -0.000000010212  0.000000044425  0.602484961555
  H  -0.000009075862  0.000000896472 -1.669106428570
  H   0.000009319050 -0.000001954388  1.669106657424

  Alkyne C-C distance    :  1.205 Å
  Alkyne bond angles     : 180.00°, 180.00°
```

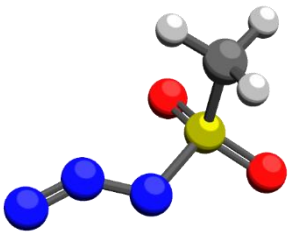
B3LYP/6-31G(D) frequency analysis

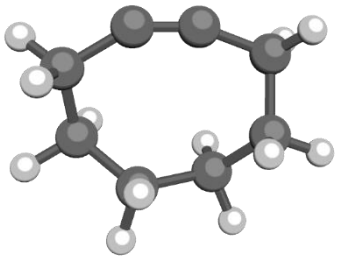
```
  Number of imaginary frequencies: 0

   E0 :     -77.32563186 Ha
   ZPE:     -77.30021899 Ha
   H  :     -77.29654192 Ha
   S  :       0.07809315 mHa/K
   G  :     -77.31982539 Ha
  evaluated at 298.15 K

      HOMO-1         HOMO         LUMO       LUMO+1
  -11.168183   -11.168183     1.141436     1.277385  eV   HF/6-311++G(2D,P)
```

TS_{CHAIR}





B3LYP/6-31G(D) optimised cartesian coordinates in Å

C	-3.148356606691	2.579235149662	-0.629254936799
C	-3.027257989458	1.046133973733	-0.481679825435
C	-2.489050159376	3.431648407520	0.483020338988
C	-1.612112977838	0.657849554129	-0.330011101966
C	-1.001734129975	3.866989184529	0.309246065630
C	-0.456104384370	0.974430838826	-0.040441426088
C	0.090117519094	3.083299470390	1.076267803709
C	0.659987310033	1.826462452254	0.370388697199
C	2.676426564695	-2.785659093179	-1.312864560995
H	-4.220091931329	2.816298001876	-0.665577489478
H	-3.588451562976	0.706613721437	0.400176913716
H	-3.486082475129	0.548420341769	-1.344059877114
H	-3.079243116013	4.353741915128	0.553211334665
H	-2.736038842590	2.874177337299	-1.603212644586
H	-2.615515008982	2.931194267156	1.453487257949
H	-0.934373145855	4.905502230570	0.656457264528
H	-0.749004009673	3.900597074728	-0.760118784000
H	-0.300024319340	2.788748259424	2.058998297846
H	0.938486660294	3.752844146722	1.269023735382
H	1.242813376475	2.123138717616	-0.512461867438
H	1.350608128839	1.297673465552	1.035015464400
H	1.958406934123	-3.439511933723	-1.811274383124
H	2.957848476371	-1.946364012920	-1.950348244872
H	3.560306365280	-3.352539616321	-1.010371192347
N	-1.597783731448	-1.491540562685	-0.772255161078
N	-0.475011006244	-1.752813705039	-0.628079762228
N	0.635833790780	-1.164113703577	-0.412163200442
O	1.413984488191	-3.262291132365	0.975516552379
O	2.833894298629	-1.148992777790	0.777690933893
S	1.928267026432	-2.137016393881	0.195501909826

N1-N2 distance	:	1.276 Å
N2-N3 distance	:	1.162 Å
Alkyne C-C distance	:	1.233 Å
N1-C distance	:	2.430 Å
N3-C distance	:	2.194 Å
Azide N-N-N angle	:	139.36°
Alkyne bond angles	:	158.54°, 148.86°

```
B3LYP/6-31G(D) frequency analysis

  Number of imaginary frequencies: 1

   E0 :   -1064.65235543 Ha
   ZPE:   -1064.41014712 Ha
   H  :   -1064.39312311 Ha
   S  :       0.21064736 mHa/K
   G  :   -1064.45592762 Ha
  evaluated at 298.15 K

  Difference from GS1 and GS2 ground states
  ΔE0 :       0.01340461 Ha          8.411 kcal/mol
  ΔH  :       0.01399160 Ha          8.780 kcal/mol
  ΔS  :      -0.06327509 mHa/K      -39.705 cal/mol/K
  ΔG  :       0.03285707 Ha         20.618 kcal/mol
  evaluated at 298.15 K

Azide at transition state geometry

   E0 :    -752.63732419 Ha   B3LYP/6-31G(D)
   E0 :    -749.98581599 Ha   HF/6-311++G(2D,P)

  ΔEdist from GS1 ground state   17.72458 kcal/mol    B3LYP/6-31G(D)

      HOMO-1         HOMO         LUMO       LUMO+1
  -12.326763   -12.053560     0.085689     0.906194  eV   HF/6-311++G(2D,P)

Alkyne at transition state geometry

   E0 :    -311.99750562 Ha   B3LYP/6-31G(D)
   E0 :    -309.84573460 Ha   HF/6-311++G(2D,P)

  ΔEdist from GS2 ground state    1.68432 kcal/mol    B3LYP/6-31G(D)

      HOMO-1         HOMO         LUMO       LUMO+1
   -9.627120    -9.532969     1.156756     1.320542  eV   HF/6-311++G(2D,P)

HF/6-311++G(2D,P) Ground State HOMO - LUMO gaps (at distorted geometry)
  HOMO Alkyne GS2 - LUMO Azide GS1 :   10.523 eV  (   9.619 eV)
  HOMO Azide GS1 - LUMO Alkyne GS2 :   12.982 eV  (  13.210 eV)

B3LYP/6-31G(D) distortion-interaction analysis
  ΣΔEdist:                  19.40890 kcal/mol
  Eint = ΣΔE0 - ΣΔEdist:   -10.99737 kcal/mol
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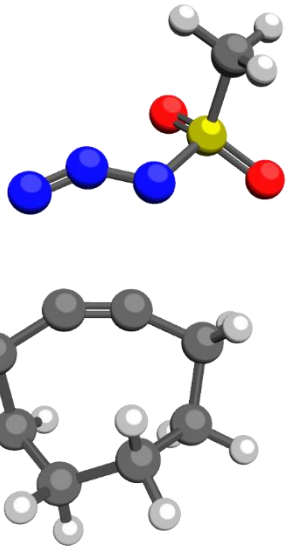
TS$_{TBOAT}$



B3LYP/6-31G(D) optimised cartesian coordinates in Å

C	-3.814327507983	-1.394750966378	0.206579938031
C	-3.777672091143	1.133399924495	1.034614290293
C	-3.702471547481	-0.378156122576	1.375451188955
C	-2.882149588257	1.741515674558	-0.068353088188
C	-2.481432973129	-2.125329207266	-0.106017787976
C	-1.416133753937	-1.113370163731	-0.259590602739
C	-1.351788479386	1.507327834185	0.042249168121
C	-1.111488205961	0.075576891993	-0.153116995268
C	3.749053797688	0.657384563334	-1.581064872580
H	-4.813778930246	1.370385797590	0.754127177046
H	-4.571003011876	-2.154737234510	0.439022247531
H	-4.516943263027	-0.566593564616	2.086521197250
H	-4.157379732861	-0.890372002702	-0.705597917494
H	-3.594000415330	1.680456857640	1.970184636637
H	-3.203318855001	1.376022468928	-1.051719501562
H	-3.058537752500	2.825653671662	-0.072507441254
H	-2.779057834212	-0.575568781357	1.932064266842
H	-2.580392960345	-2.746139722477	-1.004835205124
H	-2.222572478770	11-2.809501192303	0.713078709417
H	-0.966844094477	1.835139236120	1.016695871317
H	-0.830256945033	2.106981835527	-0.711823729114
H	3.176999496128	1.211270441796	-2.326678033809
H	3.941235286717	-0.366198941442	-1.907901509094
H	4.689391758878	1.168332110708	-1.360121425226
N	0.498002835340	-2.244210341872	-0.570478812182
N	1.254441713852	-1.366453830628	-0.562359133440
N	1.306395076643	-0.094975093052	-0.547052659884
O	2.418688100520	1.978184029290	0.306597887972
O	3.500196134224	-0.258245691303	0.899886072293
S	2.803747391511	0.614431486754	-0.044779829900

N1-N2 distance	:	1.273 Å
N2-N3 distance	:	1.159 Å
Alkyne C-C distance	:	1.232 Å
N1-C distance	:	2.456 Å
N3-C distance	:	2.245 Å
Azide N-N-N angle	:	141.59°

```
  Alkyne bond angles     : 156.10°, 146.14°

B3LYP/6-31G(D) frequency analysis

  Number of imaginary frequencies: 1

   E0 :   -1064.64950649 Ha
   ZPE:   -1064.40710624 Ha
   H  :   -1064.39020432 Ha
   S  :       0.20950529 mHa/K
   G  :   -1064.45266832 Ha
  evaluated at 298.15 K

  Difference from GS1 and GS3 ground states
  ΔE0 :       0.01121893 Ha          7.040 kcal/mol
  ΔH  :       0.01176703 Ha          7.384 kcal/mol
  ΔS  :      -0.06285803 mHa/K      -39.444 cal/mol/K
  ΔG  :       0.03050815 Ha         19.144 kcal/mol
  evaluated at 298.15 K

Azide at transition state geometry

   E0 :    -752.64080643 Ha   B3LYP/6-31G(D)
   E0 :    -749.98971914 Ha   HF/6-311++G(2D,P)

  ΔEdist from GS1 ground state   15.53946 kcal/mol    B3LYP/6-31G(D)

      HOMO-1         HOMO         LUMO       LUMO+1
  -12.333103   -12.055247     0.222562     0.902221  eV   HF/6-311++G(2D,P)

Alkyne at transition state geometry

   E0 :    -311.99330244 Ha   B3LYP/6-31G(D)
   E0 :    -309.84062101 Ha   HF/6-311++G(2D,P)

  ΔEdist from GS3 ground state    1.16301 kcal/mol    B3LYP/6-31G(D)

      HOMO-1         HOMO         LUMO       LUMO+1
   -9.659502    -9.487526     1.106361     1.290718  eV   HF/6-311++G(2D,P)

HF/6-311++G(2D,P) Ground State HOMO - LUMO gaps (at distorted geometry)
  HOMO Alkyne GS3 - LUMO Azide GS1 :   10.459 eV  (   9.710 eV)
  HOMO Azide GS1 - LUMO Alkyne GS3 :   12.932 eV  (  13.162 eV)

B3LYP/6-31G(D) distortion-interaction analysis
  ΣΔEdist:                  16.70248 kcal/mol
  Eint = ΣΔE0 - ΣΔEdist:    -9.66205 kcal/mol
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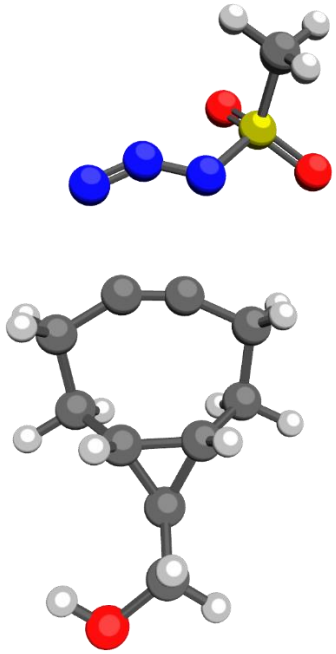
TS_{BCN}



B3LYP/6-31G(D) optimised cartesian coordinates in Å

C	-2.247992867865	-2.329819928318	0.473595801012
C	-2.225378921772	-0.975393520781	1.228386976518
C	-1.314435320509	-0.050404167537	0.525828796285
C	-0.884708812114	-2.996891818907	0.359928275826
C	-0.589976688493	-4.035553189293	-0.706674011804
C	-0.475933351005	0.111278248556	-0.362243315560
C	0.018632448803	-1.734496275492	-1.865216866559
C	0.100645841965	-5.334317772490	-0.357955522202
C	0.159457766353	-2.723702595477	-0.717582262738
C	0.387482850937	-0.273910288600	-1.481367214020
C	0.930684892882	4.979840157129	-0.628221318372
H	-3.239969480026	-0.563366833268	1.291938650225
H	-2.934979175975	-3.010080398026	0.997427602276
H	-2.675992095206	-2.166667287576	-0.522587027848
H	-1.887878668591	-1.118035855367	2.263736269282
H	-1.360150569986	-4.142564339906	-1.471445162266
H	-1.263236766879	-5.938461352805	0.885175673036
H	-1.006253794830	-1.744909859526	-2.254472793634
H	-0.439765122501	-3.206997484129	1.335402769303
H	0.217201708411	5.409019266130	0.077583233876
H	0.250614476378	0.388242966623	-2.343851802959
H	0.464453773159	4.785272019212	-1.595033480134
H	0.565056841039	-5.775254920689	-1.246909696024
H	0.669733685999	-2.051555344051	-2.691553671101
H	0.907941103203	-5.139147586694	0.368860500046
H	1.182419021155	-2.781752055261	-0.341922148491
H	1.444315298309	-0.196798431537	-1.198227515620
H	1.794905266914	5.638662943396	-0.743165551481
N	-1.392235416506	1.872245767882	1.678430565409
N	-0.595913643699	2.482983128244	1.098749694802
N	0.124012312279	2.432774869365	0.049707731777
O	-0.799746381418	-6.325861945347	0.125781855449
O	2.026160978892	3.656157258977	1.399023371770
O	2.382619721070	2.777779527532	-0.972582276529
S	1.546490775216	3.420560863016	0.037709971608

```
  N1-N2 distance         :  1.273 Å
  N2-N3 distance         :  1.159 Å
  Alkyne C-C distance    :  1.232 Å
  N1-C distance          :  2.433 Å
  N3-C distance          :  2.243 Å
  Azide N-N-N angle      : 141.24°
  Alkyne bond angles     : 156.52°, 147.70°

B3LYP/6-31G(D) frequency analysis

  Number of imaginary frequencies: 1

   E0 :   -1217.25074867 Ha
   ZPE:   -1216.96997305 Ha
   H  :   -1216.95008539 Ha
   S  :       0.23481139 mHa/K
   G  :   -1217.02009441 Ha
  evaluated at 298.15 K

  Difference from GS1 and GS4 ground states
  ΔE0 :       0.01147079 Ha          7.198 kcal/mol
  ΔH  :       0.01202995 Ha          7.549 kcal/mol
  ΔS  :      -0.06181155 mHa/K      -38.787 cal/mol/K
  ΔG  :       0.03045906 Ha         19.113 kcal/mol
  evaluated at 298.15 K

Azide at transition state geometry

   E0 :    -752.64011816 Ha   B3LYP/6-31G(D)
   E0 :    -749.98884605 Ha   HF/6-311++G(2D,P)

  ΔEdist from GS1 ground state   15.97136 kcal/mol    B3LYP/6-31G(D)

      HOMO-1         HOMO         LUMO       LUMO+1
  -12.338572   -12.028199     0.216439     0.906031  eV   HF/6-311++G(2D,P)

Alkyne at transition state geometry

   E0 :    -464.59471048 Ha   B3LYP/6-31G(D)
   E0 :    -461.56845666 Ha   HF/6-311++G(2D,P)

  ΔEdist from GS4 ground state    1.21644 kcal/mol    B3LYP/6-31G(D)

      HOMO-1         HOMO         LUMO       LUMO+1
   -9.726550    -9.615337     1.033380     1.152457  eV   HF/6-311++G(2D,P)

HF/6-311++G(2D,P) Ground State HOMO - LUMO gaps (at distorted geometry)
  HOMO Alkyne GS4 - LUMO Azide GS1 :   10.591 eV  (   9.832 eV)
  HOMO Azide GS1 - LUMO Alkyne GS4 :   12.853 eV  (  13.062 eV)

B3LYP/6-31G(D) distortion-interaction analysis
  ΣΔEdist:                  17.18780 kcal/mol
  Eint = ΣΔE0 - ΣΔEdist:    -9.98987 kcal/mol
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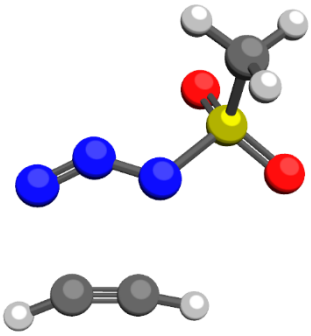
TS$_{ACETYLENE}$



B3LYP/6-31G(D) optimised cartesian coordinates in Å

C	-2.739635483330	0.775690313641	1.293251677467
C	-1.845072207042	1.538666465355	0.923791422009
C	1.409303265664	-0.516354327130	-2.056292985287
H	-3.652576283571	0.476594525023	1.761638671629
H	-1.179930526456	2.342842462708	0.698867336253
H	0.912993045703	0.211438887901	-2.699568394561
H	0.980392971178	-1.512717313123	-2.177247268723
H	2.483652133035	-0.537796547430	-2.255314883106
N	-2.172692392396	-1.179621990615	0.666267398821
N	-1.159427975084	-0.937588718638	0.140207201235
N	-0.516342897870	0.115053009108	-0.189188468793
O	1.627225503708	1.392971381461	-0.211176310430
O	1.737206309212	-1.050994529889	0.525481693670
S	1.208567381609	0.000075350137	-0.340672719257

N1-N2 distance	:	1.277 Å
N2-N3 distance	:	1.167 Å
Alkyne C-C distance	:	1.232 Å
N1-C distance	:	2.243 Å
N3-C distance	:	2.130 Å
Azide N-N-N angle	:	136.43°
Alkyne bond angles	:	169.03°, 157.61°

B3LYP/6-31G(D) frequency analysis

Number of imaginary frequencies: 1

E0 :	-829.96554018	Ha
ZPE:	-829.87630716	Ha
H :	-829.86552540	Ha
S :	0.15716510	mHa/K
G :	-829.91238418	Ha

evaluated at 298.15 K

Difference from GS1 and GS5 ground states

ΔE0 :	0.02566210	Ha	16.103 kcal/mol
ΔH :	0.02754059	Ha	17.282 kcal/mol
ΔS :	-0.05863049	mHa/K	-36.791 cal/mol/K
ΔG :	0.04502126	Ha	28.251 kcal/mol

evaluated at 298.15 K

Azide at transition state geometry

E0 :	-752.63114165 Ha	B3LYP/6-31G(D)
E0 :	-749.97767517 Ha	HF/6-311++G(2D,P)

```
  ΔEdist from GS1 ground state   21.60414 kcal/mol    B3LYP/6-31G(D)

      HOMO-1         HOMO         LUMO       LUMO+1
  -12.268068   -11.929204    -0.049389     0.907418  eV   HF/6-311++G(2D,P)

Alkyne at transition state geometry

   E0 :     -77.31705545 Ha   B3LYP/6-31G(D)
   E0 :     -76.80371615 Ha   HF/6-311++G(2D,P)

  ΔEdist from GS5 ground state    5.38172 kcal/mol    B3LYP/6-31G(D)

      HOMO-1         HOMO         LUMO       LUMO+1
  -11.026657   -11.008153     1.179913     1.367672  eV   HF/6-311++G(2D,P)

HF/6-311++G(2D,P) Ground State HOMO - LUMO gaps (at distorted geometry)
  HOMO Alkyne GS5 - LUMO Azide GS1 :   12.071 eV  (  10.959 eV)
  HOMO Azide GS1 - LUMO Alkyne GS5 :   12.957 eV  (  13.109 eV)

B3LYP/6-31G(D) distortion-interaction analysis
  ΣΔEdist:                  26.98587 kcal/mol
  Eint = ΣΔE0 - ΣΔEdist:   -10.88284 kcal/mol
```

8.3 Reaction rate determination by IR

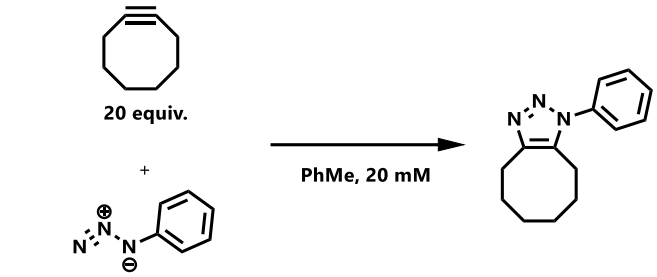
General procedure for the determination of rate constants by IR

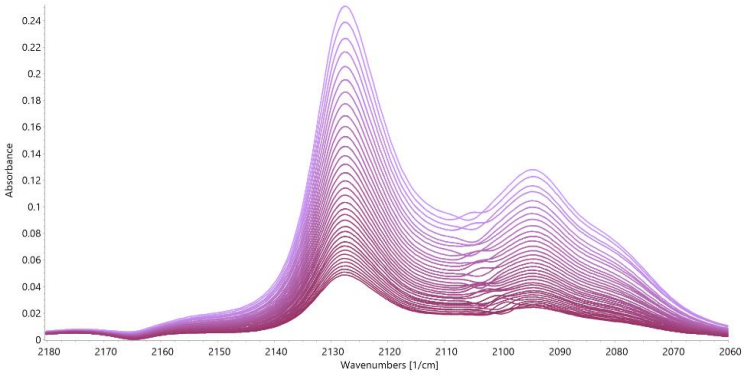
A solution of azide (600 µL, 40 mM) in PhMe and a solution of cyclooctyne (600 µL, 400 mM) in PhMe were mixed and quickly transferred to an IR cell (100 µL, BaF_2). IR spectra were recorded at pre-set time intervals and the rate of reaction was determined by measuring the decrease in integral of the azide stretching frequency around 2130 cm^{-1} until the integral had decreased by approximately 60% except for during the temperature variation where the data points were from approximately t = 0 to t = 60 to ensure the temperature remained constant. The second order rate constants were determined from the integrated rate equation:

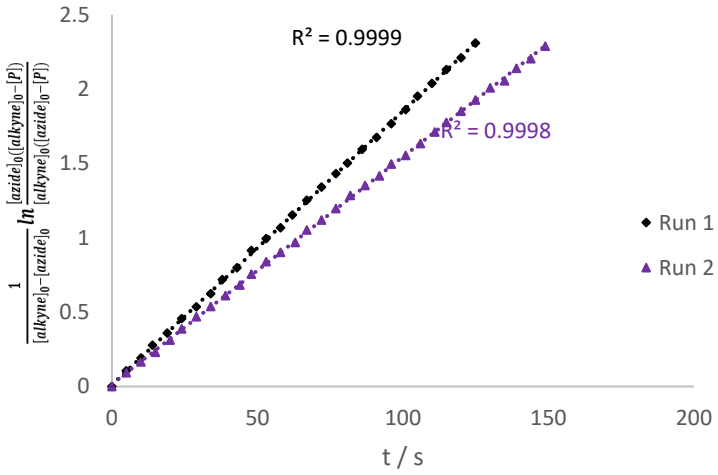
$$kt = \frac{1}{[alkyne]_0 - [azide]_0} ln \frac{[azide]_0([alkyne]_0 - [P])}{[alkyne]_0([azide]_0 - [P])}$$

k = second order rate constant ($M^{-1}s^{-1}$), t = reaction time in seconds, $[azide]_0$ = initial concentration of azide (M), $[alkyne]_0$ = initial concentration of alkyne (M), and [P] = concentration of triazole product (M). From a plot of *kt vs t*, the second order rate constant was given by the gradient. Where possible, all rate experiments were performed *in duplo*.

