The Chemistry of Ynamides and Yndiamides



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Ynamides and Yndiamides

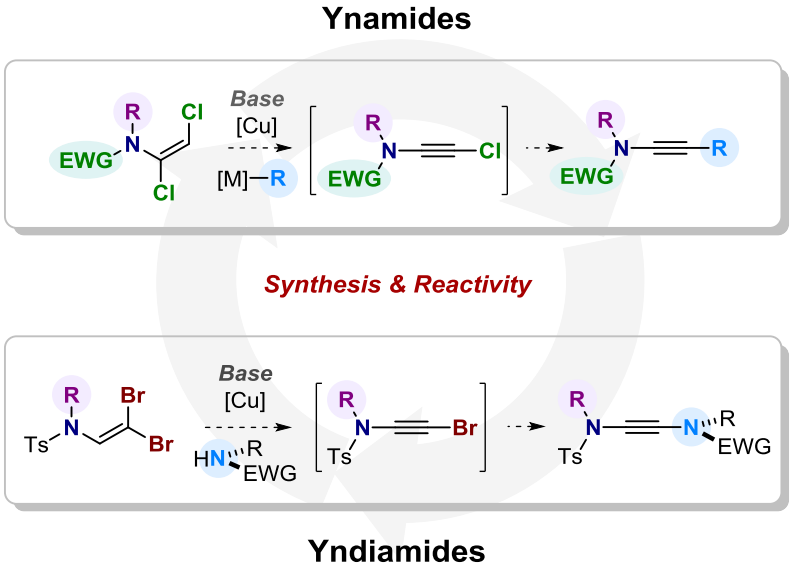
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There have been significant developments in both the synthesis and applications of nitrogen-substituted alkynes since the turn of the millennium, but there is still much that remains unexplored. In continuing these developments, two projects have been completed:

(i) A general copper-catalysed synthesis of ynamides from 1,2-dichloroenamides was achieved with broad substrate scope. This includes the use of acyclic secondary amides, acyclic ureas and sterically hindered enamide partners.

(ii) The first known synthesis of yndiamides was developed, which involves the copper-catalysed coupling of 1,1-dibromoenamides with sulfonamides and phosphoramidates. A preliminary study of yndiamide reactivity in transition metal- and Brønsted acid-catalysed processes was also performed.



Combined with the aid of crystallographic, spectroscopic and computational analyses, more fundamental aspects of these compounds have been uncovered during these studies, including conformational preferences. Questions were also raised as to how these preferences can affect the reactivity and stability of ynamides and yndiamides.

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Abbreviations

[cat.]	generic metal catalyst	Fc	ferrocenyl
[M]	generic metal species	FBW	Fritsch-Buttenberg-Wiechell
(1,10-)phen	1,10-phenanthroline	FGI	functional group interconversion
1,2-DMI	1,2-dimethylimidazole	Hall	homoallyl
2-MeTHF	2-methyl tetrahydrofuran	HOMO	highest occupied molecular orbital
Ac	acetyl	HMBC	heteronuclear multiple bond correlation
acac	acetylacetonate	HMDS	hexamethyldisilazane
AcC	2-acetylcyclohexanone	HOMO	highest occupied molecular orbital
Ar	generic aryl group	HRMS	high-resolution mass spectrometry
atm	atmosphere	HSQC	heteronuclear single quantum correlation
bbeda	*N*,*N*'-bisbenzylidene ethylene-1,2-diamine	ICT	intramolecular charge transfer
BCP	bicyclo[1.1.1]pentane	IPr	1,3-bis(2,6-di-*iso*-propylphenyl)imidazolidene
BKA	bromoketene aminal	*i*-Pr	*iso*-propyl
bmeda	*N*,*N*'-bis(*p*-methoxybenzylidene) ethylene-1,2-diamine	*J*	coupling constant
Bn	benzyl	KHMDS	potassium hexamethyldisilazide
Boc	*tert*-butyloxycarbonyl	LDA	lithium di-*iso*-propylamide
Bt	1*H*-benzotriazol-1-yl	LiHMDS	lithium hexamethyldisilazide
Bz	benzoyl	LiTMP	lithium 2,2,6,6-tetramethylpiperidinide
Cbz = Z	benzyloxycarbonyl	LUMO	lowest unoccupied molecular orbital
cod	cyclooctadiene	M	molar = mol dm^{-3}
conv.	conversion	*m*-	*meta*-
COSY	homonuclear correlation spectroscopy	Mes	mesityl = 2,4,6-trimethylphenyl
Cp*	pentamethylcyclopentadienyl	MS	molecular sieves
CPME	cyclopentyl methyl ether	MW	microwave irradiation
Cy	cyclohexyl	*n.d.*	not determined
d.r.	diastereomeric ratio	*n.r.*	no reaction
dba	dibenzylidene acetone	NBS	*N*-bromosuccinimide
DBAD	di-*tert*-butyl azodicarboxylate	*n*-Bu	*normal*-butyl
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene	*n*-Hex	*normal*-hexyl
DCA	dichloroacetylene	NMP	*N*-methyl pyrrolidinone
DCC	dicyclohexyl carbodiimide	nOe	nuclear Overhauser effect
DCE	1,2-dichloroethane	NOESY	nuclear Overhauser effect spectroscopy
dmeda	*N*,*N*'-dimethylethylenediamine	*n*-Pr	*normal*-Propyl
DMF	dimethyl formamide	Ns	nosyl = 4-nitrobenzenesulfonyl
DMPU	*N*,*N*'-dimethylpropylene urea	Nu	generic nucleophile
DMSO	dimethylsulfoxide	*o*-	*ortho*-
E	generic electrophile	*p*-	*para*-
e.e.	enantiomeric excess	PEG-400	polyethylene glycol 400
equiv.	molar equivalents	Piv	pivaloyl
ESI	electrospray ionisation	pmdta	*N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenediamine
EWG	generic electron withdrawing group	Ps	5,5-dimethyl-1,3,2-dioxaphosphinane-2-oxide-2-yl

PTAD	4-phenyl-1,2,4-triazole-3,5-dione
py	pyridine
R	generic group
r.r.	regioisomeric ratio
R_f	retention factor
rt	room temperature (21 °C)
T	temperature (°C)
t	time
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogensulfate
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TC	thiophene-2-carboxylate
TCE	1,1,2-trichloroethylene
Tf	trifluoromethanesulfonyl
Tfs	4-(trifluoromethyl)benzenesulfonyl
THF	tetrahydrofuran
tht	tetrahydrothiophenyl
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
tmeda	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidinyl
TMS	trimethylsilyl
tol / tolyl	methylphenyl
Tris	2,4,6-tri-*iso*-propylbenzenesulfonyl
Ts	tosyl = 4-methylbenzensulfonyl
v/v	volume by volume
w/v	weight by volume
X	generic halogen or leaving group
Y	generic group or heteroatom

"*Success is the ability to go from one failure to another with no loss of enthusiasm.*"

– Anonymous

A Disconnection Approach to Ynamide Synthesis

0

Alkynes are among the most versatile functional groups in chemistry. They possess unique electronic properties that stem from the presence of two mutually orthogonal π-systems, and they are inherently reactive functionalities.[1,2] This behaviour can be modulated by tuning the electronic influence of their substituents[3] and, as such, alkynes are of wide interest to chemists,[1–11] physicists and materials scientists alike. They have seen significant applications in molecular optical and electronic materials,[14,15] and as molecular wires for use in nanotechnology.[16–21] Together with straightforward methods for their preparation, it is a combination of these features that account for the rich chemistry of alkynes, and they have been employed in a whole manner of transformations including ionic, radical and transition metal-catalysed processes.[1]

There has been a long-standing interest in the Anderson group to utilise alkynes in ring-forming reactions,[22–30] with a particular focus on the application of nitrogen-substituted alkynes called ynamides.[31–37] These compounds display a marked increase in nucleophilicity as compared to "typical" alkynes,[38] and the polarising effect of the nitrogen substituent grants reliable regioselectivity in their reactions. Since the turn of the millennium, there has been a renaissance in the chemistry of ynamides that was driven primarily by the development of general methods for their synthesis.[39–54] Nevertheless, much remains unexplored in the field of ynamide chemistry.

In this thesis, two projects were completed (Chapters 1 & 2) which, combined with the aid of crystallography and computation, uncovered more fundamental aspects of these compounds (Chapter 3). Before describing these efforts, this chapter will introduce the reader to ynamides and review the current methods available for their synthesis. This will highlight key observations and provides the necessary background for discussions that will ensue in later chapters.

0.1 Introduction.

To begin the story of ynamides, one must first consider seminal work involving their more reactive cousins, ynamines. Ynamines are compounds in which an alkyne is bonded directly to the nitrogen atom of an amine and, as might be expected from the joining of these two reactive functional groups, they are exceptionally nucleophilic. A further consequence of their structure is the inherent polarisation of the alkyne that differentiates the two carbon atoms and grants exceptional regioselectivity in their reactions (Figure 0.1). Since the isolation of the first ynamine in 1958,[55] interest in their chemistry surged and the synthetic community quickly realised the potential of such reactive functionalities in both organic and organometallic chemistry.[40,41,56–61] Ultimately, the attractiveness of any functional group hinges on whether it can be readily prepared and used, and it was the extreme reactivity of ynamines, in particular their hydrolytic sensitivity, that made them difficult to purify and handle, which seriously hampered the development of their chemistry.

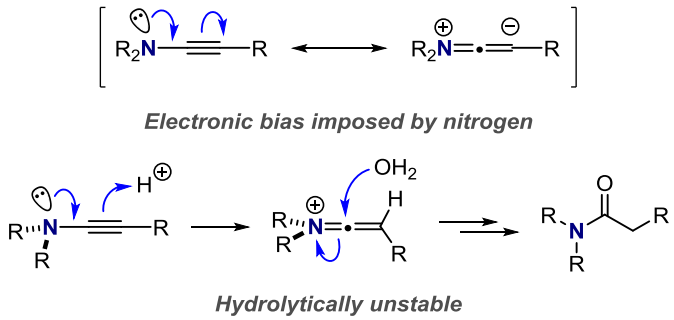


Figure 0.1: Ynamine reactivity.

It was therefore apparent that something was needed to temper this reactivity and to make these compounds more accessible to the general community; this is where ynamides take the spotlight. The nucleophilicity of the amine can be attenuated by the addition of an electron withdrawing group on nitrogen (Figure 0.2), but this seemingly simple modification has much greater ramifications than just the taming of a reactive functional group. It is the specific choice of electron withdrawing group that not only modulates ynamide reactivity by tuning its nucleophilicity,[45,46] but also serves as a handle that can direct reactions,[52] engage in cyclisations,[62] or induce diastereoselectivity.[49,51] These additional features undoubtedly grant ynamides greater synthetic versatility, whilst maintaining the overall reactivity and increased nucleophilicity[38] that made ynamines so attractive in the first place.

Methods for the synthesis of ynamides were reported as far back as 1972 by Viehe (Figure 0.2),[63] but it was only at the turn of the millennium when ynamides rose to prominence. This coincided with the development of copper-catalysed processes for their synthesis, which often followed a more simplistic design idea (as will be discussed in Sections 0.2b–d). It is perhaps the simplicity and

generality of these approaches that have made ynamides much more accessible to non-specialists, and have fuelled the development of ynamide applications. As such, ynamides have seen tremendous utility in the past 15–20 years, for example, as convenient precursors to an array of reactive intermediates[52,64–70] and to a variety of azacycles,[62,71–75] and they are seeing increased utility in medicinal chemistry.[76–82]

There are many classes of ynamides and related electron-deficient ynamines now available, and their diversity increased alongside the developments in ynamide applications. It is, therefore, interesting to briefly summarise these developments from a more historical context (Figure 0.2). Whilst attempts to prepare *ynamines* date as far back as 1892,[83,84] it was only much later in 1958 that the first well-characterised ynamine was reported, followed by the first general synthesis of ynamines in 1963 by Viehe.[85] Whilst the first copper-catalysed syntheses of ynamines[86] and an ynamide[87] were described in 1968 and 1985, respectively, it was many years before they were developed into general and robust conditions for the synthesis of ynamides.

The first, generally applicable method for ynamide synthesis was disclosed in 1996, which involved the reaction of alkynyliodonium salts with sulfonamides or acyclic secondary amides.[88–94] Hsung and co-workers later focussed on the use of oxazolidinones and imidazolidinones[95] because these substrates were not useful in reactions with alkynyliodonium salts,[46] presumably resulting in decomposition. This necessitated a reinvestigation of methods for ynamide synthesis and, alongside the work of Danheiser, led to the first, general copper-catalysed syntheses of ynamides from bromoalkynes in 2003.[96,97] The scope of ynamide classes at this time encompassed sulfonamides, amides, lactams, carbamates, oxazolidinones, imidazolidinones and various aromatic azacycles. This explosion in diversity was soon exploited by the community and as a consequence, further synthetic methods were developed that used alternative alkyne precursors, including terminal alkynes, dibromoalkenes and copper(I) acetylides. Other ynamide classes, for example, using imides, phosphoramidates and hydrazides, were developed later to solve problems encountered in the chemistry of the "original" ynamide classes. For example, phosphoramidates proved to be more useful than sulfonamides in aza-Claisen rearrangements of ynamides to ketenimines.[98] Later developments dispensed with the use of purely electron-withdrawing groups altogether, and less nucleophilic nitrogen substrates, for example, with imines and triazenes, were successful and useful alternatives to ynamides and ynamines. Cumulatively, these developments led to the commercialisation of a selection of ynamides in 2015 (Sigma Aldrich). In fact, perhaps one of the best examples of progress in this field is the development of an ynamide synthesis in water,[99] which contrasts utterly with the intolerance of ynamines towards moisture. Such developments are likely only the tip of the iceberg for what can be achieved, and the creativity of applications thus far is surely indicative of a rich future for ynamide chemistry.

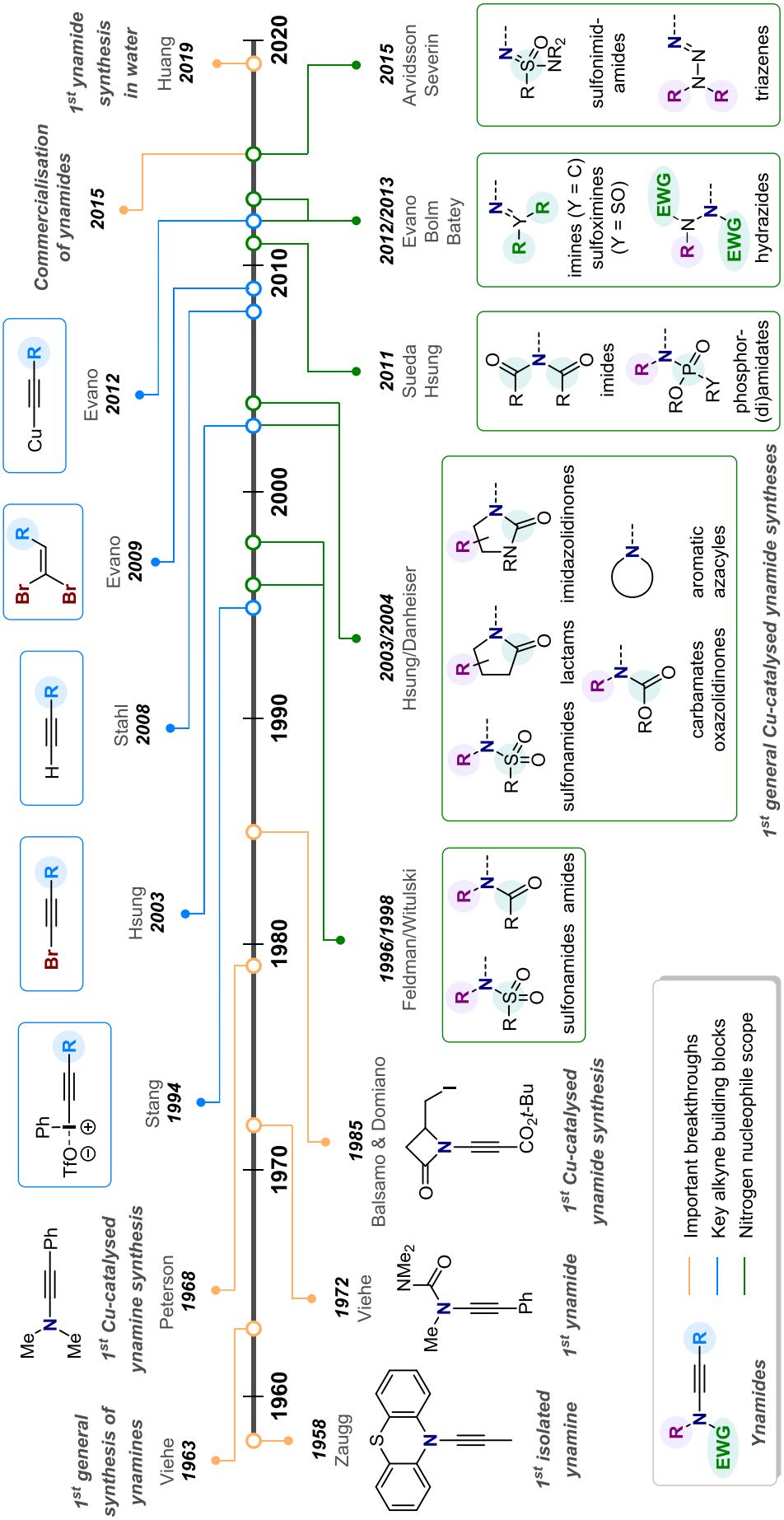


Figure 0.2: Timeline of key events in the field of ynamide chemistry, including the development of key building blocks and scope of ynamide classes.

0.2 Synthesis of ynamides.

There have been many excellent reviews covering both the synthesis and chemistry of ynamides.[39–54] When considering how best to discuss the various methods for their preparation, it is useful to organise them by key disconnection. The majority of methods can be classified either by a C–N or C–C disconnection of the ynamide (Figure 0.3) and, as such, it is convenient to divide discussions along these lines.

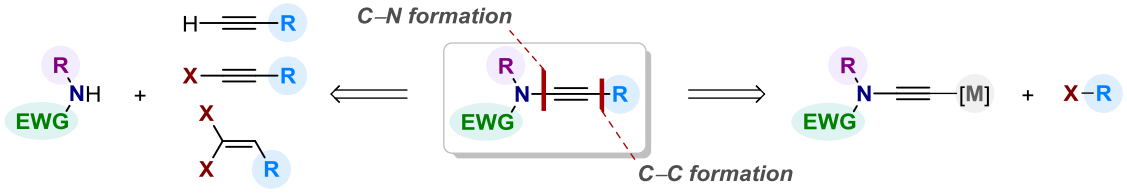


Figure 0.3: Key disconnections.

Methods used to construct the C–N bond will be considered first and, taking this disconnection approach further, three key strategies have been explored that will be discussed in the sections indicated: (i) the use of an amide nucleophile reacting with an electrophilic alkyne (Section 0.2a); (ii) the copper-catalysed coupling of an amide nucleophile with haloalkynes (Section 0.2b), dihaloalkenes (Section 0.2c) or terminal alkynes (Section 0.2d); or (iii) a reversal of polarity in which a nucleophilic alkyne reacts with an electrophilic nitrogen partner (Section 0.2e). Methods for C–C formation will be then be addressed in Section 0.2f, followed by a summary of the other methods for ynamide synthesis, including the more classical approaches (Section 0.2g).

At this point, it is also important to note that for simplicity in all following discussions, all electron-deficient nitrogen-substituted alkynes will be collectively referred to as “ynamides”, except in certain cases where specific mention of a particular ynamide class is warranted.

0.2a C–N Disconnections: Reactions of alkynyliodonium/sulfonium salts.

Stang first described the use of alkynyliodonium triflates and *N*-lithiated amines for the preparation of ynamines in 1994.[100] This was later developed by Feldman,[88] Witulksi[89–94] and others[101–108] to enable the synthesis of ynamides from *N*-metallated amides (amidates) and alkynyliodonium triflates (Figure 0.4). KHMDS or *n*-butyllithium are typically used to deprotonate the amide, although Cs_2CO_3 can be effective in some cases.[91] These reactions are thought to proceed via nucleophilic addition of amidate **1** to the alkyne **2**, which after α-elimination of iodobenzene produces carbene **3**. A 1,2-shift then gives the ynamide **4**. The most effective nitrogen nucleophiles in this chemistry are sulfonamides but others, including acyclic secondary amides (e.g. benzamides, trifluoroacetamides),[89,91,104] imidazoles[105] and benzotriazoles, can be used with variable

success.[106,107] However, the major drawback of this route is the preparation and scope of the alkynyliodonium salts: these are often poorly stable compounds, which renders both their preparation and handling non-trivial and generally inconvenient. Furthermore, the scope of the alkyne is limited to those substituted with a proton, aryl, silyl or electron-withdrawing group; alkylated alkynyliodonium salts do not give the ynamide and instead give cyclisation products such as **5**, which likely arise from C–H insertion of the carbene intermediate **3** (e.g. R^1 = *n*-Pr and R^2 = Me). Perhaps as a result of these difficulties, the most often used iodonium partner is phenyl((trimethylsilyl)ethynyl)iodonium triflate **6**, which invariably requires two further steps to access *C*–functionalised ynamides.

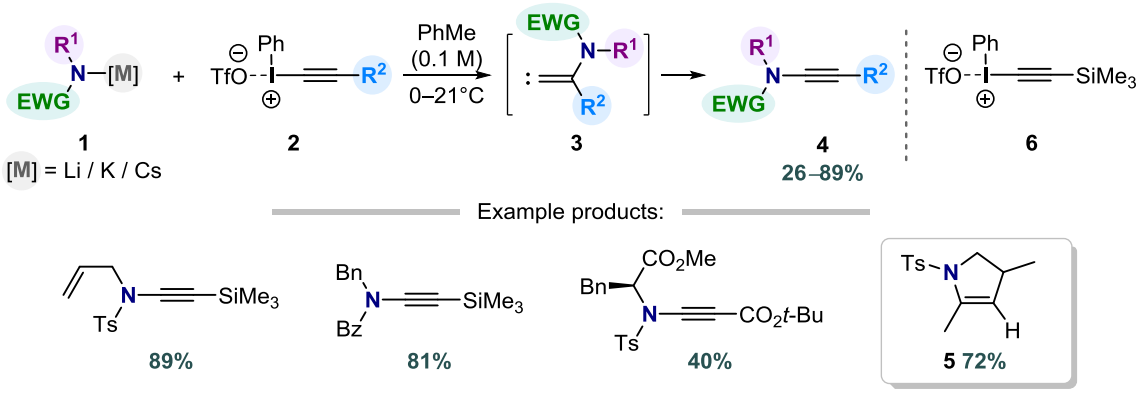


Figure 0.4: Amidation of alkynyliodonium salts.

An alternative procedure was reported much later in 2012 by Muňiz,[109] whereby readily available phenyliodonium bis(sulfonyl)imides **7** are used as precursors to ynamides (**a**, Figure 0.5). These studies concluded that alkynyliodonium salts **8** are generated in situ, which underwent subsequent conversion to the ynamide. Although the nucleophile scope was not explored beyond bis(sulfonyl)imides, this reaction is potentially more convenient than the previous work as it avoids the need to prepare and isolate alkynyliodonium salts; nevertheless, this method possessed the same inherent limitations faced when using alkylated alkynes (**9**, R = *n*-Pr).

Even more recently, alkynylsulfonium salts **10** were shown to behave in a similar manner to the iodonium salts (**b**, Figure 0.5).[110] Whilst these salts also require a rather lengthy procedure for their preparation, the main advantage of this route is that a range of nucleophiles, including sulfonamides, imides, thiols and 1,3-dicarbonyl species, can be used with Cs_2CO_3 as the base. However, only aryl and silyl alkynes were applied in this scope and the efficacy of alkylated alkynes was not reported.

Overall, these methods provide interesting entries to ynamides but have been overshadowed by the wealth of applications demonstrated using copper catalysis. With this, our discussion will enter the domain of copper-catalysed alkynylation of various nitrogen nucleophiles.

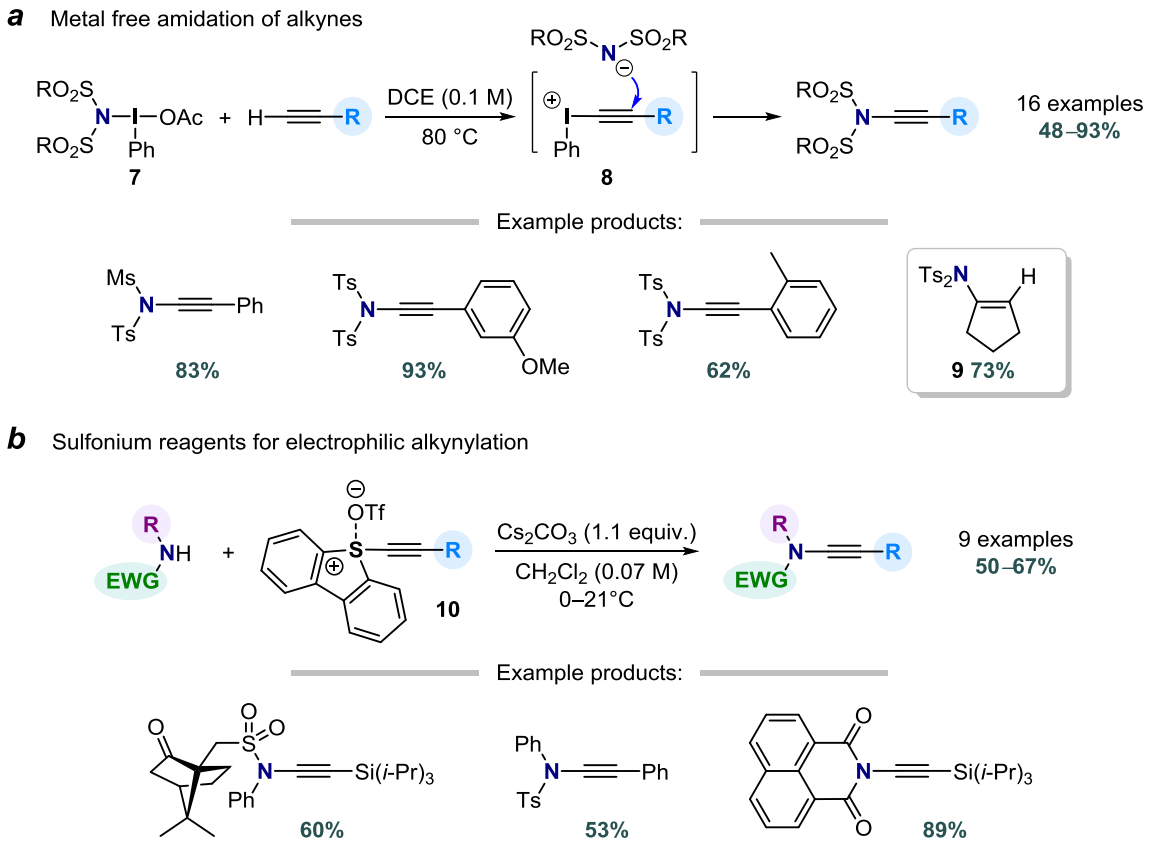


Figure 0.5: Further methods to prepare ynamides using electrophilic alkyne reagents.

0.2b C–N Disconnections: Copper-catalysed amidation of bromoalkynes.

Inspired by developments in the field of copper-catalysed Ullmann-Goldberg couplings,[43,111–114] the first general copper-catalysed ynamide synthesis came in 2003 from the group of Hsung.[96] This first generation approach made use of CuCN (5 mol%) in the presence of dmeda (10 mol%) to effect the coupling between amide nucleophiles and various bromoalkynes (**a**, Figure 0.6). A range of amide substrates could be applied in this chemistry, but by far the most successful partners were oxazolidinones; later modifications also enabled the use of sulfonamides.[115–117] Whilst this procedure had a number of limitations, namely poor substrate scope and the use of high temperatures, it was very successful in laying the groundwork for future developments. Almost immediately after Hsung's initial report, Danheiser published an alternative, general procedure to synthesise ynamides, whereby the alkynylation of amides could be performed at room temperature (**b**, Figure 0.6).[97] This was, however, contingent on the pre-formation of a copper(I) amidate using KHMDS and CuI, but the coupling was effective for a much broader amide scope, including sulfonamides, oxazolidinones, imidazolidinones and acyclic carbamates. An important note here is that high purity pyridine was required to attain the highest yields. This procedure was also applicable for large scale reactions and could be used to synthesise more heavily functionalised ynamides.[118,119]

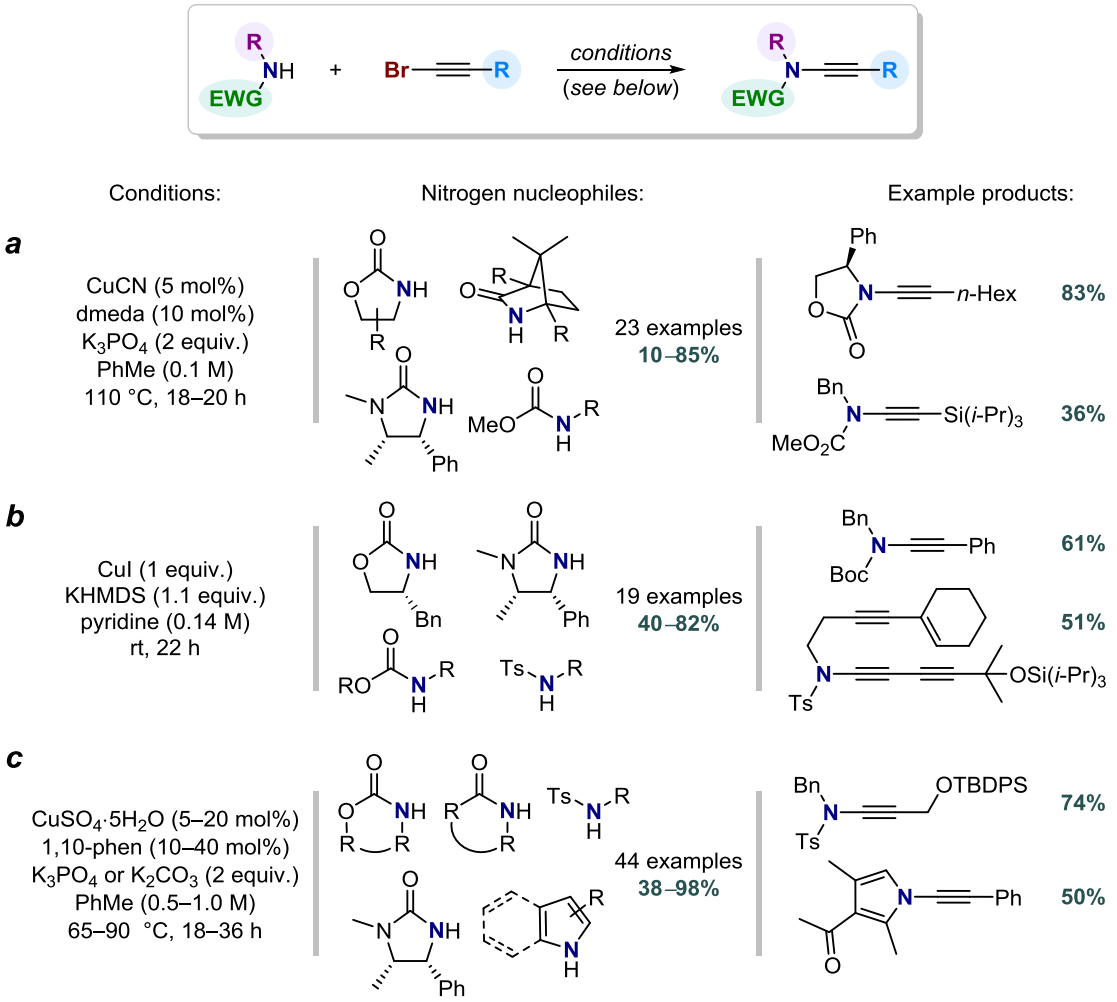


Figure 0.6: Copper-catalysed synthesis of ynamides from bromoalkynes.

However, it is Hsung's second generation route (**c**, Figure 0.6) that is arguably one of the most practical and generally applicable of the other copper-catalysed methods reported to date (described throughout the course of this review).[120] The optimised catalyst system involved the use of inexpensive $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline as the ligand and used either K_3PO_4 or K_2CO_3 as the base. In comparison with the first generation protocol, these reactions could be performed at lower temperatures (65–90 °C) and were applicable to a vast range of bromoalkynes and amide-analogues, including those which were previously poorly reactive such as sulfonamides[121] and imidazolidinones. This reaction is also very effective on a large scale,[122] and was used in intramolecular ynamidations to create macrocyclic ynamides in good yields (Figure 0.7).[123] One notable limitation was the general inability for acyclic secondary amides to undergo coupling with most bromoalkynes; only silylated bromoalkynes underwent coupling in 52–87% yield.[123] In addition, the use of acyclic ureas was never reported. Similarly, bulky and *N*-aryl amide nucleophiles are also less effective than primary aliphatic amide-analogues. Nevertheless, this procedure can be applied to a range of other nitrogen nucleophiles, including indoles and pyrroles,[120,124,125] some bulky carbamates,[126–128] phosphoramidates,[98] and sulfoximines[129] using

only a slight variation in conditions, for example by changing the base, solvent or copper salt.[127,130,131] A fascinating modification of these conditions uses a copper-doped zeolite catalyst for the formation of pyrrole-ynamide **11** en route to acortatarin A (Scheme 0.1).[132,133] It is important to note that whilst anhydrous base was found to give higher yields of the ynamide in organic solution,[134,135] later developments demonstrated that this coupling can be performed in water with the aid of surfactants.[99] It is likely that the morphology and granularity of the powdered base are of greater importance for the reactions in organic solution.[134]

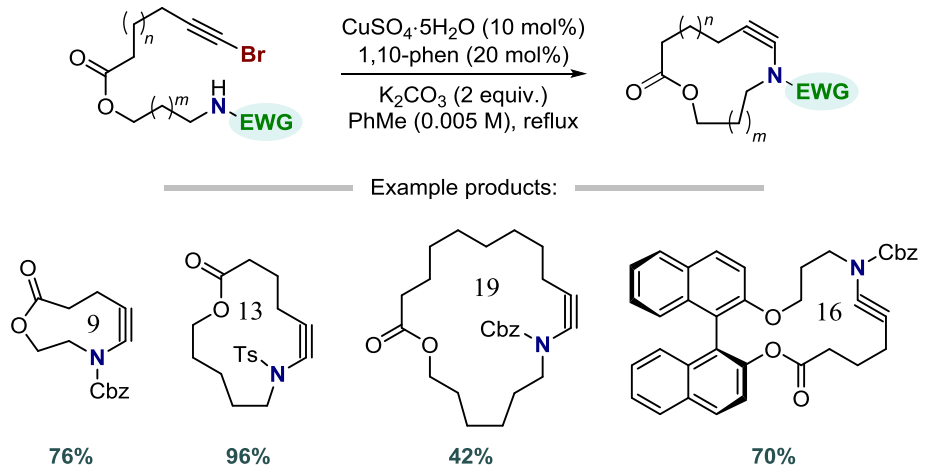
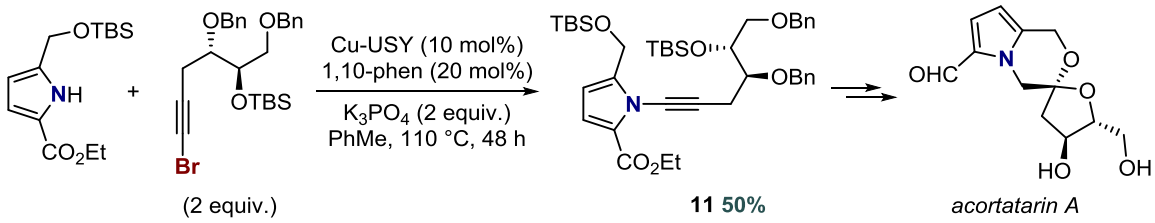


Figure 0.7: Synthesis of macrocyclic ynamides.



Scheme 0.1: Application of copper metal-organic-frameworks in the synthesis of an ynamide en route to Acortatarin A. Cu-USY = Copper(I)-doped, ultrastable Y-type zeolite.

A related protocol using $FeCl_3 \cdot 6H_2O$ was reported which was highly effective in the formation of a range of ynamides from sulfonamides, oxazolidinones and indoles (Figure 0.8).[136] Although it has been shown that trace copper is sometimes responsible for the outcomes of iron-catalysed couplings,[137] this was not investigated here and cannot be discounted. However, this methodology can be used to make ynamides, such as **12**, from amido/hydroxy-amides, which is not possible for most copper-catalysed methods and instead lead almost exclusively to cyclisation products such as **13** (Figure 0.8).[117] This can be rationalised by a greater affinity for copper to coordinate to the ynamide prior to cyclisation and is important to note for discussions later in Chapter 2.[117,138–141]

In comparison, aromatic azacycles such as imidazoles or pyrazoles require a slightly different set of

conditions to facilitate couplings with bromoalkynes,[53,142–144] and in some cases copper is not even required.[145] For example, Kerwin reported a procedure for the synthesis of *N*-alkynylimidazoles from bromoalkynes using CuI (5 mol%) and 2-acetylcyclohexanone (AcC) (20 mol%) (**a**, Figure 0.9).[142] The authors specifically commented that in these cases, diamine ligands such as dmeda or 1,10-phenanthroline were ineffective.

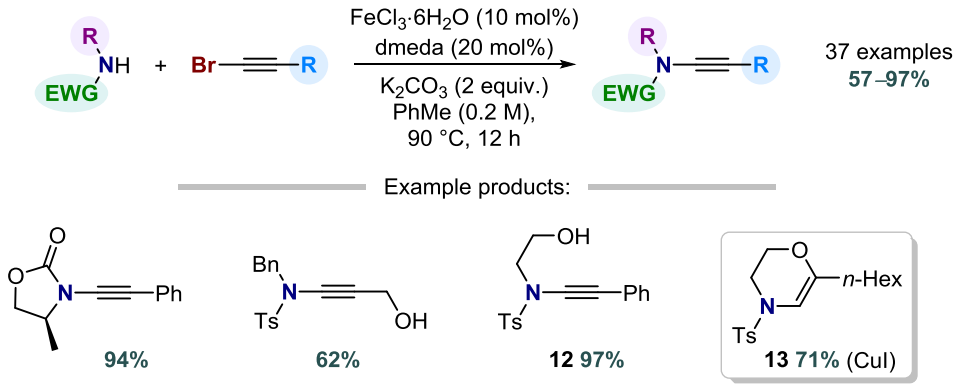


Figure 0.8: Iron-catalysed synthesis of ynamides. Protection of pendant hydroxy/amido functionality is not required to prevent cyclisation - this is an issue when using copper catalysts.

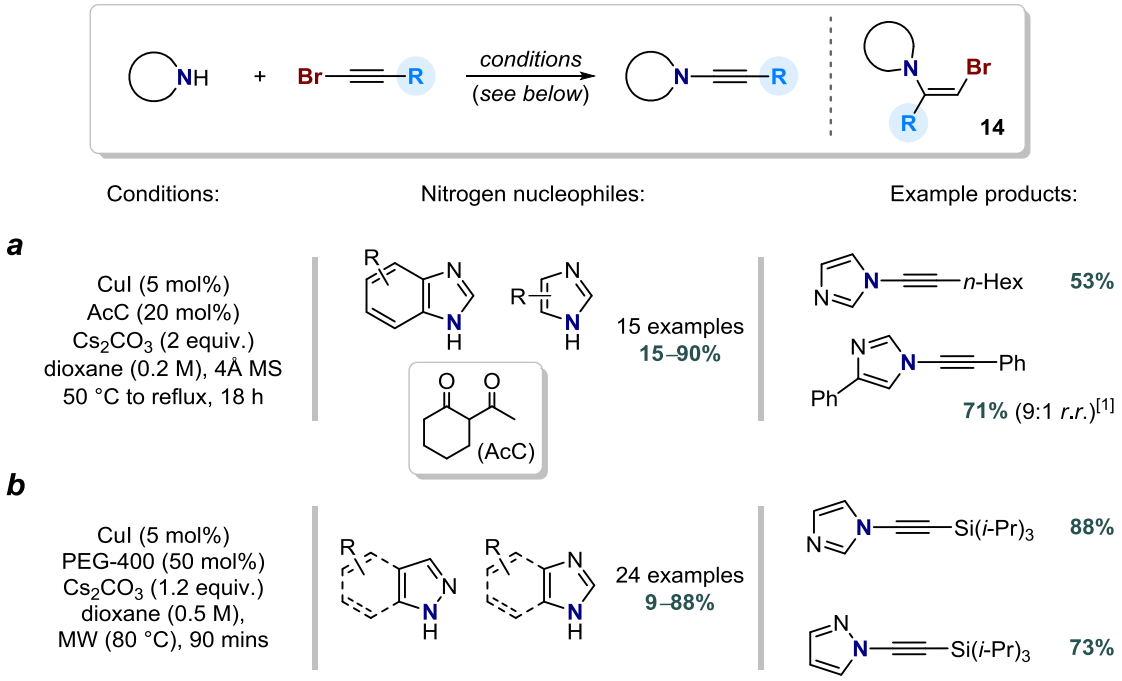


Figure 0.9: Reactions of imidazoles and pyrazoles with bromoalkynes. [1] Ratio of 1,4- and 1,5-regioisomeric products.

A related procedure demonstrated both the remarkable effects of PEG-400 and microwave irradiation in the reactions of imidazoles and pyrazoles (**b**, Figure 0.9).[143] The beneficial role of PEG-400 was attributed to this being both a phase transfer agent and a ligand for copper. Furthermore, microwave irradiation increased both the yield of the product and decreased the

reaction time from 36 hours to just 90 minutes. In both reactions bromoenamides **14** were observed as side products, particularly in cases using more electron deficient and unhindered alkyne partners, and it is possible that these come from a direct nucleophilic attack on the alkyne. Nevertheless, these modifications have not been reported for any other ynamide synthesis but could be applied to other reactions which proceed sluggishly.

In summary, many of these procedures have their origins in the conditions first reported by Hsung or Danheiser, but modifications in base, copper salt, ligand and solvent are often required to further optimise the reaction for specific substrates. Despite this variety, a number of conclusions can still be made. Firstly, whilst many different copper salts can be employed in these reactions, including CuI, CuTC, $Cu(OAc)_2$, and $CuSO_4{\cdot}5H_2O$, it is the choice of ligand that has a greater overall influence and, in many cases, 1,10-phenanthroline was seen to outperform other diamine ligands such as pyridine, dmeda or tmeda. However, in some cases stronger σ-donors such as dmeda or AcC can be beneficial. This could be indicative of a mechanistic difference, although to date there have been no studies or evidence gained to support any mechanism for the amidative couplings of bromoalkynes (see Chapter 2 for further discussions). The use of inorganic bases such as K_2CO_3, Cs_2CO_3 or K_3PO_4 in non-polar solvents (toluene or dioxane) is generally preferred, though when using less reactive nucleophiles, stronger bases and more polar solvents can provide better outcomes.[120,131] For example, the use of KHMDS is often beneficial for bulky acyclic carbamates,[126–128] but here slow addition of the base is required. This correlates with similar observations in related copper-catalysed Buchwald-couplings,[146] where it was important to match the rate of deprotonation to the rate of amidative coupling. Many of these reactions required heating to between 60–110 °C, which can be problematic in cases where the starting bromoalkyne or the product ynamide is unstable. Nevertheless, the main limitation of these methods is the preparation of the bromoalkyne partners. Although this is often accomplished in high yield from readily available precursors, it becomes quite problematic for unstable or volatile partners, as bromoalkynes tend to be highly odorous and lachrymatory.

0.2c C–N Disconnections: Copper-catalysed amidation of dihaloalkenes.

In circumventing these limitations, Evano reported the use of 1,1-dibromoalkenes as conveniently prepared precursors to ynamides (Figure 0.10).[147,148] This not only avoids problematic bromoalkynes but offers a more streamlined approach to ynamides in cases where the bromoalkynes are themselves prepared from dibromoalkenes. These couplings were found to require a specific combination of base (Cs_2CO_3) and solvent (dioxane or DMF) to obtain high yields of the ynamide (whilst suppressing the formation of ketene aminals **15**), and a range of oxazolidinones and sulfonamides could be coupled with (hetero)aryl and alkyl dibromoalkenes to give the ynamides in 34–97% yields.

Furthermore, and unlike for the reactions using bromoalkynes, evidence has been gathered to support a mechanism for the conversion of dibromoalkenes to the ynamide. A simplified mechanism is shown in Figure 0.10b, whereby an initial coupling gives a bromoenamide **16**, which undergoes β-elimination to the ynamide. It was fortunate that in some cases, bromoenamides could be obtained from these reactions simply by lowering the temperature, and treatment of these with Cs_2CO_3 smoothly afforded the expected ynamides. The use of deuterium labelled dibromoalkenes **17** lent further support for this mechanism,[47] in which the deuterium label is fully retained during their conversion to bromoenamides such as **18** (see inset, Figure 0.10).

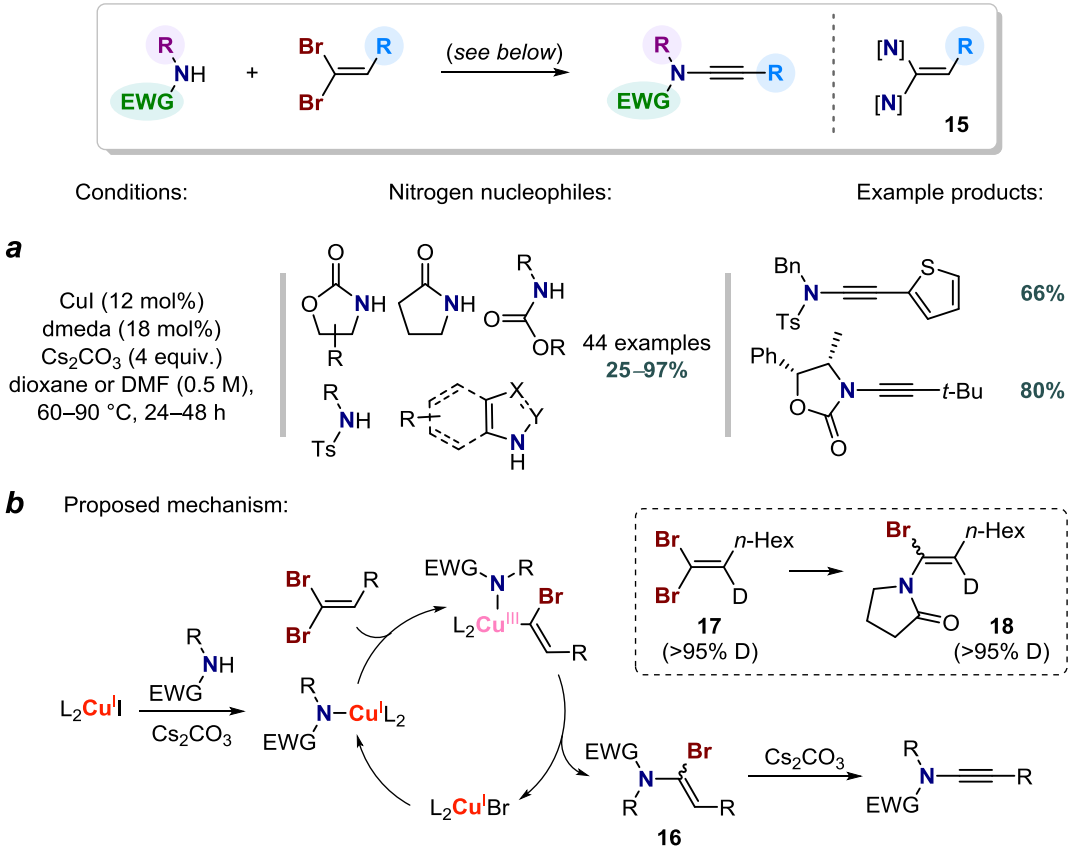


Figure 0.10: Synthesis of ynamides from 1,1-dibromoenamides, [N] = R(EWG)N.

The dibromoalkene strategy was extended further to include the use of benzimidazoles and benzopyrazoles,[47,149,150] albeit the use of tmeda instead of dmeda was found to provide higher product yields; further improvements could also be made by using the preformed complex [Cu(phen)PPh_3Br].[151] 1,10-Phenanthroline was an effective ligand in these transformations and a range of sulfonamide[152,153] and sulfoximine[154,155] substrates can be successfully converted to ynamides. Unlike any of the other C–N couplings en route to ynamides, the reaction between benzimidazoles and 2-alkynylaryl dibromoalkenes **19** required the use of a dual catalyst system involving CuI, 1,10-phenanthroline and $Pd(OAc)_2$ (Figure 0.11).[156] It is unfortunate that no further studies were performed to rationalise this curious observation. In addition to these developments,

1,2-dihalostyrenes can also be coupled with sulfonamides, albeit these reactions have a much narrower substrate scope.[157,158]

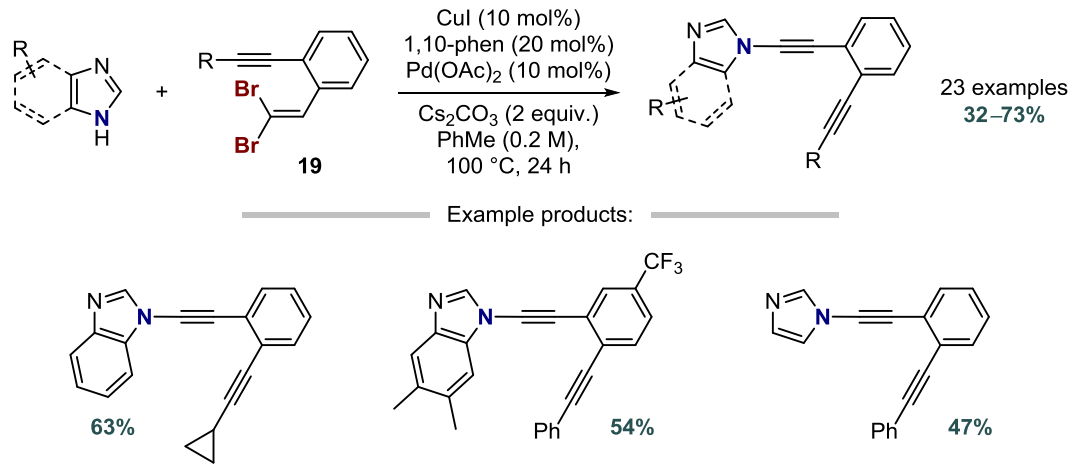


Figure 0.11: Unusual application of a dual catalytic system involving both copper and palladium salts.

More recently,[159,160] a transition metal-free synthesis of ynamides was reported in which vinyl dichloride or other dichloroalkenes undergo reaction with a range of sulfonamides, oxazolidinones and aromatic azacycles to give the corresponding terminal or internal alkynes in good yields (Figure 0.12). Nevertheless, the major limitations of this method are firstly the preparation of the 1,1-dichloroalkene itself from CCl_4, which unlike CBr_4, is both more hazardous and difficult to acquire. Secondly, only (hetero)aryl dichloroalkenes were useful in the formation of ynamides and the analogous alkyl partners instead gave the chloroenamides such as **20**.

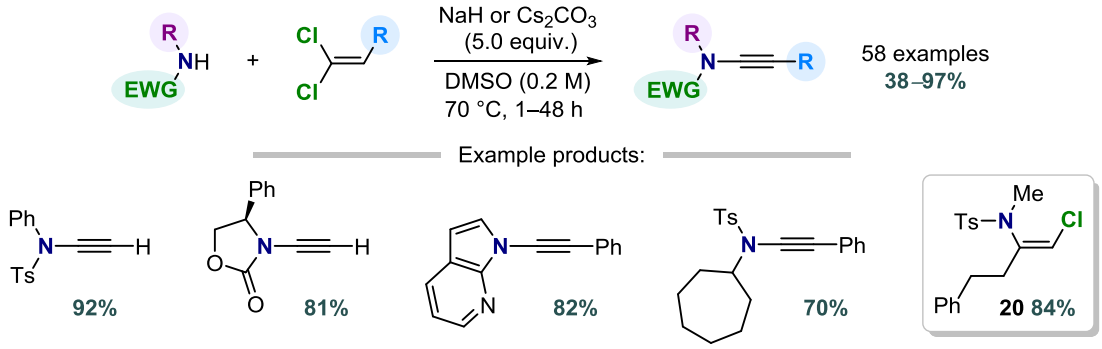


Figure 0.12: Synthesis of ynamides from 1,1-dichloroalkenes.

Overall, the coupling of bromoalkynes and dibromoalkenes with amide nucleophiles has been a significant development for the synthesis of ynamides, and it is of no doubt that these methods helped spark the fire of interest for the community. However, these methods are somewhat limited by the necessary preparation of the bromoalkyne/dibromoalkene partners. Whilst these are often readily prepared from commercial materials, it would be much more convenient to use terminal alkynes directly. Naturally, conditions have been developed to achieve exactly this.

0.2d C–N Disconnections: Copper-catalysed oxidative amidation of alkynes.

Taking advantage of the discoveries made by Peterson,[86] Balsamo and Domiano,[87] Stahl and co-workers reported the first general copper-catalysed oxidative amidation of terminal alkynes (Figure 0.13).[161] An extensive optimisation highlighted that a combination of $CuCl_2$ (20 mol%) and pyridine (2.0 equiv.), under an oxygen atmosphere, was the most effective catalyst system for a range of sulfonamides, oxazolidinones, imidazolidinones, lactams and indoles. In the case of the less reactive pyrrolidinones, the use of Cs_2CO_3 and a more polar solvent (DMSO) was beneficial. These conditions were later applied to a range of other nitrogen nucleophiles, including imines,[162,163] sulfoximines,[164] sulfonimidamides[165] and imides;[166,167] the latter of which supersedes the use of alkynyl(triaryl)bismuthonium salts for the formation of yne-imides.[168] Despite the apparent atom economy of these procedures, the main drawback is the necessary use of excess amide and the slow addition of the alkyne (over 4 hours) that is required to suppress both homodimerisation of the alkyne (**21**) and the formation of chloroalkynes **22**; nevertheless, this excess amide can be recovered at the end of the reaction in good yield.

To account for these observations, it was proposed that sequential activation of the alkyne and the amide, followed by reductive elimination, gives the ynamide (**b**, Figure 0.13); aerobic oxidation of the resulting copper(0) species would conceivably regenerate copper(II).[169] This putative mechanism would also explain the requirement of excess amide, in which the formation of an amido copper(II)-acetylide **23** would outcompete the formation of copper(II)-bisacetylide **24**. However, the formation of a diyne from **24** is not consistent with the current understanding of related Glaser-Hay couplings, which are thought to proceed via dimeric copper(II) acetylides (e.g. **25**, Figure 0.13).[170,171] Furthermore, there have been direct observations of reduction of copper(II) complexes to copper(I) by terminal alkynes to give 1,3-diynes.[172,173] Therefore, a mechanism that also accounts for these observations in the formation of ynamides is proposed (**c**, Figure 0.13). It is also interesting to consider the involvement of two copper atoms in the amidation (**26**), a situation that is well known for related azide-alkyne click reactions,[174–177] but has not yet been considered in the formation of ynamides from (bromo)alkynes.

To address these shortcomings, the groups of Mizuno and Xia reported the use of $Cu(OH)_2$ and Cu_2O, respectively, in these couplings,[178,179] which suppressed diyne formation and provided a better overall selectivity for the ynamide. This overcame the need for slow alkyne addition and the amount of amide required could be reduced to two equivalents. In addition, a rather interesting study made use of Cu-MOFs (MOFs = metal-organic-frameworks), which also enabled a highly efficient transformation that had the added benefit of catalyst recyclability.[180]

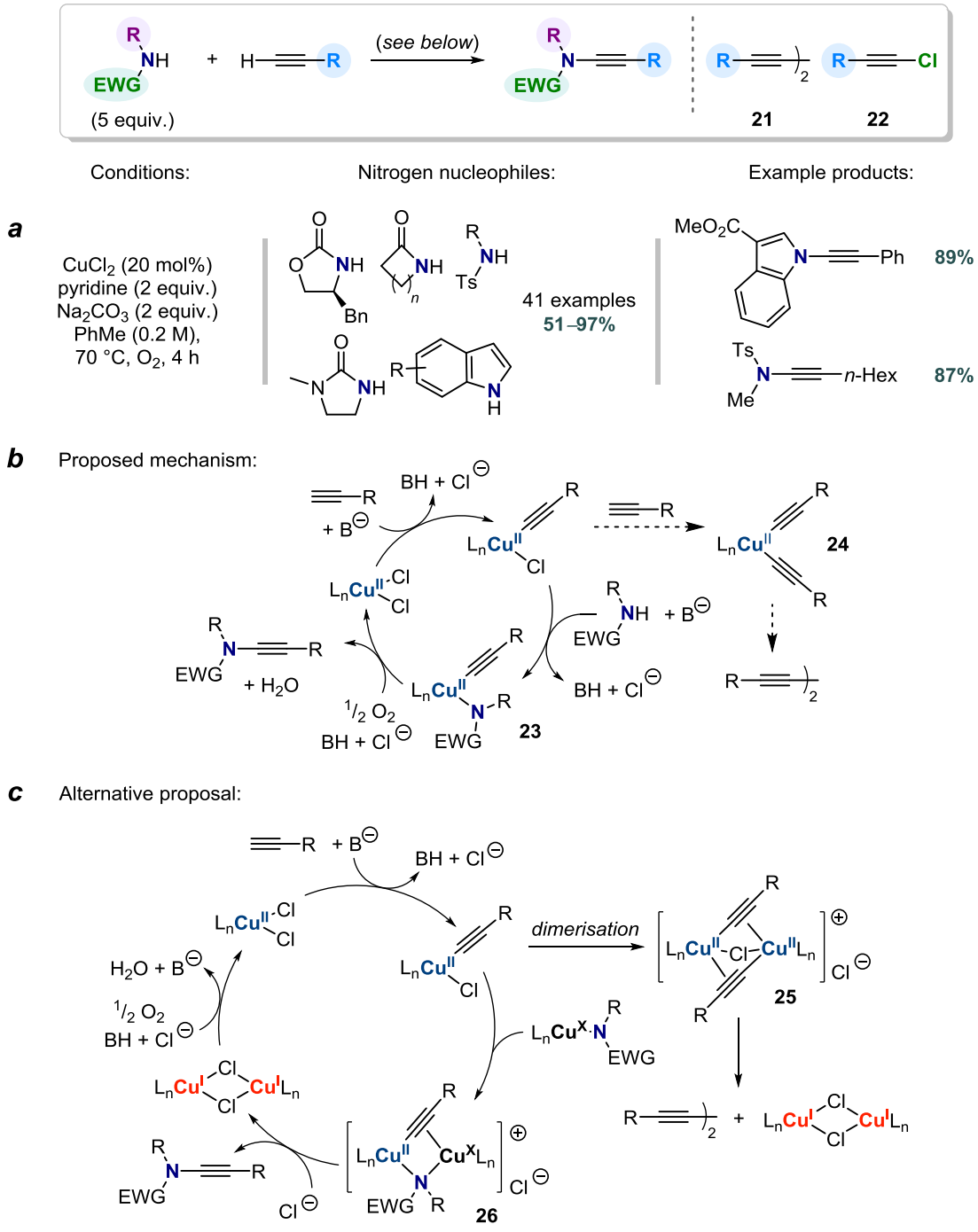


Figure 0.13: Oxidative coupling for the synthesis of ynamides from terminal alkynes. In section **c**, the oxidation state for Cu^X is undefined and could be a Cu(I) or Cu(II) species.

Propiolic acids could also be used in these reactions and, in comparison with the previous method, proceeded without added ligand and use air as the terminal oxidant (**a**, Figure 0.14).[181] This is a considerable safety advantage and also eliminates the need for slow addition of the alkyne; though an excess of amide (2 equiv.) is still required. The amide scope encompasses a range of oxazolidinones, imidazolidinones, and indoles, and a range of alkyl and aryl alkynes perform well. In the case of indole substrates, the addition of pyridine (2 equiv.) shortened both the reaction times

and led to increased yields of the ynamides. Sulfoximines were also successful, albeit requiring a slight modification of conditions.[182]

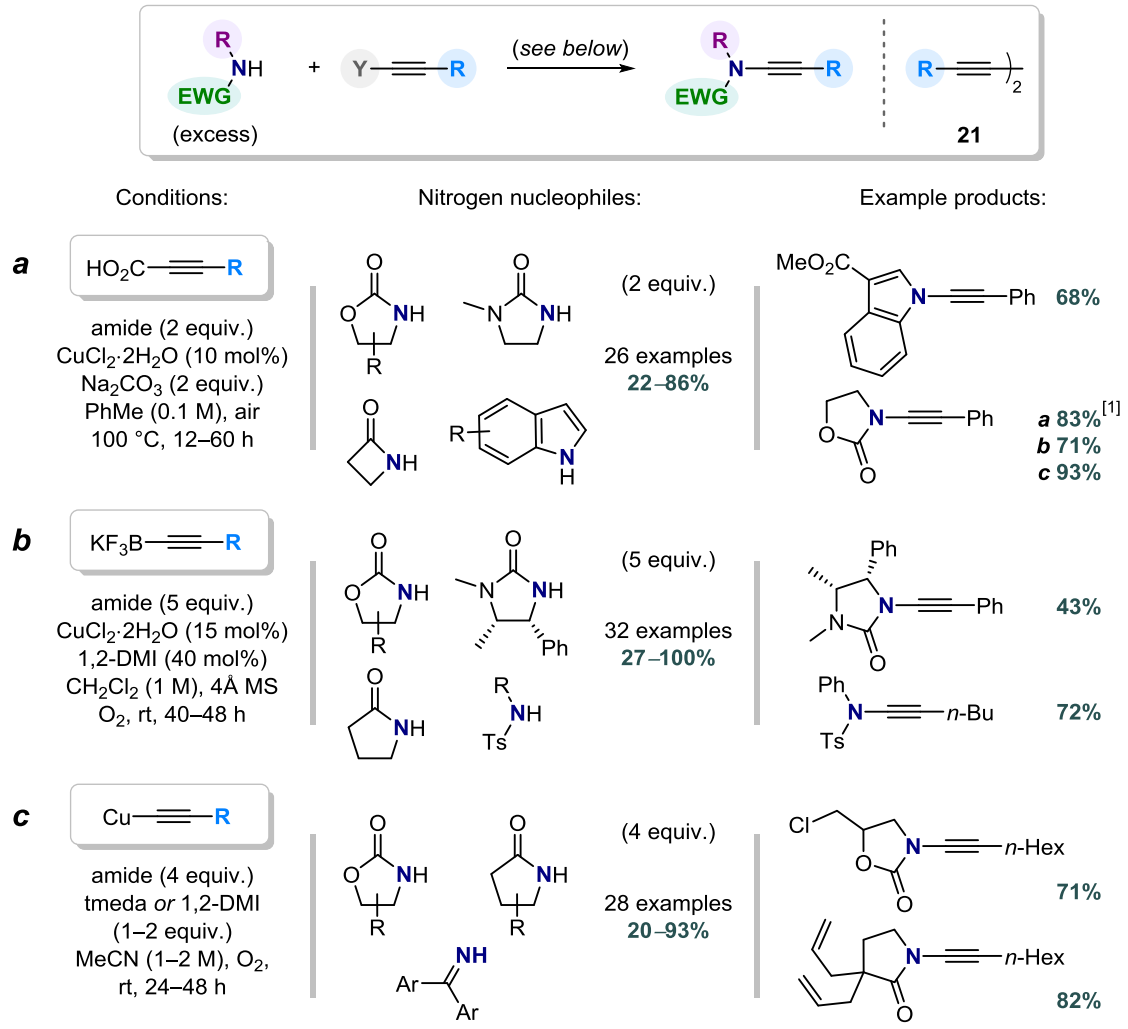


Figure 0.14: Synthesis of ynamides from various alkyne precursors. 1,2-DMI = 1,2-dimethylimidazole. [1] These values refer to isolated yields of the ynamide shown, using methods **a**, **b** or **c**.

Evano and co-workers further sought milder conditions that were both base free and could be performed at room temperature. The first of these solutions came from a Chan-Lam type coupling,[183] in which alkynyltrifluoroborate salts were coupled with oxazolidinones, imidazolidinones and sulfonamides, using $CuCl_2 \cdot 2H_2O$ (15 mol%) and 1,2-dimethylimidazole (1,2-DMI, 40 mol%) under an oxygen atmosphere (**b**, Figure 0.14). Although this reaction matched the criteria of being base free and can be performed at room temperature, the preparation of the alkynyltrifluoroborate salts requires the use of toxic and corrosive KHF_2, which, as a glass etching agent, necessitates the use of Teflon coated reaction vessels to prevent the damage of glassware. Furthermore, five equivalents of amide are required to achieve the observed efficiencies, although it is unclear whether the excess amide is recoverable at the end of these reactions.

These limitations sparked a reconsideration of alkyne precursors, which were required to meet the strict criteria put forth by Evano: "*should be readily available and easy to make, even on a multigram scale, bench-stable, non-hazardous, non-volatile, non-lachrymatory [...] unreactive but still easily activated under mild conditions*."[184] Copper(I) acetylides were investigated as a means to fulfil these criteria, as they are often readily prepared, including on large scale, easily purified by filtration from the reaction mixture and are generally bench stable. In fact, due to the polymeric nature of many of these compounds, such acetylides are notoriously unreactive. But in the presence of diamines, they become much more prone to oxidation.[185,186] Taking advantage of these properties, copper(I) acetylides were used in oxidative coupling reactions with oxazolidinones and pyrrolidinones at room temperature to afford the corresponding ynamides (**c**, Figure 0.14).[187,188] Though acyclic amide analogues are poorly reactive partners, and the use of excess amide (4 equiv.) is a limitation, this strategy is highly effective for many other nucleophiles, including imines,[189] phosphines,[190] phosphites[187] and others.[51,191]

In summary, the oxidative couplings using both terminal alkynes and propiolic acids share very similar conditions, namely the use of copper(II) salts ($CuCl_2$ or $Cu(OAc)_2$) in the presence of pyridine (typically 2 or more equivalents). Carbonate bases are typically used (most often Na_2CO_3) and an oxygen atmosphere is generally more effective than air as the terminal oxidant. The advantage of these conditions is that there is no need to modify the alkyne coupling partners, although the use of excess amide that is required to suppress alkyne homodimerisation can be a serious limitation, especially when using precious precursors. Alkynylborates and copper(I) acetylides are also effective partners in this oxidative chemistry, the latter being very convenient to prepare and handle, and can be used effectively on a large scale.

0.2e C–N Disconnections: Reactions of metallated alkynes.

Finally, we come to the use of nucleophilic acetylides in an "umpolung" approach to C–N formation. In their research to prepare medicinally relevant heterocycles, Batey required access to yne-hydrazides and although the iodonium triflate methodology was shown to be effective in certain cases,[103] a more straightforward approach was to react lithium acetylides with sterically hindered diazo dicarboxylate derivatives (**a**, Figure 0.15).[192,193] The yields for these reactions were variable but this route is very convenient and subsequent *N*-alkylation gives access to a number of functionalised yne-hydrazides.[33,35]

A related approach to yne-triazines involves the addition of a lithium dialkyamide to nitrous oxide, followed by the addition of an alkynyl Grignard reagent (**b**, Figure 0.15).[194,195] Other triazene products can also be accessed with equal efficiency using alkyl or arylmagnesium halides, and this work also characterised the intermediate nitrous oxide adducts **27**; which were unambiguously

determined to have (*Z*)-configuration by single crystal X-ray analysis. Unfortunately, few ynamide analogues are amenable to these kinds of synthesis and the copper-catalysed C–N couplings remain the "gold-standard" of ynamide synthesis to date. Whilst these techniques are not able to prepare every such ynamide that one might wish - a challenge for any methodology - an expanded toolbox has been developed to extend the scope of ynamide products by functionalisation of terminal or metallated ynamides.

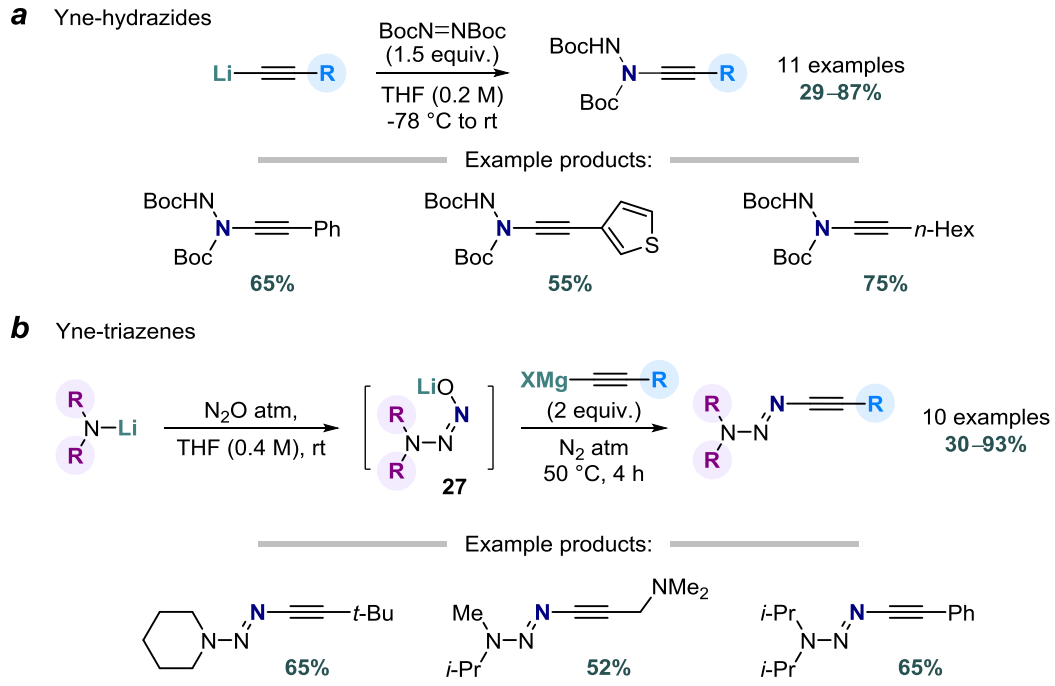
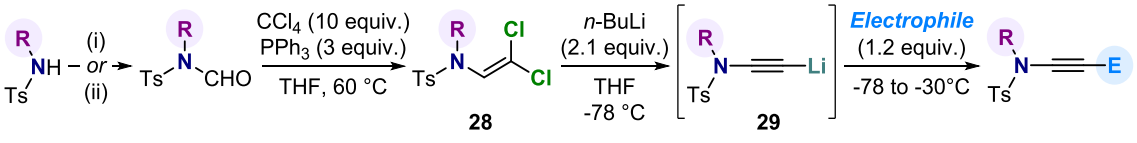


Figure 0.15: Synthesis of ynamide analogues from alkynylmetal reagents.

0.2f C–C Disconnections.

One of the original methods to prepare *C*-functionalised ynamides was from 1,1-dichloroenamides **28** (Scheme 0.2), pioneered by Brückner[196,197] and later developed by Saá[198–201] and Cossy.[202] In the majority of cases, the dichloroenamide was converted to the alkynyllithium **29**, which reacted with electrophiles to give the corresponding ynamides in good yields (**a**, Figure 0.16). However, the necessary use of CCl_4 in the preparation of **28** reduces the appeal of this method and, coupled with the advent of copper-catalysed methods, was superseded by the application of terminal ynamides **31**, which are readily prepared by desilylation of **30** (Figure 0.16).[50,89,96,159,196]



Scheme 0.2: Synthesis of ynamides from 1,1-dichloroenamides; (i) *n*-butyllithium (1.1 equiv.), 1*H*-benzotriazole-1-carbaldehyde (1.2 equiv.), THF, 0 °C to rt; (ii) HCO_2H (2.0 equiv.), *N*,*N*′-dicyclohexylcarbodiimide (2.5 equiv.), CH_2Cl_2, rt.

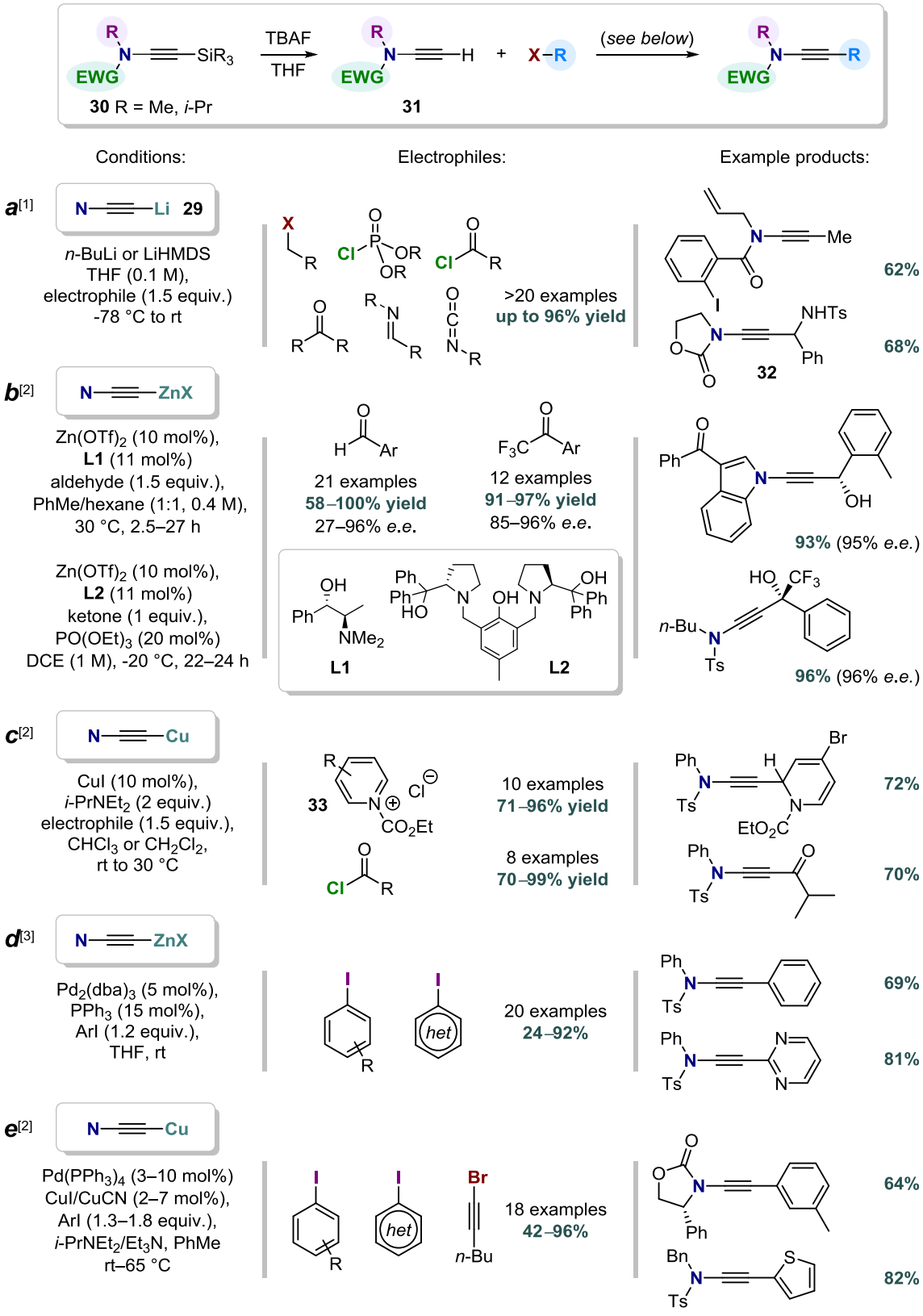


Figure 0.16: Utility of metallated ynamides. [1] *n*-Butyllithium was used for the conversion of 1,1-dichloroenamides **28** to the alkynyllithium **29**; LiHMDS was preferred when converting the terminal ynamide **31** to **29**; [2] The terminal ynamide is likely converted to the alkynylmetal during the course of the reaction; [3] The alkynylzinc was generated from the alkynyllithium by transmetallation with $ZnBr_2$ (1.1 equiv.).

In addition to the methods using 1,1-dichloroenamides, we also disclosed a procedure that utilised 1,2-dichloroenamides for the generation of alkynyllithiums,[203] and the reader is referred to Chapter 1 for full details of this work. In any case, alkynyllithiums **29** proved to be highly versatile building blocks and a range of electrophiles, including carbonyl derivatives (aldehydes/ketones,[204] imines[205] and Ellman's sulfinimines),[206,207] primary alkyl iodides,[96] halogens[208–210] and others,[201,211] can be used to afford an array of functionalised ynamides (**a**, Figure 0.16). This route offers a very effective approach to hydroxy/amido ynamides such as **32** because the alkyne/dibromoalkene partners that would be required for C–N coupling are often prepared via multi-step procedures, which includes protection of the pendant functionality. More recently, Wolf and co-workers reported the direct functionalisation of terminal ynamides, which, importantly, avoided the need for metallation with strong bases. For example, enantioenriched propargylic alcohols were prepared from aldehydes or ketones using catalytic zinc(II) triflate and an enantiopure ligand (**b**, Figure 0.16).[212,213] Nucleophilic addition to acid chlorides, activated nitrogen heterocycles (**33**)[214] and isatins[215] can also be catalysed by copper salts, giving ynamides in comparable yields to those obtained via lithiation (**c**, Figure 0.16).

It is therefore evident that catalytic methods for C–C bond formation offer potentially milder conditions and broader product scope than the use of alkynyllithiums when preparing functionalised ynamides. In this regard, transition metal catalysed coupling of alkynylzinc or copper species enabled ready access to *C*-arylated ynamides via Negishi or Sonogashira couplings, respectively (**d** and **e**, Figure 16),[198,216] However, in the latter case, homocoupling of the terminal ynamide is a significant issue that can be minimised by using very low concentrations of copper salt. Later reports detailed an alternative, copper-free Sonogashira coupling using aryl iodides,[217,218] which, importantly, was found to completely suppress the homodimerisation of the terminal ynamides. The homodimerisation of terminal ynamides in the presence of copper was similarly observed by Saá and co-workers,[199] who optimised this to prepare a selection of diynes **34** (Figure 0.17); alternative "head-to-tail" dimerisation can also be achieved.[219,220] Polyyne ynamides **35** can also be prepared by a Cadiot-Chodkiewicz coupling of terminal ynamides with bromoalkynes (Figure 0.18);[221–223] these polyynes possess interesting electronic properties that will be discussed further in Chapter 3.

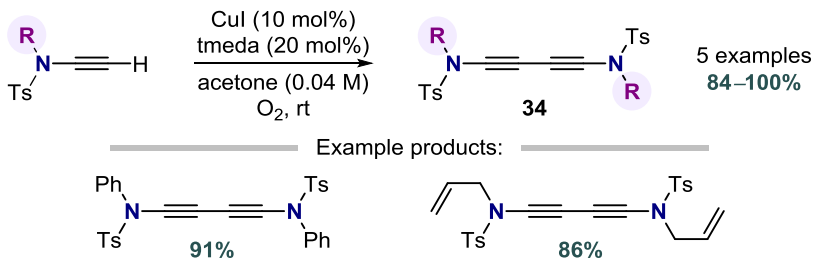


Figure 0.17: Glaser-Hay oxidative dimerisation of terminal ynamides.

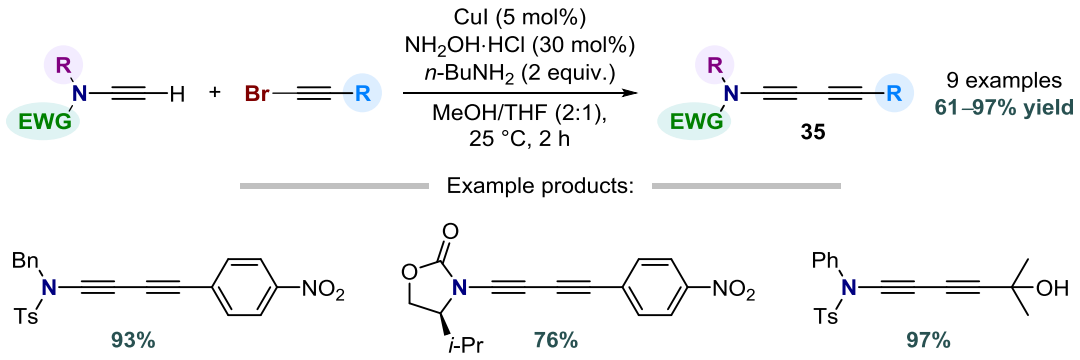


Figure 0.18: Cadiot-Chodkiewicz couplings of terminal ynamides.

0.2g Miscellaneous: Functional group interconversions.

In addition to methods based on the two key disconnection strategies, a few other routes have been developed that relied on the elimination of H–X from an enamide precursor (Figure 0.19). These elimination strategies, as well as the isomerisation of propargylic amides,[95,224–226] were reported prior to the development of the copper-catalysed transformations and had only limited efficiency and product scope.

The elimination strategy was first described in 1972 by Viehe, in which reaction of amide **36** with phosgenimonium chloride afforded the chloroenamide **37** (Figure 0.19). The elimination was performed using potassium *t*-butoxide and gave the ynamide **38** in good yield.[63] This strategy was later revisited by Katritzky and co-workers,[227,228] who reported the synthesis of benzotriazol-1-yl alkynes **39** from the corresponding ketones **40** via the enol triflate (**a**, Figure 0.20). A related synthesis also grants access to triazol-2-yl alkynes **41**[229] and strained cyclic ynamides.[230]

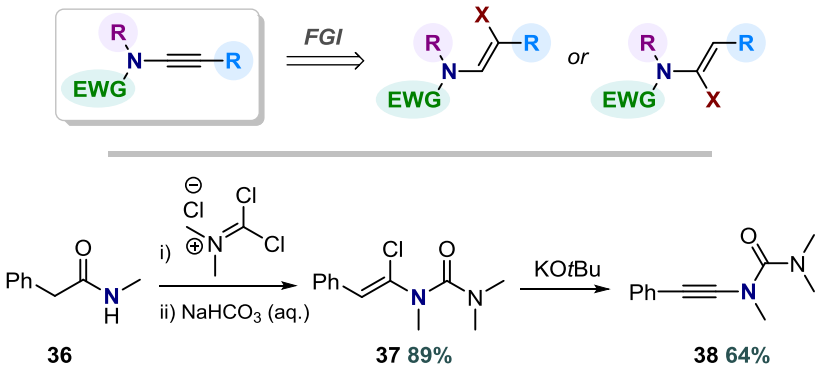


Figure 0.19: Functional group interconversion (FGI) of ynamides to haloenamides and Viehe's synthesis of ynamides.

Hsung and co-workers also described a similar route that involved the use of β-bromoenamides **43** (**b**, Figure 0.20).[95] These bromoenamides were prepared as an (*E*)-/(*Z*)-mixture by refluxing the enamides **42** with either bromine or *N*-bromosuccinimide. Only the (*Z*)-isomer underwent elimination to give the ynamides and attempts to convert the (*E*)-isomers were unsuccessful.