The analysis of IR spectra was carried out using Spectragryph software version 1.2.15, developed by F. Menges: http://www.effemm2.de/spectragryph/



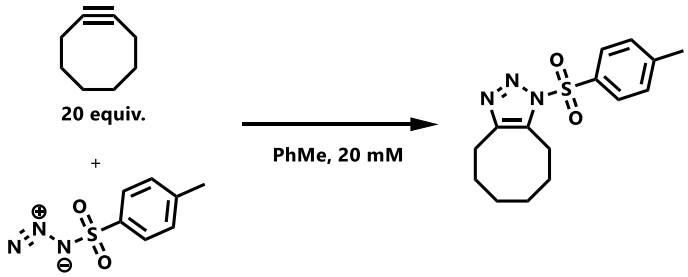


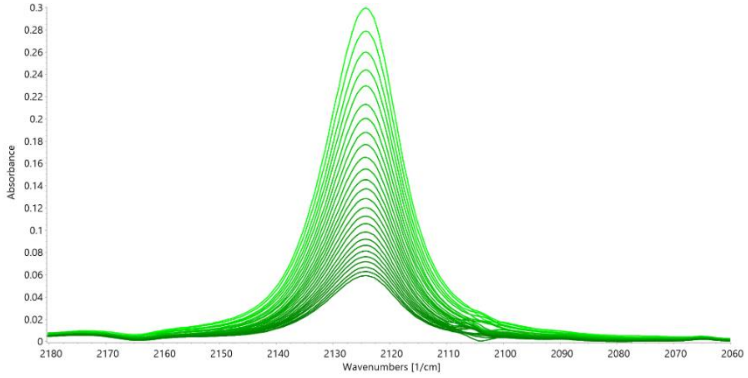


t (s)	integral
0	1.000
5	0.963
10	0.936
15	0.912
20	0.883
24	0.857
29	0.829
34	0.807
39	0.784
44	0.762
48	0.741
53	0.716
58	0.699
63	0.681
67	0.659
72	0.641
77	0.623
82	0.601
87	0.586
92	0.571
96	0.554
101	0.541
106	0.524
111	0.509
115	0.496
120	0.482
125	0.468
130	0.453
135	0.445
139	0.431
144	0.420
149	0.407

t (s)	integral
0	1.000
5	0.959
10	0.926
14	0.895
19	0.866
24	0.834
29	0.808
34	0.780
38	0.751
43	0.728
48	0.696
53	0.674
58	0.655
62	0.633
67	0.609
72	0.588
77	0.568
81	0.552
86	0.533
91	0.516
96	0.498
101	0.480
105	0.463
110	0.448
115	0.432
120	0.419
125	0.403

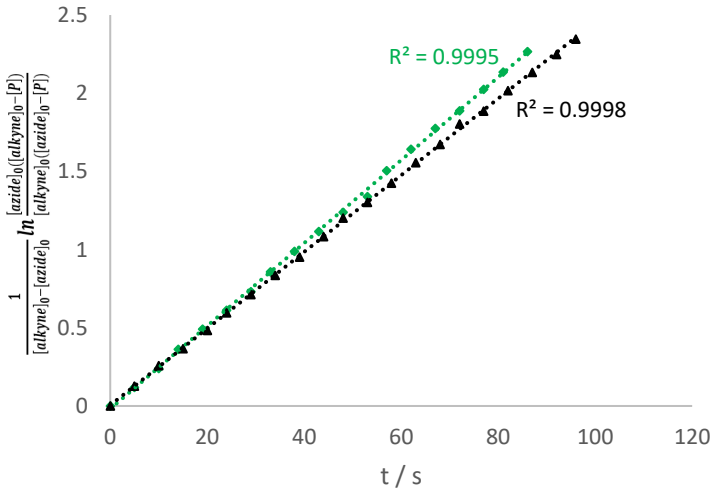
Integration range = 2170–2070 cm^{-1}



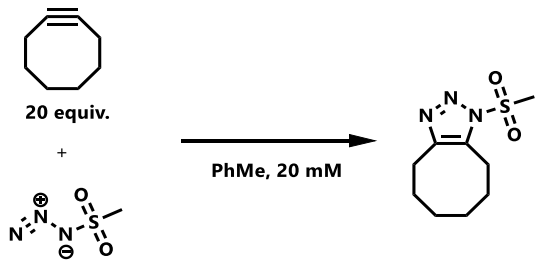


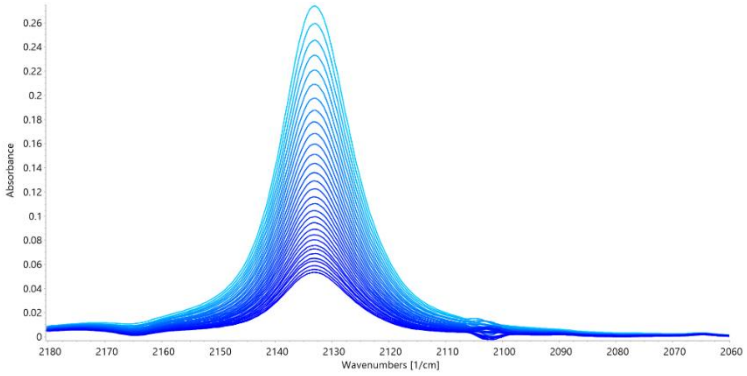
t (s)	integral
0	1.000
5	0.954
10	0.909
14	0.866
19	0.822
24	0.784
29	0.748
33	0.711
38	0.676
43	0.643
48	0.613
53	0.589
57	0.552
62	0.523
67	0.497
72	0.475
77	0.451
81	0.432
86	0.410

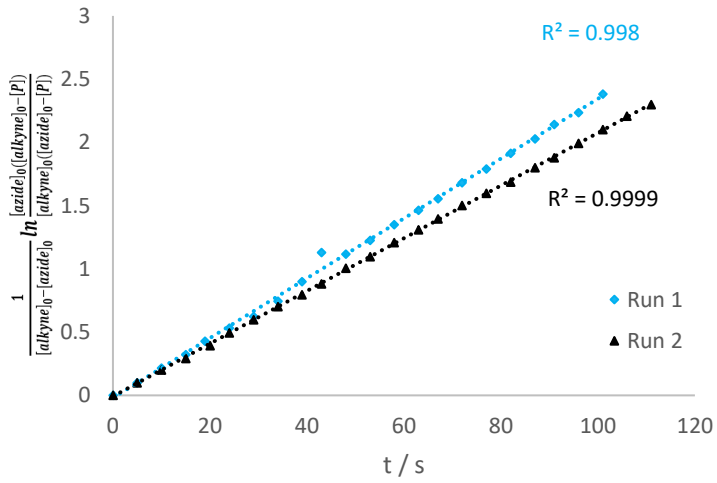
t (s)	integral
0	1.000
5	0.950
10	0.902
15	0.864
20	0.825
24	0.789
29	0.753
34	0.718
39	0.685
44	0.651
48	0.622
53	0.597
58	0.569
63	0.541
68	0.517
72	0.491
77	0.476
82	0.452
87	0.432
92	0.413
96	0.398



Integration range = 2170–2070 cm^{-1}



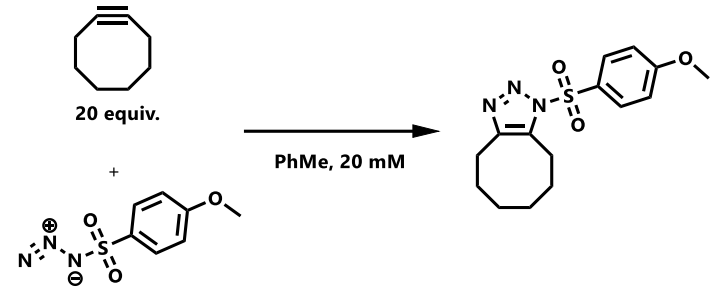


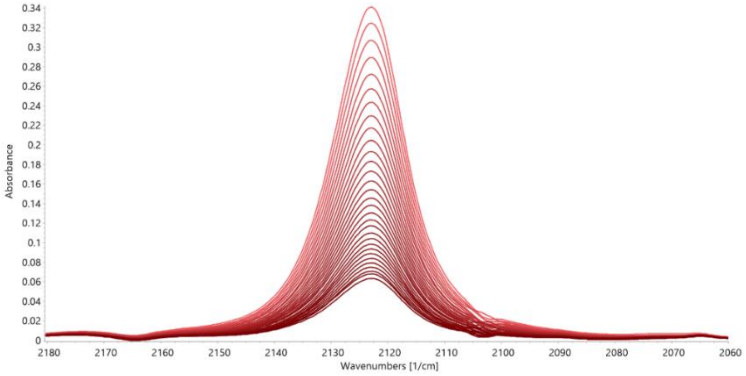


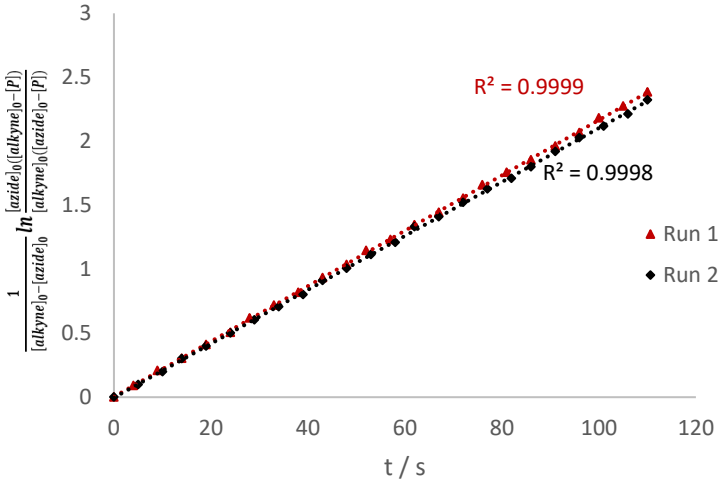
t (s)	integral
0	1.000
5	0.961
10	0.918
15	0.879
19	0.843
24	0.809
29	0.781
34	0.744
39	0.700
43	0.639
48	0.643
53	0.615
58	0.586
63	0.561
67	0.541
72	0.515
77	0.494
82	0.470
87	0.450
91	0.431
96	0.415
101	0.392

t (s)	integral
0	1.000
5	0.961
10	0.923
15	0.890
20	0.855
24	0.822
29	0.788
34	0.756
39	0.729
43	0.705
48	0.671
53	0.647
58	0.620
63	0.596
67	0.576
72	0.553
77	0.532
82	0.514
87	0.492
91	0.477
96	0.456
101	0.437
106	0.420
111	0.405

***Integration range = 2170–2070 cm^{-1}**



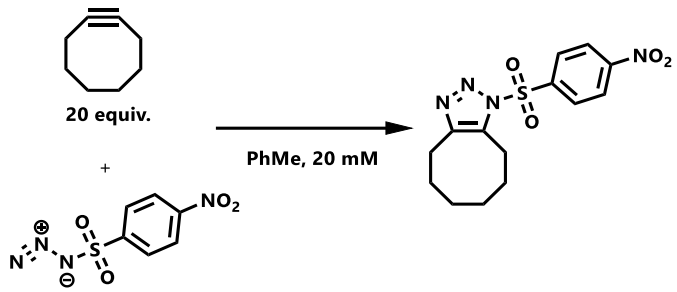




t (s)	integral
0	1.000
4	0.964
9	0.920
14	0.886
19	0.849
24	0.818
28	0.782
33	0.751
38	0.722
43	0.691
48	0.663
52	0.635
57	0.614
62	0.587
67	0.565
72	0.541
76	0.520
81	0.500
86	0.481
91	0.461
96	0.443
100	0.424
105	0.409
110	0.392

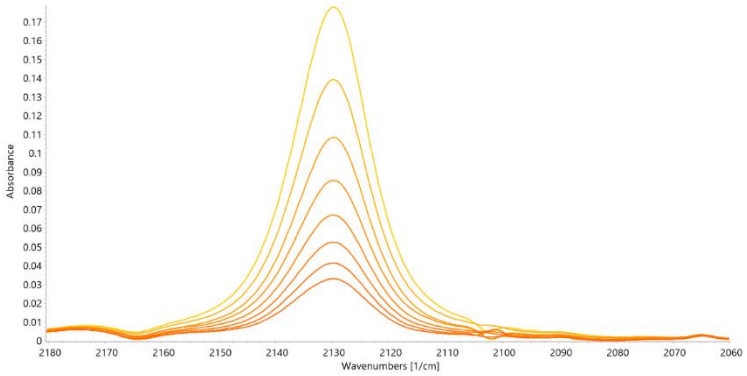
t (s)	integral
0	1.000
5	0.961
10	0.924
14	0.887
19	0.853
24	0.819
29	0.787
34	0.755
39	0.727
43	0.696
48	0.671
53	0.643
58	0.620
62	0.590
67	0.573
72	0.548
77	0.526
82	0.509
86	0.492
91	0.469
96	0.450
101	0.435
106	0.419
110	0.401

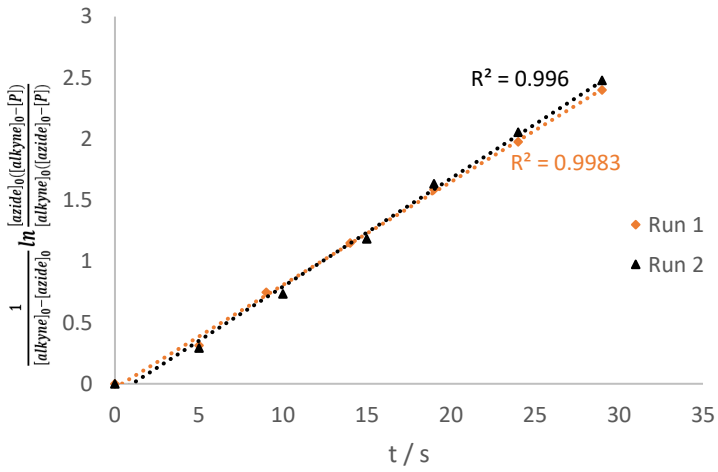
Integration range = 2170–2070 cm^{-1}



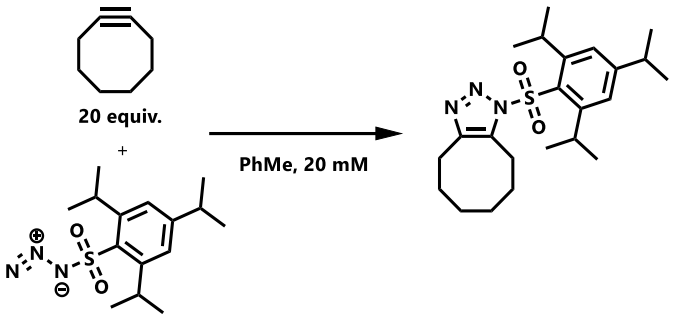
t (s)	integral
0	1.000
5	0.883
9	0.743
14	0.634
19	0.534
24	0.459
29	0.389

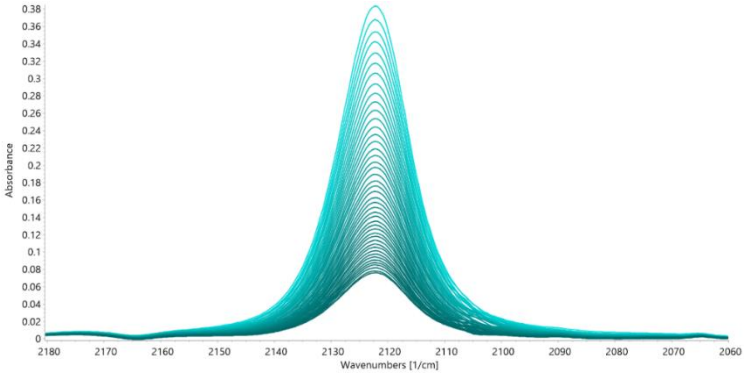
t (s)	integral
0	1.000
10	0.798
19	0.644
29	0.509
39	0.430

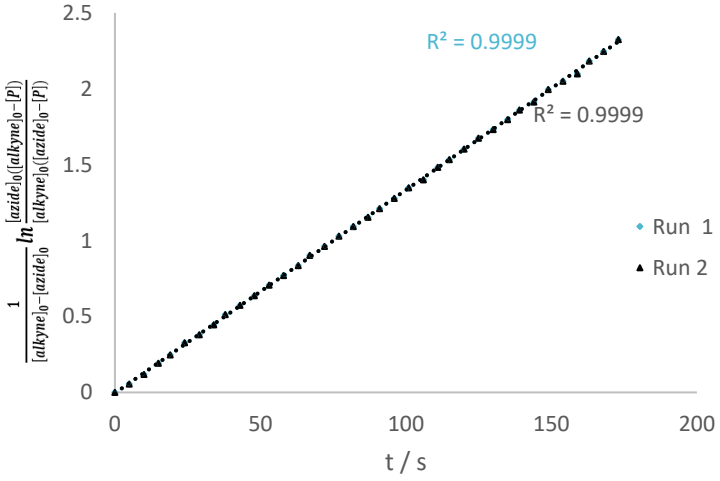




Integration range = 2170–2070 cm^{-1}



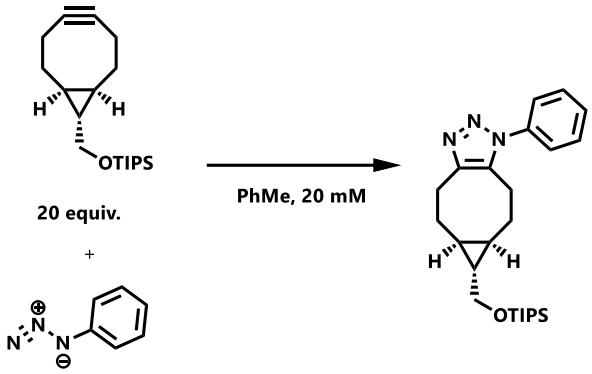




t (s)	integral
0	1.000
5	0.978
10	0.953
15	0.926
19	0.906
24	0.878
29	0.859
34	0.837
38	0.815
43	0.795
48	0.776
53	0.755
58	0.736
63	0.718
67	0.699
72	0.683
77	0.665
82	0.649
87	0.633
91	0.619
96	0.603
101	0.587
106	0.575
111	0.557
115	0.545
120	0.531
125	0.516
130	0.505
135	0.492
139	0.480
144	0.471
149	0.456
154	0.446
159	0.438
163	0.423
168	0.413
173	0.401

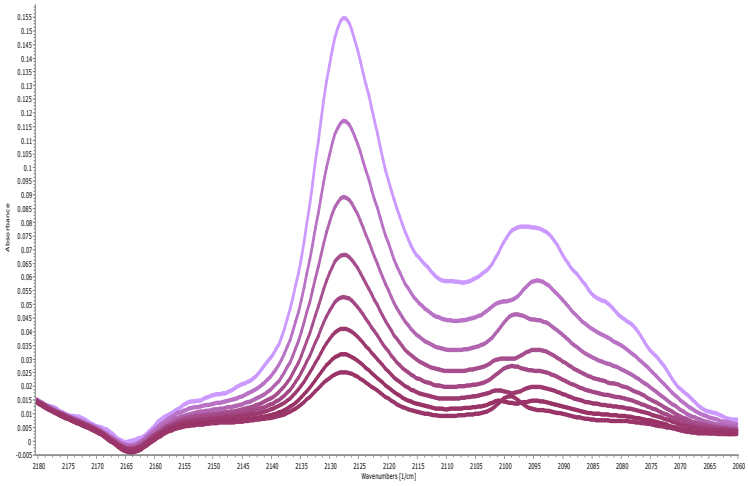
t (s)	integral
0	1.000
5	0.976
10	0.952
14	0.927
19	0.902
24	0.880
29	0.858
34	0.834
38	0.814
43	0.790
48	0.767
53	0.749
58	0.729
62	0.709
67	0.695
72	0.673
77	0.657
82	0.644
86	0.623
91	0.606
96	0.590
101	0.573
105	0.563
110	0.544
115	0.528
120	0.520
125	0.505
129	0.492
134	0.477
139	0.467
144	0.456
149	0.442
153	0.432
158	0.420
163	0.408
168	0.399

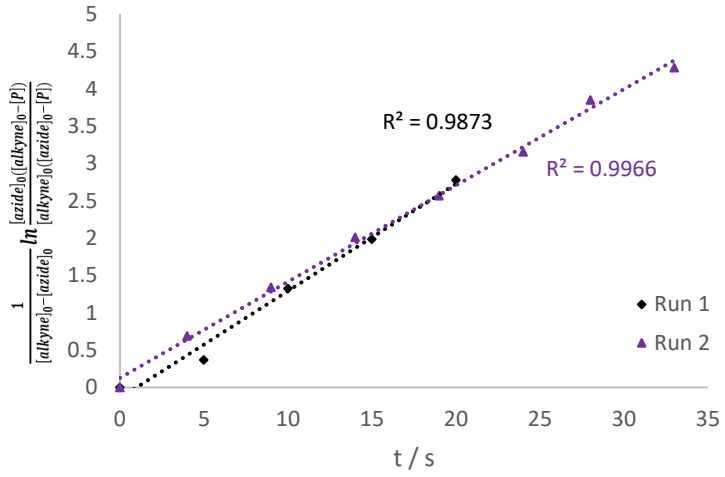
Integration range = 2170–2070 cm^{-1}



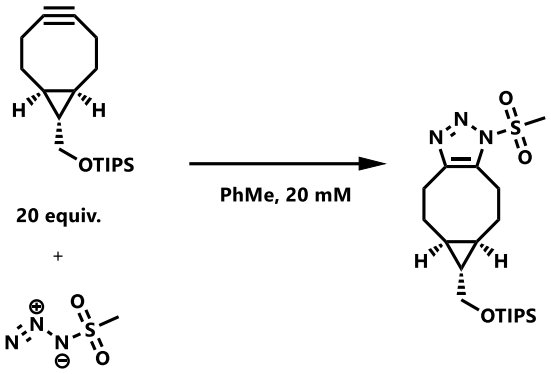
t (s)	integral
0	1.000
4	0.760
9	0.588
14	0.453
19	0.365
24	0.291
28	0.223
33	0.189

t (s)	integral
0	1.000
5	0.863
10	0.592
15	0.457
20	0.336



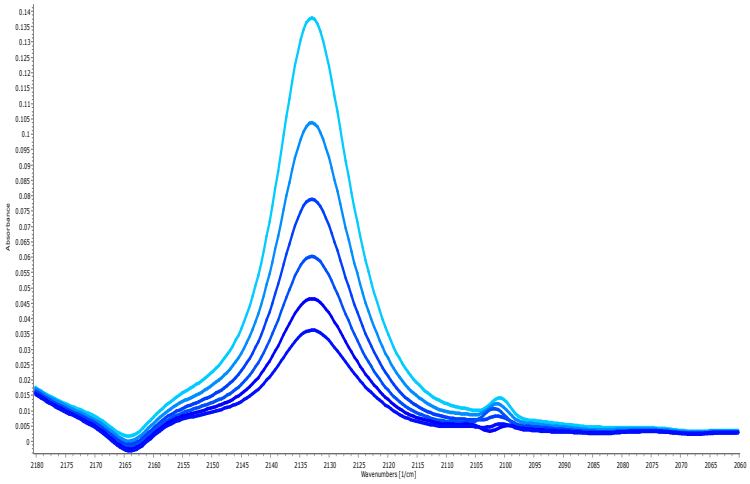


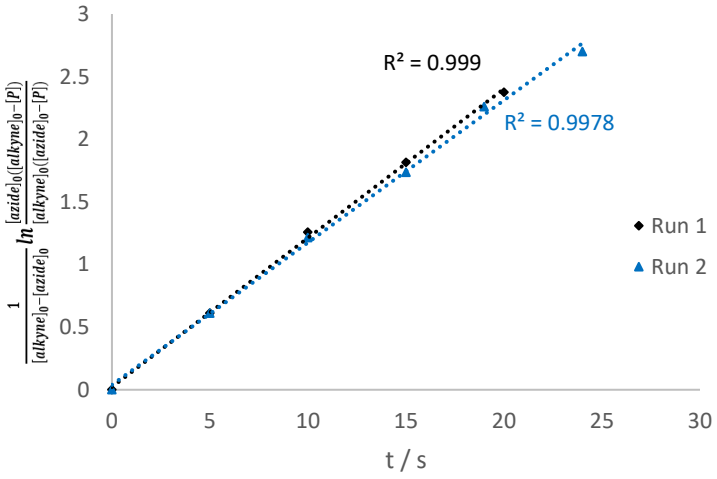
Integration range = 2170–2070 cm^{-1}



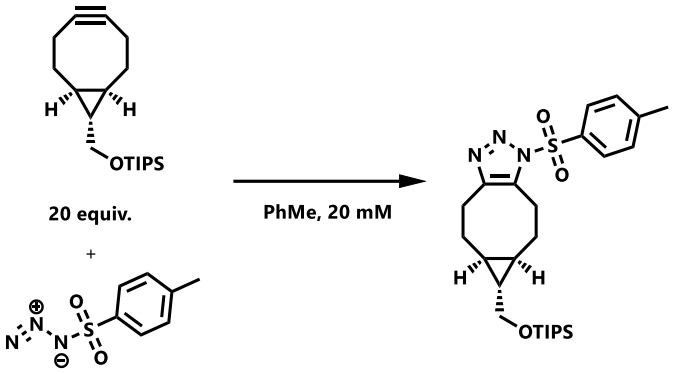
t (s)	integral
0	1.000
5	0.784
10	0.618
15	0.504
19	0.411
24	0.347

t (s)	integral
0	1.000
5	0.784
10	0.608
15	0.489
20	0.393



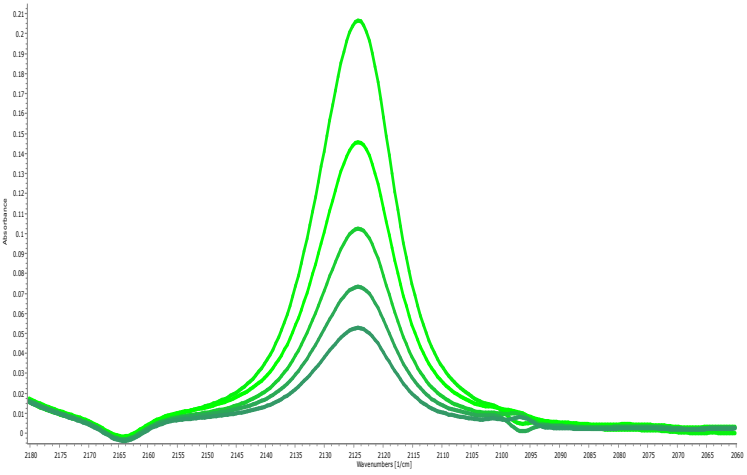


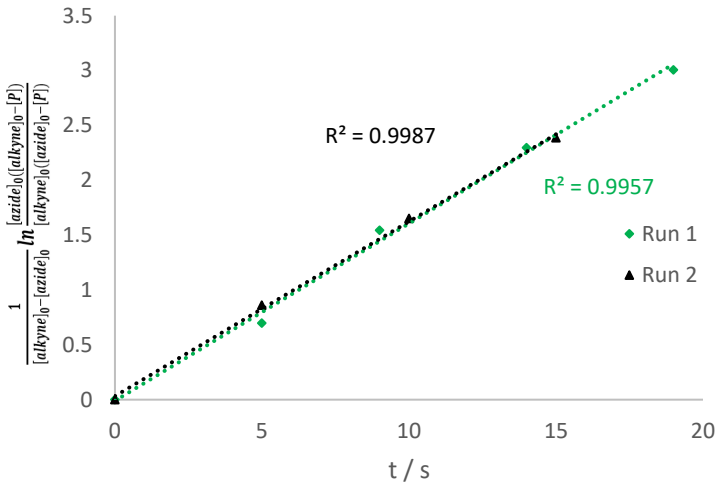
Integration range = 2170–2070 cm^{-1}



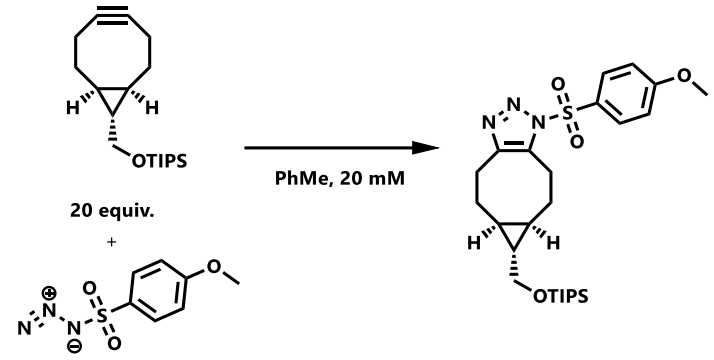
t (s)	integral
0	1.000
5	0.758
9	0.544
14	0.405
19	0.308

t (s)	integral
0	1.000
5	0.710
10	0.521
15	0.391



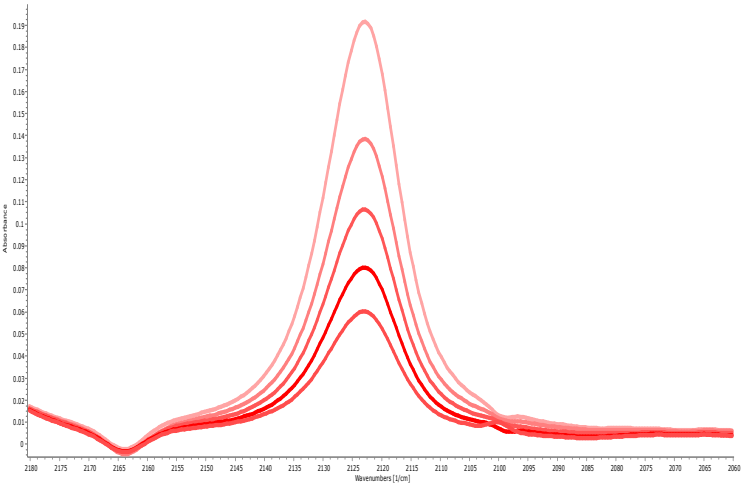


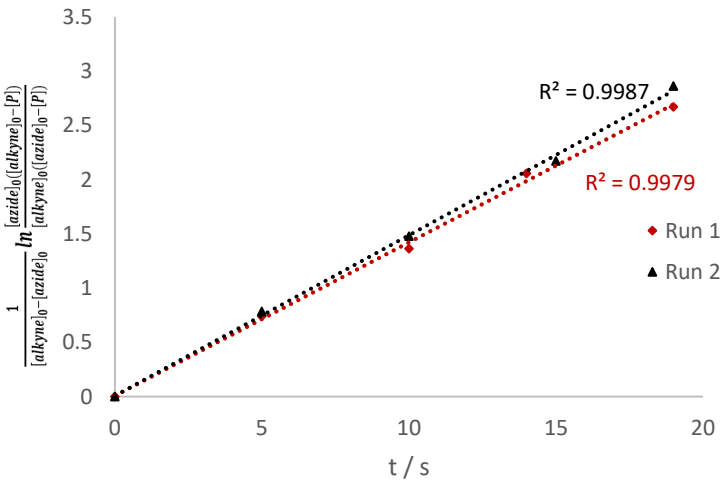
Integration range = 2170–2070 cm^{-1}



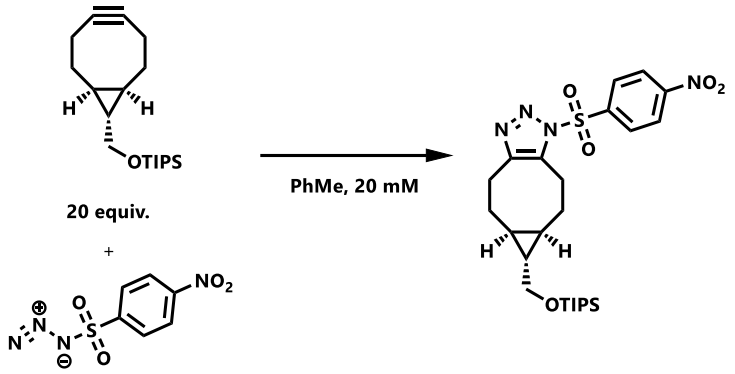
t (s)	integral
0	1.000
5	0.746
10	0.583
14	0.445
19	0.351

t (s)	integral
0	1.000
5	0.733
10	0.558
15	0.426
19	0.326



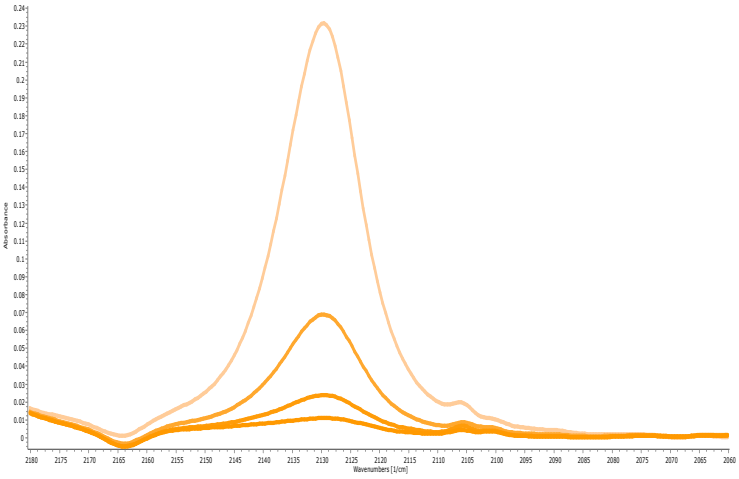


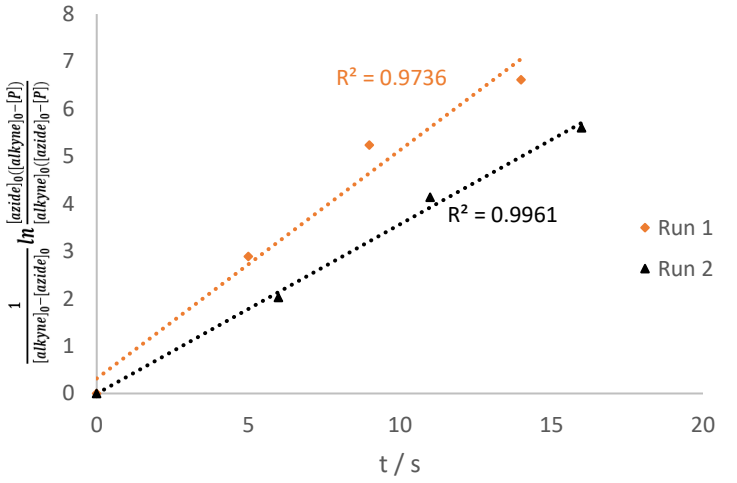
Integration range = 2170–2070 cm^{-1}



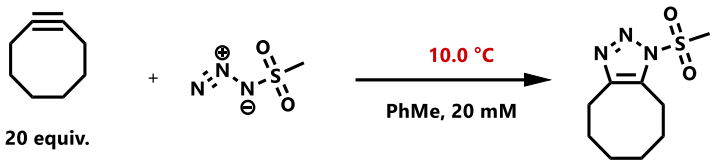
t (s)	integral
0	1.000
5	0.323
9	0.131
14	0.077

t (s)	integral
0	1.000
6	0.450
11	0.199
16	0.114

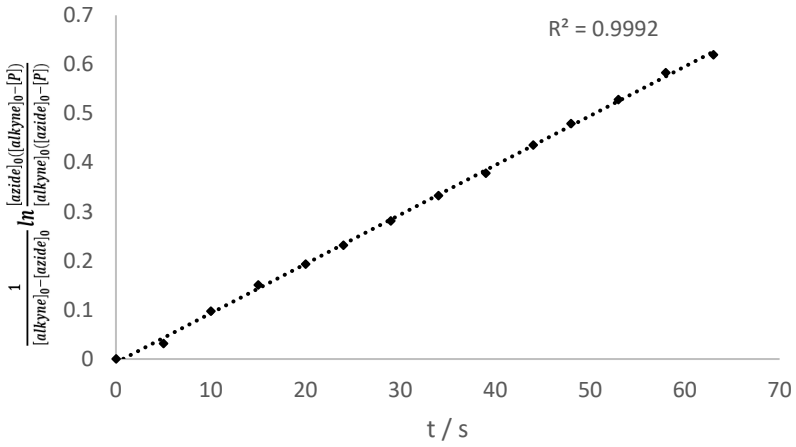




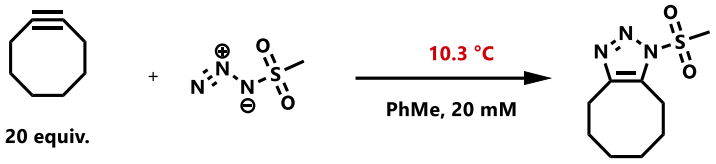
Integration range = 2170–2070 cm^{-1}



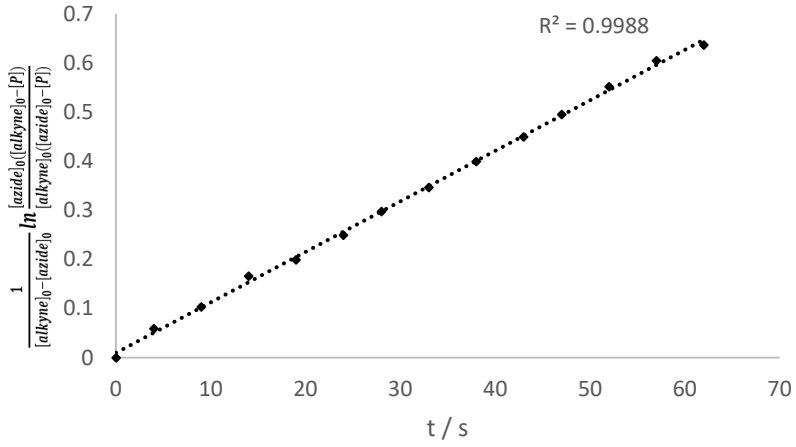
t (s)	integral
0	1.000
5	0.988
10	0.962
15	0.942
20	0.926
24	0.912
29	0.894
34	0.876
39	0.860
44	0.841
48	0.826
53	0.810
58	0.793
63	0.782



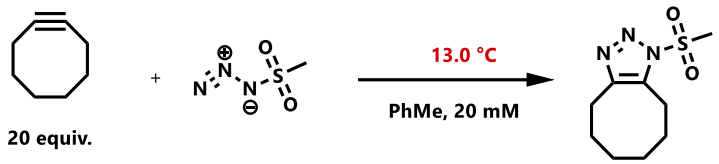
Integration range = 2170–2070 cm^{-1}

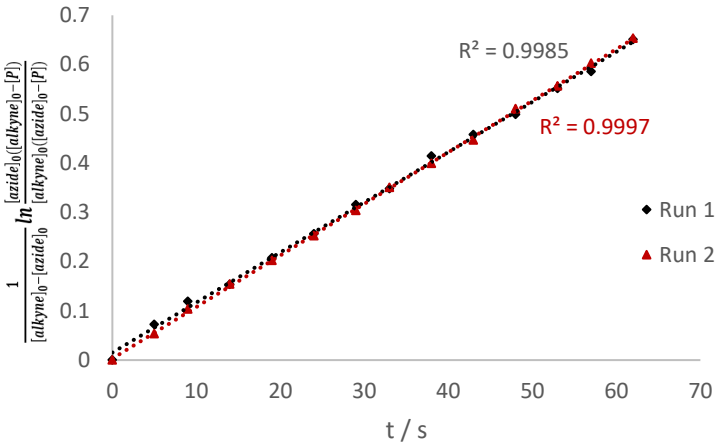


t (s)	integral
0	1.000
4	0.977
9	0.960
14	0.936
19	0.923
24	0.905
28	0.888
33	0.871
38	0.853
43	0.836
47	0.821
52	0.803
57	0.786
62	0.776



Integration range = 2170–2070 cm^{-1}

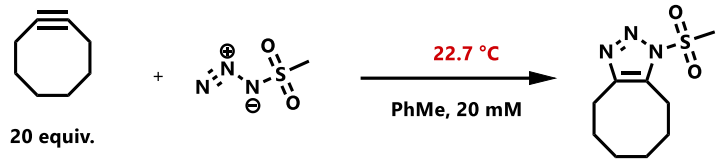


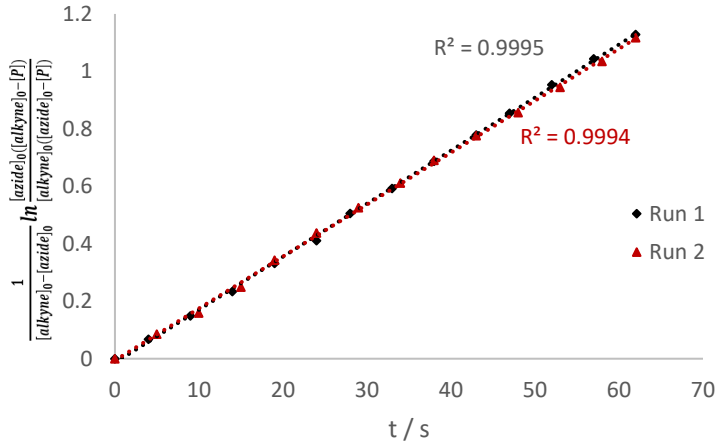


t (s)	integral
0	1.000
5	0.971
9	0.954
14	0.941
19	0.920
24	0.903
29	0.882
33	0.870
38	0.848
43	0.833
48	0.820
53	0.803
57	0.792
62	0.772

t (s)	integral
0	1.000
5	0.979
9	0.959
14	0.940
19	0.923
24	0.904
29	0.886
33	0.870
38	0.853
43	0.837
48	0.816
53	0.801
57	0.787
62	0.771

Integration range = 2170–2070 cm^{-1}

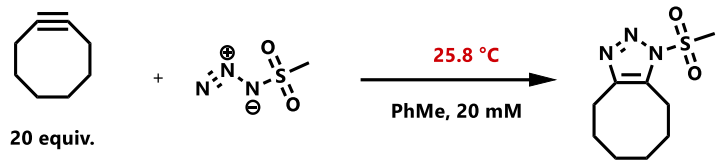


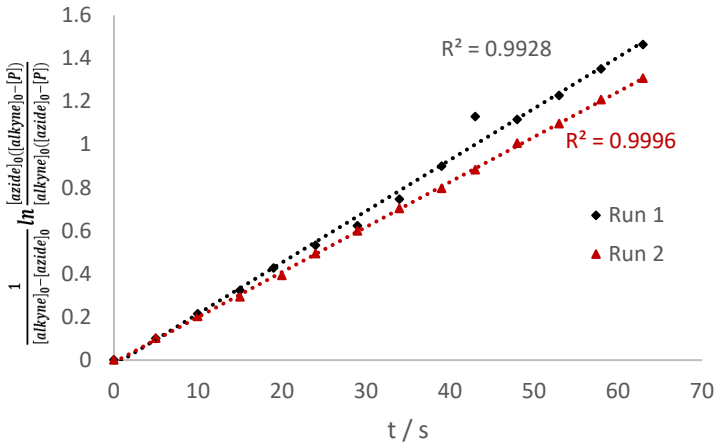


t (s)	integral
0	1.000
4	0.973
9	0.942
14	0.911
19	0.876
24	0.849
28	0.817
33	0.790
38	0.761
43	0.734
47	0.712
52	0.685
57	0.661
62	0.639

t (s)	integral
0	1.000
5	0.966
10	0.938
15	0.905
19	0.872
24	0.840
29	0.811
34	0.784
38	0.760
43	0.734
48	0.712
53	0.687
58	0.663
62	0.642