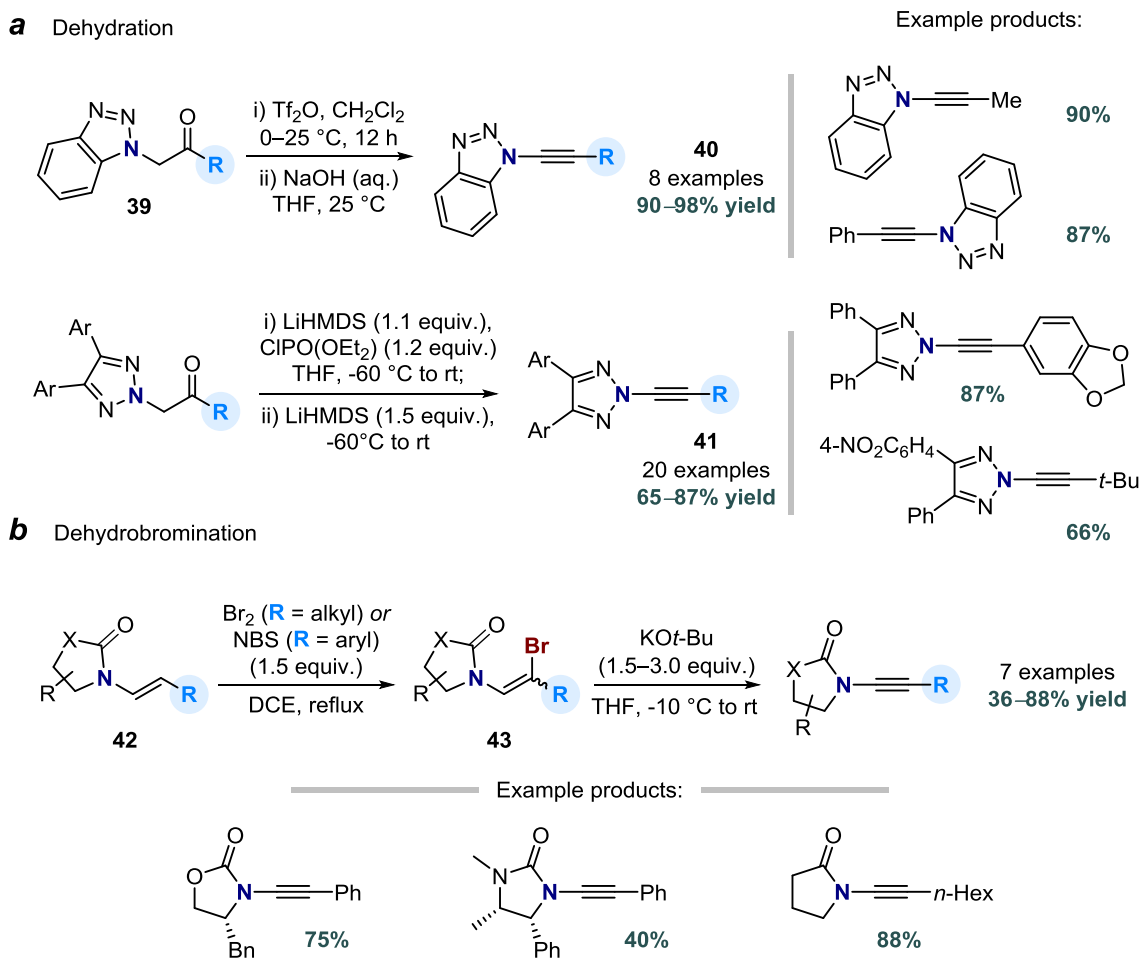


Figure 0.20: Elimination strategies to prepare ynamides.

A few other methods remain that rely on perhaps unconventional disconnection strategies. These will be highlighted for interest, because they not only show potential to synthesise more problematic ynamides, but also illustrate that possible solutions to problems can come from unexpected directions. For example, two analogous routes to ynamides involve the ring opening of azoles **44** and **45** with strong bases (**a**, Figure 0.21).[231,232] Though these are not mild conditions, nor are they necessarily generally applicable, they do illustrate a kinship between ynamides and azoles. Furthermore, use of the triazole conceivably allows for the installation of *any* electron withdrawing group on the ynamide - a strategy that has potentially enormous value. A related approach involves the conversion of one electron withdrawing group into another (**b**, Figure 0.21). This was developed recently by Evano and co-workers to address the use of problematic acyclic secondary amides in C–N coupling.[233] Here, readily accessible yne-oxazolidinones **46** undergo ring opening with organolithiums to give lithium alkoxide **47**. The hydroxy ynamides that result from protonation of **47** were found to be unstable and in situ trapping of the lithium alkoxide **47** was performed using acyl chlorides or other reactive electrophiles. Unfortunately, the use of Grignard reagents was unsuccessful but, mindful of the potential involvement of the alkyne in carbometallation chemistry,

one wonders whether the addition of "hard" Lewis acids, for example, cerium(III) salts, would be successful in aiding oxazolidinone cleavage in these cases.

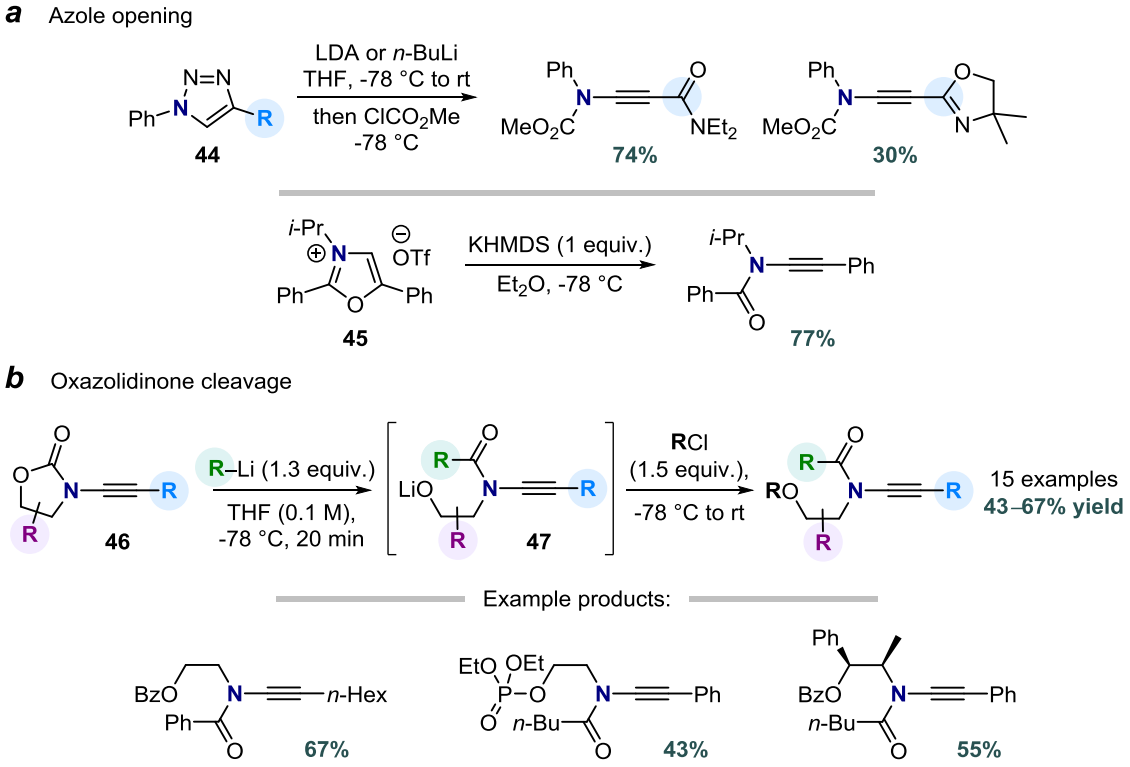


Figure 0.21: Alternative approaches to ynamides via ring-opening.

0.3 Conclusions.

Throughout this review, we have endeavoured to indicate nucleophiles that participate well for each method, which includes a range of oxazolidinones, lactams, sulfonamides, unhindered acyclic carbamates, phosphoramidates, indoles, pyrroles, imidazoles, pyrazoles, imines, and others. Consequently, these developments have enabled access to a wide range of ynamide classes, with an almost free choice of substituents that can be installed on the alkyne terminus. However, it is also prudent to mention non- or poorly-participating nitrogen nucleophiles in these chemistries (**a**, Figure 0.22). By far the most difficult substrates to use are acyclic secondary amides, acyclic ureas and bulky amide-analogues (**48**) and, to date, the reactions with alkynyliodonium triflates remain the most effective method to *N*-alkynylate acyclic secondary amides. In cases using more specialised nitrogen-derivatives, (hetero)aryl sulfonamides are often poorly effective partners for cross couplings and reactions using hydroxylamines[234] and guanidines[235] are unsuccessful. It is unclear why all of these nucleophiles display such recalcitrance in these reactions, and it has been suggested that this may be due to poor acidity, poor nucleophilicity and/or steric hindrance. Furthermore, non-ynamide products are afforded in cases where oxazolidine-thiones **49** and amidines **50** are used in copper-catalysed couplings (**b** and **c**, Figure 0.22). In the former case (**49**), the coupling occurs at

sulfur instead of nitrogen, which leads to thioethers **50** and, for the latter, amidinyl ynamides **51** were proposed to form as intermediates en route to pyrroles **52**. These observations likely indicate that reactions using related nucleophiles, for example, thioamides, could also produce cyclisation products instead of the ynamide.

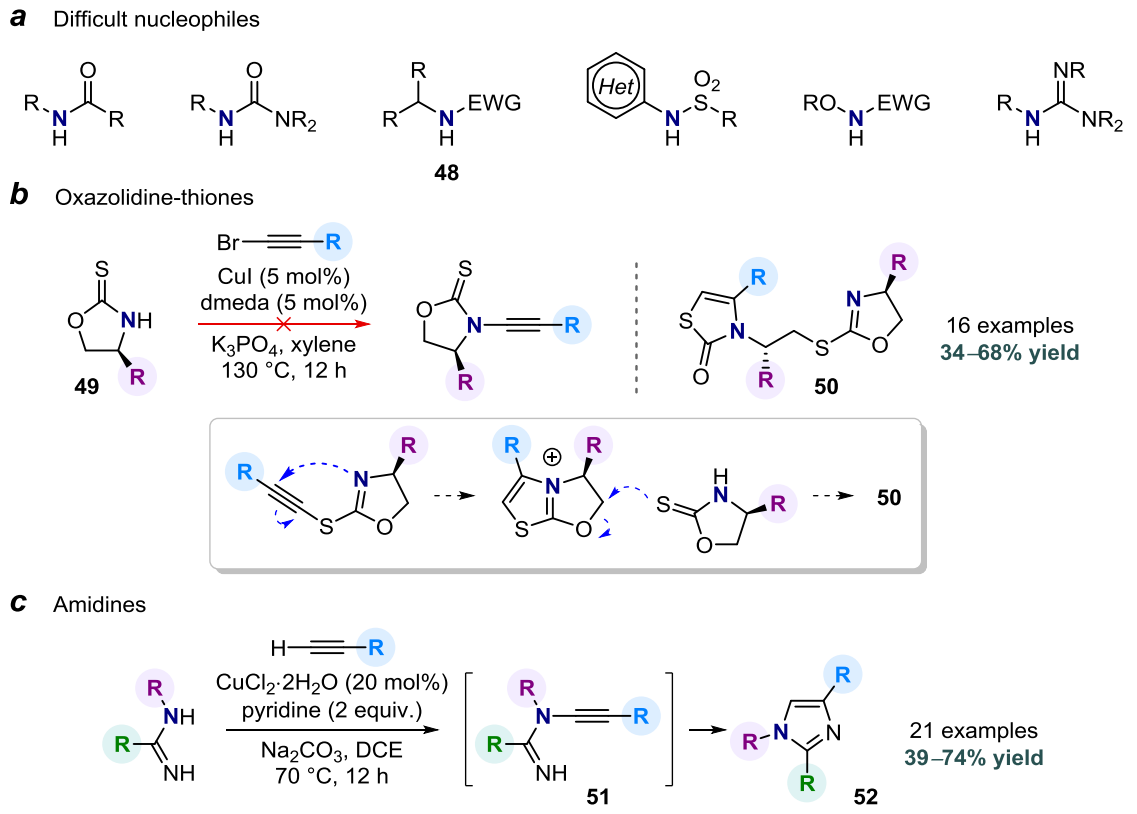


Figure 0.22: Poorly-participating nucleophiles for ynamide synthesis, and the reactions of oxazolidine-thiones and amidines.

In conclusion, there are clearly many methods to prepare ynamides and it is of little doubt that these developments have contributed to the rising interest to utilise these building blocks. To date, and if the number of citations are any indication, the most general and popular methods to prepare a majority of ynamides are Hsung's 2nd generation and Danheiser's protocols using bromoalkynes (Figure 0.6), Evano's 1st generation protocol using dibromoenamides (Figure 0.10) and Stahl's oxidative coupling of terminal alkynes (Figure 0.13); with many hundreds, likely thousands, of different ynamides having been prepared and characterised using these methods. Whilst the synthesis of ynamides is not a fully solved problem, insights gleaned from individual approaches could offer prospects to further tune these procedures in the case of poorly reactive nucleophiles, for example, using microwave irradiation[236] or sonication.[237] It is unclear whether the quest for a truly universal ynamide synthesis can ever be completed but if achieved, could facilitate a greater expansion and interest in ynamide chemistry.

Synthesis of Ynamides from 1,2-Dichloroenamides

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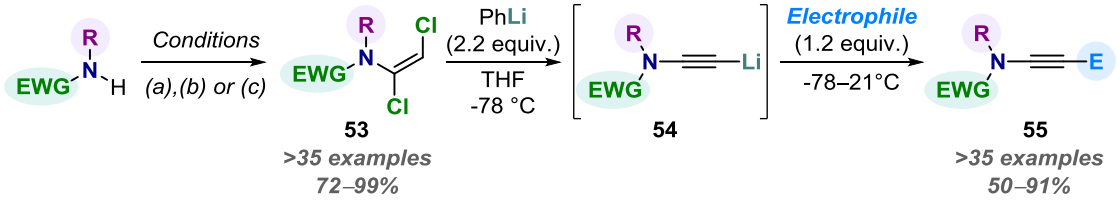
As a testament to their value, there has been a significant rise in the number of synthetic applications of ynamides and, as discussed in the previous chapter, this has resulted in an ever-increasing diversity of methods for their preparation. Whilst these developments are impressive achievements in their own right, it is apparent that no single methodology reigns supreme over any other and a truly general synthetic method remains elusive. To date, sulfonamides and oxazolidinones remain the most successful amide analogues in ynamidative couplings and, perhaps as a consequence, many of the ynamide applications only utilise such substrates. One question that invariably arises is "what other nitrogen protecting groups can be used?", ultimately because of the reputed challenge of sulfonamide cleavage, which often requires harsh conditions that are not compatible with many other functional groups. Acyclic carbamates, particularly Boc-protected amines, and acyclic secondary amides are considered more desirable partners because milder conditions are often sufficient for their cleavage. Unfortunately, it is these substrates that are much less successful in ynamidative couplings and their urea cousins have also received scant attention. It is surprising that acyclic *N*-carbonyl ynamides have been so neglected as compared to other ynamide classes, and their potential applications remain untapped simply because of the difficulty to prepare them in synthetically useful quantities.

We thus envisaged a modular approach to ynamides that utilised a two-carbon building block, in which a variety of functionality could be added conveniently at both ends. This chapter describes our efforts in this regard and is divided into two sections. Section 1.1 deals with our previous work, the preparation and utility of 1,2-dichloroenamides, and provides an overview of observations that informed many of the decisions made in subsequent work, as described in section 1.2.

1.1 Previous work.

1.1a Synthesis and utility of 1,2-dichloroenamides.

Our initial work[203] showed that (*E*)-1,2-dichloroenamides **53** can be prepared in one step from a range of amide analogues and dichloroacetylene (generated in situ from trichloroethylene (TCE)). Subsequent lithiation using phenyllithium (2.2 equiv.) gave alkynyllithiums **54** and addition of the desired electrophile afforded the functionalised ynamides **55** in good yield (Scheme 1.1). While the latter step proceeded rather uneventfully, the synthesis of the dichloroenamides warrants further discussion.



Scheme 1.1: Synthesis of ynamides from 1,2-dichloroenamides *via* alkynyllithiums. ***Conditions***: (a) TCE (1.1 equiv.), Cs_2CO_3 (1.5 equiv.), DMF, 50 °C; (b) TCE (3.0 equiv.), 25% w/v aq. NaOH or 50% w/v aq. KOH, *n*-Bu_4NHSO_4 (TBAHS) (0.25 equiv.), PhMe, 21–60 °C; (c) TCE (1.0 equiv.), NaH (2.1–3.0 equiv.), DMF, 0–21 °C.

The first conditions that were optimised for the preparation of 1,2-dichloroenamides used 1.1 equiv. of trichloroethylene (TCE) and 1.5 equiv. of Cs_2CO_3 in DMF at 50 °C (Scheme 1.1). These conditions were highly successful for sulfonamides, electron-deficient aromatic heterocycles and certain unhindered carbamates, such as methyl and *i*-propyl phenylcarbamates. The reactions were typically complete within 1–4 hours and the crude dichloroenamide products were usually of sufficient purity for direct use in the subsequent lithiation chemistry.[238] On the other hand, *t*-butyl carbamates, ureas and amides were typically poor substrates. In these cases, the reaction mixture turned black and there was negligible conversion. As a general observation for all of these reactions: the darker the final reaction mixture, the lower the yield of the desired product.

It was hypothesised that the amide/urea reactivity issue was primarily one of acidity (both kinetic acidity and pK_a), though the nucleophilicity of the resulting anion was also in question, particularly for hindered substrates such as *t*-butyl carbamates. Considering the issue of pK_a, our next approaches to prepare dichloroenamides involved the use of stronger bases, specifically sodium or potassium hydroxide with phase transfer catalysis, or the yet more basic sodium hydride (Scheme 1.1). Industrially, phase transfer catalysed (PTC) reactions using sodium or potassium hydroxide have generally superseded the use of expensive and pyrophoric bases such as sodium hydride; it is often overlooked that hydroxide is a remarkably strong base in organic solutions (pK_a 31.4 in DMSO)[239] and, in exceptional cases, has been known to deprotonate materials with pK_a values up

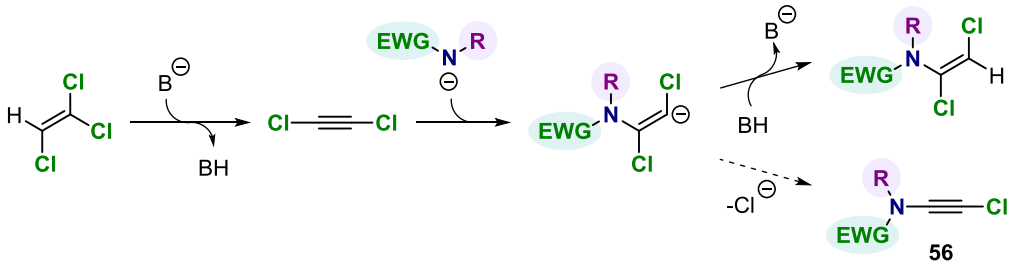
to ~38.[240] Furthermore, sodium hydride is usually avoided when safer[241] and more reliable[242] alternatives are viable, with the use of sodium hydride in DMF being a notably dangerous reaction mixture, particularly on scale.[243,244] It is unfortunate, however, that this is often very convenient for use in an academic setting, as it generally requires less optimisation than the PTC reactions.

In our work, the phase transfer conditions found a niche in which *N*-aryl amides/carbamates/ureas, some *N*-alkyl amides, and *N*,*N*′-di-Boc hydrazines would react smoothly to give the dichloroenamide, but most *N*-alkyl derivatives were poorly reactive. These reactions could be heated to improve conversion for those poorly reactive substrates, but this was sometimes accompanied by the following issues: (i) the tetrabutylammonium salt degraded upon heating in basic solution over time (though the reaction could be "topped up" with more ammonium salt); and (ii) dichloroacetylene tended to evaporate out of solution at higher temperatures, retarding the reaction. Alternative catalysts for base-mediated phase transfer reactions include crown ethers, cryptands and open chain polyethers[240] and, whilst these were not screened here, they may offer advantages over the use of tetraalkylammonium salts in this chemistry.

Switching the base to sodium hydride offered only a partial solution. While it was certainly sufficiently basic to deprotonate even the least acidic amides, the reaction outcome was often poorly reproducible: conversion fluctuated significantly between reactions (with isolated yields ranging from 5–70%). Typically, a suspension of the amide and sodium hydride was stirred for an hour at room temperature, followed by the dropwise addition of a solution of trichloroethylene. These reactions darkened significantly with a build-up of an unidentified insoluble black matter and the dichloroenamide product was often contaminated with minor amounts of the chloroynamide **56** (Scheme 1.2). Using potassium hydride gave better conversion, but was accompanied by greater amounts of the chloroynamide and insoluble black material.[245] After further experimentation, these reproducibility issues did not seem to correlate solely with factors such as reagent and solvent purity, dilution, temperature or the rate of addition of trichloroethylene. It was more likely that a combination of factors was at play, and the outcome of the reaction was substrate dependent.

However, all of these reactions did lead to two important conclusions: (i) the amide pro-nucleophiles were not nucleophilic enough to add to dichloroacetylene and deprotonation *was* required (though imidazole will react with dichloroacetylene without additional base);[246] and (ii) dehydrochlorination of TCE was slow in the absence of an organic-soluble base (the elimination is likely facilitated by the amidate ion itself, and the insoluble inorganic base is the final proton sink).[247] A generic mechanism is thus proposed in Scheme 1.2. There are many possible species that could serve as the base B^- in these reactions, including the inorganic base or any of the anionic intermediates. Similarly, BH could be the protonated inorganic base, the amide or another molecule of trichloroethylene. Where the concentration of BH is small or zero, as for the cases using sodium

hydride, the final protonation is retarded and β-elimination of chloride can occur instead to produce the chloroynamide **56**.



Scheme 1.2: Generic reaction mechanism for the formation of (*E*)-1,2-dichloroenamides.

1.1b Detection of intermediates en route to lithiated ynamides.

By analogy to the work of Poisson,[248] it was reasonable to presume that the conversion of a dichloroenamide to alkynyllithium **54** (Scheme 1.1) proceeded via lithiation and *syn*-elimination of chloride to give a chloroynamide (Figure 1.1). Lithium-halogen exchange would then afford the alkynyllithium. In confirming this sequence, the intermediate vinyllithium **57** was generated from **53a** using *n*-butyllithium at -78 °C and, after five minutes, was trapped with reactive electrophiles to give the functionalised dichloroenamides **58a**–**58e** in good yield (Figure 1.1). Only a single isomer of the dichloroenamide product was detected in these reactions and single crystal X-ray analysis of **58e** showed this to have (*E*)-geometry; the geometries of the other dichloroenamides were assigned by analogy. If the intermediate vinyllithium **57** was not trapped within five minutes at -78 °C,[249] it underwent complete conversion to the chloroynamide **56a** within an hour; this could be isolated in 62% yield and its identity was confirmed by X-ray analysis.

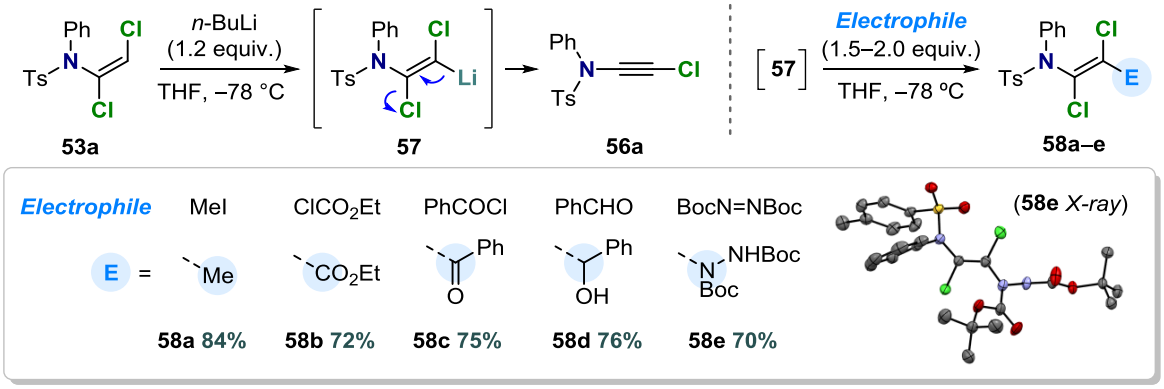


Figure 1.1: Generation and trapping of the intermediate vinyllithium **57**. Displacement ellipsoid plot for **58e** is displayed at 50% probability; hydrogen atoms and the disordered component are omitted for clarity.

Treatment of **56a** with phenyl or *n*-butyllithium (1.2 equiv.), either in situ or using purified material, gave full conversion to the alkynyllithium, as determined by TLC analysis. Here, the alkynyllithium is protonated when spotted onto the TLC plate, and the resulting terminal ynamides (**55**, E = H,

Scheme 1.1) have different R_f values as compared to the chloroynamides. Subsequent reaction of **54** with electrophiles gives ynamides **55** (Scheme 1.1).

A range of bases was also screened to enable a more reliable chloroynamide formation. Ultimately the use of LiHMDS (1.2 equiv.) at 0 °C in THF proved optimal (Figure 1.2); these reactions were typically "spot to spot" as judged by TLC analysis. Overall, this base consistently outperformed other metal amides (including NaHMDS, LDA or LiTMP), which generally resulted in decomposition, and was preferred to organolithium species, which often gave competing lithium-halogen exchange. Metal alkoxides such as KO*t*-Bu were unreactive, even upon prolonged heating.

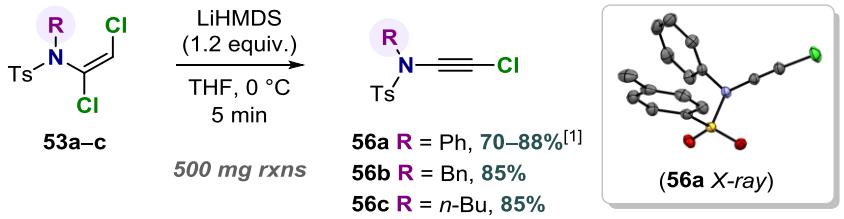


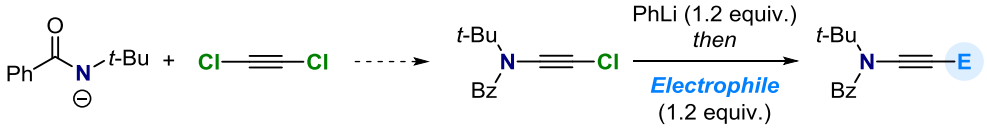
Figure 1.2: Synthesis of chloroynamides from (*E*)-1,2-dichloroenamides. [1] Yield range over five runs. Single crystal X-ray data collection, processing and solution refinement for **56a** was performed by Dr Mike Jones. Displacement ellipsoid plot for **56a** is displayed at 50% probability and hydrogen atoms are omitted for clarity.

The general stability of the chloroynamides **56a**–**56c** was also assessed. They could withstand typical aqueous workup conditions using water or saturated aqueous ammonium chloride, with no discernible degradation. Purification by flash column chromatography on silica gel (pretreatment with Et_3N was unnecessary) gave isolated yields between 70–88%, though prolonged exposure to silica gel resulted in significantly decreased yields. Purified *N*-tosyl chloroynamides were found to be sensitive to concentration in vacuo above 20 °C: upon concentration of the colourless, purified column fractions, the mixture would often become a yellow to orange/brown oil or solid. In these cases, a mixture of polar compounds had formed, as analysed by TLC, but their identities were not determined. In general, the *N*-alkyl chloroynamides were less stable than the *N*-aryl analogue, and crystalline chloroynamides, for example, **56a**, were more stable towards general handling and manipulation than those that were oils (**56c**). Thus in our later chemistry, it was desirable to generate and use the chloroynamides in situ, without isolation, to avoid these issues.

1.1c Further investigations towards ynamides.

Considering an alternative strategy to ynamides, we sought to develop a more streamlined approach to chloroynamides by using pre-formed amidate and dichloroacetylene (Scheme 1.3). Conceivably, this could be performed in one of two ways: (i) generation of both in the same reaction mixture, at a temperature low enough such that all subsequent reactions are suppressed, followed by warming the reaction mixture up to an appropriate temperature; or (ii) preparation of a solution of each in

separate vessels, followed by mixing of the two in a third vessel. *N*-*t*-Butyl benzamide was chosen as the test substrate for this reaction because there are no acidic α-protons that could interfere, and hindered *N*-alkyl amides are one of the least competent substrates for any ynamide methodology; we anticipated that successful reaction conditions here would be applicable to less hindered substrates.



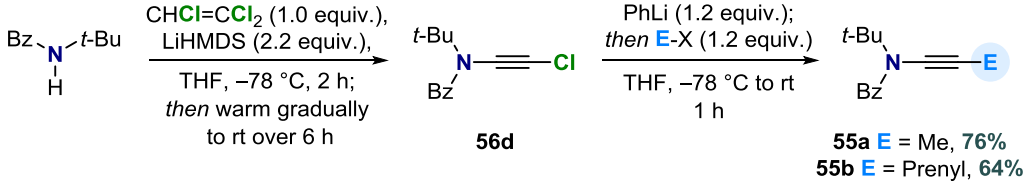
Scheme 1.3: Proposed route to ynamides directly via chloroynamides.

Addressing idea (i), it is known that amidates can be generated conveniently using most soluble strong bases, including LiHMDS, ethylmagnesium bromide or *n*-butyllithium. However, the formation of a solution of dichloroacetylene from TCE required a specific choice of base - a problem that has been visited a number of times.[246,247,250–252] For example, the use of 2 equiv. of *n*-butyllithium or phenyllithium, which is required to deprotonate both TCE and the amide, also gave a competing lithium-chlorine exchange of dichloroacetylene. Both LiHMDS and pentynyl-lithium were excellent bases, being selective for both amide deprotonation and dehydrochlorination of TCE, but the deprotonation of pentyne in later lithiation steps was an issue; this was not the case for HMDS. We hoped to alleviate this issue by having a volatile byproduct, acetylene, and the reactions were also performed using dilithium acetylide[253] or ethynylmagnesium bromide as bases. However, these were much less effective than LiHMDS, which was chosen for our studies.

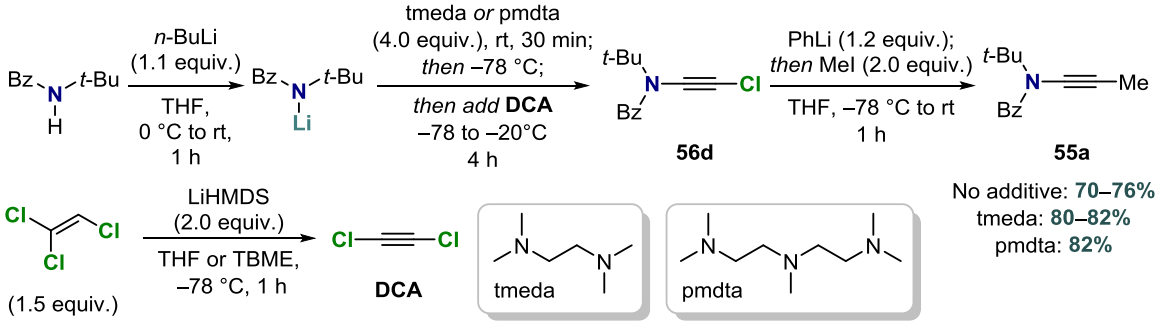
Thus a THF solution of *N*-*t*-butyl benzamide and trichloroethylene was treated with 2.2 equiv. of LiHMDS at -78 °C and the reaction stirred for 2 hours (Scheme 1.4). The mixture was then allowed to warm gradually to room temperature over a period of 6 hours. TLC analysis of the reaction mixture at 10 °C intervals indicated that the reaction between the amidate and dichloroacetylene begins at around -20 °C. The reaction mixture would also begin to darken at -20 °C, turning from a pale yellow solution to a dark orange/brown solution at -5 °C, and this coincided with the increased formation of the chloroynamide **56d**. The dichloroenamide was consistently formed as a minor byproduct and the reaction would rarely reach full conversion of the amide (~75–85% conversion). Doubling the amount of LiHMDS and TCE did not appreciably alter this. Nevertheless, in situ lithiation of the chloroynamide with phenyllithium (1.2 equiv.), followed by reaction with methyl iodide or prenyl bromide, afforded the desired ynamides **55a** and **55b** in 76 and 64% yields, respectively.

Idea (ii) gave much the same result. Firstly, the choice of metal counterion for the amidate was found to be very important: Li^+ outperformed Na^+ and K^+, with the latter two giving rapid decomposition even at -78 °C, and there was negligible conversion with $[MgBr]^+$. The temperature

at which the two components were mixed was also important (Scheme 1.5). In line with previous observations, mixing at temperatures significantly above -20 °C led to very poor conversion, and it was best to mix the two components below -40 °C and allow the mixture to warm gradually. The aggregation states of the various lithium species at these temperatures is likely important here. Additives such as tmeda or pmdta facilitated the reaction and the formation of the chloroynamide began around -40 °C. Warming to -20 °C produced the usual darkening of the reaction mixture and, for reasons unknown, it was beneficial to maintain the reaction temperature between -20 °C and -15 °C until completion (~4–5 hours), which gave full conversion to the chloroynamide. Subsequent lithiation and reaction with methyl iodide afforded the corresponding ynamide **55a** in good yield.



Scheme 1.4: First approach to yne-amides via chloroynamides.



Scheme 1.5: Second approach to yne-amides via chloroynamides and the use of chelating amines.

During these studies using *N*-*t*-butyl benzamide, we also observed that prolonged stirring of chloroynamide **56d** gave the oxazole **59** (Figure 1.3). This mode of reactivity is known for carbamate-derived ynamides, but usually requires the presence of a π-acidic metal catalyst.[254–257] It is therefore proposed that an electrocyclisation affords the mesoionic carbene shown, possibly coordinated to lithium, which undergoes protonation and loss of *t*-butyl cation in some fashion, possibly via the intramolecular proton shift shown. This could be a general feature of yne-amides, but nevertheless provides a simple route to oxazoles. Later discussions will elaborate on the significance of this cyclisation.

Returning to the formation of ynamides, it was unfortunate that this method was unreliable when applied to less bulky amides. For example, using *N*-*n*-butyl benzamide or *N*-phenyl benzamide, the overall conversions were unsatisfactory (~60%) and there was a concomitant formation of insoluble black matter. Although a promising route to ynamides, we ceased our efforts here in search of a superior methodology.

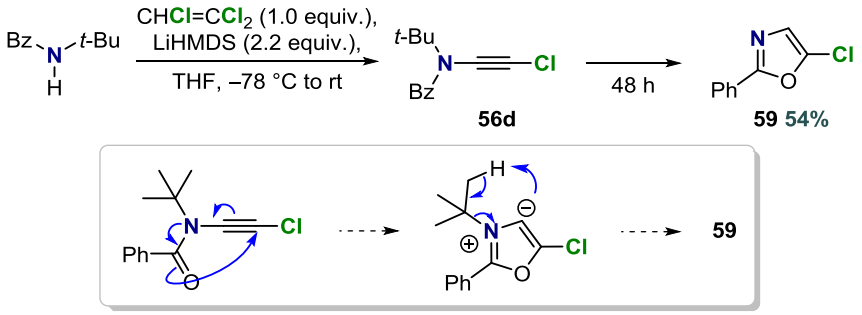


Figure 1.3: Cyclisation of *N*-*t*-butyl chloroynamide **56d** to an oxazole.

In summary, reproducibility issues were observed when changing the reaction from a "steady-state" generation and consumption of dichloroacetylene (e.g. with sulfonamides and weak bases such as Cs_2CO_3), to reactions in which significant quantities of dichloroacetylene were produced, but with slower consumption to product (e.g. using weak or strong bases with amides and ureas). The latter reactions often gave dark reaction mixtures and poorly-soluble black precipitates. Generally, weak bases were unable to convert amides and ureas to dichloroenamides, and strong bases such as LiHMDS or sodium hydride were required. The reactions using LiHMDS favoured the formation of chloroynamides over dichloroenamides (the chloroynamide was observed as a side product when using sodium hydride). Whilst the exact reasons for the irreproducibility could not be ascertained at the time, it was likely that a combination of factors such as temperature and the rate of addition of trichloroethylene/dichloroacetylene were important when matching the substrate-dependent consumption of dichloroacetylene. As dichloroacetylene is highly reactive and thus susceptible to oxidation/polymerisation, it is perhaps not surprising that non-specific degradation was observed as a side reaction,[258,259] possibly facilitated by trace impurities formed in the reaction mixture. Later discussions will again touch on these observations.

1.2 Copper-catalysed umpolung synthesis of ynamides.

The strategy described previously (Scheme 1.1) enabled a modular approach to ynamide synthesis, and could utilise many of the amide analogues that are typically difficult partners for C–N coupling methodologies, such as hindered or *N*-aryl sulfonamides, *t*-butyl carbamates and acyclic ureas. It also avoided the need to prepare (bromo)alkyne or dibromoalkene coupling partners, and an array of electrophiles including carbonyl derivatives (e.g. aldehydes, ketones, imines and enones), epoxides, primary alkyl halides and disulfides were successful. However, there were some inherent drawbacks: first and foremost, the necessary use of phenyllithium is not generally compatible with reactive functionalities such as esters, nitriles and nitro groups. Furthermore, secondary and tertiary alkyl groups could not be installed conveniently, and arylation of the alkynyllithium was particularly challenging and ultimately low yielding.[260] In developing the strategy further and circumventing these issues, we considered reversing the reaction polarity, instead using an ynamide as the

electrophilic component (Figure 1.4). A haloynamide was a natural choice but, despite being potentially useful building blocks, they have been largely neglected in synthesis.[203,208–210,261,262] Nevertheless, it was envisioned that coupling of a chloroynamide with an organometallic nucleophile, such as a Grignard or organozinc reagent, would provide a useful and novel "umpolung" entry to ynamides. Unlike the well-known Sonogashira couplings of alkynes, the coupling of a haloalkyne and an organometallic nucleophile has been very poorly studied,[263–265] with only a single case reporting the use of chloroalkynes;[266] these are, for the most part, considered to be "*of little practical importance because of their low reactivity*."[186] Nevertheless, such an approach would give us the opportunity to explore the chemistry of a poorly investigated building block, and would complement our previous work by increasing the versatility of 1,2-dichloroenamide building blocks for ynamide synthesis.

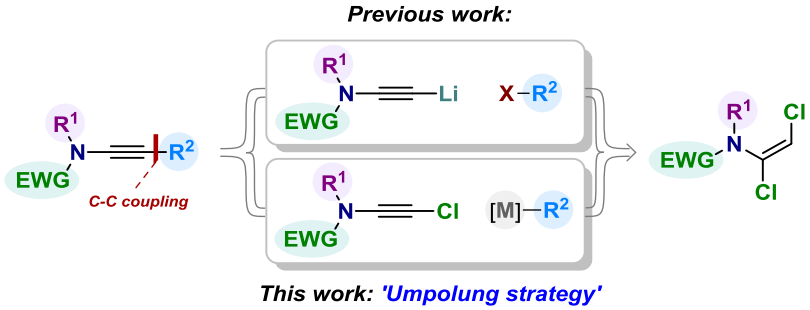
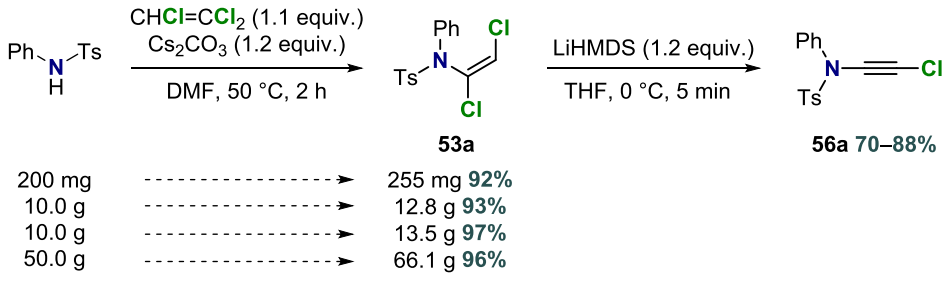


Figure 1.4. Comparison of strategies: the synthesis of ynamides via nucleophilic alkynyllithiums and the planned umpolung synthesis using electrophilic chloroynamides.

1.2a Reaction optimisation.

Dichloroenamide **53a** (Scheme 1.6) was chosen as a suitable test substrate in this study for the following reasons: (i) no chromatography was necessary for this compound as it was readily purified by recrystallisation from *t*-butyl methyl ether (TBME); and (ii) it was anticipated that many of the product *N*-phenyl ynamides would be crystalline, giving the opportunity for recrystallisation and ultimately enabling product analysis using single crystal X-ray diffraction techniques (Chapter 3). Furthermore, the synthesis of *N*-tosyl dichloroenamides is generally very effective at large scale (≥10 g),[267] and a large quantity of **53a** was readily prepared for our study (Scheme 1.6).



Scheme 1.6: Synthesis of dichloroenamide **53a** at multiple scales, and subsequent conversion to the chloroynamide.

The viability of the route was first tested using spectroscopically pure (>98%) *N*-phenyl-*N*-tosyl chloroynamide **56a**, as this would avoid potentially spurious outcomes that may result from the inclusion of HMDS and LiCl byproducts (produced during *syn*-elimination from the dichloroenamide). Four Grignard reagents were selected as coupling partners to test: phenylmagnesium bromide (1.0 M solution in THF), *i*-propylmagnesium chloride (1.0 M solution in THF), cyclohexylmagnesium chloride (1.0 M in toluene/THF) and *t*-butylmagnesium chloride (1.0 M solution in THF). Using the conditions reported by Cahiez (dropwise addition of a solution of RMgX (1.2 equiv.) over 1 hour to a solution of chloroalkyne and $CuCl_2$ (5 mol%) at 0 °C),[266] there was full conversion of the chloroynamide and the ynamide products **60a**–**60d** were isolated in reasonable yields (Figure 1.5). Somewhat unexpectedly, (*Z*)-chloroenamide **61** was a significant byproduct when using phenylmagnesium bromide and its geometry was identified using single crystal X-ray analysis. Chloroenamides were not observed when using the alkyl Grignard reagents. Switching the counteranion from bromide to chloride by using of phenylmagnesium chloride (1.0 M solution in THF) did not affect this outcome. Without added copper salt, the use of phenylmagnesium bromide led to no conversion, while 2°/3° Grignard reagents underwent magnesium-chlorine exchange to give the terminal ynamide (R = H).

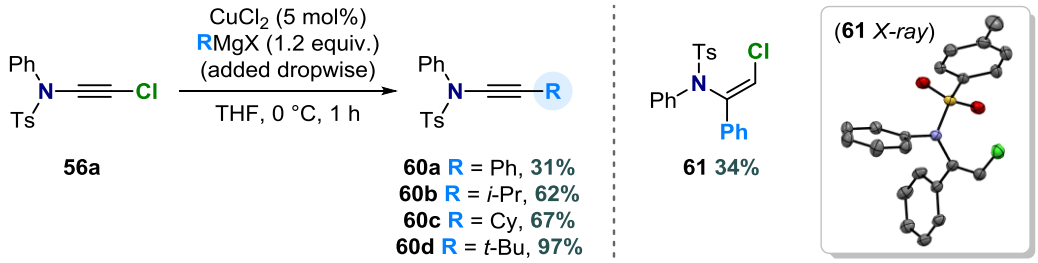
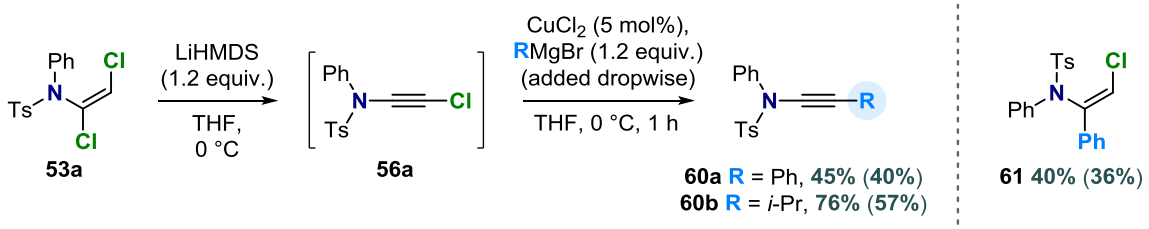


Figure 1.5: Viability test for the coupling of chloroynamide with Grignard reagents. Displacement ellipsoid plot for **61** is displayed at 50% probability and hydrogen atoms are omitted for clarity.

With this success, the preceding reactions were repeated with the chloroynamide generated in situ (rather than with purified material), using phenylmagnesium bromide and *i*-propylmagnesium chloride as coupling partners, to determine if the HMDS and LiCl byproducts would affect the reaction outcome (Scheme 1.7). These reactions proceeded without issue, affording the desired ynamides in comparable yields to those obtained previously. It was also noted that higher yields of the chloroynamide, and hence coupled ynamides **60a** and **60b**, could be obtained when switching from a commercial solution of LiHMDS (1.0 M in THF, Sigma Aldrich) to using a freshly prepared solution from freshly distilled HMDS and good quality, salt-free *n*-butyllithium (Scheme 1.7).

At this point it is prudent to note that in analogous work,[266] Cahiez proposed that the copper-catalysed chloroalkyne-Grignard coupling likely proceeded via a carbocupration/elimination sequence, as shown in Figure 1.6. If this were true for the reaction of the chloroynamide, then the ynamide and chloroenamide products observed when using phenylmagnesium bromide could result

from a poorly selective carbometallation. However, it is unclear from this simple mechanism why alkyl Grignards would show "perfect" selectivity for the formation of ynamides.



Scheme 1.7: Initial results for the conversion of dichloroenamide **53a** to ynamides. Yields in parentheses are for reactions carried out using commercial LiHMDS, as opposed to freshly prepared from distilled, anhydrous HMDS and *n*-butyllithium.

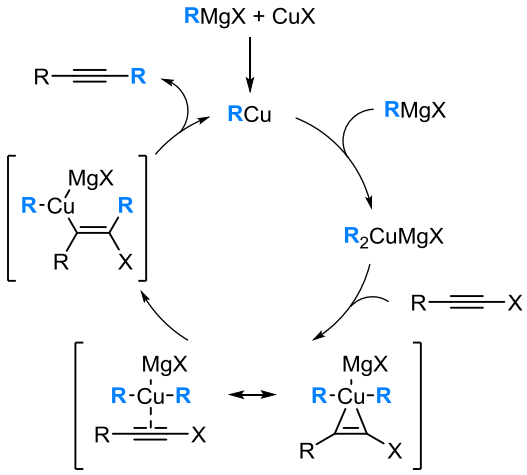
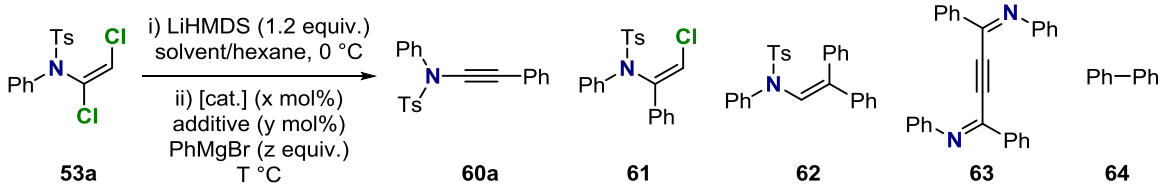


Figure 1.6: Putative mechanism proposed by Cahiez (ref [266]) for the coupling of Grignard reagents with haloalkynes.

With this mechanistic hypothesis in mind, the reaction with phenylmagnesium bromide was chosen for optimisation in order to suppress formation of the chloroenamide. This reaction was repeated using 500 mg of dichloroenamide **53a** to enable isolation of sufficient amounts of all byproducts for characterisation; however, the identities of products **62** and **63** (Scheme 1.8) required single crystal X-ray analysis for absolute structure determination. Diphenylenamide **62** likely results from carbometallation of the product ynamide **60a** but the regioselectivity is noteworthy when considering a possible mechanism for the chloroynamide coupling. At this stage, the origins of imine **63** were unknown, but it seemed plausible that it derived from two molecules of **56a**.



Scheme 1.8: General reaction scheme showing the products formed during the elimination/coupling of dichloroenamide **53a**. *Conditions*: THF (0.34 M), $CuCl_2$ (5 mol%), no additive, PhMgBr (1.2 equiv.), 0 °C.

Firstly, the influence of certain additives (PhC≡CMe, PPh_3, tmeda, *N*-methyl pyrrolidinone (NMP)), which have previously been shown to enhance similar reactions,[266] was investigated using $CuCl_2$ as the catalyst (**a**, Figure 1.7). Unfortunately, these had a negligible effect on the selectivity. Next, the carbometallation reactions of "typical" ynamides, as developed by Marek,[268,269] were considered.[270] These reactions, which also use Grignard reagents and copper salts, typically required low temperatures (<-30 °C) and poorly coordinating solvents such as Et_2O to achieve high regioselectivity in favour of the adduct required in our chemistry, as predicted from the mechanistic hypothesis in Figure 1.6. Surprisingly, the chloroynamide behaved in the opposite fashion: *increased* temperature gave increased selectivity for the desired ynamide (**b**, Figure 1.7). Whilst Et_2O provided a slight increase in selectivity (2:1 at 0 °C, 81% combined yield), the dichloroenamide and chloroynamide were poorly soluble and the reaction required 8 hours.

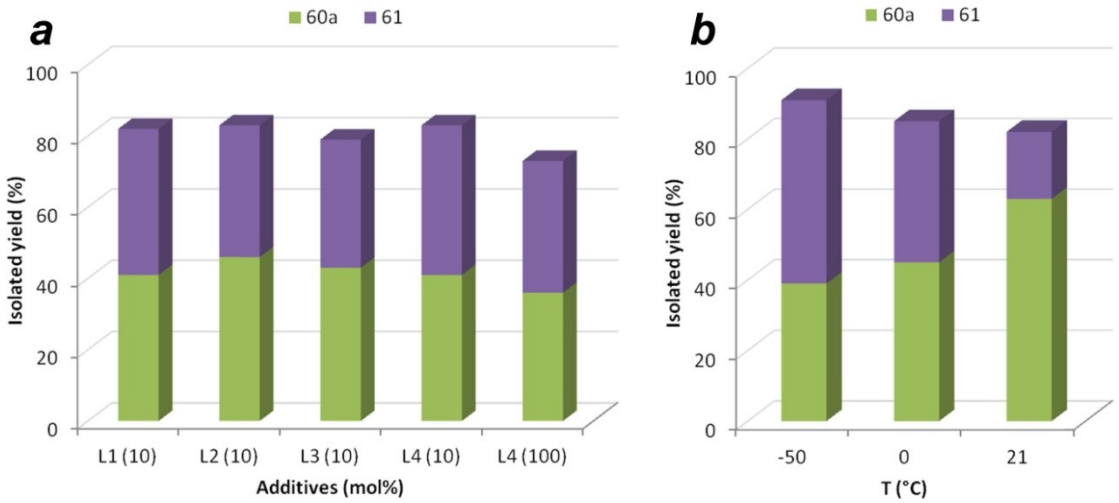


Figure 1.7: **a**: The effect of additives on the ratio of ynamide **60a** and chloroenamide **61**. Reactions were each performed using 500 mg of **53a**. *Conditions*: THF (0.34 M), $CuCl_2$ (5 mol%), additive (y mol%), PhMgBr (1.2 equiv.), 0 °C. L1 = PhC≡CMe; L2 = PPh_3; L3 = tmeda; L4 = NMP; **b**: The effect of temperature on the ratio of ynamide **60a** and chloroenamide **61**. *Conditions*: THF (0.34 M), $CuCl_2$ (5 mol%), no additive, PhMgBr (1.2 equiv.), T °C.

Curiously, reverse addition (whereby a solution of chloroynamide is added to a solution of Grignard and copper salt, in THF at 0 °C) gave increased selectivity for the product ynamide **60a**, albeit the gain was insufficient (3.9:1, 64% combined yield). All of these coupling reactions were exothermic and it was important to add the solution of the organometallic *dropwise* to control the temperature. Cooling was not a viable option as this alters the reaction selectivity.

The effect of various copper salts was then evaluated at room temperature (21 °C) (**a**, Figure 1.8). Whilst the use of CuCl, $CuBr{\cdot}SMe_2$ and CuI did not provide satisfactory results, CuCN gave a significant enhancement (>20:1) with only a trace (<1%) of the chloroenamide observed in the ^{1}H NMR spectrum of the crude reaction mixture. Decreasing the amount of phenylmagnesium bromide from 1.2 to 1.03 equiv. suppressed the formation of diphenylenamide **62** (**b**, Figure 1.8) and

the inclusion of trimethyl phosphite (10 mol%) reduced the formation of biphenyl from 11% to 2% (**c**, Figure 1.8).[271] Furthermore, the use of TBME as solvent provided a cleaner overall reaction and greater overall yield, with minimal formation of tarry byproducts from chloroynamide degradation.

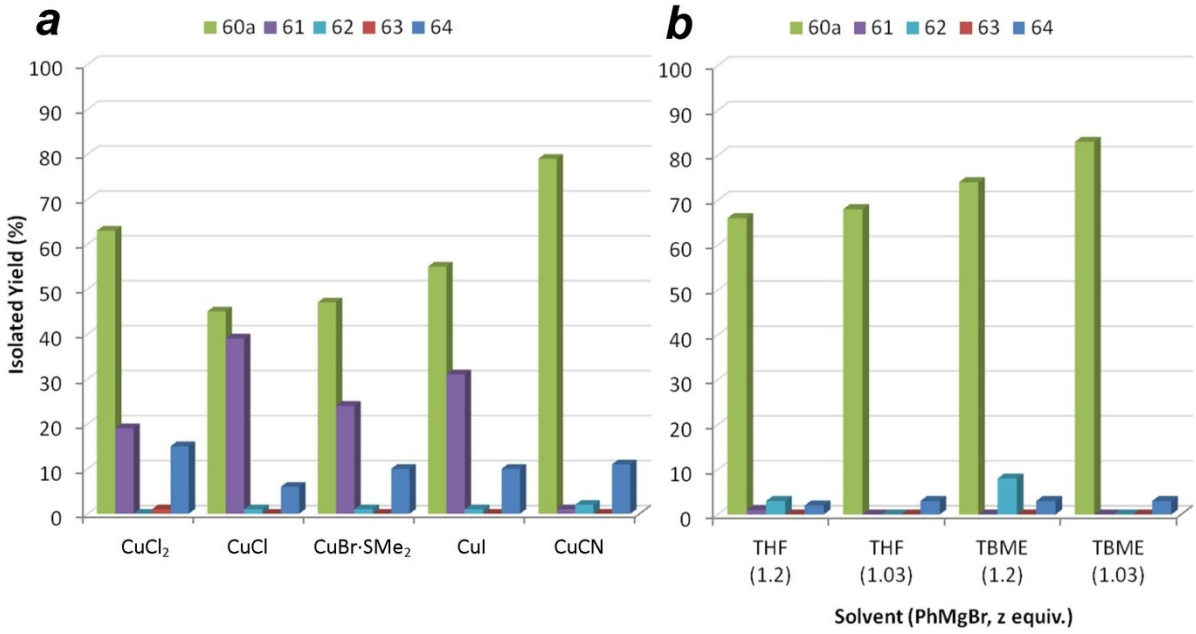


Figure 1.8: **a**: The effect of various copper salts on the ratio of products in the couplings. Reactions were each performed using 500 mg of **53a**. *Conditions*: copper salt (5 mol%), no additive, PhMgBr (1.2 equiv.), THF (0.34 M), 21 °C; **b**: The effect of decreasing the amount of PhMgBr to 1.03 equiv. *Conditions*: CuCN (5 mol%), $P(OMe)_3$ (10 mol%), PhMgBr (z equiv.), solvent.

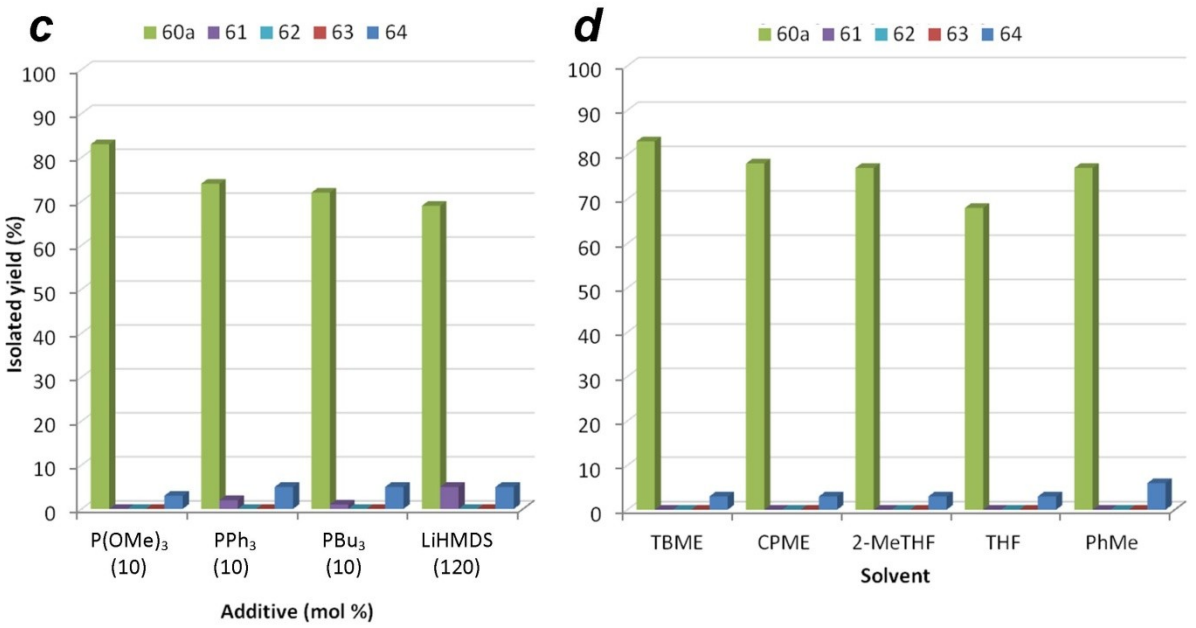


Figure 1.8: **c**: The effect of additives. Reactions were each performed using 500 mg of **53a**. *Conditions*: CuCN (5 mol%), additive (y mol%), PhMgBr (1.03 equiv.), TBME (0.24 M), 21 °C; **d**: The effect of solvent. *Conditions*: CuCN (5 mol%), $P(OMe)_3$ (10 mol%), PhMgBr (1.03 equiv.), solvent (0.24 M), 21 °C. CPME = cyclopentyl methyl ether.

Throughout our optimisation, it was apparent that the "yield-determining" step in this sequence was the chloroynamide formation. In this step, polar solvents such as DMSO or NMP gave only decomposition, and THF, although convenient at the outset, did not provide a sufficiently clean reaction, affording dark polymeric byproducts in the reaction mixture. Having found a suitable catalyst for the transformation, chloroynamide formation was revisited to improve the overall yield and a range of solvents was examined (**d**, Figure 1.8). The study began by comparing the reactions in TBME and THF. The dichloroenamide was less soluble in TBME at 0.34 M so the reaction was diluted to 0.24 M to provide both increased solubility and faster reaction with LiHMDS (from 1 hour to ~30–40 minutes). Whilst the reaction was cleaner upon dilution, the yield of ynamide **60a** decreased from 86% to 81%. Performing the same comparison with THF had a similar effect in the elimination step, but a decreased yield (from 79% to 66% yield) of the desired ynamide. Cyclopentyl methyl ether (CPME), 2-methyl THF (2-MeTHF) and toluene behaved almost identically in this reaction but were less effective than TBME.

The use of $Fe(acac)_3$ (5 mol%) instead of a copper salt was also investigated, which led to a slightly different outcome: the ynamide was formed in 55% yield and the chloroenamide was not observed, but there was a significant increase of biphenyl (28%) and imine **63** (6%). As supported by later observations, it is feasible that the imine **63** resulted from dimerisation of the chloroenamide. Due to the success of the reaction with copper salts, the use of iron salts was not considered further.

Overall, the chloroynamide **56a** was prepared in ~95% yield in TBME (0.24 M) and, using 5 mol % of $CuCN{\cdot}2P(OMe)_3$ with 1.03 equiv. of phenylmagnesium bromide (1.0 M in THF), the ynamide **56a** was isolated in 83% yield. Reducing the catalyst loading to 1.25 mol% afforded the ynamide in 85% yield, though the proportion of chloroenamide byproduct increased to ~1% (as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture). This reaction was repeated a further four times and gave 82–86% yields. Dr Russell Smith (Janssen Pharmaceuticals, La Jolla, CA) also performed this reaction using commercially available anhydrous TBME and LiHMDS (1.0 M solution in TBME, Sigma Aldrich) and this afforded ynamide **56a** in 79% yield.

1.2b Scope of organometallic partners and application to *N*-sulfonyl dichloroenamides.

A range of Grignard and organozinc reagents were then applied in this reaction (Figure 1.9). Many of these Grignard reagents are available commercially and they were used as supplied after titration to determine actual concentration. For those Grignard and organozinc reagents that are not commercially available, these were prepared according to a number of procedures,[272] including:

(i) direct reaction of the halide with magnesium turnings;

(ii) transmetallation of the (hetero)arylbromide/iodide with either *i*-PrMgCl or *i*-PrMgCl·LiCl;[273,274]

(iii) lithiation with *n*-butyllithium, followed by transmetallation with either $MgBr_2$ or $ZnCl_2$;[275]

(iv) direct metallation with TMPZnCl·LiCl;[276]

(v) alkynylmagnesium reagents were generated by deprotonation using EtMgBr.

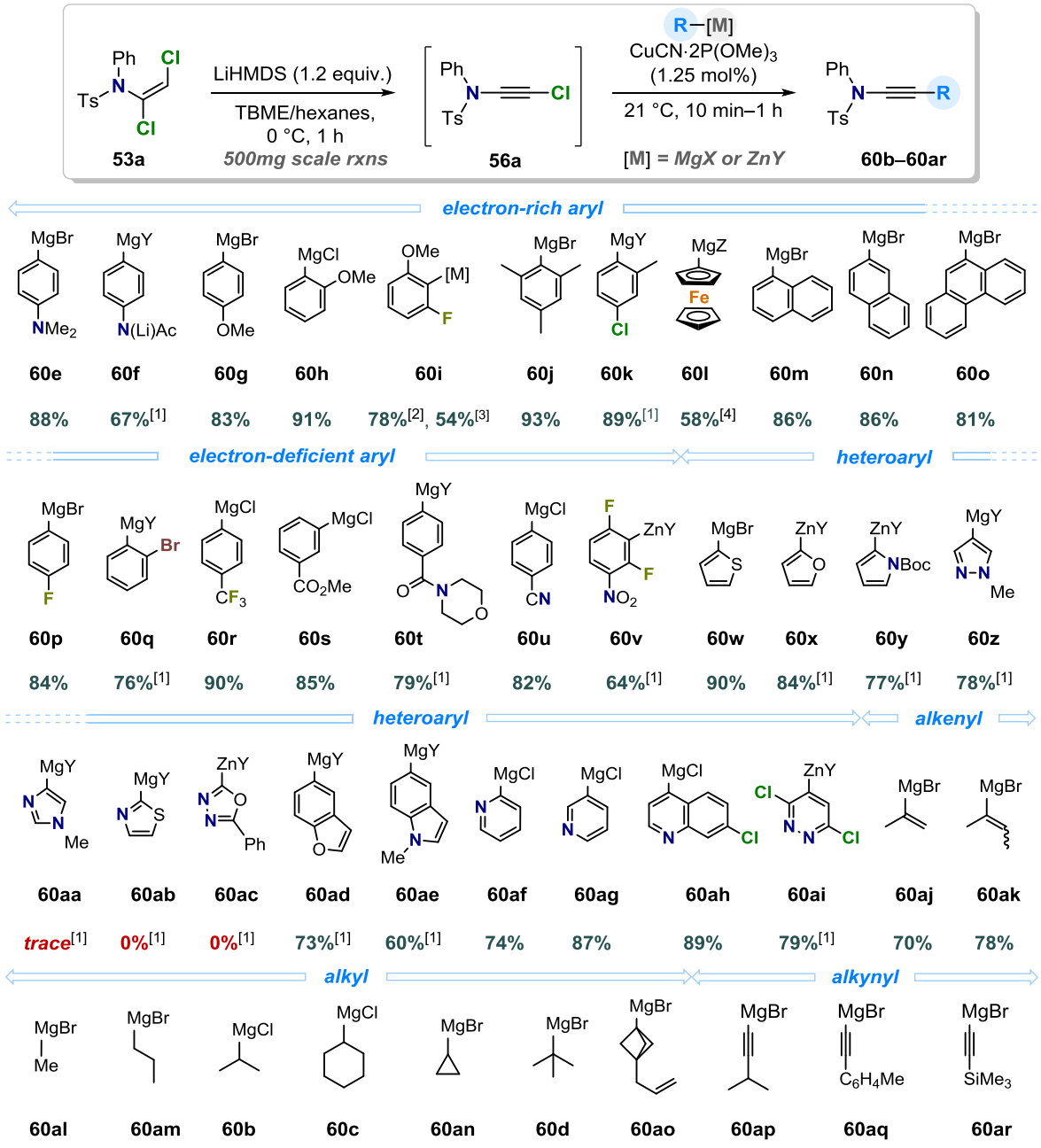


Figure 1.9: Scope of organometallic coupling partners. [1] Y = Cl·LiCl; [2] ArMgBr·LiBr was used; [3] ArZnCl·LiCl was used, [4] Z = TMP·LiCl. DMF = dimethylformamide; TMP = 2,2,6,6-tetramethylpiperidinyl.

Overall, both Grignard and organozinc reagents were applicable, with 38 organometallic partners across a range of electron-rich and electron-poor (hetero)aryl, alkenyl and alkyl groups being successful (Figure 1.9). Notable examples include the use of bulky nucleophiles (**60i**–**60m**) and the

tolerance of ester, amide, nitrile and nitro functionalities (**60s**–**60v**). These latter coupling partners were necessarily generated at low temperature (<0 °C) by transmetallation with *i*-PrMgCl, or zincation with TMPZnCl·LiCl in the case of **60v**, to suppress self-decomposition, but there were no discernible side reactions during the couplings at room temperature. A more interesting result is the use of 4-chloro-2-methylphenyl and 2-bromophenylmagnesium chloride/lithium chlorides to give ynamides **60k** and **60q**, respectively: no competitive reaction with the pendant halide was observed and the ynamides were isolated in 89% and 76% yield. The selectivity for coupling of a chloroalkyne over an aryl bromide/chloride is intriguing and could provide a mechanistic insight for the reaction. Among sp^3 couplings, the use of short chain alkyl partners such as methyl or cyclopropylmagnesium bromides overcomes the need for volatile coupling partners as would be required for many C–N coupling strategies, and the synthesis of bicyclo[1.1.1]pentane (BCP) ynamide **60ao** also demonstrates an interesting entry to alkynyl BCPs.[277,278] This is notable because BCPs have seen increased utility as surrogates for 1,4-disubstituted arenes, *t*-butyl groups and alkynes in drug development, which can impart desirable properties such as increased membrane permeability and metabolic stability.[279] Organozinc partners required longer reaction times (12 hours versus 10–30 minutes for the Grignard reagents), but their use proved to be particularly convenient in cases where the corresponding Grignard reagents were either unavailable or unstable, which included a number of (hetero)aromatic species (**60v**, **60x**, **60y**, **60ac**, **60ai**).

Six coupling partners were unsuccessful in this chemistry. Imidazol-4-yl and thiazol-2-ylmagnesium chlorides, and 5-phenyl-1,3,4-oxadiazol-2-ylzinc chloride gave negligible conversion to the desired ynamides. On the other hand, the reactions of alkynylmagnesium bromides favoured the formation of chloroenamides **65a**–**65c** instead of the desired diyne (Figure 1.10). These had (*E*)-geometries, as determined by single crystal X-ray analysis, and the (*Z*)-isomer was not found. Only when using *i*-propylacetylene was a small amount of the desired diyne observed (**60ap**, 3%, Figure 1.9).

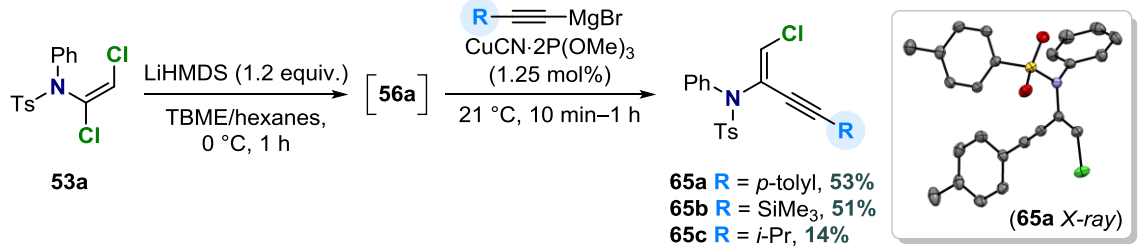
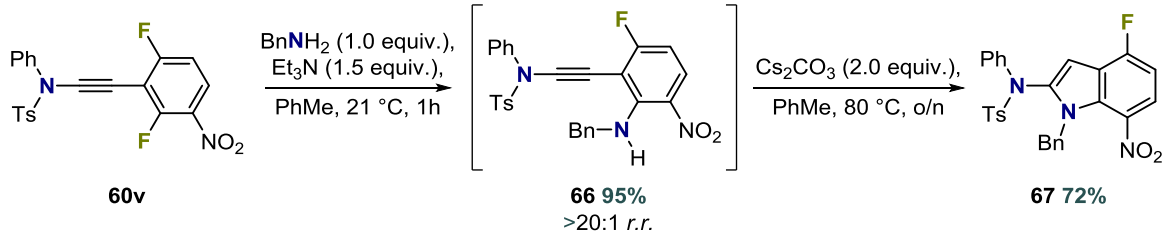


Figure 1.10: Application of alkynyl Grignard reagents. *p*-tolyl = 4-MeC_6H_4. Displacement ellipsoid plot for **65a** is displayed at 50% probability and hydrogen atoms are omitted for clarity.

In comparison with more typical C–N coupling strategies, the avoidance of prolonged heating and the use of readily accessible Grignard or organozinc reagents (which obviates the need to pre-form haloalkene / alkyne coupling partners) enhance the range of functionality that can be introduced on the alkyne terminus. This also affords opportunities to develop novel ynamide reactivity. For

example, a concise synthesis of indole **67** can be readily achieved from the reaction of ynamide **60v** with 1.0 equiv. of benzylamine (Scheme 1.9). This reaction proceeded with complete regioselectivity[280] (the regioisomer was not observed in the ^{1}H NMR spectrum of the crude reaction mixture) via the ynamide **66**. Whilst **66** was isolable and was characterised using single crystal X-ray analysis, it slowly undergoes spontaneous cyclisation to the indole. It was, therefore, more convenient to perform this transformation in one pot, by heating the crude mixture of ynamide **66** with Cs_2CO_3 to give the indole.



Scheme 1.9: Application of ynamide **60v** in the regioselective formation of an indole.

With the scope of the organometallic partner established, a selection of *N*-sulfonyl dichloroenamides was tested to explore the reaction tolerance towards various bulky or functionalised sulfonamide substituents (Figure 1.11).

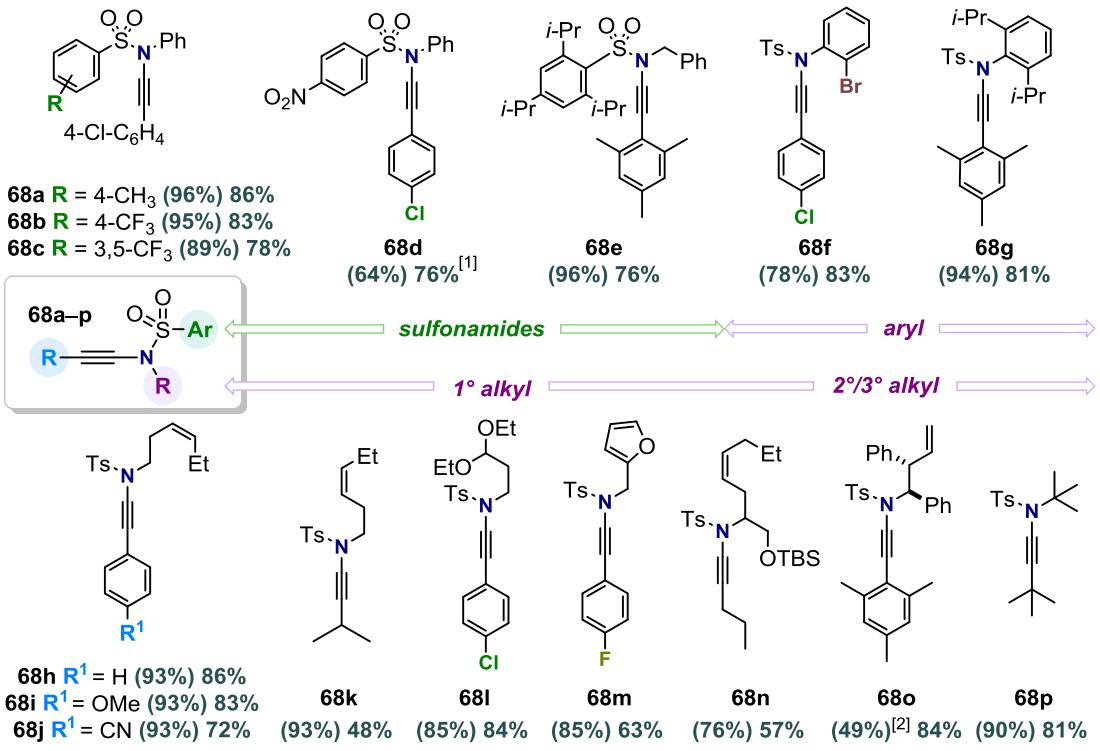


Figure 1.11: Products obtained from the elimination/coupling of a range of *N*-sulfonyl 1,2-dichloroenamides. Values in parentheses are isolated yields for the formation of the dichloroenamides, prepared using TCE (1.1 equiv.), Cs_2CO_3 (1.5 equiv.), DMF, 50 °C; [1] $Ar_2Zn{\cdot}MgBr_2{\cdot}MgCl_2$ (0.55 equiv.) was used. [2] Yield over 2 steps starting from *N*-benzylidene tosylamide; The dichloroenamide precursors to **68c** and **68h**–**68n**, and ynamides **68h**–**68n** were prepared by Jonathan Yong. The dichloroenamide precursors to **68b**, **68d**, **68e** and **68g**, and ynamide **68a** were prepared by Olivia Garry.

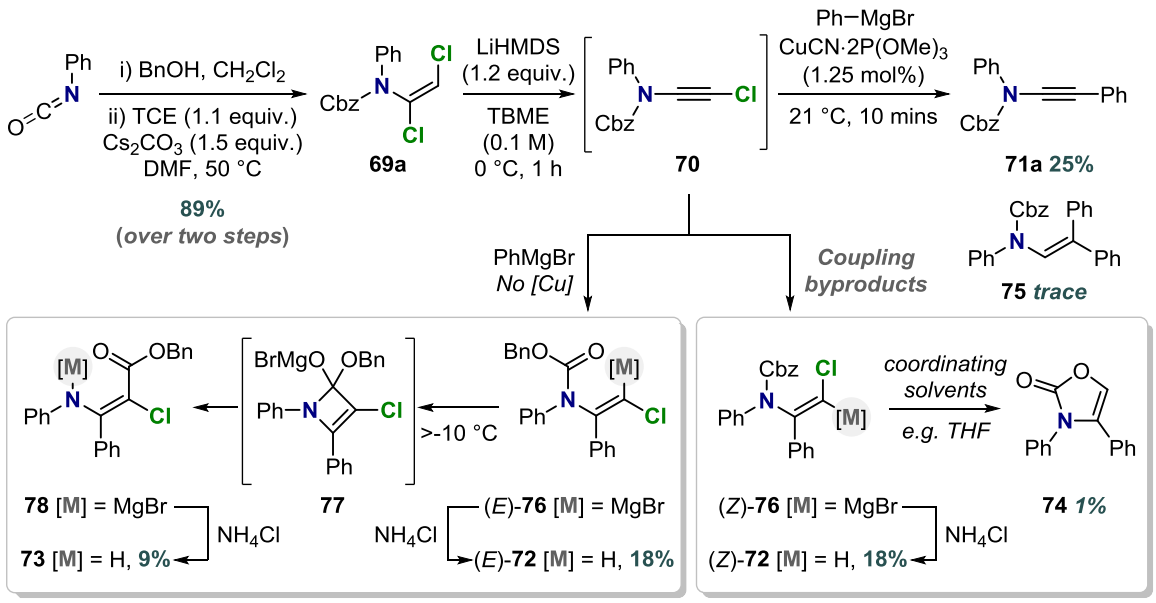
The dichloroenamides were all prepared in good yield using TCE (1.1 equiv.), Cs_2CO_3 (1.5 equiv.), DMF, 50 °C, and subsequent elimination/coupling reactions were found to be very efficient, irrespective of the nature of either the sulfonyl motif (**68a**–**68e**) or the aryl/alkyl substituent on the nitrogen atom (**68f**–**68p**). Notable examples are ynamides **68e**, **68g**, **68o** and **68p** featuring bulky substituents on *both* the nitrogen and alkyne (76–84%), and the electron-deficient sulfonyl ynamides **68c** and **68d** (78% and 76%). The decreased yield for the couplings with alkyl Grignard reagents is possibly due to the increased sensitivity of the product ynamides to silica gel chromatography.

1.2c Application of *N*-carbonyl dichloroenamides.

Having completed the scope of organometallic partners and the synthesis of a range of sulfonyl ynamides, attention shifted to the utility of carbonyl-protected dichloroenamides in this chemistry. These represent a different ynamide class and whilst many unhindered acyclic carbamates are successful substrates using traditional cross-coupling methods, acyclic ureas and amides are not.

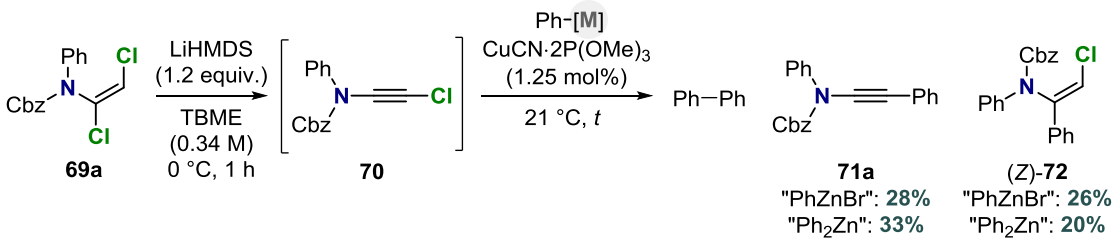
Carbamate **69a** was selected as a test substrate for our investigations and was conveniently prepared on multigram scale (42 mmol/12 g, 89%) (Scheme 1.10). Using the previously optimised conditions, the coupling of **70** with phenylmagnesium bromide led to the formation of the desired ynamide **71a** alongside chloroenamides (*Z*)- and (*E*)-**72** and chloroester **73** as significant byproducts. The structures of (*E*)-**72** and **73** were identified by single crystal X-ray analysis. In addition, the oxazolone **74** was isolated in 1% yield and diphenylenamide **75** was tentatively identified, by ^{1}H NMR spectroscopic analysis, as the minor impurity that co-eluted with the desired ynamide. In the absence of copper salt, the reaction of chloroynamide **70** with phenylmagnesium bromide gave only (*E*)-**72** and **73**, which likely arise from protonation of the alkenylmagnesium bromide (*E*)-**76** and magnesium amide **78**, respectively. Further investigations showed that (*E*)-**76** formed initially (and was stable below -10 °C) and rearranged to **78** over time at higher temperatures. After stirring for 12 hours (overnight) at room temperature and quenching the reaction, ^{1}H NMR spectroscopic analysis of the crude mixture indicated approximately 80% conversion of (*E*)-**76** to **78**. A reasonable mechanism for the formation of **78** would, therefore, be cyclisation of the alkenylmagnesium bromide (*E*)-**76** to azetine **77**, followed by ring opening (Scheme 1.10).

Although the direct nucleophilic addition was an unexpected result, certainly when compared to the sulfonyl cases discussed previously, this mode of reactivity is known: the nucleophilic addition of heteronucleophiles with *N*-tosyl chloroynamides gives the same regio- and stereoselectivity; albeit requiring heating with mild base (Chapter 2).[262] Nevertheless, it is evident that this carbamate-derived chloroynamide was more reactive towards Grignard nucleophiles than its sulfonylated cousins, although it is unclear whether this is a measure of the different inherent electrophilicities of the two or an increased ability of the electron withdrawing group to direct nucleophilic attack.



Scheme 1.10: Distribution of products formed in the initial screening using carbamate dichloroenamide **69a**. PhMgBr (1.2 equiv., 1.0 M in THF) was used. Cbz = CO_2CH_2Ph.

Less reactive organozinc reagents were therefore chosen as coupling partners; they are often readily prepared[281] and transmetallation of a Grignard reagent with $ZnCl_2$ was most convenient here. It should be noted that the chemistry of organozinc reagents is often more complex than that of Grignard reagents, and the stoichiometry of reagents and additives used in their preparation can often be crucial to their reactivity.[272] Furthermore, where the addition of lithium salts to Grignard reagents gives "turbo-Grignards", a species of intermediate reactivity between organolithiums and Grignards, an analogous effect on the reactivity of organozinc reagents can also be achieved with the addition of lithium and/or magnesium salts. Whilst it is often convenient to ignore these inorganic salt "byproducts", they are rarely innocent spectators and should be accounted for when possible, even if the actual structures of the heterometallic reagents are not accurately represented (or even known).[282,283]

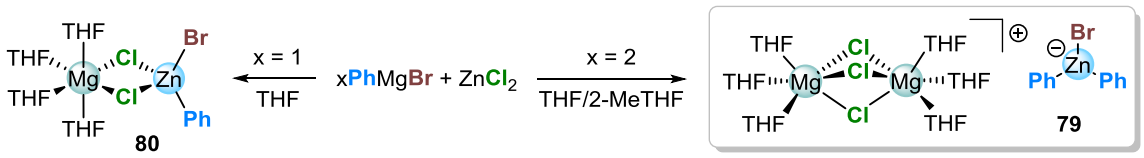


Scheme 1.11: Distribution of products formed during coupling between chloroynamide **70** and organozinc reagents. PhMgBr (1.0 M in THF) and $ZnCl_2$ (1.9 M in 2-MeTHF) were used.

Mindful of these effects, both $PhZnBr{\cdot}MgCl_2$ and $Ph_2Zn{\cdot}MgCl_2{\cdot}MgBr_2$ were prepared using phenylmagnesium bromide (1.0 M solution in THF) and $ZnCl_2$ (1.9 M in 2-MeTHF). Fortunately, both monoarylzinc and diarylzinc reagents gave full conversion in the coupling reaction (Scheme

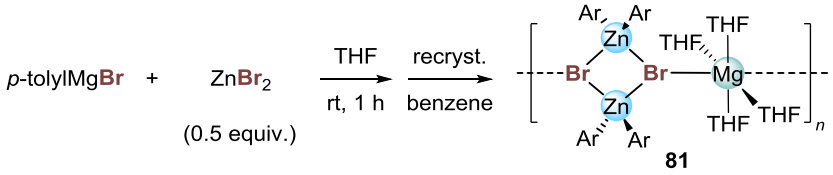
1.11). A few interesting features were noted: first, using either 1.1 equiv. of the monoarylzinc or 0.55 equiv. of the diarylzinc gave full conversion to the ynamide at room temperature. As hoped, there was no discernible background nucleophilic addition reaction between the organozinc and the chloroynamide, and only biphenyl, ynamide **71a** and the (*Z*)-chloroenamide were observed as products. The reaction with the monoarylzinc required stirring overnight at room temperature to reach completion (cf. sulfonamide cases previously) whereas the diarylzinc reacted within 30 minutes. Given the isolated yields, it is unclear whether both phenyl groups were transferred from zinc during the reaction. The use of $Ph_2Zn{\cdot}2LiCl$ (prepared using phenyllithium (1.9 M in dibutyl ether, diluted to 1.0 M using anhydrous THF) and $ZnCl_2$ (1.9 M in 2-MeTHF)) was also successful in this reaction, giving a 30% yield of the ynamide and 16% of the chloroenamide.

The seemingly simple reaction of phenylmagnesium bromide (2.0 equiv. 1.0 M in THF) with $ZnCl_2$ (1.0 equiv., 1.9 M in 2-MeTHF) gave a rather unexpected outcome during our preliminary investigations. When the reaction mixture was left unagitated for about 1 hour at room temperature, fine colourless needles crystallised from solution. This outcome was repeated successfully a number of times, and the crystallisation could also be induced with gentle stirring. Interestingly, the use of the crystals alone, the solution alone, or the combined mixture in the coupling reaction all gave conversion to the ynamide **71a**. The identity of this solid was determined to be $[Ph_2ZnBr][Mg_2Cl_3(THF)_6]$ (**79**) by single crystal X-ray analysis (Scheme 1.12). It is also worth noting that a 1:1 ratio of phenylmagnesium bromide and zinc(II) chloride is known to give **80**.[283]



Scheme 1.12: Solid state structures of the monoarylzinc and diarylzinc species prepared by salt metathesis of phenylmagnesium bromide with $ZnCl_2$.

A search of the Cambridge Crystallographic Data Centre (CCDC) only found two similar compounds.[284–287] $[Bu_4N][Ph_2ZnBr]$ was prepared from the reaction of tetrabutylammonium bromide (TBAB) and diphenylzinc,[287] and the heterometallic species **81** (Scheme 1.13) was isolated from the reaction of *p*-tolylmagnesium bromide with $ZnBr_2$ in THF.[286]

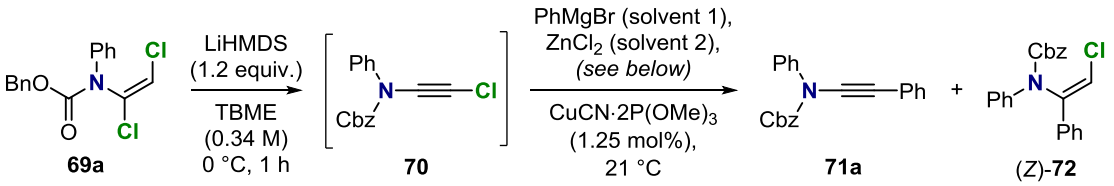


Scheme 1.13: Salt metathesis of *p*-tolylmagnesium bromide with $ZnBr_2$. Ar = *p*-tolyl = 4-Me-C_6H_4.

By comparing the reactions in Schemes 1.12 and 1.13, one immediately notices that the metal/halide ratio of the reagents differs with that for the products *isolated*. Evidently, in our case, there was a larger proportion of chloride in the crystal (bromide:chloride = 1:3) and it is reasonable to assume that the solution contained a bromide-rich organometallic species; though its composition or identity was not determined. It is therefore important to note that the structures of these organometallic species are often in equilibrium, such that a species in the solid state may not represent that which exists in solution.

The investigations continued and the effect of temperature was re-examined. As with the reactions of sulfonamides (see Figure 1.7 previously), decreased temperature also led to increased chloroenamide formation, and all subsequent reactions were performed at room temperature. Nevertheless, a significant amount of the (*Z*)-chloroenamide was still generated at room temperature, which we attributed to a solvent effect, and the synthesis of the organozinc reagent was revisited (Table 1.1). Entries 2, 3 and 4 show a marked effect of a less coordinating solvent on the reaction selectivity, with the yield of ynamide **71a** increasing from 33% to 51% and a concomitant decrease in the formation of chloroenamide (*Z*)-**72** (from 20% to 4%). There was a practical concern when using Et_2O alone, as the formation of the diarylzinc in this solvent was accompanied by a significant build-up of white precipitate, which made transferral to the reaction flask difficult due to needle blockages. However, this could be remedied by the use of toluene in the preparation of the diarylzinc, which gave a finer precipitate and could be transferred more easily. The identity of this white precipitate was not determined. Finally, it was found that $CuCN{\cdot}2P(OMe)_3$ and the commercially available CuCN.2LiCl (1.0 M solution in THF, 1.25 mol%) performed equally in these reactions (entries 5 and 6); thus for convenience, the latter was used in later reactions. Importantly, the tiny amount of THF associated with this catalyst did not noticeably alter the reaction selectivity.

Throughout the optimisation, the combined yield of the ynamide and chloroenamide coupling products did not significantly exceed 50%. This prompted us to revisit the chloroynamide formation, and in particular, re-examine the effect of the reaction solvent and the concentration. In considering possible routes for investigation, attention was drawn to the work of Collum,[288–294] in which the combination of LiHMDS in toluene/Et_3N was shown to be a highly effective system for the enolisation of ketones, as compared to the use of THF or other ethereal solvents. This was attributed to the reaction of the dimeric form of LiHMDS,[290,292] whereas the reaction in THF generally proceeds via the monomer.[288] This significant rate enhancement is a steric effect: there is greater destabilisation of the Et_3N-bound, dimeric LiHMDS reagent than in the transition structure for enolisation. The addition of the chelating ligands tmeda or pmdta also favours monomer formation in hydrocarbon solvents.[293] Intrigued by these data, the reactions were next performed using **69a** in toluene with the following co-solvents in a 2:1 ratio: Et_2O, *n*-Bu_2O, TBME, Et_3N, tmeda, pmdta.

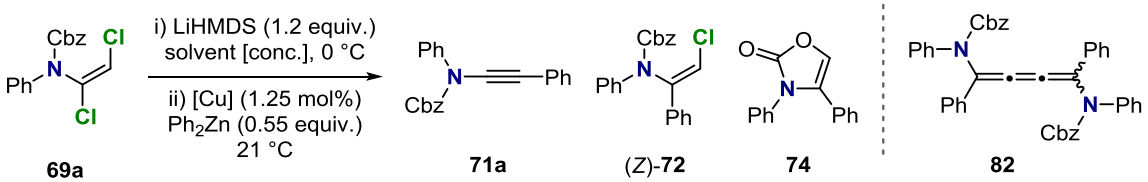


69a **70** **71a** (*Z*)-**72**

entry	PhMgBr (x equiv. in solvent 1)	$ZnCl_2$ (y equiv. in solvent 2)	additive	**71a** : (*Z*)-**72** (NMR yield)[1]
1	1.1 (THF)	1.1 (2-MeTHF)	THF	28:26
2	1.1 (THF)	0.55 (2-MeTHF)	THF	33:20
3	1.1 (Et_2O)	0.55 (2-MeTHF)	Et_2O	41:13
4	1.1 (Et_2O)	0.55 (Et_2O)	Et_2O	51:4
5	1.1 (Et_2O)	0.55 (Et_2O)	PhMe	53:3
6[2]	1.1 (Et_2O)	0.55 (Et_2O)	PhMe	52:3

Table 1.1: The effect of solvent in the preparation of arylzinc reagent on product selectivity. *Conditions:* Dichloroenamide **69a** (500 mg), PhMgBr (1.0 M solution in solvent 1, x equiv.), $ZnCl_2$ (1.0 M solution in solvent 2, y equiv.), additive (1.0 mL), $CuCN{\cdot}2P(OMe)_3$ (1.25 mol%), TBME (0.34 M), 21 °C. [1] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard. [2] $CuCN{\cdot}2LiCl$ (1.0 M solution in THF, 1.25 mol%) was used instead of $CuCN{\cdot}2P(OMe)_3$.

Overall, the elimination reactions using amine co-solvents were notably faster than using TBME alone and were typically complete within 20 minutes. The use of toluene alone or toluene with *n*-Bu_2O, tmeda or pmdta co-solvents gave significant decomposition of **69a** and these reactions were not investigated further. On the other hand, the use of Et_2O, TBME or Et_3N co-solvents was much more successful and subsequent coupling led to the formation of ynamide **71a** (32–76% yield, see Figure 1.12) alongside chloroenamide (*Z*)-**72** and oxazolone **74** byproducts (Scheme 1.14). Interestingly, the use of Et_3N favoured the formation of the oxazolone (6:1 **74**:**72**, 7% combined yield) and Et_2O/TBME favoured the formation of (*Z*)-**72** (~3:1 **72**:**74**, 7% combined yield). Small amounts of cumulene **82** (1%) were also observed in the reaction using Et_3N. The formation of the oxazolone and the cumulene is reminiscent of carbene reactivity, both of which likely originate from carbenoid (*Z*)-**76** (Scheme 1.10), but it is unclear whether their formation is copper-catalysed or not.



69a **71a** (*Z*)-**72** **74** **82**

Scheme 1.14 General reaction scheme showing the products formed during the elimination/coupling of dichloroenamide **69a**. *Conditions*: **69a** (500 mg), PhMe/co-solvent (2:1), $CuCN{\cdot}2LiCl$ (1.25 mol%, 1.0 M in THF), $Ph_2Zn{\cdot}MgCl_2{\cdot}MgBr_2$ (0.55 equiv., ~0.15 M solution in Et_2O/PhMe).

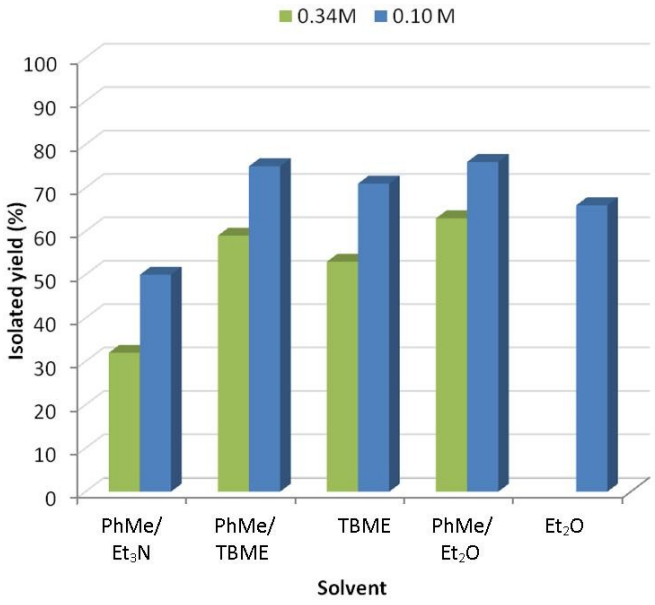
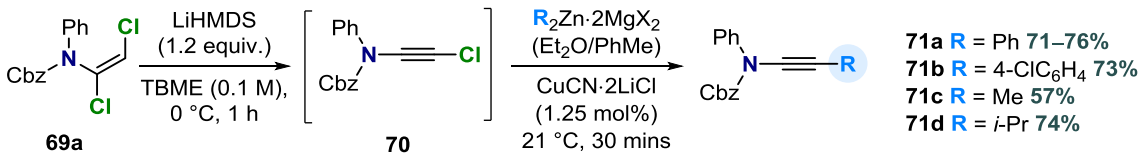


Figure 1.12: The effect of concentration and solvent mixtures on the yield of ynamide **71a**. Reactions were each performed using 500 mg of **53a**. *Conditions:* "Ph_2Zn" (0.55 equiv., ~0.15 M solution in Et_2O/PhMe), CuCN·2LiCl (1.25 mol%), solvent (0.X M) or PhMe/co-solvent (2:1, 0.X M), 21 °C.

Contrasting with sulfonamide cases, there was also a noticeable concentration effect observed in these reactions (Figure 1.12). Increased dilution gave a significantly higher yield in all of these reactions (shown in blue, Figure 1.12), and the use of toluene/co-solvent mixtures gave slightly higher yields of the ynamide as compared to the use of Et_2O or TBME alone. ^1H Spectroscopic analysis of the crude reaction mixtures also indicated a slight decrease in chloroenamide observed upon dilution (from 7–8% to 3–4%). For convenience, TBME (0.10 M) was chosen as the solvent for our continuing studies and the reaction of **69a** was repeated three additional times, using 1.25 mol% CuCN·2LiCl with 0.55 equiv. of diphenylzinc (~0.15 M in Et_2O/PhMe), to afford ynamide **71a** in 71–76% yield.

With these new optimised conditions, a brief scope of diorganozinc reagents was evaluated using dichloroenamide **69a**. Three Grignard reagents were selected for the preparation of these zinc reagents: 4-chlorophenylmagnesium bromide (1.0 M solution in Et_2O), methylmagnesium iodide (1.0 M in Et_2O) and *i*-propylmagnesium chloride (1.0 M in Et_2O). The organozinc coupling reactions proceeded well and ynamides **71b**–**71d** were formed in 57–74% yields (Scheme 1.15).



Scheme 1.15: Brief scope of diorganozinc coupling partners.

It is noted that where only 0.55 equiv. of the diarylzinc reagent was required to achieve full conversion of the chloroynamide, an excess dialkylzinc reagent (1.05 equiv.) was required. Furthermore, small amounts of chloroenamide byproducts were consistently formed when using diarylzinc reagents, but chloroenamides were never observed when using dialkylzinc reagents. This is a consistent feature of this chemistry for both Grignard and organozinc reagents, and might indicate a mechanistic difference between alkyl and aryl species. The stoichiometry of Grignard reagent to $ZnCl_2$ was also found to be very important, with a ratio of 2.0–2.1 molar equiv. Grignard reagent to 1.0 molar equiv. of zinc deemed optimal. This necessitated titration of the Grignard beforehand to establish the true concentration of the reagent. If the proportion of Grignard reagent was significantly lower than this, the resulting solution had a significant build of white precipitate, making transferral to the reaction mixture problematic, and the coupling reaction was also slow. On the other hand, increased amounts of Grignard reagent were also suboptimal as this led to competing chlorine-metal exchange on the chloroynamide, with small amounts of the terminal ynamide produced in the reaction. This was more of an issue when using the alkyl Grignard reagents, as the terminal ynamide was not observed during our optimisation using phenylmagnesium bromide. The involvement of trialkylzincates would be a reasonable explanation for this metal-halogen exchange, as these have been shown to undergo exchange with aryl halides much more effectively than dialkylzincs.[295]

In all subsequent couplings, di(4-chlorophenyl)zinc was chosen as the coupling partner. This was primarily to facilitate product analysis: firstly the ^{1}H NMR spectra of these compounds were easier to interpret because the resonances for the chlorophenyl group appeared downfield from many of the other aromatic resonances, and had a characteristic AB quartet splitting pattern. Secondly, by considering all of the ynamides prepared thus far, those which featured a 4-substituted phenyl group on the alkyne terminus were often highly crystalline. In addition to aiding recrystallisation, crystals that possess 3rd row (or heavier) elements generally give greater scattering of X-rays, which greatly aids data collection and analysis (Chapter 3). Whilst a 4-bromo substituent would also have accomplished this, 4-bromophenylmagnesium bromide/iodide is not commercially available and 4-chlorophenylmagnesium bromide was thus more convenient to use.

A selection of dichloroenamides was prepared in good yield using conditions (a) as described in Scheme 1.1. However, the increased bulk of *t*-butyl *N*-phenylcarbamate required the use of hydroxide and PTC conditions to prepare the dichloroenamide. The acyclic carbamate dichloroenamides underwent facile conversion to the expected ynamides (Figure 1.13). Unhindered and hindered *N*-phenyl carbamates were equally effective, with the ethyl carbamate **71e** (77%) and *t*-butyl carbamate **71g** (73%) being a good comparison. On the other hand, cyclic carbamates were not viable substrates in this chemistry and the dichloroenamides did not survive the elimination step. It is possible this was due to the instability of the chloroynamide in the reaction. Lastly, as a

comparison with sulfonamide **68f** (see Figure 1.11 previously), the analogous methyl carbamate **71h** was prepared in comparable yield (75% versus 83% for **68f**).

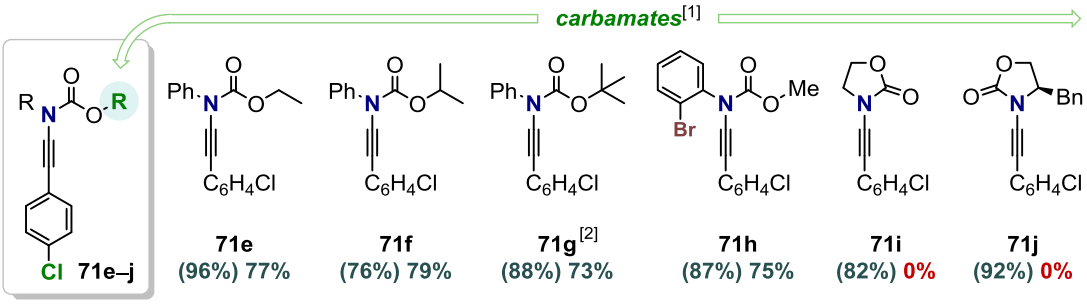


Figure 1.13: Scope of carbamate ynamides. Values in parentheses are isolated yields for the formation of the dichloroenamides, prepared using TCE (1.1 equiv.), Cs_2CO_3 (1.5 equiv.), DMF, 50 °C; [1] *Conditions:* (i) LiHMDS (1.2 equiv.), TBME (0.1 M), 0 °C, (ii) $Zn(C_6H_4Cl)_2{\cdot}MgBr_2{\cdot}MgCl_2$ (~0.15 M solution in Et_2O/PhMe, 1.1 equiv.), CuCN·2LiCl (1.25 mol%), 21 °C. [2] Dichloroenamide was prepared using trichloroethylene (3.0 equiv.), TBAHS (0.25 equiv.), 50% aq. KOH, PhMe, 60 °C.

Acyclic urea-derived dichloroenamides were next investigated using these conditions and **83a** was chosen for test experiments (Figure 1.14). Although chloroynamide formation proceeded well, the coupling reaction was less selective for the ynamide (**85a**) as compared to the analogous reactions of carbamates, although the combined yield of ynamide and chloroenamide (86%) was good. The poor solubility of (*Z*)-**86** in the reaction mixture hindered TLC analysis and (*Z*)-**87** was only observable after workup. There was insufficient time at this point in the project to perform another full optimisation, but the use of the "salt-free" diarylzinc was partially investigated.[296]

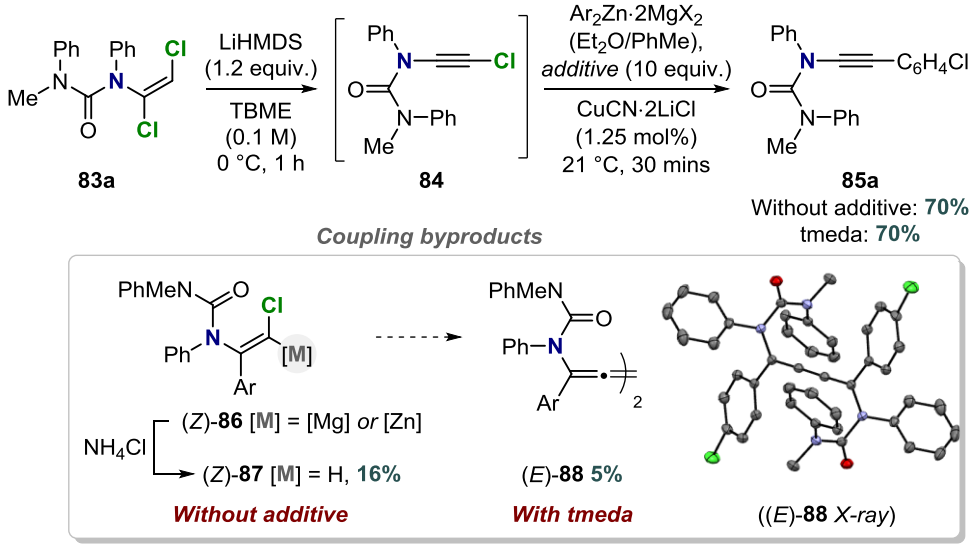


Figure 1.14: Distribution of products formed when using urea dichloroenamide **83a**. Ar = 4-Cl-C_6H_4.

The most convenient preparation here was the precipitation of the magnesium halide with excess tmeda or dioxane. After allowing the precipitate to settle for 20 minutes, only the solution was used. Single crystal X-ray analysis of the former precipitate confirmed the formation of $MgX_2(tmeda)_2$

(X = $Br_{0.67}Cl_{0.33}$). Though the use of dioxane did not affect the reaction outcome, tmeda provided some success: the chloroenamide was significantly reduced to trace levels and the ynamide was isolated in 70% yield. Unlike for the carbamates, in which an oxazolone was the primary side product in the presence of amines, the cumulene (*Z*)-**88** (5% yield) was produced here (Figure 1.14). Whilst tmeda did not provide any enhancement to this reaction, the result was more of a practical success: the R_f difference between the chloroenamide (*Z*)-**87** and the ynamide **85a** was slight, and careful chromatography was required for their separation, whereas the cumulene was significantly more polar and was easily separated. No further screening was performed and our attention shifted to explore the substrate scope.

A selection of dichloroenamides was prepared using the PTC conditions (b) described in Scheme 1.1. The *N*-phenyl ureas performed well and gave the dichloroenamides in 86–94% yield. The low yield observed for the tribenzylurea dichloroenamide **83e** (20%) is an unfortunate limitation of the PTC conditions employed, and later discussions will touch on possible improvements to this reaction. In contrast with the sulfonyl and carbamate dichloroenamides, these urea-dichloroenamides were not stable and would undergo partial hydrolysis when left on the bench for a period of about a week; this decomposition was often accompanied by an acrid odour. These compounds were therefore stored under argon and in the freezer at -20 °C, though the long term stability of these products is unknown. The dichloroenamides were all successfully converted to the desired ynamides in 56–72% yield (Figure 1.15) and, in strong contrast to the hydrolytic sensitivity of the dichloroenamides, dibenzyl urea ynamide **85b** withstood boiling ethanol in an attempt to grow single crystals of sufficient quality for X-ray diffraction and hydrolysis was not observed. This is not a general phenomenon for ynamides, which would typically decompose when subjected to this treatment. Overall, this represents the first general route for the synthesis of acyclic urea ynamides.

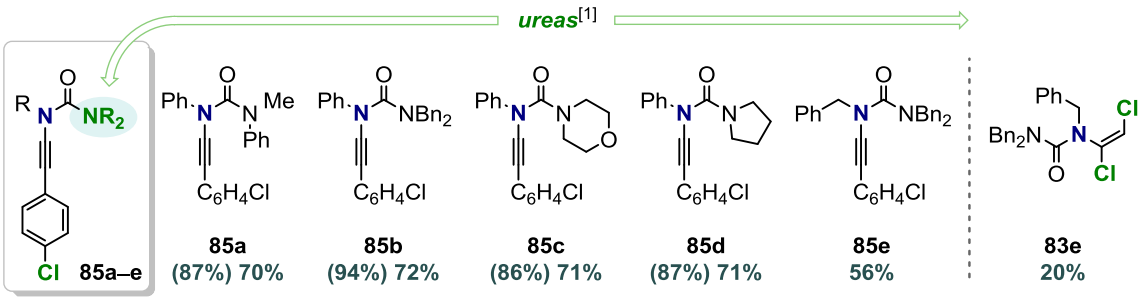
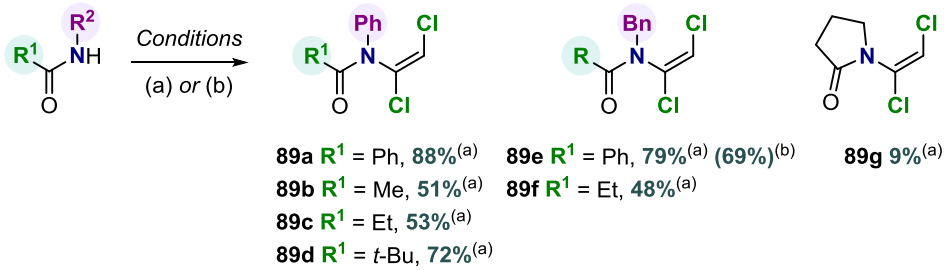


Figure 1.15: Scope of urea ynamides. Values reported in parentheses are isolated yields for the formation of the dichloroenamides, using TCE (3.0 equiv.), TBAHS (0.25 equiv.), 50% aq. KOH, PhMe, 60 °C. [1] *Conditions:* (i) LiHMDS (1.2 equiv.), TBME (0.1 M), 0 °C, (ii) $Zn(C_6H_4Cl)_2{\cdot}MgBr_2{\cdot}MgCl_2$ (~0.15 M solution in Et_2O/PhMe, 1.5 equiv.), tmeda (10 equiv.), CuCN·2LiCl (1.25 mol%), 21 °C.

1.2d Yne-amides.

Our final foray with this chemistry looked at preparing the much coveted yne-amides. Alongside the yne-ureas mentioned previously, these could be considered as a "missing class" of ynamides and a general synthesis remains elusive. To investigate this here, a range of amide-derived dichloroenamides were prepared using the PTC conditions (b) described in Scheme 1.1. Whilst the formation of benzamides **89a** and **89e**, and pivalamide **89d** proceeded well, reactions using substrates with α-protons were generally lower yielding (Scheme 1.16).



Scheme 1.16: Synthesis of amide-derived dichloroenamides. *Conditions* (a) trichloroethylene (TCE) (3.0 equiv.), TBAHS (0.25 equiv.), 50% aq. KOH, PhMe, 21 °C or 60 °C; (b) TCE (1.5 equiv.), NaH (2.5 equiv.), 2-MeTHF, 75 °C;

Following the observations of a process development route,[241] the use of sodium hydride in 2-MeTHF was also investigated for the preparation of *N*-benzyl dichloroenamide **89e** (Scheme 1.16). This proved to be quite informative, especially given the observations made in Section 1.1 for cases using dichloroacetylene and strong bases. Thus a solution of *N*-benzyl benzamide was added dropwise to a suspension of sodium hydride in 2-MeTHF under argon at 75 °C, such that the rate of evolution of hydrogen gas was controlled by the rate of addition of the amide. This was stirred for an hour before a solution of trichloroethylene (TCE) (1.5 equiv.) in 2-MeTHF (~3.6 M) was added dropwise to this reaction mixture at 75 °C. This was the crucial point in the reaction - the solution of TCE should be added over 3–4 minutes to the reaction. If the addition was too fast (<1 minute) the reaction stalled at ~20% conversion, and if the addition was too slow (>5 minutes) then the chloroynamide was also formed, the reaction became very dark and there was a poor yield of the desired product. At room temperature, the addition of TCE over 5 minutes was also unsuccessful, with the reaction stalling at <10%. This was repeated exactly for *N*-phenyl benzamide, at 75 °C, and the reaction stalled at ~50% conversion; this likely reflects the lower nucleophilicity and basicity of the *N*-phenyl benzamidate anion. This was the first direct evidence that the required rate of addition of trichloroethylene was substrate *and* temperature dependent; though it is unclear why the reaction would stall if it were added too quickly, because dichloroacetylene was formed in all cases.

In hindsight, these observations would also explain why the *N*-alkyl carbamates and ureas were less successful in the PTC reactions: they are less acidic (pK_a) than the *N*-aryl analogues and the sulfonamides, and the rate of equilibrium between the amide and amidate could be an important

factor. Refluxing the amide with sodium hydride would drive the equilibrium entirely to the amidate and negate this. Being aware of the substrate and temperature dependence of these reactions, it is therefore recommended that TCE is added slowly to the reaction mixture.

The dichloroenamides prepared in Scheme 1.16 were then applied in our reaction in an attempt to prepare yne-amides. A range of behaviours were observed in these reactions that were quite unlike the other *N*-carbonyl ynamides. For pivalamide **89d** and benzamide **89e**, the entire reaction sequence from the dichloroenamide to the coupled ynamides **90d** and **90e** proceeded without issue. Pivalamide **90d** was also readily crystallised and its structure was confirmed by X-ray analysis.

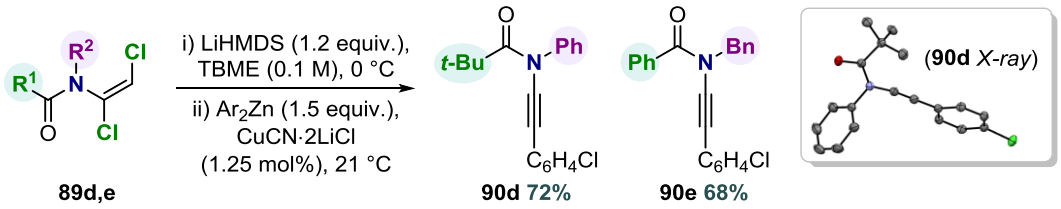


Figure 1.16: Synthesis of yne-amides. Ar = 4-ClC_6H_4. Displacement ellipsoid plot for **90d** is displayed at 50% probability and hydrogen atoms are omitted for clarity.

However, these compounds were quite unstable in $CDCl_3$ and C_6D_6 solution, and decomposed within hours. This behaviour was seen for all subsequent yne-amides and the NMR spectroscopic data were collected immediately upon dissolution in C_6D_6. Storage of the compounds as a frozen matrix in C_6D_6 (-20 °C) was sufficient to suppress decomposition for at least one month. Prolonged storage of these ynamides as solutions in either $CDCl_3$ or C_6D_6 at room temperature led to another curious outcome: fine colourless needles of 4-chlorobenzoic acid (identified by single crystal X-ray analysis) had grown over a matter of weeks. However, NMR spectroscopic analysis of the remaining solution was inconclusive and showed only a complex mixture of compounds - the identities of which were not determined.

The attempted conversion of *N*-phenyl benzamide **89a** to ynamide **90a** indicated that both this and the intermediate chloroynamide **91** were unusually reactive (Figure 1.17). Firstly, the elimination at 0 °C was accompanied by the formation of trichloroenamide **92**, the structure of which was identified by single crystal X-ray analysis. Secondly, while the coupling of chloroynamide **91** gave full conversion to the ynamide, attempted isolation led to the formation of ketone **93a**, which was isolated in 49% yield. The formation of trichloroenamide **92** could be minimised by conducting the elimination at room temperature and/or by decreasing the reaction concentration further, and this led to an increased (63%) yield of ketone **93a**. Further investigations showed that whilst ynamide **90a** survived workup using aqueous saturated ammonium chloride, it undergoes decomposition upon concentration of the crude organic phases. Similarly, the coupling of **91** with diethylzinc also gave full conversion to the expected yne-amide **94**, but this decomposed to a brown tar and was not pursued further.

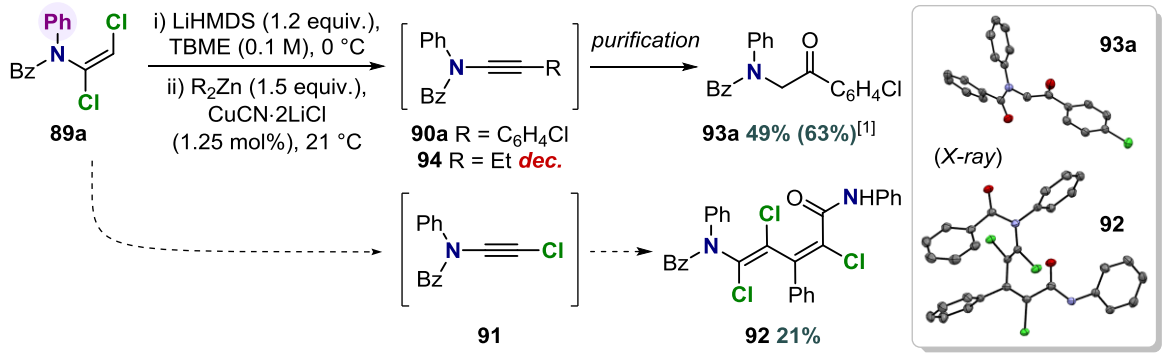
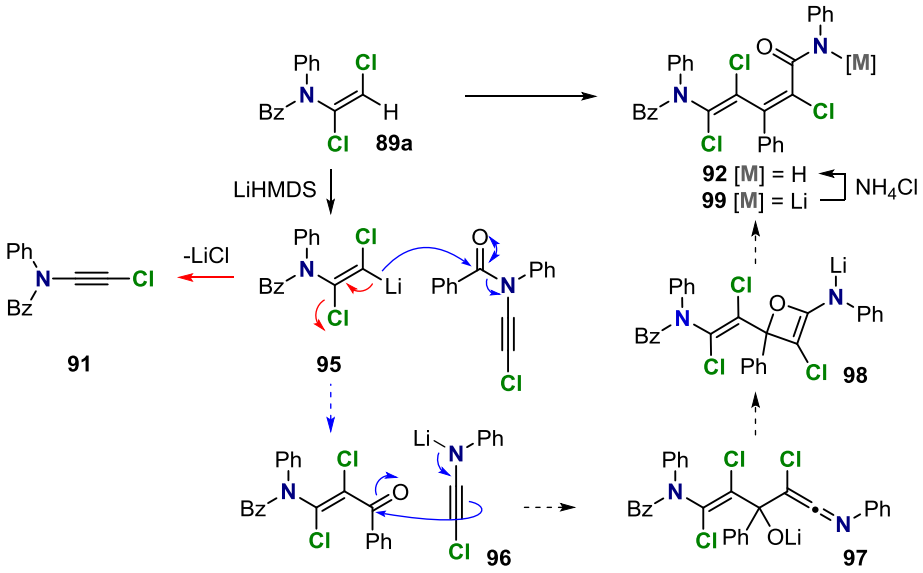


Figure 1.17: Isolated products from the attempted conversion of dichloroenamide **89a** to ynamides **90a** and **94**. [1] Yield of **93a** when step i) was performed at 21 °C. Displacement ellipsoid plots for **92** and **93a** are displayed at 50% probability and hydrogen atoms are omitted for clarity.

A putative mechanism that explains the formation of the trichloroenamide is outlined in Scheme 1.17. Lithiation of **89a** affords **95**, which can either undergo elimination of chloride to give the chloroynamide, or give nucleophilic addition/elimination onto a second molecule of chloroynamide **91**. This would give the *N*-lithio ynamine **96**, a species that is expected to be highly nucleophilic, which could add to the carbonyl through the alkyne β-carbon to give ketenimine **97**. Cyclisation to oxetene **98** and subsequent electrocyclic ring-opening would give **99** and then **92** upon workup. This would be consistent with the increased electrophilicity of the amide carbonyl as compared to the pivalamide (steric effect) and the carbamates and ureas (electronic effect).



Scheme 1.17: Proposed mechanism for the formation of trichloroenamide **92**.

N-Acetyl/propionyl dichloroenamides **89b**, **89c**, **89f** and pyrrolidinone **89g** were not successful in this chemistry. By TLC analysis, there was complete decomposition of these dichloroenamides upon treatment with 1.2 equiv. of LiHMDS, but substoichiometric amounts (0.6 equiv.) of LiHMDS led to the formation of a compound with an R_f consistent with the formation of the desired

chloroynamide. This compound could not be isolated, the mass spectra obtained from the reaction mixtures were inconclusive and attempted coupling led to decomposition. It is also unknown whether there was competitive enolisation occurring.

Four more substrates were thus prepared to explore two possible aspects of yne-amide stability (Figure 1.18): the dimethylaniline (**89h**) and furoyl (**89i**) dichloroenamides were chosen to explore a potential electronic effect and to mimic the urea and carbamate dichloroenamides. 2,4,6-Trimethyl and 2,6-dichlorobenzoyl dichloroenamides **89j** and **89k** were chosen to explore the effect of sterics, though the loss of conjugation upon twisting would also constitute an electronic factor.

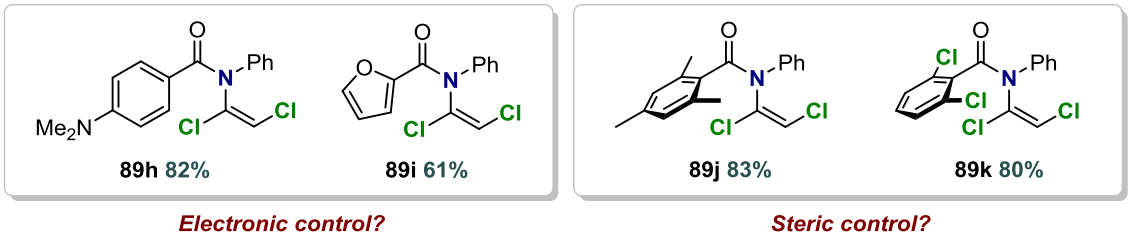


Figure 1.18: Substrates to investigate electronic and steric effects on yne-amide stability. Yields refer to isolated yields of the dichloroenamide. *Conditions* (a) TCE (3.0 equiv.), TBAHS (0.25 equiv.), 50% aq. KOH, PhMe, 21 °C.

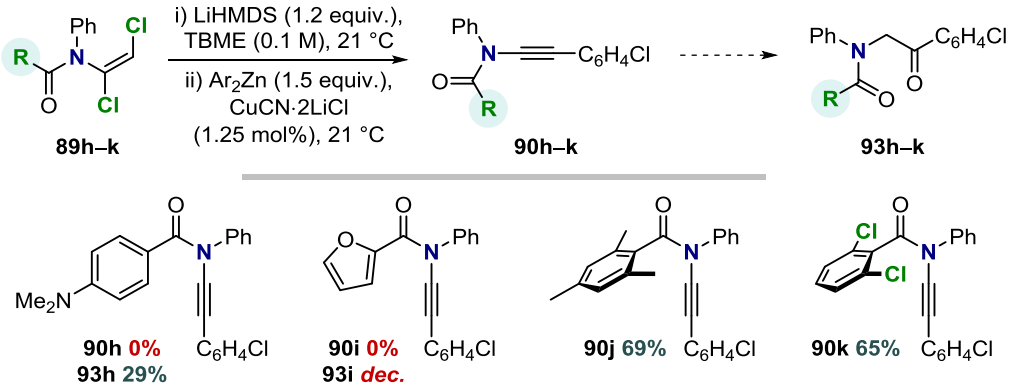


Figure 1.19: Resultant electronic and steric effects on yne-amide stability. Ar = 4-ClC_6H_4.

Overall, the dimethylaniline and furyl dichloroenamides behaved comparably with the *N*-phenyl benzamide **89a**, albeit the formation of the furoyl chloroynamide occurred with some decomposition. The subsequent couplings both proceeded without issue but, after extraction, concentration of the organic phases gave a complex mixture of products. Only for the dimethylaniline case could the hydration product **93h** be isolated from this mixture (29% yield); the final mixture for the furan was too complex to enable isolation and identification of the products. On the other hand, the reactions and purifications of the hindered yne-amides went well, affording **90j** and **90k** in 69% and 65% yields, respectively. These compounds were still sensitive to prolonged exposure to hydrophilic solvents such as $CDCl_3$ or methanol, and were stored as a frozen matrix in C_6D_6.

It is intriguing that the hydration of these yne-amides occurred with the opposite regioselectivity observed for most other ynamides: mesomeric donation of the nitrogen lone pair into the alkyne π-system gives regioselective protonation at the β-carbon, with subsequent hydration at the α-position (**a**, Figure 1.20). The observed β-hydration of yne-amides most likely occurs via a different mechanism, possibly via an oxazolium ion **100** (**b**, Figure 1.20). Supporting this, it is known that *t*-butyl carbamate ynamides undergo gold-catalysed cyclisations to afford oxazolones **102** (**c**, Figure 1.20).[254] This presumably occurs via an intermediate oxazolylidene-complex **101**, followed by loss of the *t*-butyl cation and protodemetallation. In addition, Bertrand demonstrated the kinship between oxazoles (**103**) and yne-amides (**104**) through base- and metal-mediated transformations, respectively (**d**, Figure 1.20).[232] Note, also, a similar transformation was observed in our work with the formation of oxazole **59** from *N*-*t*-butyl chloroynamide **56d** (see Figure 1.3 previously). Unlike in that case, the *N*-aryl yne-amides here cannot lose a cation of comparable stability (*t*-butyl versus aryl cation) and hydrolysis is, therefore, a reasonable outcome.

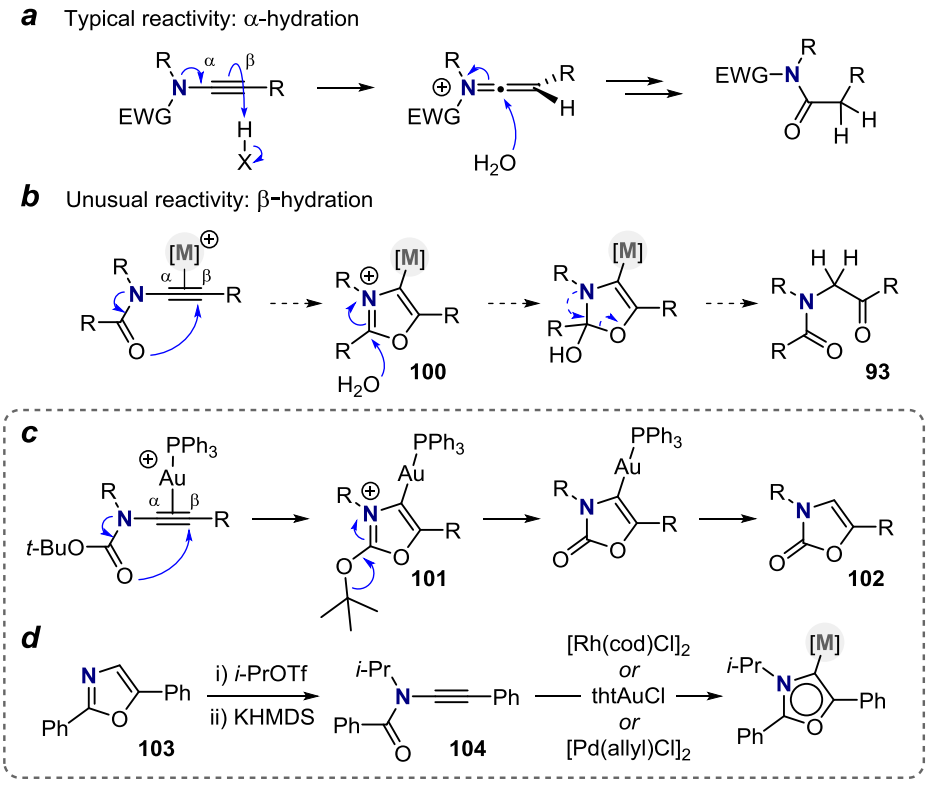


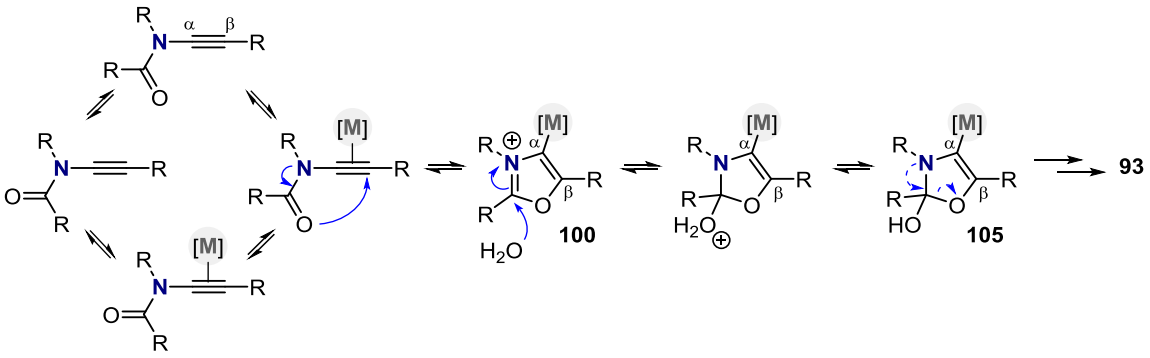
Figure 1.20: Comparison between (a) typical ynamide reactivity and (b) a proposed mechanism for the formation of ketones **93**; [M] is proposed to be a Lewis acid. (c) Formation of oxazolones using $[Ph_3PAu(NCMe)]SbF_6$ (1 mol%), CH_2Cl_2, 20 °C. (d) Interconversion of oxazoles and yne-amides, [M] = Rh(cod)Cl, AuCl, Pd(allyl)Cl. tht = tetrahydrothiophenyl.

Additionally, the formation of 4-chlorobenzoic acid from **90d** and **90e** could occur from the oxidation of hydration products **93**. The oxidation of α-hydroxy or α-aryloxy ketones using Cu(II) salts, with either a Lewis or Bronsted acid, is well documented,[297–299] but these generally require an

oxygen atmosphere and heating to 90 °C or greater. Nevertheless, these outcomes are difficult to rationalise without the involvement of a catalyst, and it is possible that the presence of trace amounts of copper species could account for these unanticipated outcomes.

Given these results, one question stood out clearly: why is there such a difference between amides and the carbamates/ureas? The carbonyls of the carbamates and ureas are certainly less electrophilic than for the amide and the (in)stabilities of the *N*-carbonyl ynamides seem to correlate with the electrophilicity of the carbonyl itself. At first glance, this would not explain why the yne-amide is more reactive; a stronger electron-withdrawing group would be expected to render the alkyne *less* nucleophilic and *less* prone to protonation or coordination to a Lewis acid. Secondly, there was certainly a steric influence that enhanced the stability of the bulky yne-amides.

For the following discussion, one has assumed that hydration was more likely to be catalysed by residual copper species than trace acid, especially because the yne-amides prepared from alkynyliodonium salts (Chapter 0), which had no involvement of copper, were not reported to be unstable. In considering the hydration of these yne-amides via an oxazolium-like species, a number of elementary steps must be considered (Scheme 1.18): (i) coordination to copper; (ii) rate of rotation about the C–N bond; (iii) rate of cyclisation and (iv) rate of oxazolium hydrolysis. Each of these will be considered in a qualitative manner in the absence of conclusive data.



Scheme 1.18: Mechanistic model for the β-hydration of yne-amides. [M] is presumed to be a π-Lewis acid.

(i) The nucleophilicity of the alkyne would be a key factor for coordination to copper, as mentioned previously. One must be mindful that the nature of the catalyst is unknown, thus any stereoelectronic preferences of the metal are purely speculative, and additional binding modes (e.g. coordination of the carbonyl) or the involvement of multimetallic species may also be important in this step.

(ii) The rotation about the C–N bond would be an equilibrium effect that allows for adoption of the reactive conformation. This is governed by (a) the polarity and hydrogen bonding ability of the solvent - increased solvent polarity leads to increased rotational

barriers for amides, and ureas to a lesser extent, while carbamates are relatively unaffected; (b) the temperature of the reaction; (c) the addition of Lewis/Brønsted acids, which relates directly to point (i); (d) the electronics at the carbonyl - also relates to point (i); and (e) the bulkiness of both the *N*- and *C*-substituents.

Considerations (a) and (b) do not seem particularly important here, because all of these compounds were treated identically. Nevertheless, points (c), (d) and (e) are likely to be the most important factors. It is known that for typical amides, carbamates and ureas that the C–N bond rotational barrier decreases in this order: from 14–22 kcal mol^{-1} for amides,[300–305] to 13–16 kcal mol^{-1} for carbamates[301,303,306–309] and 6–14 kcal mol^{-1} for ureas.[310–314] Factors that are found to decrease the rotational barrier are electron withdrawing substituents on nitrogen (even a phenyl group is sufficient to decrease the barrier by ~3 kcal mol^{-1}),[306,308] and electron donating substituents at the carbonyl. In addition, bulky substituents lead to an increased rotational barrier.

(iii) Cyclisation to the oxazolium would likely depend on two factors: (a) the nucleophilicity of the carbonyl oxygen, and (b) the bulkiness of the *N*- and *C*-substituents.

Addressing point (a), carbamates are less nucleophilic than either amides or ureas. While there are σ-withdrawing and π-donating effects granted by the additional heteroatom (O or N), the increased electronegativity of oxygen gives increased σ-withdrawal as compared to both the urea and amide, and decreased π-donation as compared to the urea. For (b), upon adoption of the required s-*cis* conformation for cyclisation, any steric repulsion between the *N*- and *C*-substituents would push the carbonyl closer to the alkyne (i.e. the deformation energy required for reaching the transition state would likely be lower).

(iv) If the ring closing to the oxazolium **100** was a reversible process, then the rate of hydrolysis of **100** might be an important factor. As there is no conclusive evidence for any of these steps, it is difficult to predict at which point the hydration would effectively become irreversible. It is possible that the first irreversible step in this reaction would be the ring opening of oxazoline **105**.

From these considerations and previous observations, some conclusions can be drawn. The amides shown in Figure 1.21 are considered first before comparison with carbamates and ureas. The decreased stability of *N*-phenyl yne-amide **90a** as compared to *N*-benzyl yne-amide **90e** can be attributed to the electron withdrawing effect of the *N*-phenyl substituent. This would render the nitrogen atom less nucleophilic and would lead to a decreased C-N rotational barrier. A comparison of *N*-phenyl benzamide **90a** and *N*-phenyl pivalamide **90d** is also supportive of an increased

rotational barrier and a decreased carbonyl electrophilicity (steric hinderance) for the latter. Furthermore, the electron-rich yne-amides **90h** and **90i** would have a decreased rotation barrier and increased carbonyl nucleophilicity, whilst the opposite would be true for the hindered amides **90j** and **90k**. These observations would indicate that the degree of conjugation of the nitrogen lone pair into the carbonyl is important for the yne-amides.

Comparing the reactivity of the amides with the ureas and carbamates, it seems unlikely that C–N rotation would be a limiting factor because the C–N rotational barriers for carbamates and ureas are generally lower than for amides. The carbonyl nucleophilicity of the three would also not match the observed (in)stabilities, as one might expect the more nucleophilic ureas to cyclise preferentially. In this case, however, increased carbonyl nucleophilicity may disfavour coordination at the alkyne, with binding occurring at the carbonyl instead. What is certainly known is that more π-electrophilic catalysts (**c**, Figure 1.20) are typically required to induce cyclisation of yne-carbamates. This may be indicative of an otherwise poor rate of cyclisation.

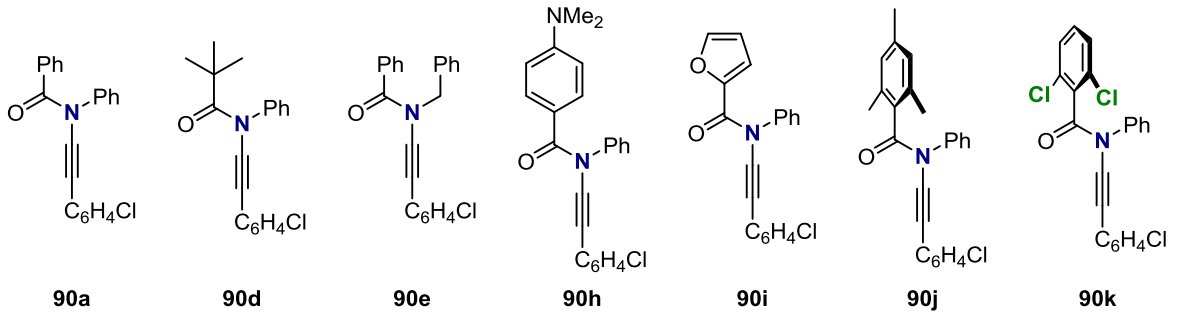
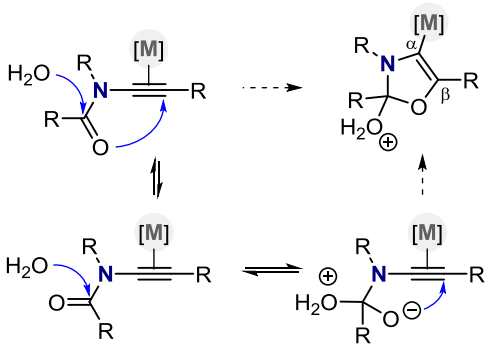


Figure 1.21: Yne-amides.

Assuming the mechanism in Scheme 1.18 to be a reasonable model, there remain two possibilities: (a) coordination to copper, or (b) rate of hydrolysis assuming ring closing was reversible. The overall stabilities of the *N*-carbonyl ynamides better match the electrophilicities of the carbonyl, and this could implicate reversible oxazolium formation as the defining step in these reactions. There is another possibility. Though binding of the Lewis acid to the alkyne is anticipated to be less favourable for the yne-amide, the resulting complex could be more electrophilic than for the carbamates and ureas. A cyclisation might instead be facilitated by the simultaneous nucleophilic attack of water at the carbonyl (Scheme 1.19).

As of yet, the reasons for the yne-amide instability are unknown, but it is reasonable to assume the involvement of trace copper left from the coupling reaction.[315] Further experiments using increased copper loadings and/or ICP-MS analysis of the products would be required to validate this. In addition, kinetic and computational studies would also be required to understand the stark reactivity differences for these *N*-carbonyl ynamides.

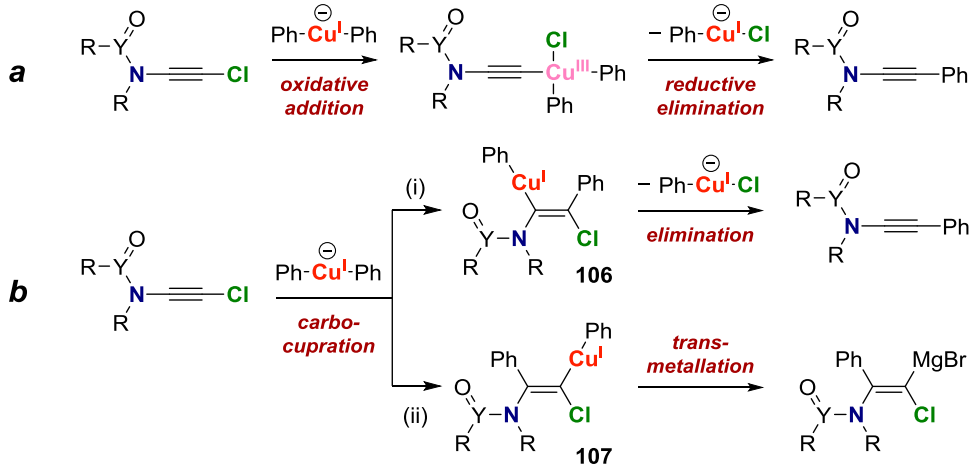


Scheme 1.19: Mechanistic model for the β-hydration of yne-amides. [M] is presumed to be a π-Lewis acid.

1.3 Mechanistic discussion.

Having discussed the synthesis of a range of ynamides, we shall now consider possible mechanisms for this coupling reaction. Firstly, any mechanistic understanding would need to address the following questions: (i) Why do aryl organometallics give chloroenamide byproducts, but alkyl ones do not? (ii) How does the use of CuCN alleviate this selectivity problem? (iii) Why is the coupling selective for the chloroalkyne over bromo or chloroarenes (see **60k** and **60q** in Figure 1.9)? (iv) How does Grignard homocoupling occur and why does trimethyl phosphite suppress this?

Question (iii) is particularly intriguing when considering a mechanism involving the oxidative insertion of a copper species into the C–Cl bond of the chloroynamide (**a**, Scheme 1.20). Considering only C–X bond strengths, where X is Br or Cl, the C(sp)–Cl would be a much stronger bond than C(sp^2)–Br or C(sp^2)–Cl. If an oxidative insertion pathway to give an alkynylcopper is occurring in this chemistry, then the coordination of the chloroalkyne to copper would likely need to be significantly more favourable than coordination of the haloarene to enable this reaction.



Scheme 1.20: General mechanistic hypotheses: **a**. C-Cl oxidative insertion; **b**. carbocupration. Y = C or SO.

Nevertheless, the increased reduction potential of alkyl versus aryl ligands may explain the poor

selectivity for arylation, with competitive carbocupration occurring as a side reaction (**b**(ii), Scheme 1.20). How then, would CuCN give increased selectivity?

Conversely, a carbometallation pathway is perhaps more feasible (**b**, Scheme 1.20). Carbocupration could conceivably give regioisomeric products **106** and **107**, where only **106** undergoes elimination of chloride to give the ynamide, and protonation of **107** would give the (*Z*)-chloroenamide. Why, therefore, would alkyl organometallic reagents be completely selective for the ynamide, but the aryl analogues give a mixture? How would CuCN increase the selectivity in the latter cases?

There have been very few mechanistic investigations into the copper catalysed carbometallation of alkenes/alkynes using either magnesium or zinc reagents,[316,317] but there have been significant studies with organolithiums.[318–323] However, aggregation of these organometallic species will certainly be metal and ligand dependent, and will also be influenced by the solvent and temperature. In our coupling reactions, one equivalent of lithium chloride was necessarily present and, if a proper mechanistic study were ever to be attempted, the involvement of up to four different metals should be considered. Despite such complexity, it is still informative to consider the established mechanisms using organolithiums.

1.3a Structures of lithium and magnesium organocuprates.

First, it is necessary to discuss the nature of the organocopper species generated from an excess of organometallic reagent.[87–97] Halides (X) are readily displaced from CuX by organometallics RM to give the linear [R-Cu-R]$^-$ anion, and cuprates of this structure are typically described as *lower order cuprates*. Organolithiums are frequently used and solutions of these "Gilman cuprates",[335] R_2CuLi, invariably contain the non-innocent, Lewis acidic LiX.[336] A number of structures have been proposed for the species $R_2CuLi{\cdot}LiX$ (Figure 1.22), but a significant body of data suggests that **108** is likely to be the ground state structure in THF.[331,334] Though the exact structures are unknown in Et_2O solution, it is believed that the coordination of LiX to the cuprate is suppressed, and structure **109** has been observed by single crystal X-ray diffraction studies.[330,337] Theoretical calculations indicate a significant residual positive charge on lithium, such that structures **109** and **110** could be considered as contact ion pairs. Though the existence of *higher order cuprates*, $[CuR_3]^{2-}$, in ethereal solution is not yet clear, this fragment has been observed as part of a higher aggregate $[Li_3(CuPh_3)(CuPh_2)(SMe_2)_4]$, **111**.

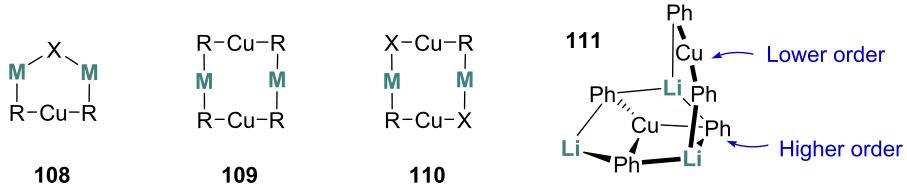
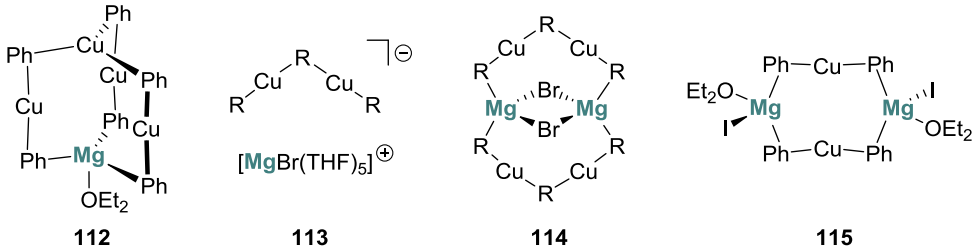


Figure 1.22: Structures of lithium organocuprates. The solvating dimethyl sulfide molecules coordinated to lithium in **111** have been omitted for clarity.[327]

The enhanced reactivity of "Lipshutz reagents", formed from 2RLi + CuCN, in conjugate addition reactions has also received significant attention[320,331] and, whilst a higher order cuprate such as $[R_2CuCN]^{2-}$ was proposed to be involved, cumulative evidence indicates that a structure akin to **108**, X = CN, is likely to be the true ground state species in THF. In this case, it is also interesting to note the presence of Li··C and N··Li interactions. In Et_2O, aggregates such as **109** have been observed by X-ray diffraction studies, although the location of LiCN was not identified.[338]

Overall, lithium diorganocuprates are less aggregated in solvents that coordinate well to lithium cations, i.e. THF, DME or crown ethers, and the converse is generally true in less coordinating solvents such as Et_2O, Me_2S or benzene. One should also be mindful that the less stable, minor constituents of these aggregates could indeed be the true reactive species. These discussions have not mentioned the role of species such as RCu·MX and, whilst they seem less likely to exist in the presence of an excess of organometallic reagent, their involvement cannot be discounted.

The structure of the analogous "Normant reagents", RMgBr + CuBr, has been less well studied. Nevertheless, Ashby[316,317] examined the reaction of phenylacetylene with a 1:1 mixture of methylmagnesium bromide and CuBr in THF, and identified Cu_4MgMe_6 and Cu_6MgMe_8 to be responsible for addition to the alkyne. Curiously, reactions using either Cu_4MgMe_6, Cu_6MgMe_8 or 1:1 MeMgBr + CuBr gave conflicting rate differences, and the regioselectivity of these reactions also decreased with time. These observations were attributed "*to differences in the nature of the reagents in the latter stages of reaction*." Increased amounts of $MgBr_2$ were also found to give significantly increased rates of carbometallation, but there was also a minor decrease in regioselectivity. Later structural studies[331] identified cluster structures such as **112** (Figure 1.23), prepared from diphenylmagnesium, and structures such as **113** and **114** were observed when using Grignard reagents, as well the dimeric contact ion pair **115** analogous to those of lithium diorganocuprates. As for the lithium cuprates, less coordinating solvents such as Et_2O led to increased aggregation.



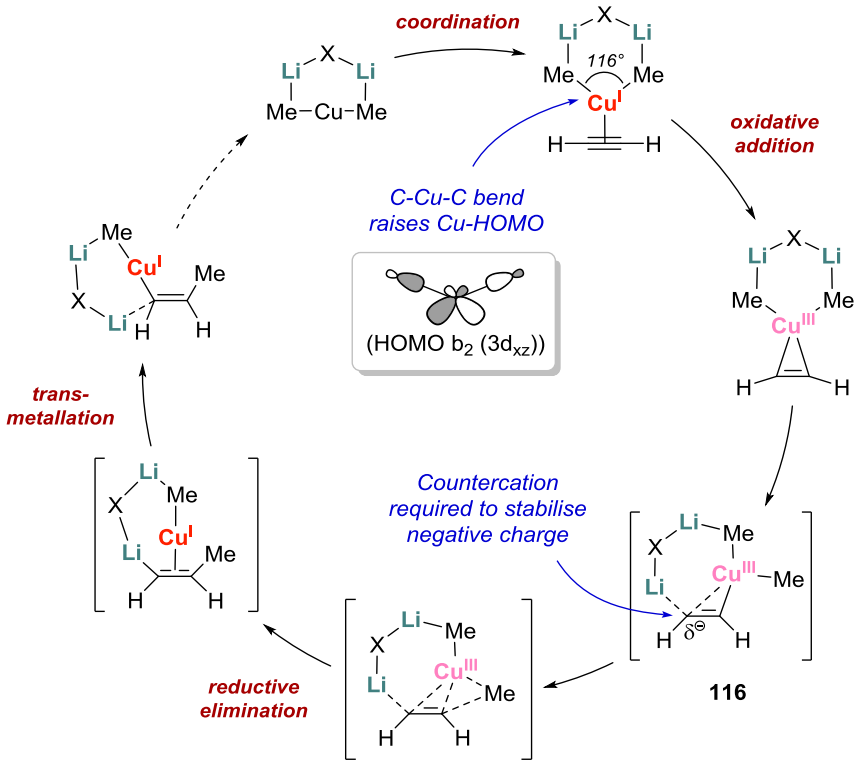
112 **113** **114** **115**

Figure 1.23: Observed structures of magnesium organocuprates. R = mesityl.

1.3b Reactivity of organocuprates.

Moving on to the mechanism of copper-catalysed alkyne carbometallation, the reaction of

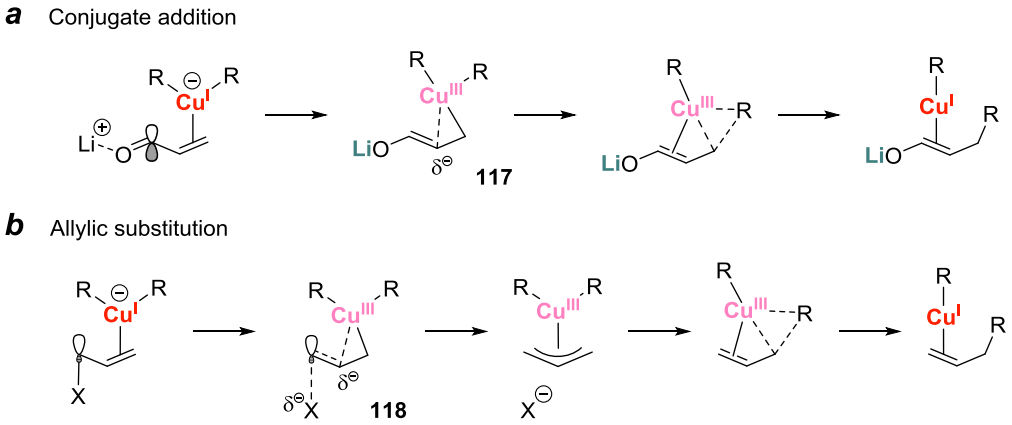
$Me_2CuLi{\cdot}LiCl$ with acetylene was subject to a combined kinetic and computational study.[322] Firstly, this showed that the "typical" carbocupration mechanism, which involves the concerted addition of Cu–C across an alkyne, is a very high energy process which requires the breaking of the strong Cu(I)–C bond (55 kcal mol^{-1}). Furthermore, the reactions of MeCu or $[Me_2Cu]^-$ were calculated to have high activation barriers (~44 and 20 kcal mol^{-1}, respectively) as compared to the reaction of the $Me_2CuLi{\cdot}LiCl$ cluster (~14–16 kcal mol^{-1}). The lithium countercation was therefore very important in lowering this barrier. In more detail (Scheme 1.21), coordination of the $Me_2CuLi{\cdot}LiCl$ cluster to acetylene causes a C–Cu–C bend, which raises the HOMO on copper. Transfer of electrons from copper to acetylene gives a Cu(III) transition species that undergoes reductive elimination without the formation of a stable intermediate. The build-up of negative charge on acetylene is stabilised by lithium as shown (**116**). Transmetallation of the vinyllithium to copper completes the carbocupration to give the σ-alkenyl copper(I) complex. Overall, this process is best described as proceeding via a lithio-cupration, followed by reductive elimination and transmetallation.



Scheme 1.21: Theoretical "trap and bite" mechanism (B3LYP/631A//B3LYP/631A); X = Cl or Me_2Cu. 631A denotes a modified version of the 6-31G basis set, see ref [322] for details.

It is also important to note the mechanistic parallels of carbocupration with 1,4-conjugate addition and allylic substitution: in these scenarios, a build-up of charge is instead stabilised by conjugation into the adjacent carbonyl π*-orbital (**117**) or the C–X σ*-orbital (**118**), respectively, the latter of which ultimately results in the loss of X^- (Scheme 1.22). Furthermore, in light of natural population

analyses for many of these reactions, our view of the formal Cu(III) oxidation state should be adjusted,[328] as the calculated change in electronic state is primarily based on the ligand and the oxidation state of copper is actually between I and II.[339] Whatever the true oxidation state is, it has been calculated that strong σ-donors such as phosphines can stabilise organocopper(III) species, CuR_3, which could explain the observed rate acceleration of these reactions with phosphines.[340–342]



Scheme 1.22: Comparison of copper-catalysed 1,4-conjugate addition (**a**) versus allylic substitution (**b**) mechanisms.

There has been significant work to determine the role of cyanide in these interrelated reactions and, whilst the predominant ground state structure for these Lipshutz reagents was determined not to have a Cu(I)–CN contact, both kinetic and theoretical studies indicate the possibility of a key binding of cyanide to the Cu(III) transition species.[343–347] In particular, it was calculated that the species **120** was more reactive than **119** (Figure 1.24) and that a copper bound cyanide stabilised both the acetylene bound complex and the transition structure **121** due to an extra C··Li electrostatic interaction (Scheme 1.24). This work also highlighted the potential importance of the kinetic reactivities of minor organometallic species in these reactions.

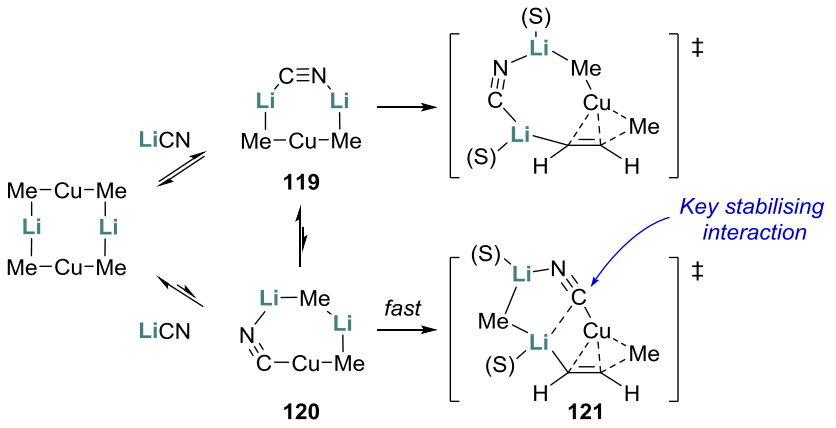


Figure 1.24: Theoretical model for role of cyanide in acetylene carbocupration using $Me_2CuLi{\cdot}LiCN$. (S) = Me_2O.

When investigating the nucleophilic substitution of allylic acetate **122**, MeCu(CN)Li was found to give remarkable regioselectivity as compared to Me_2CuLi (Figure 1.25).[348] Gas phase calculations

indicate that this selectivity is determined in the initial oxidative addition, and transition state **123** was lower in energy than **124**. The difference in σ-donor ability of the alkyl (stronger) and cyanide (weaker) ligands on the $3d_{xz}$ orbital is key, and leads to orbital desymmetrisation such that the lobe opposite CN is significantly larger. The C–OAc cleavage leads to a greater LUMO coefficient at the γ-position and therefore gives better HOMO-LUMO overlap here. Whilst oxidative additive of $[MeCu(CN)]^-$ is slower than for $[Me_2Cu]^-$, it was noted that the electron withdrawing cyanide group destabilises the Cu(III) intermediate and facilitates reductive elimination.

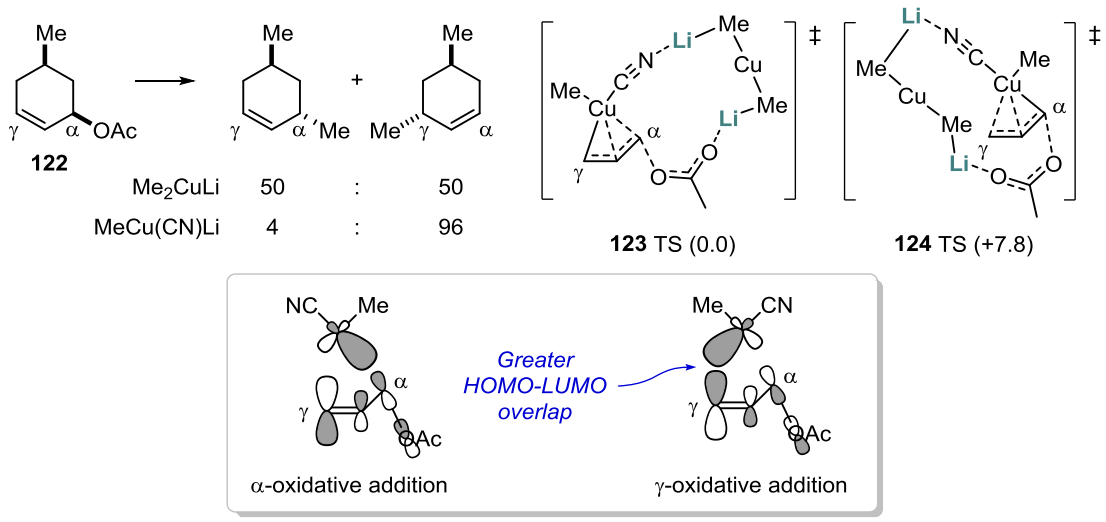


Figure 1.25: Effect of cyanide in regioselective allylic subsitution reactions. Relative energies are shown in kcal mol^{-1}.

Finally, the substitution of vinyl bromide using organocuprates was also studied, with a particular focus on the role of the polymetallic clusters that are essential to organocuprate reactivity.[349] The calculated mechanism (Figure 1.26) bears a striking resemblance to that of alkyne carbocupration and, parenthetically, it is also interesting to note that the formation of a π-complex with vinyl bromide was found to be less favourable than with the more electrophilic cyclohexenone.

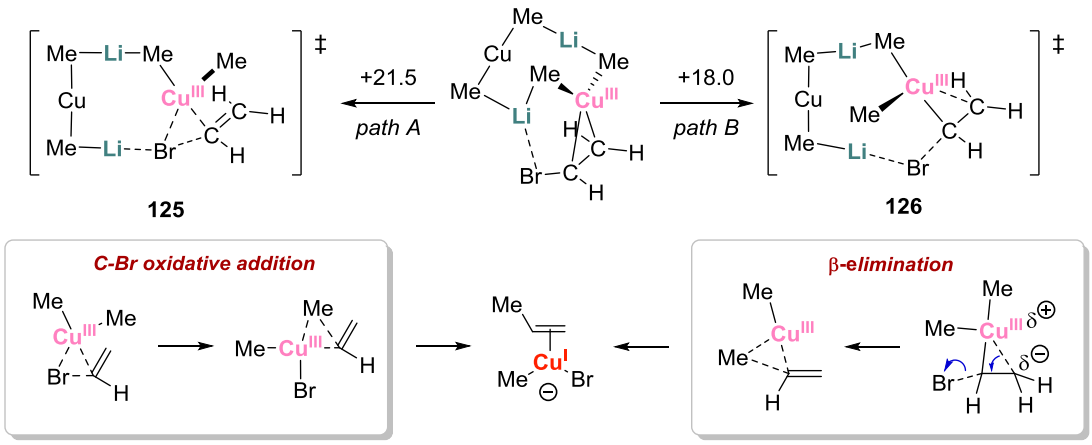


Figure 1.26: Copper catalysed nucleophilic substitution of vinylbromide using Me_2CuLi in Et_2O. Relative energies are shown in kcal mol^{-1}

The transition state for direct C–Br oxidative addition (**125**) was calculated to be less favourable than β-elimination of bromide from the cuprio(III)cyclopropane (**126**). A simplified mechanism is also highlighted in Figure 1.26. Furthermore, the calculated and experimental $^{12}C/^{13}C$ kinetic isotope effect values for the reaction between Me_2CuLi and 1-bromocyclooctene better supported a β-elimination pathway and, for related calculations, the authors state that "*the three-centred TS was higher in energy and could not be located as a stationary point*".

1.3c Mechanistic proposal.

The previous discussions have provided sufficient background to propose a mechanistic pathway for the copper-catalysed coupling of chloroynamides with organometallic nucleophiles (Figure 1.27). Note that the following proposal describes only one of many possible mechanistic scenarios.

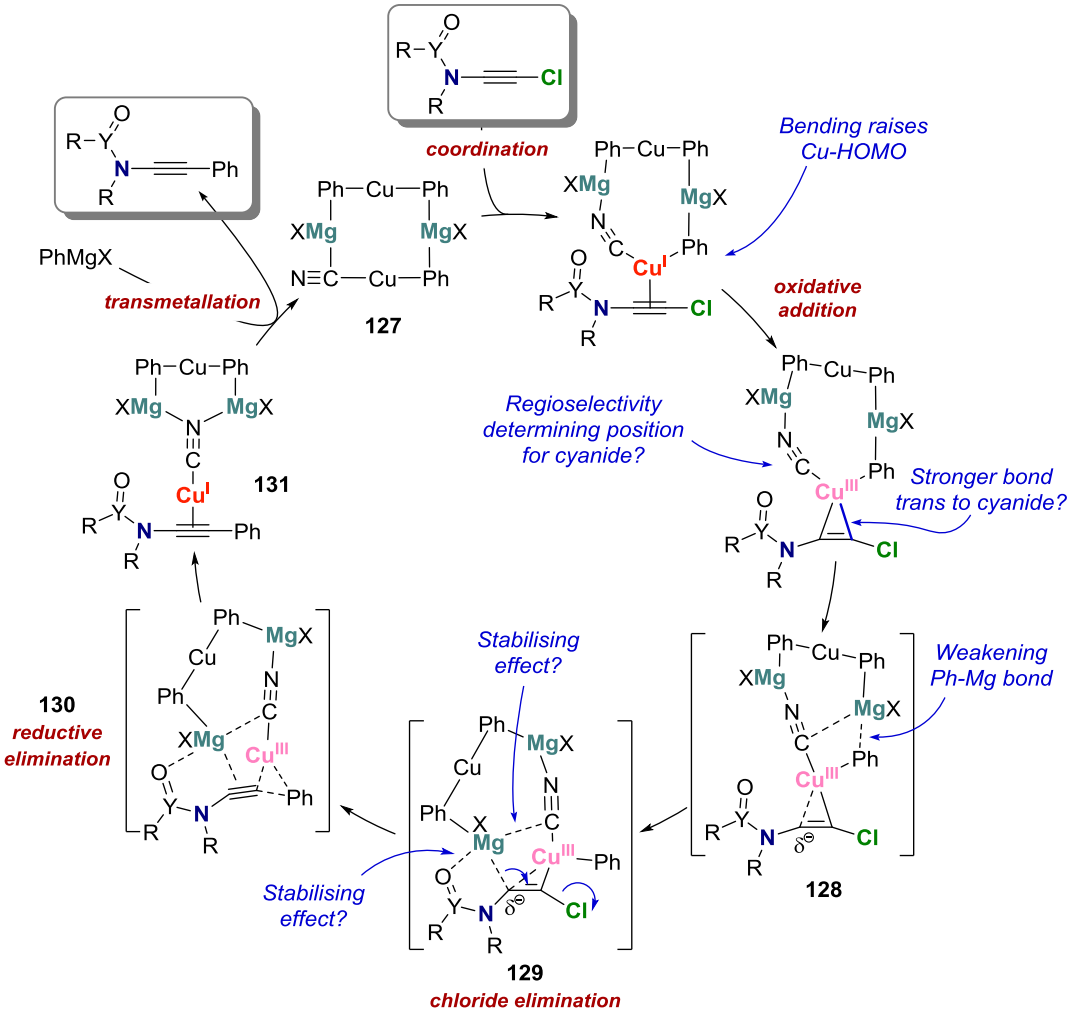


Figure 1.27: Proposed mechanism for the coupling of chloroynamides with Grignard reagents. Additional solvent molecules coordinated to magnesium have been neglected for clarity. X = halide, CN or Ph, Y = SO or C.

First, the formation of a cyano-magnesium-cuprate cluster such as **127** seems reasonable in TBME; this solvent is expected to show properties more akin to Et_2O than THF. The effect of trimethyl phosphite on the deaggregation of species such as **127** is, however, uncertain. Coordination of

copper(I) to the chloroynamide would induce a C–Cu–C bend, raising the HOMO on copper and enabling oxidative addition. Here, the position of cyanide is likely important and, assuming that it is copper-bound, would perhaps confer increased regioselectivity due to a favourable HOMO-LUMO interaction, as seen for allylic substitution in Figure 1.25. The phenyl group would be liberated from coordination to magnesium (**128**), opening up the cluster; a NC··Mg contact could be important in facilitating this (akin to that in Figure 1.24). A build-up of charge α- to nitrogen could be stabilised by magnesium (**129**) and aided by coordination of the electron withdrawing group to magnesium. Subsequent β-elimination of chloride, similar to that observed in the coupling of vinylbromide (Figure 1.26), would give an alkynylcopper(III) transition species that is analogous to that obtained by a direct C–Cl insertion. Reductive elimination (**130**) then gives the Cu(I)-ynamide complex **131**.

This proposal neglects the potential role of lithium, and one could imagine replacement of magnesium for zinc in relevant examples. The exact nature of the organometallic species in these reactions is purely speculative at this time, and the observed effects of increased temperature and the regioselective enhancements with cyanide could correlate with differing aggregation states. In considering the observed chemoselectivities, it is conceivable that the electronegativity of chlorine renders the chloroynamide more electrophilic than the product ynamide, giving more favourable coordination of the former species to copper and thus enabling the desired coupling to outcompete both carbocupration of the product ynamide, and reaction with the haloarenes.

The regioselectivity differences observed for alkyl and aryl organometallics must be considered further and, in light of Ashby's work, it is unfortunate that any changes in regioselectivity over the course of the reaction with the aryl Grignard reagents are unknown. Whilst our mechanistic proposal offers a potential explanation for the role of cyanide in *enhancing* the regioselectivity with aryl organometallics, these considerations do not explain the inherent difference between aryl and alkyl reagents: in all cases, the reactions of the latter displayed complete selectivity using either CuI or CuCN. If an oxidative pathway was operative, then a key factor would be the reduction potential of the ligands on copper. Strong σ-donors, such as alkyl ligands or phosphines, are required to stabilise $Cu(III)R_3$ species and these are generally stronger donors than aryl groups. Incidentally, this would also provide an explanation for why trimethyl phosphite can suppress aryl Grignard homocoupling, which presumably occurs via reductive elimination from a diphenylCu(III) species. This raises the following question: if a Cu(III) species is less stabilised with aryl ligands, would coordination of the electron withdrawing group to Cu(III) now be an important interaction? If so, a decreased temperature might favour this interaction and would provide an explanation for our observations. The decreased selectivity with ureas could also be attributed to their enhanced ability to coordinate to metals via the carbonyl, which could mitigate the regiocontrol offered by cyanide. This discussion is of course purely speculative in the absence of conclusive data, but it does outline a hypothesis that could be explored further.