Integration range = 2170–2070 cm^{-1}

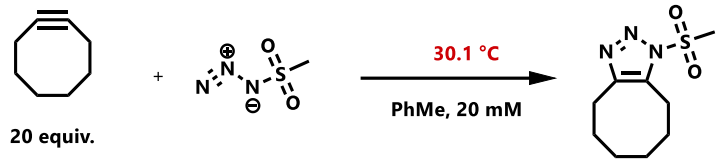


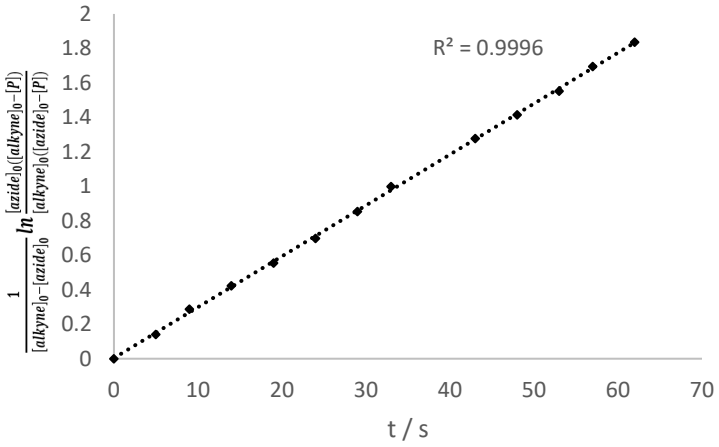


t (s)	integral
0	1.000
4	0.973
9	0.942
14	0.911
19	0.876
24	0.849
28	0.817
33	0.790
38	0.761
43	0.734
47	0.712
52	0.685
57	0.661
62	0.639

t (s)	integral
0	1.000
5	0.966
10	0.938
15	0.905
19	0.872
24	0.840
29	0.811
34	0.784
38	0.760
43	0.734
48	0.712
53	0.687
58	0.663
62	0.642

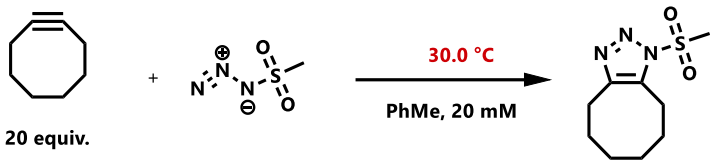
Integration range = 2170–2070 cm^{-1}

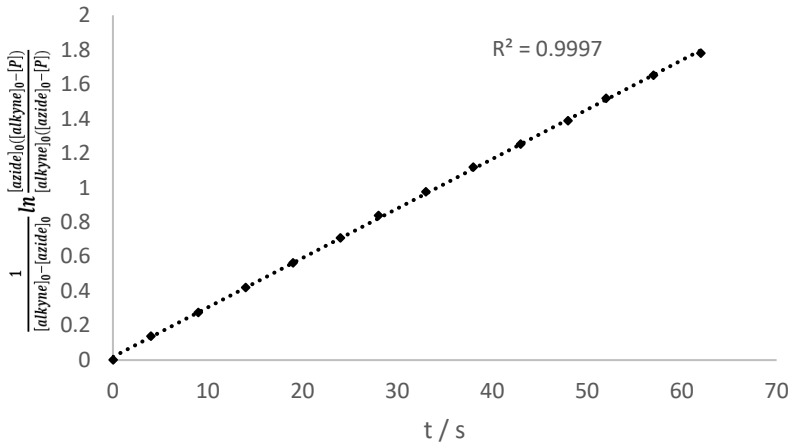




t (s)	integral
0	1.000
5	0.945
9	0.891
14	0.845
19	0.802
24	0.758
29	0.713
33	0.673
43	0.603
48	0.571
53	0.542
57	0.512
62	0.485

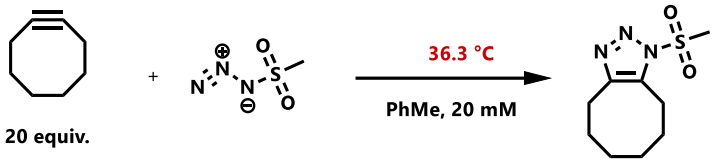
Integration range = 2170–2070 cm^{-1}

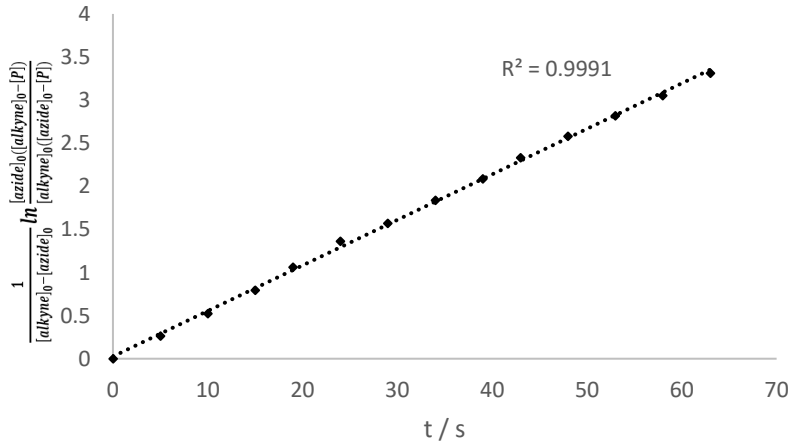




t (s)	integral
0	1.000
4	0.946
9	0.896
14	0.846
19	0.799
24	0.755
28	0.717
33	0.679
38	0.642
43	0.609
48	0.578
52	0.549
57	0.521
62	0.496

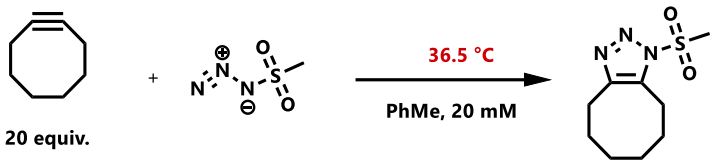
Integration range = 2170–2070 cm^{-1}



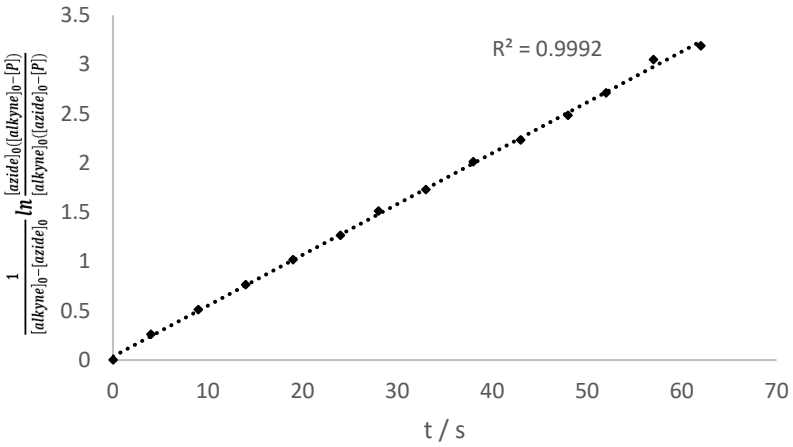


t (s)	integral
0	1.000
5	0.900
10	0.811
15	0.730
19	0.657
24	0.583
29	0.538
34	0.484
39	0.440
43	0.400
48	0.363
53	0.331
58	0.303
63	0.274

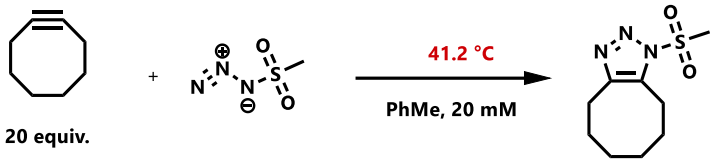
Integration range = 2170–2070 cm^{-1}



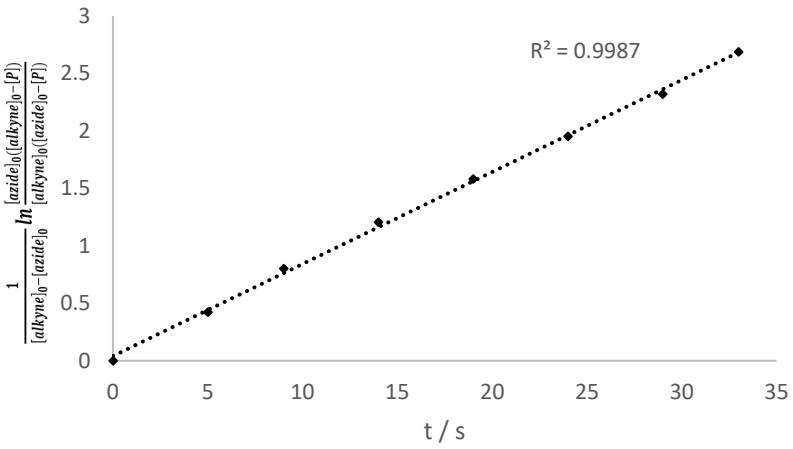
t (s)	integral
0	1.000
4	0.902
9	0.816
14	0.738
19	0.668
24	0.606
28	0.550
33	0.505
38	0.453
43	0.415
48	0.377
52	0.345
57	0.303
62	0.287



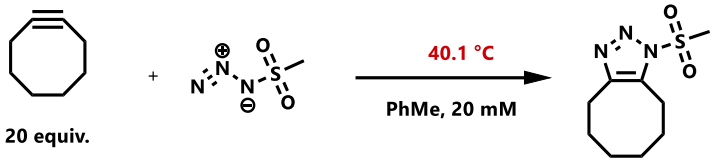
Integration range = 2170–2070 cm^{-1}



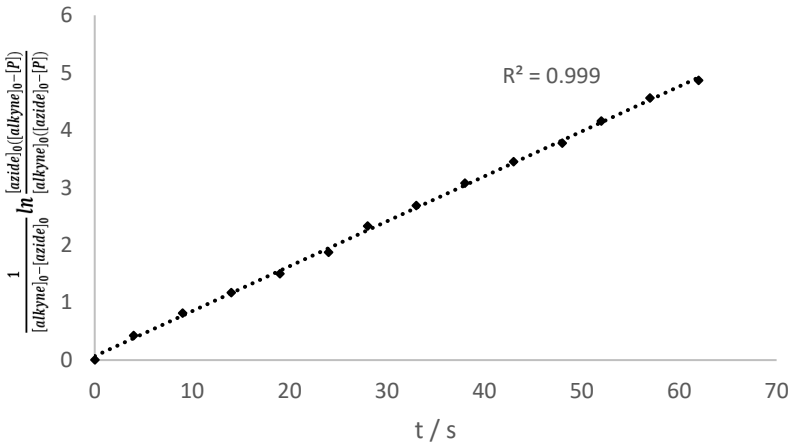
t (s)	integral
0	1.000
5	0.844
9	0.727
14	0.620
19	0.536
24	0.463
29	0.402
33	0.348



Integration range = 2170–2070 cm^{-1}

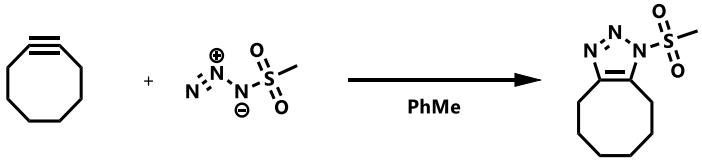


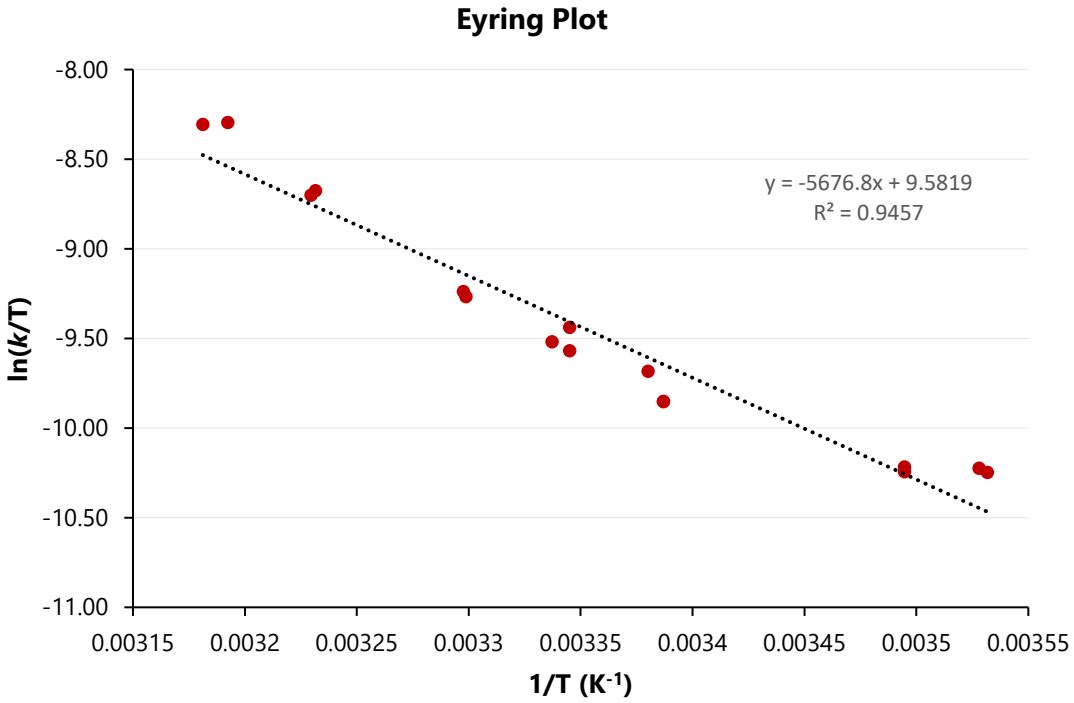
t (s)	integral
0	1.000
4	0.844
9	0.723
14	0.629
19	0.553
24	0.478
28	0.400
33	0.349
38	0.300
43	0.260
48	0.229
52	0.198
57	0.170
62	0.151

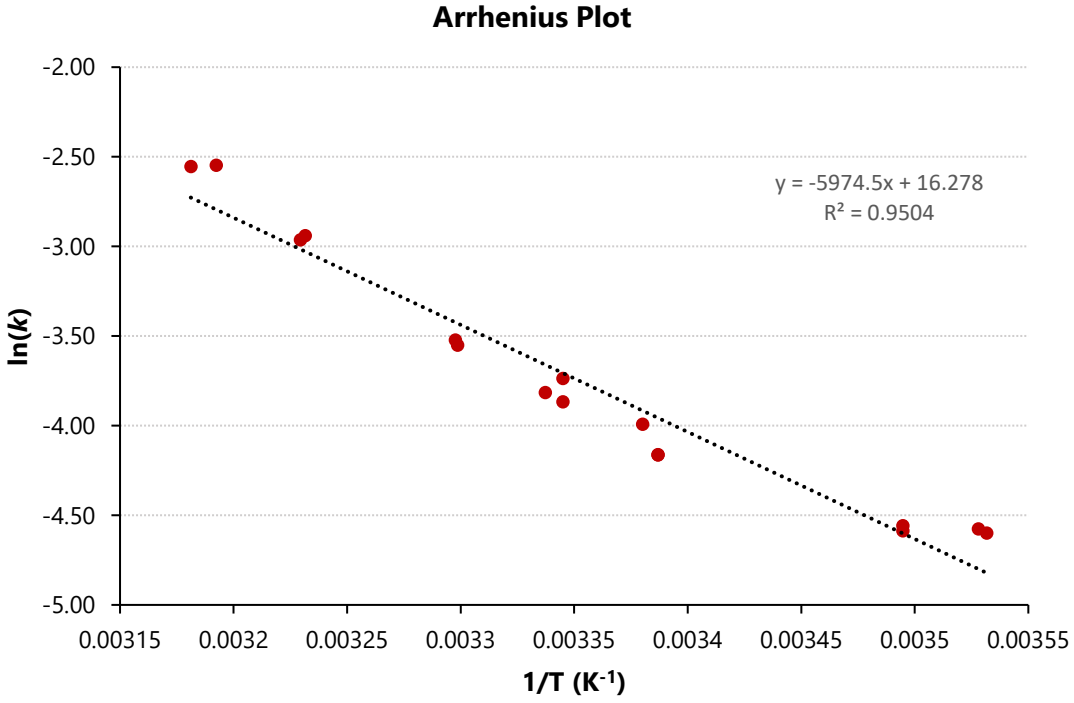


Integration range = 2170–2070 cm^{-1}

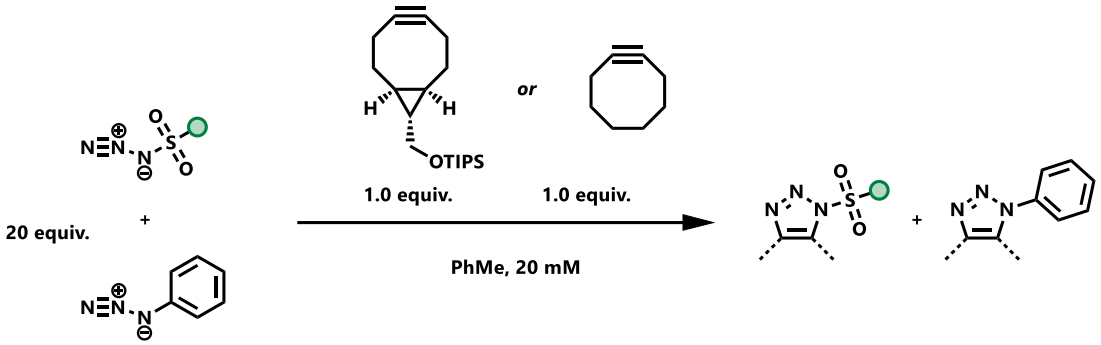
T	T	k	1/T		
°C	K	s^{-1}	K^{-1}	ln(k/T)	ln(k)
10.0	283.15	0.0101	0.00353	−10.25	−4.60
10.3	283.45	0.0103	0.00353	−10.22	−4.58
13.0	286.15	0.0102	0.00349	−10.24	−4.59
13.0	286.15	0.0105	0.00349	−10.22	−4.56
22.1	295.25	0.0155	0.00339	−9.85	−4.16
22.1	295.25	0.0156	0.00339	−9.85	−4.16
22.7	295.85	0.0185	0.00338	−9.68	−3.99
25.8	298.95	0.0238	0.00335	−9.44	−3.74
25.8	298.95	0.0209	0.00335	−9.57	−3.87
26.5	299.65	0.0220	0.00334	−9.52	−3.82
30.1	303.25	0.0295	0.00330	−9.24	−3.52
30.0	303.15	0.0287	0.00330	−9.27	−3.55
36.3	309.45	0.0528	0.00323	−8.68	−2.94
36.5	309.65	0.0516	0.00323	−8.70	−2.96
41.2	314.35	0.0777	0.00318	−8.31	−2.55
40.1	313.25	0.0782	0.00319	−8.30	−2.55




Eyring Plot
y = -5676.8x + 9.5819
R² = 0.9457
ln(k/T)
1/T (K-1)
-8.00
-8.50
-9.00
-9.50
-10.00
-10.50
-11.00
0.00315
0.0032
0.00325
0.0033
0.00335
0.0034
0.00345
0.0035
0.00355

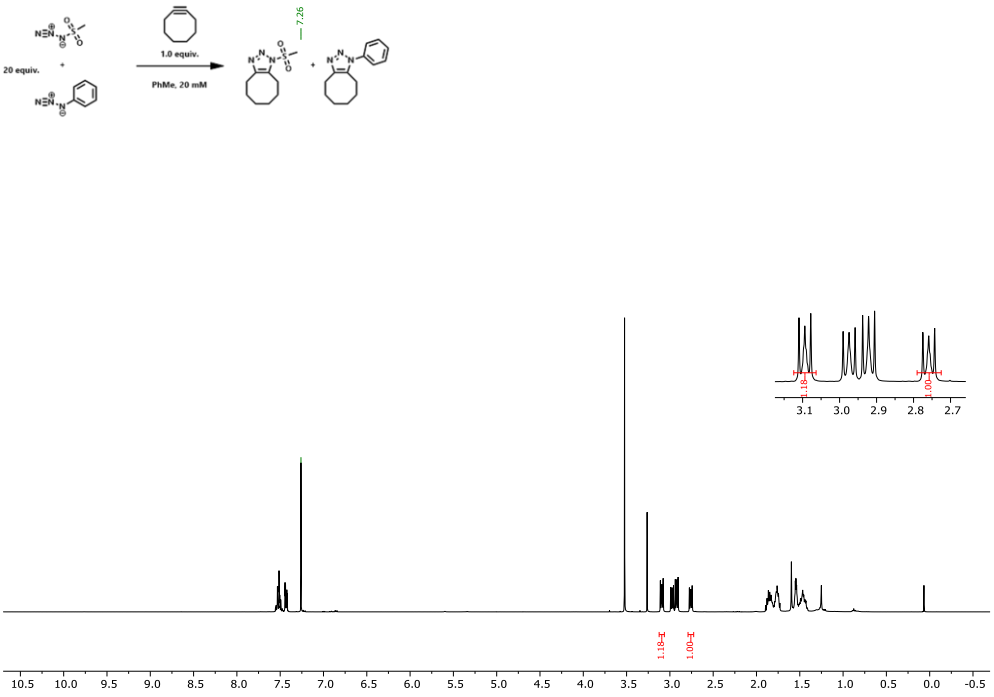

Arrhenius Plot
y = -5974.5x + 16.278
R² = 0.9504
ln(k)
1/T (K-1)
-2.00
-2.50
-3.00
-3.50
-4.00
-4.50
-5.00
0.00315
0.0032
0.00325
0.0033
0.00335
0.0034
0.00345
0.0035
0.00355