1.4 Conclusions.

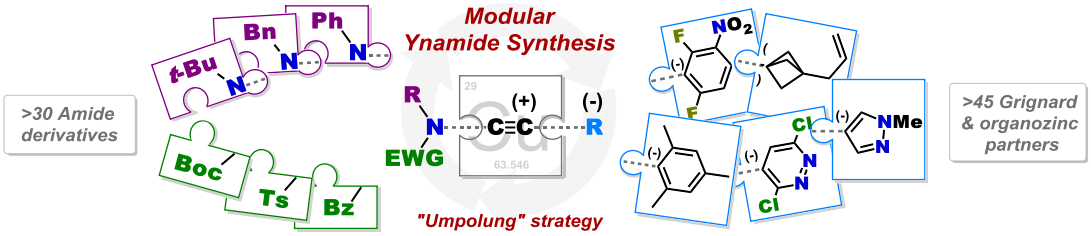
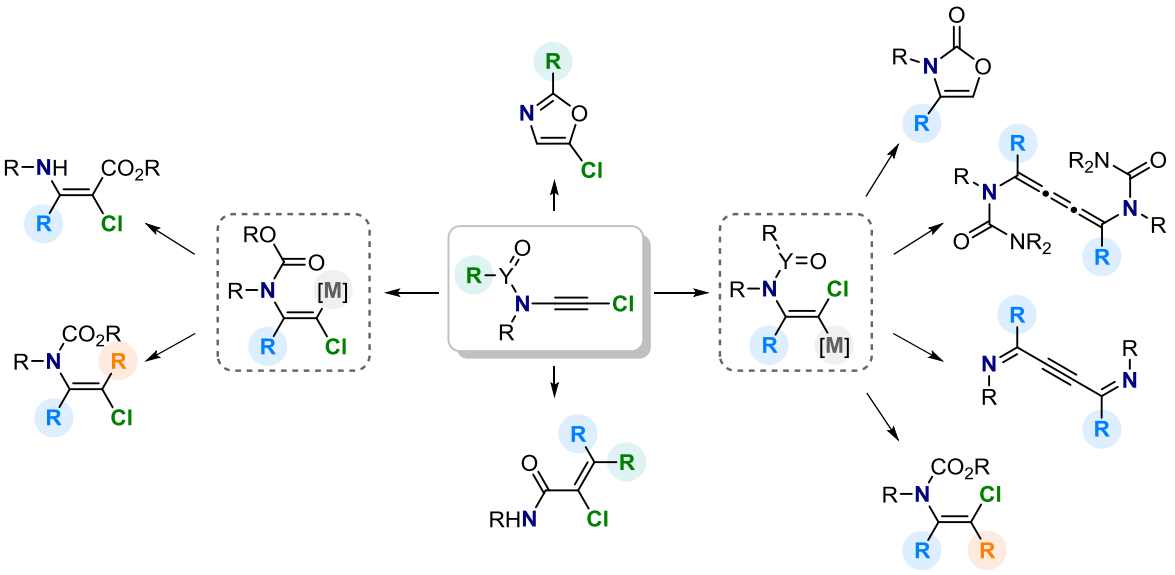


Figure 1.28: General copper-catalysed umpolung synthesis of ynamides.

In summary, a novel umpolung strategy that accesses ynamides from readily available dichloroenamides has been developed, in which a chloroynamide acts as the "electrophilic" coupling partner. It offers a milder route to ynamides that is complementary to the more conventional use of alkynyllithiums and electrophiles, and demonstrates that 1,2-dichloroenamides are incredibly useful building blocks for the synthesis of ynamides. This umpolung reaction has a broad scope, accommodating a wide range of Grignard and organozinc reagents, and tolerates a diverse range of functionality, electronic character and steric bulk on both coupling partners. Unlike many of the procedures mentioned in Chapter 0, these reactions occur at room temperature with a typical reaction taking 2–3 hours from dichloroenamide to the ynamide, even in the cases of highly substituted partners.

Alongside these advances, the side products isolated during these studies not only enabled a greater understanding of the coupling reaction itself, which elicited a deeper study to understand the fundamental reactivity of the organometallic species employed, but also highlighted the unique reactivity of a chloroynamide as compared to more "typical" ynamides. In this light, the enhanced reactivity of the *N*-carbonyl chloroynamides over their sulfonyl cousins enables access to a range of interesting products from a single precursor. These included the stereocontrolled formation of (*E*)- and (*Z*)-chloroenamides, and subsequent conversion to oxazolones, cumulenes and α,β-unsaturated amides (Scheme 1.23).

Finally, this chemistry also provides the first general route to acyclic amide/urea-derived ynamides, and valuable insight has been gained with respect to their stability and reactivity. Whilst this grants opportunities to investigate their chemistry, a greater fundamental understanding of the reactivity differences between the amides, carbamates and ureas could allow for a more informed approach when investigating future applications. An extensive understanding of ynamide reactivity differences, particularly the influence of the substituents at each of the three positions, remains elusive to date[350] and much of their behaviour remains somewhat anecdotal - particularly in the area of transition metal catalysis. To this end, the reader is referred to the discussions in Chapter 3.



Scheme 1.23: Potential applications of chloroynamide.

Synthesis and Applications of Yndiamides

2

The electron withdrawing group of an ynamide not only improves the overall stability of the functional group, but also grants further control in subsequent chemistry, for example, by directing carbometallation.[269,351] However, the *C*-substituent at the end of the ynamide also has a role in modulating ynamide reactivity, and we questioned whether an additional heteroatom on the alkyne would result in a more reactive ynamide, which could enable access to other 1,2-difunctionalised products. There have been very few reports that describe such ynamides, with only halogen and thioether-substituents known.[203,211,352] Already in this work, we have demonstrated the unique reactivity of chloroynamides, and we were particularly drawn to an ynamide that possessed a second amido substituent on the alkyne, so-called "yndiamides". Prior to this work, such compounds were unknown, though the analogous yndiamines are known to be very reactive functional groups.[353–362] Reports on their synthesis cautioned the reader to their ease of hydrolysis and their air sensitivity, making both their preparation and handling particularly difficult; consequently, this confined many of their applications to the synthesis of organometallic complexes. Our curiosity was piqued, why had yndiamides not been reported? Throughout this work, it became apparent that yndiamides had achieved an almost mythical status, with tales being told of various research groups trying to prepare these elusive functionalities. Unfortunately, these ventures were never reported and there was little doubt that we were treading a well-trodden path at the start of this project.

This chapter describes our studies that explored the chemistry of yndiamides and is divided into four sections. Section 2.1 will introduce the synthesis of yndiamines, which informed our initial attempts using 1,2-dihaloenamides discussed in Section 2.2. Section 2.3 concerns the synthesis of yndiamides from 1,1-dibromoenamides and Section 2.4 details our preliminary study of yndiamide reactivity, which poses the question of achieving regioselectivity in these reactions.

2.1 Yndiamines.

Yndiamines are compounds in which an alkyne is directly bonded to the nitrogen atoms of two separate amines (Figure 2.1). These compounds are highly reactive but, unlike related ynamines, there is no dipole across the alkyne and, consequently, there is no regioselectivity reported in their reactions. Furthermore, the resonance forms shown below also bring into question what the nature of the bonding is for these unusual compounds.

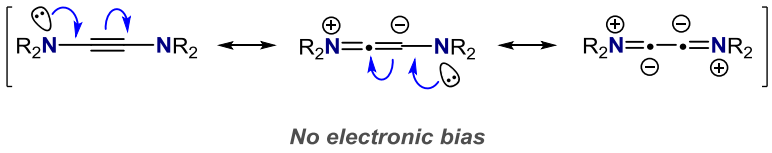
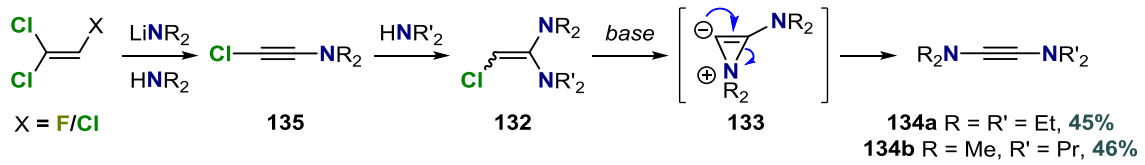


Figure 2.1: Yndiamines.

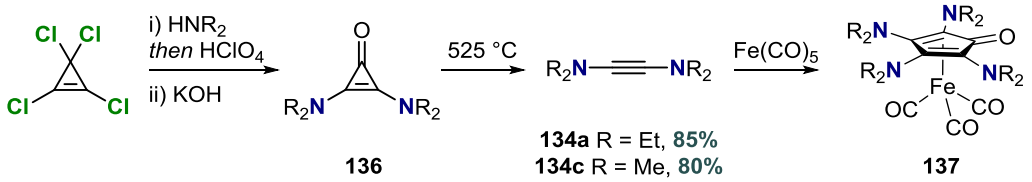
Reports of yndiamines first surfaced with a Union Carbide patent and a communication by Viehe in 1964,[363,364] in which 1,1-dichlorofluoroethylene was reacted with lithium diethylamide (3.3 equiv.) to afford a symmetrical yndiamine. Further publications in 1970 gave a detailed account of a more optimised version of this synthesis (Scheme 2.1),[365,366] in which 1,1-dichlorofluoroethylene or trichloroethylene react with lithium amides (1 equiv.) and dialkylamines (5 equiv.) to form chloroketene aminals **132**. Treatment of these with a strong base ($LiNR_2$ or PhLi) enabled the α-elimination of HCl and an "onium" rearrangement (**133**) (which is analogous to a Fritsch-Buttenberg-Wiechell (FBW) rearrangement of a vinylidene carbene) afforded yndiamines **134**. The direct use of dichloroacetylene is also possible and generally gave higher yields (50–60% as compared to 40–50% for the haloalkenes).



Scheme 2.1: Synthesis of yndiamines via chloroketene aminals. *Conditions for preparation of* **134a**: (i) $LiNEt_2$ (1 equiv.), $HNEt_2$ (5 equiv.), Et_2O, -78 °C to rt, 4 h, then 100 °C, 15 h, sealed tube; (ii) $LiNEt_2$ or PhLi (1 equiv.), Et_2O, 0 °C.

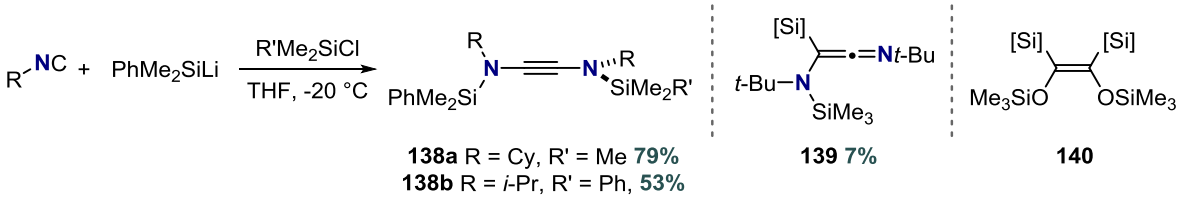
The reaction can be halted at the chloroynamine **135** and the addition of a different amine, e.g. dipropylamine, ultimately gives access to unsymmetrical yndiamines such as **134b**. Unfortunately, the generality of this route was never reported and only simple alkyl amines have been used. Nevertheless, it was this work that sparked a general interest in yndiamines and a selection of reports detailing alternative approaches resulted soon after.[355,367–371] A few described only simple improvements to Viehe's work,[355,370] but two routes warrant some discussion.

In their synthesis of cyclopentadienones,[368] Wilcox and Breslow devised a rather interesting strategy to yndiamines from cyclopropanone **136** (Scheme 2.2). They avoided Viehe's route to yndiamines due to "*considerable hazards involved in the preparation and handling of toxic unstable dichloroacetylene*" and instead preferred pyrolytic decarbonylation of **136** at 525 °C. The resulting yndiamines were isolated in good yields, however, and reaction with iron pentacarbonyl afforded the corresponding tetraaminocyclopentadienones **137**.



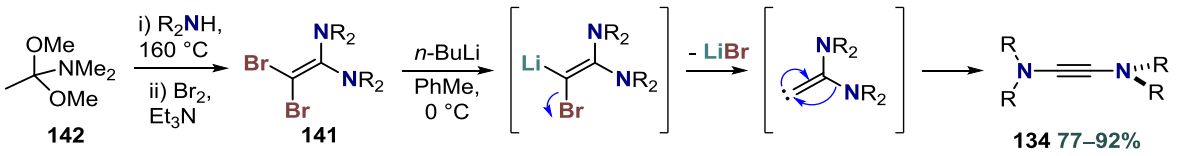
Scheme 2.2: Synthesis of yndiamines by cheletropic extrusion of CO from cyclopropenones.

In 1986, Ito disclosed the conversion of alkyl isocyanides to *N*-silylated yndiamines **138** using silyllithiums and chlorotrialkylsilanes (Scheme 2.3).[369] In the case of the hindered *t*-butyl isocyanide, a very low yield (11%) of yndiamine was isolated together with the ketenimine **139** (7%). The isoelectric carbon monoxide instead gives the enediol ether **140**,[372] the yield of which was unreported.

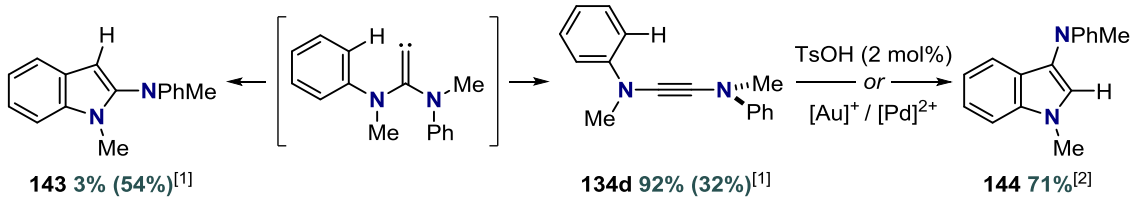


Scheme 2.3: Dimerisation of isocyanides with silyllithiums. [Si] = $SiPhMe_2$.

It was only much later in 2010 when the synthesis of yndiamines was revisited by Tamm and co-workers,[373] who chose to prepare them from 1,1-dibromoketene aminals **141**, themselves prepared from ortho-amide **142** (Scheme 2.4). Treatment of **141** with *n*-butyllithium afforded a lithium carbenoid, which underwent FBW rearrangement[374] to give yndiamines in good yields (77–92%) (Scheme 2.4). This mechanism is equivalent to the onium rearrangement proposed by Viehe in 1970 (Scheme 2.1). The simultaneous formation of 2-amino indole **143** alongside **134d** is supportive of a carbenoid intermediate (Scheme 2.5) and performing the reaction in THF or with coordinating additives such as tmeda increased the yield of indole from 3% to 54% yield. Unlike the organometallic chemistry established with aliphatic yndiamines, *N*-aryl yndiamine **134d** afforded indole **144** upon treatment with electrophilic metals (Scheme 2.5). This could also be achieved with catalytic *p*-toluenesulfonic acid (TsOH) to afford **144** in 71% yield.



Scheme 2.4: Synthesis of yndiamines from 1,1-dibromoketene aminals.



Scheme 2.5: Formation of regioisomeric indoles. [1] Yields in parentheses for reaction in THF; [2] Yield using TsOH.

Tamm also reported the first X-ray crystal structures of yndiamines, proving that, in accordance with the theoretically predicted conformation[375] and at least in the crystal lattice, the substituents on the two nitrogen atoms sit in almost orthogonal planes (with dihedral angles of 75º and 79º; the deviation from orthogonality could be due to crystal packing effects). The reader is referred to Chapter 3 for further discussions on the structures of yndiamines and yndiamides.

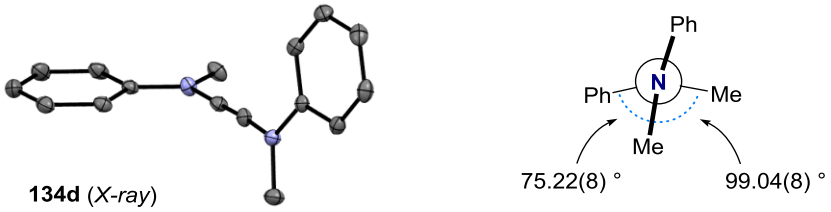


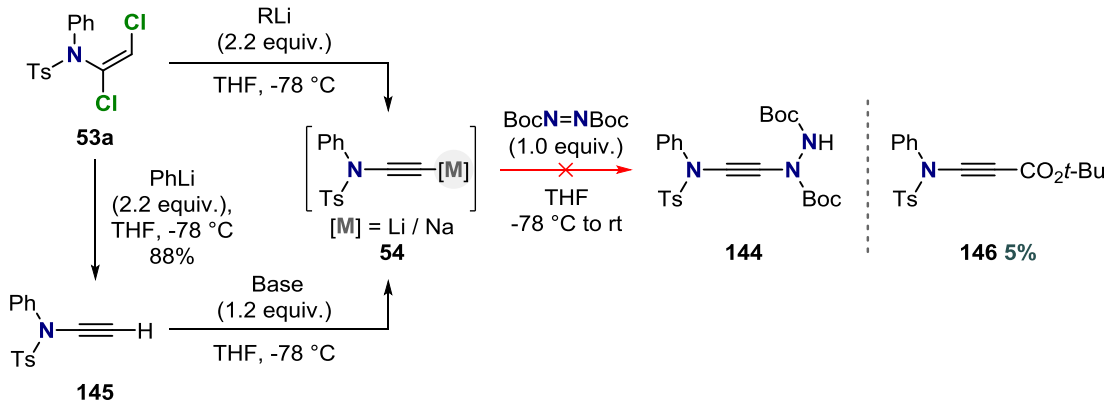
Figure 2.2: Yndiamines exhibit a twisted conformation in the crystal lattice. Single crystal X-ray data for **134d** were obtained from the CCDC (784155). The displacement ellipsoid plot is displayed at 50% probability and hydrogen atoms are omitted for clarity.

2.2 Previous work.

2.2a Attempted synthesis of yndiamides from 1,2-dichloroenamides.

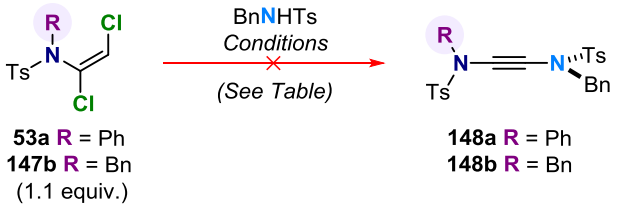
Given our previous success in trapping lithiated ynamides **54** with carbon electrophiles,[203] our first strategy[376] towards yndiamides was to add of an electrophilic nitrogen component (Scheme 2.6).[192,262] Here we used di-*t*-butyl azodicarboxylate (DBAD) but this failed to give the desired compound **144**. Varying the methods used to generate **54** (e.g. from dichloroenamide **53a** using *n*-butyllithium or phenyllithium, or from the terminal ynamide **145** using LiHMDS, NaHMDS, LDA, *n*-butyllithium or phenyllithium) consistently resulted in complex mixtures, though in some cases ynamide **146** could be isolated. Attempted bromination/iodination[208] of **54**, or direct oxidative

amidation[161] of **145**, also proved unsuccessful (the latter only resulted in ynamide hydrolysis and homodimerisation) and, given this lack of success, our attention switched to cross-coupling strategies.



Scheme 2.6: First attempts to prepare an yndiamide by treatment of an alkynyllithium with DBAD.

The use of 1,2-dichloroenamides was investigated with conditions more typically applied for ynamide synthesis (Table 2.1). It was hoped that an excess of base would enable in situ elimination to the chloroynamide, which would undergo coupling with *N*-benzyl tosylamide to give yndiamides **148**. Unfortunately both dichloroenamides **53a** and **147** were unreactive and were fully recovered in each case (Table 2.1).



Substrate	[Cu] *(equiv.)*	Ligand *(equiv.)*	Base *(equiv.)*	Solvent	T (°C)	t (h)	Yield (%)
53a **147b**	$CuSO_4.5H_2O$ *(0.2)*	1,10-phen *(0.4)*	K_3PO_4 *(2.5)*	PhMe	110	48	*n.r.* *n.r.*
53a **147b**	CuI (0.1)	1,10-phen *(0.2)*	Cs_2CO_3 *(4.0)*	THF	85	48	*n.r.* *n.r.*
53a **147b** **147b**	CuI (0.12)	dmeda *(0.18)*	Cs_2CO_3 *(4.0)*	DMF DMF dioxane	60	48	*n.r.* *n.r.* *n.r.*

Table 2.1: Attempted couplings of 1,2-dichloroenamides with *N*-benzyl tosylamide; *n.r.* = no reaction, as determined by TLC and ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

On the other hand, attempted coupling of chloroynamide **56a** with *N*-benzyl tosylamide failed to give the yndiamide **148a** and, instead, gave full conversion to the chloroketene aminal **149a**. This reaction also proceeded smoothly in the absence of copper salts, and a selection of

heteronucleophiles were used to afford the ketene aminals **149a–d** in excellent yield and as single geometrical isomers (Figure 2.3).[135] Compounds **149a** and **149b** were shown to possess (*E*)-geometries by single crystal X-ray analysis, which result from the *trans* addition of Nu–H across the alkyne; the configuration of the other ketene aminals was assigned by analogy. These compounds are also superficially equivalent to the ketene aminals utilised by Viehe (see Scheme 2.1).

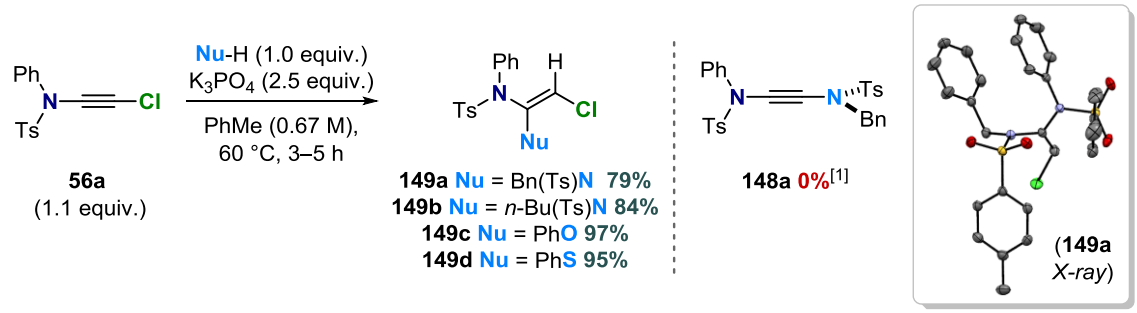


Figure 2.3: Formation of chloroketene aminals from chloroynamide **56a**. [1] The following conditions failed to produce **148a**: $CuSO_4 \cdot 5H_2O$ or CuI (0.2 equiv.), 1,10-phenanthroline (0.4 equiv.), K_3PO_4 or Cs_2CO_3 (2.5–4.0 equiv.), PhMe or THF (0.33–0.67 M), 85–110 °C, N_2 atmosphere, 24 hours. Single crystal X-ray data collection, processing and solution refinement for **149a** and **149b** were performed by Dr Mike Jones. The displacement ellipsoid plot is displayed at 50% probability and hydrogen atoms are omitted for clarity.

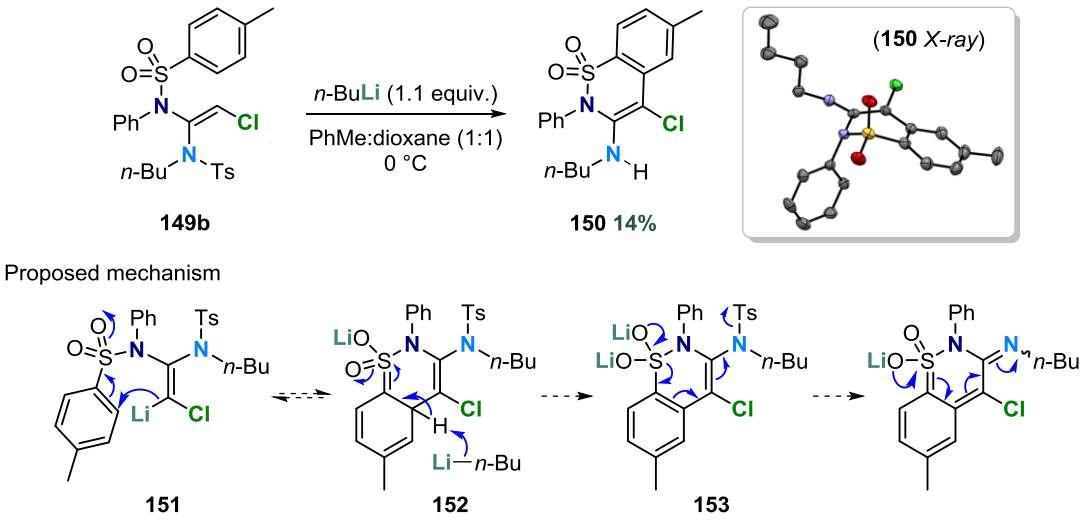


Figure 2.4: Conversion of chloroketene aminal **149b** to benzothiazine **150**. Single crystal X-ray data collection, processing and solution refinement for **150** were performed by Dr Mike Jones. The displacement ellipsoid plot is displayed at 50% probability and hydrogen atoms are omitted for clarity.

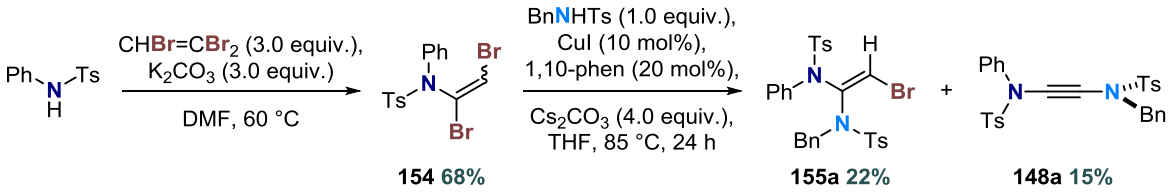
As such, we attempted to convert **149b** to the yndiamide (via FBW rearrangement) using the conditions described by Tamm (Figure 2.4). Remarkably, this gave the benzothiazine **150** instead, albeit with only 20% conversion, and the yndiamide was not observed. To explain the formation of **150**, a vicarious nucleophilic substitution mechanism is proposed. It is likely that lithiation occurred

to give the carbenoid **151**; however, instead of chloride loss, nucleophilic attack on the neighbouring tosyl group leads to a dearomatised intermediate **152**, which regains aromaticity with further deprotonation and loss of the remote tosyl leaving group (**153**). An alternative mechanism via tosyl ortho-lithiation may operate instead. Due to time constraints, this transformation was never re-investigated but it does offer a potentially interesting route to benzothiazines from ynamides.[377–379]

2.2b Attempted synthesis of yndiamides from 1,2-dibromoenamides.

In light of these observations, we wondered if dibromenamides would be more useful substrates. By analogy to the dichloroenamides, the reaction of *N*-phenyl tosylamide with tribromoethylene and K_2CO_3 in DMF gave the expected dibromoenamide **154**, but as a 1.7:1 mixture of (*E*)- and (*Z*)-isomers. There was also a third compound in the mixture, possibly the bromoynamide, which co-eluted with the enamides. Recrystallisation enabled isolation of the mixture of (*E*)-/(*Z*)-**154** in 68% yield. On the other, the use of *N*-benzyl and *N*-*n*-butyl tosylamides was much less successful, with poorly reproducible conversion of starting material, and the product dibromoenamides were sensitive to silica gel chromatography. The use of Cs_2CO_3 instead offered no benefit, and the yields of those dibromoenamide products never exceeded 15%.

Nevertheless, and considering all of the previous failures, the use of dibromoenamide **154** was to give a sensational result. The use of Liang's conditions[157] successfully afforded bromoketene aminal **155a** and yndiamide **148a** (Scheme 2.7), alongside several other unidentified products. Single crystals of **148a** and **155a** were grown and X-ray analysis provided absolute proof of their identities. Despite this result, we were never able to gain reliable yields for the formation of 1,2-dibromoenamides and, coupled with their increased sensitivity to silica gel chromatography, that route was abandoned in favour of using 1,1-dibromoenamides.



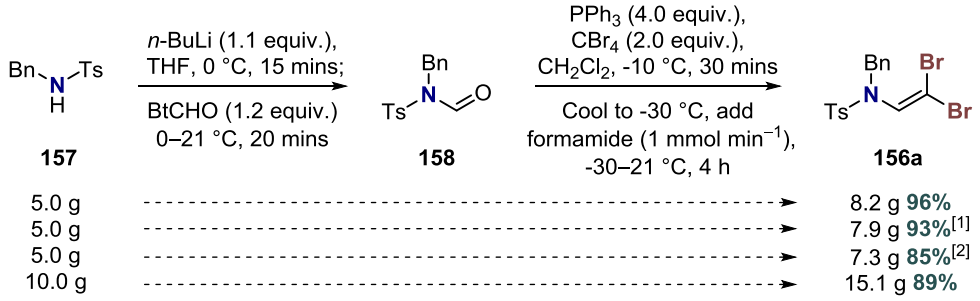
Scheme 2.7: First synthesis of an yndiamide from a dibromoenamide: 1.1 equiv. of dibromoenamide **154** was used.

2.3 Copper-catalysed synthesis of yndiamides.

2.3a Reaction optimisation.

1,1-Dibromoenamides are readily prepared in two steps from the sulfonamide by formylation and Ramirez dibromoolefination (Scheme 2.8).[197,380] *N*-Benzyl dibromoenamide **156a** was selected as a

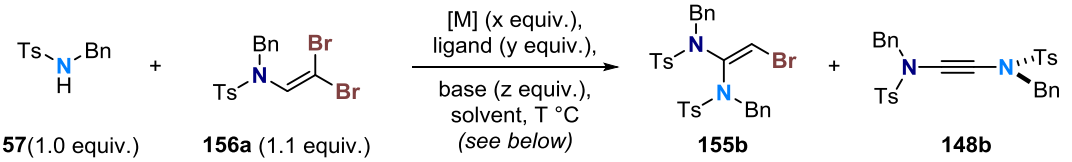
test substrate and its synthesis was streamlined to enable more rapid access. First, a THF solution of *N*-benzyl tosylamide (**157**) was treated with *n*-butyllithium at 0 °C to give the *N*-lithiated sulfonamide. This reaction was effectively a titration and full conversion was observed when the pale yellow reaction mixture turned an intense orange at the reaction endpoint. Treatment of this with a solution of 1*H*-benzotriazole-1-carbaldehyde (BtCHO)[381] afforded the formamide **158**. Though **158** is highly crystalline, neither recrystallisation nor chromatography was effective for removing the byproduct benzotriazole and remaining BtCHO. This issue was circumvented by performing a basic extraction with 2 M aqueous K_2CO_3, which was mild enough to hydrolyse the remaining BtCHO whilst leaving the formamide intact and the resulting potassium benzotriazolide was extracted into the aqueous phase. The crude formamide was of sufficient purity for use in the next step. The dibromoolefination step was somewhat capricious, often resulting in incomplete conversion, and the high crystallinity of both the formamide **158** and dibromoenamide **156a** made isolation of **156a** exceptionally difficult. Careful temperature control and the use of strictly anhydrous solvent was required to enable reproducibly high conversions (>98%) (Scheme 8), from which the product dibromoenamide could be isolated simply by direct filtration of the reaction mixture through a silica gel pad. With this streamlined approach, we were able to routinely prepare 5–10 g of dibromoenamide **156a** from the sulfonamide within 12–18 hours. Further purification of the dibromoenamide can be achieved by recrystallisation from heptane or ethanol. Storage of these crystals in the freezer (-20 °C) under an inert atmosphere is recommended because **156a** undergoes gradual hydrolysis in air. This degradation was also accompanied by an acrid odour.



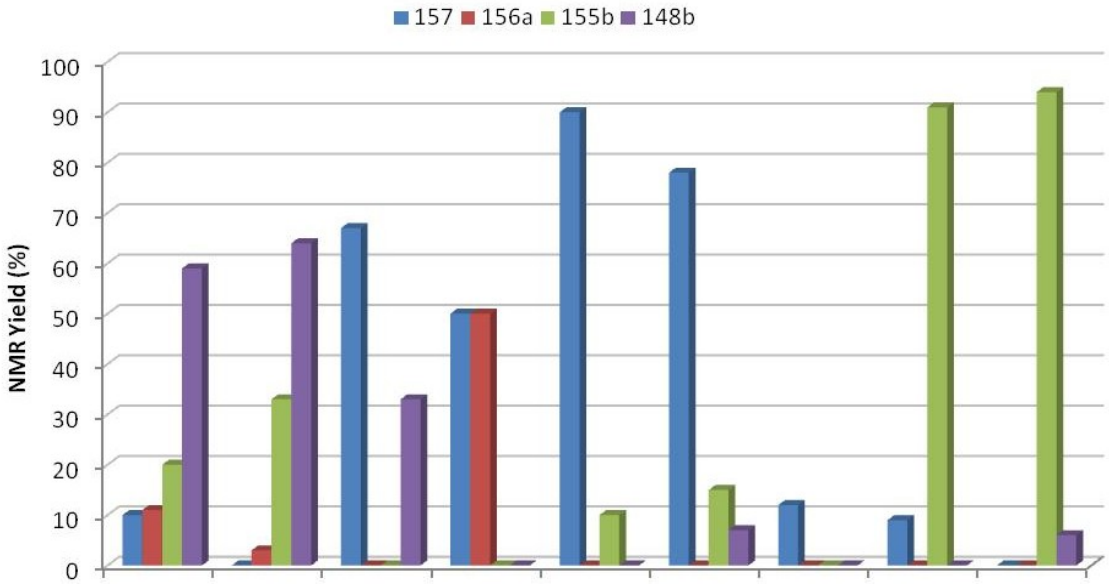
Scheme 2.8: Synthesis of dibromoenamide **156a**. [1] Recrystallised from heptane; [2] Recrystallised from ethanol.

With sufficient quantities of precursor **156a** in hand, investigations began by screening a range of conditions typically used in the amidative coupling of bromoalkynes or 1,1-dibromoalkenes (Table 2.2). The conditions used in entries 1,[120] 2,[157] 3a,[116] and 4b[147] produced some of the desired yndiamide **148b**; however, this was invariably contaminated with the bromoketene aminal **155b**. Although it is difficult to make a conclusive comparison of these conditions, hydrolysis of the dibromoenamide seemed to be more significant for the reactions using dmeda (entries 3 and 4), and the use of 1,10-phenanthroline gave a consistently better reaction profile regardless of the copper salt (entries 1 and 2). The use of iron trichloride[136] (entry 6) gave a high proportion of the

bromoketene aminal, and a comparison with entry 7 indicates that **155b** was formed in the absence of transition metal salt - here **155b** was isolated in 92% yield. It is possible the formation of **155b** in entries 1 and 2 was a background reaction, though mindful of Viehe's work, we considered that it may be an intermediate, or at least be derived from an intermediate, en route to the yndiamide. This will be addressed later in our discussions.



157(1.0 equiv.) **156a** (1.1 equiv.) **155b** **148b**



entry	1	2	3a	3b	4a	4b	5	6	7
[M] (x equiv.)	$CuSO_4 \cdot 5H_2O$ (0.2)	CuI (0.12)	CuI (0.1)		CuI (0.12)		CuI (0.1)	$FeCl_3$ (0.1)	-
ligand (y equiv.)	1,10-phen (0.4)	1,10-phen (0.2)	dmeda (0.2)		dmeda (0.18)		AcC (0.4)	dmeda (0.18)	-
base (z equiv.)	K_3PO_4 (2.5)	Cs_2CO_3 (4.0)	K_3PO_4 (4.0)		Cs_2CO_3 (4.0)		Cs_2CO_3 (4.0)	Cs_2CO_3 (4.0)	Cs_2CO_3 (4.0)
solvent (conc. / M)	PhMe (0.33)	THF (0.33)	DMF (0.1)	PhMe (0.1)	dioxane (0.1)	DMF (0.1)	dioxane (0.5)	PhMe (0.2)	THF (0.2)
T (°C)	110	85	85	85	60	60	80	90	85

Table 2.2: Screening of literature conditions for the synthesis of yndiamide **148b**. [1] Ratio determined by ^{1}H spectroscopic analysis of the crude reaction mixture after 18 hours; AcC = 2-acetylcyclohexanone,[142] dmeda = *N*,*N*′-dimethylethylenediamine, 1,10-phen = 1,10-phenanthroline.

The conditions used in entries 1 and 2 were taken forward and are subsequently described as conditions A and B, respectively. Each reaction parameter was investigated to optimise the synthesis of yndiamide **148b**. To enable a more direct comparison of the two conditions, 2.5 equiv. of base,

0.2 equiv. of copper salt and a temperature of 85 °C was chosen. A selection of ligands was first screened (Figures 2.5 and 2.6), and it was clear that 1,10-phenanthroline (L1) outperformed bipyridine (L2), terpyridine (L3) and dmeda (L4). These reactions also showed some dependence on the ligand to metal ratio. With conditions A, both a 1:1 and 2:1 ratio of 1,10-phenanthroline (L1) to metal provided a similar level of conversion after 18 hours, the latter of which only provided a 4% increase in yield of **148b**. However, the reaction outcome was extremely sensitive to the proportion of bipyridine (L2, Figure 2.5). Where a 1:1 ratio gave <10% yield of the yndiamide (and a similar product distribution to the reaction without ligand), the use of a 2:1 ratio gave a significantly increased yield of the yndiamide (59%). With conditions B, a 2:1 ratio of 1,10-phenanthroline (L1) to metal gave a greater conversion of dibromoenamide **156a** and an increased yield of the yndiamide (from 50% to 75%, Figure 2.6). In general for both conditions, the use of terpyridine (L3) and dmeda (L4) compared very similarly to those reactions without added ligand, and gave a high proportion of **155b**. In addition to these results, decreased catalyst loading (i.e. 0.1 equiv of copper salt and 0.2 equiv. of 1,10-phenanthroline) gave decreased yields of the yndiamide (52% and 57% for conditions A and B, respectively, after 18 hours).[134] As such, 0.2 equiv. of copper salt and 0.4 equiv. of 1,10-phenanthroline were chosen for our subsequent studies.

Having established suitable catalyst systems, the next reaction parameter investigated was the base and, for ease of comparison, THF was chosen as solvent for the reactions using both copper salts - the effect of solvent will be explored later. The reactions using $CuSO_4 \cdot 5H_2O$ (conditions A) are considered first. Of the bases screened (K_2CO_3, Cs_2CO_3, Ag_2CO_3, K_3PO_4 and TBAF,[382,383] 2.5 equiv.), K_3PO_4 and Cs_2CO_3 were the most effective, with the former providing a higher yield of the yndiamide **148b** (57%) as compared to Cs_2CO_3 (32%), which gave increased amounts of the bromoketene aminal. The other carbonates gave no conversion, and TBAF reacted to give an immediate pale blue slurry, which was attributed to the formation of $Cu(OH)_2$ and gave negligible conversion. For conditions B (CuI), Cs_2CO_3 and TBAF gave good conversion and the former gave the highest yield of yndiamide (75% as compared to 53% for TBAF, where hydrolysis of the enamide was an additional issue). The other bases were ineffective and gave negligible conversion after 18 hours. In cases where the base used was ineffective, increasing the loading to 4.0 equivalents also failed to provide any meaningful improvement. A strong dependence on the quality of the base was also observed,[135] particularly for reactions which used Cs_2CO_3, and anhydrous base was found to give lower amounts of the bromoketene aminal and increased proportions of the yndiamide. Because Cs_2CO_3 and K_3PO_4 are hygroscopic, newly-purchased anhydrous Cs_2CO_3 (Fluorochem) and K_3PO_4 (Sigma Aldrich) was stored and dispensed in a N_2 filled glovebox to alleviate these problems. The effect of base quantity was also investigated (Figure 2.7). Increased amounts of K_3PO_4 gave greater overall conversion and the proportion of bromoketene aminal to yndiamide did not change appreciably. However, increased amounts of Cs_2CO_3 from 2.0–4.0 equiv.

favoured an increased formation of the bromoketene aminal, which could be attributed to greater solubility of the base in THF. Considering these results, 2.5 equiv. of base was chosen for our studies using both conditions A and B, but note that 3.0 equiv. of Cs_2CO_3 (B) can be used without significant detriment.

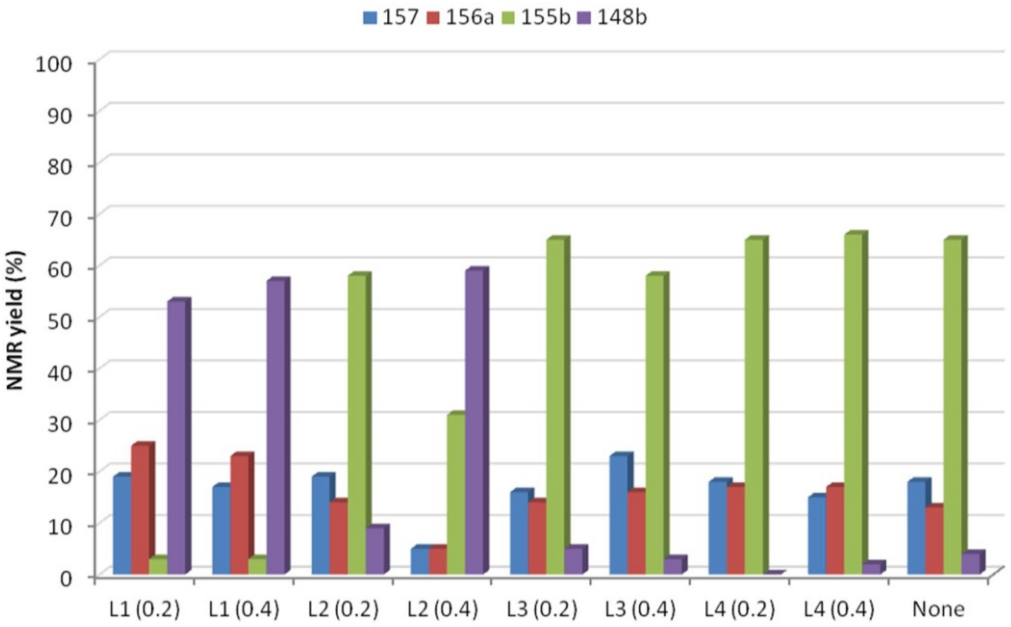


Figure 2.5: The effect of different ligands on the formation of yndiamide **148b** using C*onditions A*: PhMe (0.33 M), $CuSO_4 \cdot 5H_2O$ (0.2 equiv.), ligand (y equiv.), K_3PO_4 (2.5 equiv.), N_2 atm., 85 °C, 18 hours. L1 = 1,10-phenanthroline; L2 = 2,2'-bipyridyl; L3 = 2,2';6',2"-terpyridine; L4 = dmeda. The values in parentheses refer to equivalents of ligand used.

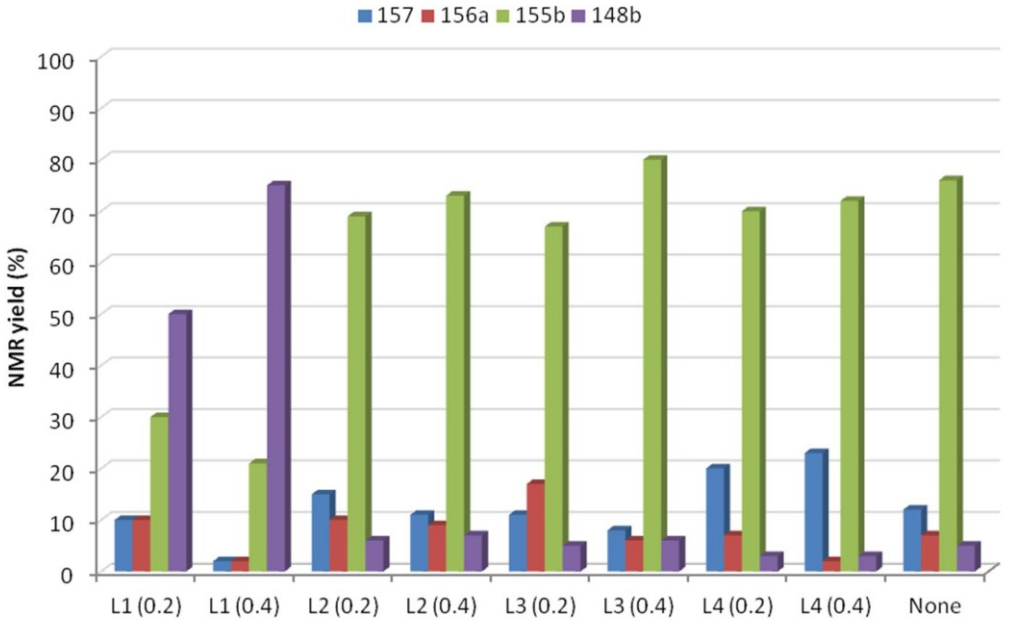


Figure 2.6: The effect of different ligands on the formation of yndiamide **148b** using *Conditions B*: THF (0.33 M), CuI (0.2 equiv.), ligand (y equiv.), Cs_2CO_3 (2.5 equiv.), N_2 atm., 85 °C, 18 hours. L1 = 1,10-phenanthroline; L2 = 2,2'-bipyridyl; L3 = 2,2';6',2"-terpyridine; L4 = dmeda. The values in parentheses refer to equivalents of ligand used.

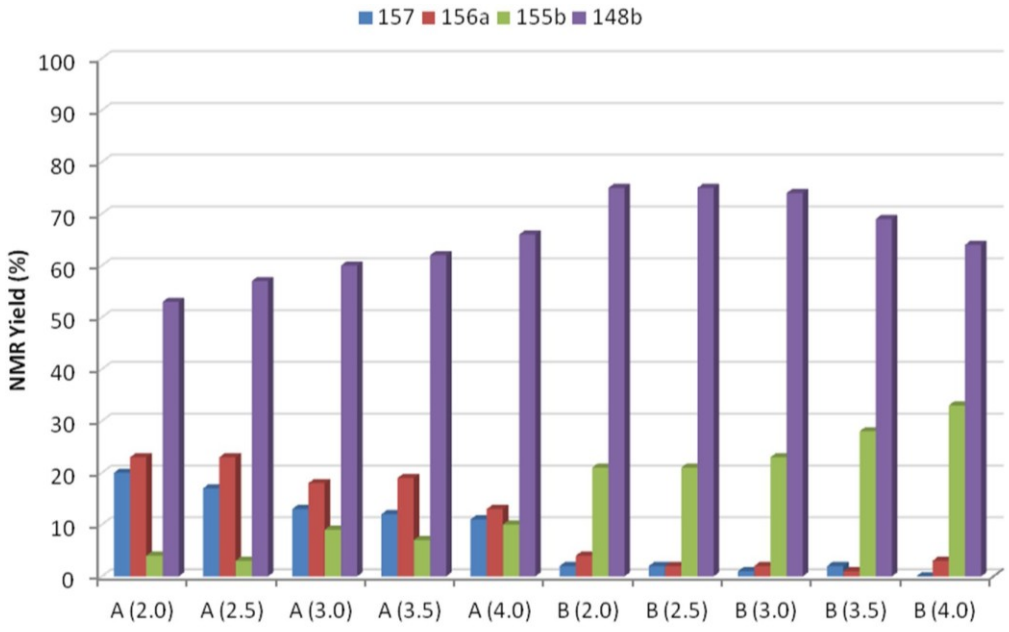


Figure 2.7: The effect of base loading on the formation of yndiamide **148b**. The values in parentheses refer to equivalents of base used. *Conditions*: THF (0.33 M), [Cu] (0.2 equiv.), 1,10-phenanthroline (0.4 equiv.), base (z equiv.), N_2 atm., 85 °C, 18 hours; **A**: [Cu] = $CuSO_4 \cdot 5H_2O$ and base = K_3PO_4; **B**: [Cu] = CuI and base = Cs_2CO_3.

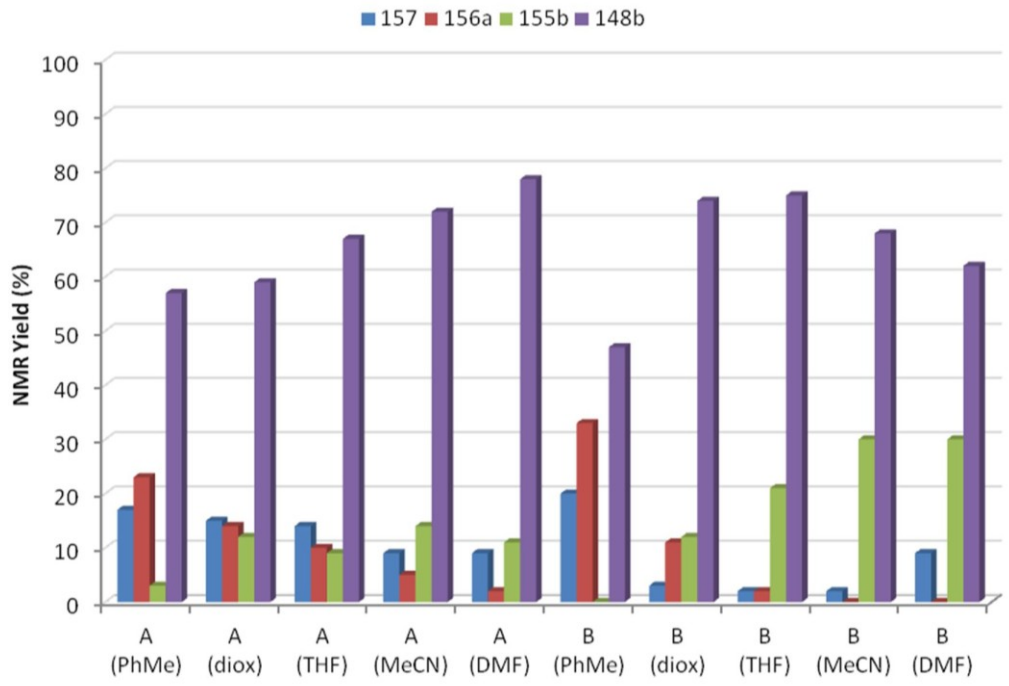


Figure 2.8: The effect of solvent on the formation of yndiamide **148b**. The values in parentheses refer to the solvent used, diox = dioxane. *Conditions*: anhydrous solvent (0.33 M), [Cu] (0.2 equiv.), 1,10-phenanthroline (0.4 equiv.), base (2.5 equiv.), N_2 atm., 85 °C, 18 hours; **A**: [Cu] = $CuSO_4 \cdot 5H_2O$ and base = K_3PO_4; **B**: [Cu] = CuI and base = Cs_2CO_3.

The solvent influence was next investigated (Figure 2.8). Returning to the original screening of conditions (Table 2.2), toluene, dioxane, THF, acetonitrile and DMF are the solvents most commonly used in ynamidative cross couplings, and the use of these solvents in our reaction led to

some interesting trends. Firstly, increased solvent polarity gave a greater conversion of the dibromoenamide with both catalyst systems, although greater hydrolysis of the enamide and greater formation of the bromoketene aminal was seen when using Cs_2CO_3; a decreased amount of yndiamide also correlated with increased amounts of bromoketene aminal. A similar observation was made when using K_3PO_4, albeit the effect was much smaller. Overall, the best conversion and yield of yndiamide was seen when using conditions B with anhydrous THF (Figure 2.8). Note that whilst the use of DMF with conditions A also gave a high yield of the yndiamide (78%), there were concerns related to the toxicity of this solvent.[384]

Final investigations looked at temperature effects and there was a distinct "Goldilocks effect" observed with these reactions, whereby the temperature had to be "just right" to afford optimum conversion and yield of the yndiamide, whilst also suppressing the bromoketene aminal. Increased temperatures (85–110 °C) gave higher amounts of bromoketene aminal, as well as some enamide hydrolysis. Curiously, there was also a larger proportion of aminal when the reaction was performed at 35 °C. Conducting the reaction at 60 °C provided optimal conversion and product ratio, highlighting the complexity of this reaction. From this screening of conditions, we settled on the use of CuI (0.2 equiv.), 1,10-phenanthroline (0.4 equiv.), Cs_2CO_3 (2.5 equiv.), THF (0.33 M) at 60 °C. This reaction was repeated three times using 100 mg (0.38 mmol) of *N*-benzyl tosylamide, and the yndiamide **148b** was isolated in 80–86% yield.

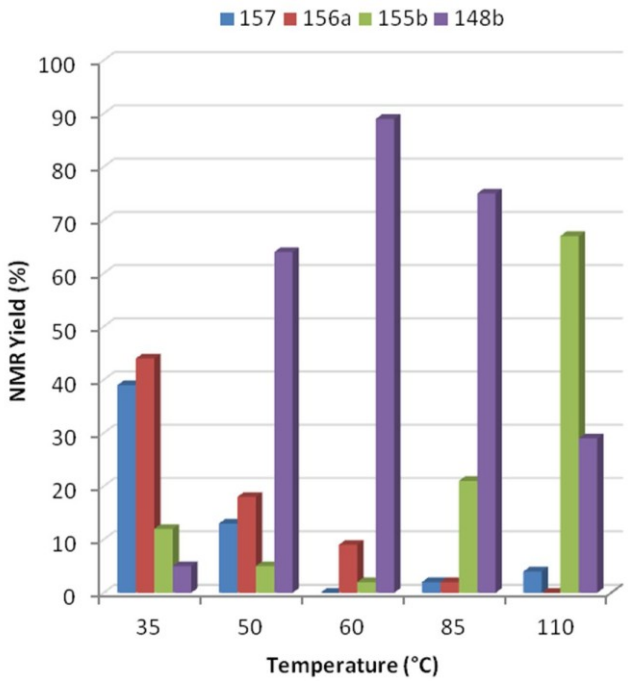


Figure 2.9: The effect of temperature on the formation of yndiamide **148b**. *Conditions*: THF (0.33 M), CuI (0.2 equiv.), 1,10-phen (0.4 equiv.), Cs_2CO_3 (2.5 equiv.), N_2 atm., T °C, 18 hours. The reaction at 110 °C was performed in a sealed tube.

2.3b Scope of amide and 1,1-dibromoenamide coupling partners.

Using dibromoenamide **156a**, a variety of amide nucleophiles were evaluated using the optimised conditions described (Figure 2.10). Sulfonamide and phosphoramidate derivatives both performed well and many of these afforded the corresponding yndiamides **148b**–**148x** (**a**, Figure 2.10). All of these yndiamides were purified by chromatography on silica gel without the need for pretreatment with Et_3N. A range of functional groups on these amides was tolerated in these reactions, including alkenes/internal alkynes (for example, **148k**–**148n**), acetals (**148u**, **148w**), esters (**148w**) and silyl ethers (**148o**); further chemistry using these compounds will be discussed in Section 2.4. These reactions were also effective on multi-gram scale, with 3.2 g (61% yield) of **148k** prepared from 5.0 g (11 mmol) of dibromoenamide **156a**. Considering the scope further, the only sulfonamides of consequence that failed to give an yndiamide were the *N*-*t*-butyl and *N*-phenyl tosylamides. Both are arguably poor nucleophiles - the former being sterically hindered and the anion of latter stabilised by conjugation - but it is the respective formation of diyne **159** and aminal **155** in these reactions instead, that potentially tells us more about the overall reaction mechanism itself. We will consider the ramifications of these observations in Section 2.3c.

Almost all of the *N*-carbonyl derivatives examined (**b**, Figure 2.10), which spanned a range of cyclic and acyclic amides, carbamates and ureas, failed to give the desired products. The reactions of pyrrolidinone (**148y**) and oxazolidinone (**148z**) both gave full conversion to a single product each, with R_f values consistent with the formation of an yndiamide (0.47 and 0.41, respectively, eluting with 20% v/v EtOAc/40-60 petroleum ether). However, NMR spectroscopic and MS analysis of the crude reaction mixtures were inconclusive, and these products proved to be quite unstable under ambient conditions, which precluded attempts to isolate them. What is more interesting is the distinct lack of ketene aminal formed in any of these reactions, with variable amounts of the diyne **159** and small amounts (<3%) of the *N*,*N*′-dibenzyl yndiamide **148b** found instead; the latter presumably arises from in situ hydrolysis of the dibromoenamide **156a** to *N*-benzyl tosylamide and subsequent coupling with more **156a**. The use of phenol as a nucleophile was also unsuccessful and instead gave the bromoketene aminal (**155c**, Nu = OPh) in 85% yield.

A brief exploration of the dibromoenamide scope was also performed (Figure 2.11), but this was significantly hampered because the Ramirez dibromoolefination of certain formamide precursors was often low yielding or gave only decomposition (**a**, Figure 11). In hindsight, the conditions reported by Marquez may have offered a successful alternative.[385] Nevertheless, only *N*-sulfonyl dibromoenamides were competent in these couplings, with amide (**156n**, **156p**) or carbamate (**156k**) derivatives being completely unreactive, even upon prolonged heating with 4 equiv. of Cs_2CO_3. The side-chain of the sulfonyl dibromoenamides were readily varied, leading to a selection of difunctionalised yndiamides (**148k**, **160a**–**160n**) (**b**, Figure 2.11).

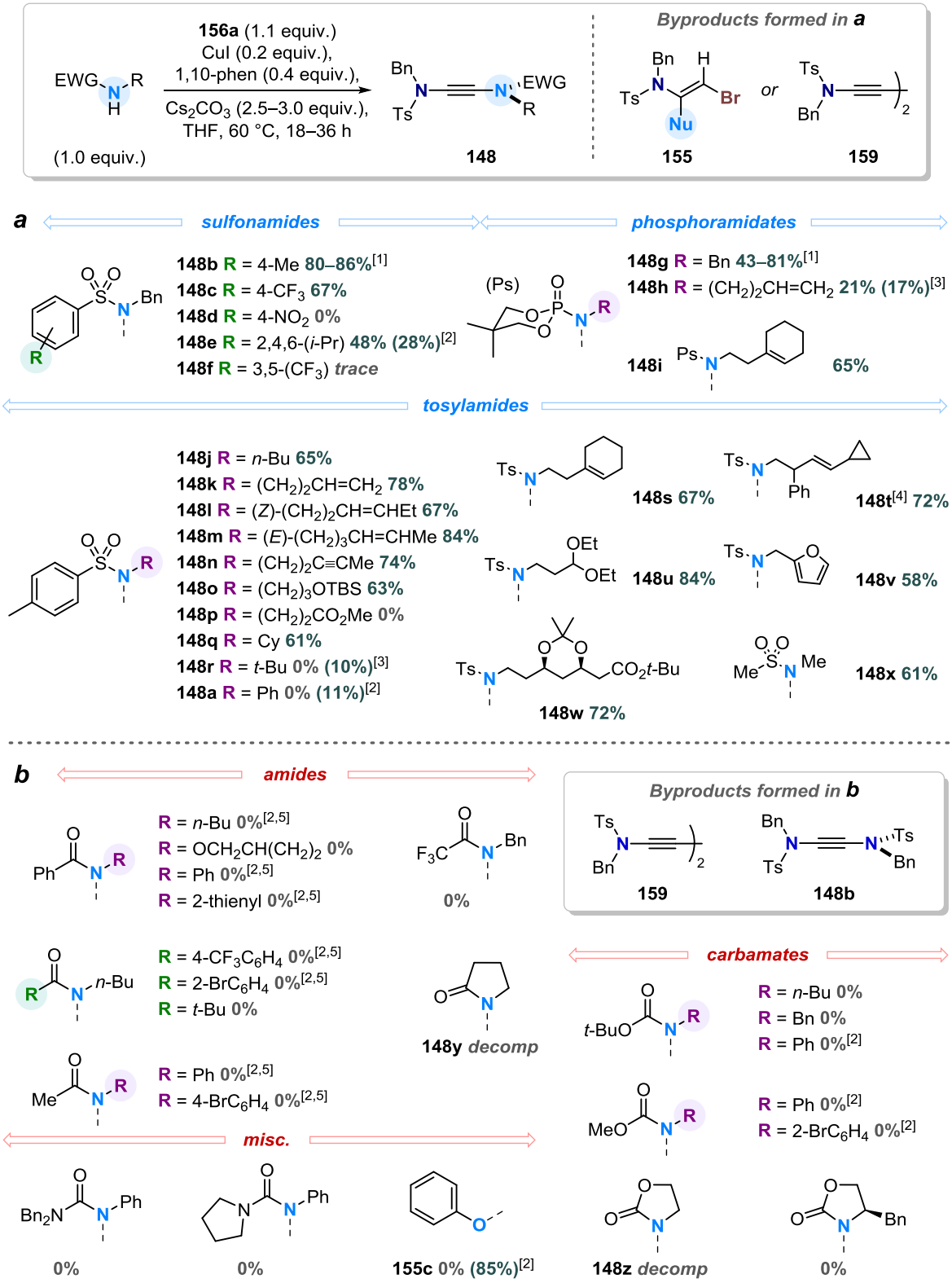


Figure 2.10: Scope of amide partners screened in the reaction, yields refer to the isolated yield of the corresponding yndiamide. **a**. scope of successful partners. **b**. scope of unsuccessful partners. [1] Yield over 3 runs; [2] The bromoketene aminal was formed in the reaction, isolated yield is in parentheses; [3] Diyne **159** was formed in the reaction, isolated yield is in parentheses; [4] The sulfonamide partner for **148t** was prepared by Kai Ma. [5] Yndiamide **148b** was formed in the reaction.

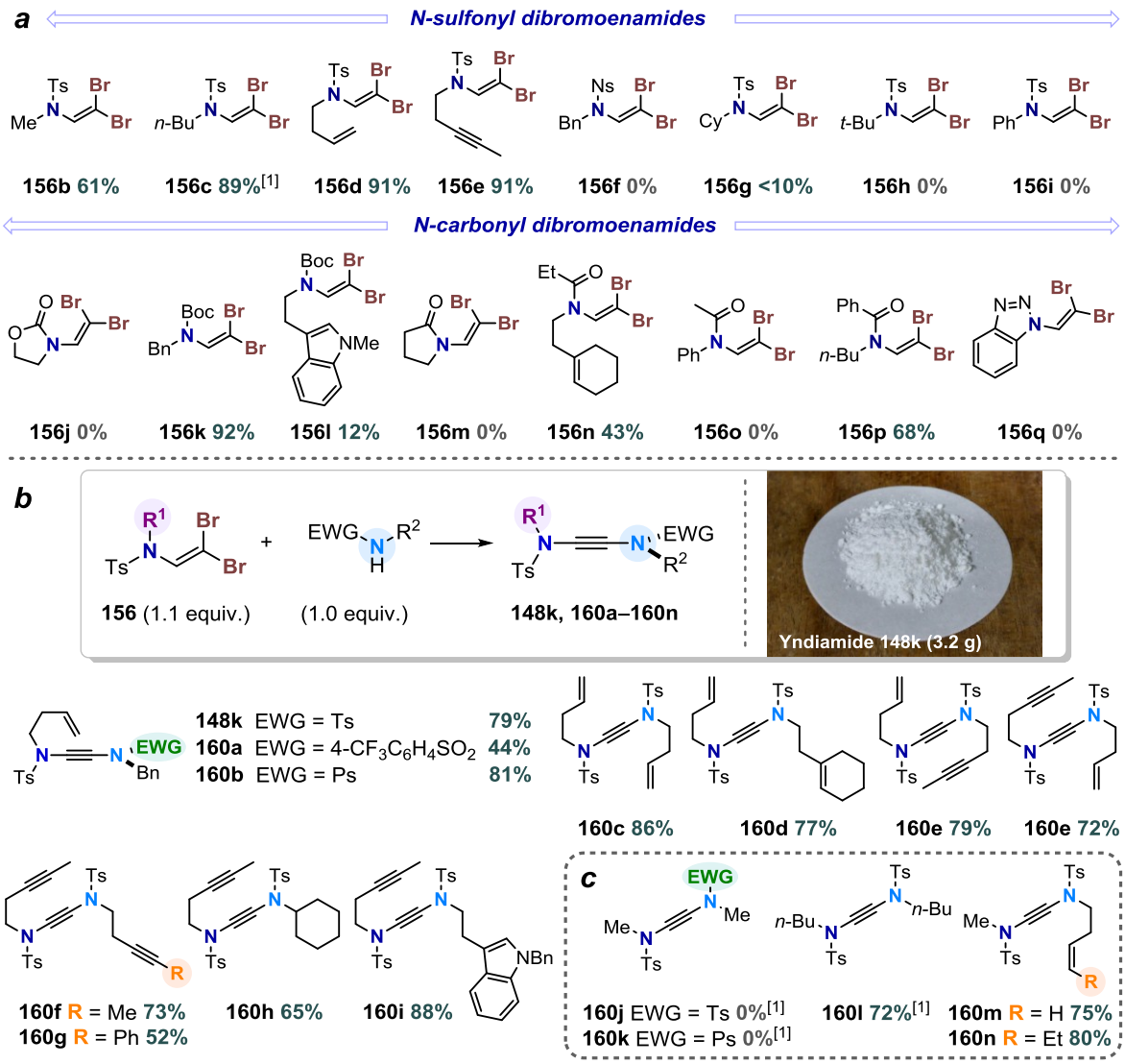


Figure 2.11: **a**. Dibromoenamides prepared in this study; **b**. scope of successful enamide partners; **c**. importance of alkylchain length. [1] These compounds were prepared by Olivia Garry. Yndiamides **160j** and **160k** were the major components in their respective crude reaction mixtures, as determined by ^{1}H NMR spectroscopic analysis. They were extremely sensitive to chromatography upon Et_3N-pretreated silica and only returned hydration and polymerisation products.

The flexibility of this approach to unsymmetrical yndiamides is also emphasised by compounds **148k** and **160e**, which were produced from either of their respective sulfonamide/enamide partners in comparable yields (**148k**: 78/79%; **160e**: 72/79%). Subsequent work also indicated a dependence of yndiamide stability on the bulkiness of the *N*-substituent (**c**, Figure 2.11). For example, whilst the *N*,*N*′-dimethyl yndiamides **160j** and **160k** could be prepared, as indicated by NMR spectroscopic analysis of the crude reaction mixtures, they were highly unstable and their isolation was fraught with difficulty. On the other hand, the dibutyl analogue **160l** displayed no such instability and was prepared and isolated without issue. This is reminiscent of the pyrrolidinone/oxazolidinone cases mentioned previously.

Before discussing possible mechanisms involved in these reactions, it is useful to provide a brief summary of key observations. Considering the conditions used, both anhydrous solvent and reagents were required to suppress degradation and hydrolysis of the dibromoenamide, and the proportion of yndiamide and bromoketene aminal formed in these reactions seemed to inversely correlate. A range of sulfonamides and *N*-sulfonyl dibromoenamides were readily converted to the corresponding symmetrical or unsymmetrical yndiamides, and purification can be achieved by chromatography upon silica gel in most cases. Furthermore, most of these compounds were air and bench-stable crystalline compounds and single crystal X-ray analysis showed that, like yndiamines, they also exhibit a twisted structure in the crystal lattice - this will be discussed in detail in Chapter 3. However, these reaction conditions were not applicable to *N*-carbonyl derivatives and, whilst this is not a surprise given their failure in related ynamide syntheses, the poor reactivity of *N*-carbonyl dibromoenamides was unexpected. Finally, the reactions with phosphoramidates were highly variable (for example, the isolated yields for **148g** ranged from 43–84%), which was partly attributed to an increased moisture sensitivity of the reaction.[98] Thus extra precaution was necessary to ensure the dryness of all reagents and solvent, including the phosphoramidate and dibromoenamide.

2.3c Further observations and mechanistic discussion.

During the course of this work, we certainly felt that the bromoketene aminals were more likely to be byproducts than intermediates, and their formation strongly implies the generation of a bromoynamide in the reaction (cf. the chloroketene aminals in Figure 2.3). The fact that increased amounts of base, increased water content and increased temperature all facilitated the formation of the aminal is consistent with increased rates of dehydrobromination of **156a** to give the bromoynamide **161**. It is striking that chloroynamides and (*E*)-/(*Z*)-1,2-dibromoenamides afforded analogous compounds in which Nu–H addition was exclusively *trans* (Figure 2.3 and Scheme 2.7). During our substrate scope investigation, the bromoketene aminals **155c**–**155e** also had geometries that are consistent with *anti*-addition (Figure 2.12). Given this evidence, we briefly revisited the synthesis of a bromoynamide in an attempt to understand the role it has in our reactions.

A range of conditions was screened in our attempts to prepare bromoynamide **161** from **155a**, including the use of Cs_2CO_3 in THF or DMF, aqueous KOH with TBAHS or $[BnEt_3N]Cl$,[211] TBAF, DBU, KO*t*-Bu or LiHMDS. Unfortunately, most led to decomposition or hydrolysis, and in the case with TBAF also gave a minor amount of a bromofluoroenamide. However, treatment of **156a** with LiHMDS gave full conversion to a single compound, as analysed by TLC (R_f 0.65, 15% v/v Et_2O/40-60 petroleum ether), which was suspected to be **161**. Attempted isolation of this compound resulted in spontaneous conversion to **162** (R_f 0.14 (15% v/v Et_2O/40-60 petroleum ether)) and its structure was determined unambiguously by single crystal X-ray analysis. This type

of haloalkyne dimerisation is known, but typically requires an electrophilic catalyst, such as Barluenga's reagent,[386] $[IPy_2][BF_4]$, or $IPrAuNTf_2$.[387] It is possible that Li^+ was sufficient to catalyse this reaction. The dimerisation of **161** was rapid and occurred upon warming or even slight concentration of the reaction mixture, but this could be minimised by dilution to <0.01 M. Attempted coupling of **161** only gave the dimer **162**, which was fully stable under the reaction conditions and did not undergo amidation or conversion to the diyne **159** (Scheme 2.9). However, these observations do not rule out the involvement of a bromoynamide in our reactions because it is entirely plausible that it was generated in sufficiently small quantities that other possible reaction pathways, e.g. nucleophilic addition (to afford the keteneaminals), amidative coupling (to form the yndiamide) or reductive coupling (to form a diyne) outcompeted dimerisation. Faced with the inherent difficulty of observing the reaction of small amounts of a bromoynamide in a heterogeneous reaction mixture, our efforts here came to an end.

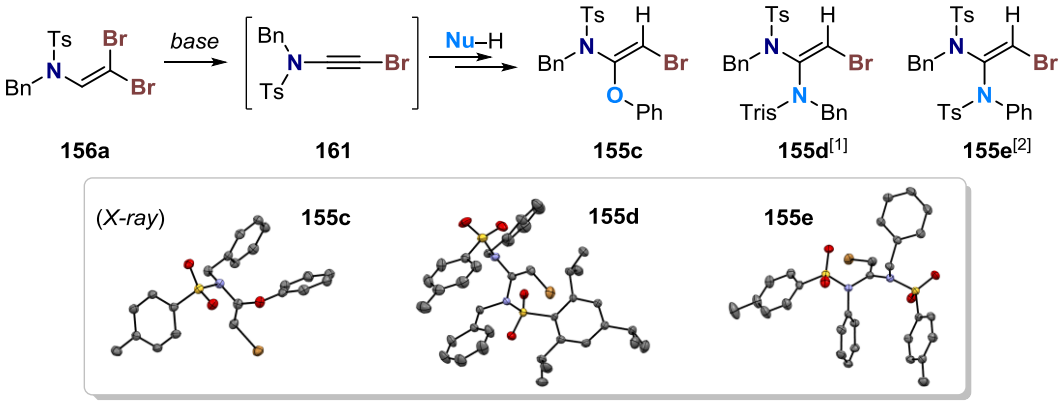
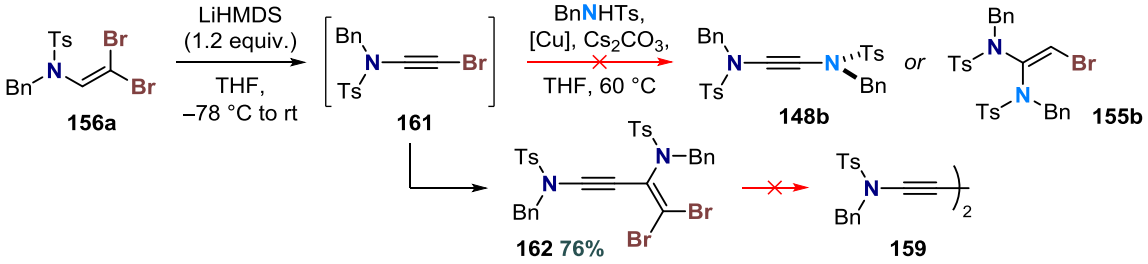


Figure 2.12: Bromoketene aminals formed during attempted yndiamide formation. [1] Tris = 2,4,6-tri-*i*-propylbenzene-sulfonyl; [2] Also prepared using the following conditions: PhNHTs (1.0 equiv.), **156a** (1.0 equiv.), Cs_2CO_3 (4.0 equiv.), DMF, 60 °C, 76% yield, (*E*)-:(*Z*)- 92:8; displacement ellipsoid plots are displayed at 50% probability. Hydrogen atoms and disordered components are omitted for clarity. X-ray data collection, processing and solution refinement for compound **155c** were performed by Dr Kirsten Christensen.

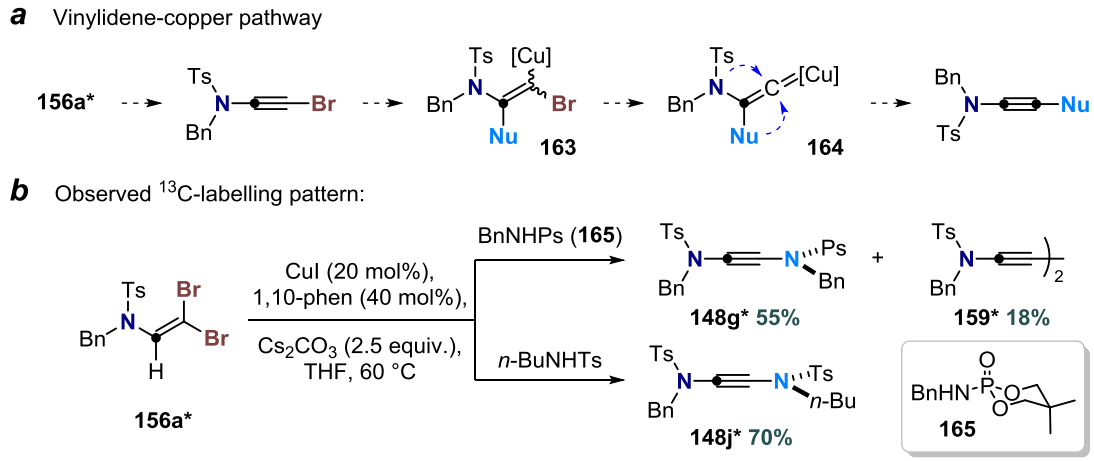


Scheme 2.9: Generation of bromoynamide **161** and conversion to dibromide **162**.

Our attention turned to the possibility of converting the bromoketene aminal to yndiamide **148b**.[262] Resubmission of **155b** to the coupling conditions gave no conversion, even at increased temperature or with increased amounts of Cs_2CO_3 (4.0 equiv.) and, curiously, the addition of silver salts had

minimal impact. Furthermore, attempts to force the FBW rearrangement also failed using KO*t*-Bu, LiHMDS, KHMDS or *n*-butyllithium, each only resulting in increased amounts of decomposition. Whilst these results strongly suggest that bromoketene aminals are not precursors to yndiamides in our coupling reactions, the intermediacy of a vinylidene species (i.e. FBW rearrangement) in the formation of the yndiamides could not be ruled out.

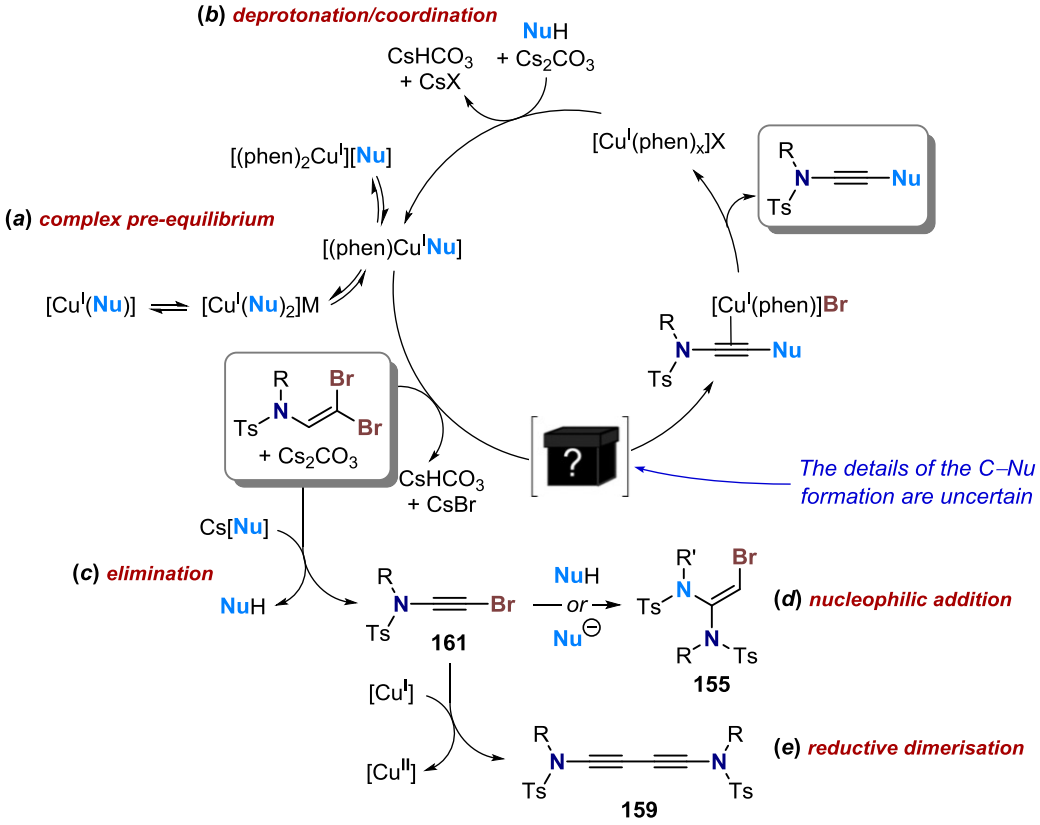
In considering a mechanism that proceeds via such a species, it is possible that amido-cupration (*anti* or *syn*-addition) across the alkyne of a bromoynamide would afford a vinylcopper species **163**,[388] which upon α-elimination of bromide would lead to the vinylidene-copper complex **164** (**a**, Scheme 2.10). A 1,2-shift of either amido group would then afford the yndiamide. Here we assume that both amido groups have a roughly equal propensity for this migration. If this were the case, then the use of ^{13}C-labelled **156a*** would give ^{13}C-enhancement of both alkyne carbons in the product. To test this, **156a*** was prepared and reacted with *N*-*n*-butyl tosylamide and *N*-benzyl phosphoramidate **165**. The products **148g***, **148j*** and **159*** each had only one enhanced ^{13}C resonance, and further analysis using ^{1}H-^{13}C coupling (both **148g*** and **148j*** had J_{CH} = 4.6 Hz) showed that the label had remained in place during the reaction. Given this cumulative evidence, it is likely that neither a bromoketene aminal nor a vinylidene species are intermediates en route to the yndiamide.



Scheme 2.10: **a**: Proposed mechanism via a copper-carbenoid; **b**: Observed position of the ^{13}C-label is shown with a black dot.

As an aside, it is worth noting that the ^{13}C NMR spectrum of the crude phosphoramidate-containing reaction mixture also showed a small amount of a fourth ^{13}C-labelled compound, identified only by the presence of a peak at δ_C = 72.1 ppm (in $CDCl_3$). After discounting many potential side products, it is possible that this corresponded to the alkyne carbon α- to nitrogen in the bromoynamide **163**. However, the compound could not be isolated and was probably only visible by virtue of the ^{13}C-enhancement.

Having discounted the involvement of bromoketene aminals in the formation of yndiamides, we considered the overall mechanism for yndiamide formation. Scheme 2.11 provides an overview of events that can be inferred from the literature and proposed from our own observations. Extensive work[114,389–392] on the Goldberg (Ullmann) reaction has shown that there is a complex equilibrium between various copper species in these reactions (**a**, Scheme 2.11),[393] and it is strongly believed that complexes of the form $[L_2Cu(NR_2)]$ are the true reactive species in these reactions.[394–396] Unlike with palladium catalysis, one role of the ligand is to compete with the N–H nucleophile for binding at copper and, in the absence of ligand, there is a preferential formation of homoleptic $[Cu(NR_2)_2]^-$ complexes, which are inert in amidative coupling reactions.[397,398] In cases where the rate of N–H deprotonation exceeds the rate of C–N coupling, there is increased formation of the unreactive $[Cu(NR_2)_2]^-$, which retards the overall reaction.[146,396,397] This would explain why a particular base can be more effective in certain cases[134,399] by enabling a better match between the rate of N–H deprotonation and C–N coupling.



Scheme 2.11: Putative reaction mechanism for yndiamide formation.

An important factor would, therefore, be the N–H acidity (**b**, Scheme 2.11).[400] There is a tendency for highly acidic N–H nucleophiles to be deprotonated prior to coordination to copper,[389] but for weakly acidic species, the formation of the copper-amidate complex can become a bottleneck for the reaction; in these cases, coordination of the amide to copper may be required to facilitate deprotonation. In our chemistry, both sulfonamides and phosphoramidates are more acidic (pK_a

15–20 in DMSO) than *N*-carbonyl derivatives such as acyclic amides or carbamates (pK_a 20–25 in DMSO), and it is possible that the mechanism for the formation of their respective copper-amidate species is different - the latter possibly requiring pre-coordination to copper.

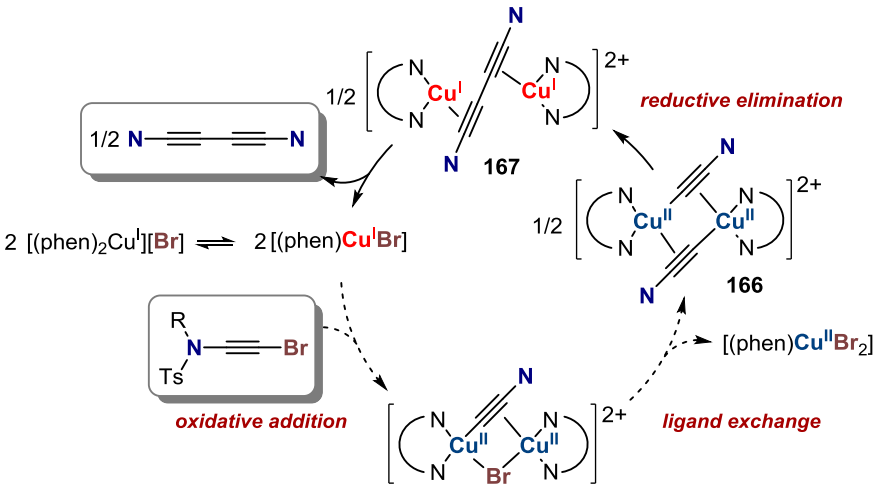
These considerations might also provide a possible explanation for why bromoketene aminals form (or do not form) in our reactions. Previous observations strongly suggest that excess amidate was responsible for the conversion of the dibromoenamide to the bromoynamide (**c**, Scheme 2.11), which reacts with a suitable nucleophile to give the bromoketene aminal (**d**, Scheme 2.11). This could be a feedback cycle that shifts the equilibrium back towards the more reactive [(phen)Cu(NR_2)] species, and lends credence to the fact that increased Cs_2CO_3 and increased water led to increased amounts of bromoketene aminal.

In contrast to the coupling reactions of sulfonamides, the reactions of phosphoramidates and *N*-carbonyl derivatives produced only the diyne **159** as the byproduct. In the latter cases, the reactions tended to stall after 18 hours, and the diyne was isolated in 10–18% yield. It is, therefore, interesting to consider whether the bromoynamide **161** was a common precursor for both the bromoketene aminal and diyne byproducts. If so, the formation of the diyne might indicate cases where reductive dimerisation outcompetes nucleophilic addition (**e**, Scheme 2.11). Indeed, in the absence of copper, the reactions using phosphoramidates did not produce any bromoketene aminal and only resulted in significant decomposition of the dibromoenamide. Assuming that a bromoynamide was formed, this might imply that phosphoramidates are less able to undergo nucleophilic addition onto the alkyne. On the other hand, as shown in Figure 2.10, the attempted couplings of *N*-phenyl tosylamide (**148a**) and *N*-benzyl tri-*i*-propylbenzenesulfonamide (**148e**) produced significant amounts of aminal instead of the desired yndiamide, which could indicate cases where coordination to copper is less favoured. By extrapolating these ideas further, it is possible that *N*-carbonyl derivatives were insufficiently nucleophilic to react with either the alkyne or copper.

These observations raised the following questions: how does dimerisation occur and do these reactions stall as a result of diyne formation? In the former case, a mechanism akin to the Glaser-Hay couplings was envisaged (Scheme 2.13),[172,173] in which the dimerisation of copper(II) acetylides **166** leads to the bis-copper(I)-diyne complex **167**. Concerning the latter question, we suggest that if this is so, it could either be due to competitive binding of the diyne to the copper species or, assuming the reduction is mediated by copper, that regeneration of copper(I) is somehow retarded.[393,401]

To gain some insight in this regard, the reaction between phosphoramidate **168** and dibromoenamide **156a** was briefly reinvestigated using sodium ascorbate (0.2 equiv.) as a reducing agent. Upon completion of the reaction, visual inspection of the final mixture indicated a potential difference in outcome (**a**, Figure 2.13). The pale blue precipitate/pale yellow solution is typical for the reactions

that produce diyne and the dark blue precipitate/brown solution is typical for those reactions that do not (e.g. with sulfonamides). Indeed, ^{1}H NMR spectroscopic analysis confirmed that the use of sodium ascorbate had suppressed the formation of the diyne (**b**, Figure 2.13) and, whilst this did not significantly increase the amount of yndiamide, it did suppress decomposition of the dibromoenamide. Increasing the amount of sodium ascorbate from 0.2 equiv. to 1.0 equiv. (in 0.2 equiv. increments) did not improve upon this and led to a steady increase in the amount of diyne (from 0% to 17%). This reaction was not investigated further but leaves the role that ascorbate plays open to investigation.



Scheme 2.12: Putative mechanism for the reductive dimerisation of a bromoynamide. Conversion of **166** to **167** is known for analogous Glaser-Hay couplings using tmeda as the ligand.[172,173]

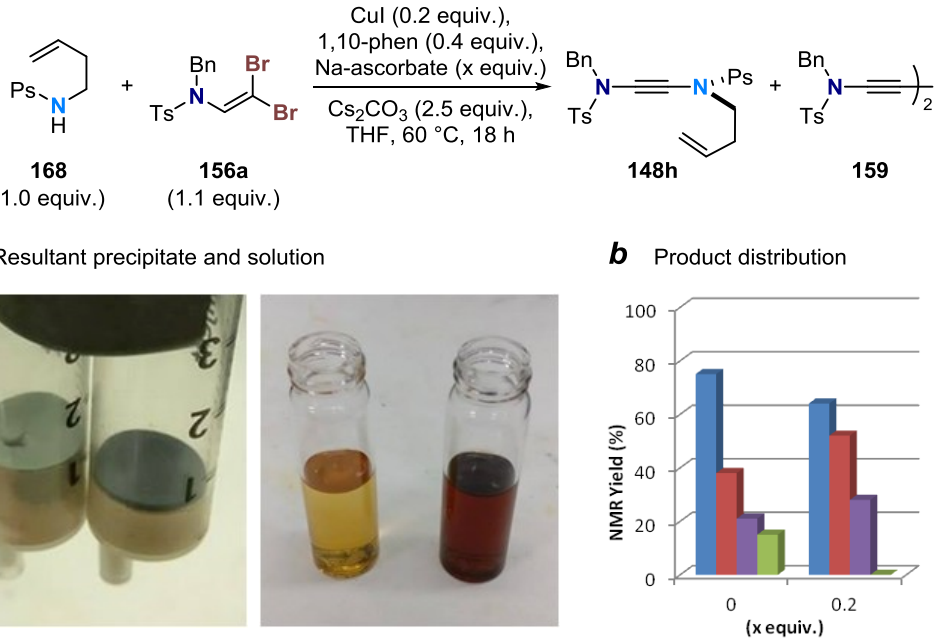
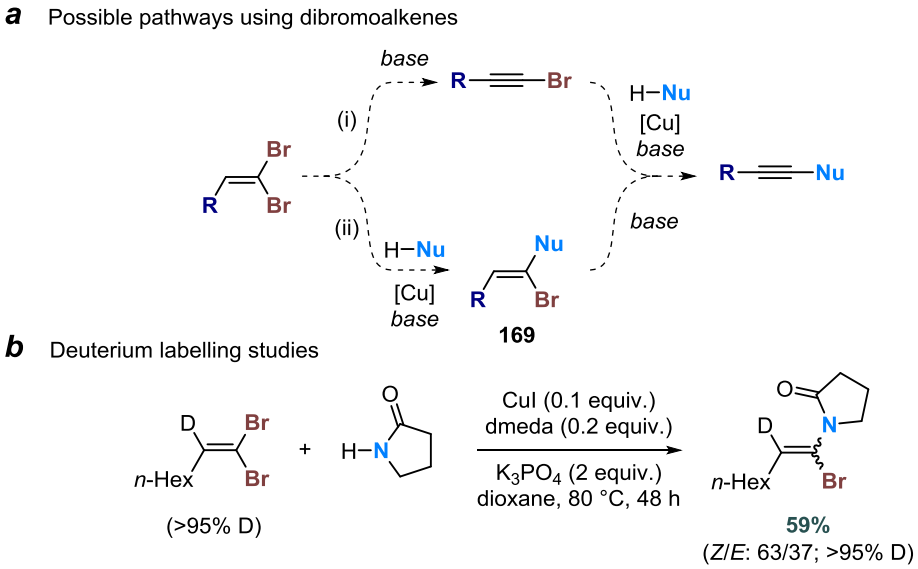


Figure 2.13: Reaction of **168** and **156a** in the absence or presence of ascorbate. **a**: (*left*) resulting precipitate without (left) and with (right) Na-ascorbate; (*right*) reaction solution without (*left*) and with (*right*) Na-ascorbate; **b**: Distribution of compounds after 18 hours.

Returning to the mechanism shown in Scheme 2.11, there remains one final question: "What is happening inside the black box?" Two possible explanations are: (i) formation of a bromoynamide that undergoes C–N coupling (or amido-cupration/elimination, c.f. Chapter 1); or (ii) direct C–N coupling to give the bromoenamide **169**, followed by elimination of HBr (**a**, Scheme 2.13). The closest related study from the Evano group used deuterium labelled 1,1-dibromoalkenes, which showed that direct C–N coupling occurred prior to dehydrohalogenation to give ynamides (**b**, Scheme 2.13);[47] furthermore, bromoalkynes were not detected in their reactions.[147] This is contrary to observations made in our reactions - intermediates such as **169** have never been observed and there is strong evidence for the generation of bromoynamides. This, of course, cannot discount a mechanism via pathway (ii), but it currently seems more likely that the formation of a bromoynamide is important, particularly when considering the complete lack of reactivity observed with *N*-carbonyl dibromoenamides.[202] The Hsung coupling is the closest system that involves a bromoalkyne (Chapter 0), but no studies have been performed to elucidate the mechanism of this or any reaction that uses bromoalkynes.



Scheme 2.13: Comparison between possible reaction pathways for dibromoalkenes and observed deuterium-labeling pattern of products.[47]

Unlike the reactions of 1,1-dibromoalkenes, which often require a strong σ-donating ligand (dmeda),[402] the reactions of 1,1-dibromoenamides had an absolute preference for 1,10-phenanthroline - arguably a poorer σ-donor and an effective π-acceptor ligand. By analogy to copper-catalysed Ullmann couplings of aryl halides,[403] the mechanism of C–Br bond activation is likely determined by the electron-donating ability of both the ligand and nucleophile. An exploration of phenanthroline derivatives and analogues could enable a greater understanding of its role in our reactions but, as of yet, there is no consensus as to how phenanthroline influences any of the copper-catalysed C–N bond formations.[401–406]

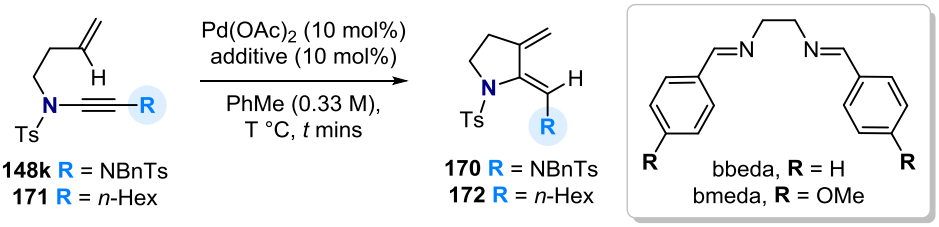
2.4 The chemistry of yndiamides.

Ynamides have proven to be valuable building blocks in organic synthesis.[45,46,51] Given such interest in nitrogen-substituted alkynes, we took the opportunity to begin exploring the chemistry of yndiamides. We were particularly interested in comparing their reactivity with their ynamide cousins and, given the breadth of potential chemistry available to explore, we chose to examine their application in selected transition metal and Brønsted acid catalysed transformations.

2.4a Cycloisomerisation and other transition metal catalysed transformations.

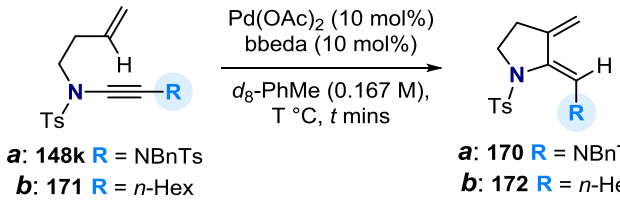
There has been a long-standing interest in the Anderson group to use ynamides in the preparation of azacycles.[31–37,407] Chief amongst the methods developed were the cycloisomerisation reactions of enynamides,[33,36,37,407] which exhibit complete atom economy in the conversion of starting materials to the cyclic product. A number of the yndiamides prepared in this study were designed with pendant alkene functionality in anticipation of their application in cycloisomerisation reactions, and this would enable a comparison between the reactivity of ynamides and yndiamides.

These studies began by evaluating the cyclisation of yndiamide **148k** with the conditions optimised for ynamides (entry 1, Table 2.3). This led to complete conversion of **148k**, but the reaction took significantly longer than that of ynamide **171** (entry 2, Table 2.3). Furthermore, where the cycloisomerisations of ynamide **171** were "spot to spot" as judged by TLC analysis, the analogous reactions of the yndiamide gave a number of side products, but these were in small amounts and could not be identified. A selection of other ligands, which are also effective in related enyne cycloisomerisations, was also employed in this reaction (entries 3–5)[408–413] but none outperformed the use of bbeda. The effect of temperature was also remarkable: at 35 °C there was incomplete conversion of the yndiamide after 4 hours, and the reaction was heated overnight (12 hours) to achieve full conversion (entry 6); however, the related ynamide required only 10 minutes using half the catalyst loading (entry 7). TLC analysis of the reaction mixture in entry 1 at 5-minute intervals indicated that unlike with the reaction of ynamide **171**, which only had a slight induction period, the reaction of yndiamide **148k** had a significant induction period of about 10 minutes before any significant product formation occurred. Intrigued by these observations, the reaction was monitored using ^{1}H NMR spectroscopy and the results are shown in Figure 2.14. As expected from our previous analysis, the reaction of the yndiamide indeed shows an induction period of between 8–12 minutes. In this period, only 2–5% of the product is obtained at the expense of 10–15% of starting material. A similar observation can be made for the ynamide, albeit to a lesser degree. This brings into question the mechanism of initiation for these reactions and the potential involvement of the starting material, but the details of this step remain unclear.



entry	substrate	ligand (mol%)	T (°C)	*t* (mins)	isolated yield (%)
1	**148k**	bbeda (10)	60	40	73 (75)[1]
2	**171**	bbeda (10)	60	<10	83 (89)[1]
3	**148k**	bmeda (10)	60	40	62
4	**148k**	PPh_3 (20)	60	40	69
5	**148k**	P(*o*-tol)$_3$ (20)	60	120	*n.d.*[2]
6[3]	**148k**	bbeda (10)	35	<720	(70)[1]
7[4]	**171**	bbeda (5)	35	10	(85)[1]

Table 2.3: Enyne cycloisomerisation. [1] Yields in parentheses were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, using 1,2,4,5-tetrachloronitrobenzene as the internal standard. [2] *n.d.* = not determined, the reaction gave very poor conversion after 2 hours and gave many byproducts; [3] Performed using d_8-toluene (0.167 M); [4] $Pd(OAc)_2$ (5 mol%) was used with d_8-toluene (0.167 M); see ref [36].



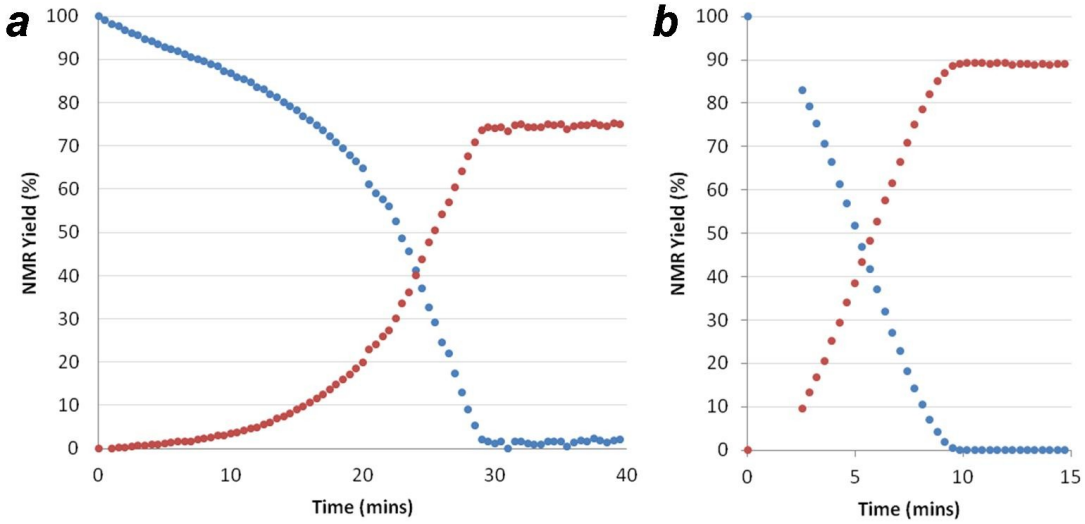


Figure 2.14: Reaction profiles for the conversion of enyn(di)amide (blue) to pyrrolidine (red); determined by ^{1}H NMR spectroscopic analysis. **a**: performed using yndiamide **148k** at 60 °C; **b**: performed using ynamide **171** at 35 °C. NMR spectroscopic data were collected by Dr Aroonroj (Yao) Mekareeya.

Furthermore, whilst the reactions with ynamides are often significantly slower in the absence of bbeda,[36] the opposite was the case with **148k** and the cycloisomerisation was *significantly* faster without bbeda (Figure 2.15). Within 5 minutes, there was 61% conversion of starting material and 37% of the expected product. In this time, a second product was also formed (14%), which, alongside unreacted **148k**, was the major species at the end of the reaction. ^{1}H NMR spectroscopic and mass spectrometric analyses were sufficient to identify this product as imine **173**, but hydrolysis of this during chromatography afforded the aldehyde **174**. This unexpected outcome further brings into question what the role of bbeda is in these reactions.

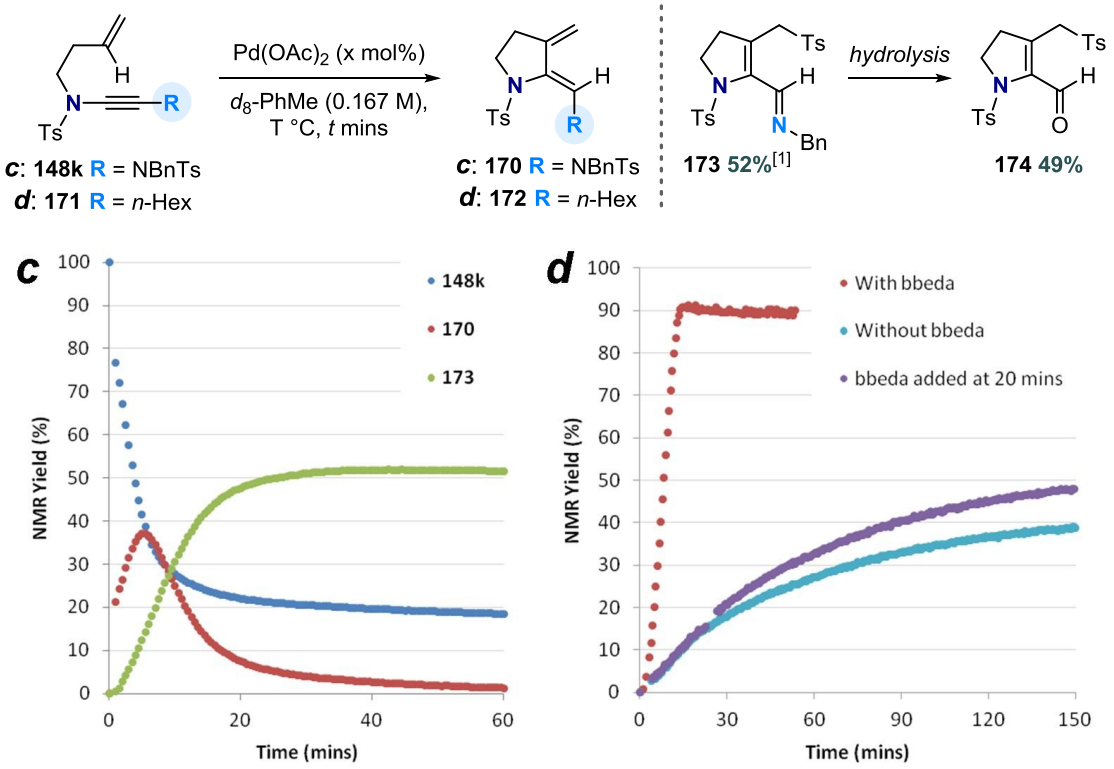
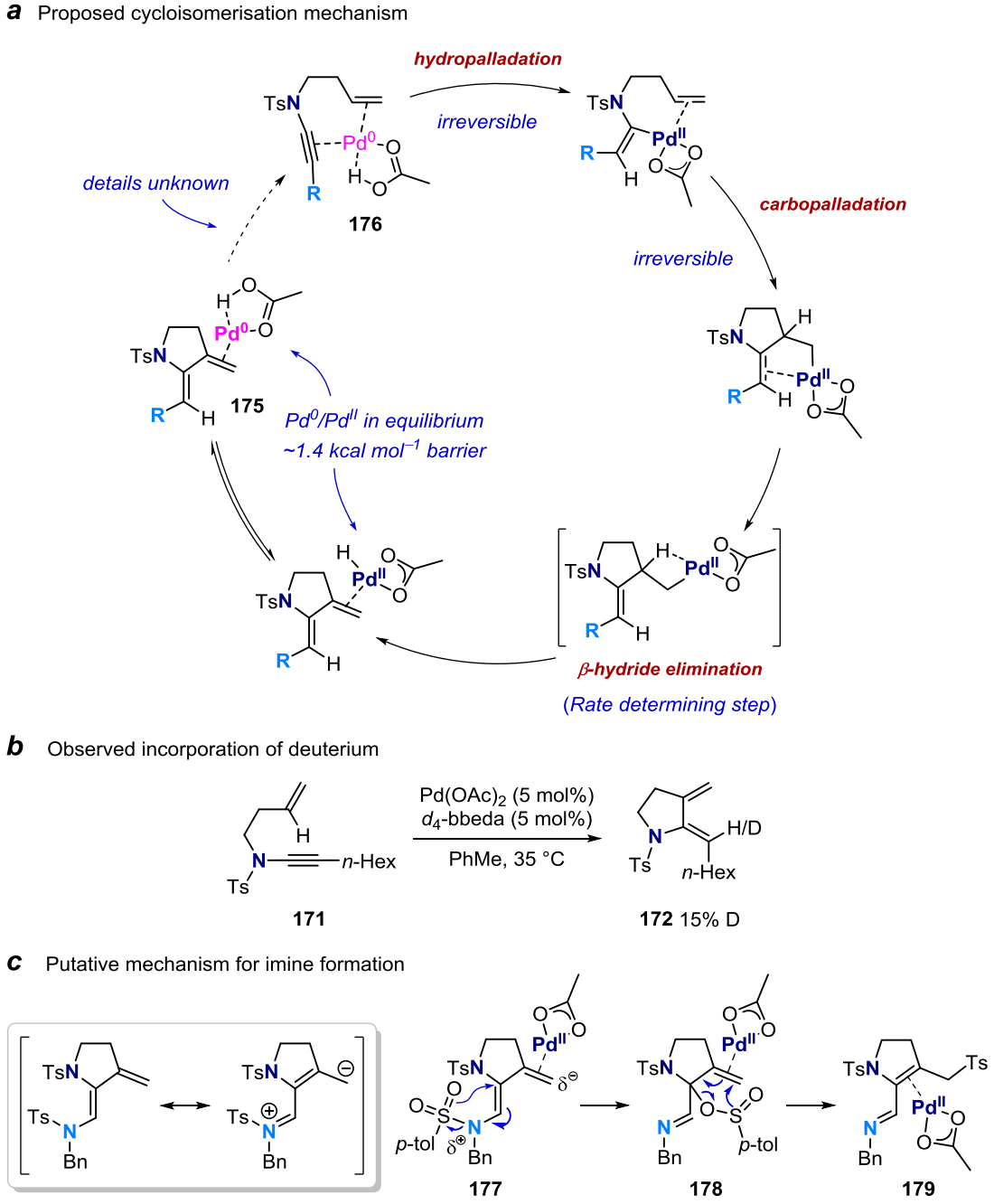


Figure 2.15: Reaction profiles for the conversion of enyn(di)amide to pyrrolidine (red) without bbeda; [1] yield determined by ^{1}H NMR spectroscopic analysis. **c**: *Conditions*: yndiamide **148k**, $Pd(OAc)_2$ (10 mol%), d_8-toluene, 60°C; **d**: ynamide **171**, $Pd(OAc)_2$ (5 mol%), d_8-toluene, 35 °C. NMR spectroscopic data were collected by Dr Aroonroj (Yao) Mekareeya.

Considering the cycloisomerisation reaction of *ynamides* in more detail, previous investigations in the Anderson group provided strong evidence for a mechanism involving regioselective hydropalladation of the ynamide,[36] and a full outline of the proposed mechanism is detailed in Scheme 2.14a. In these reactions, a neutral [Pd(0)(AcOH)] complex is purported to be the active catalytic species and, though its origins have not been confirmed, it is likely to arise from a reaction between bbeda and the in situ generated $[Pd_3(OAc)_5OH]$ (from $[Pd(OAc)_2]_3$ and water).[414] Indeed, increased water content in the reaction was found to accelerate the rate of cycloisomerisation, and the use of d_4-bbeda led to ~15% deuterium incorporation into the product (**b**, Scheme 2.14). Bbeda

is also unrecoverable at the end of these reactions and it is possible that it, or derivatives thereof, may also be involved in catalyst turnover. A related cycloisomerisation pathway involving a bbeda-complexed, cationic Pd(II)–H complex was calculated to be feasible, albeit less supported by experimental evidence. In any case, the initial ynamide hydropalladation is followed by alkene carbopalladation, both of which were calculated to be essentially irreversible, and subsequent β-hydride elimination was found to be the rate-limiting step in this process - enamide decomplexation and C–C rotation is required to align the C–Pd bond *syn*-coplanar with the C–H bond.



Scheme 2.14: **a**: Ynamide cycloisomerisation reaction mechanism, see ref [36] for details; **b**: Deuterium incorporation from d_4-bbeda; **c**: Proposed mechanism for sulfonyl migration. In general, the terminal alkene possessed increased reactivity towards electrophiles than the endiamide, as suggested by the resonance form shown (see later discussions).

Nevertheless, catalyst turnover from the product-palladium complex **175** to the substrate-palladium complex **176** is likely to be product dependent. For the yndiamide, one could assume that the extra nitrogen substituent would render the product enamide **170** more electron rich and more sterically hindered than for the ynamide case. The former would make spontaneous catalyst decomplexation more difficult, but if turnover required the involvement of an external species, e.g. a second molecule of substrate or bbeda, then the steric bulk of the nitrogen substituent would also affect this. Our observations would, therefore, support a proposal in which bbeda competes with the enamide (and substrate) for coordination to palladium. In the absence of bbeda, the product enamide could re-coordinate to a palladium(II) species at the terminal alkene (**c**, Scheme 2.14). Migration of the tosyl group could occur via fragmentation/recombination of a sulfonium ion,[415–420] or via two sequential [2,3]-sigmatropic shifts (**177**–**179**, Scheme 2.14).[421,422] Nevertheless, this is a new mode of reactivity for cycloisomerisation reactions and would require further study to elaborate its potential application.

A selection of other enyndiamide substrates was next subjected to palladium-catalysed cycloisomerisation (Table 2.4). In comparison with previous observations, we observed a marked enhancement of the reaction rate upon replacement of the groups on the exocyclic nitrogen (entries 1 and 2). For example, switching from a tosyl to a cyclic phosphoryl group halved the reaction time and gave a highly reactive product (**180**) that defied isolation. Similarly, replacing the *N*-benzyl group for a methyl substituent gave a yet faster rate of cycloisomerisation that was much more in line for "typical" ynamides. This product (**181**) was also highly reactive and was trapped with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to give cycloadduct **182** in 51% yield (**a**, Scheme 2.15). This further supports our previous conclusions that steric factors play an important role here.

Comparing entries 3 and 4, we observed a similar steric effect affecting the product distribution. Additionally, there is also a choice in the β-hydride elimination step and a 1,3-diene or (*E*)-/(*Z*)-1,4-dienes are possible products resulting from this (**b**, Scheme 2.15). However, there was no 1,3-diene product observed, and the reaction of **148l** gave an 81:15:4 ratio of (*E*)-**183**:(*Z*)-53:1,5-diene; the latter likely resulting from reversible β-hydride elimination. The *N*-methyl analogue **160n** reacted at a significantly faster rate, and gave an 89:11 ratio of (*E*)-**184**:(*Z*)-**184**. No 1,5-diene was observed. On the other hand, cyclohexene **148s** gave a significant proportion of the 1,5-diene (15%) (entry 5) and these observations all seem to indicate a strong product dependence on catalyst turnover. Extending the ene-yndiamide tether length was also successful, albeit slower, and resulted in the formation of piperidine **186** (entry 6) as a mixture of 1,3- and 1,4-dienes. The reaction of **148t** also demonstrated a high level of substrate stereocontrol (entry 7), in which the triene **187** was formed as a single diastereomer at the newly formed centre, although with a ~1:1 mixture of alkene geometries.

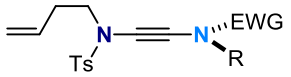
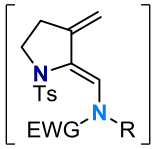
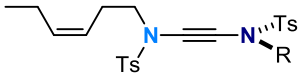
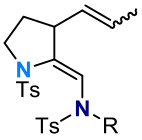
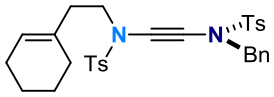
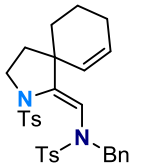
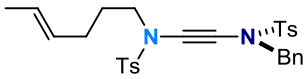
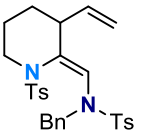
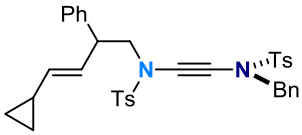
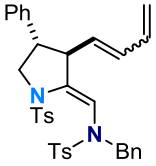
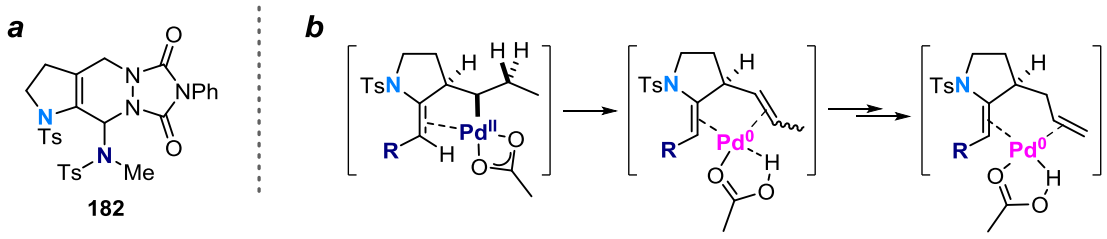
entry	substrate		*t* (mins)	major product		isolated yield (%)[1]
1		**160b** EWG = Ps R = Bn	20		**180**	(58)[2]
2		**160m** EWG = Ts R = Me	10		**181**	(62)[2]
3		**148l** R = Bn	30		**183** R = Bn	79[3]
4		**160n** R = Me	<10		**184** R = Me	80[4]
5		**148s**	30		**185**	73[5]
6		**148m**	90		**186**	72[6]
7		**148t**	60		**187**	66[7]

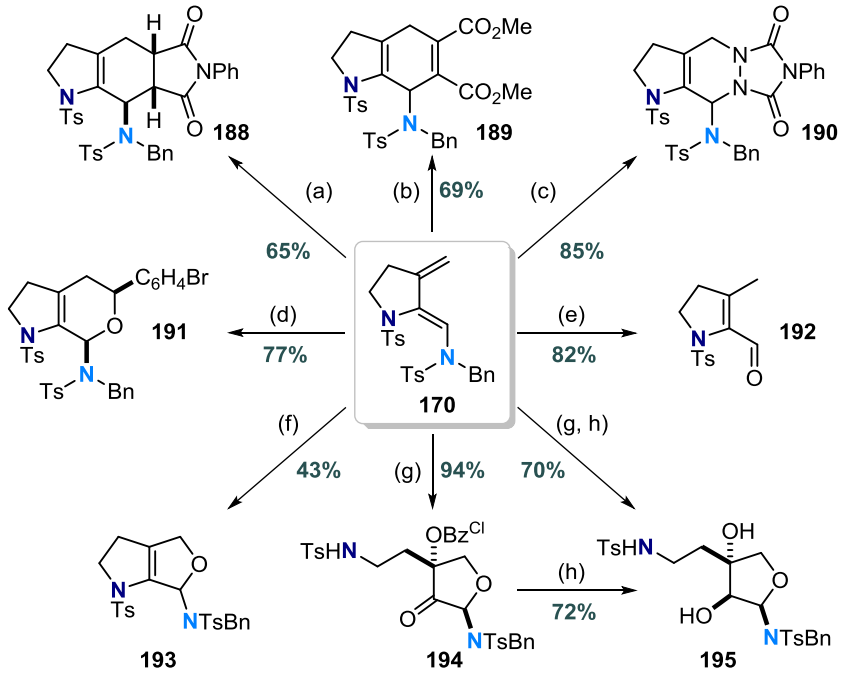
Table 2.4: Application of enyndiamides in cycloisomerisation reactions. *Conditions*: $Pd(OAc)_2$/bbeda (10 mol%), PhMe (0.33 M), 60 °C; [1] In cases where a mixture of alkene isomers was formed, the isolated yield refers to the combined yield of the mixture of isomers, which were not separable. All product ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction and did not change upon isolation of the mixture. [2] Yield in parentheses determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, using 1,2,4,5-tetrachloronitrobenzene as the internal standard; [3] 81:15:4 (*E*)-**183**:(*Z*)-**183**:1,5-diene; [4] 89:11 (*E*)-**184**:(*Z*)-**184**; [5] 85:15 **185**:1,5-diene; [6] 85:15 **186**:1,3-diene; [7] 57:43 (*Z*)-**187**:(*E*)-**187**.



Scheme 2.15: **a**: Cycloadduct of **181** and PTAD; **b**: β-hydride elimination can afford regioisomeric alkene products.

With a range of diamido-diene products in hand, time was taken to investigate their reactivity further.[32] Diene **170** was a potent substrate for Diels-Alder reactions and underwent [4+2] cycloadditions with a number of dienophiles to give heterocycles **188**–**190**. The direct reaction between **170** and 4-bromobenzaldehyde was unsuccessful at room temperature, and upon heating led to degradation, but the use $BF_3{\cdot}OEt_2$ at -78 °C was extremely effective, affording **191** as a single

regio- and diastereoisomer - a result that shows the powerful donating effect of the exocyclic enamide compared to the pyrrolidine nitrogen atom. The related reaction of an ynamide-derived diene showed the same regioselectivity,[35] a result that further indicates that there is negligible conjugation of the endocyclic nitrogen lone pair into the diene π-system. This is very likely a conformational effect, in which the 5-membered ring twists to minimise $A^{1,3}$ strain between the pyrrolidine tosyl group and the alkene substituent. In the solid state, dienes **183**–**187** also adopted a conformation that places this tosyl group in a pseudo-axial position (Figure 2.16). Acid hydrolysis of **170** was also highly regioselective and afforded enal **192** exclusively.



Scheme 2.16: Chemistry of 1,3-diene **170**; *Conditions*: (a) *N*-phenyl maleimide (1.0 equiv.), PhMe, 60 °C; (b) $MeO_2CC{\equiv}CCO_2Me$ (1.0 equiv.), PhMe, 60 °C; (c) PTAD (1.0 equiv.), PhMe, 21 °C; (d) 4-BrC_6H_4CHO (1.1 equiv.), $BF_3{\cdot}OEt_2$ (0.5 equiv.), CH_2Cl_2, –78 °C; (e) CF_3CO_2H (2.0 equiv.), CH_2Cl_2, –60 °C; (f) *m*-CPBA (1.5 equiv.), CH_2Cl_2, –78 °C; (g) *m*-CPBA (5.0 equiv.), CH_2Cl_2, –78 °C; (h) $NaBH_4$ (5.0 equiv.), $MeOH/CH_2Cl_2$, rt, then 15% NaOH (aq.), rt. Bz^{Cl} = 3-ClC_6H_4CO.

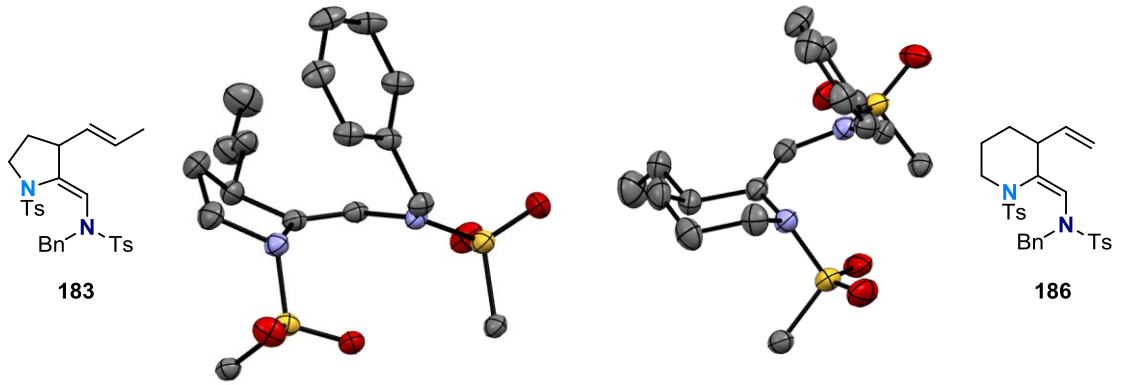
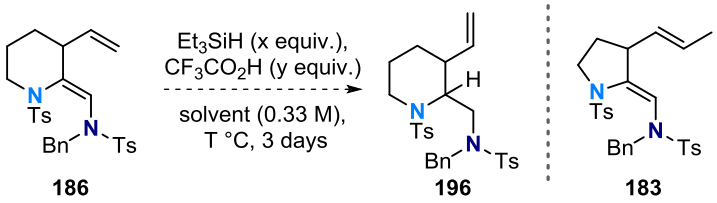


Figure 2.16: Solid state conformation of dienes **183** (left) and **186** (right). Displacement ellipsoid plots are displayed at 50% probability. Disordered components, *p*-tolyl groups and hydrogen atoms are omitted for clarity.

However, it was the reaction of **170** with *m*-CPBA that sparked an exciting voyage of serendipity. Treatment of **170** with 1.5 equiv. of *m*-CPBA gave incomplete conversion and afforded two products, the major being the heterocycle **193**, isolated in 43% yield. The minor product was too impure to determine its structure unambiguously but NMR and IR spectroscopic analyses indicated the presence of two carbonyls, one an ester (δ_c = 164.0 ppm, ν_{max} = 1782 cm^{-1}) and the other ketonic (δ_c = 204.3 ppm, ν_{max} = 1718 cm^{-1}). The reaction was repeated and the crude mixture was carefully treated with $NaBH_4$ to give an alcohol, which was hoped to be of sufficient polarity to enable separation. This was not the case and the crude mixture was treated with aqueous sodium hydroxide to hydrolyse the ester, which gave a compound that was separable from the detritus. NMR spectroscopic and X-ray crystallographic analysis showed this to be compound **195**, formed as a single diastereomer. Upon reinvestigation, treatment of diene **170** with 5.0 equiv. of *m*-CPBA afforded ketone **194** in 94% yield, which was readily converted to the tetrahydrofuran **195** (72% yield). In situ reaction of **194** was also possible and gave compound **195** in 70% isolated yield over two steps. Overall, yndiamide **148k** was converted to a single diastereomer of a highly functionalised amino-sugar analogue in 53% yield, via a four-step, two-pot operation. This showcases the potential value of yndiamides in organic synthesis.

Similarly, 1,4-dienes **183** and **186** are also potentially interesting fragments for drug discovery,[423–425] especially considering that diastereoselective endiamide reduction would give access to chiral 1,2-diamine derivatives. Given the reported success of enamine/acetal reduction using hydrosilanes and acids,[426–428] a variety of conditions were evaluated and are briefly summarised in Table 2.5.



186 **196** **183**

entry	substrate	Et_3SiH (x equiv.)	CF_3CO_2H (y equiv.)	solvent	T (°C)	Conversion (yield)[1]
1	**186**	6	10	CH_2Cl_2	21	19 (<5)
2	**186**	6	10	$(CH_2Cl)_2$	60	83 (12)
3	**186**	12	20	$(CH_2Cl)_2$	60	>90 (<5)
4	**186**	12	20	PhMe	60	>90 (8)
5	**183**	12	20	$(CH_2Cl)_2$	60	>90 (<5)

Table 2.5: Summary of conditions for the reduction of 1,4-dienes **183** and **186**. [1] Conversions estimated by ^1H NMR spectroscopic analysis of the crude reaction mixture, these values are approximate due to overlapping resonances. Furthermore, the yields reported are not accurate as the products contained significant impurities.

Overall, these compounds were prone to non-specific decomposition and, although conversion could be maximised upon heating, the products were isolated in low yield and with low purity (estimated to be ~75% pure by ^{1}H NMR spectroscopic analysis). Other acids either gave very poor conversion (*rac*-BINOL phosphoric acid, *p*-toluenesulfonic acid, or HCl solution in dioxane) or decomposition (triflic acid or bistriflimide) and other silanes (tris(trimethylsilyl)silane or tetramethyldisiloxane)[429] were less effective than triethylsilane. Our efforts ceased here, but alternative methods such as hydrogenation[430,431] or detosylation and in situ reduction could be more successful.

Having explored palladium-catalysed enyne cycloisomerisations, our attention shifted to investigate the application of yndiamides in other transition metal catalysed transformations. The rhodium(I)-catalysed [5+2] cycloisomerisation[37] of (–)-**148t** was examined by Kai Ma and key observations are summarised for the reader (Figure 2.17). Firstly, similar reactions with branched ynamides often display significant substrate diastereocontrol (ranging from 2:1 to >20:1 *d.r.*) and the reactions also showed a significant time dependence on the nature of the alkyne substituent, with reactions at room temperature ranging from 15 minutes with 1° alkyl groups, to 20 hours for electron-rich aromatic substituents. The [5+2] reaction of yndiamide (–)-**148t** was sluggish at room temperature and heating at 80 °C for 16 hours was required to enable full conversion. This gave (–)-**197** in 58% yield. The *d.r.* could not be determined by ^{1}H NMR spectroscopic analysis because the compound was rotameric and the spectrum contained broad unresolved peaks; variable temperature NMR experiments failed to improve resolution and resulted in product decomposition. Single crystal X-ray analysis identified the diastereomer (and enantiomer) of (–)-**197** (Figure 2.17), and a sample of these crystals gave identical NMR spectroscopic data as compared to the bulk. This would at least indicate a high *d.r.* for the isolated product. This reaction was not investigated further but, in line with previous cycloisomerisations, it is likely that the steric bulk at nitrogen was problematic in these reactions.

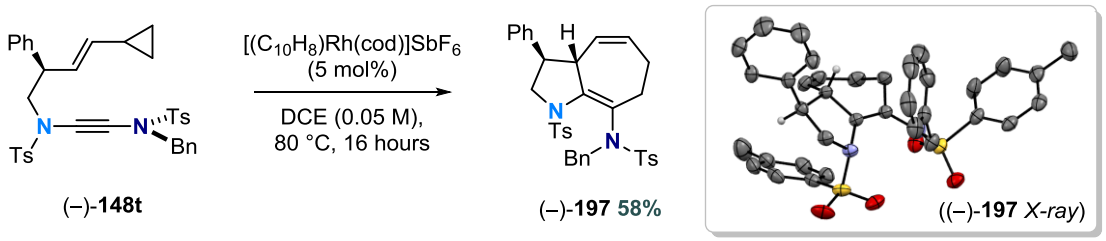


Figure 2.17: [5+2] Cycloisomerisation of (–)-**148t**; reactions were performed by Kai Ma. These reactions were extremely oxygen sensitive and were performed using Schlenk techniques under a N_2 atmosphere, with rigorously dried and degassed solvent. Displacement ellipsoid plot is displayed at 50% probability. Hydrogen atoms (except at the stereocentres) are omitted for clarity.

In contrast, cyclotrimerisation of triynes **160f** and **160g** using Wilkinson's catalyst, $RhCl(PPh_3)_3$, proceeded much more rapidly than the analogous reactions of ynamides (which typically take 15–24

hours at >100 °C),[90,93,432] giving the pyrroloindolines **198** and **199** in excellent yield (Figure 2.18). These reactions were very clean and product purification was facile, with catalyst removal achieved by filtration through a silica gel plug. Single crystal X-ray analysis also revealed that these compounds adopted a chiral conformation (as shown in Figure 2.18), in which the tosyl groups are positioned on opposite sides of the ring system. One could imagine that the incorporation of a substituent α- or β- to nitrogen could control the position of the tosyl groups and influence the overall conformation of these compounds; their use in ligand design is potentially significant.

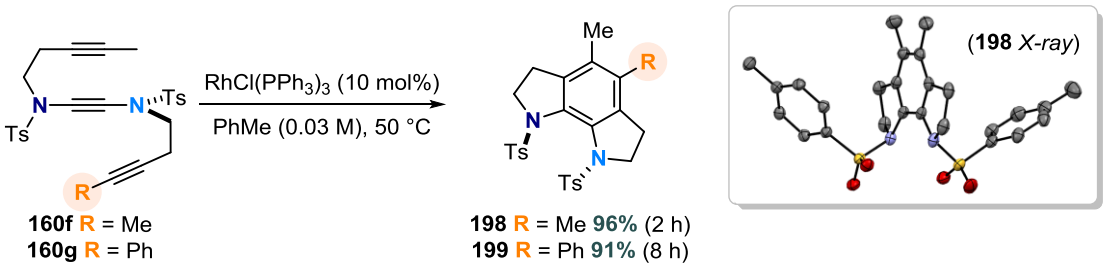
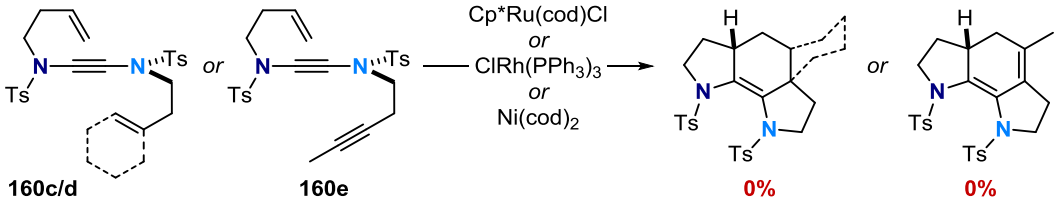


Figure 2.18: [2+2+2] Cyclotrimerisation of yndiamides, values in parentheses refer to the reaction duration. Displacement ellipsoid plot is displayed at 50% probability. Hydrogen atoms are omitted for clarity.

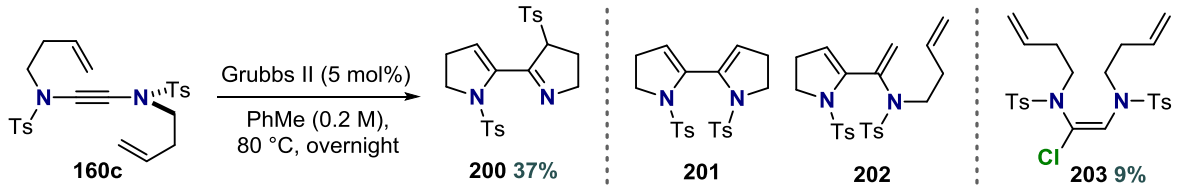
In comparison with triyne [2+2+2] reactions, the analogous transformations using a mono or bis-alkene containing substrates were unsuccessful (Scheme 2.18).[433–437] Using the catalysts shown, our preliminary investigation failed to afford the desired cyclotrimerisation products at temperatures below 60 °C (although the reaction mixtures did undergo colour changes) and heating above 70 °C only led to decomposition of the starting material.



Scheme 2.17: Attempted [2+2+2] reactions of ene-yne- or diene-yndiamides using 5 mol% of catalyst.

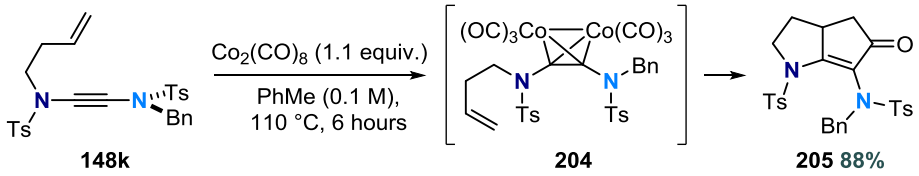
Unlike for ynamides,[226,438–441] the ring-closing metathesis of yndiamide **160c** was found to be exceptionally difficult using Grubbs II catalyst. No reaction was observed at room temperature over 6 hours, and heating to 80 °C overnight was required to afford complete conversion of **160c** (Scheme 2.18). Products **200**–**203** were all identified at the end of the reaction, with the major product being imine **200** (its structure confirmed by single crystal X-ray analysis) instead of the expected bis-dihydropyrrole **201**. Further investigation found that purified **201** also underwent spontaneous rearrangement to **200**; however, it is possible that remaining ruthenium residues facilitated this transformation. The chloroendiamide **203** evidently comes from hydrochlorination of the alkyne and the only source of HCl is the catalyst itself, likely formed via phosphine mediated

catalyst degradation.[442,443] Addition of a sacrificial copper salt is known to sequester liberated phosphines[444–446] and, although there is a veritable smörgåsbord of metathesis catalysts available for further investigations,[447–450] this reaction was not pursued further.



Scheme 2.18: Ene-yne-ene metathesis of **160c** using Grubbs II catalyst. **201** and **202** were also isolated in small amounts but contained significant contaminants, including *N*-(but-3-en-1-yl)tosylamide.

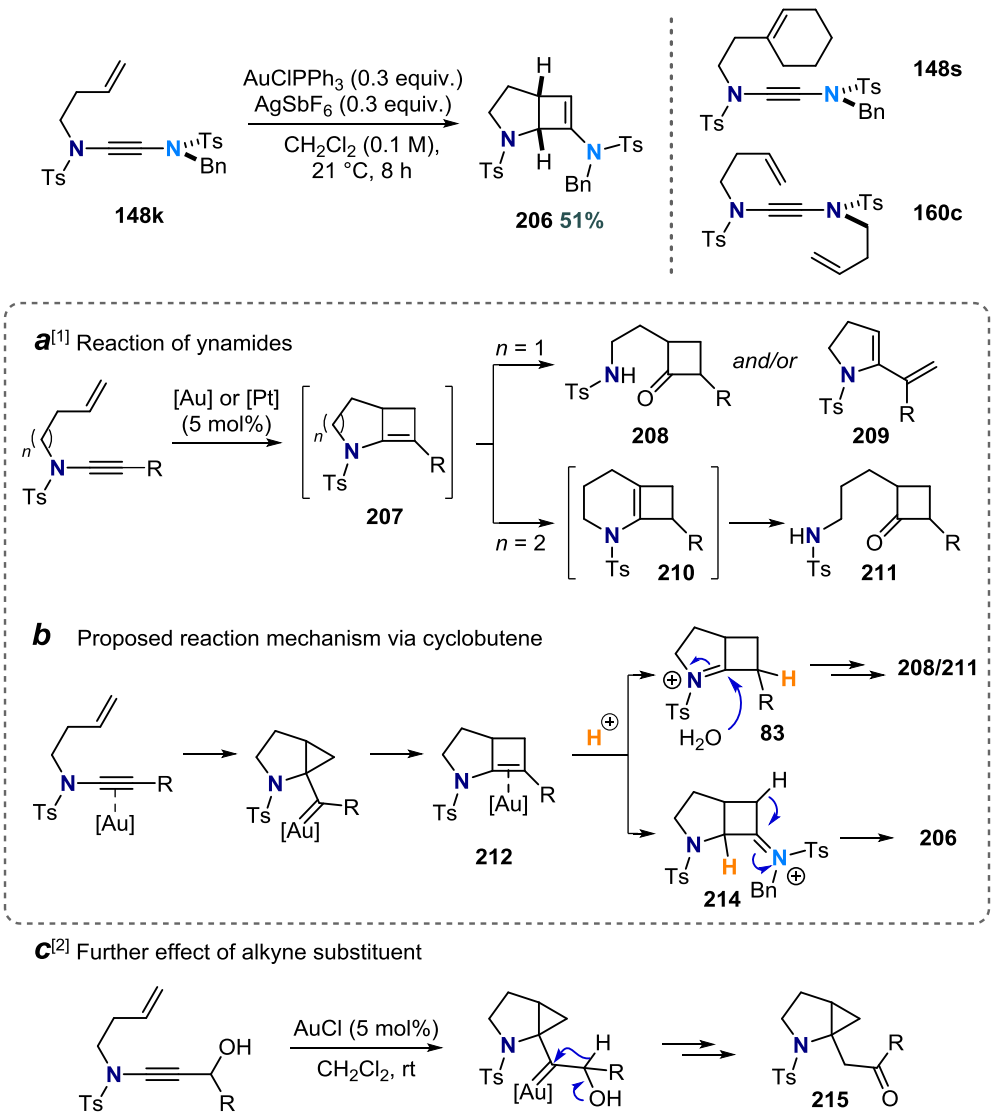
The Pauson-Khand reaction of **148k** was also successful, albeit requiring somewhat forcing conditions (Scheme 2.19).[89,91,451] The cobalt-complex **204** formed relatively easily upon gentle heating to 40 °C (with a concomitant colour change from orange/red to dark green). However, the cyclisation itself was more challenging and additives that are typically used to facilitate such reactions (e.g. trimethylamine *N*-oxide and *N*-methylmorpholine *N*-oxide) were only mildly effective at temperatures above 80 °C; the use of cyclohexylamine was also unsuccessful. Prolonged heating at 110 °C was therefore required, which gave the desired product **205** in 88% yield.



Scheme 2.19: Pauson-Khand reaction of **148k** using $Co_2(CO)_8$.

Given the diversity of alkyne chemistry that uses gold and platinum catalysts,[452–455] we also took the opportunity to explore this using yndiamide **148k** (Scheme 2.20). Following the conditions reported for ynamides,[456] reactions were performed using either AuCl or $PtCl_2$ (5 mol%), but these gave negligible conversion, even upon prolonged heating. Switching to the in situ generated $[AuPPh_3]SbF_6$ (5 mol%) afforded the cyclobutene **206** - albeit the reaction stalled at approximately 25% conversion. The catalyst loading was increased incrementally and 30 mol% of $[AuPPh_3]SbF_6$ afforded full conversion at room temperature, giving cyclobutene **206** in 51%. Related reactions of yndiamides **148s** and **148c** were similarly capricious, giving poor conversion and numerous side products. The formation of the cyclobutene **206** is distinct from that of equivalent ynamide chemistry, which typically gives ring-opened products **208**–**211**. In considering a mechanism to account for these observations (**b**, Scheme 2.20), a common cyclobutene intermediate **212** could undergo regiodivergent protonation that would depend on the nature of the former alkyne R-

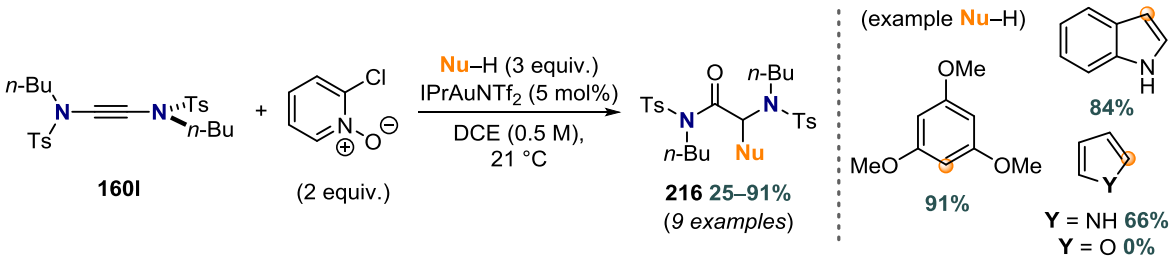
substituent (i.e. leading to the formation of **213** or **214**). In the case of yndiamides, the exocyclic electron-donating substituent appears to control this protonation event (**214**) and accounts for the product difference. On a related note, moving the electron-donating substituent one carbon away from the alkyne gives yet another outcome,[456] in which 1,2-hydride shift leads to the cyclopropane **215**; further demonstrating that a significant difference can result from a seemingly small change.



Scheme 2.20: Cycloisomerisation using gold or platinum catalysis. **a**: [1] *Conditions*: AuCl (5 mol%), CH_2Cl_2, rt (ref [456]) or $PtCl_2$ (5 mol%), PhMe, 80 °C (ref [452]); **b**: Proposed reaction mechanism - regioselective protonation determined by alkyne substituent; **c**: Possibility for 1,2-migrations or other transformations from a common intermediate, [2] see ref [456].

Yndiamides are also excellent precursors to α-amino amide derivatives **215** (Scheme 2.21). This chemistry was explored by a Part II (Master's) student, Olivia Garry, and is highlighted for the reader's interest.[457–460] $IPrAuNTf_2$ was found to promote the reaction between yndiamide **160l** and the pyridine *N*-oxide much more effectively than bistriflimide,[461] and a brief substrate scope

indicated that electron-rich aromatics, heterocycles and enol ethers performed best in this transformation. This work would naturally extend to both the regioselective and asymmetric synthesis of α-amino acids,[462,463] but preliminary work with chiral-phosphine/gold complexes has thus far given only negligible enantioselectivities.



Scheme 2.21: α-Amino amide synthesis. This work was performed by Olivia Garry.

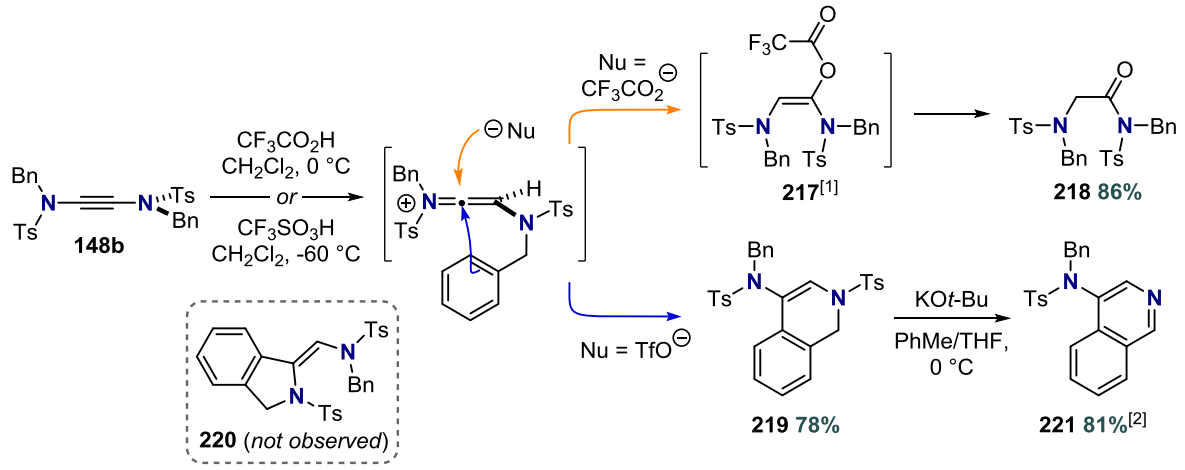
Having explored the effect of a range of transition metal species in these reactions, it has become clear that whilst yndiamides are likely to be more electron rich than ynamides - by virtue of the second nitrogen substituent - it is often difficult to bring this to bear in reactions when there are sufficiently bulky substituents at nitrogen. Further investigations are required to verify and explore this, but there are two reactions of note that illustrate this: firstly, altering the steric and electronic properties of this second nitrogen substituent enabled up to four-fold rate acceleration in the palladium-catalysed enyne cycloisomerisations at 60 °C (Table 2.4), and the reactivity of the resulting products was also affected by these changes. Secondly, the cyclotrimerisation of diyne-yndiamides to pyrroloindolines was also significantly faster than for ynamides, which could be evidence of their increased nucleophilicity. Nevertheless, it is apparent that whilst an *N*-benzyl substituent is sufficiently bulky to retard many of these reactions, it has the benefit of improving general yndiamide stability. It would, therefore, be very interesting to determine how variation of these substituents can be used to achieve a balance between reactivity and stability for yndiamides.

2.4b Brønsted acid catalysed transformations.

A number of transformations of ynamides are promoted by Brønsted acids,[45,46,51,64,464–480] and these all show complete regioselectivity in favour of protonation β- to nitrogen - the electron donating power of the single nitrogen substituent being evident here. This naturally leads to an important question - how could regioselectivity be imparted in the reactions of yndiamides? This concept will be explored later, but first, the utility of yndiamides in acid catalysed transformations will be discussed.

In line with analogous transformations of ynamides,[465,470] the reactions of yndiamide **148b** with either trifluoroacetic acid or triflic acid gave counteranion dependent outcomes (Scheme 2.22). The former reaction gave the unstable enol trifluoroacetate **217**, as identified by ^{1}H NMR spectroscopic

analysis of the crude reaction mixture, which underwent partial conversion to the amide **218** upon aqueous workup and full conversion during silica gel chromatography, giving **218** in 86% isolated yield. On the other hand, the use of triflic acid gave the dihydroisoquinoline **219** in 78% yield, but this was contingent on using anhydrous conditions, which otherwise led to **218**. It is interesting to note that cyclisation occurs with complete regioselectivity and cyclisation to give the 5-membered ring **220** was not observed. Furthermore, the use of catalytic amounts of bistriflimide, followed by addition of potassium *t*-butoxide, gave a streamlined approach to 4-aminoisoquinoline **221**, isolated in 81% yield.



Scheme 2.22: Counteranion dependent outcomes in the reactions of yndiamides with acids; 2.5 equiv. of acid used in each case. [1] Major product observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, hydrolysis occurs upon workup and chromatography; [2] This yield refers to the sequential reaction from **148b** to **221**, performed by Olivia Garry, using Tf_2NH (10 mol%), PhMe, 0 °C then KO*t*-Bu (2.0 equiv.), THF.

Similarly, during attempts to obtain single crystals of furyl yndiamide **148v** via vapour diffusion techniques, crystals of pyrrole **222** were obtained instead (Figure 2.19). This compound crystallised as a 3:1 (*E*):(*Z*) mixture, but the bulk contained a ~1.2:1 ratio of (*E*)-/(*Z*)-isomers as determined by ^{1}H NMR spectroscopic analysis. This was not investigated further but demonstrates a remarkably facile route to functionalised amino-pyrroles.

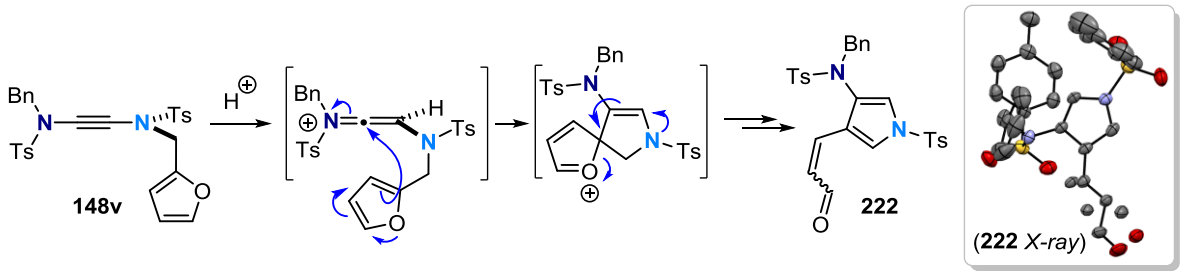


Figure 2.19: Serendipitous formation of amino-pyrrole **222**. Displacement ellipsoid plot for **222** is displayed at 50% probability. Disordered components are retained and hydrogen atoms are omitted for clarity.

The chemistry of tryptamine derived yndiamides was also enlightening, in which acid and base-

mediated cyclisations had different regioselectivities (Figure 2.20). In the first case, the use of anhydrous hydrochloric acid (as a solution in dioxane) gave regioselective cyclisation of **160i** to endiamide **223**. This compound was unstable towards aqueous workup and hydrolysed to the aldehyde **224**; unfortunately, **224** co-eluted with the sulfonamide byproduct and was isolated in ~90% purity. The yield reported (63%) takes this into account. Reduction with sodium borohydride gave alcohol **225**, which was separated from residual byproducts in excellent yield. In contrast, the attempted coupling of sulfonamide **226** with dibromoenamide **156a**, which was performed by a visiting student, Pavel Fedoseev, failed to deliver the expected yndiamide **227** and instead afforded the spiro-indolenine **228**. This presumably arises from an in situ, copper-catalysed cyclisation of the indol(ate) **227**.[141] The syntheses of analogous ynamides are not troubled by this cyclisation and are typically isolated in good yield,[123,481] but this is reminiscent of related cyclisations of unprotected sulfonamides or alcohols (Chapter 0). Given the preponderance of indoles and spiro-indolenines in natural products and drug design,[482–487] this regioselective divergence could be of interest.

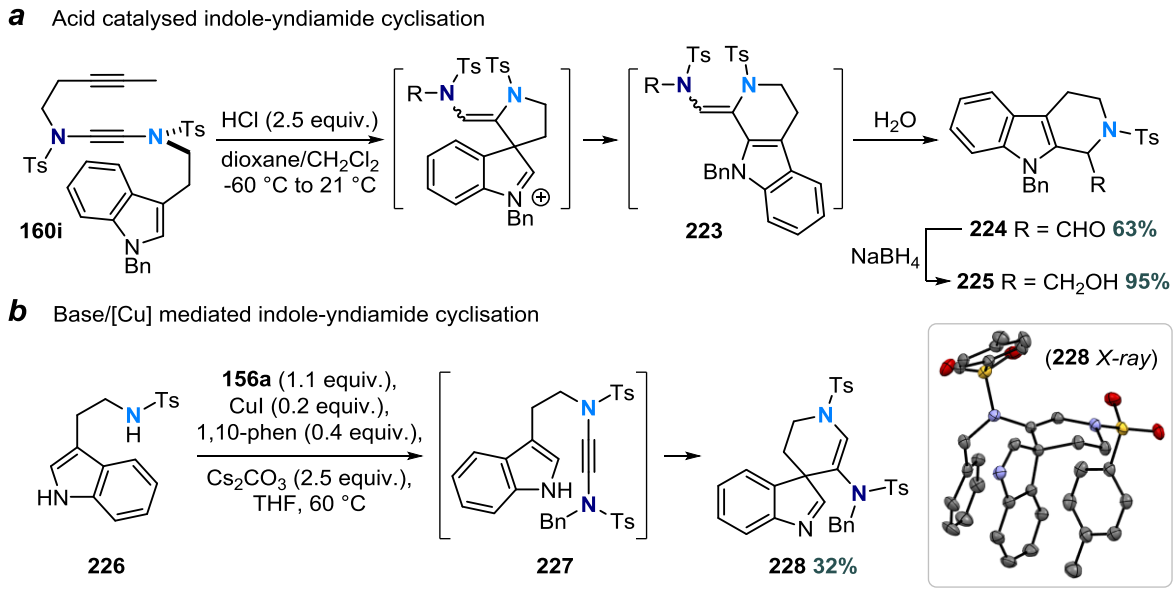
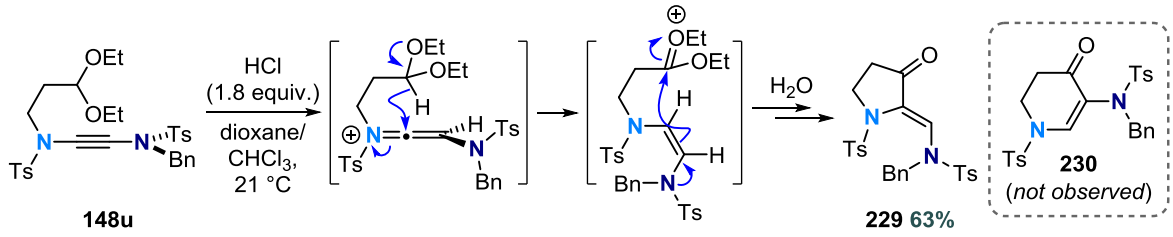


Figure 2.20: **a**: Regioselective acid-catalysed cyclisation of indole **160i**; **b**: Attempted synthesis indole yndiamide **227** led to spiroindolenine **228**, this reaction was performed by Pavel Fedoseev. Displacement ellipsoid plot for **228** is displayed at 50% probability, hydrogen atoms are omitted for clarity.

Finally, the acetal-appended yndiamide **148u** contains two acid-sensitive functional groups, and the question was raised as to which would be more susceptible to reaction with acid. The use of anhydrous hydrochloric acid (as a solution in dioxane) gave full conversion to the pyrrolidinone **229** (Scheme 2.23); here, again, this was contingent on the use of anhydrous conditions, with otherwise led to a mixture of products, including yndiamide hydration and cleavage. This outcome is reminiscent of previous work from the Evano group, in which pyridine/piperidine derivatives were obtained exclusively.[466] Piperidinone **230** was not observed and the structure of **229** was confirmed

by single crystal X-ray analysis. In considering a mechanism for this transformation, it appears that there was a cooperative effect from both nitrogen atoms, in which one controlled keteniminium formation and the other controlled the cyclisation. This further illustrates that the reactivity of an yndiamide can be distinctly different from an ynamide.

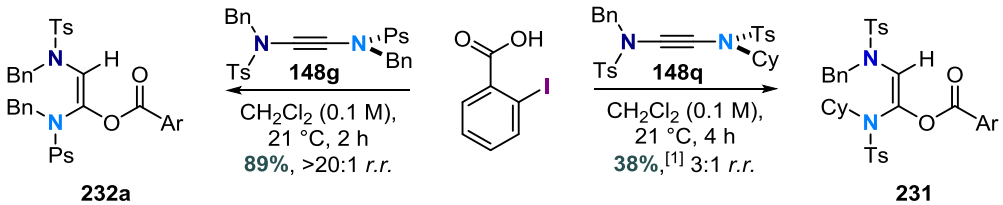


Scheme 2.23: Acid-mediated cyclisation of acetal yndiamide **148u** to pyrrolidine **229**.

2.4c Regioselective transformations.

An important aspect of yndiamide chemistry would be the ability to perform *inter*molecular reactions regioselectively. It is apparent that the polarising effect of a single nitrogen atom is key for the reactions of ynamides, but the ability is effectively lost when considering an yndiamide. Whilst tethering circumvents this issue, we hypothesised whether a steric and/or electronic bias could be imposed by variation of the substituents at one or both nitrogen atoms. This work was carried out by a Part II student, Olivia Garry, and is summarised below for the reader.[457]

Unsymmetrical yndiamides **148g** and **148q** were selected to test the electronic and steric bias in their reactions with 2-iodobenzoic acid (Scheme 2.24). Whilst *N*-cyclohexyl yndiamide **148q** gave moderate regioselectivity in favour of **231** (3:1 *r.r.*, >20:1 (*E*):(*Z*), 38% yield), it was the reaction of the *N*-phosphoryl yndiamide that was most surprising, which gave >20:1 regioselectivity in favour of **232a** (isolated in 89% yield). The absolute structures of the major isomers **231** and **232a** were confirmed by single crystal X-ray analysis.



Scheme 2.24: Reaction of unsymmetrical yndiamides with Brønsted acids, product ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [1] Isolated yield of the major regioisomer; Ar = 2-I-C_6H_4.

Next, a range of Brønsted acids including carboxylic acids, phenols and thiols were screened in the reaction with yndiamide **148g** (Figure 2.21). Carboxylic acids were by far the most effective and, in general, Brønsted acids with pK_a values (in DMSO) outside the range of 9–12 gave either decomposition (pK_a <9) or no reaction (pK_a >12). The reactions with phenols often gave

concomitant formation of the aryl phosphate **233**, which could arise either from dephosphorylation of the yndiamide or the keteniminium ion. Carbon acids were unsuccessful and gave either no conversion or complete decomposition. One particular oddity that emerged from this investigation was the stark reactivity difference between thiophenol and 2-bromothiophenol. Whilst the former gave no conversion, the latter gave a small amount of the expected endiamide and preferential formation of the dihydroisoquinoline **234**. Both were formed with excellent regioselectivity (20:1 *r.r.*), as determined by ^{1}H NMR spectroscopic analysis, and **234** was isolated in 60% yield. Our curiosity was piqued and this outcome was investigated further (Figure 2.23).

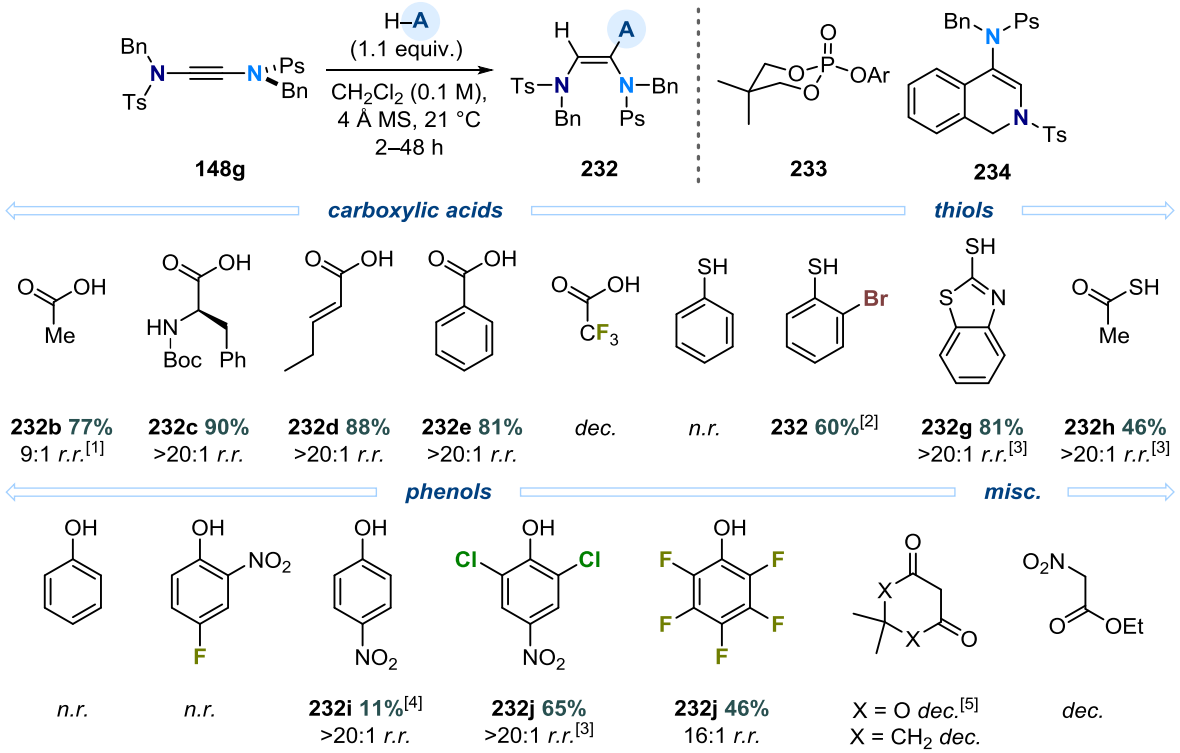
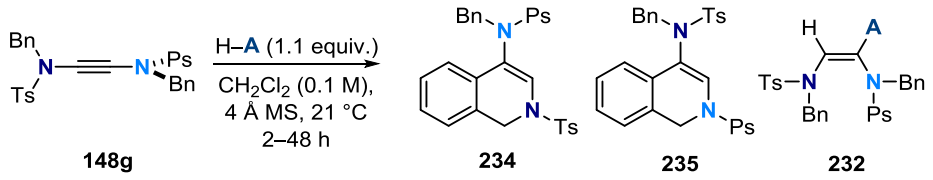
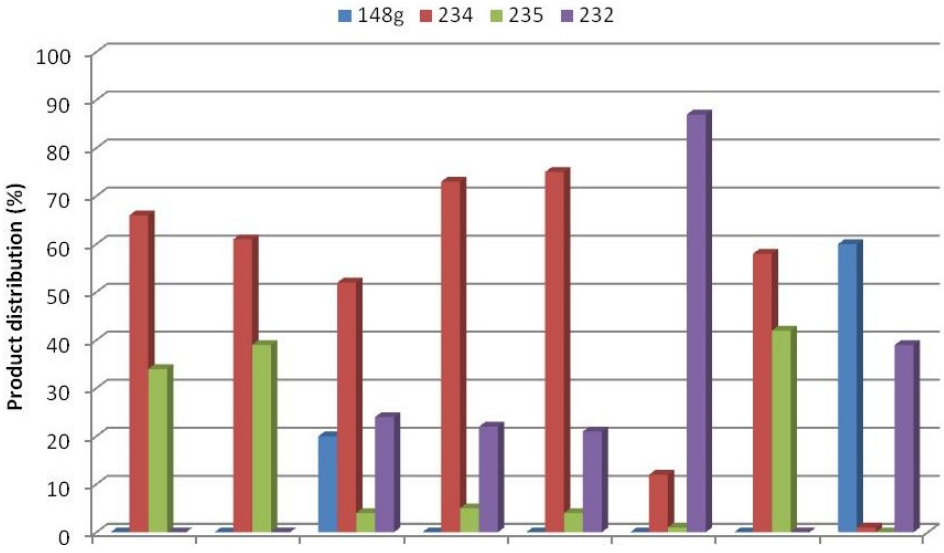


Figure 2.21: Reaction of **148g** with Brønsted acids, product ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture unless otherwise stated. Isolated yields are shown for the indicated compound. [1] Conducted in neat acetic acid. When the reaction was performed in CH_2Cl_2, the product was obtained with >20:1 *r.r.* but was contaminated by an unidentified byproduct. [2] **232**:**234** formed in approximately 1:3 ratio, isolated yield is reported for **234**, **232** was not isolated; [3] Ratio determined by ^{1}H NMR spectroscopic analysis of the isolated material; [4] The reaction of *p*-nitrophenol gave a 1:6 ratio of **232i**:**233** as an inseparable mixture. The yield is a calculated yield based on the combined isolated mass of the two compounds; [5] No reaction at room temperature and decomposition upon heating to 80 °C in DCE. *dec.* = decomposition of starting material. These reactions were all conducted by Olivia Garry.

A selection of other acids was screened to examine their ability to induce cyclisation. Pyridinium *p*-toluenesulfonate (PPTS), camphorsulfonic acid (CSA) and anhydrous hydrochloric acid (solution in dioxane) each gave significant amounts of yndiamide decomposition, with only minor amounts of the desired products observed (not shown). Triflic acid and bistriflimide gave cyclisation products **234** and **235** exclusively, albeit with poor selectivity (entries 1 & 2, Table 2.6). In comparison, 2-bromothiophenol was unique amongst these acids. Firstly, 24 hours was insufficient time to reach

full conversion of yndiamide **148g** and up to 48 hours was required (entries 3 & 4). The proportion of isoquinoline **234** increased during this time (entry 4). Increased amounts of thiol enabled faster conversion but did not affect the final selectivity (entries 4 & 5). At first glance, these observations could imply the presence of an equilibrium between endiamide **232** and the intermediate keteniminium ion. Contrary to this, heating the reaction to 75 °C instead gave a significantly increased proportion of **232** (entry 6), though the required solvent change to dichloroethane could also affect this. The use of catalytic amounts of bistriflimide demonstrated that protonation and cyclisation outcompeted thiol addition (entries 2 & 7), and increased amounts of thiol (5.5 equiv.) here resulted in 1:1 mixture of **234** and **235**. However, the addition of DTBMP (entry 8) gave remarkable selectivity for the endiamide **232**, albeit the reaction only reached 40% conversion after 24 hours. It is perhaps feasible to assume the involvement of the ion pair $[PyH]^+[ArS]^-$ in this reaction.





entry	1	2	3	4	5	6[1]	7	8
acid (equiv.)	TfOH (2.5)	Tf_2NH (2.5)	ArSH (1.1)	ArSH (1.1)	ArSH (2.5)	ArSH (1.1)	ArSH (1.1)	ArSH (1.1)
t (h)	0.1	0.1	24	48	45	24	24	24
T (°C)	-60	21	21	21	21	75	21	21
additive (equiv.)	-	-	-	-	-	-	Tf_2NH (0.1)	DTBMP (1.1)

Table 2.6: Reaction of yndiamide **148g** with acids. ArSH = 2-BrC_6H_4SH. [1] Reaction performed in $(CH_2Cl)_2$. DTBMP = 2,6-di-*t*-butyl-4-methylpyridine. These reactions were all conducted by Olivia Garry.

Whilst these data do not allow for any definitive conclusions about the reaction, it would be interesting to see how the product distribution in these reactions changes during the first 24 hours, especially considering the roughly constant amounts of endiamide in entries 3–5. One wonders whether there is a build up of some species (possibly another acid) that, upon reaching a critical concentration, alters the reaction in favour of the dihydroisoquinoline. At increased temperature or in the presence of base, this may not be able to accumulate. Further experiments are required to investigate this, and the effect of the ortho-substituent warrants study, for example, by replacing bromine with different halogens or other substituents.

Overall, two criteria were identified that could enable regioselective reactions with an yndiamide. First, differential protection of the nitrogen atoms was critical, although it is not certain whether this was a steric and/or electronic effect. The reader is referred to Chapter 3 for relevant discussions. Furthermore, the acid itself was also very important in affecting the product selectivity in these reactions. Whilst it was convenient to categorise a success or failure based on pK_a alone, the nature of the counteranion was also very important. Acid dependent outcomes have also been observed for ynamides and those reactions also displayed a strong dependency on the nature of the counteranion.[64,472,475,481,488] Those studies also indicated that the keteniminium ion pair $[YnH]^+[X]^-$ is transient and readily converts to the enamide.

2.5 Conclusions.

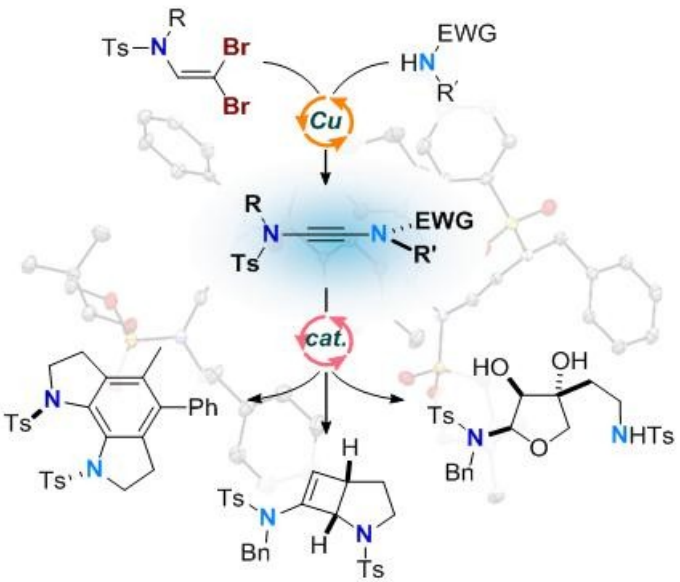


Figure 2.22: Copper-catalysed synthesis and applications of yndiamides.

In summary, the first route to yndiamides - novel, bis-nitrogen substituted alkynes - has been developed in which nitrogen nucleophiles undergo copper-catalysed coupling with 1,1-dibromoenamides. These reactions showed a strong dependence on the nature of all components

involved, with the nucleophile and "electrophile" seemingly limited to sulfonyl and phosphoryl derivatives. Furthermore, 1,10-phenanthroline had the unique ability to facilitate this reaction and a further study, including a full screening of phenanthroline derivatives and analogues, would be useful to enable a fuller understanding of this reaction. Not only would this have mechanistic implications that could allow for further reaction optimisation, but it could also enable a greater understanding of ynamide formation as a whole; this is very relevant given the absence of kinetic studies in the literature for the copper-catalysed alkynylation of heteronucleophiles.

Yndiamides are, for the most part, air and bench stable compounds, and many of them are also crystalline. These properties not only facilitated general handling and purification of these compounds, certainly compared to yndiamines, but they also enabled a large amount of structural data to be obtained. 22 of these compounds were studied using single crystal X-ray diffraction techniques and they all exhibited a significantly twisted structure. The same effect was observed for yndiamines and is discussed in detail in Chapter 3.[373,489] A preliminary study was performed to explore the behaviour of yndiamides in a range of transition metal- and acid-catalysed transformations, which led to the synthesis of a variety of nitrogen-substituted frameworks. By analogy to the reactivity of ynamides, variation of the substituents at both nitrogen atoms was important in modulating yndiamide reactivity, with steric and electronic influences being implicated in their chemistry. Overall, this led us to investigate regioselectivity in the reactions of yndiamides, which opens up a potential wealth of future applications. Far from behaving like a "simple" ynamide, yndiamides possess a reactivity profile that both mirrors and contrasts with that of ynamides.