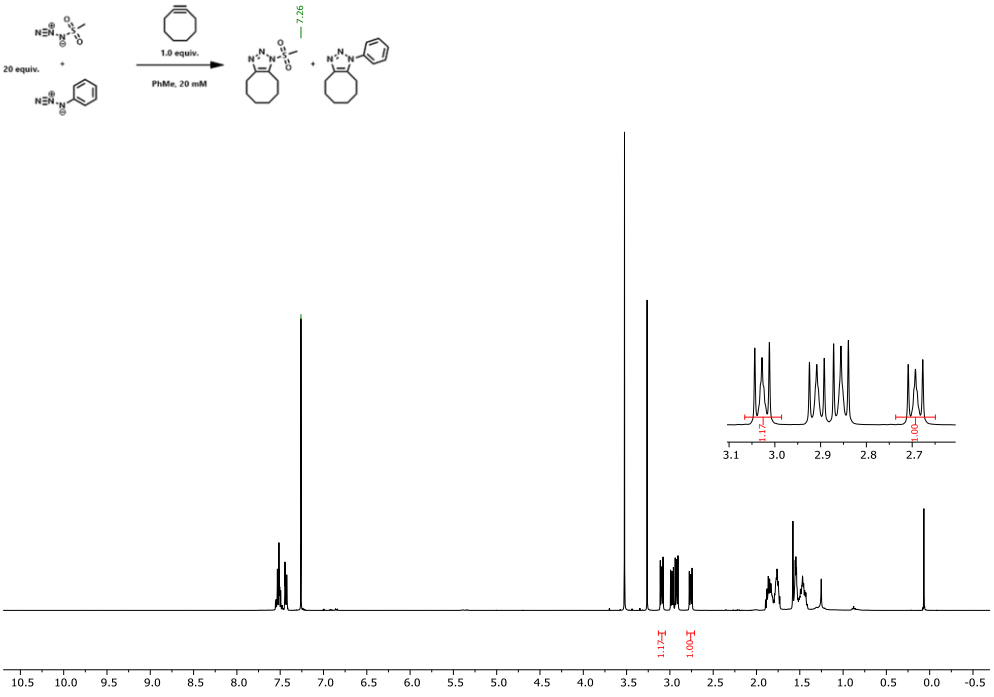
8.4 NMR competition experiments

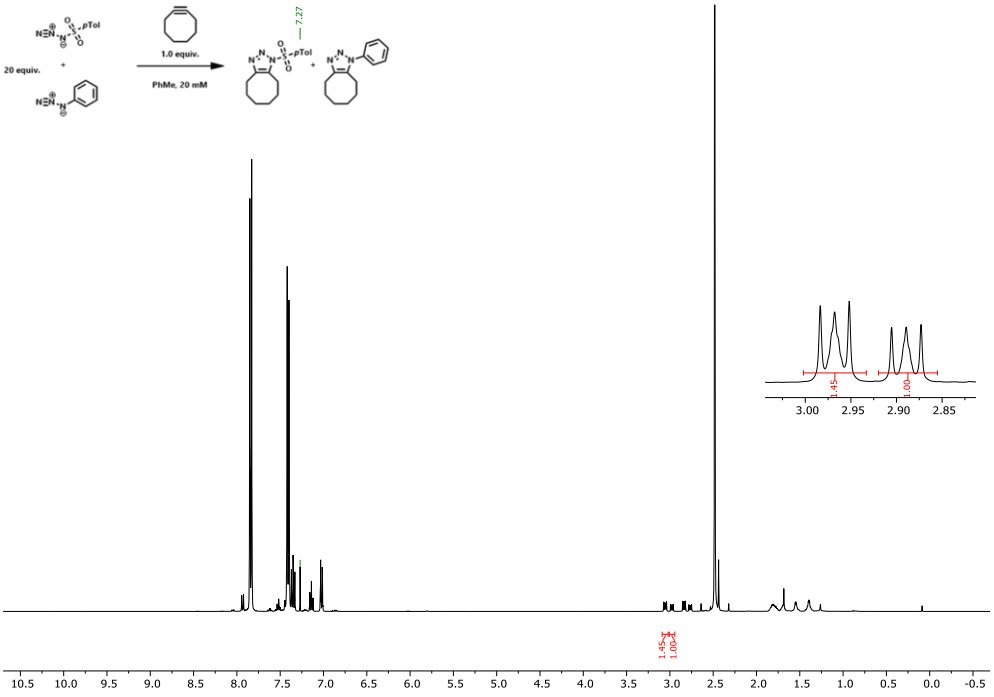


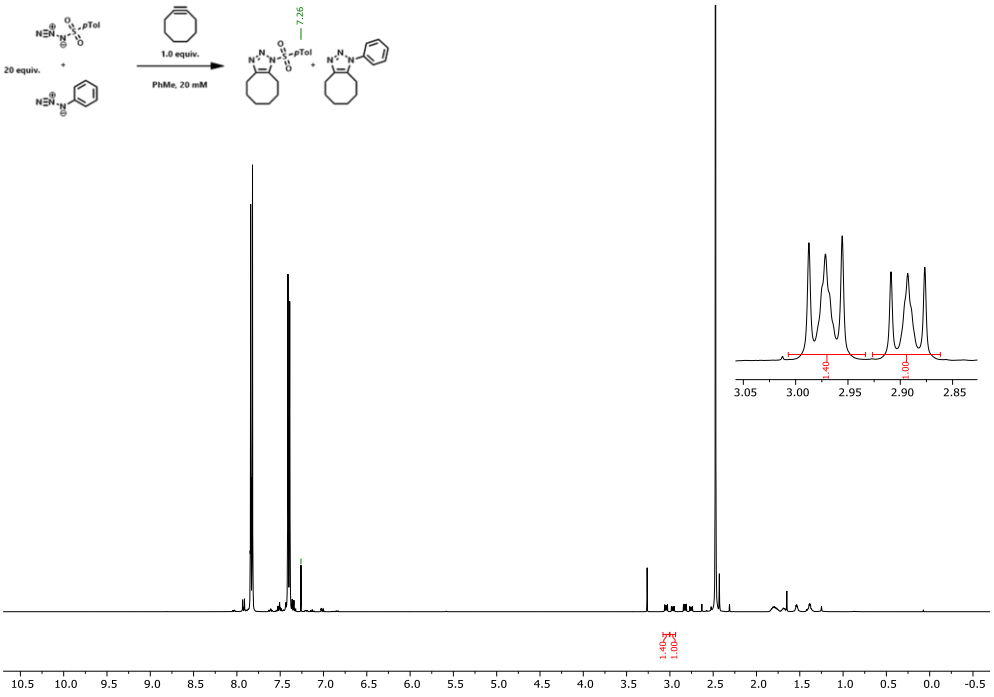
Phenyl azide (20 equiv.) and the requisite sulfonyl azide (20 equiv.) were dissolved in PhMe (0.02 M) at ambient temperature. The cyclic alkyne (1.0 equiv.) was added in one portion with vigorous stirring and the reaction stirred for 30 min. An aliquot was removed, concentrated *in vacuo* and analysed by ^{1}H NMR spectroscopy. The relative rate of cycloaddition for each sulfonyl azide was calculated by comparing the integration of the distinct signal corresponding to the methylene protons of the 1-ST product and comparing to the corresponding signal of the methylene protons in the *N*-phenyl triazole product. The full and zoomed ^{1}H NMR spectra for each experiment are shown.

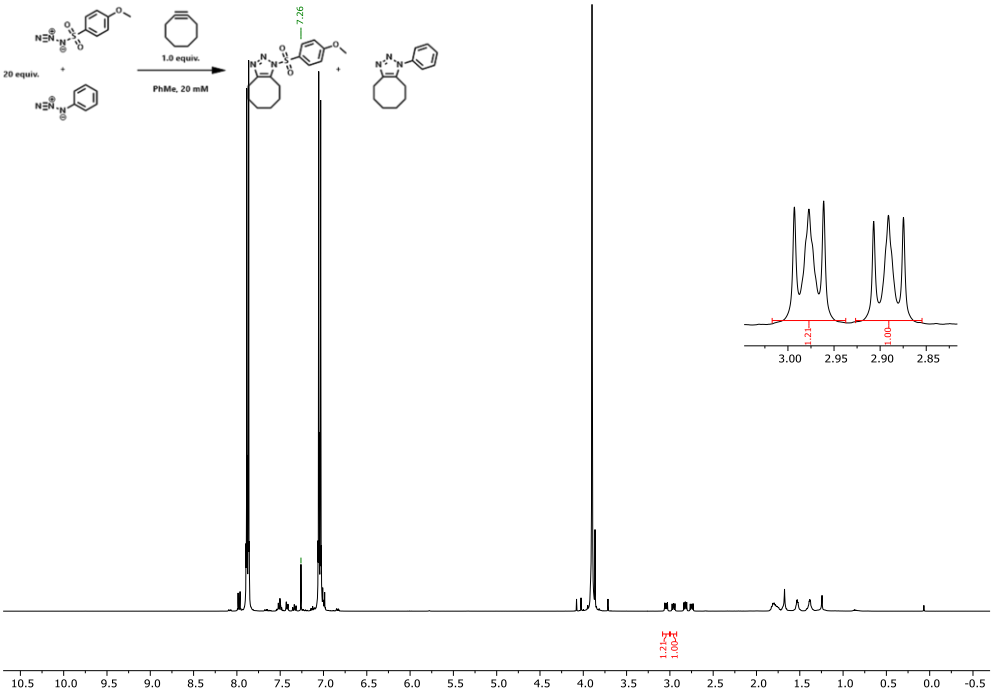
Full and zoomed spectra of competition experiments

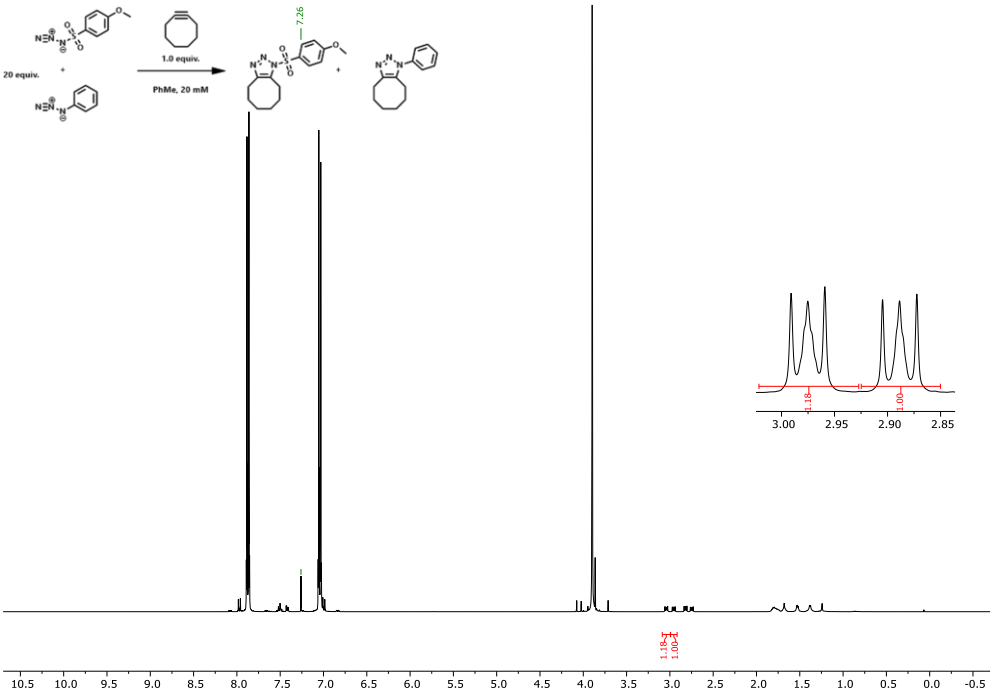


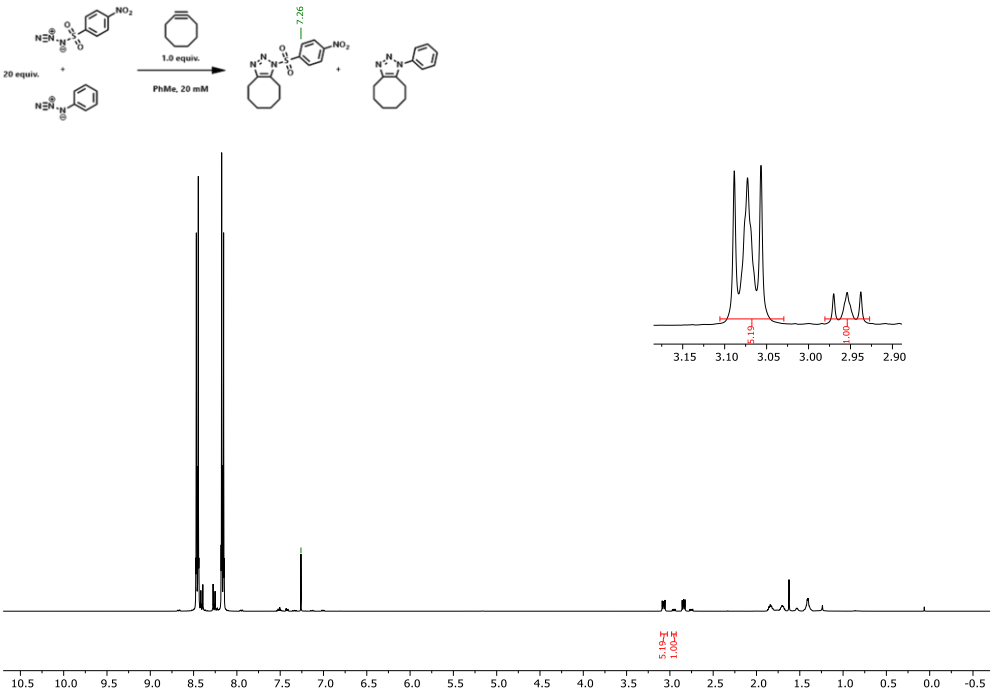


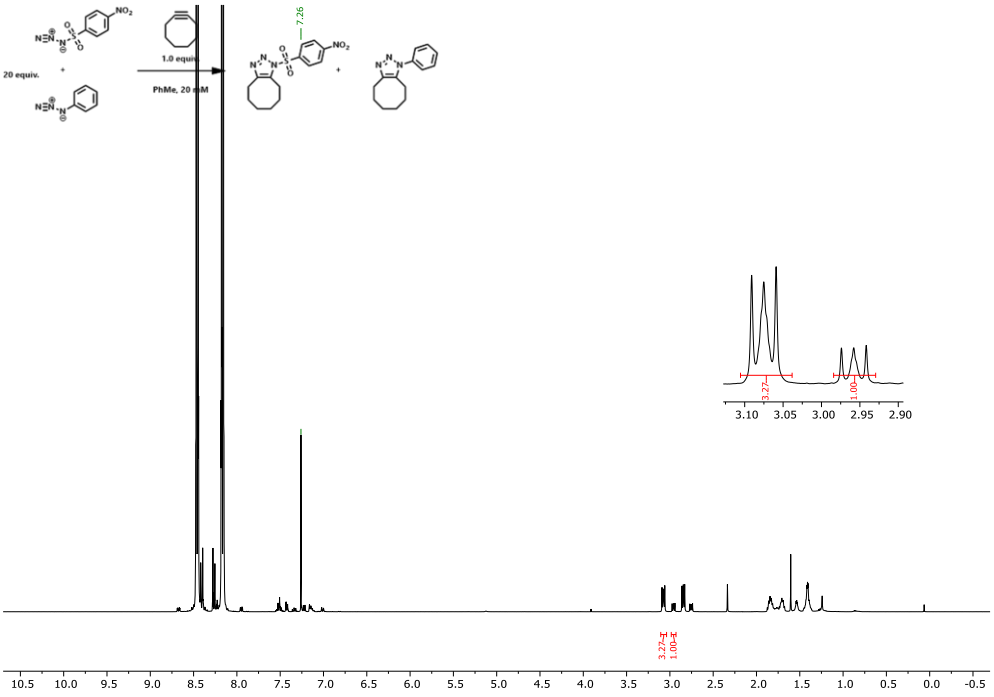

20 equiv.
1.0 equiv.
PhMe, 20 mM
7.27
1.45
1.00
3.00
2.95
2.90
2.85
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

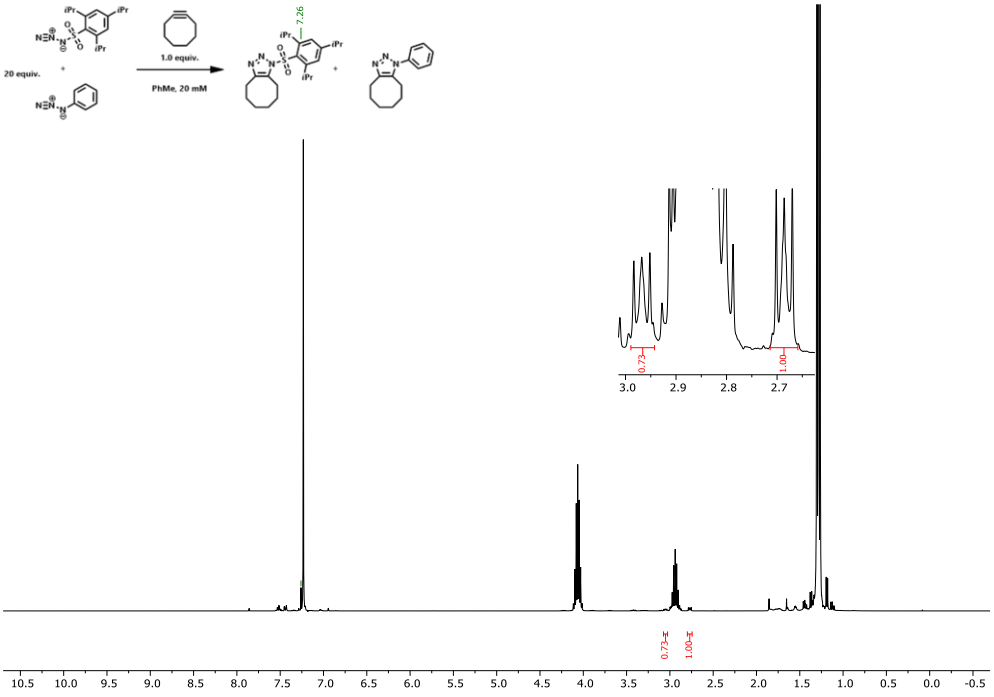

20 equiv.
1.0 equiv.
PhMe, 20 mM
7.26
1.40
1.00
3.05
3.00
2.95
2.90
2.85
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

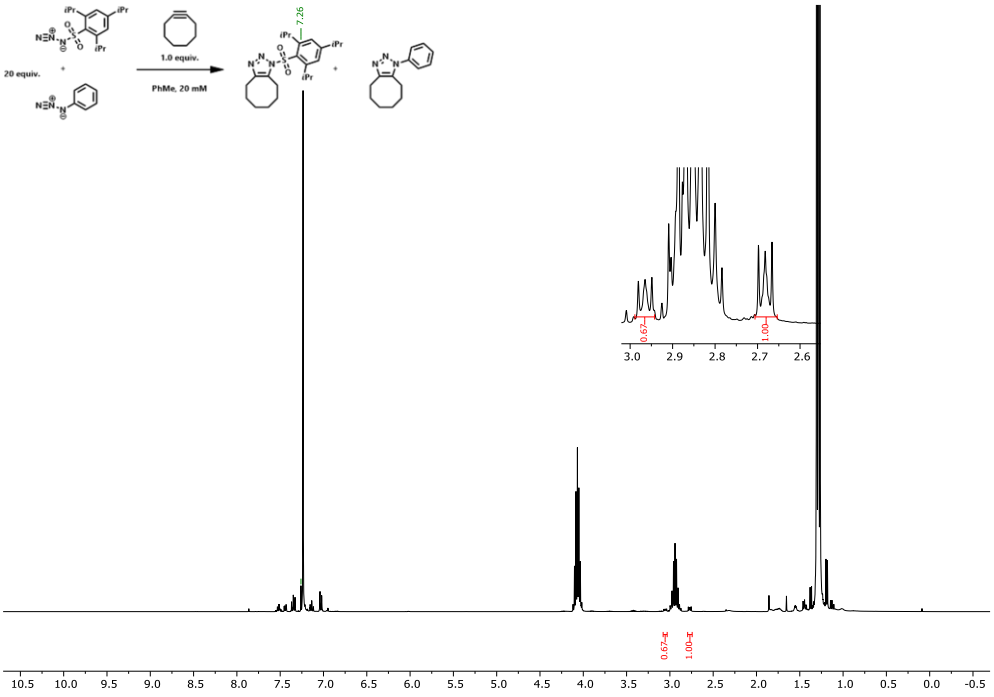

20 equiv.
1.0 equiv.
PhMe, 20 mM
7.26
1.21
1.00
3.00
2.95
2.90
2.85
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


20 equiv.
1.0 equiv.
PhMe, 20 mM
7.26
1.18
1.00
3.00
2.95
2.90
2.85
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


20 equiv.
1.0 equiv.
PhMe, 20 mM
7.26
5.19
1.00
3.15 3.10 3.05 3.00 2.95 2.90
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


20 equiv.
1.0 equiv.
PhMe, 20 mM
7.26
3.27
1.00
3.10 3.05 3.00 2.95 2.90
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