Physical and Spectroscopic Properties of Ynamides and Yndiamides

3

In the past 20 years, there have been significant advances made in both the synthesis and applications of ynamides, many of which have been described or referred to in previous chapters. Given such interest, it is perhaps surprising that very few studies investigating more fundamental aspects of these compounds have been reported, for example, a comparison of the electronic and steric effects of the different substituents. Whilst it is known that ynamides are more nucleophilic than "typical" alkynes, by virtue of the electron-donating amido group, a detailed understanding of ynamide reactivity, particularly the influence of their substituents, remains elusive. Nevertheless, a greater understanding would be helpful to facilitate further developments in ynamide chemistry. Within our own work (Chapters 1 and 2), the following questions remained unanswered: (i) What is the nature of the bonding in ynamides? (ii) How do the substituents affect this? (iii) How does this compare to yndiamides? A significant number of these compounds were prepared throughout the course of this work and many were amenable to crystallisation. Though not an initial goal for these projects, we sought to understand whether structural insights gained from single crystal X-ray analysis of ynamides and yndiamides, coupled with spectroscopic and computational studies, would enable a greater understanding of these building blocks.

This chapter will be divided into two main sections. Section 3.1 will introduce the reader to previous studies obtained from the literature, which looks at both the physical and spectroscopic properties of electron-deficient ynamines and ynamides. Kinetic and computational experiments will also be discussed in this section, as they provide valuable insights into ynamide reactivity. This will lead to Sections 3.2 and 3.3, which discuss the X-ray crystallographic and spectroscopic data collected during our studies. It is important to note that these discussions relate only to the solid and ground state properties of these compounds, respectively, and any changes in structure that occur upon reaching a reaction transition state will very likely be reaction dependent.

3.1 Introduction.

Ynamides are often described as nucleophilic building blocks and a resonance description such as in Figure 3.1 is drawn to illustrate this. This description is reasonable from first principles: delocalisation of an electron pair into an unoccupied orbital, for example, belonging to an alkyne or arene, is a stabilising interaction that reduces inter-electron repulsion and lowers the energy of the HOMO. It is important to point out here that "resonance" does not involve the actual movement of electrons or nuclei, and is used to better describe the electronic distribution in cases where a single Lewis structure does not accurately represent observed properties.

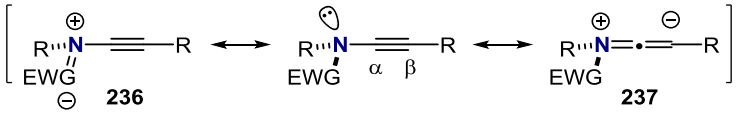
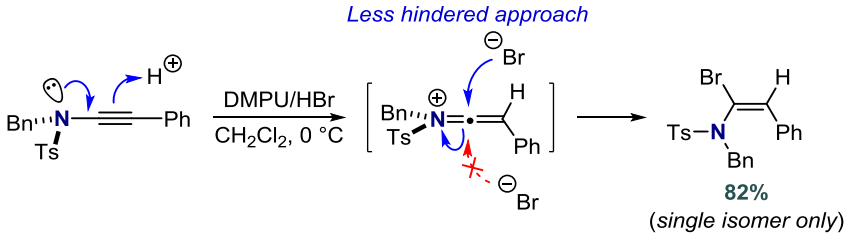


Figure 3.1: Resonance forms of ynamides.

For example, reactions in which ynamides behave as nucleophiles or bases, particularly with Brønsted acids,[64] show exceptional regioselectivity for electrophilic addition/protonation at the β-position (Scheme 3.1),[470] which, at the very least, is consistent with a build-up of negative charge on this atom upon reaching the transition state. Assuming thermodynamic effects to be less important than kinetics, the following questions are raised: "Is the regioselectivity pre-determined by the ground state electronic configuration, or does it rather arise from stabilising interactions that develop upon reaching a transition state?" I.e. To what extent can these resonance forms be used to approximate the electronic wavefunctions for the ground and transition states during a reaction?



Scheme 3.1: Regio- and stereoselectivity in reaction of ynamides with Brønsted acids.

Considering the reactions that use ynamides as *electrophilic* partners, the regio- and stereoselectivity of nucleophilic attack is less obvious, and can occur at either the α- or β-positions with *anti*- or *syn*-selectivity.[45,46,51,52] The nature of the electron withdrawing group is very important in these reactions and coordination to a metal species is often invoked to explain the regioselectivity differences, especially in light of the different selectivities for ynamines and ynamides (**a**, Figure 3.2).[268] Another curious example is the intramolecular carbolithiation of ynamides **238**, which generally proceeded via 5-exo-dig cyclisation to give **239** (**b**, Figure 3.2); however, a 6-endo-dig

cyclisation occurred when using a phosphoramidate (**240**).[490] After conducting DFT studies, the authors concluded that this cannot be rationalised by purely electronic factors alone and a clear explanation of this result remains elusive.

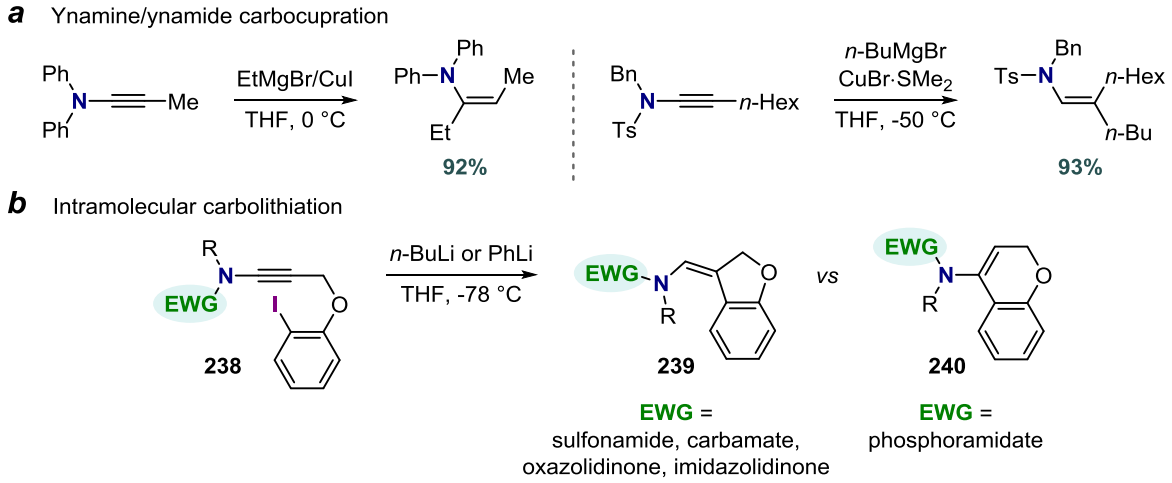


Figure 3.2: Example reactions using ynamides as an electrophilic component.

All of these observations bring into question how to weigh the different resonance forms when describing *all* aspects of ynamide reactivity, especially as this will depend on the nature of the electron withdrawing group and the effect of the other substituents. Many of the explanations for ynamide behaviour remain anecdotal, and a survey of the ynamide literature (which contains over 800 publications) returned only a small fraction (15–20) that contained any kinetic, structural and/or computational studies. Most of these were performed to help rationalise the outcomes of a particular reaction, but some provided valuable insight into the chemical and physical properties of ynamides.

3.1a Literature review: Physical and spectroscopic properties of *N*-alkynyl amines/amides.

We shall first discuss the characteristics of *C*-boryl ynamines (Figure 3.3), remarkable compounds that are analogous to frustrated Lewis pairs,[492] which represent the most extreme cases of push-pull delocalisation for ynamines and give an "upper limit" for what might be expected in related ynamides. Yamashita and co-workers performed a detailed structural analysis of dimesityl borane **241** using single crystal X-ray diffraction.[491] In the solid state, the amino and boryl substituents of **241** were oriented almost coplanar to each other (torsion angle = 164.82(18)°), with a trigonal planar arrangement at boron (sum of bond angles $\sum\theta_B$ = 359.9(3)°) and a slight pyramidal arrangement at nitrogen ($\sum\theta_N$ = 356.7(3)°). The C≡C bond length was found to be lengthened (1.227(3) Å) as compared to typical alkyne (1.18–1.20 Å), but was smaller than the central C=C bond length of a butatriene (1.25 Å, see also the urea cumulene (*E*)-**88**, Figure 1.14, Chapter 1).[493] The corresponding C–N (1.312(2) Å) and C–B (1.476(3) Å) bonds were also shorter than typical C(sp)–N (1.33–1.37 Å, see later discussions) and C(sp)–B bonds (1.50–1.63 Å).[493]

The C≡C stretching frequencies for *C*-boryl ynamines were markedly lower than most disubstituted alkynes (Figure 3.3), which typically exhibit frequencies in the range of 2260–2190 cm^{-1}, and indicate a weakening of the triple bond. The large ^{13}C chemical shift differences for C(α) and C(β) were also attributed to the strong polarisation of the alkyne.

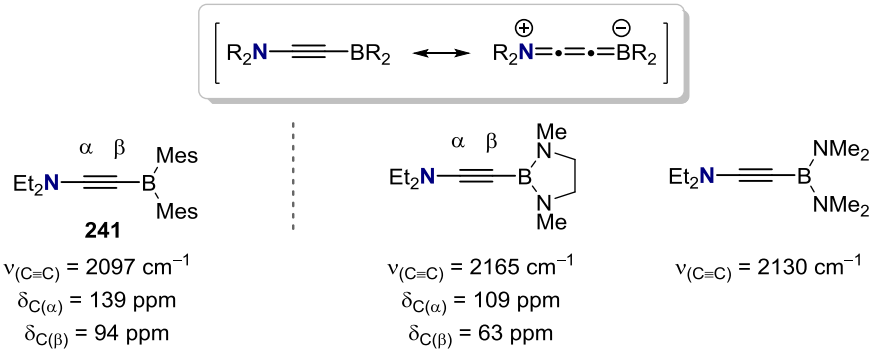


Figure 3.3: Selected data for boryl-ynamines are shown. NMR spectroscopic data were collected in C_6D_6.

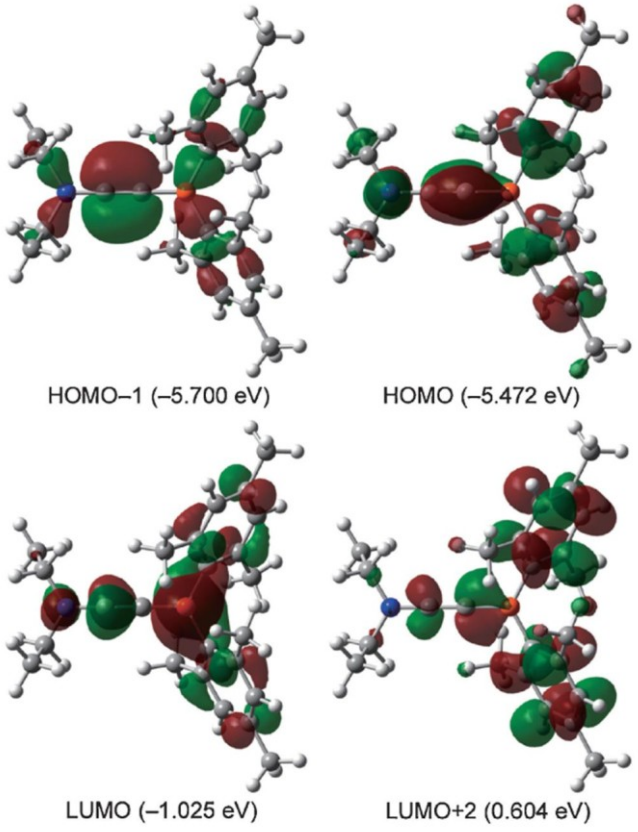


Figure 3.4: This figure was taken from ref [491], showing selected molecular orbitals and their energy levels for the geometry optimised borane **241**, calculated at the B3LYP/6-31G(d) level of theory.

DFT calculations were also performed to provide insight into the bonding of these compounds. The HOMO shows the alkyne π-orbital is slightly polarised towards C(β) and boron, and the LUMO is localised on C(α) and boron (Figure 3.4). Natural population analysis also predicted a positive charge (+0.22) at C(α) and negative charge (−0.39) at C(β). In addition, the solution UV-vis

absorption spectrum of **241** gave an absorption maximum, λ_{max}, at 320 nm, which was assigned to an electronic transition between the alkyne and the mesityl groups in the HOMO and LUMO respectively. Overall, characterisation by spectroscopic, X-ray diffraction and computational analyses indicated a butatriene-like ground state structure for boryl ynamines.

Though there are many X-ray crystal structures of ynamides in the CCDC, discussions about their physical and spectroscopic properties are sparing at best. The nearest related study was described by Witulski with the related 1,3-buta-1,4-diynamide **242** (Figure 3.5). The C≡C stretching frequency (2169 cm^{-1}) is lower than for typical disubstituted alkynes, which indicates a weaker alkyne bond. The alkyne ^{13}C resonances occur at 75.4 ppm and 59.6 ppm in $CDCl_3$ and, although the resonance for C(β) (59.6 ppm) has a slightly lower chemical shift than many other alkynes, these values are not unusual. This compound also exhibits axial chirality in the solid state. There is a significant twisting of the end groups (Figure 3.5) and the substituents around the nitrogen atoms are close to a trigonal planar geometry ($\sum\theta_N$ = 358.7(3)° and 354.3(2)°). The C(α)≡C(β) and C(β)–C(β') bonds lengths are 1.199(4) Å and 1.365(4) Å, respectively, and, whilst the bond length for the alkyne falls in the expected range, the C(β)–C(β') is much closer to that expected for an alkene (typically around 1.33–1.34 Å). The C(sp)–N bond lengths (1.345(3) Å and 1.348(3) Å) are not unusual and, in comparison with boryl-ynamine **241**, it is unclear from these values as to the degree of lone pair conjugation.

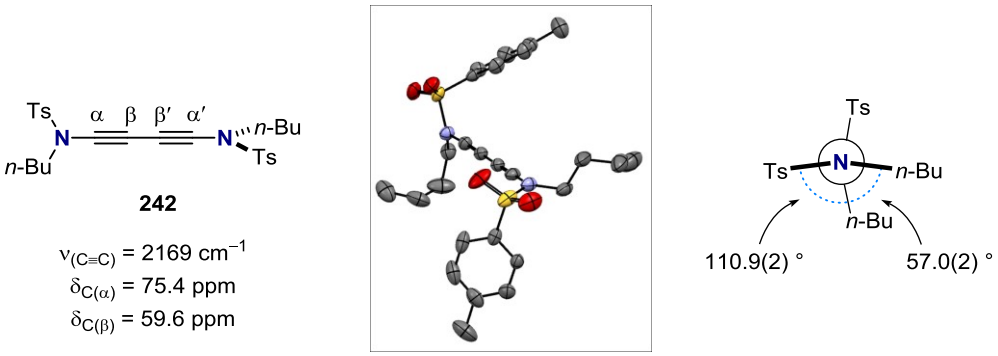


Figure 3.5: Selected data and molecular structure of 1,3-butadi-1,4-diynamide **242**, showing twisted conformation. NMR spectroscopic data collected in $CDCl_3$. Single crystal X-ray data for **242** were obtained from the CCDC (1449990). Displace-ment ellipsoid plot is displayed at 50% probability, disordered components and hydrogen atoms are omitted for clarity.

However, calculations for a related butadiynamide **243** indicated that the twisting is likely an electronic effect as opposed to a crystal packing effect.[494] A result (or cause?) of this twisting was a series of helical MOs that extend across the NC_4N unit (Figure 3.6) - a phenomenon that will be discussed further in Section 3.4.[494–496] The properties of **242** were further characterised by UV-vis (λ = 319, 295, 277, 254 nm) and fluorescence spectroscopy, as well as cyclic voltammetry and thermogravimetric analysis. A later study also investigated the photophysical and thermal properties of polymeric ynamides,[497] and the reader is referred to these reports for further details.

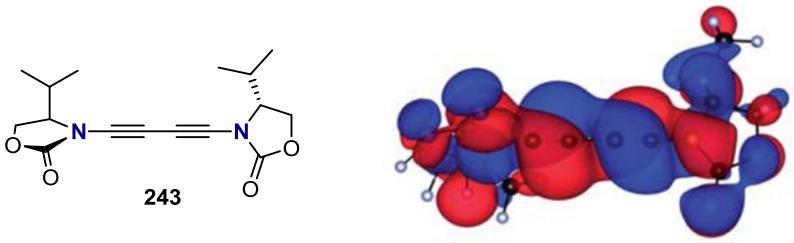
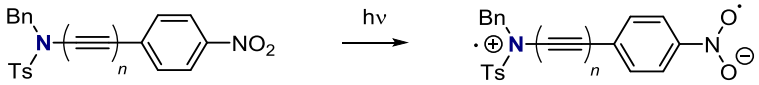


Figure 3.6: This figure was taken from ref [494], depicting the HOMO (DFT-TPSSh) for diyne **243**. Note the right-handed helix with the (*R*)- configured oxazolidinone.

Witulski also examined the photophysical properties of a range of push-pull ynamides which possessed one to four alkyne spacer-units between donor (nitrogen) and acceptor (4-nitro- or 4-cyanophenyl) groups (Scheme 3.2).[222] The solution UV-vis absorption spectra showed that increased spacer length (n = 1–4) shifted the intramolecular charge transfer (ICT) absorptions from 340 to 415 nm (incrementally in 20–30 nm intervals). Furthermore, calculations indicated a large increase in dipole moment between ground and excited electronic states upon photo-excitation, particularly for ynamides capped with a 4-nitrophenyl substituent, as compared to other oligoyne linked donor-(π-spacer)-(aryl-acceptor) arrays.[498,499] This increase was attributed to an efficient N to NO_2/CN charge transfer, which was most pronounced in cases with one or two alkyne spacer units. Compared to these tosyl ynamides, oxazolidinone analogues showed a lower overall change in dipole moment upon photo-excitation, which reflects a less effective charge transfer and likely indicates the greater electron withdrawing effect of a carbonyl versus a sulfonyl group. These results are in full agreement with related observations, in which ynamide reactivity can be modulated by altering either/or both the electron withdrawing group and the alkyne terminal substituent.[45,46,51,52]



Scheme 3.2: Photoinduced intramolecular charge transfer of push-pull ynamides with n = 1–4 alkyne spacer units.

3.1b Literature review: Nucleophilicity and electrophilicity of ynamides.

Mayr and Evano determined the kinetic nucleophilicity parameter, N, for a selection of ynamides by studying their reactions with benzhydrylium salts **244** (**a**, Figure 3.7).[350] They concluded that the second-order rate constant, k, reflected an irreversible first step - the formation of keteniminium **245** - for which eq. 1 could be used to determine the values N and s_N (sensitivity parameter) by plotting log$k$ against the electrophilicity parameters, E, of the benzhydrylium salts **244**. Note that N and E are kinetic parameters and eq.1 is not applicable to reactions under thermodynamic control.

$$\log k = s_N(N + E) \qquad \text{(eq. 1)}$$

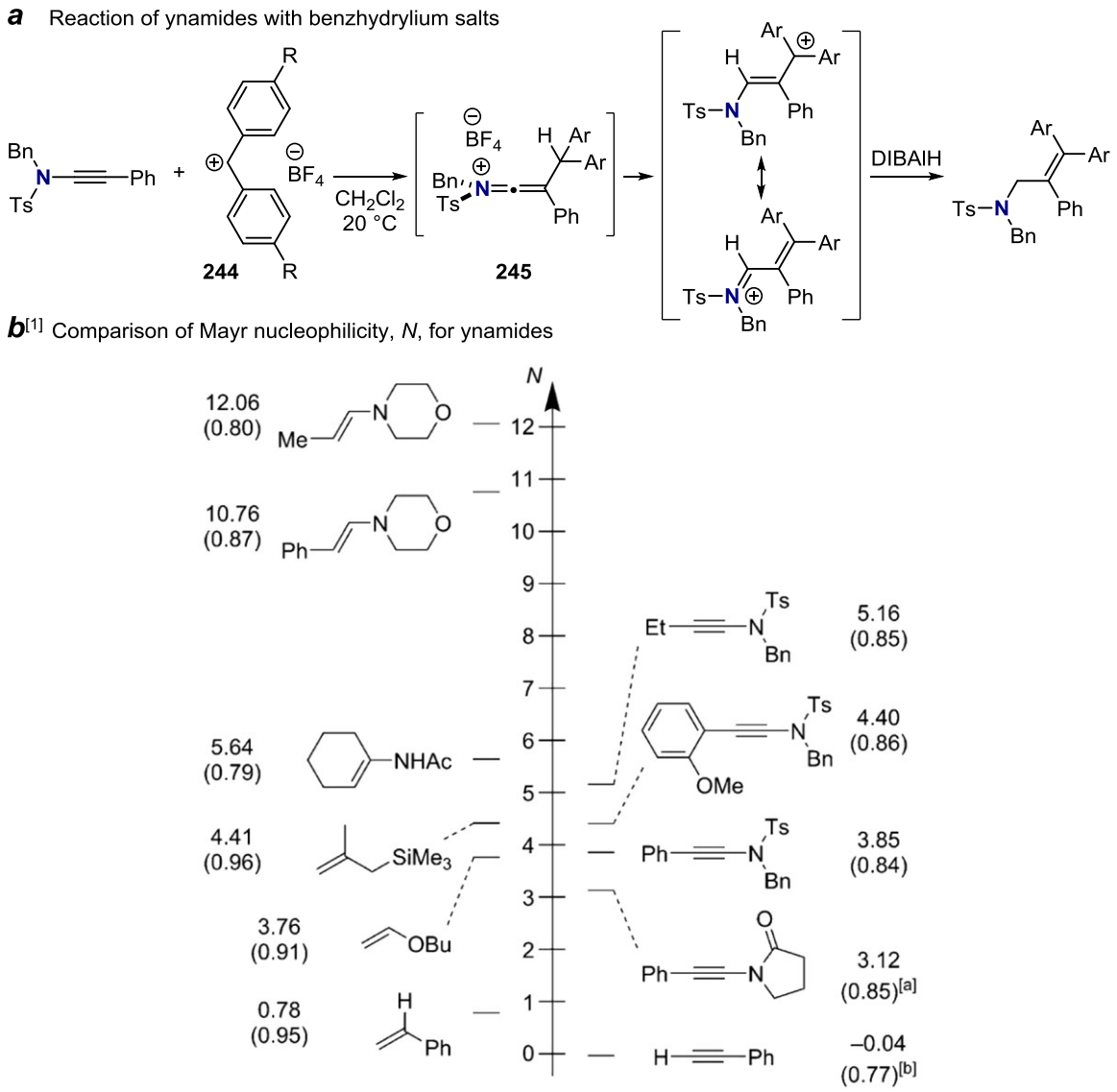


Figure 3.7: Quantification of ynamide nucleophilicity, as performed by Mayr and co-workers. **a**: Example reaction, R = NPh_2, $N(Me)CH_2CF_3$ and $N(Ph)CH_2CF_3$; **b**: Mayr nucleophilicity scale. [1] This figure was taken from ref [350]. The values *N* are on a logarithmic scale and are determined for reactions in performed CH_2Cl_2 (acetonitrile for the enamide) and the values in parentheses are the s_N values (nucleophile specific sensitivity parameter).[a] estimated values of s_N; [b] nucleophilicity parameter adjusted to the revised electrophilicity parameters, *E*, of the reference electrophiles in ref [500].

The nucleophilicities of the ynamides were of a similar order of magnitude as enol ethers, allyl silanes and enamides, but were approximately 10^3–10^5 times more nucleophilic than phenylacetylene (**b**, Figure 3.7). The effect of both the electron withdrawing group and the alkyne *C*-substituent was also apparent given the 100-fold difference in these values. In addition, these studies showed that ynamides are approximately 10^5–10^7 times *less* nucleophilic than enamines and it remains to be seen how these compare to ynamines, which were not studied.

A number of DFT calculations have been performed in an attempt to understand particular outcomes in the reactions of ynamides.[36,141,465,470,483,485,496–505] Whilst many of these involved analyses that

were targeted at answering specific questions relating to those transformations, and did not provide many general insights, a few described natural population analyses to determine the residual charges on the ynamides.[490,501,505,506] It is difficult, however, to make a definitive conclusion by comparing these results because the calculations were performed with different ynamides using different functionals and different basis sets. However, they all indicate that C(α) bears a slight positive charge (ranging from +0.09 to +0.14) and C(β) bears a slight negative charge (−0.02 to −0.12) in the ground state; which is at least consistent with a resonance hybrid that includes **237** (Figure 3.1). Nevertheless, the nucleophilicity of any species relies not only on the charge but on the energy, size and shape of the frontier molecular orbitals involved. In one case,[501] the HOMO of an ynamide (**246**) was calculated and was mainly localised on the alkyne (Figure 3.8). However, it seems unreasonable to consider *only* the electronic ground state and an investigation of possible transition states is much more likely to give a clearer explanation for any selectivity observed in the reactions of ynamides.

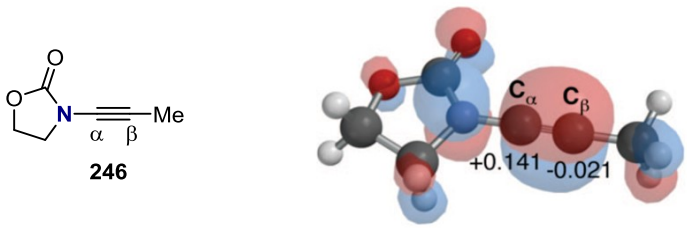


Figure 3.8: HOMO of geometrically optimised ynamide **246**. The values show natural charge at C(α) and C(β). This figure was taken from ref [501], and was calculated at the B3LYP/6-31G* level of theory.

A more detailed computational study of the nucleophilic and electrophilic behaviour of ynamides was disclosed by Bertrand and co-workers.[507] The carbometallation of oxazolidinone, pyrrolidinone, imido and sulfonyl ynamides was investigated using dialkylzinc reagents in the presence of iron or copper salts (Figure 3.9), which afforded the enamides **247** with complete regioselectivity. The use of CuI gave consistently higher yields of **247** and the reactions of $FeCl_2$ exhibited strong substrate dependence, although both salts failed to enable a reaction with the yne-sulfonamide **248c**. Computational analyses were performed in an attempt to rationalise these outcomes. The global electrophilicities of ynamides **248a**–**c** (Figure 3.9) were low, although the sulfonamide was the most electrophilic. Condensed Fukui functions and dual descriptors were calculated to produce maps of nucleophilic and electrophilic regions for ynamides **248a**–**c** (**b**, Figure 3.9),[511,512] which indicated that C(β) was the most nucleophilic site for all of these ynamides and was greatest for the sulfonyl ynamide; note that this is in accordance with Mayr's previous study. The authors, therefore, concluded that the reactivity of these ynamides towards carbometallation increased as the nucleophilicity of C(β) decreased. Furthermore, the carbonyl oxygen atoms for **248a** and **248b** were more nucleophilic than the sulfonyl oxygens in **248c** and it was suggested that

this increased nucleophilicity was important for coordination to zinc, which explained the increased reactivity of **248a** and **248b**, and enabled regiocontrol in the carbometallation.

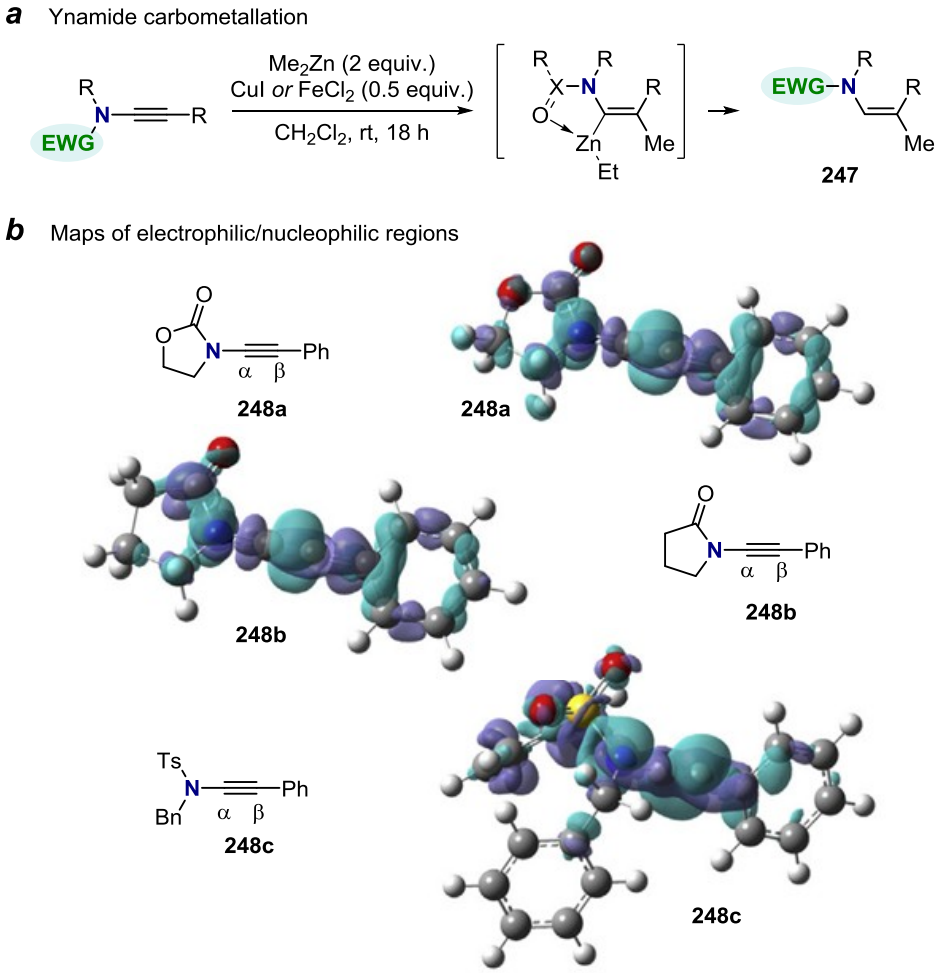


Figure 3.9: **a**: Carbozincation of ynamides. **b**: These figures were taken from ref [507], and show the calculated maps of Fukui's dual descriptors. Nucleophilic (turquoise) and electrophilic (purple) regions are shown for carbonyl and sulfonyl ynamides. Calculations were performed at the B3LYP/6-31+G(d,p) level of theory.

Another interesting reaction was reported by Dodd and co-workers, who described the regio- and stereoselective nucleophilic attack of indolate anions on *N*-alkyl terminal ynamides to give enamides **249** (Figure 3.10).[503,513] This selectivity is remarkable and DFT calculations were performed to rationalise this unexpected outcome. The calculated natural charges of the ynamide were similar to those discussed previously and C(β) was found to bear a negative charge (−0.270). Whilst one might expect the reaction between two nucleophilic sites to be a high energy process dominated by charge repulsion, the activation energy was calculated to be quite low (9.6 kcal mol^{-1}) (**b**, Figure 3.10); it is uncertain whether this value is consistent across a range of functionals. Interestingly, calculations for the formation of the (*E*)-isomer did not converge and collapsed to the (*Z*)-isomer, which was attributed to charge repulsion between the developing anion at C(α) and the incoming nucleophile. The role of the electron withdrawing group was also apparent: the build-up of charge was not

localised on C(α) and was also carried by the indole and the tosyl group, which was very important in determining the regioselectivity.[510]

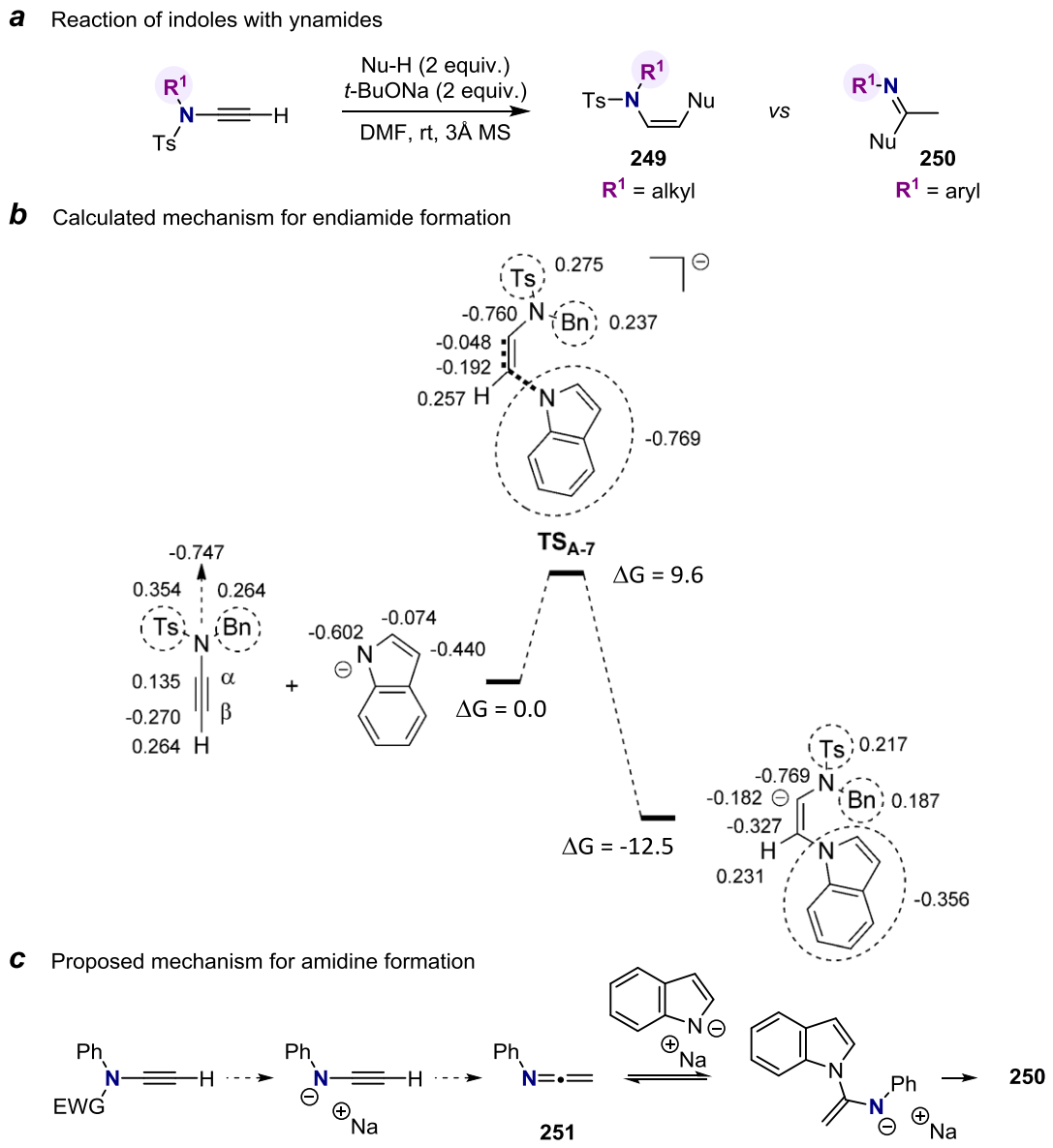


Figure 3.10: **a**: Reaction of terminal ynamides with indoles (Nu-H). **b**: This figure was taken from ref [503]. This figure shows the computed free-energy profile (ΔG, kcal mol^{-1}) for the nucleophilic addition of an indolate to a terminal ynamide (natural bond orbital (NBO) charges of atoms and circled fragments are indicated). Calculations were performed at the M05-2X/6-31+G(d,p) level of theory. **c**: Proposed mechanism for amidine formation.

On the other hand, a seemingly slight change from an *N*-alkyl to an *N*-phenyl ynamide changed the reaction pathway completely in favour of amidine **250**. *N*-Aryl methanesulfonamides, acetamides and carbamate derivatives also led to the same product. This reaction was not subject to DFT analysis and the authors proposed that in situ deprotection of the *N*-aryl ynamide led to the ketenimine **251**,[514] which underwent nucleophilic attack of indole or indolate at C(α). It is possible that the electron withdrawing effect of the *N*-phenyl group was important to facilitate the

nucleophilic attack of *t*-butoxide or indolate at the electron withdrawing group.

Overall, computational studies indicate that there is a slight polarisation of the ynamide alkyne in the ground state, with natural population analyses indicating a slight negative charge at C(β). Furthermore, the map of Fukui dual descriptors also indicated that C(β) possesses increased nucleophilicity as compared to C(α), and these observations support a conclusion that the resonance hybrid **237** (Figure 3.1) has some contribution to the ground state for ynamides. It is possible that such ground-state polarisation offers some regioselectivity bias for the reactions of ynamides but, in general, it is unclear as to the significance of this effect. Further kinetic and computational evidence showed that the electron withdrawing group plays an important role in determining the behaviour of ynamides as nucleophiles (Figure 3.9) *and* electrophiles (Figure 3.10). As of yet, it is unclear whether crystallographic or spectroscopic data are useful in aiding reaction analysis.

3.2 Structural comparison of nitrogen substituted alkynes.

Throughout the work described in Chapters 1 and 2, it was fortunate that many of the ynamides and yndiamides could be made to crystallise and afford single crystals of sufficient quality for X-ray diffraction analyses. Whilst these analyses began as somewhat idle curiosity, certain trends were observed and, despite the significant wealth of data available in the CCDC, no studies have been reported that compare structural features of ynamines or ynamides.

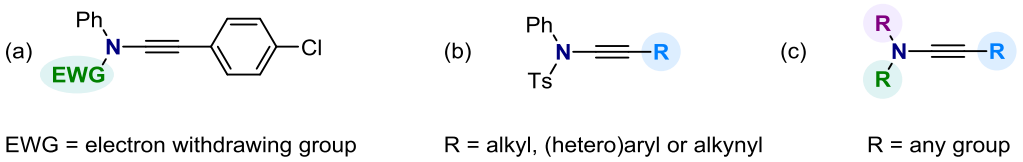


Figure 3.11: Sub-groups for structural discussions.

This study will compare the structural characteristics of ynamides and yndiamides from this work with related data from the CCDC. The discussions will be divided into the following sections: (a) the effect of the electron withdrawing group; (b) the effect of substituents at the alkyne terminus and (c) a comparison of these with data for the nitrogen substituted alkynes published in the CCDC (Figure 3.11). Unfortunately, there is insufficient data available to make a reliable comparison of the effect *N*-alkyl/aryl substitution for ynamides. Following these discussions, the structural features of yndiamides will be described in Section 3.2d, before summarising the key overall findings.

Crystallographic data collection, processing and refinement details for all compounds prepared in this thesis have been included as supplementary data (.cif) with the associated chapters. All other data were obtained from the CCDC and are not included, but can be accessed free of charge from the CCDC.

3.2a Effect of electron withdrawing group.

Different electron withdrawing groups display different conformational preferences in the crystal lattice, which can provide useful insights into the bonding in ynamides. For example, carbamates and amides adopt planar conformations, with the carbonyl oxygen pointing either towards or away from the alkyne (**71e** and **71f**, Figure 3.12). The planarity implies sp^2 hybridisation of nitrogen, with conjugation of the *N*-lone pair into the C=O π*-orbital. The ureas adopted slightly twisted conformations (**85b**), which likely minimises both $A^{1,2}$- and $A^{1,3}$-strain that would exist in a fully planar conformation, whilst maintaining n→π* conjugation of the *N*-lone pairs into the carbonyl. Sulfonamides are not planar, indicating sp^3-like hybridisation at nitrogen, and the *N*-lone pair is aligned between the sulfonyl oxygen atoms (**68a**) to enable conjugation with the S–C σ*-orbital. This stereoelectronic effect grants excellent conformational control and the vast majority of sulfonamides analysed in this work (and in the CCDC) adopt this conformation in the solid state. In general, these geometrical preferences are not unique to ynamides and, in contrast with carbonyl-derivatives, mesomeric effects are much less significant than inductive effects for sulfonamides. This has been attributed to poorer orbital overlap (2p/3p) for lone pair delocalisation.[515]

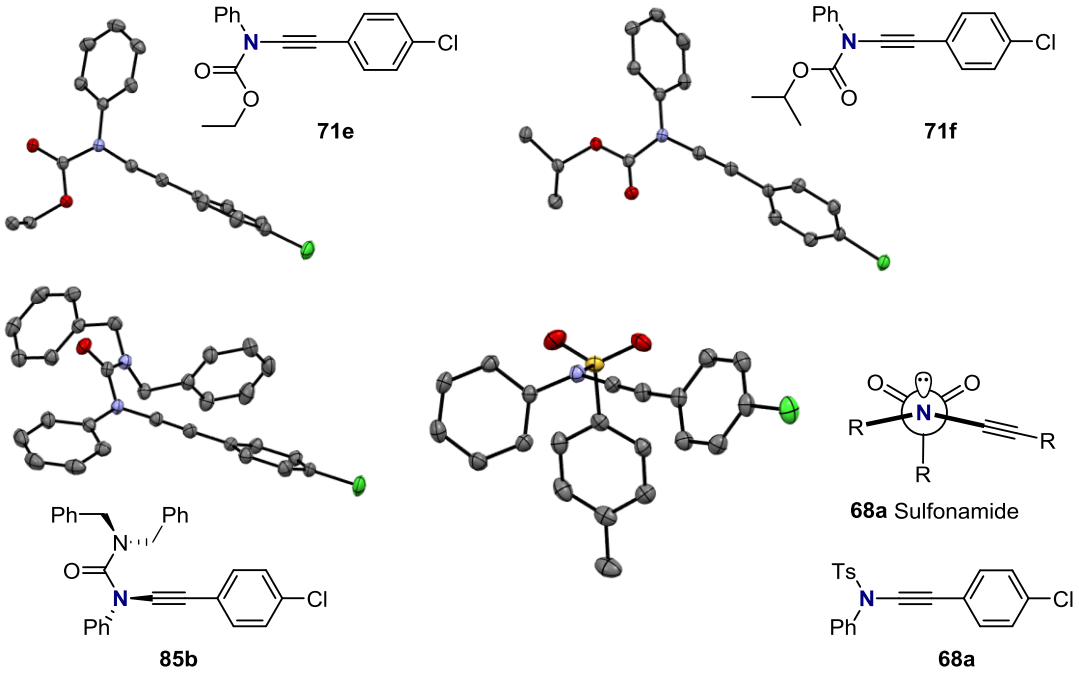


Figure 3.12: Example electron withdrawing group conformations for ynamides. Displacement ellipsoid plots are displayed at 50% probability and hydrogen atoms are omitted for clarity. X-ray data collection, processing and solution refinement for compound **71e** was performed by Dr Kirsten Christensen.

A plot comparing N–C bond lengths and degree of pyramidality about nitrogen ($\sum\theta_N$) for the ynamides in Figure 3.13, where $\sum\theta_N$ is determined by summing the bond angles around nitrogen, shows three distinct regions (Figure 3.14). As indicated previously, the sulfonamides adopted

distinctly pyramidal geometries and carbamates, ureas and the yne-amide **90d** possessed planar or near planar geometries. The N–C bonds lengths fell in the range of 1.354(2)–1.369(2) Å (M = 1.361 Å, SD = 0.004 Å) (see also Figure 3.15); however, shorter N–C bonds were observed for the yne-ureas **85a**–**c** (ranging from 1.354(2)–1.358(1) Å).

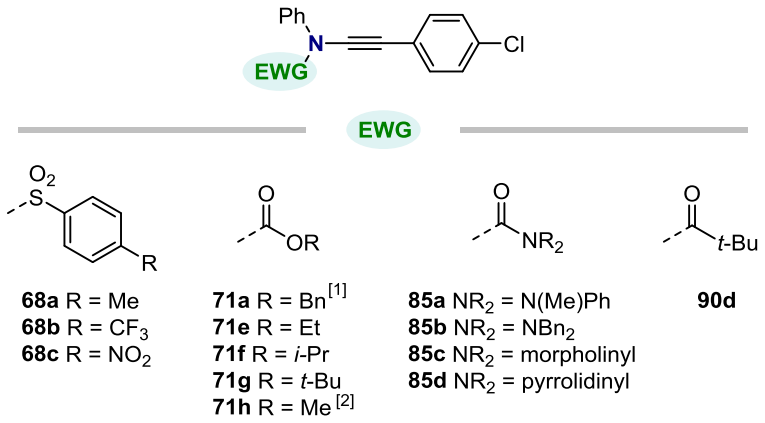


Figure 3.13: Ynamides used for analysis. [1] The asymmetric unit contains two molecules (*Z*' = 2); a phenyl group replaces the 4-chlorophenyl group on the alkyne terminus. [2] This compound possesses a 2-bromophenyl group instead of phenyl on nitrogen.

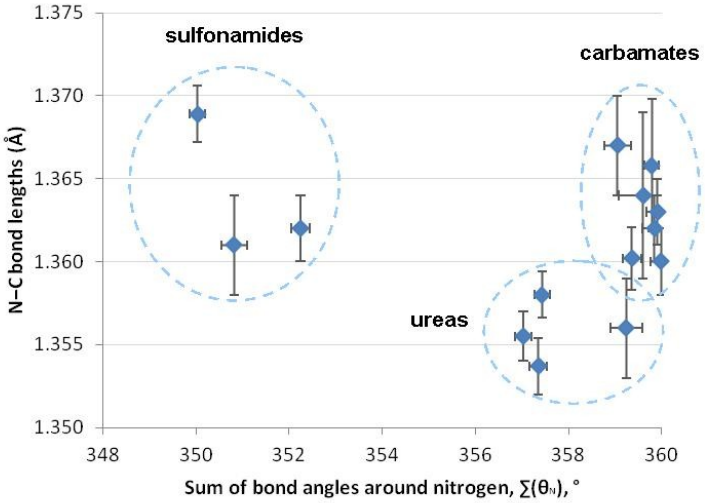


Figure 3.14: Plot of N–C bond lengths against the planarity of substituents about nitrogen for the ynamides shown in Figure 3.13.

Variation of the electron-withdrawing group had no discernible effect on the C≡C and C–C bonds lengths, which fell in the range of 1.185(5)–1.198(2) Å (M = 1.193 Å, SD = 0.004 Å) and 1.432(2)–1.447(2) (M = 1.437 Å, SD = 0.004 Å), respectively. These values are consistent with other C≡C and C(sp)–C(aryl) bond lengths for alkynes. However, more data would be required to determine whether these are general phenomena and, particularly in the case of ureas, to properly determine the effects of different substituents on the electron withdrawing groups.

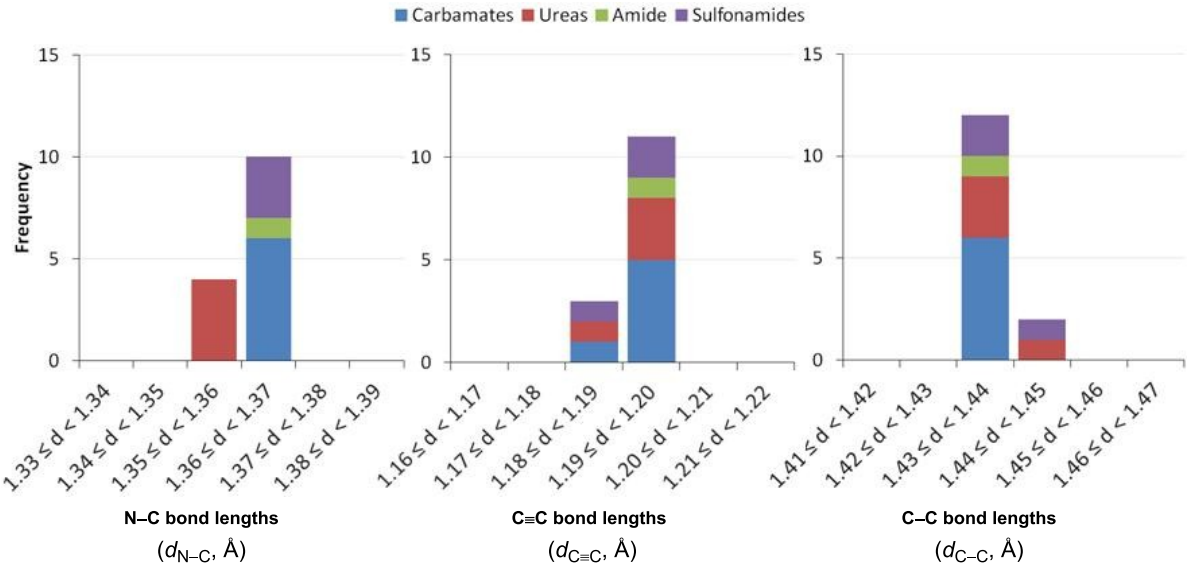


Figure 3.15: Distribution of N–C, C≡C and C–C bond lengths for the ynamides shown in Figure 3.13.

3.2b Effect of substituents on the alkyne terminus.

The nucleophilicity of an ynamide is not only determined by the electron withdrawing group but also the functionality on the *C*-terminus of the alkyne (Mayr nucleophilicities, Figure 3.7). The yne-sulfonamides prepared in Chapter 1 (Figure 3.16) will be considered to determine if there are any discernible structural insights that might aid this conclusion. Diynamide **252** was obtained from the homodimerisation of a terminal ynamide en route to yndiamides (Section 2.2a, Chapter 2). Data for compounds **253** and **254** were obtained from the CCDC (CCDC entries 1841826 and 1423446, respectively). Interestingly, for all examples, the *N*-phenyl groups were not coplanar with the alkyne and were twisted significantly out the plane (mean dihedral angle = 50.43°, SD = 13.54°).

Overall, the alkyne (C≡C) bond lengths fell in the range of 1.184(3)–1.201(2) Å (M = 1.194 Å, SD = 0.004 Å) and were not noticeably affected by variation of the group on the *C*-terminus. However, the N–C bond lengths were generally shorter for ynamides that possess alkynes on the *C*-terminus (**60ap** and **252**, N–C = 1.347(3)–1.3564(15) Å), heteroaryl groups (thien-2-yl (**60w**), fur-2-yl (**60x**), pyrrol-2-yl (**60y**), pyrazol-4-yl (**60z**), quinolinyl (**60ah**) and pyridazinyl (**60ai**), N–C = 1.345(3)–1.3556(15) Å), benzoyl (**254**, 1.345(3) Å) and 2-fluoro-6-methoxyphenyl (**60i**, 1.3585(18) Å) groups. These bond lengths are consistent with the increased electron withdrawing effect of these groups. The conformation of these ynamides in the crystal lattice is also informative: the 5-membered heterocycles and 2-fluoro-6-methoxyphenyl group were twisted by 58.2(2)–87.4(4)° away from the C–N–S plane of the sulfonamide (Figure 3.18), and the quinoline, pyridazine and benzoyl substituents were almost coplanar, with torsion angles between 2.1(1)–4.6(3)°. Whilst the latter three support the conclusion for conjugation, it is possible the 5-membered heterocycles and the 2-fluoro-6-methoxyphenyl group were inductively electron withdrawing. Although not prepared for this study, ynamides capped with thien-3-yl or fur-3-yl groups would be useful for comparison.

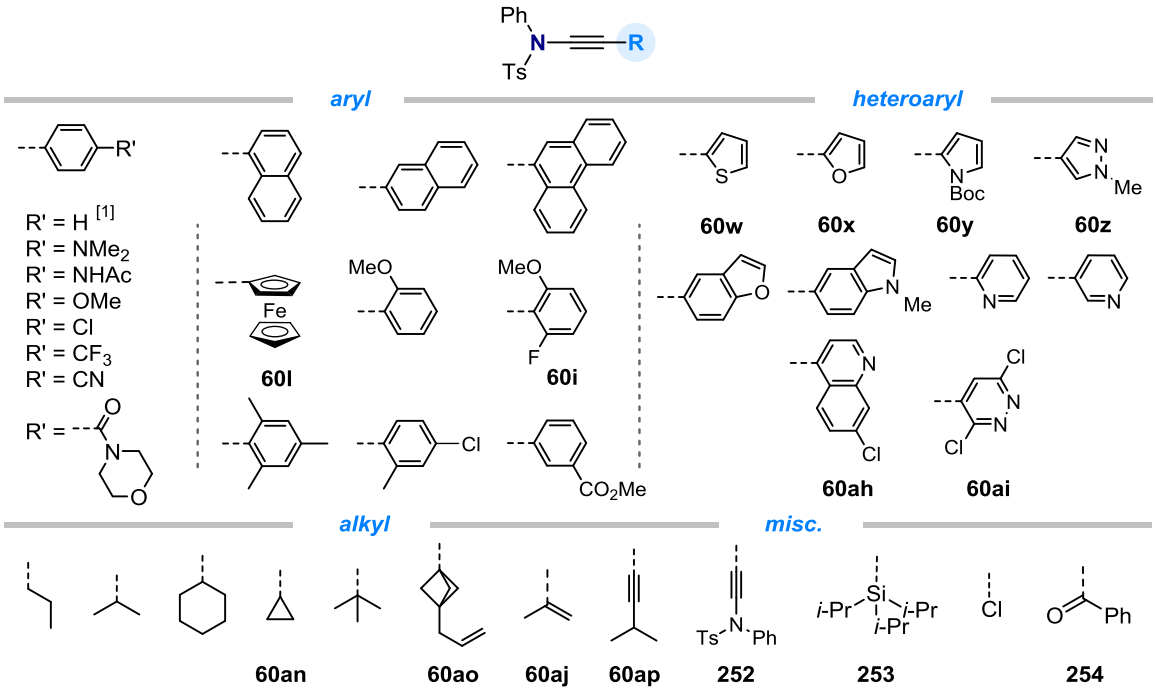


Figure 3.16: Scope of ynamides used for analysis. [1] Two polymorphs were characterised for this compound.

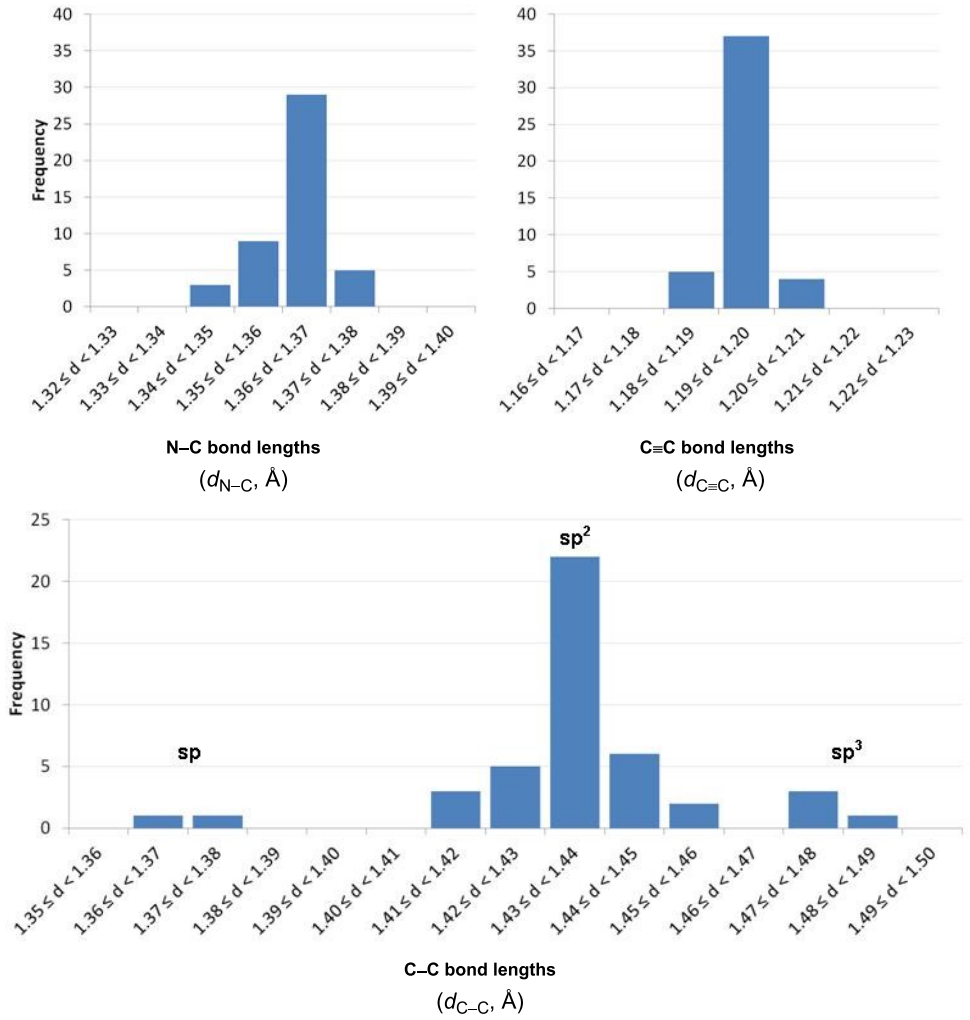


Figure 3.17: Distribution of N–C, C≡C and C–C bond lengths for ynamides in Figure 3.16.

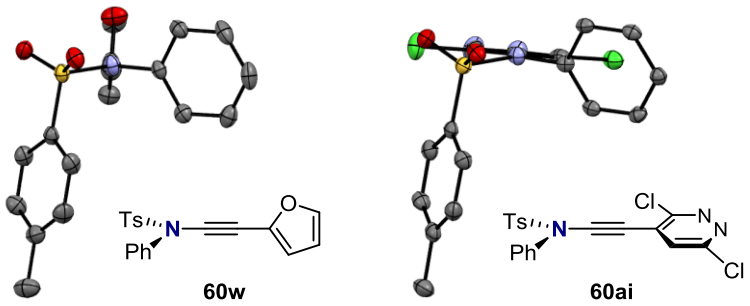


Figure 3.18: Conformations of furyl and pyridazinyl ynamides in the crystal lattice. Displacement ellipsoid plots are displayed at 50% probability and hydrogen atoms are omitted for clarity.

There is a strong correlation between C–C bond lengths and the hybridisation of the terminal group: sp-hybridised groups (e.g. alkynyl) have C–C bond lengths in the range of 1.36–1.38 Å, sp^2-hybridised (e.g. aryl/alkenyl) between 1.4140(18)–1.447(5) Å (M = 1.433 Å, SD = 0.007 Å) and sp^3-hybridised (e.g. alkyl) between 1.441(2)–1.4806(18) Å (M = 1.465 Å, SD = 0.017 Å). This trend is not surprising, because increased s-character contracts σ-bonding orbitals and there is also a possibility of conjugation for the alkynyl and aryl substituted ynamides. The previously mentioned heteroaryl groups (thien-2-yl (**60w**), fur-2-yl (**60x**), pyrrol-2-yl (**60y**), pyrazol-4-yl (**60z**), quinolinyl (**60ah**) and pyridazinyl (**60ai**)) and ferrocene **60l** all possessed short C(sp)–C(sp^2) bonds (1.4140(18)–1.4293(18) Å), which can be attributed to increased conjugation with the alkyne. Longer C(sp)–C(sp^2) bonds (1.44–1.46 Å) were found for benzoyl (**254**, 1.4475(19) Å) and propenyl ynamides (**60aj**, Z' = 2, 1.452(2) & 1.456(2) Å); however, it is interesting to see the cyclopropyl (**60an**, 1.441(2) Å) and BCP (**60ao**, 1.4474(19) Å) ynamides also in this range. This is consistent with increased s-character in the σ-bonds to these strained alkyl groups.

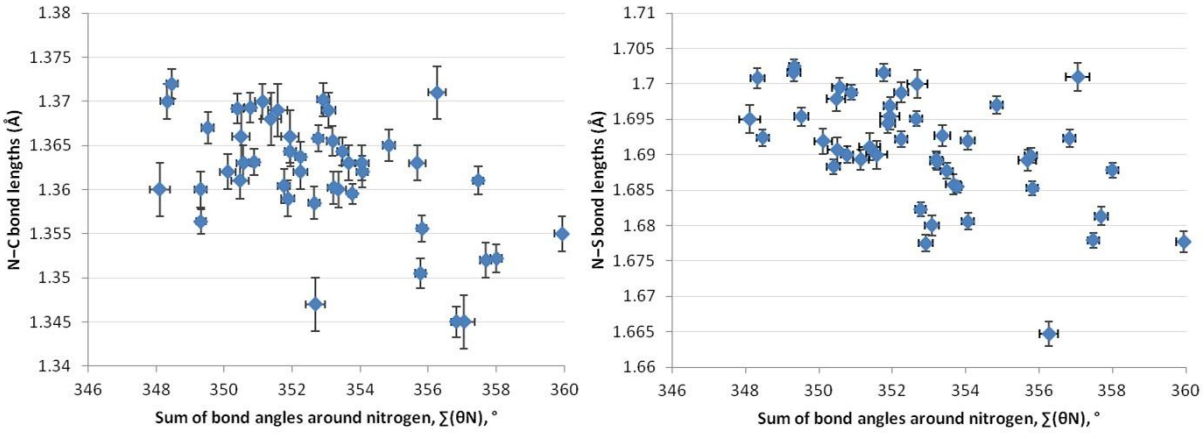


Figure 3.19: Plot of N–C and N–S bond lengths against $\sum\theta_N$ for the ynamides in Figure 3.16.

In general, the substituents about the sulfonamide nitrogen typically adopted a pyramidal geometry, though there is, at best, only a slight correlation between the degree of pyramidality, $\sum\theta_N$, and either

of the N–C or N–S bonds lengths, which may otherwise have indicated increased or decreased electron delocalisation (Figure 3.19). $\sum\theta_N$ typically clustered around 350–354°, but the heteroaryl and benzoyl substituted ynamides tended to fall outside of this range, their substituents adopting positions closer to planarity ($\sum\theta_N$ = 355.77(16)–359.94(22)°). There was also no correlation between the torsion angles for *C*-aryl ynamides and N–C, C–C or $\sum\theta_N$ (Figure 3.20). However, these plots did show an unpopulated region of torsion angles between 20–30°, but it is unclear whether this is a crystal packing phenomenon or indicative of an otherwise disfavoured conformation. The outlier at (1.347 Å, 70.9°) in plot **c** is for the Ph–N–N–Ph torsion angle for diynamide **252**, which is useful to include for later discussions with yndiamides.

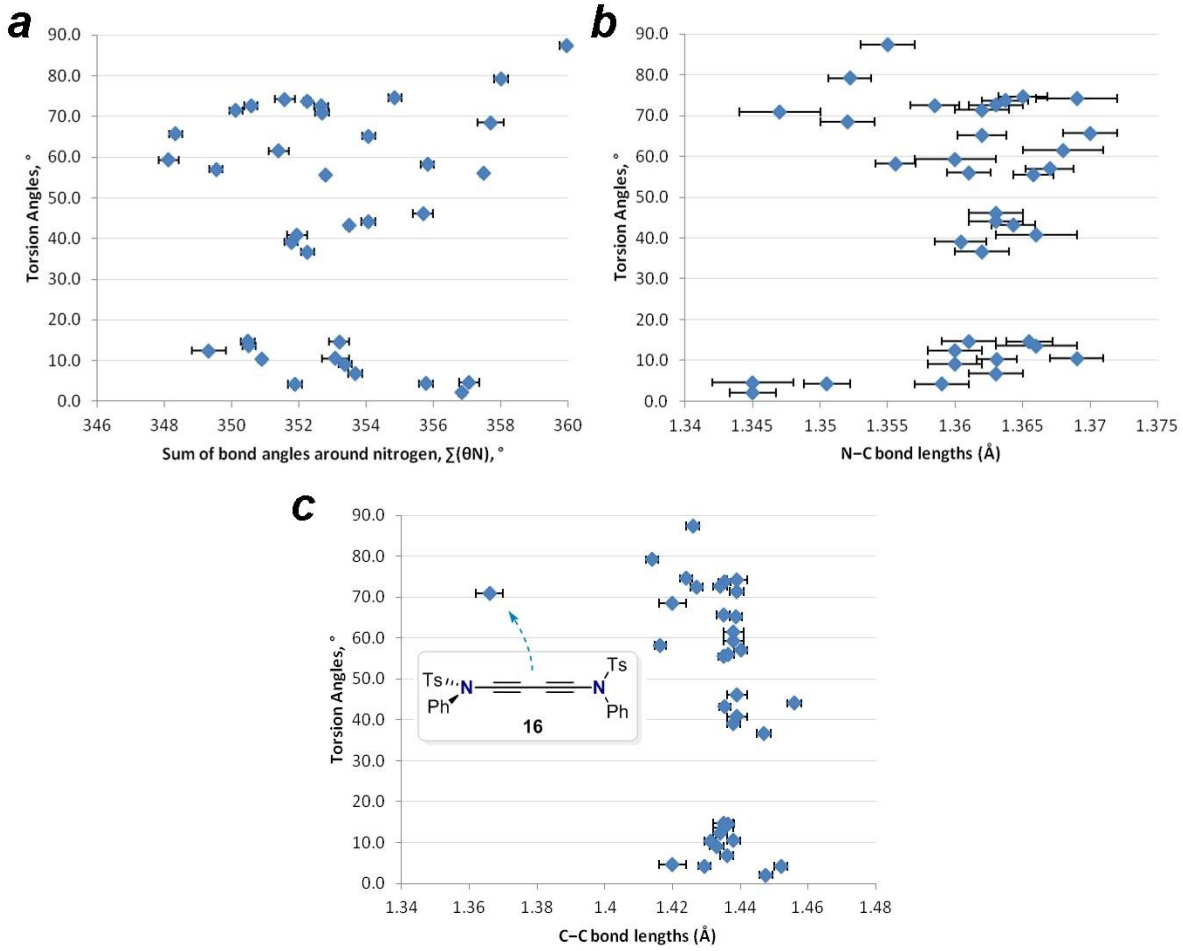


Figure 3.20: Plots of torsion angles against $\sum\theta_N$, N–C and C–C bond lengths for the ynamides in Figure 3.16.

The data so far indicates that the planarity of the substituents around nitrogen is almost exclusively influenced by the electron withdrawing group: carbonyl protected ynamides tend to give a planar arrangement and sulfonamides tend to be pyramidal. In general, the electron withdrawing group does not appear to affect the N–C, C≡C or C–C bond lengths to any significant degree; though it is unclear as to the importance of strain versus stereoelectronic effects for ureas. Considering the nature of the substituent on the alkyne terminus, variation in C–C bond lengths are consistent with

the hybridisation of this group. In general, only cases of strong inductive or conjugative electron withdrawing functionalities at the *C*-terminus were found to impart a discernible structural effect (i.e. a small decrease in N–C and C–C bond lengths).

It is also interesting to note that whilst the Ph(Ts)N moiety for each ynamide adopted almost identical positions in the crystal lattice (examples in Figure 3.18), the group on the alkyne displayed much a greater conformational variation. The torsion angles did not correlate with bond lengths or angles, except for the ynamides capped with heterocyclic groups, and it is likely that the observed conformations arise due to favourable packing forces rather than a strong electronic predisposition.

3.2c Comparison with data from the Cambridge Crystallographic Data Centre (CCDC).

To conclude our crystallographic study, we shall compare the previous data with that obtained from the CCDC and with the remaining data collected during our studies. The CCDC contains a wealth of data for various nitrogen substituted alkynes (Figure 3.21), including those coordinated to organometallic complexes and, for this study, only structures of uncomplexed alkynes that possess final R indices ($I>2\sigma(I)$) of 0.05 or less have been considered. These values indicate how well the refined crystallographic model represents the experimental diffraction data, and smaller R indices signify smaller discrepancies between the calculated values and experimental values. The data presented previously has been combined with that obtained from the CCDC and the results, shown in Figures 3.22 and 3.23, have been colour coded: data for ynamines (amine, aniline or phenothiazine substituted alkynes, which represent only a small proportion of the data) are coloured red and data for yne-sulfonamides and other ynamides are coloured blue and green, respectively.

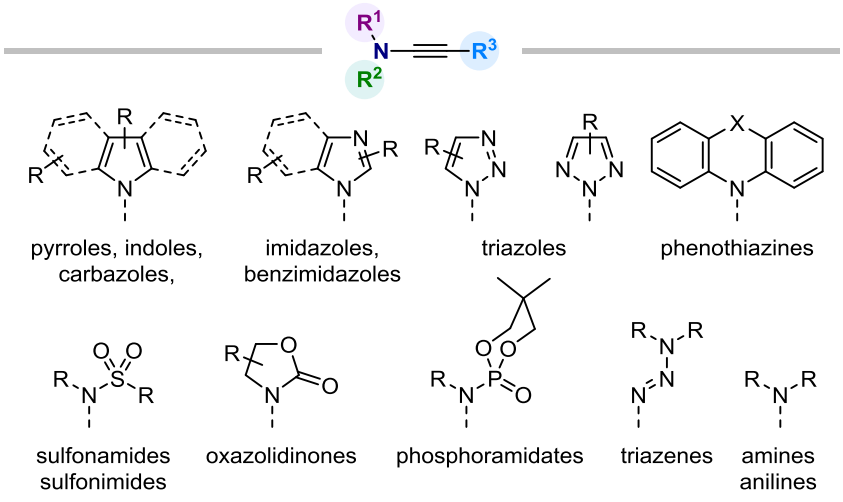


Figure 3.21: Scope of nitrogen-substituted alkynes. R^3 includes H, alkyl, aryl, alkynyl and silyl .

In general, the trends described previously are also consistent with the data from the CCDC. N–C and C≡C bond lengths are predominantly in the regions of 1.34–1.38 Å (M = 1.359 Å, SD = 0.008 Å) and 1.18–1.21 Å (M = 1.193 Å, SD = 0.007 Å), respectively, and C–C bonds lengths all

display a dependence on the nature of the terminal group (Figure 3.22). Ynamines were observed to have shorter N–C bond lengths than the other nitrogen substituted alkynes, though the data set contained many *N*,*N*-diaryl and/or polyyne-ynamines, biasing the results due to conjugative effects.

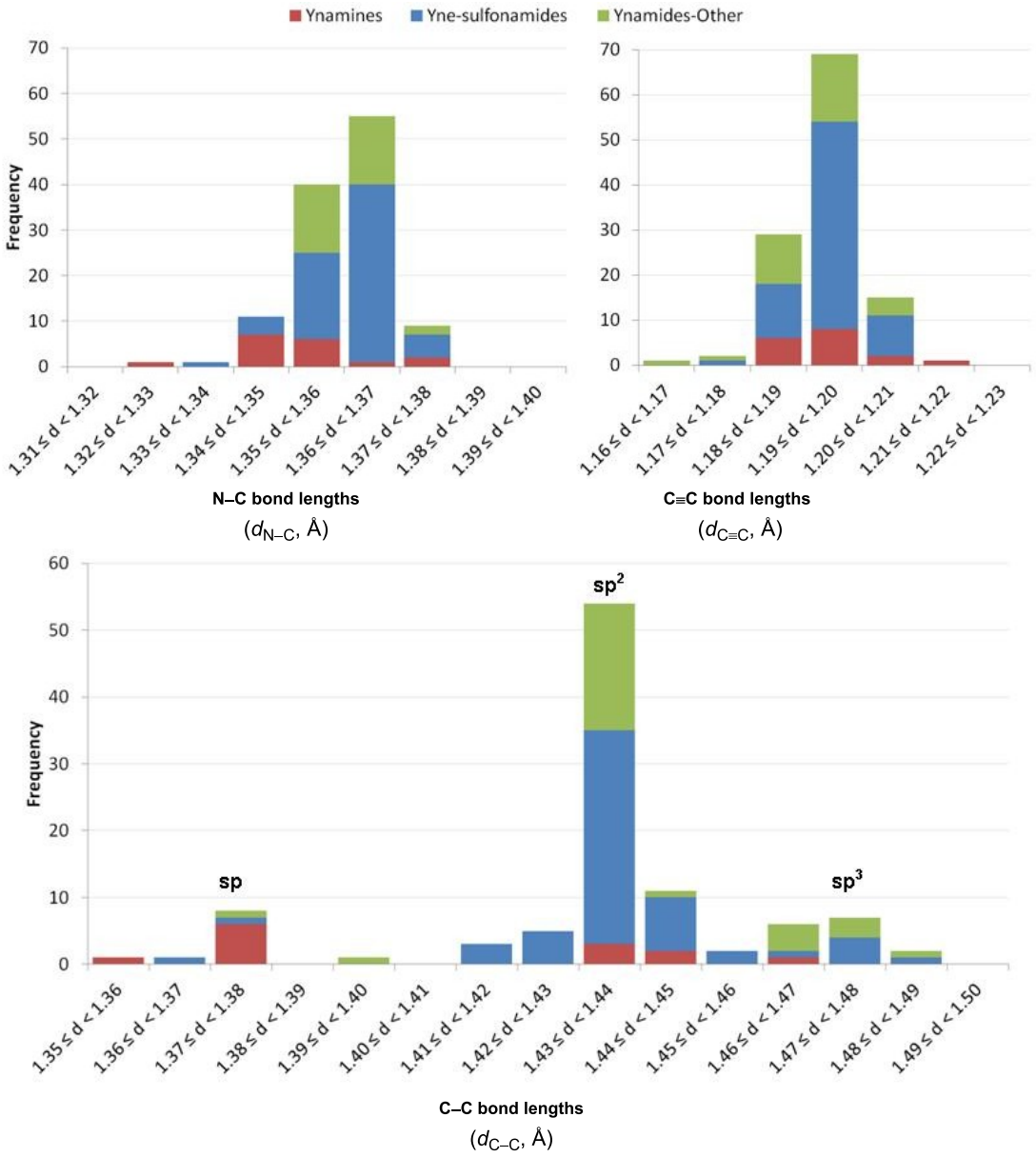


Figure 3.22: Distribution of N–C, C≡C and C–C bond lengths for nitrogen substituted alkynes. Blue represents all electron deficient nitrogen substituted alkynes (termed "ynamides" for convenience) and red for ynamines.

A map of planarity versus N–C bond angles further demonstrated the effect of the electron withdrawing group on the geometry of substituents at nitrogen (Figure 3.23); for the single triazene example, the sum of angles about the R_2N–N group was taken (Z' = 2, 359.2(1)° and 359.8(1)°). Two regions exist in this map: sulfonamides tend to possess a pyramidal arrangement of substituents ($\sum\theta_N$ = 350–354°). The others, for example, oxazolidinones, indoles and triazoles, tend to adopt planar or near planar geometries. The ynamines also display a tendency for planar or near planar geometries, but this is unlikely to be a general phenomenon due to the aforementioned conjugation.

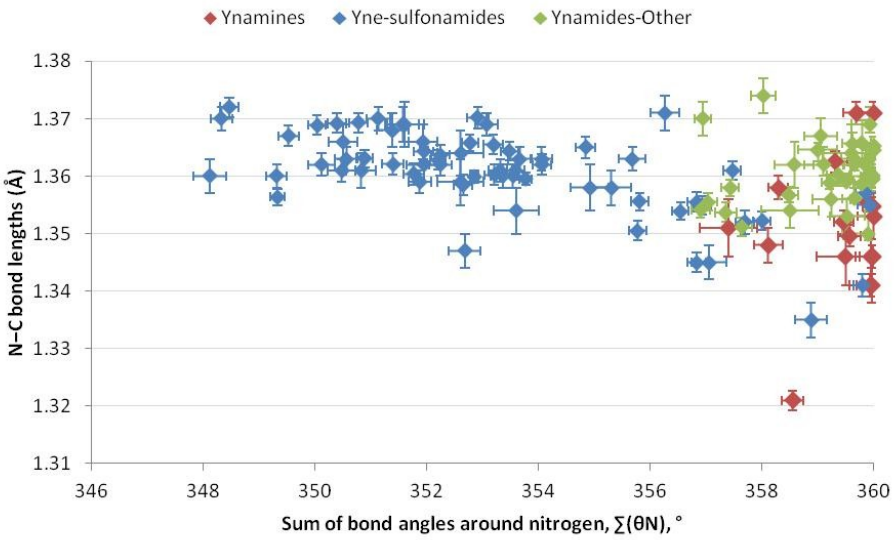


Figure 3.23: Plot of N–C bond lengths against the planarity of substituents about nitrogen. Blue represents all electron deficient nitrogen substituted alkynes (termed "ynamides" for convenience) and red for ynamines.

Overall, the strong electronic bias of the electron withdrawing group affords the greatest conformational control in the crystal lattice, which also determines the geometry of the substituents around nitrogen: e.g. trigonal planar for carbamates and azacycles or pyramidal for sulfonamides. Except in cases of increased electronic bias, the group on the alkyne terminus displayed no particular conformational preference and was more likely influenced by packing forces in the crystal lattice. This could be indicative of a low barrier for interconversion of conformers at the temperatures used to crystallise these compounds (typically 0–25 °C).

Furthermore, variation of the electron withdrawing group did not measurably influence the N–C or alkyne (C≡C) bond lengths. Whilst C–C bond lengths varied according to the hybridisation of the terminal substituent, for example, alkynyl, aryl or alkyl groups, the effect of variation within these subgroups was often too small to determine crystallographically. Only in certain cases, i.e. ynamides that possess an electron withdrawing substituent on the alkyne terminus, were slightly shorter N–C and C–C bonds observed, which could be due to inductive and/or conjugative effects of this group.

3.2d Yndiamides.

We will next compare the data for ynamides with the structural preferences exhibited by yndiamides and yndiamines. Data for yndiamines **255**–**257** (Figure 3.24) were obtained from the CCDC (CCDC entries 784155, 784156 and 970596, respectively). Furthermore, we wondered whether structural data, for example, variation in bond lengths or degree of pyramidality, could provide any insight into the reactivity of *N*-phosphoryl yndiamides, particularly in light of the regioselectivity discussed at the end of Chapter 2; shorter N–C bond lengths could possibly indicate greater conjugation with the alkyne.

Unlike for ynamides, all of the yndiamides/yndiamines adopted a significantly twisted conformation in the crystal lattice. These conformations are analogous to those seen for diynamides **242** and **252** (see Figures 3.5 and 3.16, respectively), and all of these molecules possess axial chirality (at least in the solid state). Except for (–)-**148t** and **148w**, which were prepared from enantiopure sulfonamide precursors, every other yndiamide was necessarily obtained as a racemate. Of the 22 yndiamide crystal structures obtained (Figure 3.24), 18 crystallised as true racemates in centrosymmetric space groups. This was also the case for the yndiamine structures obtained from the CCDC. The enantiopure yndiamide **148w** crystallised in the chiral space group C2 (Flack (x) = −0.007(17)) and the remaining 3 compounds, **160b**, **160h** and **160m**, each crystallised in the chiral space group $P2_12_12_1$; albeit the structures for **160b** and **160h** were found to be twinned (Flack (x) = 0.450(19) and 0.432(19), respectively) and contained an approximate 1:1 ratio of (*R*)- and (*S*)-domains. The Flack (x) parameter for **160m** (0.00(2)) suggests that this compound spontaneously resolved during crystallisation to give a conglomerate mixture of enantiomerically pure crystals. However, no further studies were performed to verify this and it is entirely possible that the bulk crystalline material also contained twinned crystals and/or polymorphic mixtures. Indeed, it is uncertain whether the twisted conformations adopted by yndiamides in the solid state are maintained in solution, and the reader is referred to subsequent discussions in Sections 3.3b and 3.4.

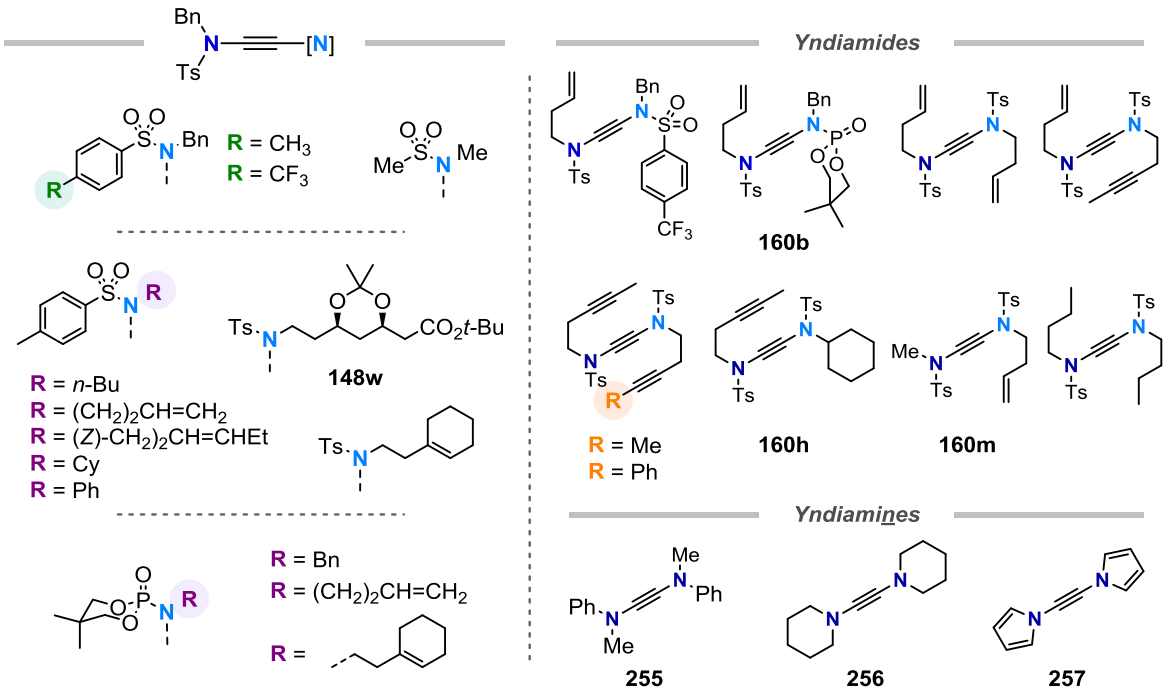


Figure 3.24: Yndiamides and yndiamines for which X-ray crystallographic data has been obtained and used in our study.

Nevertheless, a plot of C–N–N–C and S–N–N–C torsion angles, φ and ψ, respectively, for *N*-sulfonyl ynamides and yndiamides shows a much narrower range of angles as compared to ynamides (Figure 3.25). It is also interesting to note that the angle φ was typically less than 90° for

yndiamides. In all cases, data points that fall on the line $\psi = 180 - \varphi$ represent cases in which the substituents adopt a planar geometry about nitrogen, with data points closer to the origin indicating a greater degree of pyramidality.

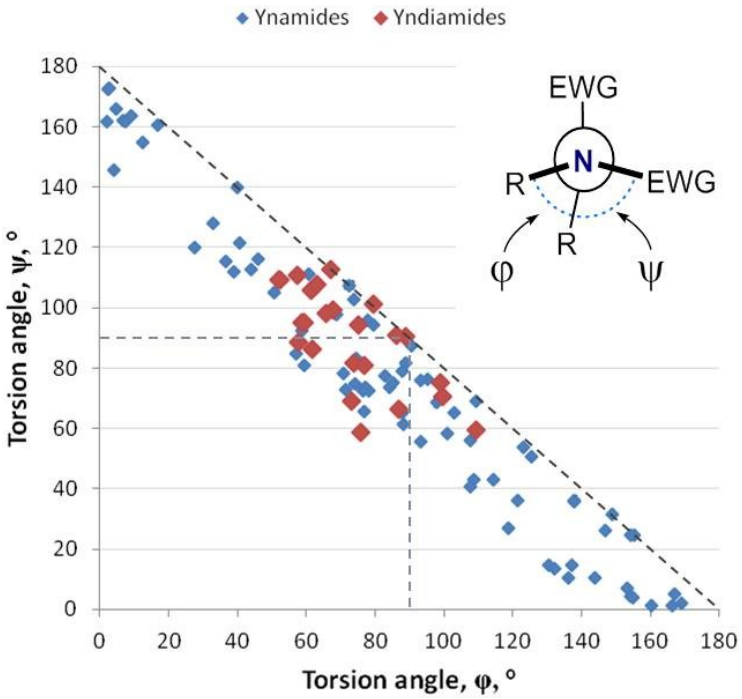


Figure 3.25: Plot of torsion angles φ and ψ for *N*-sulfonyl ynamides (blue) and yndiamides/yndiamines (red).

In addition to these twisted conformations, the electron withdrawing groups also adopted a number of orientations in the crystal lattice. In the cases of *N*,*N*'-disulfonyl yndiamides, three different orientations of the sulfonyl groups were observed (Figure 3.26): most had conformation **258**, three of **259** and one of **260**. There were no discernible trends for S–N or N–C bond length differences and the key stereoelectronic factor (N lone pair → S–C σ* donation) is retained for all sulfonamides.

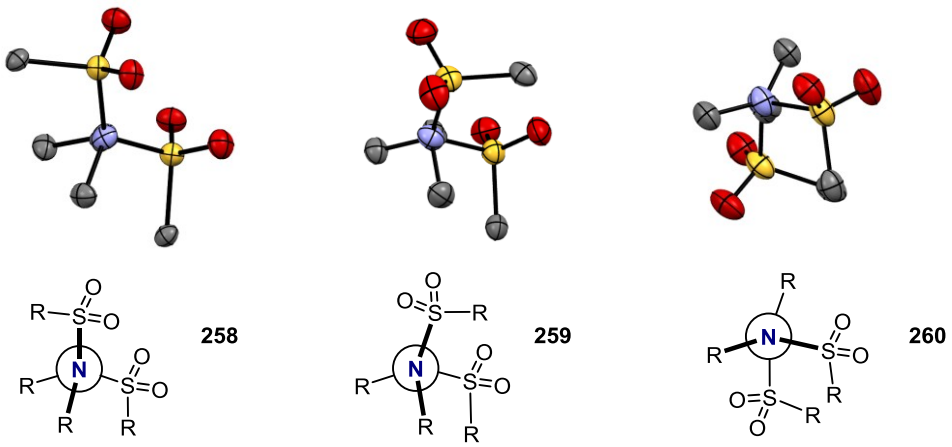


Figure 3.26: Conformations of yndamides in the crystal lattice, as viewed down the N–C≡C–N axis. Displacement ellipsoid plots are displayed at 50% probability with tosyl and alkyl groups, and hydrogen atoms omitted for clarity.

The phosphoramidates also adopted various conformations in the crystal lattice (Figure 3.27): two of which had the nitrogen atom positioned axial on the chair-like 6-membered ring (**261**/**262**) and another in the equatorial position (**263**). There was also a slight correlation between phosphoryl orientation and P–N/N–C bond lengths: in the cases where nitrogen was axial (**261**/**262**), the N(1)–C(2) bond lengths were shorter (1.342(4)–1.346(3) Å) and P–N(1) bonds longer (1.671(2)–1.674(2) Å) than for the equatorial conformer (N(1)–C(2) = 1.359(3)–1.360(3) Å and P–N(1) = 1.6445(18)–1.6498(18) Å).

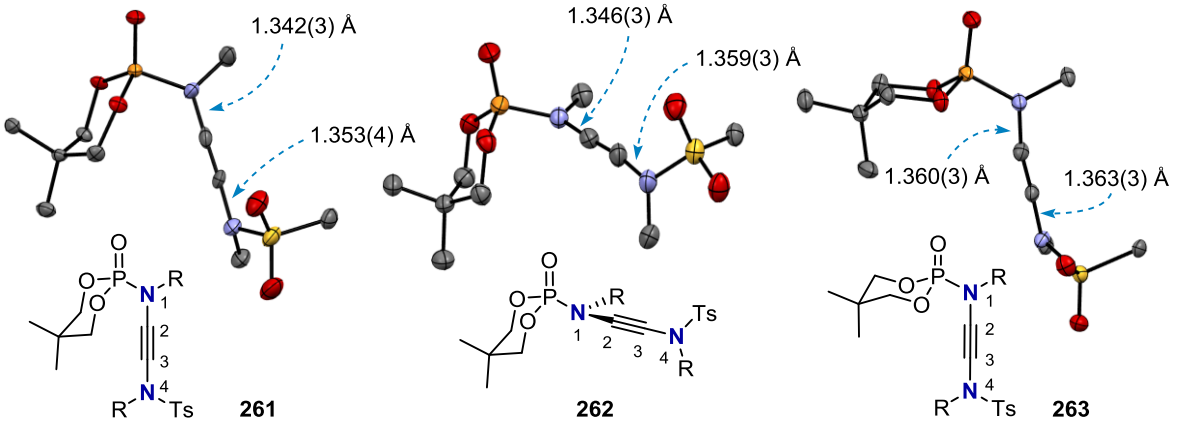


Figure 3.27: Conformations of phosphoryl groups in the crystal lattice. Displacement ellipsoid plots are displayed at 50% probability, with tosyl and alkyl groups, and hydrogen atoms omitted for clarity.

Nevertheless, the interconversion of these sulfonyl and phosphoryl conformers is expected to be rapid in solution at room temperature (i.e. the temperature at which all of these crystals can be grown) and it is intriguing to speculate whether a Curtin-Hammett like scenario operates in the reactions of phosphoryl yndiamines, in which the reactivity of specific conformers is important for determining the overall reactivity. Furthermore, and assuming a sufficiently low racemisation barrier for yndiamides in solution, it might also be reasonable to expect reactivity differences between the twisted and planar conformations that would be accessible via rotation of the amido groups.

In general for yndiamines and yndiamides, the mean N–C (1.352 Å, SD = 0.007 Å) and alkyne (C≡C) (1.187 Å, SD = 0.007 Å) bond lengths were slightly shorter than those of ynamides (Figure 3.28). A plot of N–C lengths against planarity ($\sum\theta_N$) for yndiamides and yndiamines showed a much greater spread of $\sum\theta_N$ values as compared to the ynamides (Figure 3.29). This did not correlate with the identity of the *N*-alkyl groups on either end of the yndiamide, nor the orientation of the electron withdrawing group. The phosphoramidate groups tended to adopt more planar geometries as compared to the sulfonamides, which is also the case for related *N*-phosphoryl ynamides (CCDC entries 848644 and 905007, $\sum\theta_N$ = 358.1(3)–359.6(2)°).[98,516] Considering the yndiamines, it is interesting to note that the dipiperidine yndiamine (**256**) had a distinctly pyramidal geometry about nitrogen ($\sum\theta_N$ = 344.57(18)° and 341.61(17)°) as compared to the *N*-phenyl (**255**) and pyrrolyl (**257**) analogues, which were distinctly planar - likely due to conjugative effects and pyrrole aromaticity.

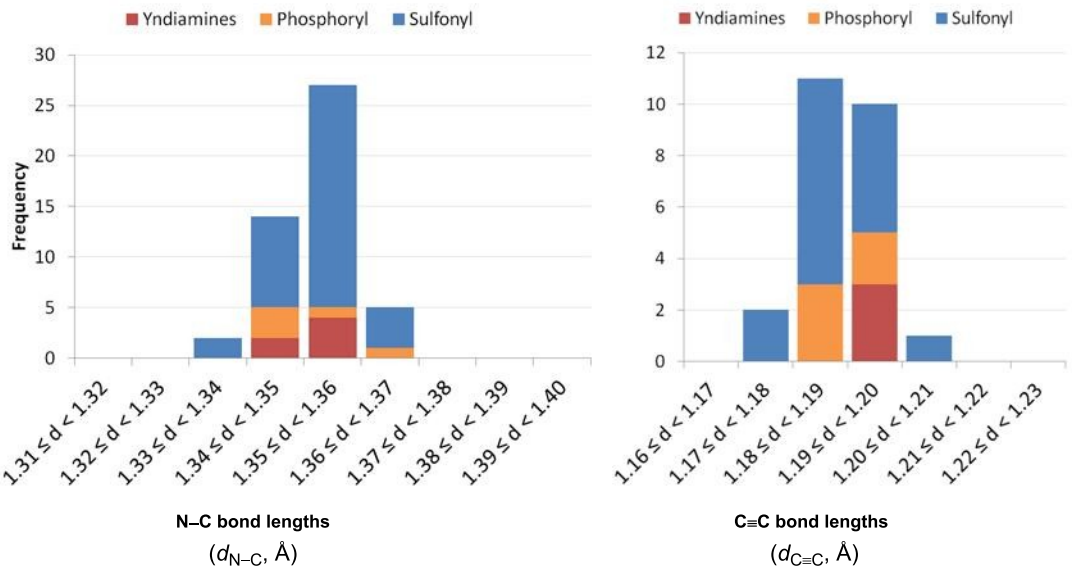


Figure 3.28: Distribution of N–C and C≡C bond lengths for yndiamines, *N*-phosphoryl and *N*,*N* ′-disulfonyl yndiamides.

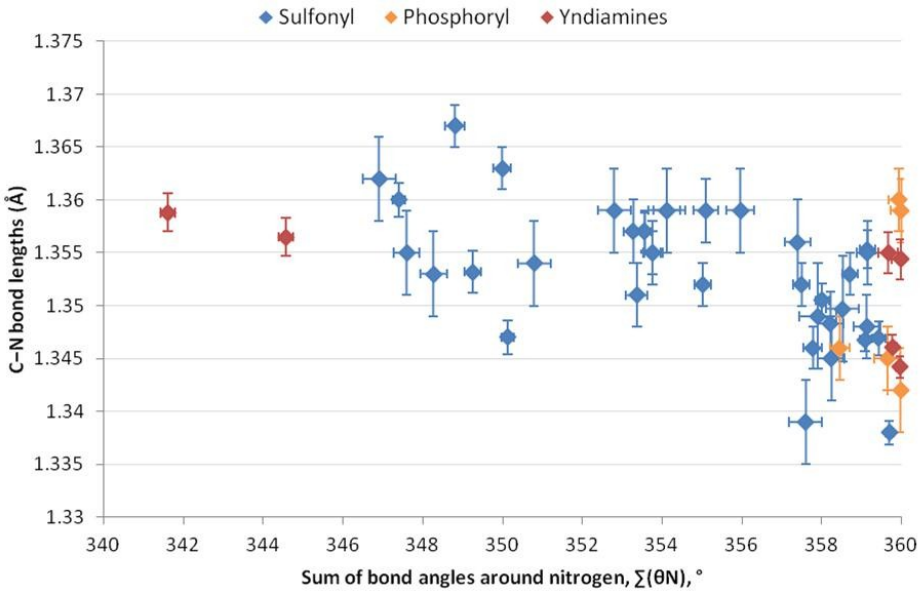


Figure 3.29: Plot of N–C bond lengths against $\sum\theta_N$. In the legends, sulfonyl and phosphoryl refer to $\sum\theta_N$ about the sulfonamide and phosphoramidate, respectively.

Overall, the key structural difference between ynamides and yndiamides was the strong preference for the latter to adopt a twisted conformation in the crystal lattice. The consistency of this phenomenon suggests an electronic bias as opposed to a crystal packing effect. The orientation of the electron withdrawing groups provided stereoelectronic insights about their bonding, for example, n $\rightarrow$ π^* or n $\rightarrow$ σ^* delocalisation, but it was the conformational freedom of the two electron withdrawing groups in yndiamides that could be very important for determining their overall reactivity. In general for both ynamides and yndiamides, the N–C(sp) and C≡C bond lengths fell within the ranges of 1.34–1.37 Å (M = 1.357 Å, SD = 0.008 Å) and 1.17–1.21 Å (M = 1.192 Å,

SD = 0.007 Å), respectively. Slightly shorter N–C bond lengths (Δd_{N-C} ~0.02 Å) were observed where inductive or conjugative electron withdrawing groups were also present on the alkyne. Furthermore, it was generally not useful to consider differences in C≡C bond lengths and a comparison of N–C lengths was more valuable, albeit the differences were very small.

3.3 Spectroscopic comparison of ynamides and yndiamides.

3.3a Vibrational spectroscopy.

In comparison with X-ray crystallographic techniques, it can often be easier to detect the electronic influence of substituents on a functional group by using vibrational spectroscopy. Here we will focus on the effect of ynamide substitution on the alkyne stretching frequencies, $\nu_{(c\equiv c)}$, and in the IR spectrum, $\nu_{(c\equiv c)}$ occurs between 2150–2100 cm^{-1} for mono-substituted alkynes and 2260–2190 cm^{-1} for disubstituted alkynes.[517] We will also consider the effect of the alkyne on carbonyl stretching frequencies $\nu_{(c=o)}$, (typically between 1800–1630 cm^{-1}) for relevant examples. A better diagnostic might be an evaluation of the N–C stretching frequencies but, unfortunately, these are often harder to locate due to overlap with other bands in the 1350–1050 cm^{-1} range.

Data for a range of *N*-alkyl and *N*-aryl tosyl ynamides were gathered to explore the effect of substituents at nitrogen, and to compare these with alkyl and aryl groups on the alkyne terminus.[31,33,37,132,203,518–520] Overall, *N*-alkyl and *N*-aryl groups had only a slight influence on the alkyne stretching frequencies as compared to having alkyl or aryl groups directed attached to the alkyne terminus (Figure 3.30): typically, *C*-alkyl ynamides possessed stretching frequencies in the range of 2270–2240 cm^{-1} and *C*-aryl ynamides were at lower frequencies in the range of 2245–2220 cm^{-1}. This difference can be attributed to both inductive and conjugative electron withdrawing effects of the *C*-aryl group. However, variation of electron donating or withdrawing groups on the arene did not significantly alter the alkyne stretching frequencies and only in the case 4-cyanophenyl was the stretching frequency decreased to 2221 cm^{-1}.

The effect of the electron withdrawing group was next investigated using *C*-aryl ynamides; in most cases, the aryl group was either a phenyl or 4-chlorophenyl substituent (Figure 3.31). Surprisingly, variation of the electron withdrawing group did not have a significant influence on the alkyne stretching frequencies, which were typically in the range of 2260–2230 cm^{-1}. Absorption frequencies for oxazolidinones and aromatic azacycles, for example, indoles and pyrroles, tended to be at the higher end of this range and ureas, phosphoramidates and sulfonamides came at the lower end (2249–2230 cm^{-1}). Moreover, there was little difference in alkyne stretching frequencies for azetidinone ($\nu_{(c\equiv c)}$ = 2241 cm^{-1}) and pyrrolidinone ynamides ($\nu_{(c\equiv c)}$ = 2247–2241 cm^{-1}).

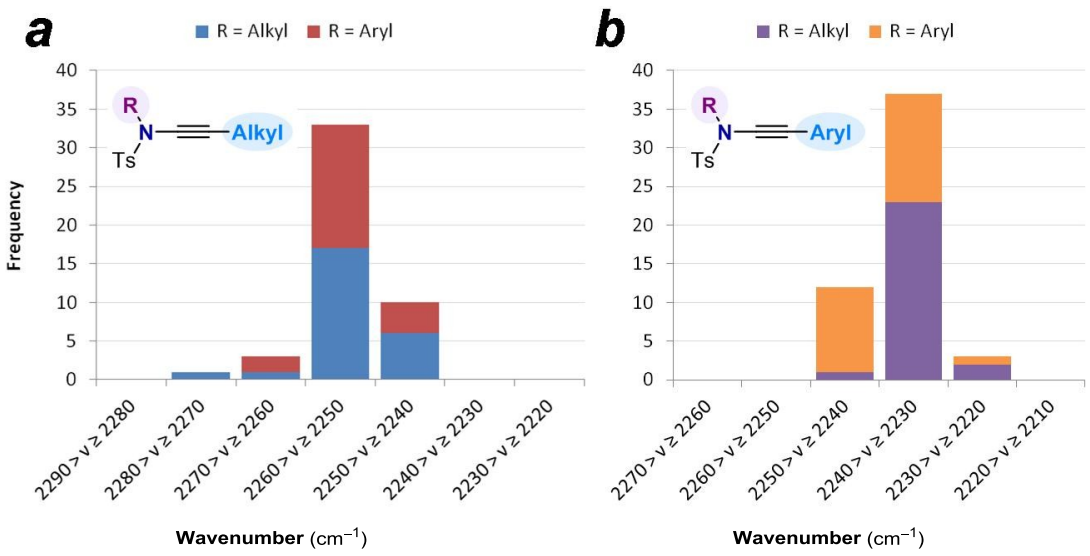


Figure 3.30: Comparison of C≡C stretching frequencies, ν (cm^{-1}), for *N*-alkyl and *N*-aryl ynamides. **a**: R = alkyl (M = 2252 cm^{-1}, SD = 6 cm^{-1}), R = aryl (M = 2254 cm^{-1}, SD = 5 cm^{-1}); **b**: R = alkyl (M = 2234 cm^{-1}, SD = 4 cm^{-1}), R = aryl (M = 2238 cm^{-1}, SD = 4 cm^{-1}).

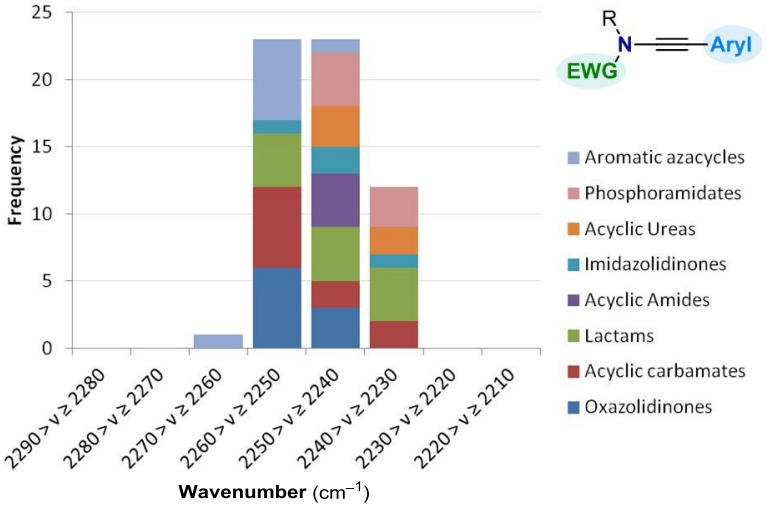


Figure 3.31: Effect of electron withdrawing group on C≡C stretching frequencies, ν (cm^{-1}).

The effect of the alkyne on carbonyl stretching frequencies, $\nu_{(c=o)}$, was also informative. Typically, acyclic amides, ureas and carbamates possess carbonyl stretching frequencies in the ranges of 1670–1630 cm^{-1}, 1705–1635 cm^{-1} and 1740–1680 cm^{-1}, respectively.[517] *N*-aryl compounds tend to shift these frequencies to the higher end of these ranges and benzanilides fall in the range of 1710–1695 cm^{-1}. For cyclic amide analogues, i.e. pyrrolidinones and oxazolidinones, the carbonyl stretching frequencies are typically higher than their acyclic counterparts due to ring strain and fall in the ranges of 1710–1680 cm^{-1} and 1760–1730 cm^{-1}, respectively.[521] In comparison, there was only a small increase on $\nu_{c=o}$ for acyclic urea and carbamate ynamides (~5–10 cm^{-1}); however, there was a significant increase for acyclic amides and pyrrolidinones (~20–40 cm^{-1}), and oxazolidinones (~20 cm^{-1}). These data imply that the alkyne behaves as a mild electron withdrawing group. This

conclusion is consistent with Hammett σ_p-values for alkynes[1] and, based on the Swain-Lupton constants for inductive/field and resonant effects of alkynes,[522] is attributed to a greater inductive withdrawing effect of the alkyne.

The substituent on the ynamide terminus provides the greatest influence on the alkyne stretching frequencies, although the electron withdrawing group does modulate this to a small degree. A greater survey of functionality on the ynamide terminus, ranging from alkyl, aryl, heteroaryl, carbonyl (e.g. esters or ketones) and hydrogen, showed a distinct range of stretching frequencies for each functional group (Figure 3.32). The increased electron withdrawing power of the terminal group is apparent, in which the characteristic alkyne stretch moves from a high frequency (up to 2275 cm^{-1} in the cases of *C*-alkyl oxazolidinone-derived ynamides)[96,123] down to 2220–2200 cm^{-1} for ynamides with carbonyl groups on the terminus.[211] Terminal ynamides (R^2 = H) fall within the expected range for monosubstituted alkynes.

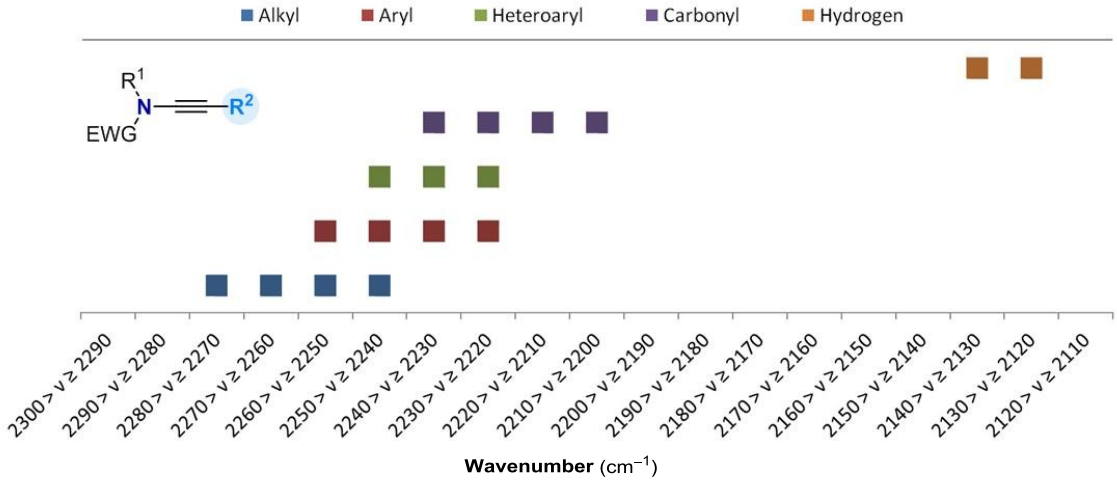


Figure 3.32: Comparison of C≡C stretching frequencies for *C*-functionalised ynamides (variation of R^2).

For *C*-heterosubstituted ynamides, the alkyne stretching frequencies span a wide range from 2250–2150 cm^{-1} (Figure 3.33). It is difficult to make any definitive conclusions from these data, because unlike those displayed in Figures 3.30–3.32, which amount to >150 data points, very few hetero-substituted ynamides have been prepared and characterised using IR spectroscopy (34 data points used here). In general, however, $\nu_{(c\equiv c)}$ increases for ynamides capped with second-row elements with increasing electronegativity and decreasing π-acceptor ability (Si→P→S→Cl). No valuable comparison can be made with X-ray data because there is insufficient available for analysis; however, preliminary evidence suggests that trialkylsilyl ynamides tended to have slightly longer C≡C bonds (CCDC entries 1518789, 1840581, 1840582 and 1841828, 1.2034(13)–1.2092(11) Å).[110] The thioether examples mainly included *S*-methyl and *S*-phenyl groups but the effect of the strongly electron withdrawing 2-nitrophenylthio group was apparent ($\nu_{(c\equiv c)}$ = 2158 cm^{-1}). For

[1] Hammett σ_p values: C≡CMe (0.03), C≡CPh (0.16), C≡CH (0.23), C≡CCF_3 (0.51); see ref [522] for details.

yndiamides, the alkyne stretch was not visible in the IR spectrum, presumably due to the lack of dipole on the alkyne, and Raman spectroscopy was used for the examples shown in Figure 3.34.

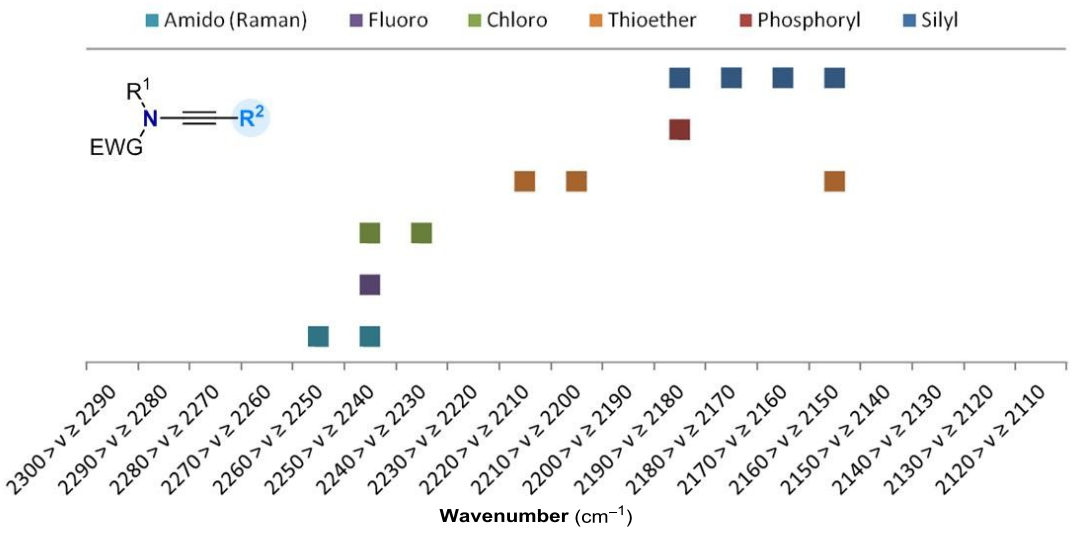
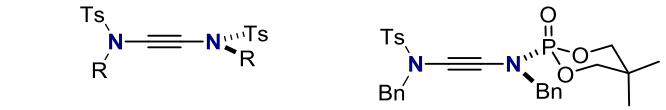


Figure 3.33: Comparison of C≡C stretching frequencies for *C*-heterofunctionalised ynamides (variation of R^2).



148b R = Bn, $\nu_{(C\equiv C)}$ = 2246 cm^{-1}
160l R = *n*-Bu, $\nu_{(C\equiv C)}$ = 2246 cm^{-1}

160g $\nu_{(C\equiv C)}$ = 2251 cm^{-1}

Figure 3.34: Alkyne stretching frequencies for yndiamides were determined by Raman spectroscopy.

Overall, IR and Raman spectroscopic analysis of ynamides and yndiamides indicated that the alkyne stretching frequency is most affected by the substituent directly bonded to the ynamide terminus; the nature of the electron withdrawing group had a less significant effect. Furthermore, by comparing carbonyl stretching frequencies for *N*-carbonyl ynamides, the alkyne can also be considered a mild electron withdrawing group itself - an effect that was much more apparent for pyrrolidinone derived ynamides. *C*-Alkyl and aryl *ynamines* possess stretching frequencies that are slightly lower than for ynamides, typically in the range of 2250–2220 cm^{-1}, and showed the same substituent dependence as for ynamides.[523–529] In light of their reactivity differences, these data are surprising. Nevertheless, it is dangerous to use crystallographic and IR spectroscopic data to predict or rationalise reactivity outcomes because they very often lack the necessary information required for predicting reactive conformations or transition states.

3.3b NMR spectroscopy.

The interpretation of ^{13}C NMR data for quantifying the push-pull effect in alkynes should also be treated with caution. A previous study sought to quantify the effect of charge polarisation by comparing the ^{13}C chemical shift differences between the two alkyne carbons, Δδ/ppm, with alkyne

bond lengths, $d_{C\equiv C}$.[530] The correlation was very poor because chemical shift differences are dependent on a number of factors that includes polarisation.[531] A better quantification of conjugation comes from a comparison of $d_{C\equiv C}$ with the occupation quotient for alkyne antibonding π*- and bonding π-orbitals. However, this method was not effective in cases of strongly inductive electron withdrawing groups, for example with F, Cl or OR substituents, on the alkyne. Ynamides were not included in this study and, whilst this could potentially be an extremely useful measure of the push-pull effect of nitrogen substituted alkynes, it is far beyond the scope of this thesis and is only mentioned for interest and as a potential future endeavour in the field.

Nevertheless, the ^{13}C NMR spectra showed clear polarisation of the alkyne for *C*-aryl ynamides, in which C(α) was significantly deshielded as compared to C(β). This is illustrated in Figure 3.35 using the data obtained for the ynamides prepared in Chapter 1. These data were obtained for sulfonamides, acyclic carbamates and ureas as solutions in $CDCl_3$, and for acyclic amides in C_6D_6. ^{13}C chemical shift assignments were made using HMBC experiments. On the other hand, the polarisation effect was not clear for *C*-alkyl ynamides:[531] the chemical shifts for C(α) and C(β) were highly substituent dependent and, in many cases with branched alkyl substituents, C(β) was found to be more deshielded than C(α).

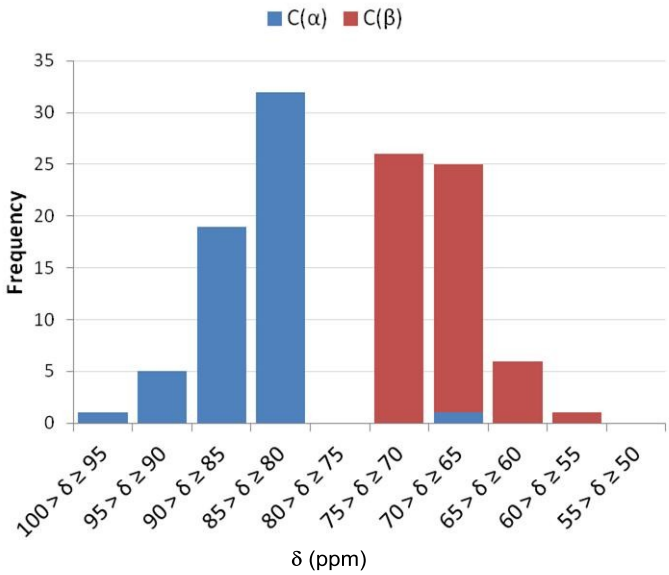


Figure 3.35: Comparison of ^{13}C chemical shifts for alkyne carbons of *C*-aryl ynamides.

The greatest effects on C(α) were seen in cases with strongly electron withdrawing aryl groups, i.e. compounds **60i**, **60v**, **60ah** and **60ai** (Figure 3.36); similar effects were identified previously from X-ray crystallographic analysis in Section 3.2b. Accordingly, the inductively electron withdrawing fluoroarenes **60i** and **60v** also possessed very low chemical shifts for C(β). However, C(α) for *C*-mesityl ynamides (e.g. **60j**) was also found to be deshielded (δ_C = 87.3–90.0 ppm). These compounds did not adopt any preferential conformation in the crystal lattice that might aid an explanation and, whilst the reasons for this are unclear, this may not be a conjugative effect. The

shielding effect of the ferrocene (**60l**) was also apparent, with low ^{13}C chemical shifts observed for both C(α) and C(β). Heterocycles **60w**–**60z** also displayed a notable shielding of C(β), though it is not clear whether this is a conjugative or magnetic field effect.

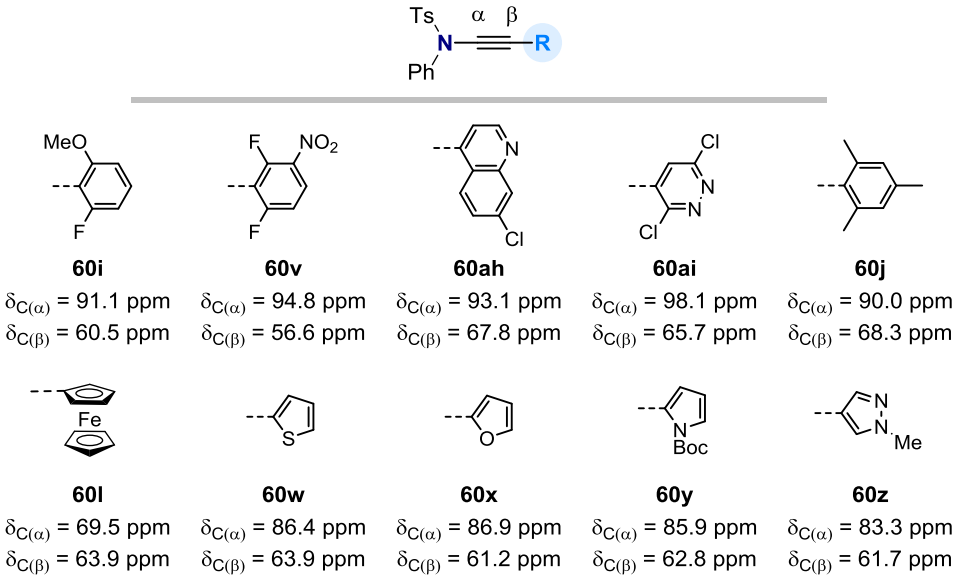


Figure 3.36: Comparison of ^{13}C chemical shifts for alkyne carbons of ynamides.

In comparison with ynamides, the ^{13}C chemical shifts for yndiamide alkynes fell within the range of 63.8–72.8 ppm. In general, the chemical shift differences for the alkyne carbons in *N*,*N*′-ditosyl yndiamides were very small and it was not generally possible to unambiguously characterise each resonance using HMBC correlations. However, there was a clear chemical shift difference for the two alkyne carbons in *N*-phosphoryl yndiamides, which were typically around 72 and 64 ppm. Unambiguous assignments were made using ^{13}C labelled yndiamides **148g*** and **148j*** (Figure 3.37), where ^{13}C-^{1}H coupling (J_{CH} = 4.6 Hz) enabled the identification of C(α) (which was ^{13}C labelled) and hence C(β) (Section 2.3c, Chapter 2).

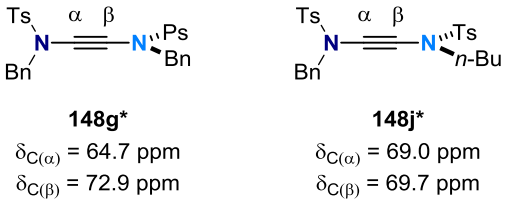


Figure 3.37: Comparison of ^{13}C chemical shifts for alkyne carbons of ynamides.

Whilst a meaningful conclusion about yndiamide polarisation cannot be made from these data, for example, the chemical shift differences could be due to a magnetic field effect, it is intriguing to consider whether this data provides an explanation for the regioselective reactions of *N*-phosphoryl yndiamide **148g** with Brønsted acids (protonation was selective for C(α), see Chapter 2).

Despite ample evidence for yndiamides adopting a twisted conformation in the solid state, it is uncertain as to whether this is perpetuated in solution. It is possible that the molecule undergoes facile racemisation at room temperature and a twisted conformation was "frozen out" in each case due to favourable crystal packing. Indeed, we wondered whether NMR spectroscopy could also lend support for the twisted nature of yndiamides in solution. In the ^{1}H NMR spectra, the signals for the methylenes attached to the nitrogen atoms may be expected to broaden or split. For example, in the cases of compounds **148t** and **148w**, both of which possess stereocentres on the pendant alkyl chains, the signals for benzylic CH_2 protons appear as AB quartets (Figure 3.38). However, for other yndiamides, such as **148j**, that lack additional stereocentres, the benzylic CH_2 appeared as a sharp singlet, suggesting a lack of magnetic inequivalence on the NMR timescale that would otherwise have been associated with the presence of axial chirality. Similarly, the signals for the methylenes attached to the other nitrogen atom did not provide any indication of axial chirality (Figure 3.39); the imperfect triplet peak shapes are a consequence of the presence of *anti* and *gauche* conformations of the alkyl chain and not due to any source of chirality.

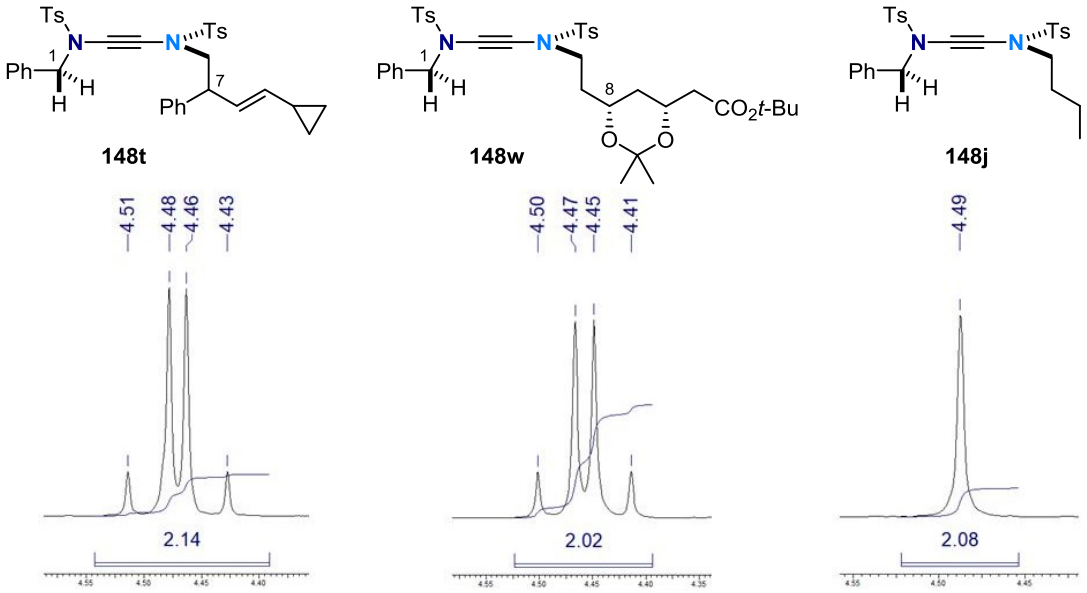


Figure 3.38: Observed signals for the benzylic CH_2 group in the ^{1}H NMR spectrum of yndiamides **148j**, **148t** and **148w**. Spectra were recorded at 400 MHz in $CDCl_3$.

Nevertheless, for compounds **148t** and **148w**, the observed splitting of the benzylic methylenes suggests a relatively constrained system that is able to transmit stereochemical information over 7 or 8 atoms.[532,533] In general, however, the current NMR data does not support the presence of any significant populations of atropisomers on the current NMR timescale. This also begs the question of how rotationally flexible these compounds are at room temperature. For the related hypothetical molecule $H_2NC{\equiv}CNH_2$, the conformer with the amino groups oriented orthogonally was predicted to be more stable than the planar conformer by ~5 kcal mol^{-1}.[375] Related calculations for

yndiamides are currently underway in collaboration with Dr Alexander Dürr, and variable temperature NMR experiments would also be required to investigate this phenomenon further.

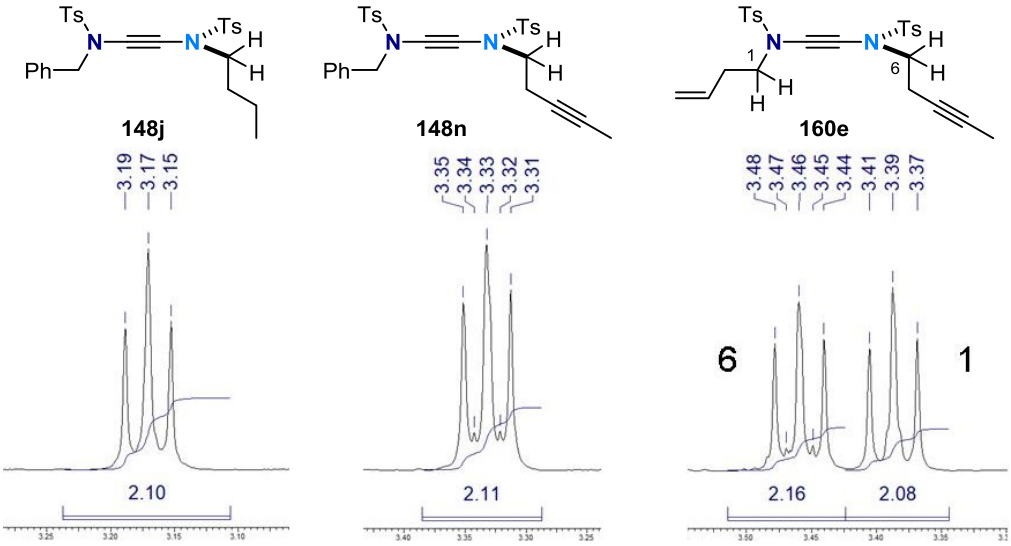


Figure 3.39: Observed signals for the indicated methylene groups in the ^{1}H NMR spectrum of yndiamides **148n**, **148j** and **160e**. Spectra were recorded at 400 MHz in $CDCl_3$.

3.4 Computational analyses of ynamides and yndiamides.

As indicated previously for the diynamides (see Figure 3.5 previously), it is possible that the twisted nature of the yndiamide resulted from an electronic effect, which conceivably allows each nitrogen lone pair to conjugate with the orthogonal alkyne π*-antibonding orbitals. DFT calculations were performed by Niels Marien to explore the structure and frontier molecular orbitals of an ynamide (**264**) and an yndiamide (**265**) (Figure 3.40). This was implemented in Gaussian09[534] and geometry optimisations were carried out at the B3LYP/6-31(d,p) level of theory.

The frontier molecular orbitals for the ynamide are primarily located on the alkyne. Only the HOMO has a significant contribution from the nitrogen lone pair, and this orbital also possesses a nodal plane between nitrogen and the alkyne. The LUMO shares a contribution from the N–S σ*-orbital, which is potentially very important in determining the outcome of the electrophilic reactions of ynamides, for example, the nucleophilic attack of indolate on terminal ynamides, which was discussed in Section 3.1.

In the yndiamide case, the frontier orbitals are also primarily located on the alkyne. In contrast, the HOMO–1 and HOMO orbitals were almost degenerate (ΔE = 0.158 eV), and had a distinctly helical shape, which possessed a contribution from both nitrogen lone pairs. The LUMO is similarly helical with both N–S σ*-orbitals contributing. Whilst the HOMO–LUMO energy difference is similar for both compounds, the small difference between HOMO–1 and HOMO for the yndiamide suggests

that both π-orbitals are available for reaction.

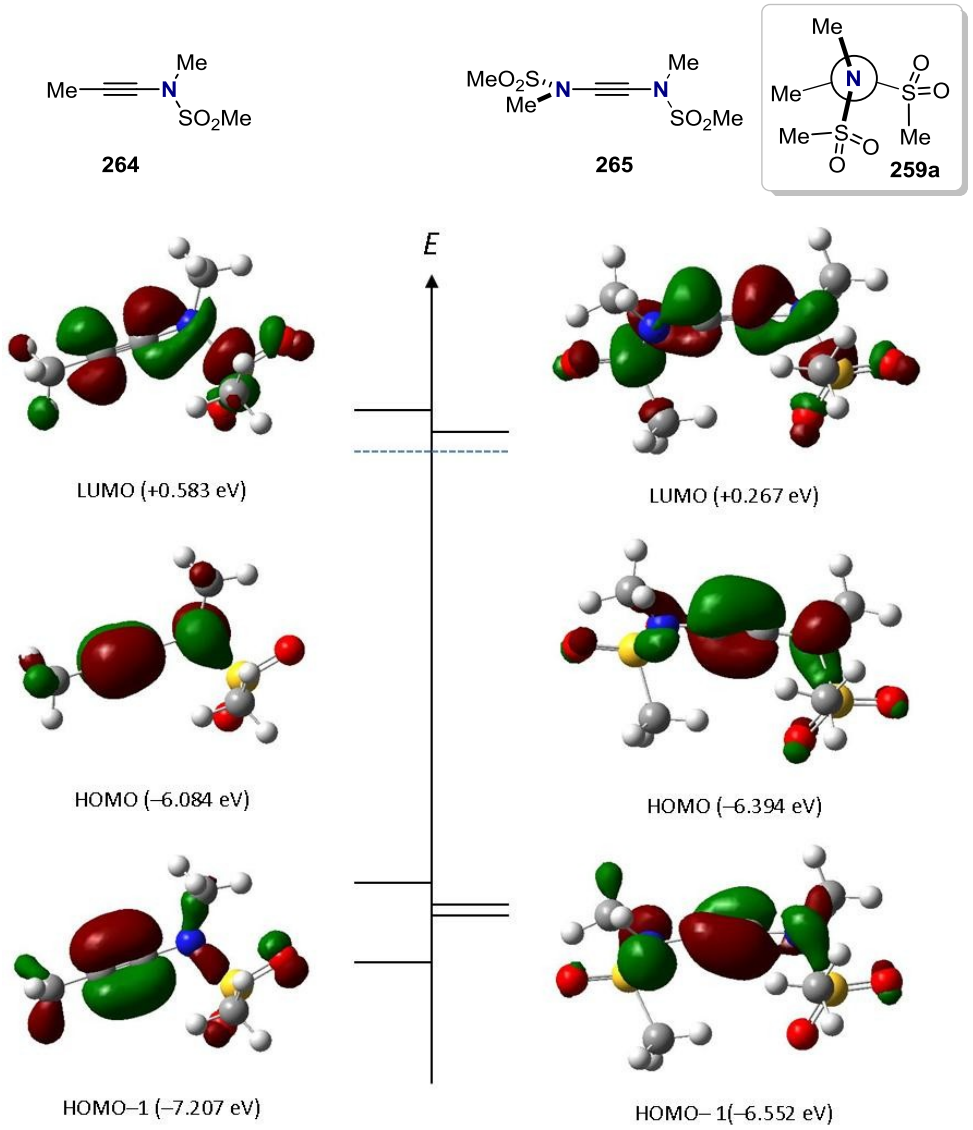


Figure 3.40: Calculated frontier molecular orbitals for an ynamide and an yndiamide, relative energies are shown. Calculations were performed by Niels Marien.

One potential issue with this calculation is the orientation of the sulfonyl groups. As mentioned in Section 3.2d, the two sulfonyl groups were found to orient in any of three ways in the crystal lattice. A screening of these conformers was not performed and, as such, only the orbitals for conformer **259a** can be considered. A more reliable interpretation would require consideration of *at least* these three conformers. This is highlighted with the related *N*,*N*'-dibenzyl yndiamide **148b**, which adopted conformation **258a** in the crystal lattice. Taking the crystallographically determined atomic coordinates for **148b**, DFT calculations were performed by Dr Alexander Dürr without further geometry optimisation. Both ωB97XD/def2tzvp and B3LYP/def2tzvp computational methods were found to give consistent results with respect to orbital helicity (Figure 3.41).

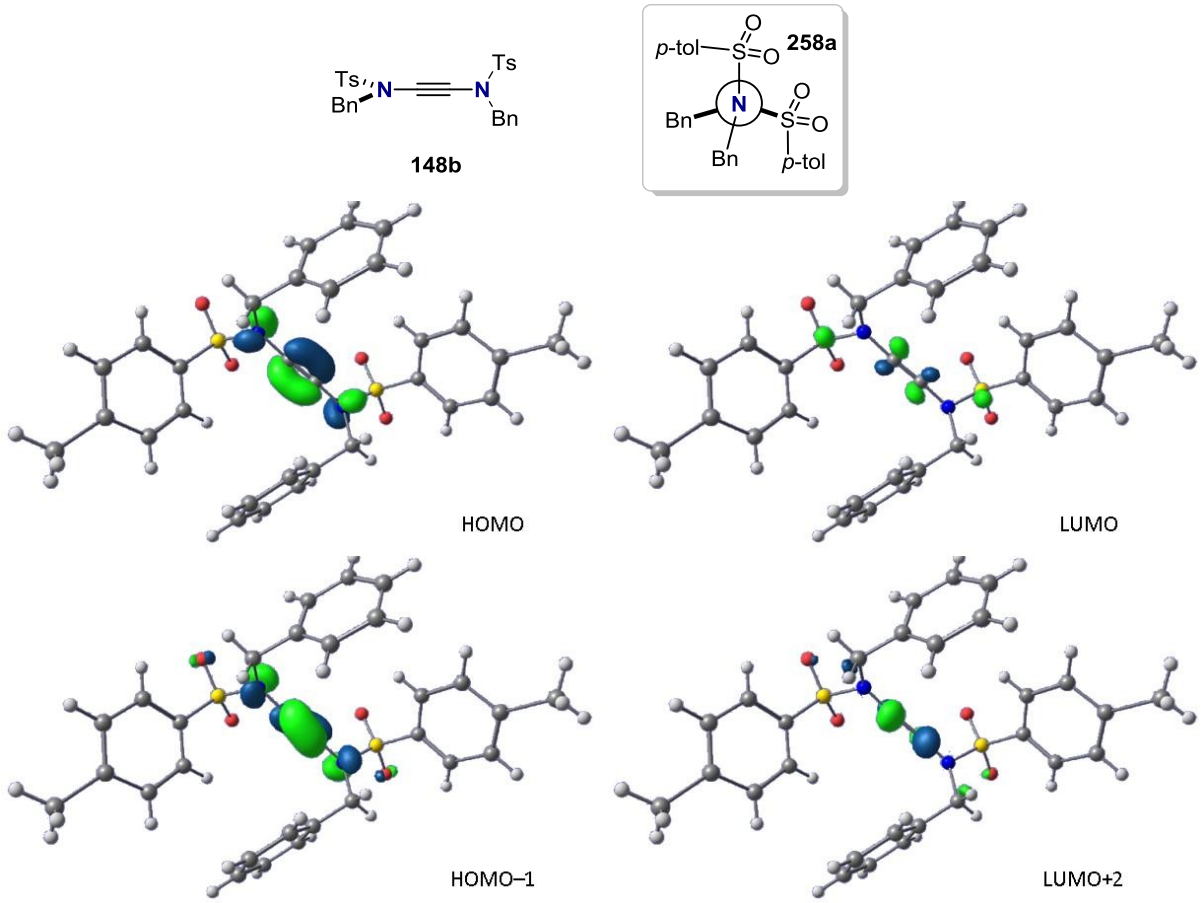


Figure 3.41: Frontier molecular orbitals for yndiamide **148b**. Contour value = 0.08. Calculations were performed by Dr Alexander Dürr.

The occupied orbitals for yndiamide **148b** share the same characteristics as for the previous yndiamide: both are helical and the energy gap between the two is small (ΔE = 0.087 eV). However, the alkyne centred LUMO and LUMO+2 are not helical in this conformation.

Furthermore, DFT calculations were also performed for *C*-mesityl ynamide **60j**, again using the atomic coordinates determined using X-ray analysis and at the same levels of theory as for the yndiamide (Figure 3.42). It is evident that in this conformation, HOMO–1 is helical and spans across the alkyne, nitrogen lone pair and *N*-phenyl group. The HOMO also indicates conjugation of the lone pair into the mesityl ring; however, the HOMO, LUMO and LUMO+2 were not helical in this conformation.

Overall, the effect of conformation on orbital shape for these alkynes raises the following questions: What is/are the reactive conformation(s) for an yndiamide and an ynamide? How would different substituents, particularly the electron withdrawing group, affect this? These questions are likely pertinent for understanding the reactivity of *N*-phosphoryl yndiamides and further kinetic and computational studies would be required to help answer these questions and to provide a greater understanding of the reactivity of both ynamides and yndiamides.

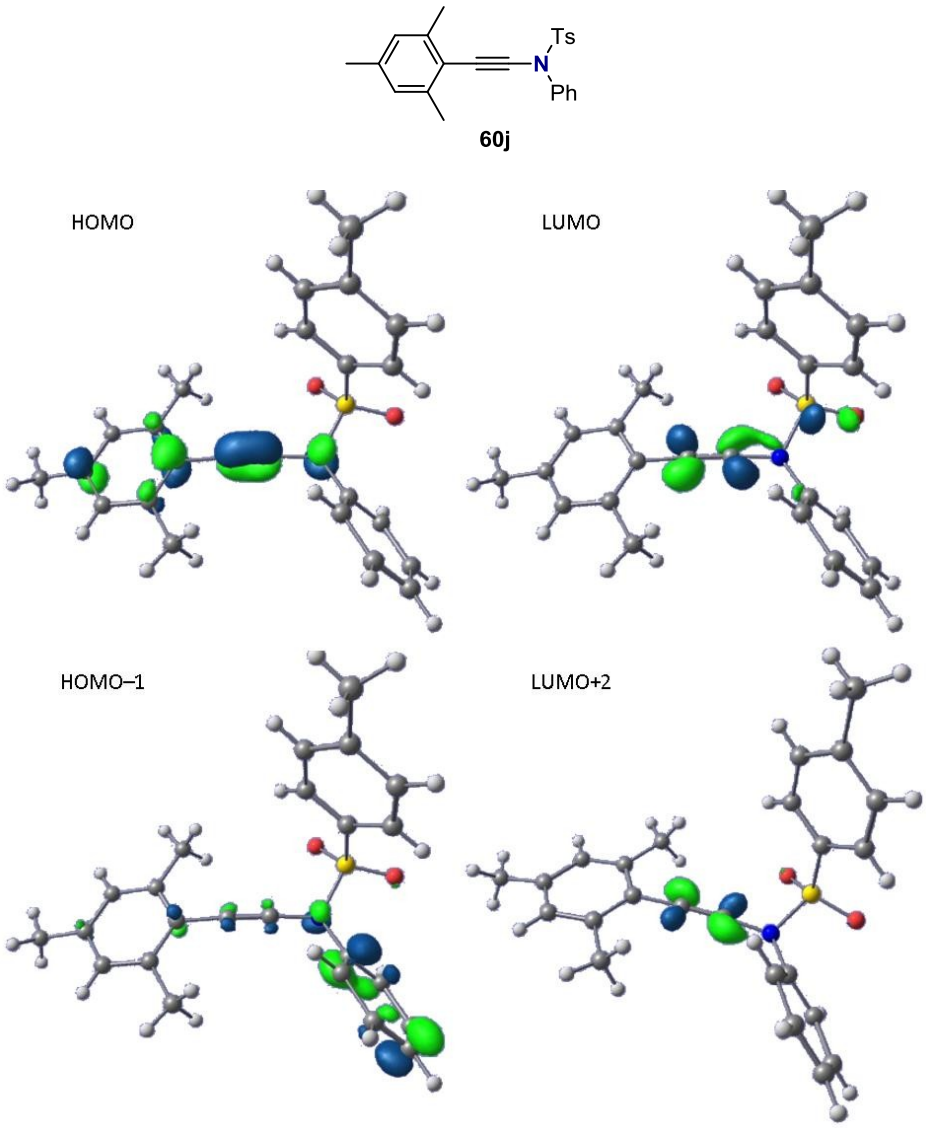


Figure 3.42: Frontier molecular orbitals for ynamide **60j**. Contour value = 0.08. $\Delta E_{(HOMO-1/HOMO)}$ = 1.016 eV. Calculations were performed by Dr Alexander Dürr.

3.5 Conclusions.

Ynamides are inherently nucleophilic, approximately 10^3–10^5 times more nucleophilic than phenylacetylene, which is comparable with that of enamides and enol ethers. The effect of both the electron withdrawing group and the *C*-terminal substituent is also apparent given the 100-fold difference in values (Mayr nucleophilicity scale). It is, however, unknown whether these reactions proceeded via similar transition states and/or whether they possess similar reactive conformations. For nucleophilic reactions of ynamides, there is complete regioselectivity for reaction at C(β), which would indicate a build-up of charge at this atom upon reaching the transition state. The electrophilic reactions of ynamides are less predictable and the electron withdrawing group is very important for determining regioselectivity. This chapter has brought together physical, spectroscopic, kinetic and

computational data, both from the literature and from our own work, in an attempt to understand the fundamental properties and reactivity of ynamides, and to enable a comparison with yndiamides. We began this chapter by posing a number of questions and shall conclude by providing answers and considering different, more refined questions. Firstly: what is the nature of the bonding in ynamides? How do the substituents affect this?

In terms of experimental evidence, the polarisation of the ynamide alkyne is particularly apparent in the ^{13}C NMR data for *C*-aryl ynamides, in which the chemical shifts for C(α) are significantly deshielded as compared to C(β). IR spectroscopic data also indicated that ynamides possessing an electron withdrawing *C*-substituent tended to have a lower stretching frequency (for example, pyridazinyl (2224 cm^{-1}), *t*-butoxycarbonyl (2217 cm^{-1}) and benzoyl (2202 cm^{-1})[214] groups); the alkyne stretching band was particularly intense in these cases, which would indicate increased alkyne polarisation and a weakening of the triple bond (likely through conjugation). Furthermore, crystallographic analysis of these cases indicated a shortening of the N–C bond, which is likely a better measure for nitrogen lone pair delocalisation than comparing minute differences in alkyne bond length. Natural population analyses also showed a slight polarisation of the alkyne in the ground state, with C(β) possessing a slight negative charge, and maps of Fukui dual descriptors also predicted C(β) to be the most nucleophilic site. These data are all consistent with the polarisation of the ynamide in the ground state.

Surprisingly, IR/NMR spectroscopic and X-ray crystallographic analyses indicated that variation of the electron withdrawing group had a less significant impact on the properties of the ynamide, as compared to the effects of differing alkyne *C*-substituents. For example, C(sp)–R bond lengths decreased in the order of R = alkyl, aryl, alkynyl and likely reflect the sp^3, sp^2 and sp hybridisation, respectively, for these groups. The ^{13}C chemical shifts for C(α) and IR stretching frequencies for the alkyne also varied much more significantly with variation of the terminal group, as compared to switching between sulfonamides, acyclic carbamates, amides and ureas. These data support a conclusion that orbital hybridisation of the terminal group is important, which could relate to the observed nucleophilicity differences for *C*-alkyl and *C*-aryl ynamides.

Now we come to consider the effect of varying the electron withdrawing group, which generally provides the biggest reactivity differences, but afforded only small spectroscopic differences. The most important physical evidence for the effect of this group is the geometry of the substituents about nitrogen, which could be used as a measure of the hybridisation of nitrogen: planar geometries ($\sum\theta_N = 360°$) imply sp^2, pyramidal geometries ($360° > \sum\theta_N \geq 328°$) imply hybridisation closer to sp^3. *N*-carbonyl amide analogues and aromatic azacycles had a strong tendency for planarity ($360 \geq \sum\theta_N \geq 358°$), and sulfonamides were most often pyramidal ($354 \geq \sum\theta_N \geq 348°$). It is unclear whether this measure correlates with nucleophilicity and, in comparison with previously discussed data, it is

not yet possible to draw any conclusion about the effect of the substituents on the frontier molecular orbitals. What is clear from the preliminary computational analysis is that the orthogonal π-orbitals on the alkyne are differentiated by interaction with the nitrogen lone pair; i.e. $\Delta E_{(\mathrm{HOMO/HOMO-1})} \approx 1$ eV. Further computational analyses would be required to enable more quantitative conclusions regarding the bonding effect of various substituents, and a Hammett-style kinetic analysis would seem appropriate to explore substituent effects for a given reaction, for example, ynamide protonation.

This leads directly to the next questions: Is the regioselectivity pre-determined by the ground state electronic configuration, or does it rather arise from stabilising interactions that develop upon reaching a transition state? I.e. To what extent can these resonance forms be used to approximate the electronic wavefunctions for the ground and transition states during a reaction?

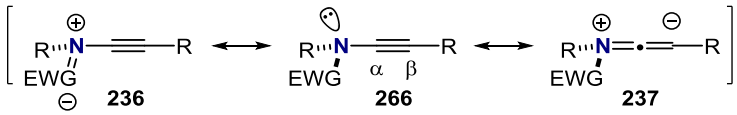


Figure 3.43: Resonance forms of ynamides.

The spectroscopic data and natural population analyses are all consistent with polarisation of the ynamide in the ground state. It is possible that this affords some regioselectivity bias for nucleophilic reactions of ynamide, but it is unclear as to the significance of this as compared to the electronic distribution for a particular reactive conformation in the ground or transition state in a reaction. In cases where the ynamide behaves as an electrophile, it is the electron withdrawing group that plays a more crucial role, though increased nucleophilicity at C(β) can retard carbometallation. Therefore, it is reasonable to presume that the ionic resonance forms **236** and **237** are better approximations of the electronic wavefunction upon approaching a transition state for an electrophilic or nucleophilic reaction of an ynamide, respectively, (i.e. corresponding to a stabilising interaction) and the ground state is likely better represented by the neutral alkyne **266**.

Finally, how do yndiamides compare with ynamides? The most significant difference is the fact that all of the yndiamides studied displayed a complete preference for a twisted conformation in the crystal lattice, which was not the case for ynamides. As to whether this is manifested in solution is unclear and would require variable temperature NMR studies to elucidate this further. There are, of course, implications regarding the barrier to rotation about the N–C(sp) bond for ynamides and yndiamides. DFT analyses indicated that the twisted yndiamides possess helical frontier molecular orbitals, which was particularly apparent for both the HOMO and HOMO–1. However, the preliminary data for both ynamides and yndiamides suggest that this bonding situation is possibly related to their conformation. If this were to be the case, the implications for ynamide and

yndiamide reactivity could be significant, especially when considering the effects of different orientations of the electron withdrawing group. Investigations are currently underway to explore this phenomenon.

Conclusions and Prospects for Ynamide Chemistry

4

There have been significant developments in the field of ynamide synthesis that were, primarily, spurred on by the increasing number of their applications. With regard to the availability and utility of ynamides, it is apparent that two criteria are of particular importance to chemists: (i) they should be cheap and convenient to prepare from readily available precursors and reagents; and (ii) it should be possible to incorporate a whole range of different substituents at all positions on the ynamide. In general, for most ynamide classes, both of these criteria have been met, even to the point that a small number are now commercially available. However, certain substrate classes, particularly the use of acyclic ureas and amides, are difficult and inconvenient to prepare using the previously available methodologies; a direct effect of this is the lack of applications that make use of these compounds.

To directly address these issues, 1,2-dichloroenamides were developed to enable the syntheses of these more troublesome ynamide classes, in particular with the use of sterically hindered amide-analogues, acyclic ureas and acyclic secondary amides. Previously, 1,2-dichloroenamides were utilised to generate lithiated ynamides, *nucleophiles* that reacted with various electrophiles to give internal ynamides. In this work, they were utilised as precursors to chloroynamides, *electrophilic* components that react with readily available organometallic nucleophiles. This umpolung strategy was broadly applicable, accommodated a wide range of Grignard and organozinc reagents, and tolerated a diverse range of functionality and steric bulk on both coupling partners. These reactions proceed at room temperature and take between 2–3 hours from dichloroenamide to ynamide. 1,2-dichloroenamides have, therefore, become versatile building blocks for ynamide synthesis.

In continuing these developments, the first synthesis of yndiamides was also achieved by the coupling of 1,1-dibromoenamides with nitrogen nucleophiles. Unlike analogous yndiamines, these

compounds are, for the most part, air and bench stable, and can be purified via silica gel chromatography. Whilst yndiamides could be considered a new class of ynamide, this does not accurately describe their behaviour in transition metal and acid-catalysed transformations. Certainly compared to ynamides, the presence of bulky groups on nitrogen offsets their potential nucleophilicity; however, and particularly with Brønsted or Lewis acids, both nitrogen atoms are able to react cooperatively during intramolecular reactions and can give remarkable selectivity for a single product. As for ynamides, the steric and electronic influences of the substituents on nitrogen are important for yndiamide reactivity and a preliminary investigation uncovered the potential to perform regioselective, intermolecular reactions of yndiamides with Brønsted acids.

However, it is difficult to make reasonable comparisons between the reactivity of yndiamides and ynamides, because there have been very few studies that investigate the electronic and steric effects of the different substituents. In the final chapter, a comparison of crystallographic and spectroscopic data for ynamides indicated that, at least in the ground and solid states, the nature of the substituents on the alkyne have a greater influence than the substituents on nitrogen. Whilst there is no doubt that an ynamide alkyne is polarised, it is still unclear how and why the nature of the substituents affects reactivity. From crystallographic studies, it was clear that yndiamides had an absolute preference for adopting a twisted structure, which is quite unlike the behaviour of ynamides. Ultimately, this raises, perhaps, one of the most important questions from this work: How do the stereoelectronic influences of the ynamide and yndiamide substituents affect the conformation and, ultimately, the reactivity of these functional groups?

4.1 Future work.

Answering such a question would not be an easy task. However, a potential strategy that could provide conclusions about the reactivity of different ynamides and, possibly by extension, yndiamides can be made by considering the following questions:

(i) What are the stereoelectronic influences of a particular group for an ynamide or yndiamide?

(ii) How do these effects influence the different conformation(s) of an ynamide and yndiamide?

(iii) What are the reactive conformations for different ynamides and yndiamides? Here it would be necessary to assess the accessibility of these conformers from the ground state, and to determine barriers for the interconversion between all relevant conformers.

(iv) What are the shapes, sizes and energy differences of the frontier molecular orbitals for all relevant conformers? Is orbital helicity a result or cause of a conformational preference? Is helicity a result of a particular substituent on the alkyne?

(v) Where are the nucleophilic and electrophilic sites on different ynamides and yndiamides? How do they compare? This would involve the use of Fukui dual descriptors to develop maps of both electrophilic and nucleophilic regions.

(vi) What influences do these have on the possible transition states for a particular reaction? Protonation would be an example reaction to consider here.

(vii) These calculations would need to be performed alongside kinetic studies. A Hammett style kinetic analysis may provide insight about substituent effects for *C*- or *N*-aryl ynamides. Mayr style analyses of nucleophilicities (and possibly electrophilicities?) would be an alternative.

(viii) Finally, a comparison of agreement between computational models and kinetic studies would be required throughout this process.

By answering these questions, we will likely gain insights as to why there are observed reactivity/stability differences between various ynamides, including yne-amides and yne-ureas, and to develop an understanding of how the nature of the substituents affects this. This could also provide insights for why the unsymmetrical, *N*-phosphoryl yndiamide reacted regioselectively with Brønsted acids. It is very likely that these reactions are dependent on the natures of both the yndiamide and the Brønsted acid, and specific consideration of the latter could help explain the outcome of the reactions with 2-bromothiophenol. Computational investigations are currently being performed by Dr Alexander Dürr and seek to understand the stereoelectronic influences of sulfonyl and phosphoryl electron withdrawing groups on the conformations and reactivities of ynamides and yndiamides.

Whilst new syntheses of ynamides and yndiamides were achieved in this thesis, it is the fundamental questions that arose from these studies that are of potentially greater value. There is no doubt that ynamide chemistry will continue to have a rich future, but answering these questions could spark a revolution in our understanding.

"*Nothing in life is to be feared, it is only to be understood.*
Now is the time to understand more, so that we may fear less."

– Marie Curie

Supporting Information

Chapter 1 - Synthesis of Ynamides from 1,2-Dichloroenamides

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1 General.

1.1 General information.

Reagents, solvents and techniques: All reagents, obtained from Acros, Alfa and TCI (Fisher Scientific), Fluorochem, Sigma-Aldrich and Strem fine chemical suppliers, were used directly as supplied. Anhydrous hexamethyldisilazane (HMDS) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (tmeda) were both obtained by first stirring overnight (~12 h) with CaH_2 under nitrogen, followed by distillation under low vacuum (for HMDS) or at ambient pressure under a nitrogen atmosphere (for tmeda). They were used either immediately or stored over CaH_2 under a nitrogen atmosphere. The concentrations of the Grignard and organolithium reagents used were determined by iodometric titration[535] and it is highly recommended to titrate all organometallic solutions prior to use. Solvents were either used as commercially supplied, or as purified by standard techniques. Anhydrous *t*-butyl methyl ether (TBME), THF and toluene were each obtained from solvent dispenser units having been passed through an activated alumina column under argon. Unless otherwise stated, all non-aqueous reactions were performed in oven-dried apparatus under a nitrogen atmosphere at room temperature.

Chromatography: Reactions were monitored by thin layer chromatography on pre-coated aluminium-backed plates (Merck Kieselgel 60 with fluorescent indicator UV254). Spots were visualised by quenching of UV fluorescence or by staining with potassium permanganate or vanillin, and retention factors are reported with the solvent system in parentheses. Flash column chromatography was performed on silica gel obtained from Macherey Nagel (MN 60, 230–400 mesh) under a positive pressure of nitrogen, using the stated solvent system.

Melting Points: Melting points were obtained using a Griffin melting point apparatus and are uncorrected.

Infrared Spectroscopy: Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer equipped with a diamond ATR module, with the sample being prepared as a thin film. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

NMR Spectroscopy: ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker AV400 or Bruker AVII500 spectrometers using TOPSPIN software, with the deuterated solvent acting as the internal deuterium lock. ^{1}H NMR spectra were recorded at 400 or 500 MHz, ^{13}C NMR spectra were recorded at 101 or 126 MHz with ^{1}H decoupling, and ^{19}F NMR spectra were recorded at 376 or 470 MHz.

The residual protic solvent signal(s) acted as the internal reference for ^{1}H NMR spectra [$CDCl_3$ (δ 7.26), C_6D_6 (δ 7.16) or toluene-d_8 (δ 7.09)], and the deuterated solvent signal acted as the internal

reference for ^{13}C NMR spectra [$CDCl_3$ (δ 77.0), C_6D_6 (δ 128.1) or toluene-d_8 (δ 137.5)]. ^{19}F NMR spectra were not externally referenced.

Chemical shifts (δ) are quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and ^{19}F NMR spectra, and 0.1 ppm for ^{13}C NMR spectra. Only those signals in the ^{13}C NMR spectra that are within 0.1 ppm are reported to the nearest 0.01 ppm. Peak multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, spt = septet, m = multiplet, br. = broad, app. = apparent. Coupling constants (*J*) are reported to the nearest 0.1 Hz. Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HSQC, HMBC, and/or NOESY experiments.

High-Resolution Mass Spectrometry: Electrospray ionisation (ESI) HRMS were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using water:methanol:formic acid (10:89.9:0.1) as eluent. The system uses a heated electrospray ionisation (HESI-II) probe and has a resolution of 50,000 FWHM under conditions for maximum sensitivity. The mass reported is that containing the most abundant isotopes, with all values reported to 4 decimal places and within a 5 ppm tolerance.

Chemical ionisation (CI) HRMS was performed on an Agilent 7200 Q-ToF instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software, and the reagent gas used was ammonia. All values are reported to 4 decimal places and are within a 5 ppm tolerance.

1.2 General procedures.

1.2a Example procedure for the synthesis of 1,2-dichloroenamides using Cs_2CO_3.

To a 500 mL round-bottomed flask equipped with a magnetic stirrer bar and a septum, was added *N*-phenyl tosylamide (50.0 g, 202 mmol, 1.0 equiv.) and powdered Cs_2CO_3 (79.1 g, 243 mmol, 1.2 equiv.). ***Note***: In general for most substrates, and particularly on a smaller scale (<1 g of amide), 1.5 equivalents of Cs_2CO_3 was found to be more effective. The flask was then evacuated under high vacuum for 30 seconds to remove air and backfilled with nitrogen (this vacuum cycle was repeated twice more – see ***Safety Note***). Next was added DMF (150 mL, 0.75 mL $mmol^{-1}$ of amide substrate) and the resulting suspension was then stirred vigorously at 50 °C for 10 minutes. ***Note***: Strictly anhydrous DMF is not required, and reactions performed using DMF straight from the bottle often perform better – this is likely due to trace water increasing Cs_2CO_3 solubility.

Safety Note*:* Extreme care must be taken when working with dichloroacetylene (DCA), generated here in situ from trichloroethylene, as exposure to air (particularly oxygen) may result in sparking. As a general precaution, it is recommended to conduct these reactions under an inert atmosphere (Ar or N_2), and to add the trichloroethylene dropwise over 2–30 minutes (depending on the scale, also see section **1.1c**). For most sulfonamides, the generation and consumption of DCA occur at a comparable rate, and there is minimal to no accumulation of DCA in the reaction vessel. For the carbamate, urea and amide substrates, the rate of consumption is generally slower than generation and DCA can accumulate in the vessel (generally seen as a white vapour that dissipates as the reaction proceeds).

Using a syringe pump, trichloroethylene (20.0 mL, 222 mmol, 1.1 equiv.) was added dropwise over 30 minutes to the vigorously stirring reaction mixture, and the resulting mixture was stirred at 50 ºC until reaction completion (2 hours), as analysed by TLC (20% Et_2O/petroleum ether). Upon cooling to room temperature, the reaction mixture was poured into a 2 L separating funnel containing EtOAc (~300 mL) and brine (~1200 mL). The reaction vessel was thoroughly rinsed with EtOAc and water (3×50 mL each, alternately) and these washings were poured into the separating funnel. The organic layer was then separated and further washed with brine (2×800 mL). At this point, TLC analysis (20% Et_2O/petroleum ether) of both the organic and aqueous layers was conducted to confirm complete separation of the desired product from DMF (stain with $KMnO_4$ or vanillin to visualise). ***Note***: If the separation is not complete, continue extraction as necessary. The organic was then dried ($MgSO_4$), filtered and concentrated in vacuo to afford crude (*E*)-*N*-(1,2-dichlorovinyl)-*N*-phenyltosylamide (68.3 g) as a yellow solid.

To this solid in a 1 L round-bottomed flask was added TBME (~500 mL) and a magnetic stirrer bar, and the mixture was stirred at ~50 °C to dissolve the material. The solution was allowed to cool to room temperature and allowed to stand overnight, by which time colourless crystals of (*E*)-*N*-(1,2-dichlorovinyl)-*N*-phenyltosylamide, **53a**, had grown. This suspension was further cooled to −10 °C for ~2 hours to enable further crystallisation. Once crystallisation had ceased, the remaining pale yellow solution was decanted into a second 1 L round-bottomed flask, and the colourless crystals were washed with ice-cold TBME (2×20 mL). These crystals were then dried under high vacuum for ~5 hours. The combined decanted solution and washings were concentrated to approximately 150–200 mL, by which time more of the desired compound had precipitated. This mixture was again stirred at 50 °C to dissolve the material, and the crystallisation proceeded as before.

The colourless crystals obtained from these 2 crops were both determined to be >98% pure (by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as internal standard). These 2 crops of crystals were combined to give 65.2 g (190 mmol, 94%) of (*E*)-*N*-(1,2-dichlorovinyl)-*N*-phenyltosylamide, **53a**, as colourless blocks. These crystals were suitable for X-ray diffraction.

The remaining solution from these crystallisations was concentrated to give a dark orange oil that contained residual (*E*)-*N*-(1,2-dichlorovinyl)-*N*-phenyltosylamide, **53a**. Column chromatography (10% Et_2O/petroleum ether) afforded a further 890 mg (96% pure, as determined by ^{1}H NMR spectroscopic analysis) of the desired compound.

1.2b Example procedure for the synthesis of 1,2-dichloroenamides using 50% w/v aq. KOH.

To a 100 mL round-bottomed flask, equipped with a magnetic stirrer bar and a septum, was added *t*-butyl phenylcarbamate (850 mg, 4.40 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (373 mg, 1.10 mmol, 0.25 equiv.). Toluene (44 mL) was then added and the mixture was stirred to dissolve the material. The flask was then purged with argon using a balloon and outlet needle. (Alternatively, evacuation under high vacuum and backfilling with Ar or N_2 is also effective, see the previous ***Safety Note***).

Next was added a 50% w/v aqueous solution of KOH (20 mL), and the reaction was stirred vigorously at 60 °C for ~10 minutes. To the vigorously stirring mixture was then added trichloroethylene (1.18 mL, 13.2 mmol, 3.0 equiv.) dropwise over 2 minutes and the mixture was stirred vigorously at 60 °C for 2 hours. Complete conversion was then confirmed by TLC (10% Et_2O/petroleum ether). ***Note***: The reaction mixture often turns dark brown.

Upon cooling to room temperature, the mixture was poured into a 100 mL separating funnel. The reaction flask was thoroughly rinsed with Et_2O and water (2×5 mL each) and these washings were poured into the separating funnel. The organic layer was separated and was washed with brine

(2×20 mL), dried (Na_2SO_4) and concentrated in vacuo to afford a brown oil. Column chromatography (5% Et_2O/pentane) afforded dichloroenamide **69d** (1.12 g, 3.89 mmol, 88%) as a colourless oil.

1.2c Example procedure for the preparation of functionalised organomagnesium reagents.[536]

To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added 4-iodobenzonitrile (402 mg, 1.75 mmol, 1.2 equiv.) and the flask purged under high vacuum for ~1 minute. The flask was backfilled with N_2, anhydrous THF (4 mL) was added, and the solution cooled to −20 °C whilst stirring. Next, *i*-propylmagnesium chloride (1.02 mL of a 2 M solution in THF, 2.05 mmol, 1.4 equiv.) was added dropwise over 10 minutes and the reaction was stirred for a further 30 minutes at −20 °C. This solution was used directly in the subsequent reaction.

1.2d Preparation of $CuCN{\cdot}2P(OMe)_3$ solution (0.1 M in THF).

To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous CuCN (100 mg, 1.12 mmol, 1.0 equiv.) and the flask purged under high vacuum for 30 minutes. The flask was backfilled with N_2 followed by the addition of anhydrous THF (11.2 mL) and trimethyl phosphite (264 μL, 2.23 mmol, 2.0 equiv.). Stirring was continued until the salts were dissolved.

1.2e Example procedure for the synthesis of ynamides from *N*-sulfonyl-1,2-dichloroenamides.

To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous TBME (1.5 mL) and freshly distilled hexamethyldisilazane (0.37 mL, 1.75 mmol, 1.2 equiv.), and the solution was cooled to 0 °C whilst stirring. To this solution was added dropwise *n*-butyllithium (0.70 mL of a 2.5 M solution in hexanes, 1.75 mmol, 1.2 equiv.) and the mixture stirred for 1 hour at 0 °C. ***Note***: The use of good quality *n*-butyllithium - i.e. a colourless, precipitate-free solution in hexanes – is required to obtain high yields. The resulting solution of LiHMDS should then be colourless. Otherwise, the subsequent reactions will be lower yielding.

To a second, oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added powdered (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide, **53a**, (500 mg, 1.46 mmol, 1.0 equiv.) and anhydrous TBME (2.0 mL), and the suspension was cooled to between −5 and 0 °C whilst stirring. To this suspension was added the previously prepared solution of LiHMDS dropwise over 30 seconds, and the reaction was stirred between −5 and 0 °C for 30 minutes. The cooling bath was then removed and the reaction stirred for 1 hour at room temperature (approx. 21 °C) (see Figure SE1). Complete consumption of the dichloroenamide was verified at this point by TLC (10% Et_2O/petroleum ether).

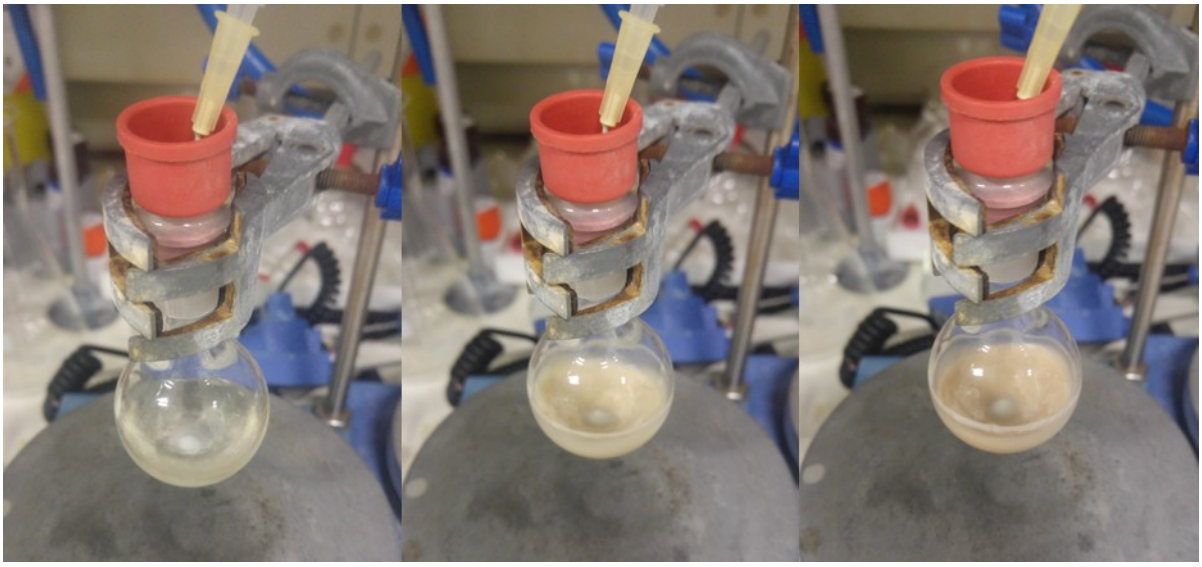


Figure SE1: Images showing the expected colour changes for this reaction; ***(Left)*** The reaction mixture once a freshly prepared solution of LiHMDS in TBME/hexane has been added to a suspension of (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide in TBME (cooling bath was removed to obtain the above image); ***(Centre)*** The reaction mixture after complete conversion of the dichloroenamide to the corresponding chloroynamide. This is the expected colour for these transformations - a brown or darker reaction mixture generally indicates a lower yield of the chloroynamide; ***(Right)*** Reaction mixture after the addition of a solution of $CuCN{\cdot}2P(OMe)_3$.

Next, a solution of $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) was added and the reaction stirred for 5 minutes (see Figure S14). A solution of *i*-propylmagnesium chloride (1.50 mL of a 1.0 M solution in THF/TBME (1:1), 1.50 mmol, 1.03 equiv.) was then added dropwise over 1 minute, and the reaction was stirred for 30 minutes at room temperature. Reaction completion was then verified by TLC (10% Et_2O/petroleum ether). ***Note***: In this case, the reaction mixture turned orange upon reaction completion, but in general, the colour is highly dependent on the Grignard reagent added and the reaction colour may range from pink to dark red, or from yellow to orange to dark brown. The reaction was quenched with aqueous saturated NH_4Cl (5 mL), stirred for 10 minutes and then poured into a 250 mL separating funnel containing Et_2O (~50 mL) and aqueous saturated NH_4Cl (~50 mL). The reaction vessel was thoroughly rinsed with Et_2O and water (2×5 mL each, alternately) and these washings were poured into the separating funnel. The organic layer was then separated and the aqueous was further extracted with Et_2O (2×30 mL). The organic extracts were then combined, dried ($MgSO_4$) and concentrated in vacuo. ***Note***: Alternatively, the extractions can be performed using TBME, EtOAc or toluene.

Column chromatography (3% Et_2O/40–60 petroleum ether) afforded the ynamide as a pale yellow solid. To this solid was added hexane (~4 mL) and the mixture heated to ~50 °C to dissolve the material. The solution was allowed to cool to room temperature and allowed to stand overnight, by

which time thin crystalline plates of *N*-(3-methylbut-1-yn-1-yl)-*N*-phenyltosylamide, **60b**, had grown. This suspension was further cooled to −10 °C for ~2 hours to enable further crystallisation. Once crystallisation had ceased, the remaining pale yellow solution was decanted and the colourless crystals were washed with ice-cold pentane (2×1 mL). The crystals were then dried under high vacuum for 1 hour. This afforded 390 mg (1.24 mmol, 85%) of *N*-(3-methylbut-1-yn-1-yl)-*N*-phenyltosylamide, **60b**, as colourless plates. These crystals were suitable for X-ray diffraction.

1.2f Example procedure for the synthesis of ynamides from *N*-carbonyl-1,2-dichloroenamides.

To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous TBME (1.5 mL) and freshly distilled hexamethyldisilazane (0.39 mL, 1.86 mmol, 1.2 equiv.), and the solution was cooled to −5 °C whilst stirring. To this solution was added dropwise *n*-butyllithium (0.75 mL of a 2.5 M solution in hexanes, 1.86 mmol, 1.2 equiv.) and the mixture stirred for 1 hour at 21 °C. ***Note***: The use of good quality *n*-butyllithium - i.e. a colourless, precipitate-free solution in hexanes – is required to obtain high yields. The resulting solution of LiHMDS should then be colourless. Otherwise, the subsequent reactions will be lower yielding.