20 equiv.
1.0 equiv.
PhMe, 20 mM
7.26
0.73
1.00
3.0
2.9
2.8
2.7
0.73
1.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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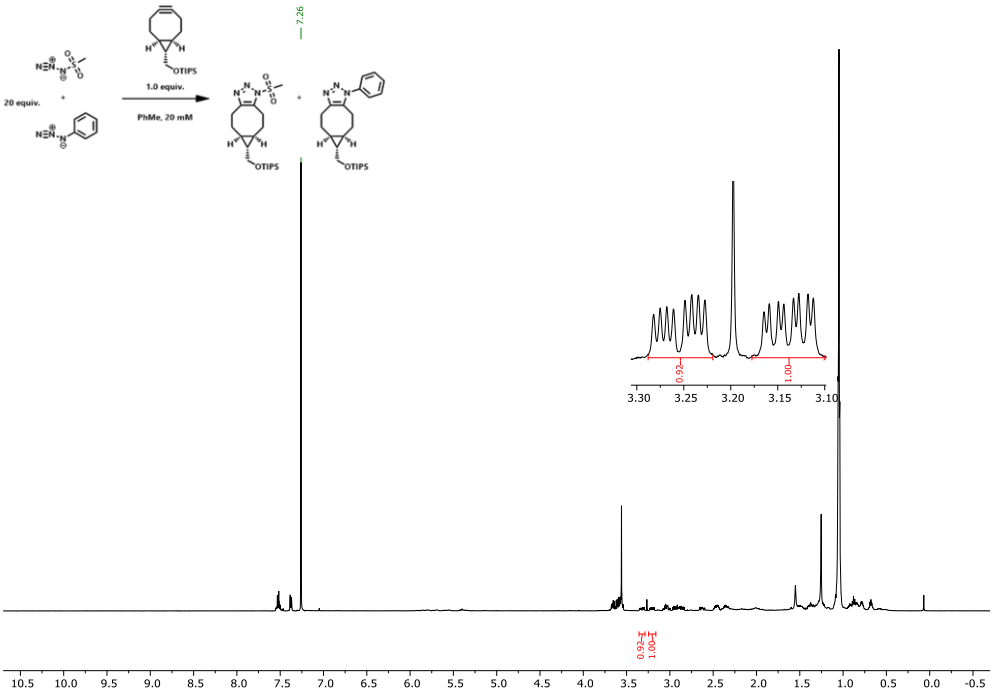
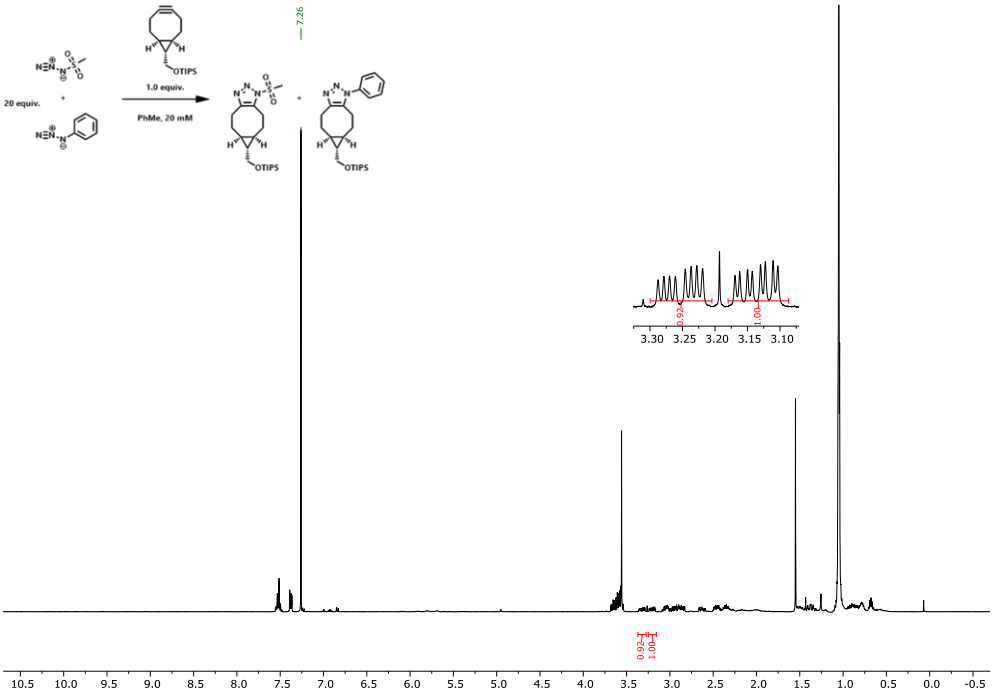
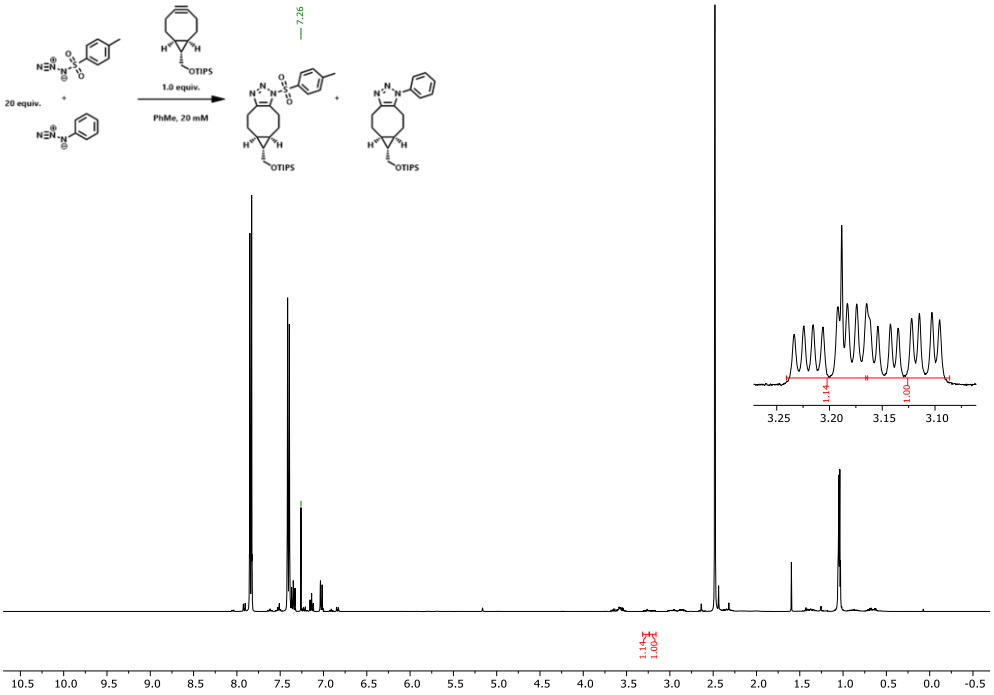
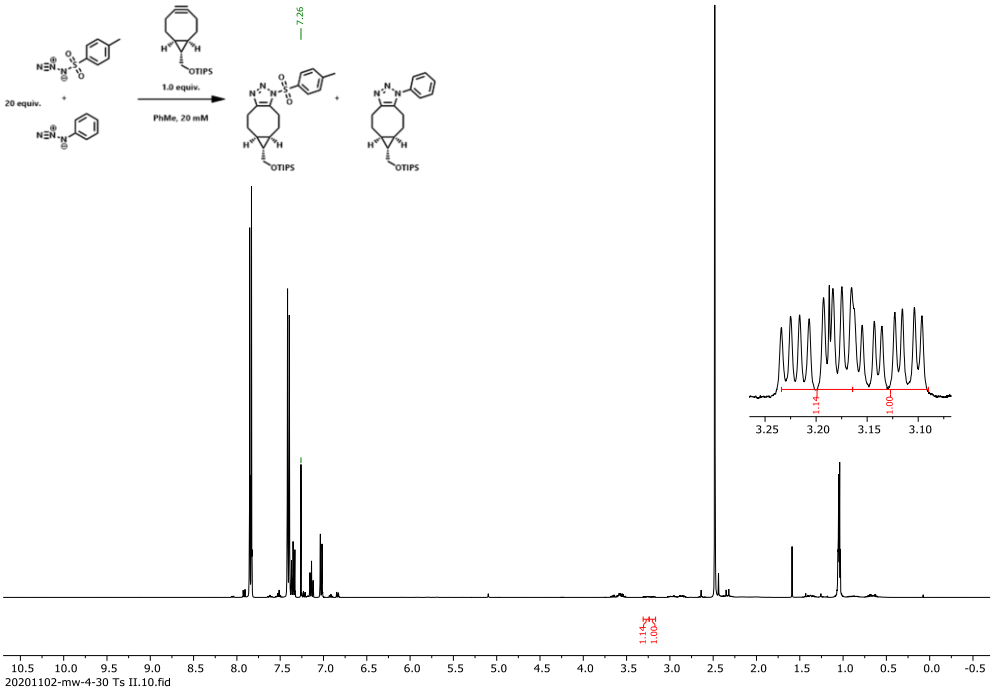
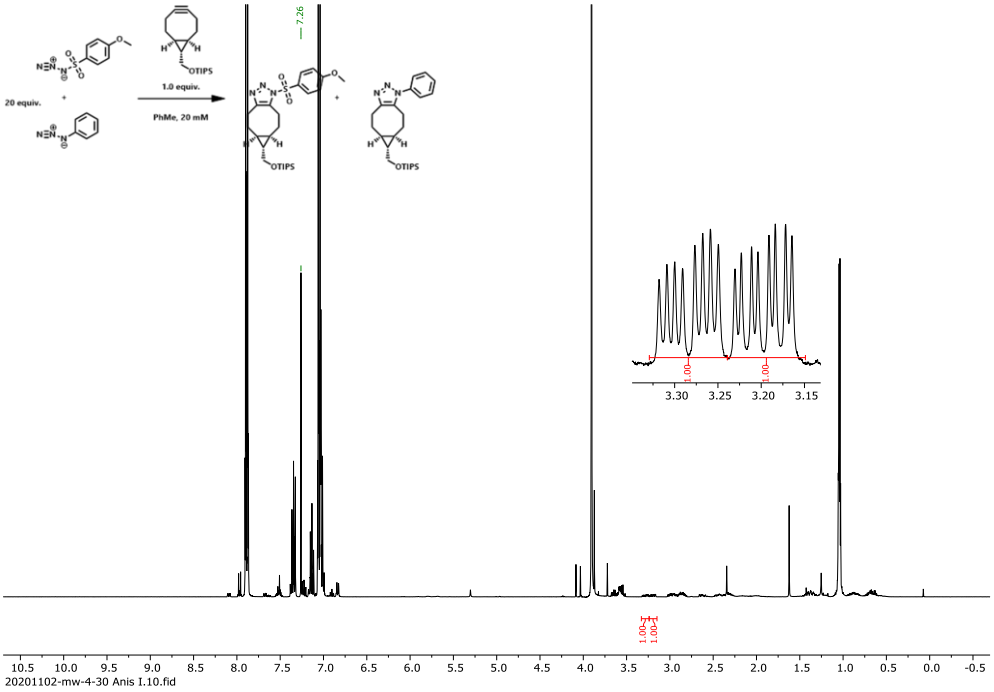
1.0 equiv.
PhMe, 20 mM
7.26
0.67
1.00
3.0
2.9
2.8
2.7
2.6
0.67
1.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

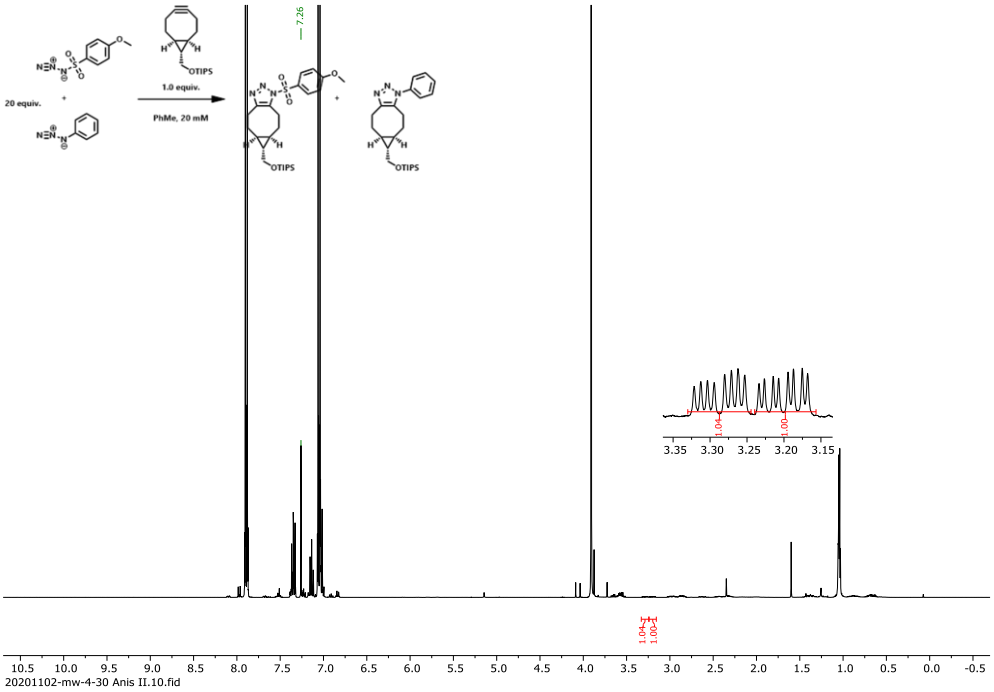

20 equiv.
1.0 equiv.
PhMe, 20 mM
OTIPS
7.26
0.92
1.00
3.30 3.25 3.20 3.15 3.10
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

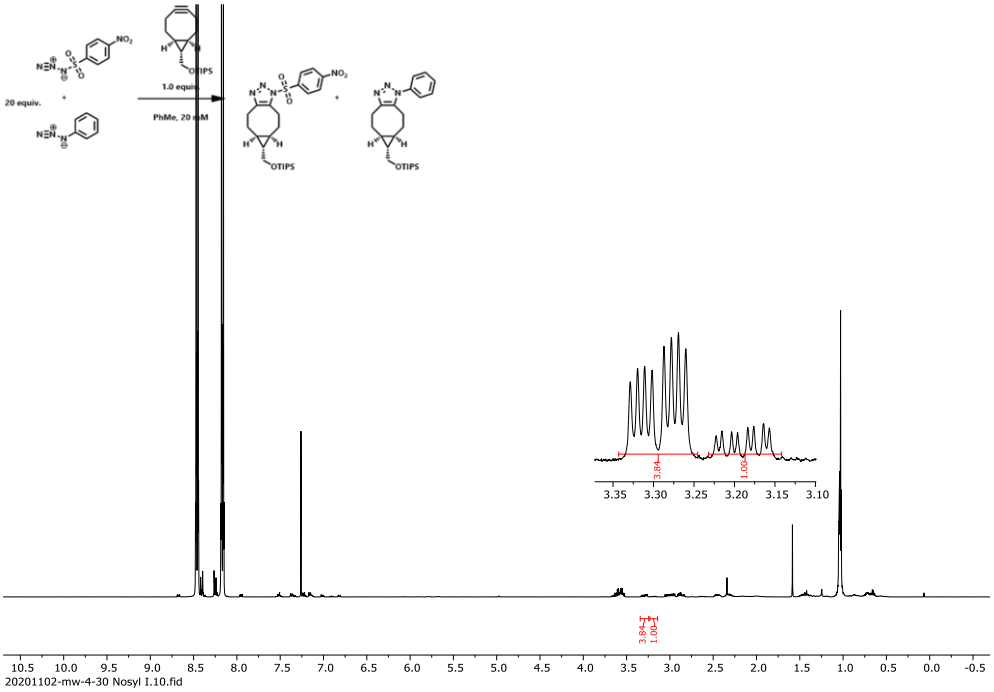

20 equiv.
1.0 equiv.
PhMe, 20 mM
OTIPS
7.26
0.92
1.00
3.30 3.25 3.20 3.15 3.10
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


20 equiv.
OTIPS
1.0 equiv.
PhMe, 20 mM
OTIPS
OTIPS
7.26
1.14
1.00
3.25
3.20
3.15
3.10
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


20 equiv.
OTIPS
1.0 equiv.
PhMe, 20 mM
OTIPS
OTIPS
7.26
1.14
1.00
3.25
3.20
3.15
3.10
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
20201102-mw-4-30 Ts II.10.fid


20 equiv.
OTIPS
1.0 equiv.
PhMe, 20 mM
7.26
OTIPS
OTIPS
3.30 3.25 3.20 3.15
1.00
1.00
1.00
1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
20201102-mw-4-30 Anis I.10.fid


20 equiv.
OTIPS
1.0 equiv.
PhMe, 20 mM
7.26
OTIPS
OTIPS
3.35 3.30 3.25 3.20 3.15
1.04
1.00
1.04
1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
20201102-mw-4-30 Anis II.10.fid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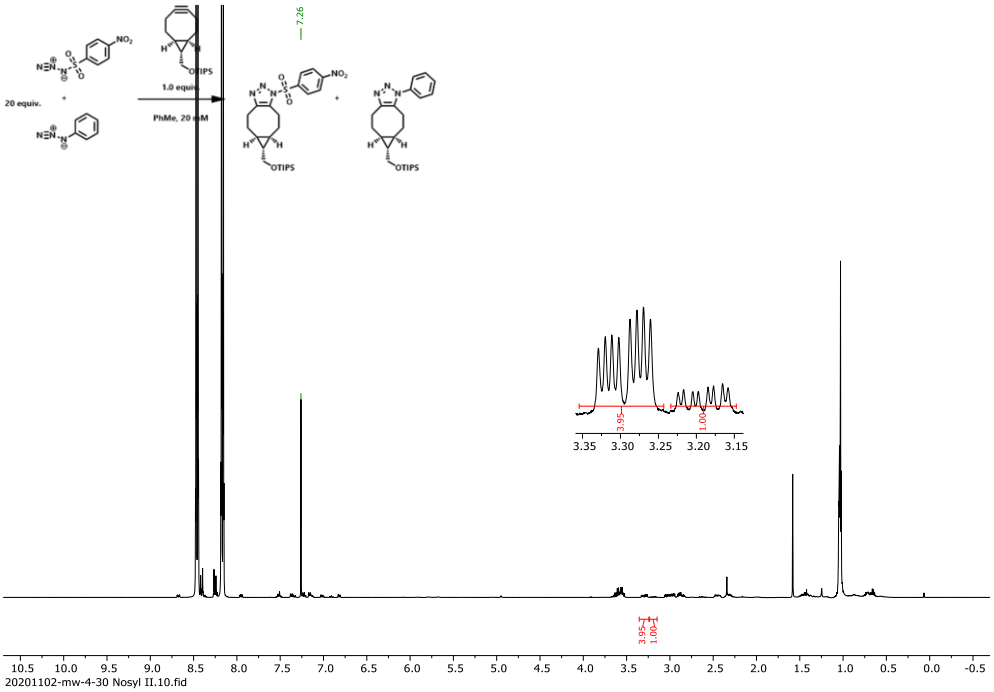
1.0 equiv.
PhMe, 20 mM
OTIPS
3.84
1.00
3.35 3.30 3.25 3.20 3.15 3.10
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
20201102-mw-4-30 Nosyl I.10.fid


7.26
20 equiv.
1.0 equiv.
PhMe, 20 mM
OTIPS
3.95
1.00
3.35 3.30 3.25 3.20 3.15
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
20201102-mw-4-30 Nosyl II.10.fid

9 References

1 R. A. Moss, *Chem. Rev.*, 2013, **113**, 6903–6904.

2 A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115**, 9981–10080.

3 L. Wolff, *Justus Liebigs Ann. Chem.*, 1902, **325**, 129–195.

4 G. Burdzinski, Y. Zhang, J. Wang and M. S. Platz, *J. Phys. Chem. A*, 2010, **114**, 13065–13068.

5 J. Wang, G. Burdzinski, J. Kubicki, T. L. Gustafson and M. S. Platz, *J. Am. Chem. Soc.*, 2008, **130**, 5418–5419.

6 P. Visser, R. Zuhse, M. W. Wong and C. Wentrup, *J. Am. Chem. Soc.*, 1996, **118**, 12598–12602.

7 P. de Frémont, N. Marion and S. P. Nolan, *Coord. Chem. Rev.*, 2009, **253**, 862–892.

8 M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, 1998.

9 H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2904.

10 J. Wang, F. Liang and B. Chen, *J. Org. Chem.*, 1998, **63**, 8589–8594.

11 L. Liu and J. Zhang, *Chem. Soc. Rev.*, 2016, **45**, 506–516.

12 X. Qi and J. M. Ready, *Angew. Chemie Int. Ed.*, 2007, **46**, 3242–3244.

13 N. D. Koduri, Z. Wang, G. Cannell, K. Cooley, T. M. Lemma, K. Miao, M. Nguyen, B. Frohock, M. Castaneda, H. Scott, D. Albinescu and S. R. Hussaini, *J. Org. Chem.*, 2014, **79**, 7405–7414.

14 J. Adams and D. M. Spero, *Tetrahedron*, 1991, **47**, 1765–1808.

15 S. M. Sheehan, A. Padwa and J. P. Snyder, *Tetrahedron Lett.*, 1998, **39**, 949–952.

16 J. P. Snyder, A. Padwa and T. Stengel, *J. Am. Chem. Soc.*, 2001, **123**, 11318–11319.

17 F. A. Cotton, B. G. DeBoer, M. D. LaPrade, J. R. Pipal and D. A. Ucko, *Acta Crystallogr. Sect. B Struct. Crystallogr. Cryst. Chem.*, 1971, **27**, 1664–1671.

18 G. A. Rempel, P. Legzdins, H. Smith, G. Wilkinson and D. A. Ucko, *Inorg. Synth.*, 2007, **13**, 90–91.

19 E. Martínez-Castro, S. Suárez-Pantiga and A. Mendoza, *Org. Process Res. Dev.*, 2020, **24**, 1207–1212.

20 C. G. Espino, K. W. Fiori, M. Kim and J. Du Bois, *J. Am. Chem. Soc.*, 2004, **126**, 15378–15379.

21 A. Padwa, J. P. Snyder, E. A. Curtis, S. M. Sheehan, K. J. Worsencroft and C. O. Kappe, *J. Am. Chem. Soc.*, 2000, **122**, 8155–8167.

22 E. Nakamura, N. Yoshikai and M. Yamanaka, *J. Am. Chem. Soc.*, 2002, **124**, 7181–7192.

23 F. M. Wong, J. Wang, A. C. Hengge and W. Wu, *Org. Lett.*, 2007, **9**, 1663–1665.

24 C. Werlé, R. Goddard, P. Philipps, C. Farès and A. Fürstner, *J. Am. Chem. Soc.*, 2016, **138**, 3797–3805.

25 H. M. L. Davies and E. G. Antoulinakis, *Org. React.*, 2001, 1–326.

26 S. Dong, X. Liu and X. Feng, *Acc. Chem. Res.*, 2022, **55**, 415–428.

27 H. M. L. Davies and J. R. Denton, *Chem. Soc. Rev.*, 2009, **38**, 3061–3071.

28 M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911–935.

29 H. Lebel, J. F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977–1050.

30 H. Pellissier, *Tetrahedron*, 2008, **64**, 7041–7095.

31 S. Ma, D. Mandalapu, S. Wang and Q. Zhang, *Nat. Prod. Rep.*, 2022, **39**, 926–945.

32 T. T. Talele, *J. Med. Chem.*, 2016, 59, 8712–8756.

33 Y. Lian, L. C. Miller, S. Born, R. Sarpong and H. M. L. Davies, *J. Am. Chem. Soc.*, 2010, **132**, 12422–12425.

34 H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2903.

35 J. Busch-Petersen and E. J. Corey, *J. Am. Chem. Soc*, 1976, **98**, 1641–1643.

36 Y. Xia, Z. Liu, L. Zhen, R. Ge, F. Ye, M. Hossain, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2014, **136**, 3013–3015.

37 B. S. P. David C. Forbes and B. S. P. Mark C. McMills, *Curr. Org. Chem.*, 2005, **5**, 1091–1105.

38 V. Bagheri, M. P. Doyle, J. Taunton and E. Elizabeth Claxton, *J. Org. Chem.*, 1988, **53**, 6158–6160.

39 X. Xu, P. Y. Zavalij and M. P. Doyle, *Angew. Chemie Int. Ed.*, 2012, **51**, 9829–9833.

40 J. Xue, H. L. Luk and M. S. Platz, *J. Am. Chem. Soc.*, 2011, **133**, 1763–1765.

41 A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, 1991, **91**, 263–309.

42 J. S. Clark, R. Berger, S. T. Hayes, H. M. Senn, L. J. Farrugia, L. H. Thomas, A. J. Morrison and L. Gobbi, *J. Org. Chem.*, 2013, **78**, 673–696.

43 M. C. Pirrung, H. Liu and A. T. Morehead, *J. Am. Chem. Soc.*, 2002, **124**, 1014–1023.

44 E. J. Roskamp and C. R. Johnson, *J. Am. Chem. Soc.*, 1986, **108**, 6062–6063.

45 M. C. Pirrung and J. A. Werner, *J. Am. Chem. Soc.*, 1986, **108**, 6060–6062.

46 J. S. Clark, T. C. Fessard and C. Wilson, *Org. Lett.*, 2004, **6**, 1773–1776.

47 F. Arndt and B. Eistert, *Ber. Dtsch. Chem. Ges.*, 1935, **68**, 200–208.

48 T. Ye and M. A. McKervey, *Chem. Rev.*, 1994, **94**, 1091–1160.

49 M. Jia and S. Ma, *Angew. Chemie Int. Ed.*, 2016, **55**, 9134–9166.

50 L. D. Proctor and A. J. Warr, in *Org. Process Res. Dev.*, 2002, **6**, 884–892.

51 H. Yang, B. Martin and B. Schenkel, *Org. Process Res. Dev.*, 2018, **22**, 446–456.

52 T. L. Gilchrist, G. E. Gymer and C. W. Rees, *J. Chem. Soc. Perkin Trans. 1*, 1975, 1–8.

53 T. L. Gilchrist, C. W. Rees and C. Thomas, *J. Chem. Soc. Perkin Trans. 1*, 1975, 8.

54 A. R. Katritzky, Z. Wang, M. Tsikolia, C. D. Hall and M. Carman, *Tetrahedron Lett.*, 2006, **47**, 7653–7654.

55 A. S. Kumar, V. D. Ghule, S. Subrahmanyam and A. K. Sahoo, *Chem. – A Eur. J.*, 2013, **19**, 509–518.

56 V. Hugenberg, B. Riemann, S. Hermann, O. Schober, M. Schäfers, K. Szardenings, A. Lebedev, U. Gangadharmath, H. Kolb, J. Walsh, W. Zhang, K. Kopka and S. Wagner, *J. Med. Chem.*, 2013, **56**, 6858–6870.

57 G. Aromí, L. A. Barrios, O. Roubeau and P. Gamez, *Coord. Chem. Rev.*, 2011, **255**, 485–546.

58 T. Duan, K. Fan, Y. Fu, C. Zhong, X. Chen, T. Peng and J. Qin, *Dye. Pigment.*, 2012, **94**, 28–33.

59 T. Zheng, S. H. Rouhanifard, A. S. Jalloh and P. Wu, *Top Heterocycl Chem*, 2012, **28**, 163–183.

60 A. H. El-Sagheer and T. Brown, *Chem. Commun.*, 2011, **47**, 12057–12058.

61 S. G. Agalave, S. R. Maujan and V. S. Pore, *Chem. – An Asian J.*, 2011, **6**, 2696–2718.

62 H. C. Kolb and K. B. Sharpless, *Drug Discov. Today*, 2003, **8**, 1128–1137.

63 C. H. Zhou and Y. Wang, *Curr. Med. Chem.*, 2012, **19**, 239–280.

64 O. Piloty and J. Neresheimer, *Ber. Dtsch. Chem. Ges.*, 1906, **39**, 514–517.

65 O. Dimroth, *Justus Liebig's Ann. der Chemie*, 1909, **364**, 183–226.

66 O. Dimroth and W. Michaelis, *Justus Liebig's Ann. Chem.*, 1927, **459**, 39–46.

67 P. Grünanger, P. V. Finzi and C. Scotti, *Chem. Ber.*, 1965, **98**, 623–628.

68 R. E. Harmon, F. Stanley, S. K. Gupta and J. Johnson, *J. Org. Chem.*, 1970, **35**, 3444–3448.

69 M. E. Hermes and F. D. Marsh, *J. Am. Chem. Soc.*, 1967, **89**, 4760–4764.

70 Y. A. Rozin, E. A. Vorob'ova, Y. Y. Morzherin and V. A. Bakulev, *Chem. Heterocycl. Compd.* 2001, **37**, 294–304.

71 M. E. Hermes and F. D. Marsh, *J. Am. Chem. Soc.*, 1967, **89**, 4760–4764.

72 C. L. Habraken, C. Erkelens, J. R. Mellema and P. Cohen-Fernandes, *J. Org. Chem.*, 1984, **49**, 2197–2200.

73 Y. Y. Morzherin, Y. A. Rozin, E. A. Savel'eva and V. A. Bakulev, *Chem. Heterocycl. Compd.,* 2003, **39**, 168–173.

74 Y. A. Rosin, *Mendeleev Commun.*, 1998, **8**, 240–241.

75 S. Chuprakov, F. W. Hwang and V. Gevorgyan, *Angew. Chemie Int. Ed.*, 2007, **46**, 4757–4759.

76 R. E. Harmon, F. Stanley, S. K. Gupta and J. Johnson, *J. Org. Chem.*, 1970, **35**, 3444–3448.

77 T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 14972–14974.

78 B. Chattopadhyay and V. Gevorgyan, *Angew. Chemie Int. Ed.*, 2012, **51**, 862–872.

79 H. M. L. Davies and J. S. Alford, *Chem. Soc. Rev.*, 2014, **43**, 5151–5162.

80 P. Anbarasan, D. Yadagiri and S. Rajasekar, *Synth.*, 2014, **46**, 3004–3023.

81 Y. Li, H. Yang and H. Zhai, *Chem. - A Eur. J.*, 2018, **24**, 12757–12766.

82 T. Miura and M. Murakami, *Rhodium Catalysis in Organic Synthesis*, Wiley, Weinheim, Germany, 2019, vol. 7, pp. 449–470.

83 M. Akter, K. Rupa and P. Anbarasan, *Chem. Rev.*, 2022, **122**, 13108–13205.

84 T. Miura, M. Yamauchi and M. Murakami, *Chem. Commun.*, 2009, **7345**, 1470.

85 J. S. Alford and H. M. L. Davies, *Org. Lett.*, 2012, **14**, 6020–6023.

86 A. Boyer, *Org. Lett.*, 2014, **16**, 1660–1663.

87 D. Yadagiri and P. Anbarasan, *Org. Lett.*, 2014, **16**, 2510–2513.

88 D. J. Lee, J. Shin and E. J. Yoo, *Chem. Commun.*, 2014, **50**, 6620–6622.

89 F. Medina, C. Besnard and J. Lacour, *Org. Lett.*, 2014, **16**, 3232–3235.

90 E. E. Schultz, V. N. G. Lindsay and R. Sarpong, *Angew. Chemie*, 2014, **126**, 10062–10066.

91 X. H. Pan, P. Jiang, Z. H. Jia, K. Xu, J. Cao, C. Chen, M. H. Shen and H. D. Xu, *Tetrahedron*, 2015, **71**, 5124–5129.

92 S. W. Kwok, L. Zhang, N. P. Grimster and V. V. Fokin, *Angew. Chemie Int. Ed.*, 2014, **53**, 3452–3456.

93 H. D. Xu, K. Xu, Z. H. Jia, H. Zhou, P. Jiang, X. L. Lu, Y. P. Pan, H. Wu, Y. Ding, M. H. Shen and X. H. Pan, *Asian J. Org. Chem.*, 2014, **3**, 1154–1158.

94 T. Miura, T. Tanaka, T. Biyajima, A. Yada and M. Murakami, *Angew. Chemie Int. Ed.*, 2013, **52**, 3883–3886.

95 S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit and V. V Fokin, *J. Am. Chem. Soc.*, 2014, **136**, 195–202.

96 J.-M. Yang, C.-Z. Zhu, X.-Y. Tang and M. Shi, *Angew. Chemie*, 2014, **126**, 5242–5246.

97 V. N. G. Lindsay, H. M. F. Viart and R. Sarpong, *J. Am. Chem. Soc.*, 2015, **137**, 8368–8371.

98 J. Meng, M. Wen, S. Zhang, P. Pan, X. Yu and W. P. Deng, *J. Org. Chem.*, 2017, **82**, 1676–1687.

99 T. Miura, T. Tanaka, A. Yada and M. Murakami, *Chem. Lett.*, 2013, **42**, 1308–1310.

100 A. Boyer, *Org. Lett.*, 2014, **16**, 1660–1663.

101 A. Boyer, *Org. Lett.*, 2014, **16**, 5878–5881.

102 D. Yadagiri and P. Anbarasan, *Chem. – A Eur. J.*, 2013, **19**, 15115–15119.

103 S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher and V. V. Fokin, *J. Am. Chem. Soc.*, 2009, **131**, 18034–18035.

104 T. Miura, T. Nakamuro, S. G. Stewart, Y. Nagata and M. Murakami, *Angew. Chemie Int. Ed.*, 2017, **56**, 3334–3338.

105 H. Shang, Y. Wang, Y. Tian, J. Feng and Y. Tang, *Angew. Chemie Int. Ed.*, 2014, **53**, 5662–5666.

106 T. Miura, T. Nakamuro, C. J. Liang and M. Murakami, *J. Am. Chem. Soc.*, 2014, **136**, 15905–15908.

107 T. Miura, T. Nakamuro, T. Biyajima and M. Murakami, *Chem Lett.*, 2015, **44**, 700–702.

108 C. E. Kim, S. Park, D. Eom, B. Seo and P. H. Lee, *Org. Lett.*, 2014, **16**, 1900–1903.

109 B. T. Parr, S. A. Green and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 4716–4718.

110 T. Miura, M. Yamauchi and M. Murakami, *Chem. Commun.*, 2009, **0**, 1470.

111 Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 7734–7735.

112 S. Chuprakov, J. A. Malik, M. Zibinsky and V. V. Fokin, *J. Am. Chem. Soc.*, 2011, **133**, 10352–10355.

113 L. Li, X.-H. Xia, Y. Wang, P. P. Bora and Q. Kang, *Adv. Synth. Catal.*, 2015, **357**, 2089–2097.

114 A. A. Ogunlana, J. Zou and X. Bao, *J. Org. Chem.*, 2019, **84**, 8151–8159.

115 D. J. Lee and E. J. Yoo, *Org. Lett*, 2015, **17**, 1830–1833.

116 G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563–639.

117 X. He, Y. Wu, T. Zhou, Y. Zuo, M. Xie, R. Li, J. Duan and Y. Shang, *Synth. Commun.*, 2020, **50**, 2685–2697.

118 H. J. Jeon, D. J. Jung, J. H. Kim, Y. Kim, J. Bouffard and S. G. Lee, *J. Org. Chem.*, 2014, **79**, 9865–9871.

119 Y. S. Zhang, X. Y. Tang and M. Shi, *Chem. Commun.*, 2014, **50**, 15971–15974.

120 X. Y. Tang, Y. S. Zhang, L. He, Y. Wei and M. Shi, *Chem. Commun.*, 2014, **51**, 133–136.

121 M. L. Martin and A. Boyer, *European J. Org. Chem.*, 2021, **43**, 5857–5861.

122 N. Selander and V. V. Fokin, *J. Am. Chem. Soc.*, 2012, **134**, 2477–2480.

123 T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 17440–17443.

124 N. Selander, B. T. Worrell and V. V. Fokin, *Angew. Chemie Int. Ed.*, 2012, **51**, 13054–13057.

125 M. Zibinsky and V. V. Fokin, *Angew. Chemie Int. Ed.*, 2013, **52**, 1507–1510.

126 W. B. Zhang, S. D. Xiu and C. Y. Li, *Org. Chem. Front.*, 2015, **2**, 47–50.

127 D. J. Lee, H. S. Han, J. Shin and E. J. Yoo, *J. Am. Chem. Soc.*, 2014, **136**, 11606–11609.

128 S. Samala, D. H. Ryu, C. E. Song and E. J. Yoo, *Org. Biomol. Chem.*, 2019, **17**, 1773–1777.

129 J. Y. Lee, R. K. Varshnaya and E. J. Yoo, *Org. Lett.*, 2022, **24**, 3731–3735.

130 W. Kirmse and M. Kapps, *Chem. Ber.*, 1968, **101**, 994–1003.

131 A. Boyer, *J. Org. Chem.*, 2015, **80**, 4771–4775.

132 R. Huisgen, *Angew. Chemie Int. Ed.*, 1963, **2**, 633–645.

133 R. Huisgen, *Proc. Chem. Soc.*, 1961, 357–396.

134 R. Huisgen, *Angew. Chemie Int. Ed. English*, 1963, **2**, 565–598.

135 R. Huisgen, G. Szeimies and L. Möbius, *Chem. Ber.*, 1967, **100**, 2494–2507.

136 R. Huisgen, *Angew. Chemie Int. Ed.*, 1963, **2**, 633–645.

137 R. Huisgen, R. Knorr, L. Möbius and G. Szeimies, *Chem. Ber.*, 1965, **98**, 4014–4021.

138 T. Curtius and W. Klavehn, *J. für Prakt. Chemie*, 1930, **125**, 498–523.

139 M. L. Martin and A. Boyer, *European J. Org. Chem.*, 2021, **2021**, 5857–5861.

140 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chemie Int. Ed.*, 2002, **41**, 2596–2599.

141 C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064.

142 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chemie Int. Ed.*, 2001, **40**, 2004–2021.

143 J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, 39, 1302–1315.

144 E. Haldón, M. C. Nicasio and P. J. Pérez, *Org. Biomol. Chem.*, 2015, **13**, 9528–9550.

145 J. González, V. M. Pérez, D. O. Jiménez, G. Lopez-Valdez, D. Corona and E. Cuevas-Yañez, *Tetrahedron Lett.*, 2011, **52**, 3514–3517.

146 C. G. Gordon, J. L. Mackey, J. C. Jewett, E. M. Sletten, K. N. Houk and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2012, **134**, 9199–9208.

147 R. Berg and B. F. Straub, *Beilstein J. Org. Chem. 9308*, 2013, **9**, 2715–2750.

148 E. Haldón, M. C. Nicasio and P. J. Pérez, *Org. Biomol. Chem.*, 2015, **13**, 9528–9550.

149 S. Neumann, M. Biewend, S. Rana and W. H. Binder, *Macromol. Rapid Commun.*, 2019, **41**, 1900359.

150 J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302.

151 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210–216.

152 Y. Özkllç and N. S. Tüzün, *Organometallics*, 2016, **35**, 2589–2599.

153 I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 2038–2039.

154 J. Y. Eun, M. Ahlquist, I. Bae, K. B. Sharpless, V. V. Fokin and S. Chang, *J. Org. Chem.*, 2008, **73**, 5520–5528.

155 S. H. Kim, S. H. Park, J. H. Choi and S. Chang, *Chem. - An Asian J.*, 2011, **6**, 2618–2634.

156 E. J. Yoo and S. Chang, *Curr. Org. Chem.*, 2009, **13**, 1766–1776.

157 E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless and S. Chang, *Angew. Chemie Int. Ed.*, 2007, **46**, 1730–1733.

158 J. Raushel and V. V. Fokin, *Org. Lett.*, 2010, **12**, 4952–4955.

159 J. R. Johansson, T. Beke-Somfai, A. Said Stålsmeden and N. Kann, *Chem. Rev.*, 2016, 116, 14726–14768.

160 M. E. Meza-Aviña, M. K. Patel and M. P. Croatt, *Tetrahedron*, 2013, **69**, 7840–7846.

161 G. R. Harvey, *J. Org. Chem.*, 1966, **31**, 1587–1590.

162 S. Rajasekar and P. Anbarasan, *Chem. – An Asian J.*, 2019, **14**, 4563–4567.

163 J. H. Boyer, C. H. Mack, N. Goebel and L. R. Morgan, *J. Org. Chem.*, 1958, **23**, 1051–1053.

164 M. E. Meza-Aviña, M. K. Patel, C. B. Lee, T. J. Dietz and M. P. Croatt, *Org. Lett.*, 2011, **13**, 2984–2987.

165 Reaxys search performed January 2023.

166 A. T. Blomquist and L. H. Liu, *J. Am. Chem. Soc.*, 1953, **75**, 2153–2154.

167 G. Wittig and A. Krebs, *Chem. Ber.*, 1961, **94**, 3260–3275.

168 N. J. Agard, J. A. Prescher and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2004, **126**, 15046–15047.

169 J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli and C. R. Bertozzi, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 16793–16797.

170 J. M. Baskin and C. R. Bertozzi, *QSAR Comb. Sci.*, 2007, **26**, 1211–1219.

171 P. V. Changa, J. A. Preschera, E. M. Sletten, J. M. Baskin, I. A. Miller, N. J. Agard, A. Lo and C. R. Bertozzi, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 1821–1826.

172 D. Heber, P. Rösner and W. Tochtermann, *European J. Org. Chem.*, 2005, **2005**, 4231–4247.

173 L. Brandsma and H. D. Verkruijsse, *Synthesis*, 1978, **1978**, 290–290.

174 This route to cyclooctyne was also performed by Ruaraidh Wells in the Boyer Research Group.

175 The intermolecular reactions were first performed by Ruaraidh Wells in the Boyer Research Group.

176 H. Wang, H. Qiao, H. Zhang, H. Yang, Y. Zhao and H. Fu, *European J. Org. Chem.*, 2015, **2015**, 4471–4480.

177 A. C. Cope, H. Lee and H. E. Petree, *J. Am. Chem. Soc.*, 1958, **80**, 2849–2852.

178 L. A. Paquette, Y. Miyahara and C. W. Doecke, *J. Am. Chem. Soc.*, 1986, **108**, 1716–1718.

179 D. Stead, P. O'Brien and A. Sanderson, *Org. Lett.*, 2008, **10**, 1409–1412.

180 P. Müller and P. Nury, *Helv. Chim. Acta*, 2001, **84**, 662–677.

181 D. M. Hodgson and I. D. Cameron, *Org. Lett.*, 2001, **3**, 441–444.

182 D. M. Hodgson, T. J. Buxton, I. D. Cameron, E. Gras and E. H. M. Kirton, *Org. Biomol. Chem.*, 2003, **1**, 4293–4301.

183 M. Regitz and J. Rüter, *Chem. Ber.*, 1969, **102**, 3877–3890.

184 G. Engling, T. Emrick, J. Hellmann, E. McElroy, M. Brandt and I. D. Reingold, *J. Org. Chem.*, 1994, **59**, 1945–1945.

185 P. M. Üller and E. M. Aîtrejean, 1999, **64**, 1807–1826.

186 A. Krebs and H. Kimling, *Angew. Chemie Int. Ed.*, 1971, **10**, 409–410.

187 C. B. Reese and A. Shaw, *J. Chem. Soc. Chem. Commun.*, 1972, 787–788.

188 A. T. Blomquist, R. E. Burge and A. C. Sucsy, *J. Am. Chem. Soc.*, 1952, **74**, 3636–3642.

189 A. T. Blomquist, L. H. Liu and J. C. Bohrer, *J. Am. Chem. Soc.*, 1952, **74**, 3643–3647.

190 C. B. Reese and A. Shaw, *J. Chem. Soc. D Chem. Commun.*, 1970, 1172.

191 R. F. Lockwood and K. M. Nicholas, *Tetrahedron Lett.*, 1977, **18**, 4163–4165.

192 K. M. Nicholas and R. Pettit, *J. Organomet. Chem.*, 1972, **44**, C21–C24.

193 T. Hagendorn and S. Bräse, *RSC Adv.*, 2014, **4**, 15493–15495.

194 R. Ni, N. Mitsuda, T. Kashiwagi, K. Igawa and K. Tomooka, *Angew. Chemie Int. Ed.*, 2015, **54**, 1190–1194.

195 J. Dommerholt, S. Schmidt, R. Temming, L. J. A. Hendriks, F. P. J. T. Rutjes, J. C. M. van Hest, D. J. Lefeber, P. Friedl and F. L. van Delft, *Angew. Chemie Int. Ed.*, 2010, **49**, 9422–9425.

196 J. Dommerholt, F. P. J. T. Rutjes and F. L. van Delft, *Top. Curr. Chem.*, 2016, 374.

197 C. Rücker, *Chem. Rev.*, 1995, **95**, 1009–1064.

198 M. Schelhaas and H. Waldmann, *Angew. Chemie Int. Ed.*, 1996, **35**, 2056–2083.

199 E. J. Corey and M. Sodeoka, *Tetrahedron Lett.*, 1991, **32**, 7005–7008.

200 F. Xiao and J. Wang, *J. Org. Chem.*, 2006, **71**, 5789–5791.

201 N. Jiang, Z. Qu and J. Wang, *Org. Lett.*, 2001, **3**, 2989–2991.

202 N. Ikota, N. Takamura, S. D. Young and B. Ganem, *Tetrahedron Lett.*, 1981, **22**, 4163–4166.

203 D. H. Ess, G. O. Jones and K. N. Houk, *Org. Lett.*, 2008, **10**, 1633–1636.

204 F. Schoenebeck, D. H. Ess, G. O. Jones and K. N. Houk, *J. Am. Chem. Soc.*, 2009, **131**, 8121–8133.

205 J. Dommerholt, O. van Rooijen, A. Borrmann, C. F. Guerra, F. M. Bickelhaupt and F. L. van Delft, *Nat. Commun.*, 2014, **5**, 5378.

206 D. H. Ess and K. N. Houk, *J. Am. Chem. Soc.*, 2007, **129**, 10646–10647.

207 F. M. Bickelhaupt and K. N. Houk, *Angew. Chemie Int. Ed.*, 2017, **56**, 10070–10086.

208 I. Fernández and F. M. Bickelhaupt, *Chem. Soc. Rev.*, 2014, 43, 4953–4967.

209 D. H. Ess, G. O. Jones and K. N. Houk, *Adv. Synth. Catal.*, 2006, **348**, 2337–2361.

210 J. M. Turney, A. C. Simmonett, R. M. Parrish, E. G. Hohenstein, F. A. Evangelista, J. T. Fermann, B. J. Mintz, L. A. Burns, J. J. Wilke, M. L. Abrams, N. J. Russ, M. L. Leininger, C. L. Janssen, E. T. Seidl, W. D. Allen, H. F. Schaefer, R. A. King, E. F. Valeev, C. D. Sherrill and T. D. Crawford, *Wiley Interdiscip. Rev. Comput. Mol. Sci.*, 2012, **2**, 556–565.

211 I. Yavari, F. Nasiri, H. Djahaniani and A. Jabbari, *Int. J. Quantum Chem.*, 2006, **106**, 697–703.

212 J. Dommerholt, F. P. J. T. Rutjes and F. L. van Delft, *Top. Curr. Chem.*, 2016, **374**, 16.

213 J. C. Jewett, E. M. Sletten and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2010, **132**, 3688–3690.

214 A. Kuzmin, A. Poloukhtine, M. A. Wolfert and V. V. Popik, *Bioconjug. Chem.*, 2010, **21**, 2076–2085.

215 J. A. Codelli, J. M. Baskin, N. J. Agard and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2008, **130**, 11486–11493.

216 L. S. Campbell-Verduyn, L. Mirfeizi, A. K. Schoonen, R. A. Dierckx, P. H. Elsinga and B. L. Feringa, *Angew. Chemie Int. Ed.*, 2011, **50**, 11117–11120.

217 L. Qian, C. J. Zhang, J. Wu and S. Q. Yao, *Chem. - A Eur. J.*, 2017, **23**, 360–369.

218 S. Yoshida, A. Shiraishi, K. Kanno, T. Matsushita, K. Johmoto, H. Uekusa and T. Hosoya, *Sci. Rep.*, 2011, **1**, 4–7.

219 E. S. Zimmerman, T. H. Heibeck, A. Gill, X. Li, C. J. Murray, M. R. Madlansacay, C. Tran, N. T. Uter, G. Yin, P. J. Rivers, A. Y. Yam, W. D. Wang, A. R. Steiner, S. U. Bajad, K. Penta, W. Yang, T. J. Hallam, C. D. Thanos and A. K. Sato, *Bioconjug. Chem.*, 2014, **25**, 351–361.

220 R. C. Chadwick, S. Van Gyzen, S. Liogier and A. Adronov, *Synth.*, 2014, **46**, 669–677.

221 M. F. Debets, J. S. Prins, D. Merkx, S. S. Van Berkel, F. L. Van Delft, J. C. M. Van Hest and F. P. J. T. Rutjes, *Org. Biomol. Chem.*, 2014, **12**, 5031–5037.

222 A. A. Poloukhtine, N. E. Mbua, M. A. Wolfert, G. J. Boons and V. V. Popik, *J. Am. Chem. Soc.*, 2009, **131**, 15769–15776.

223 K. Lang, L. Davis, S. Wallace, M. Mahesh, D. J. Cox, M. L. Blackman, J. M. Fox and J. W. Chin, *J. Am. Chem. Soc.*, 2012, **134**, 10317–10320.

224 J. P. Guthrie, *Can. J. Chem.*, 1978, **56**, 2342–2354.

225 O. A. El Seoud, W. J. Baader and E. L. Bastos, *Encyclopedia of Physical Organic Chemistry, 5 Volume Set*, John Wiley & Sons, Inc., New Jersey, USA, 2016, pp. 1–68.

226 A. Gradillas and J. Pérez-Castells, *Angew. Chemie Int. Ed.*, 2006, **45**, 6086–6101.

227 A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199–2238.

228 S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer and S. J. Taylor, *J. Chem. Soc. Perkin Trans. 1*, 2000, 3815–4195.

229 S. Sussman, *Ind. Eng. Chem.*, 1946, **38**, 1228–1230.

230 R. B. Merrifield, *J. Am. Chem. Soc.*, 1963, **85**, 2149–2154.

231 R. L. Letsinger and M. J. Kornet, *J. Am. Chem. Soc.*, 1963, **85**, 3045–3046.

232 T. Kodadek, *Chem. Commun.*, 2011, **47**, 9757–9763.

233 B. Hinzen and S. V. Ley, *J. Chem. Soc. - Perkin Trans. 1*, 1997, 1907–1908.

234 F. M. Menger, H. Shinozaki and H. C. Lee, *J. Org. Chem.*, 1980, **45**, 2724–2725.

235 E. D. Goddard-Borger and R. V. Stick, *Org. Lett.*, 2011, **13**, 2514.

236 J. C. Hodges, L. S. Harikrishnan and S. Ault-Justus, *J. Comb. Chem.*, 2000, **2**, 80–88.

237 R. A. Amos, R. W. Emblidge and N. Havens, *J. Org. Chem.*, 1983, **48**, 3598–3600.

238 Z. Moussa, Z. M. A. Judeh and S. A. Ahmed, *RSC Adv.*, 2019, **9**, 35217–35272.

239 C. A. Bell, Z. Jia, S. Perrier and M. J. Monteiro, *J. Polym. Sci. Part A Polym. Chem.*, 2011, **49**, 4539–4548.

240 J. Lu and P. H. Toy, *Chem. Rev.*, 2009, 109, 815–838.

241 P. T. Nyffeler, C. H. Liang, K. M. Koeller and C. H. Wong, *J. Am. Chem. Soc.*, 2002, **124**, 10773–10778.

242 G. M. Green, N. P. Peet and W. A. Metz, *J. Org. Chem.*, 2001, **66**, 2509–2511.

243 T. Miura, Q. Zhao and M. Murakami, *Angew. Chemie Int. Ed.*, 2017, **56**, 16645–16649.

244 M. Tian, B. Liu, J. Sun and X. Li, *Org. Lett.*, 2018, **20**, 4946–4949.

245 B. Alcaide, P. Almendros, I. Fernández, T. M. del Campo, G. Palop, M. Toledano-Pinedo and P. Delgado-Martínez, *Adv. Synth. Catal.*, 2019, **361**, 1160–1165.

246 Y. Liu, Y. Chen, A. Yihuo, Y. Zhou, X. Liu, L. Lin and X. Feng, *ACS Catal.*, 2022, **12**, 1784–1790.

247 Q. Zhao, T. Miura and M. Murakami, *Chem. Lett.*, 2019, **48**, 510–512.

248 B. Alcaide, P. Almendros, S. Cembellín, T. Martínez del Campo and G. Palop, *Chem. - A Eur. J.*, 2017, **23**, 13754–13759.

249 H. Shang, Y. Wang, Y. Tian, J. Feng and Y. Tang, *Angew. Chemie Int. Ed.*, 2014, **53**, 5662–5666.

250 Z. Liu, L. Chen, D. Zhu and S. Zhu, *Org. Lett.*, 2021, **23**, 1275–1279.

251 J. Feng, Y. Wang, Q. Li, R. Jiang and Y. Tang, *Tetrahedron Lett.*, 2014, **55**, 6455–6458.

252 R. Q. Ran, J. He, S. D. Xiu, K. B. Wang and C. Y. Li, *Org. Lett.*, 2014, **16**, 3704–3707.

253 L. Xia and Y. R. Lee, *Adv. Synth. Catal.*, 2013, **355**, 2361–2374.

254 M. P. Doyle and D. van Leusen, *J. Org. Chem.*, 1982, **47**, 5326–5339.

255 Z. Margolin and F. A. Long, *J. Am. Chem. Soc.*, 1973, **95**, 2757–2762.

256 B. R. Rushing and M. I. Selim, *Food Chem. Toxicol.*, 2019, **124**, 81–100.

257 H. Li, C. Gao, C. Liu, L. Liu, J. Zhuang, J. Yang, C. Zhou, F. Feng, C. Sun and J. Wu, *Biomed. Pharmacother.*, 2021, **137**, 111332.

258 C. H. Díaz Nieto, A. M. Granero, M. A. Zon and H. Fernández, *Food Chem. Toxicol.*, 2018, **118**, 460–470.

259 E. Loğoğlu, M. Yilmaz, H. Katircioğlu, M. Yakut and S. Mercan, *Med. Chem. Res.*, 2010, **19**, 490–497.

260 Y. Asakawa, M. Toyota and T. Takemoto, *Phytochemistry*, 1981, **20**, 257–261.

261 H. Sato, K. Konoma and S. Sakamura, *Agric. Biol. Chem.*, 1979, **43**, 2409–2411.

262 S. N. Abramson, E. E. Harold, P. Taylor, J. A. Trischman, D. M. Tapiolas and W. Fenical, *J. Med. Chem.*, 1991, **34**, 1798–1804.

263 X. Ma, F. Wu, X. Yi, H. Wang and W. Chen, *Chem. Commun.*, 2015, **51**, 6862–6865.

264 G. S. Sontakke, K. Pal and C. M. R. Volla, *J. Org. Chem.*, 2019, **84**, 12198–12208.

265 S. Kaladevi, M. Kamalraj, M. Altia, S. Rajasekar and P. Anbarasan, *Chem. Commun.*, 2019, **55**, 4507–4510.

266 X. Cheng, Y. Yu, Z. Mao, J. Chen and X. Huang, *Org. Biomol. Chem.*, 2016, **14**, 3878–3882.

267 Addition of various nucleophiles to sulfonyl imines on similar substrates was investigated by Fraser Barr in the Boyer Research Group (undergraduate research project).

268 B. Chattopadhyay and V. Gevorgyan, *Org. Lett.*, 2011, **13**, 3746–3749.

269 A. Vilsmeier and A. Haack, *Ber. Dtsch. Chem. Ges.*, 1927, **60**, 119–122.

270 J. A. Hirsch, *Top. Stereochem.*, 2007, **1**, 199–222.

271 E. L. Eliel and S. H. Wilen, *Stereochem. Org. Compd.*, 1994, 686–740.

272 T. J. Curphey, *Org. Prep. Proced. Int.*, 1981, **13**, 112–115.

273 R. C. Fischer and P. P. Power, *Chem. Rev.*, 2010, **110**, 3877–3923.

274 S. Hohloch, C. Y. Su and B. Sarkar, *Eur. J. Inorg. Chem.*, 2011, **2011**, 3067–3075.

275 T. Matsuo, K. Suzuki, T. Fukawa, B. Li, M. Ito, Y. Shoji, T. Otani, L. Li, M. Kobayashi, M. Hachiya, Y. Tahara, D. Hashizume, T. Fukunaga, A. Fukazawa, Y. Li, H. Tsuji and K. Tamao, *Bull. Chem. Soc. Jpn.*, 2011, **84**, 1178–1191.

276 T. Miura, T. Tanaka, K. Matsumoto and M. Murakami, *Chem. - A Eur. J.*, 2014, **20**, 16078–16082.

277 N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994–2009.

278 G. Fang and X. Bi, *Chem. Soc. Rev.*, 2015, **44**, 8124–8173.

279 N. Singh, S. Singh, S. Kohli, A. Singh, H. Asiki, G. Rathee, R. Chandra and E. A. Anderson, *Org. Chem. Front.*, 2021, **8**, 5550–5573.

280 I. S. Young, P. D. Thornton and A. Thompson, *Nat. Prod. Rep.*, 2010, **27**, 1801–1839.

281 A. Fürstner, *Angew. Chemie Int. Ed.*, 2003, **42**, 3582–3603.

282 G. Li Petri, V. Spanò, R. Spatola, R. Holl, M. V. Raimondi, P. Barraja and A. Montalbano, *Eur. J. Med. Chem.*, 2020, **208**, 112783.

283 V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, *RSC Adv.*, 2015, **5**, 15233–15266.

284 D. Curran, J. Grimshaw and S. D. Perera, *Chem. Soc. Rev.*, 1991, **20**, 391–404.

285 H. Maeda, *B. Chem. Soc. Jpn.*, 2013, **86**, 1359–1399.

286 A. Loudet and K. Burgess, *Chem. Rev.*, 2007, **107**, 4891–4932.

287 L. Knorr, *Ber. Dtsch. Chem. Ges*, 1884, **17**, 1635–1642.

288 C. Paal, *Ber. Dtsch. Chem. Ges.,* 1885, **18**, 367–371.

289 R. Huisgen and E. Laschtuvka, *Chem. Ber.*, 1960, **93**, 65–81.

290 A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 1474–1476.

291 D. D. Xuan, *Curr. Org. Chem.*, 2020, **24**, 622–657.

292 T. A. Moss and T. Nowak, *Tetrahedron Lett.*, 2012, **53**, 3056–3060.

293 A. C. Finlay, F. A. Hochstein, B. A. Sobin and F. X. Murphy, *J. Am. Chem. Soc.*, 1951, **73**, 341–343.

294 F. Arcamone, S. Penco, P. Orezzi, V. Nicolella and A. Pirelli, *Nature*, 1964, **203**, 1064–1065.

295 X. Han, Z. Liu, Z. Zhang, X. Zhang, T. Zhu, Q. Gu, W. Li, Q. Che and D. Li, *J. Nat. Prod.*, 2017, **80**, 1684–1687.

296 H. Zhao, A. Yang, N. Zhang, S. Li, T. Yuan, N. Ding, S. Zhang, S. Bao, C. Wang, Y. Zhang, X. Wang and L. Hu, *J. Agric. Food Chem.*, 2020, **68**, 1588–1595.

297 K. Gewald, H. Schäfer, P. Bellmann and U. Hain, *J. für Prakt. Chemie.*, 1992, **334**, 491–496.

298 J. Cobb, I. N. Demetropoulos, D. Korakas, S. Skoulika and G. Varvounis, *Tetrahedron*, 1996, **52**, 4485–4494.

299 E. E. Galenko, A. V. Galenko, A. F. Khlebnikov, M. S. Novikov and J. R. Shakirova, *J. Org. Chem.*, 2016, **81**, 8495–8507.

300 A. F. Khlebnikov, M. V. Golovkina, M. S. Novikov and D. S. Yufit, *Org. Lett.*, 2012, **14**, 3768–3771.

301 E. E. Schultz and R. Sarpong, *J. Am. Chem. Soc.*, 2013, **135**, 4696–4699.

302 T. Miura, K. Hiraga, T. Biyajima, T. Nakamuro and M. Murakami, *Org. Lett.*, 2013, **15**, 3298–3301.

303 Y. Xing, G. Sheng, J. Wang, P. Lu and Y. Wang, *Org. Lett.*, 2014, **16**, 1244–1247.

304 L. Zhang, G. Sun and X. Bi, *Chem. - An Asian J.*, 2016, **11**, 3018–3021.

305 F. Li, C. Pei and R. M. Koenigs, *Chem. Sci.*, 2021, **12**, 6362–6369.

306 Y. Shi and V. Gevorgyan, *Org. Lett.*, 2013, **15**, 5394–5396.

307 S. Rajasekar and P. Anbarasan, *J. Org. Chem.*, 2014, **79**, 8428–8434.

308 C. E. Kim, Y. Park, S. Park and P. H. Lee, *Adv. Synth. Catal.*, 2014, **357**, 210–220.

309 H. Yang, S. Hou, C. Tao, Z. Liu, C. Wang, B. Cheng, Y. Li and H. Zhai, *Chem. – A Eur. J.*, 2017, **23**, 12930–12936.

310 S. Rajasekar and P. Anbarasan, *Chem. – An Asian J.*, 2019, **14**, 4563–4567.

311 J. Bi, Q. Tan, H. Wu, Q. Liu and G. Zhang, *Org. Lett.*, 2021, **23**, 6357–6361.

312 J. E. Spangler and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 6802–6805.

313 J. S. Alford and H. M. L. Davies, *J. Am. Chem. Soc.*, 2014, **136**, 10266–10269.

314 P. P. Bora, Z. L. Luo, L. Chen and Q. Kang, *Tetrahedron*, 2016, **72**, 1467–1471.

315 L. Fu and H. M. L. Davies, *Org. Lett.*, 2017, **19**, 1504–1507.

316 Y. Z. Zhao, H. Bin Yang, X. Y. Tang and M. Shi, *Chem. - A Eur. J.*, 2015, **21**, 3562–3566.

317 A. R. Khaidarov, N. V. Rostovskii, G. L. Starova, A. F. Khlebnikov and M. S. Novikov, *Chem. Heterocycl. Compd.*, 2018, **54**, 946–950.

318 Y. Wang, X. Lei and Y. Tang, *Chem. Commun.*, 2015, **51**, 4507–4510.

319 A. R. Khaidarov, N. V. Rostovskii, A. A. Zolotarev, A. F. Khlebnikov and M. S. Novikov, *J. Org. Chem.*, 2019, **84**, 3743–3753.

320 X. Lei, L. Li, Y. P. He and Y. Tang, *Org. Lett.*, 2015, **17**, 5224–5227.

321 N. V. Rostovskii, J. O. Ruvinskaya, M. S. Novikov, A. F. Khlebnikov, I. A. Smetanin and A. V. Agafonova, *J. Org. Chem.*, 2017, **82**, 256–268.

322 J. Raushel and V. V. Fokin, *Org. Lett.*, 2010, **12**, 4952–4955.

323 R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc. Trans.*, 1915, **107**, 1080–1106.

324 J. S. Alford, J. E. Spangler and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 11712–11715.

325 T. Miura, T. Biyajima, T. Fujii and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 194–196.

326 Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866–880.

327 T. Y. Zhang, *Chem. Rev.*, 2006, **106**, 2583–2595.

328 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136.

329 N. Yasuda, *The Art of Process Chemistry*, Wiley, Germany, **2010**.

330 T. Miura, T. Tanaka, K. Hiraga, S. G. Stewart and M. Murakami, *J. Am. Chem. Soc.*, 2013, **135**, 13652–13655.

331 E. Vedejs and S. Lin, *J. Org. Chem.*, 1994, **59**, 1602–1603.

332 B. Nyasse, L. Grehn and U. Ragnarsson, *Chem. Commun.*, 1997, **11**, 1017–1018.

333 G. Sabitha, B. V. Subba Reddy, S. Abraham and J. S. Yadav, *Tetrahedron Lett.*, 1999, **40**, 1569–1570.

334 T. Javorskis and E. Orentas, *J. Org. Chem.*, 2017, **82**, 13423–13439.

335 E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless and S. Chang, *Angew. Chemie Int. Ed.*, 2007, **46**, 1730–1733.

336 Y. Liu, X. Wang, J. Xu, Q. Zhang, Y. Zhao and Y. Hu, *Tetrahedron*, 2011, **67**, 6294–6299.

337 J. He, Z. Man, Y. Shi and C. Y. Li, *J. Org. Chem.*, 2015, **80**, 4816–4823.

338 R. Ni, N. Mitsuda, T. Kashiwagi, K. Igawa and K. Tomooka, *Angew. Chemie Int. Ed.*, 2015, **54**, 1190–1194.

339 K. J. Shea and J. S. Kim, *J. Am. Chem. Soc.*, 1992, **114**, 4846–4855.

340 C. B. Reese and A. Shaw, *J. Chem. Soc. Perkin Trans. 1*, 1975, 2422.

341 J. Akester, J. Cui and G. Fraenkel, *J. Org. Chem.*, 1997, **62**, 431–434.

342 L. Wang, S. Peng, L. J. T. Danence, Y. Gao and J. Wang, *Chem. - A Eur. J.*, 2012, **18**, 6088–6093.

343 J. K. Whitesell, M. A. Minton and S. W. Felman, *J. Org. Chem.*, 1983, **48**, 2193–2195.

344 D. H. R. Barton, C. Y. Chern and C. Tachdjian, *Heterocycles*, 1994, **37**, 793–805.

345 R. R. Schmidt, M. Dimmler and P. Hemmerich, *Chem. Ber.*, 1976, **109**, 2395–2404.

346 H. J Kallmayer and E. Wagner, *Arch. Pharm.*, 1980, **313**, 315–323.

347 T. S. Jiang, L. Dai, Y. Zhou and X. Zhang, *Tetrahedron*, 2020, **76**, 130917.

348 H. Cerecetto, A. Gerpe, M. González, Y. Fernández Sainz, O. E. Piro and E. E. Castellano, *Synthesis*, 2004, **2004**, 2678–2684.

349 R. Rohlmann, T. Stopka, H. Richter and O. García Mancheño, *J. Org. Chem.*, 2013, **78**, 6050–6064.

350 G. Deng, D. Li, Z. Wu, H. Li, E. Bernhardt and X. Zeng, *J. Phys. Chem. A*, 2016, **120**, 5590–5597.