Figure SE2: Images showing the expected colour changes for this reaction; ***(Left)*** The reaction mixture once a freshly prepared solution of LiHMDS in TBME/hexane has been added to a solution of benzyl (*E*)-(1,2-dichlorovinyl)(phenyl)carbamate in TBME (cooling bath at −5 °C); ***(Right)*** The reaction mixture after complete conversion of the dichloroenamide to the chloroynamide; this (or paler) is the expected colour for these transformations - a brown or darker reaction mixture generally indicates a lower yield of the chloroynamide;

To a second, oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added benzyl (*E*)-(1,2-dichlorovinyl)(phenyl)carbamate **69a** (500 mg, 1.55 mmol, 1.0 equiv.) and anhydrous TBME (13 mL), and the solution was cooled to −5 °C whilst stirring. To this solution

was added the previously prepared solution of LiHMDS dropwise over 30 seconds, and the reaction stirred at 0 °C for 2 hours. This resulted in a heterogeneous yellow solution of the chloroynamide (see Figure S15). Complete consumption of the dichloroenamide was verified at this point by TLC (10% Et_2O/petroleum ether). The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

To a third, oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added sequentially anhydrous toluene (1.0 mL), phenylmagnesium bromide (0.57 mL of a 2.8 M solution in Et_2O, 1.63 mmol, 1.05 equiv.) and zinc(II) chloride (0.82 mL of a 1.0 M solution in Et_2O, 0.823 mmol, 0.53 equiv.) and the mixture stirred for ~1 minute. ***Note***: There was an exotherm upon the addition of each reagent.

For urea/amide dichloroenamides: To a third, oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added sequentially anhydrous toluene (~1 mL $mmol^{-1}$ of Grignard reagent), 4-chlorophenylmagnesium bromide (1.05–3.0 equiv.) and zinc(II) chloride (0.53–1.5 equiv.) and the mixture stirred for ~1 minute. ***Note***: There was an exotherm upon the addition of each reagent. To this was added anhydrous tmeda (10.0 equiv.) dropwise and the reaction stirred for 5 minutes. ***Note***: There was an immediate build-up of a white precipitate. The stirring was halted and the precipitates were allowed to settle over 20 minutes. Only the solution was transferred to the subsequent reaction, via syringe, and the remaining precipitate was washed with anhydrous toluene, with these washings also added to the reaction.

To the previously prepared solution of chloroynamide at 21 °C was added CuCN·2LiCl (20 µL of a 1.0 M solution in THF, 20 µmol, 1.25 mol%), followed by the previously prepared diarylzinc solution, and the reaction was stirred for 30 minutes at room temperature. Reaction completion was then verified by TLC (10% Et_2O/petroleum ether). ***Note***: In this case, the reaction mixture remained yellow upon reaction completion. The reaction was quenched with aqueous saturated NH_4Cl (5 mL), stirred for 10 minutes and then poured into a 250 mL separating funnel containing Et_2O (~30 mL) and aqueous saturated NH_4Cl (~50 mL). The reaction vessel was thoroughly rinsed with Et_2O and water (2×5 mL each, alternately) and these washings were poured into the separating funnel. The organic layer was then separated and the aqueous was further extracted with Et_2O (2×30 mL). The organic extracts were then combined, dried ($MgSO_4$) and concentrated in vacuo.

Column chromatography (5% Et_2O/40–60 petroleum ether) afforded the ynamide as a pale yellow oil that solidified on standing. To this solid was added hexane (1.5 mL) and the mixture heated to ~50 °C to dissolve the material. The solution was allowed to cool to room temperature and left to stand overnight, by which time colourless needles of benzyl phenyl(phenylethynyl) carbamate, **71a**, had grown. This suspension was further cooled to −10 °C for ~2 hours to enable further crystallisation. Once crystallisation had ceased, the remaining pale yellow solution was decanted and the colourless crystals were washed with ice-cold pentane (2×1 mL). The crystals were then

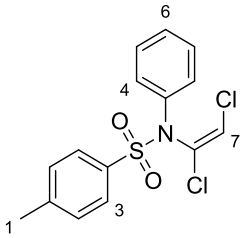
dried under high vacuum for 1 hour. This afforded 376 mg (1.15 mmol, 74%) of benzyl phenyl(phenylethynyl) carbamate, **71a**. These crystals were suitable for X-ray diffraction.

2 Characterisation data.

2.1 Organometallic Scope.

2.1a *Precursors*.

(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-phenyltosylamide, 53a



Synthesised according to example procedure **1.2a**;

m.p. 120–121 °C;

R_f 0.32 (10% Et_2O/40–60 petroleum ether);

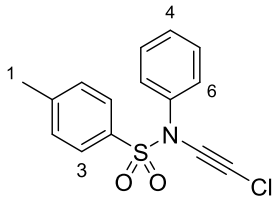
IR (thin film, ν_{max} / cm^{-1}) 3087, 1720, 1596, 1490, 1365, 1283, 1169, 1090, 948, 813, 695, 662;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67–7.62 (2H, m, *H*3), 7.40–7.30 (5H, m, *H*4, *H*5, *H*6), 7.24 (2H, d, *J* = 8.4 Hz, *H*2), 6.45 (1H, s, *H*7), 2.42 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 137.6, 135.5, 130.6, 129.4, 129.3, 129.0, 128.7, 128.6, 120.5, 21.6.

Data are consistent with literature values.[245]

_N_-(Chloroethynyl)-_N_-phenyltosylamide, 56a



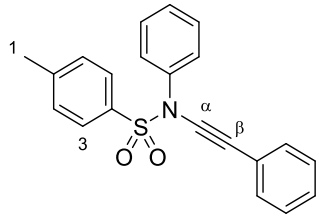
To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous TBME (1.5 mL) and freshly distilled hexamethyldisilazane (0.37 mL, 1.75 mmol, 1.2 equiv.), and the solution was cooled to 0 °C whilst stirring. To this solution was added dropwise *n*-butyllithium (0.70 mL of a 2.5 M solution in hexanes, 1.75 mmol, 1.2 equiv.) and the mixture stirred for 1 hour at 0 °C.

To a second, oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added powdered (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) and anhydrous TBME (2.0 mL), and the suspension was cooled to between −5 and 0 °C whilst stirring. To this suspension was added the previously prepared solution of LiHMDS dropwise over 30 seconds, and the reaction was stirred between −5 and 0 °C for 30 minutes. The cooling bath was then removed and the reaction stirred for 1 hour at room temperature (approx. 21 °C). Complete consumption of the dichloroenamide was verified at this point by TLC (10% Et_2O/petroleum ether). The mixture was quenched and extracted as for procedure **1.2e**. Concentration of the combined organic extracts gave a pale yellow solid. Trituration of this with Et_2O/pentane (1:5) afforded the title compound (412 mg, 1.35 mmol, 92%) as a white powder. Crystals suitable for X-ray diffraction were grown by slow evaporation of a solution of the title compound in CH_2Cl_2. ***Note***: This compound is slightly sensitive to concentration in vacuo at temperatures above 30 °C.

m.p. 95–98 °C;
R_f 0.59 (20% EtOAc/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3055, 2927, 2243, 1595, 1487, 1373, 1275, 1188, 1174, 1157, 1146, 1089, 924, 893, 811, 797, 693, 665;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 (2H, d, *J* = 8.5 Hz, *H*3), 7.37–7.31 (3H, m, *H*5, *H*6), 7.29 (2H, d, *J* = 8.5 Hz, *H*2), 7.25–7.18 (2H, m, *H*4), 2.45 (3H, s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_c 145.2, 138.2, 132.7, 129.6, 129.1, 128.4, 128.1, 126.2, 63.5, 52.0, 21.6;
HRMS (ES+) calc. for $C_{15}H_{12}{}^{35}ClNNaO_2S$ $[M+Na]^+$ 328.0169, found 328.0158.

2.1b *Ynamides*.

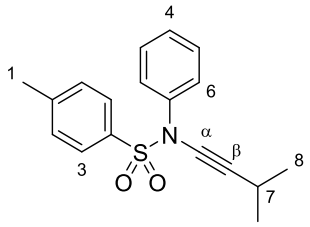
_N_-Phenyl-_N_-(phenylethynyl)tosylamide, 60a



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and phenylmagnesium bromide (1.50 mL of a 1.0 M solution in THF, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (6% Et_2O/40–60 petroleum ether) afforded the title compound (433 mg, 1.25 mmol, 85%) as colourless crystals. This compound can be recrystallised from hexane to give colourless needles, or Et_2O to give colourless blocks. These crystals were suitable for X-ray diffraction;

m.p. 102 °C (hexane), 94–95 °C (Et_2O);
R_f 0.33 (10% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3063, 2239, 1594, 1490, 1372, 1172, 1089, 1068, 1024, 921, 891, 812, 782, 754, 689, 653;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63 (2H, d, *J* = 8.3 Hz, *H*3), 7.43–7.27 (12H, m, *H*2, Ph*H* ×2), 2.45 (3H, s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.0, 138.9, 132.9, 131.4, 129.5, 129.1, 128.25 (2C), 128.22, 127.9, 126.2, 122.6, 82.9 (Cα), 70.5 (Cβ), 21.7;
HRMS (ES+) calc. for $C_{21}H_{17}NNaO_2S$ $[M+Na]^+$ 370.0872, found 370.0873.

***N*-(3-Methylbut-1-yn-1-yl)-*N*-phenyltosylamide, 60b**



Synthesised according to example procedure **1.2e**;

m.p. 56 °C;

R_f 0.38 (10% Et_2O/40–60 petroleum ether);

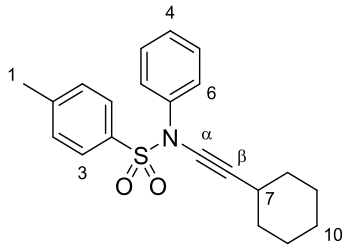
IR (thin film, ν_{max} / cm^{-1}) 2980, 2927, 2253, 1596, 1490, 1456, 1371, 1267, 1175, 1090, 908, 813, 788, 692;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54 (2H, d, *J* = 8.1 Hz, *H*3), 7.33–7.21 (7H, m, *H*2, *H*4, *H*5, *H*6), 2.66 (1H, spt, *J* = 6.8 Hz, *H*7), 2.43 (3H, s, *H*1), 1.16 (6H, d, *J* = 6.8 Hz, *H*8);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 139.3, 132.7, 129.2, 128.8, 128.3, 127.8, 126.0, 75.6 (Cβ), 73.4 (Cα), 23.0, 21.6, 20.4;

HRMS (ES+) calc. for $C_{18}H_{20}NO_2S$ $[M+H]^+$ 314.1209, found 314.1211.

***N*-(Cyclohexylethynyl)-*N*-phenyltosylamide, 60c**



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and cyclohexylmagnesium chloride (1.16 mL of a 1.3 M solution in toluene/THF (1:1), added dropwise over 1 minute, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (4% Et_2O/40–60 petroleum ether) afforded a pale orange solid which was triturated with ice-cold hexane to give the title compound (403 mg, 1.14 mmol, 78%) as colourless crystals. This compound can be recrystallised from hexane to give colourless plates that were suitable for X-ray diffraction;

m.p. 62 °C;

R_f 0.59 (20% EtOAc/40–60 petroleum ether);

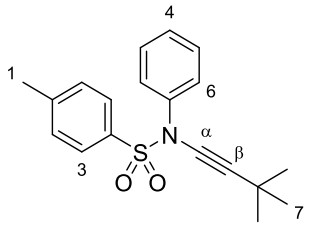
IR (thin film, ν_{max} / cm^{-1}) 2980, 2928, 2853, 2249, 1596, 1489, 1449, 1372, 1257, 1172, 1090, 813, 690;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57–7.50 (2H, m, *H*3), 7.36–7.21 (7H, m, *H*2, *H*4, *H*5, *H*6), 2.51 (1H, tt, *J* = 8.6, 3.7 Hz, *H*7), 2.43 (3H, s, *H*1), 1.81–1.71 (2H, m, *H*8), 1.71–1.60 (2H, m, *H*9), 1.53–1.38 (3H, m, *H*8, *H*10), 1.36–1.26 (3H, m, *H*9, *H*10);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 139.5, 132.8, 129.2, 128.8, 128.3, 127.7, 126.0, 74.3 (Cβ), 74.2 (Cα), 32.7, 28.8, 25.9, 24.7, 21.7;

HRMS (ES+) calc. for $C_{21}H_{23}NNaO_2S$ $[M+Na]^+$ 376.1342, found 376.1349.

_N_-(3,3-Dimethylbut-1-yn-1-yl)-_N_-phenyltosylamide, 60d



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure 1.2**e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and *t*-butylmagnesium chloride (0.89 mL of a 1.7 M solution in THF which was further diluted with 0.6 mL of anhydrous TBME, added dropwise over 1 minute, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (4% Et_2O/40–60 petroleum ether) afforded a pale yellow solid which was recrystallised from hexane to give the title compound (375 mg, 1.14 mmol, 78%) as colourless plates. These crystals were suitable for X-ray diffraction;

m.p. 87–88 °C;

R_f 0.62 (20% EtOAc/40–60 petroleum ether);

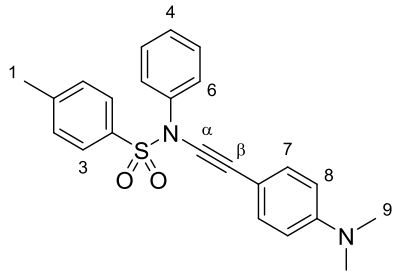
IR (thin film, ν_{max} / cm^{-1}) 2968, 2256, 1595, 1489, 1455, 1371, 1219, 1174, 1124, 1090, 813, 766, 692, 668;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56–7.46 (2H, m, *H*3), 7.34–7.15 (7H, m, *H*2, *H*4, *H*5, *H*6), 2.40 (3H, s, *H*1), 1.20 (9H, s, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 139.4, 132.5, 129.1, 128.8, 128.3, 127.7, 125.9, 78.4 (Cβ), 73.0 (Cα), 30.9, 27.4, 21.6;

HRMS (ES+) calc. for $C_{19}H_{22}NO_2S$ $[M+H]^+$ 328.1366, found 328.1368.

_N_-((4-(Dimethylamino)phenyl)ethynyl)-_N_-phenyltosylamide, 60e



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and 4-(dimethylamino) phenylmagnesium bromide (3.01 mL of a 0.5 M solution in THF, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (20 → 30% Et_2O/40–60 petroleum ether + 5% Et_3N) afforded the title compound (505 mg, 1.29 mmol, 88%) as colourless crystals. The compound crystallises spontaneously from the column fractions, and these were suitable for X-ray diffraction. ***Note***: This compound is sensitive to prolonged exposure to silica gel, and the material turns green upon melting;

m.p. 136 °C;

R_f 0.32 (30% Et_2O/40–60 petroleum ether);

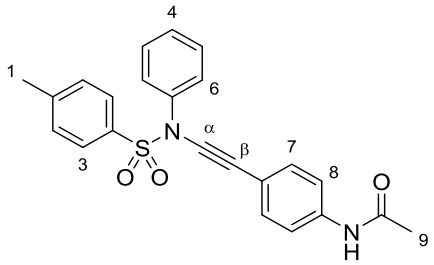
IR (thin film, ν_{max} / cm^{-1}) 2892, 2239, 1607, 1523, 1489, 1446, 1367, 1206, 1186, 1172, 1090, 815, 798, 758, 711, 692, 663;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66–7.59 (2H, d, *J* = 8.3 Hz, *H*3), 7.37–7.25 (9H, m, *H*2, *H*4, *H*5, *H*6, *H*7), 6.65–6.58 (2H, m, *H*8), 2.97 (6H, s, *H*9), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 150.2, 144.7, 139.5, 133.4, 133.0, 129.3, 128.9, 128.3, 127.9, 126.1, 111.7, 109.0, 80.7 (Cα), 71.3 (Cβ), 40.2, 21.7;

HRMS (ES+) calc. for $C_{23}H_{23}NO_3S$ $[M+H]^+$ 391.1475, found 391.1473.

_N_-(4-(((4-Methyl-_N_-phenylphenyl)sulfonamido)ethynyl)phenyl)acetamide, 60f



The chloroynamide was synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) following example procedure **1.2e**. Complete consumption of the dichloroenamide was verified by TLC. The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

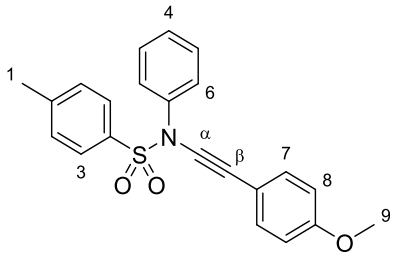
N-Lithio(4-acetamidophenyl)magnesium chloride/lithium bromide complex was prepared as follows: to an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added 4-bromoacetanilide (375 mg, 1.75 mmol, 1.2 equiv.) and anhydrous THF (8 mL), and the solution cooled to −40 °C whilst stirring. Next, *i*-propylmagnesium chloride (0.88 mL of a 2.0 M solution in THF, 1.75 mmol, 1.2 equiv.) was added dropwise and the reaction was stirred for a further 5 minutes at −40 °C. ***Note***: A pale yellow precipitate forms. The suspension was then cooled to −78 °C, and *t*-BuLi (1.89 mL of 1.7 M solution in pentanes, 3.21 mmol, 2.2 equiv.) was added dropwise over 5 minutes. The resulting yellow suspension was then allowed to warm gradually over 1 hour to 0 °C whilst stirring and was used directly in the next step.

To the previously prepared suspension of chloroynamide in TBME was added $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%), and the reaction stirred for 5 minutes at room temperature. The suspension of *N*-lithio(4-acetamidophenyl)magnesium chloride/lithium bromide complex was then transferred, by syringe, to this mixture dropwise over 1 minute, and the reaction was stirred for 30 minutes at room temperature. Reaction completion was then verified by TLC. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (50 → 60% EtOAc/40–60 petroleum ether, with the compound loaded as a concentrated solution in CH_2Cl_2) afforded a pale yellow solid that was recrystallised from EtOAc to give the title compound (394 mg, 0.973 mmol, 67%) as colourless plates. These crystals were suitable for X-ray diffraction;

m.p. >140 °C (dec.);
R_f 0.22 (60% EtOAc/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3308, 3040, 2239, 1671, 1593, 1524, 1490, 1404, 1371, 1313, 1293, 1252, 11731089, 837, 779, 689, 657;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (1H, br. s, N*H*), 7.60 (2H, d, *J* = 8.3 Hz, *H*3), 7.48 (2H, d, *J* = 8.3 Hz, *H*7), 7.36–7.26 (9H, m, *H*2, H4, H5, *H*6, *H*8), 2.44 (3H, s, *H*1), 2.16 (3H, s, *H*9);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 168.3, 145.0, 138.9, 137.9, 132.9, 132.5, 129.5, 129.1, 128.3, 128.2, 126.2, 119.3, 118.0, 82.3 (Cα), 70.2 (Cβ), 24.6, 21.7;
HRMS (ES+) calc. for $C_{23}H_{20}N_2NaO_3S$ $[M+Na]^+$ 427.1087, found 427.1087.

***N*-((4-Methoxyphenyl)ethynyl)-*N*-phenyltosylamide, 60g**



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and 4-methoxyphenylmagnesium bromide (1.50 mL of a 1.0 M solution in THF, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (6% Et_2O/40–60 petroleum ether) afforded a yellow solid which was triturated with hexane, followed by recrystallisation from hexane:TBME (2:1) to give the title compound (457 mg, 1.21 mmol, 83%) as colourless plates. These crystals were suitable for X-ray diffraction;

m.p. 99–100 °C;

R_f 0.16 (10% Et_2O/40–60 petroleum ether);

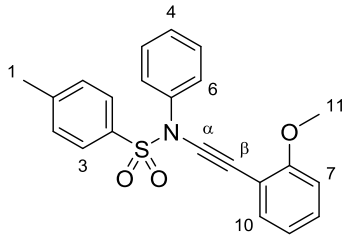
IR (thin film, ν_{max} / cm^{-1}) 2958, 2838, 2241, 1605, 1510, 1489, 1371, 1248, 1172, 1089, 1028, 922, 891, 832, 812, 721, 691, 668;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* = 8.3 Hz, *H*3), 7.38–7.22 (9H, m, *H*2, *H*4, *H*5, *H*6, *H*7), 6.86–6.78 (2H, m, *H*8), 3.79 (3H, s, *H*9), 2.43 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.6, 144.8, 139.1, 133.4, 133.0, 129.4, 129.0, 128.3, 128.1, 126.2, 114.5, 113.9, 81.5 (Cα), 70.2 (Cβ), 55.3, 21.7;

HRMS (ES+) calc. for $C_{22}H_{19}NNaO_3S$ $[M+Na]^+$ 400.0978, found 400.0978.

_N_-((2-Methoxyphenyl)ethynyl)-_N_-phenyltosylamide, 60h



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and 2-methoxyphenylmagnesium chloride (prepared according to example procedure **1.2c** from 2-iodoanisole (0.23 mL, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL) using *i*-propylmagnesium chloride (1.02 mL of a 2.0 M solution in THF, 2.05 mmol, 1.4 equiv.) and stirring for 2 hours at −20 °C). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (6% Et_2O/40–60 petroleum ether) afforded the title compound (501 mg, 1.33 mmol, 91%) as a colourless solid. This compound can be recrystallised from benzene:dibutyl ether (1:1) to give colourless crystals that were suitable for X-ray diffraction;

m.p. 57 °C;

R_f 0.24 (10% Et_2O/40–60 petroleum ether);

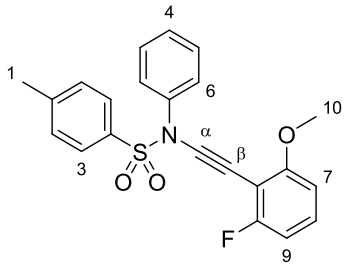
IR (thin film, ν_{max} / cm^{-1}) 3066, 2938, 2837, 2240, 1595, 1491, 1370, 1247, 1172, 1023, 812, 752, 703, 691, 679, 653;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 (2H, d, *J* = 8.3 Hz, *H*3), 7.31–7.11 (9H, m, *H*2, *H*4, *H*5, *H*6, *H*8, *H*10), 6.86–6.70 (2H, m, *H*7, *H*9), 3.77 (3H, s, *H*11), 2.34 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 160.0, 144.8, 139.0, 133.0, 132.9, 129.33, 129.30, 128.9, 128.3, 128.0, 126.1, 120.3, 111.8, 110.6, 86.5 (Cα), 67.0 (Cβ), 55.7, 21.6;

HRMS (ES+) calc. for $C_{22}H_{19}NNaO_3S$ $[M+Na]^+$ 400.0978, found 400.0978.

_N_-((2-Fluoro-6-methoxyphenyl)ethynyl)-_N_-phenyltosylamide, 60i



Preparation *via* arylmagnesium bromide/lithium bromide complex:

The chloroynamide was synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) following example procedure **1.2e**. Complete consumption of the dichloroenamide was verified by TLC. The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

(2-Fluoro-6-methoxyphenyl)magnesium bromide/lithium chloride complex was prepared as followed: To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added magnesium turnings (53.3 mg, 2.19 mmol, 1.5 equiv.), and anhydrous THF (6 mL), followed by the careful addition of 1,2-dibromoethane (190 µL, 2.19 mmol, 1.5 equiv.) at room temperature. The reaction was then heated at reflux for 2 hours and the solution was then allowed to cool to room temperature.

To a second oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous THF (1 mL) and di-*i*-propylamine (0.25 mL, 1.75 mmol, 1.2 equiv.), and the solution was cooled to 0 °C whilst stirring. To this solution was added dropwise *n*-butyllithium (0.70 mL of a 2.5 M solution in hexanes, 1.75 mmol, 1.2 equiv.) and the mixture stirred for 1 hour at 0 °C. The mixture was then cooled to −78 °C. Next, a solution of 3-fluoroanisole (0.20 mL, 1.75 mmol, 1.2 equiv.) in anhydrous THF (2 mL) was added dropwise and the solution stirred for 1 hour at −78 °C. To the resulting pale yellow solution was added the previously prepared solution of magnesium bromide in THF. The reaction was stirred for 20 minutes at −78 °C and then allowed to warm to 0 °C. This mixture was used directly in the next step.

To the previously prepared suspension of chloroynamide in TBME was added $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%), and the reaction stirred for 5 minutes at room temperature. The suspension of (2-fluoro-6-methoxyphenyl)magnesium bromide/lithium bromide complex was then transferred, by syringe, to this mixture and the reaction was stirred for 30 minutes at room temperature. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (20% Et_2O/40–60 petroleum ether), followed by recrystallisation from hexane:TBME (2:1), afforded the title

compound (451 mg, 1.14 mmol, 78%) as colourless crystals. These crystals were suitable for X-ray diffraction.

Preparation *via* arylzinc chloride/lithium chloride complex:

(2-Fluoro-6-methoxyphenyl)zinc chloride/lithium chloride complex was prepared as followed: To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous THF (1 mL) and di-*i*-propylamine (0.25 mL, 1.75 mmol, 1.2 equiv.), and the solution was cooled to 0 °C whilst stirring. To this solution was added dropwise *n*-butyllithium (0.70 mL of a 2.5 M solution in hexanes, 1.75 mmol, 1.2 equiv.) and the mixture stirred for 1 hour at 0 °C. The mixture was then cooled to −78 °C. Next, a solution of 3-fluoroanisole (0.20 mL, 1.75 mmol, 1.2 equiv.) in anhydrous THF (2 mL) was added dropwise and the solution stirred for 1 hour at −78 °C. To the resulting pale yellow solution was added a solution of zinc(II) chloride (0.92 mL of a 1.9 M solution in 2-MeTHF, 1.75 mmol, 1.2 equiv.). The reaction was stirred for 20 minutes at −78 °C and then allowed to warm to room temperature. This solution was then used following the above procedure as for the analogous magnesium bromide/lithium bromide complex, albeit the reaction required heating at 50 °C overnight to achieve completion. Column chromatography (20% Et_2O/ 40–60 petroleum ether) afforded a brown oil that was triturated with hexane/Et_2O (5:1) to afford a pale yellow solid. This solid was recrystallised from hexane:TBME (2:1) to afford the title compound (312 mg, 0.79 mmol, 54%) as colourless crystals;

m.p. 89–91 °C;

R_f 0.18 (10% EtOAc/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3150, 3065, 2241, 1594, 1489, 1469, 1371, 1336, 1173, 1130, 1110, 1090, 1029, 881, 812, 784, 766, 736, 704, 691, 654;

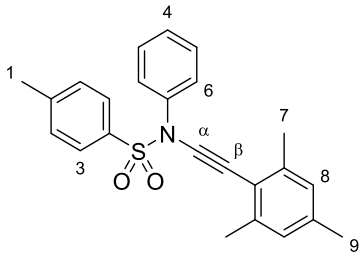
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71–7.66 (2H, m, *H*3), 7.37–7.25 (7H, m, *H*2, *H*4, *H*5, *H*6), 7.20 (1H, td, *J* = 8.4, 6.6 Hz, *H*8), 6.69 (1H, td, *J* = 8.4, 0.8 Hz, *H*9), 6.65 (1H, dt, *J* = 8.4, 0.8 Hz, *H*7), 3.87 (3H, s, *H*10), 2.43 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 163.7 (1C, d, *J* = 251 Hz), 161.4 (1C, d, *J* = 5.6 Hz), 144.8, 138.9, 132.9, 129.4 (1C, d, *J* = 11.1 Hz), 129.4, 129.0, 128.4, 128.0, 126.1, 107.7 (1C, d, *J* = 21.5 Hz), 106.2 (1C, d, *J* = 3.2 Hz), 101.3 (1C, d, *J* = 18.3 Hz), 91.1 (1C, d, *J* = 3.2 Hz, Cα), 60.5 (1C, d, *J* = 1.6 Hz, Cβ), 56.3, 21.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ_F −108.6 (1F, ddd, *J* = 8.4, 6.6, 0.8 Hz);

HRMS (ES+) calc. for $C_{22}H_{18}FNNaO_3S$ $[M+Na]^+$ 418.0884, found 418.0882.

***N*-(Mesitylethynyl)-*N*-phenyltosylamide, 60j**



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and mesitylmagnesium bromide (1.50 mL of a 1.0 M solution in THF, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (3% Et_2O/40–60 petroleum ether) afforded the title compound (352 mg, 1.36 mmol, 93%) as a white powder. This compound can be recrystallised from hexane/TBME (4:1) to give colourless crystals that were suitable for X-ray diffraction;

m.p. 79–81 °C;

R_f 0.43 (20% Et_2O/40–60 petroleum ether);

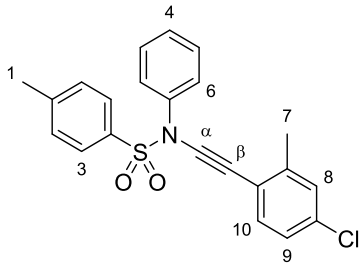
IR (thin film, ν_{max} / cm^{-1}) 2918, 2235, 1594, 1489, 1454, 1372, 1174, 1090, 921, 892, 854, 813, 771, 726, 692, 667;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.58 (2H, d, *J* = 8.1 Hz, *H*3), 7.40–7.24 (5H, m, *H*4, *H*5, *H*6), 7.20 (2H, d, *J* = 8.1 Hz, *H*2), 6.82 (2H, s, *H*8), 2.37 (3H, s, *H*1), 2.33 (6H, s, *H*7), 2.24 (3H, s, *H*9);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8, 139.8, 139.2, 137.3, 132.9, 129.3, 128.9, 128.00, 127.96, 127.4, 125.9, 119.1, 90.0 (Cα), 68.3 (Cβ), 21.5, 21.1, 20.9;

HRMS (ES+) calc. for $C_{24}H_{24}NO_2S$ $[M+H]^+$ 390.1522, found 390.1523.

_N_-((4-Chloro-2-methylphenyl)ethynyl)-_N_-phenyltosylamide, 60k



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and (4-chloro-2-methylphenyl)magnesium chloride (prepared according to example procedure **1.2c** from 2-bromo-5-chlorotoluene (0.23 mL, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL) using *i*-propylmagnesium chloride/lithium chloride complex (1.57 mL of a 1.3 M solution in THF, 2.05 mmol, 1.4 equiv.), and stirring overnight at room temperature). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (3% Et_2O/40–60 petroleum ether) afforded the title compound (514 mg, 1.30 mmol, 89%) as a white powder. This compound can be recrystallised from hexane/TBME (3:1) to give colourless crystals that were suitable for X-ray diffraction;

m.p. 93–95 °C;

R_f 0.35 (8% Et_2O/40–60 petroleum ether);

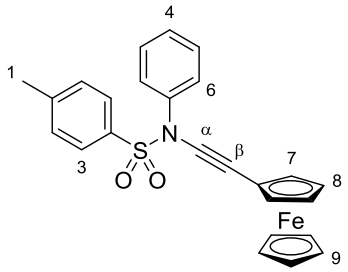
IR (thin film, ν_{max} / cm^{-1}) 3066, 2922, 2238, 1594, 1485, 1454, 1373, 1334, 1210, 1188, 1174, 1092, 1056, 922, 890, 814, 771, 704, 688, 658;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59 (2H, d, *J* = 8.1 Hz, *H*3), 7.39–7.29 (5H, m, *H*4, *H*5, *H*6), 7.29–7.21 (3H, m, *H*2, *H*10), 7.17 (1H, s, *H*8), 7.08 (1H, d, *J* = 8.1 Hz, *H*9), 2.43 (3H, s, *H*1), 2.36 (3H, s, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1, 141.6, 138.8, 133.5, 133.0, 132.6, 129.5, 129.4, 129.1, 128.3, 128.2, 126.2, 125.8, 121.0, 87.4 (Cα), 68.5 (Cβ), 21.7, 20.7;

HRMS (ES+) calc. for $C_{28}H_{18}{}^{35}ClNNaO_2S$ $[M+Na]^+$ 418.0639, found 418.0640.

_N_-(Ferrocenylethynyl)-_N_-phenyltosylamide, 60l



The chloroynamide was synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) following example procedure **1.2e**. Complete consumption of the dichloroenamide was verified by TLC. The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

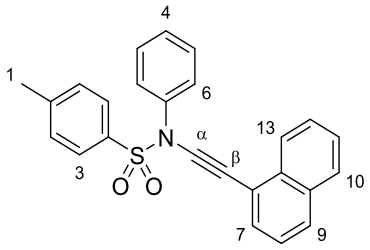
(2,2,6,6-Tetramethylpiperidinyl)ferrocenylmagnesium/lithium chloride complex was prepared as followed: to an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added bromoferrocene (581 mg, 2.19 mmol, 1.5 equiv.) and anhydrous TBME (7 mL), and the solution cooled to −20 °C whilst stirring. Next, *n*-butyllithium (0.88 mL of a 2.5 M solution in hexanes, 2.19 mmol, 1.5 equiv.) was added dropwise and the reaction was stirred for 2 hours at −20 °C. Next was added a solution of 2,2,6,6-tetramethylpiperidinylmagnesium chloride/lithium chloride complex (2.19 mL of a 1.0 M solution in toluene/THF (1:1), 2.19 mmol, 1.5 equiv.), and the solution stirred at −20 °C for 30 minutes. After this, the resulting orange suspension was allowed to warm to room temperature and was used directly in the next step.

To the previously prepared suspension of chloroynamide in TBME was added CuCN·2LiCl (18 µL of a 1.0 M solution in THF, 18 µmol, 1.25 mol%). The suspension of (2,2,6,6-tetramethylpiperidinyl) ferrocenylmagnesium /lithium chloride complex was then transferred, by syringe, to this mixture dropwise over 1 minute, and the reaction was stirred for 30 minutes at room temperature. Reaction completion was then verified by TLC. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (10% Et_2O/pentane) afforded the title compound (386 mg, 0.848 mmol, 58%) as an orange solid. This compound can be recrystallised from heptane/benzene (2:1) to give orange needles that were suitable for X-ray diffraction;

m.p. 114–115 °C;
R_f 0.21 (10% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3095, 2245, 1594, 1490, 1455, 1371, 1306, 1209, 1187, 1172, 1106, 1090, 1026, 1002, 908, 814, 763, 732, 710, 691, 659;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68–7.61 (2H, m, *H*3), 7.38–7.27 (7H, m, *H*2, *H*4, *H*5, *H*6), 4.41 (2H, t, *J* = 1.9 Hz, *H*7), 4.28–4.23 (5H, m, *H*9), 4.21 (2H, t, *J* = 1.9 Hz, *H*8), 2.47 (3H, s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8, 139.2, 133.1, 129.4, 129.0, 128.3, 128.0, 126.0, 78.8, 72.1, 69.7, 69.5 (Cα), 68.9, 63.9 (Cβ), 21.7;
HRMS (ES+) calc. for $C_{25}H_{21}{}^{56}FeNO_2S$ $[M]^+$ 455.0637, found 455.0636.

_N_-(Naphthalen-1-ylethynyl)-_N_-phenyltosylamide, 60m



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and 1-naphthylmagnesium bromide (3.20 mL of a 0.5 M solution in 2-MeTHF, 1.50 mmol, 1.1 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (6% Et_2O/40–60 petroleum ether), followed by recrystallisation from dibutyl ether afforded the title compound (498 mg, 1.25 mmol, 86%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 100–101 °C;

R_f 0.26 (50% toluene/40–60 petroleum ether);

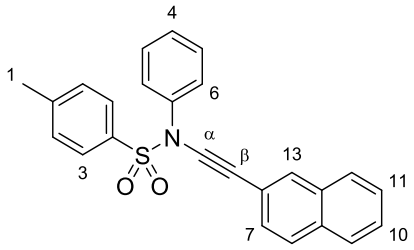
IR (thin film, ν_{max} / cm^{-1}) 3058, 2233, 1594, 1489, 1372, 1172, 1089, 800, 773, 713, 691, 674, 653;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.34–8.26 (1H, m, *H*13), 7.89–7.84 (1H, m, *H*10), 7.81 (1H, d, *J* = 8.3 Hz, *H*9), 7.71 (2H, d, *J* = 8.2 Hz, *H*3), 7.62 (1H, dd, *J* = 7.1, 1.0 Hz, *H*7), 7.58 (1H, ddd, *J* = 7.8, 6.8, 1.5 Hz, *H*12), 7.53 (1H, ddd, *J* = 7.8, 6.8, 1.5 Hz, *H*11), 7.46–7.36 (6H, m, *H*4, *H*5, *H*6, *H*8), 7.29 (2H, 2H, d, *J* = 8.2 Hz, *H*2), 2.44 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 145.0, 138.9, 133.2, 133.1, 133.0, 129.8, 129.5, 129.2, 128.3, 128.23, 128.20, 126.7, 126.3, 126.2, 126.1, 125.2, 120.3, 87.5 (Cα), 69.0 (Cβ), 21.6; ***Note**: A single ^{13}C resonance is obscured due to signal overlap.

HRMS (ES+) calc. for $C_{25}H_{19}NNaO_2S$ $[M+Na]^+$ 420.1029, found 420.1029.

_N_-(Naphthalen-2-ylethynyl)-_N_-phenyltosylamide, 60n



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and 2-naphthylmagnesium bromide (6.40 mL of a 0.25 M solution in 2-MeTHF, 1.50 mmol, 1.1 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (50% toluene/40–60 petroleum ether) afforded a yellow oil that was triturated with hexane/Et_2O (5:1) to give a pale yellow solid. This solid was recrystallised from dibutyl ether/benzene/hexane (~2:1:4) to afford the title compound (502 mg, 1.26 mmol, 86%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 84–85 °C;

R_f 0.17 (50% toluene/40–60 petroleum ether);

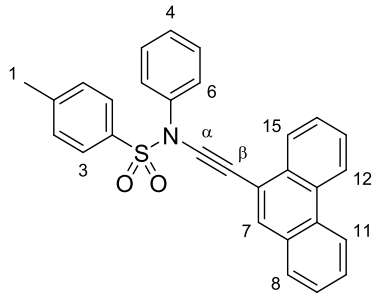
IR (thin film, ν_{max} / cm^{-1}) 3058, 2236, 1595, 1489, 1372, 1174, 1090, 815, 764, 748, 715, 691, 666, 649;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.91 (1H, br. s, *H*13), 7.85–7.74 (3H, m, *H*8, *H*9, *H*12), 7.67 (2H, d, *J* = 8.2 Hz, *H*3), 7.53–7.46 (2H, m, *H*10, *H*11), 7.45 (1H, dd, *J* = 8.4, 1.3 Hz, *H*7), 7.41–7.33 (5H, m, *H*4, *H*5, *H*6), 7.31 (2H, d, *J* = 8.2 Hz, *H*2), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.0, 138.9, 132.9, 132.6, 131.0, 129.5, 129.1, 128.28, 128.26, 127.9, 127.7, 127.6, 126.53, 126.50, 126.3, 119.9, 83.3 (Cα), 70.9 (Cβ), 21.7; ***Note**: Two ^{13}C resonances are obscured due to signal overlap.

HRMS (ES+) calc. for $C_{25}H_{19}NNaO_2S$ $[M+Na]^+$ 420.1029, found 420.1029.

***N*-(Phenanthren-9-ylethynyl)-*N*-phenyltosylamide, 60o**



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and 9-phenanthrylmagnesium bromide (3.20 mL of a 0.5 M solution in THF, 1.50 mmol, 1.1 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (50% toluene/40–60 petroleum ether) afforded the title compound (533 mg, 1.19 mmol, 81%) as a white, semi-crystalline foam. This compound can be crystallised by vapour diffusion of pentane into a concentrated solution of the title compound in benzene to give colourless crystals that were suitable for X-ray diffraction;

m.p. 120–121 °C;

R_f 0.25 (50% toluene/40–60 petroleum ether);

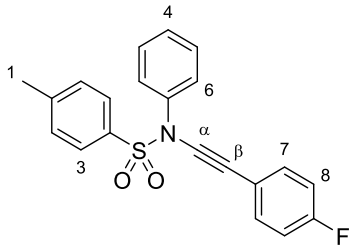
IR (thin film, ν_{max} / cm^{-1}) 3062, 2232, 1594, 1490, 1451, 1372, 1271, 1214, 1187, 1174, 892, 813, 751, 726, 705, 690, 658;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.71–8.66 (1H, m, *H*12), 8.64 (1H, d, *J* = 8.3 Hz, *H*11), 8.44–8.36 (1H, m, *H*15), 7.92 (1H, s, *H*7), 7.82 (1H, dd, *J* = 7.8, 1.3 Hz, *H*8), 7.75–7.70 (2H, m, *H*3), 7.73–7.65 (2H, m, *H*13, *H*14), 7.65 (1H, ddt, *J* = 8.3, 6.8, 1.3 Hz, *H*10), 7.59 (1H, ddt, *J* = 7.8, 6.8, 1.3 Hz, *H*9), 7.51–7.46 (2H, m, *H*5), 7.46–7.36 (3H, m, *H*4, *H*6), 7.29 (2H, d, *J* = 8.1 Hz, *H*2), 2.43 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1, 138.9, 133.0, 131.2, 131.1, 130.9, 130.02, 129.96, 129.6, 129.2, 128.33, 128.25, 128.23, 127.2, 127.1, 127.0, 126.91, 126.88, 126.3, 122.7, 122.5, 119.0, 87.2 (Cα), 69.2 (Cβ), 21.6;

HRMS (ES+) calc. for $C_{29}H_{21}NNaO_2S$ $[M+Na]^+$ 470.1185, found 470.1185.

_N_-((4-Fluorophenyl)ethynyl)-_N_-phenyltosylamide, 60p



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and 4-fluorophenylmagnesium bromide (1.50 mL of a 1.0 M solution in THF, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (3% Et_2O/40–60 petroleum ether) afforded a pale yellow solid which was recrystallisated from hexane:TBME (3:1) to give the title compound (451 mg, 1.23 mmol, 84%) as colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 78–79 °C;

R_f 0.18 (6% CH_2Cl_2/4% EtOAc/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3067, 2243, 1599, 1508, 1489, 1372, 1229, 1174, 1091, 922, 892, 836, 813, 768, 723, 691, 668, 649;

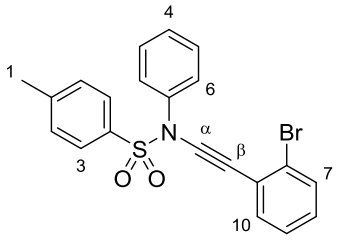
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* = 8.1 Hz, *H*3), 7.42–7.27 (9H, m, *H*4, *H*5, *H*6, *H*7), 7.00 (2H, t, *J* = 8.7 Hz, *H*8), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4 (1C, d, *J* = 249 Hz), 145.0, 138.8, 133.5 (2C, d, *J* = 7.9 Hz), 132.9, 129.5, 129.1, 128.3, 128.2, 126.3, 118.6 (1C, d, *J* = 3.2 Hz), 115.6 (2C, d, *J* = 22.3 Hz), 82.6 (Cα), 69.3 (Cβ), 21.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ_F −111.2 (1F, tt, *J* = 8.7, 5.5 Hz);

HRMS (ES+) calc. for $C_{21}H_{16}FNNaO_2S$ $[M+Na]^+$ 388.0778, found 388.0779.

***N*-((2-Bromophenyl)ethynyl)-*N*-phenyltosylamide, 60q**



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and 2-bromophenylmagnesium chloride/lithium chloride (prepared according to example procedure **1.2c** from 2-bromoiodobenzene (225 µL, 1.75 mmol, 1.2 equiv.) in anhydrous THF (3 mL) using *i*-propylmagnesium chloride/lithium chloride (1.57 mL of a 1.3 M solution in THF, 2.05 mmol, 1.4 equiv.) and stirring for 1 hour at −20 °C). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (10% Et_2O/40–60 petroleum ether) afforded a pale yellow oil that was crystallised from dibutyl ether:hexane (2:1) to afford the title compound (474 mg, 1.11 mmol, 76%) as colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 68–69 °C;

R_f 0.23 (10% Et_2O/40–60 petroleum ether);

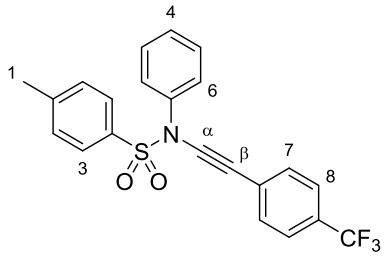
IR (thin film, ν_{max} / cm^{-1}) 3065, 2238, 1594, 1490, 1372, 1187, 1172, 1088, 1026, 891, 812, 789, 751, 732, 704, 686, 658;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69–7.63 (2H, m, *H*3), 7.54 (1H, dd, *J* = 8.1, 1.1 Hz, *H*7), 7.43 (1H, dd, *J* = 7.9, 1.8 Hz, *H*10), 7.40–7.31 (5H, m, *H*4, *H*5, *H*6), 7.26 (2H, br. d, *J* = 7.8 Hz, *H*2), 7.24 (1H, ddd, *J* = 7.9, 7.6, 1.1 Hz, *H*9), 7.13 (1H, ddd, *J* = 8.1, 7.6, 1.8 Hz, *H*8), 2.43 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.0, 138.7, 133.1, 132.9, 132.3, 129.5, 129.1, 129.0, 128.34, 128.28, 127.0, 126.3, 125.2, 124.9, 87.2 (Cα), 69.5 (Cβ), 21.7;

HRMS (ES+) calc. for $C_{21}H_{16}{}^{79}BrNNaO_2S$ $[M+Na]^+$ 447.9977, found 447.9978.

_N_-Phenyl-_N_-((4-(trifluoromethyl)phenyl)ethynyl)tosylamide, 60r



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and 4-(trifluoromethyl)phenylmagnesium chloride (prepared according to example procedure **1.2c** from 4-iodobenzotrifluoride (0.26 mL, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL), using *i*-propylmagnesium chloride (1.02 mL of a 2.0 M solution in THF, 2.05 mmol, 1.4 equiv.) and stirring for 30 minutes at −20 °C). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (10% CH_2Cl_2/10% Et_2O/40–60 petroleum ether) afforded a pale yellow solid which was recrystallised from hexane:TBME (3:1) to give the title compound (545 mg, 1.31 mmol, 90%) as colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 139–140 °C;

R_f 0.21 (10% Et_2O/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3068, 2237, 1594, 1488, 1375, 1320, 1168, 1124, 1105, 1071, 1017, 812, 684, 655;

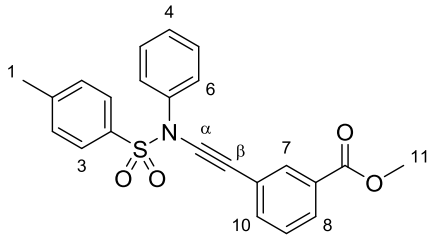
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62 (2H, d, *J* = 8.1 Hz, *H*3), 7.55 (2H, d, *J* = 8.1 Hz, *H*8), 7.47 (2H, d, *J* = 8.1 Hz, *H*7), 7.40–7.33 (3H, m, H5, *H*4), 7.33–7.27 (4H, m, *H*2, *H*6), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.2, 138.5, 132.9, 131.1, 129.6, 129.4 (2C, q, *J* = 33.4 Hz), 129.2, 128.5, 128.2, 126.6, 126.3, 125.2 (2C, q, *J* = 3.7 Hz), 123.9 (1C, q, *J* = 271.8 Hz), 85.5 (Cα), 69.6 (Cβ), 21.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ_F −62.7;

HRMS (ES+) calc. for $C_{22}H_{16}F_3NNaO_2S$ $[M+Na]^+$ 438.0746, found 438.0746.

Methyl 3-((*N*-phenyltosylamido)ethynyl)benzoate, 60s



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and (3-(methoxycarbonyl)phenyl)magnesium chloride (prepared according to example procedure **1.2c** from methyl 3-iodobenzoate (459 mg, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL), using *i*-propylmagnesium chloride (1.02 mL of a 2.0 M solution in THF, 2.05 mmol, 1.4 equiv.) and stirring for 1 hour at −20 °C). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (10% CH_2Cl_2/10% Et_2O/40–60 petroleum ether) afforded a pale yellow solid which was recrystallised from hexane:TBME (3:1) to give the title compound (545 mg, 1.31 mmol, 90%) as colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 90–91 °C;

R_f 0.21 (10% Et_2O/40–60 petroleum ether);

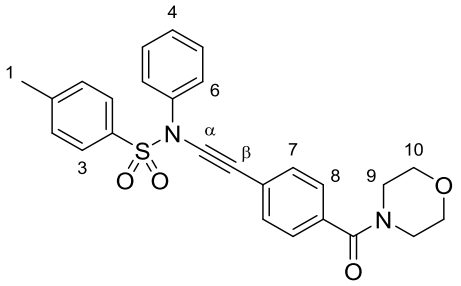
IR (thin film, ν_{max} / cm^{-1}) 2951, 2240, 1722, 1595, 1490, 1439, 1373, 1282, 1259, 1172, 1112, 1088, 980, 894, 859, 814, 784, 752, 689;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.04 (1H, s, *H*7), 7.95 (1H, d, *J* = 7.3 Hz, *H*8), 7.62 (2H, d, *J* = 8.1 Hz, *H*3), 7.57 (1H, d, *J* = 7.1 Hz, *H*10), 7.42–7.27 (8H, m, *H*2, *H*4, *H*5, *H*6, *H*9), 3.92 (3H, s, *H*11), 2.44 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.4, 145.1, 138.7, 135.4, 132.8, 132.4, 130.3, 129.6, 129.2, 128.8, 128.41, 128.37, 128.2, 126.3, 123.1, 83.8 (Cα), 69.6 (Cβ), 52.3, 21.7;

HRMS (ES+) calc. for $C_{23}H_{19}NNaO_4S$ $[M+Na]^+$ 428.0927, found 428.0925.

_N_-((4-(Morpholine-4-carbonyl)phenyl)ethynyl)-_N_-phenyltosylamide, 60t



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and (4-(morpholine-4-carbonyl)phenyl)magnesium chloride/lithium chloride complex (prepared according to example procedure **1.2c** from (4-bromophenyl) (morpholino)methanone (513 mg, 1.90 mmol, 1.3 equiv.) in anhydrous THF (4 mL), using *i*-propylmagnesium chloride/lithium chloride complex (1.69 mL of a 1.3 M solution in THF, 2.19 mmol, 1.5 equiv.) and stirring for 20 hours at −5 °C). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (20 → 30% acetone/40–60 petroleum ether) afforded the title compound (530 mg, 1.15 mmol, 79%) as a white powder. This compound can be recrystallised by vapour diffusion of pentane into a concentrated solution of the title compound in benzene to give colourless crystals that were suitable for X-ray diffraction;

m.p. 157–158 °C;

R_f 0.11 (20% acetone/40–60 petroleum ether);

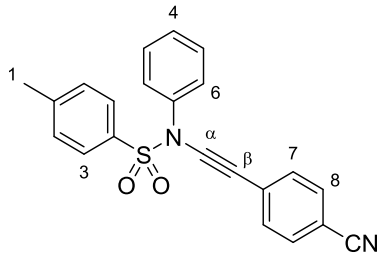
IR (thin film, ν_{max} / cm^{-1}) 2966, 2921, 2857, 2238, 1630, 1429, 1373, 1278, 1258, 1173, 1114, 1065, 1012, 840, 730, 691;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.64–6.58 (2H, m, *H*3), 7.44–7.39 (2H, m, *H*8), 7.39–7.32 (5H, m, *H*4, *H*5, *H*7), 7.32–7.26 (4H, m, *H*2, *H*6), 4.13–3.18 (8H, br. m, *H*9, *H*10), 2.44 (3H, s, *H*1);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 169.7, 145.1, 138.6, 134.3, 132.9, 131.2, 129.6, 129.2, 128.4, 128.2, 127.2, 126.3, 124.5, 84.7 (Cα), 69.9 (Cβ), 66.8, 48.3, 42.6, 21.7;

HRMS (ES+) calc. for $C_{26}H_{24}N_2NaO_4S$ $[M+Na]^+$ 483.1349, found 483.1350.

_N_-((4-Cyanophenyl)ethynyl)-_N_-phenyltosylamide, 60u



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and 4-cyanophenylmagnesium chloride (prepared according to example procedure **1.2c** from 4-iodobenzonitrile (402 mg, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL) using *i*-propylmagnesium chloride (1.02 mL of a 2.0 M solution in THF, 2.05 mmol, 1.4 equiv.)). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (5% Et_2O/40–60 petroleum ether) afforded a pale yellow solid which was recrystallised from heptane:Et_2O (2:1) to give the title compound (448 mg, 1.20 mmol, 82%) as colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 122 °C;

R_f 0.11 (6% CH_2Cl_2/4% EtOAc/40–60 petroleum ether);

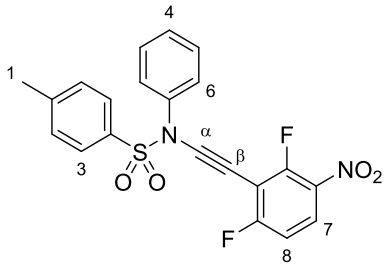
IR (thin film, ν_{max} / cm^{-1}) 3066, 2225, 1594, 1488, 1374, 1174, 1065, 923, 892, 838, 812, 761, 710, 691, 661;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 (2H, d, *J* = 8.1 Hz, *H*3), 7.57 (2H, d, *J* = 8.1 Hz, *H*8), 7.43 (2H, d, *J* = 8.1 Hz, *H*7), 7.40–7.33 (3H, m, H5, *H*4), 7.33–7.24 (4H, m, *H*2, *H*6), 2.44 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.4, 138.2, 132.8, 131.9, 131.1, 129.7, 129.3, 128.6, 128.1, 127.9, 126.3, 118.5, 110.7, 87.6 (Cα), 69.7 (Cβ), 21.7;

HRMS (ES+) calc. for $C_{22}H_{17}N_2O_2S$ $[M+H]^+$ 373.1005, found 373.0991.

_N_-((2,6-Difluoro-3-nitrophenyl)ethynyl)-_N_-phenyltosylamide, 60v



The chloroynamide was synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) following example procedure **1.2e**. Complete consumption of the dichloroenamide was verified by TLC. The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

(2,6-Difluoro-3-nitrophenyl)zinc chloride/lithium chloride complex was prepared and used as followed: To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous THF (2 mL) and freshly distilled 2,2,6,6-tetramethylpiperidine (0.32 mL, 1.90 mmol, 1.3 equiv.), and the solution was cooled to −5 °C whilst stirring. To this solution was added dropwise *n*-butyllithium (0.76 mL of a 2.5 M solution in hexanes, 1.90 mmol, 1.3 equiv.) and the mixture stirred for 1 hour at −5 °C. Next, $ZnCl_2$ (1.08 mL of a 1.9 M solution in 2-MeTHF, 2.04 mmol, 1.4 equiv.) was added and the resulting solution was stirred for 30 minutes at room temperature. ***Note***: The resulting solution was yellow. The reaction was cooled to −20 °C and 2,4-difluoro-1-nitrobenzene (192 µL, 1.75 mmol, 1.2 equiv.) was added dropwise. The reaction was stirred for 30 minutes at −20 °C and for 2 hours at room temperature, giving the requisite arylzinc chloride/lithium chloride complex as a red solution. This solution was cooled to −20 °C and CuCN·2LiCl (73 µL of a 1 M solution in THF, 73 µmol, 5 mol%) was added. The solution was then stirred for 30 minutes at room temperature and used directly in the next step.

To the previously prepared suspension of chloroynamide in TBME was added the solution of (2,6-difluoro-3-nitrophenyl)copper(I) cyanide/zinc chloride/lithium chloride complex by syringe, and the reaction was stirred overnight at room temperature. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (10% EtOAc/40–60 petroleum ether) afforded the title compound (398 mg, 928 µmol, 64%) as a white powder;

m.p. 103–105 °C;
R_f 0.21 (10% EtOAc/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3094, 2244, 1584, 1537, 1487, 1461, 1376, 1353, 1332, 1288, 1188, 1174, 1089, 1026, 887, 801, 758, 688, 659;

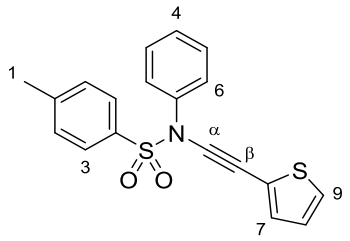
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.02 (1H, ddd, *J* = 9.3, 8.4, 5.6 Hz, *H*7), 7.63 (2H, d, *J* = 8.3 Hz, *H*3), 7.40–7.34 (3H, m, *H*4, *H*5), 7.34–7.25 (4H, m, *H*2, *H*6), 7.05 (1H, ddd, *J* = 9.3, 7.6, 1.7 Hz, *H*8), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.2 (1C, dd, *J* = 263, 5.6 Hz), 156.5 (1C, dd, *J* = 270, 5.6 Hz), 145.6, 137.9, 134.2 (1C, m), 132.5, 129.7, 129.3, 128.7, 128.2, 126.2, 125.8 (1C, d, *J* = 10.3 Hz), 111.6 (1C, dd, *J* = 23.0, 4.8 Hz), 105.0 (1C, dd, *J* = 21.5, 19.3 Hz), 94.8 (1C, t, *J* = 3.2 Hz, Cα), 56.6 (Cβ), 21.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ_F −95.3 (1F, ddd, *J* = 13.1, 8.4, 1.7 Hz), −109.1 (1F, ddd, *J* = 13.1, 7.6, 5.6 Hz);

HRMS (ES+) calc. for $C_{21}H_{14}F_2N_2NaO_4S$ $[M+Na]^+$ 451.0535, found 451.0534.

_N_-Phenyl-_N_-(thiophen-2-ylethynyl)tosylamide, 60w



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and 2-thienylmagnesium bromide (1.50 mL of a 1.0 M solution in THF, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (10% Et_2O/5% CH_2Cl_2/40–60 petroleum ether) afforded a pale yellow solid which was recrystallised from hexane:CH_2Cl_2:TBME (~5:1:1) to give the title compound (464 mg, 1.31 mmol, 90%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 129–130 °C (dec.);

R_f 0.41 (20% Et_2O/40–60 petroleum ether);

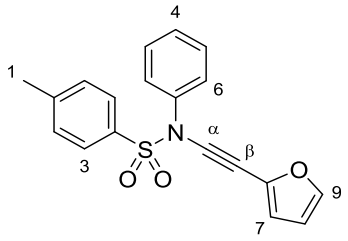
IR (thin film, ν_{max} / cm^{-1}) 3069, 2229, 1595, 1491, 1372, 1172, 1089, 1052, 1017, 921, 890, 851, 813, 765, 710, 691, 666, 651;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62 (2H, d, *J* = 8.1 Hz, *H*3), 7.39–7.24 (8H, m, *H*2, *H*4, *H*5, *H*6, *H*7), 7.22–7.17 (1H, m, *H*9), 6.97 (1H, m, *H*8), 2.46 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1, 138.8, 133.0, 132.9, 129.5, 129.1, 128.33, 128.25, 127.9, 127.0, 126.3, 122.6, 86.4 (Cα), 63.9 (Cβ), 21.7;

HRMS (ES+) calc. for $C_{19}H_{15}NNaO_2S_2$ $[M+Na]^+$ 376.0436, found 376.0438.

_N_-(Furan-2-ylethynyl)-_N_-phenyltosylamide, 60x



The chloroynamide was synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) following example procedure **1.2e**. Complete consumption of the dichloroenamide was verified by TLC. The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

(Furan-2-yl)zinc chloride/lithium chloride complex was prepared as followed: To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous THF (2 mL) and furan (128 µL, 1.75 mmol, 1.2 equiv.), and the reaction cooled to −10 °C. Next, was added dropwise *n*-butyllithium (0.76 mL of a 2.5 M solution in hexanes, 1.90 mmol, 1.3 equiv.) and the mixture stirred for 2 hours at −10 °C. $ZnCl_2$ (1.08 mL of a 1.9 M solution in 2-MeTHF, 2.05 mmol, 1.4 equiv.) was then added, followed by anhydrous tmeda (307 µL, 2.05 mmol, 1.3 equiv.), and the resulting solution was allowed to warm to 0 °C over 30 minutes whilst stirring. CuCN·2LiCl (73 µL of a 1 M solution in THF, 73 µmol, 5 mol%) was then added and the resulting solution was then stirred for 5 minutes at 0°C.

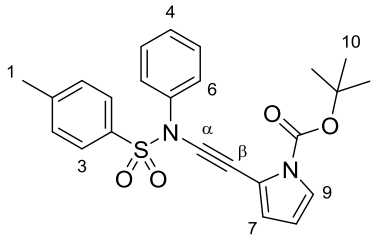
This solution was then transferred to the previously prepared suspension of chloroynamide in TBME by syringe and the reaction was stirred overnight at room temperature. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (5 → 10% Et_2O/40–60 petroleum ether) afforded a pale yellow powder, which was recrystallised from TBME/hexane (1:1) the title compound (415 mg, 1.23 mmol, 84%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 123–125 °C;
R_f 0.26 (10% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3067, 2230, 1593, 1490, 1372, 1173, 1088, 1011, 917, 886, 813, 748, 691, 659;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63 (2H, d, *J* = 8.3 Hz, *H*3), 7.40 (1H, dd, *J* = 1.9, 0.7 Hz, *H*9), 7.37–7.24 (7H, m, *H*2, *H*4, *H*5, *H*6), 6.63 (1H, dd, *J* = 3.4, 0.7 Hz, *H*7), 6.39 (1H, dd, *J* = 3.4, 1.9 Hz, *H*8), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1, 144.1, 138.6, 136.6, 133.1, 129.6, 129.2, 128.4, 128.2, 126.3, 117.2, 111.1, 86.9 (Cα), 61.2 (Cβ), 21.7;

HRMS (ES+) calc. for $C_{19}H_{15}NNaO_3S$ $[M+Na]^+$ 360.0665, found 360.0665.

_t_-Butyl 2-(((_N_-phenyltosylamido)ethynyl)-1_H_-pyrrole-1-carboxylate, 60y



The chloroynamide was synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) following example procedure **1.2e**. Complete consumption of the dichloroenamide was verified by TLC. The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

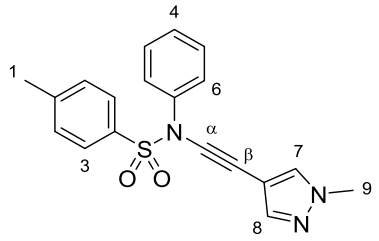
(1-(*t*-Butoxycarbonyl)-1*H*-pyrrol-2-yl)zinc chloride/lithium chloride complex was prepared as followed: To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous THF (2 mL) and freshly distilled 2,2,6,6-tetramethylpiperidine (0.32 mL, 1.90 mmol, 1.3 equiv.), and the solution was cooled to −5 °C whilst stirring. To this solution was added dropwise *n*-butyllithium (0.76 mL of a 2.5 M solution in hexanes, 1.90 mmol, 1.3 equiv.) and the mixture stirred for 1 hour at −5 °C. Next, the reaction was cooled to −78 °C and *N*-Boc pyrrole (293 μL, 1.75 mmol, 1.2 equiv.) was added and the reaction stirred at −78 °C for 1 hour. $ZnCl_2$ (1.08 mL of a 1.9 M solution in 2-MeTHF, 2.05 mmol, 1.4 equiv.) was then added, followed by anhydrous tmeda (307 μL, 2.05 mmol, 1.3 equiv.), and the resulting solution was allowed to warm to 0 °C over 30 minutes whilst stirring. CuCN·2LiCl (73 μL of a 1 M solution in THF, 73 μmol, 5 mol%) was then added and the resulting solution was then stirred for 5 minutes at 0 °C.

This solution was then transferred to the previously prepared suspension of chloroynamide in TBME by syringe and the reaction was stirred overnight at room temperature. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (5 → 10% Et_2O/40–60 petroleum ether) afforded the title compound (493 mg, 1.13 mmol, 77%) as colourless crystals. The compound crystallises spontaneously from the column fractions and these were suitable for X-ray diffraction;

m.p. 130 °C;
R_f 0.27 (10% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2981, 2238, 1744, 1594, 1490, 1404, 1371, 1347, 1317, 1288, 1173, 1144, 1089, 1054, 1002, 884, 844, 814, 768, 733, 712, 692, 660;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.63 (2H, m, *H*3), 7.35–7.24 (8H, m, *H*2, *H*4, *H*5, *H*6, *H*7), 6.51 (1H, dd, *J* = 3.4, 1.7 Hz, *H*9), 6.14 (1H, t, *J* = 3.4 Hz, *H*8), 2.43 (3H, s, *H*1), 1.55 (9H, s, *H*10);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 148.2, 144.7, 139.1, 133.2, 129.4, 129.0, 128.3, 128.0, 126.2, 123.0, 122.0, 114.5, 100.8, 85.9 (Cα), 84.1, 62.8 (Cβ), 27.9, 21.7;
HRMS (ES+) calc. for $C_{24}H_{24}N_2NaO_4S$ $[M+Na]^+$ 459.1349, found 459.1349.

_N_-((1-Methyl-1_H_-pyrazol-4-yl)ethynyl)-_N_-phenyltosylamide, 60z



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and (1-methyl-1*H*-pyrazol-4-yl)magnesium chloride/lithium chloride complex (prepared according to example procedure **1.2c** from 4-iodo-1-methyl-1*H*-pyrazole (365 mg, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL), using *i*-propylmagnesium chloride/lithium chloride (1.57 mL of a 1.3 M solution in THF, 2.05 mmol, 1.4 equiv.) and stirring for 1 hour at −20 °C). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (40% EtOAc/40–60 petroleum ether) afforded a yellow solid which was recrystallised from hexane:TBME (~1:3) to give the title compound (403 mg, 1.15 mmol, 78%) as colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 124–125 °C;

R_f 0.24 (40% EtOAc/40–60 petroleum ether);

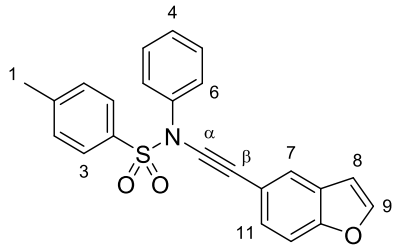
IR (thin film, ν_{max} / cm^{-1}) 3067, 2945, 2247, 1594, 1558, 1489, 1454, 1368, 1252, 1171, 1090, 981, 922, 893, 813, 769, 704, 688, 656;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63–7.57 (2H, m, *H*3), 7.52 (1H, s, *H*8), 7.47 (1H, s, *H*7), 7.36–7.26 (7H, m, *H*2, *H*4, *H*5, *H*6), 3.87 (3H, s, *H*9), 2.44 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.9, 142.8, 139.1, 133.5, 133.1, 129.5, 129.1, 128.3, 128.2, 126.2, 102.2, 83.3 (Cα), 61.7 (Cβ), 39.1, 21.7;

HRMS (ES+) calc. for $C_{19}H_{17}N_3NaO_2S$ $[M+Na]^+$ 374.0934, found 374.0935.

***N*-(Benzofuran-5-ylethynyl)-*N*-phenyltosylamide, 60ad**



The chloroynamide was synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) following example procedure **1.2e**. Complete consumption of the dichloroenamide was verified by TLC. The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

Benzofuran-5-ylmagnesium chloride/lithium chloride complex was prepared as followed: To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added magnesium turnings (107 mg, 4.38 mmol, 3.0 equiv.), anhydrous lithium chloride (92.9 mg, 2.19 mmol, 1.5 equiv.) and anhydrous THF (4 mL), followed by 5-bromobenzofuran (220 µL, 1.75 mmol, 1.2 equiv.) and the reaction was stirred at room temperature for 3 hours, followed by heating at reflux for 2 hours. The suspension was then allowed to cool to room temperature.

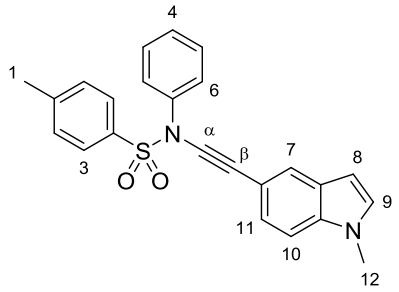
To the previously prepared suspension of chloroynamide in TBME was added $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%), and the reaction stirred for 5 minutes at room temperature. The suspension of benzofuran-5-ylmagnesium chloride/lithium chloride complex was then transferred, by syringe, to this mixture and the reaction was stirred for 1 hour at room temperature. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (5 → 10% Et_2O/40–60 petroleum ether) afforded the title compound (415 mg, 1.07 mmol, 73%) as a white powder. This compound was recrystallised from hexane/Et_2O (3:1) to give colourless crystals suitable for X-ray diffraction;

m.p. 90–91 °C;
R_f 0.13 (10% EtOAc/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3068, 2943, 2841, 2244, 1611, 1594, 1489, 1471, 1438, 1372, 1282, 1246, 1187, 1174, 1079, 1052, 922, 892, 813, 799, 778, 709, 691, 666, 651;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.90–7.67 (4H, m, *H*3, *H*7, *H*9), 7.43 (1H, dt, *J* = 8.6, 0.7 Hz, *H*11), 7.37–7.32 (6H, m, *H*4, *H*5, *H*6, *H*10), 7.32–7.27 (2H, m, *H*2), 6.74 (1H, dd, *J* = 2.2, 1.0 Hz, *H*8), 2.45 (3H, s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 154.5, 145.8, 144.9, 139.1, 133.0, 129.5, 129.1, 128.3, 128.2,

127.5, 126.2, 124.9, 117.0, 111.4, 106.4, 81.5 (Cα), 70.7 (Cβ), 21.7; ***Note***: A single ^{13}C resonance is obscured due to signal overlap.

HRMS (ES+) calc. for $C_{23}H_{17}NNaO_3S$ $[M+Na]^+$ 410.0821, found 410.0822.

_N_-((1-Methyl-1_H_-indol-5-yl)ethynyl)-_N_-phenyltosylamide, 60ae



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and (1-methyl-1*H*-indol-5-yl)magnesium chloride (prepared according to example procedure **1.2c** from 5-iodo-1-methyl-1*H*-indole (451 mg, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL), using *i*-propylmagnesium chloride/lithium chloride complex (1.57 mL of a 1.3 M solution in THF, 2.05 mmol, 1.4 equiv.) and stirring at 0 °C for 2 hours). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (20% Et_2O/40–60 petroleum ether) afforded a brown oil which was triturated with hexane/Et_2O (10:1) to afford a pale yellow solid. Recrystallisation of this solid using hexane/TBME (2:1) gave the title compound (353 mg, 882 µmol, 60%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 111–112 °C;

R_f 0.19 (20% Et_2O/40–60 petroleum ether);

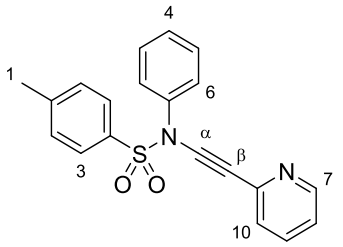
IR (thin film, ν_{max} / cm^{-1}) 3064, 2945, 2239, 1594, 1488, 1369, 1345, 1173, 1089, 912, 887, 813, 797, 759, 727, 707, 691, 659;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73–7.70 (1H, m, *H*10), 7.69–7.62 (2H, m, *H*3), 7.39–7.212 (9H, m, *H*2, *H*4, *H*5, *H*6, *H*7, *H*11), 7.06 (1H, d, *J* = 3.2 Hz, *H*9), 6.45 (1H, dd, *J* = 3.2, 0.6 Hz, *H*8), 3.78 (3H, s, *H*12), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 139.4, 136.3, 133.0, 129.8, 129.4, 129.0, 128.3, 128.2, 128.0, 126.2, 125.5, 125.2, 112.8, 109.2, 101.1, 80.5 (Cα), 71.9 (Cβ), 32.9, 21.7;

HRMS (ES+) calc. for $C_{24}H_{20}N_2NaO_2S$ $[M+Na]^+$ 423.1138, found 423.1137.

_N_-Phenyl-_N_-(pyridin-2-ylethynyl)tosylamide, 60af



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and pyridin-2-ylmagnesium chloride (prepared according to example procedure **1.2c** from 2-bromopyridine (167 μL, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL), using *i*-propylmagnesium chloride (1.02 mL of a 2.0 M solution in THF, 2.05 mmol, 1.4 equiv.) and stirring at room temperature for 2 hours). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (40 → 50% EtOAc/40–60 petroleum ether) afforded a pink solid which was recrystallised from hexane/TBME (2:1) to give the title compound (378 mg, 1.08 mmol, 74%) as pale yellow needles. These crystals were suitable for X-ray diffraction;

m.p. 100–101 °C;

R_f 0.48 (50% EtOAc/40–60 petroleum ether);

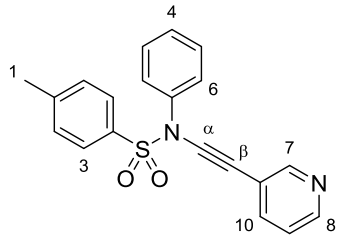
IR (thin film, ν_{max} / cm^{-1}) 3031, 2237, 1583, 1491, 1467, 1372, 1171, 1085, 892, 813, 777, 687, 655;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.53 (1H, app. dq, *J* = 4.9, 1.1 Hz, *H*7), 7.66–7.62 (2H, m, *H*3), 7.62 (1H, app. ddd, *J* = 7.8, 7.6, 2.0 Hz, *H*9), 7.41 (1H, dt, *J* = 7.8, 1.1 Hz, *H*10), 7.36–7.29 (5H, m, *H*4, *H*5, *H*5), 7.29–7.25 (2H, m, *H*2), 7.17 (1H, ddd, *J* = 7.6, 4.9, 1.1 Hz, *H*8), 2.42 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.9, 145.2, 143.3, 138.3, 136.0, 133.0, 129.6, 129.2, 128.5, 128.2, 126.7, 126.5, 122.2, 83.1 (Cα), 70.5 (Cβ), 21.7;

HRMS (ES+) calc. for $C_{20}H_{17}N_2O_2S$ $[M+H]^+$ 349.1005, found 349.1006.

_N_-Phenyl-_N_-(pyridin-3-ylethynyl)tosylamide, 60ag



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and pyridin-3-ylmagnesium chloride (prepared according to example procedure **1.2c** from 3-iodopyridine (359 mg, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL), using *i*-propylmagnesium chloride (1.02 mL of a 2.0 M solution in THF, 2.05 mmol, 1.4 equiv.) and stirring at −20 °C for 1 hour). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Recrystallisation from EtOAc gave the title compound (444 mg, 1.27 mmol, 87%) as pale yellow crystals. These crystals were suitable for X-ray diffraction;

m.p. 108–109 °C;

R_f 0.31 (40% EtOAc/40–60 petroleum ether);

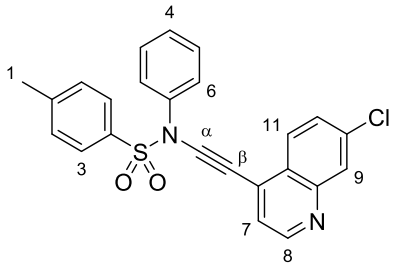
IR (thin film, ν_{max} / cm^{-1}) 3031, 2240, 1594, 1491, 1373, 1187, 1172, 1085, 1023, 892, 802, 704, 687, 655;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.60 (1H, d, *J* = 1.1 Hz, *H*7), 8.50 (1H, dd, *J* = 4.9, 1.1 Hz, *H*8), 7.67 (1H, dt, *J* = 7.8, 2.0 Hz, *H*10), 7.64–7.57 (2H, m, *H*3), 7.40–7.33 (3H, m, *H*4, *H*5), 7.33–7.27 (4H, m, *H*2, *H*6), 7.23 (1H, ddd, *J* = 7.8, 4.9, 0.7 Hz, *H*9), 2.44 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.0, 148.3, 145.2, 138.5, 138.2, 132.8, 129.6, 129.2, 128.5, 128.2, 126.3, 122.9, 119.9, 86.0 (Cα), 67.3 (Cβ), 21.7;

HRMS (ES+) calc. for $C_{20}H_{17}N_2O_2S$ $[M+H]^+$ 349.1005, found 349.1006.

_N_-((7-Chloroquinolin-4-yl)ethynyl)-_N_-phenyltosylamide, 60ah



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and (7-chloroquinolin-4-yl)magnesium chloride (prepared according to example procedure **1.2c** from 7-chloro-4-iodoquinoline (508 mg, 1.75 mmol, 1.2 equiv.) in anhydrous THF (5 mL), using *i*-propylmagnesium chloride (1.02 mL of a 2.0 M solution in THF, 2.05 mmol, 1.4 equiv.) and stirring at −20 °C for 1 hour). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (20% EtOAc/40–60 petroleum ether) afforded a dark yellow solid which was recrystallised from EtOAc to give the title compound (563 mg, 1.30 mmol, 89%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 130–132 °C;

R_f 0.13 (20% EtOAc/40–60 petroleum ether);

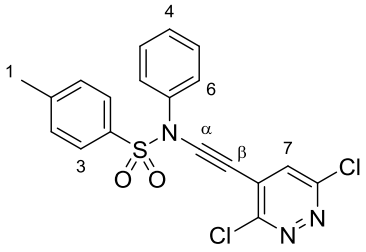
IR (thin film, ν_{max} / cm^{-1}) 3064, 2981, 2229, 1576, 1490, 1375, 1174, 1089, 1072, 996, 884, 835, 691;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.80 (1H, d, *J* = 4.4 Hz, *H*8), 8.18 (1H, d, *J* = 8.8 Hz, *H*11), 8.08 (1H, d, *J* = 2.1 Hz, *H*9), 7.68–7.61 (2H, m, *H*3), 7.55 (1H, dd, *J* = 8.8, 2.1 Hz, *H*10), 7.46–7.39 (3H, m, *H*4, *H*5), 7.39–7.34 (2H, m, *H*6), 7.32 (1H, d, *J* = 4.4 Hz, *H*7), 7.31–7.26 (2H, br. m, *H*2), 2.42 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 150.6, 148.3, 145.6, 138.1, 135.7, 132.9, 129.82, 129.78, 129.4, 128.9, 128.7, 128.10, 128.08, 127.4, 126.3, 125.8, 121.7, 93.1 (Cα), 67.8 (Cβ), 21.7;

HRMS (ES+) calc. for $C_{24}H_{18}{}^{35}ClN_2NaO_2S$ $[M+H]^+$ 433.0772, found 433.0773.

_N_-((3,6-Dichloropyridazin-4-yl)ethynyl)-_N_-phenyltosylamide, 60ai



The chloroynamide was synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) following example procedure **1.2e**. Complete consumption of the dichloroenamide was verified by TLC. The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

(3,6-dichloropyridazin-4-yl)zinc chloride/lithium chloride complex was prepared and used as followed: To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added anhydrous THF (2 mL) and freshly distilled 2,2,6,6-tetramethylpiperidine (0.32 mL, 1.90 mmol, 1.3 equiv.), and the solution was cooled to −5 °C whilst stirring. To this solution was added dropwise *n*-butyllithium (0.76 mL of a 2.5 M solution in hexanes, 1.90 mmol, 1.3 equiv.) and the mixture stirred for 1 hour at −5 °C. Next, $ZnCl_2$ (1.08 mL of a 1.9 M solution in 2-MeTHF, 2.04 mmol, 1.4 equiv.) was added and the resulting solution was stirred for 30 minutes at room temperature. ***Note***: The resulting solution was yellow. The reaction was cooled to −20 °C and a solution of 3,6-dichloropyridazine (261 mg, 1.75 mmol, 1.2 equiv.) in anhydrous THF (1 mL) was added dropwise. The reaction was stirred for 30 minutes at −20 °C and for 2 hours at room temperature, giving the requisite arylzinc chloride/lithium chloride complex as a dark red solution. This solution was cooled to −20 °C and CuCN·2LiCl (73 µL of a 1 M solution in THF, 73 µmol, 5 mol%) was added. The solution was then stirred for 30 minutes at room temperature and used directly in the next step.

To the previously prepared suspension of chloroynamide in TBME was added the solution of (3,6-dichloropyridazin-4-yl)copper(I) cyanide/zinc chloride/lithium chloride complex by syringe, and the reaction was stirred overnight at room temperature. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (10 → 20% EtOAc/40–60 petroleum ether) afforded an orange solid which was recrystallised from heptane/TBME (2:1) to afford the title compound (478 mg, 1.15 µmol, 79%) as colourless needles. This compound can be recrystallised from TBME/heptane (1:2) to give fine, colourless needles that were suitable for X-ray diffraction;

m.p. 128 °C;
R_f 0.44 (20% EtOAc/40–60 petroleum ether);

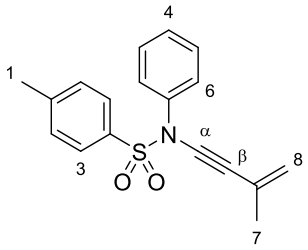
IR (thin film, ν_{max} / cm^{-1}) 3068, 2224, 1594, 1558, 1489, 1403, 1379, 1330, 1209, 1189, 1176, 1132, 1089, 876, 814, 763, 691, 677, 655;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67–7.59 (2H, m, *H*3), 7.45–7.35 (4H, m, *H*4, *H*5, *H*7), 7.34–7.29 (2H, m, *H*2), 7.29–7.04 (2H, m, *H*6), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.9, 154.4, 146.0, 137.3, 132.7, 130.0, 129.6, 129.3, 128.3, 128.2, 127.3, 126.3, 98.1 (Cα), 65.7 (Cβ), 21.8;

HRMS (ES+) calc. for $C_{19}H_{14}{}^{35}Cl_2N_3NaO_2S$ $[M+H]^+$ 418.0178, found 418.0178.

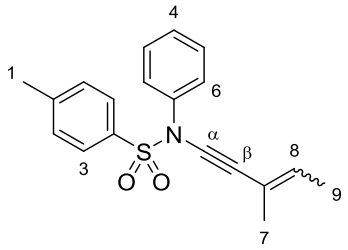
_N_-(3-Methylbut-3-en-1-yn-1-yl)-_N_-phenyltosylamide, 60aj



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and prop-1-en-2-ylmagnesium bromide (3.01 mL of a 0.5 M solution in THF, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (4% Et_2O/40–60 petroleum ether) afforded a yellow solid which was triturated with hexane, followed by recrystallisation from hexane:Et_2O (4:1) to give the title compound (319 mg, 1.02 mmol, 70%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 67–68 °C (decomp.);
R_f 0.26 (4% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2912, 2228, 1594, 1487, 1454, 1371, 1223, 1173, 1130, 1089, 1027, 921, 891, 813, 789, 745, 691, 792;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61–7.54 (2H, m, *H*3), 7.36–7.18 (7H, m, *H*2, *H*4, *H*5, *H*6), 5.22–5.12 (2H, m, *H*8), 2.43 (3H, s, *H*1), 1.88 (3H, dd, *J* = 1.2, 0.7 Hz, *H7*);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.9, 138.9, 132.9, 129.4, 129.0, 128.2, 128.1, 126.2, 126.0, 120.2, 82.3 (Cα), 72.0 (Cβ), 23.4, 21.7;
HRMS (ES+) calc. for $C_{18}H_{17}NNaO_2S$ $[M+Na]^+$ 334.0872, found 334.0873.

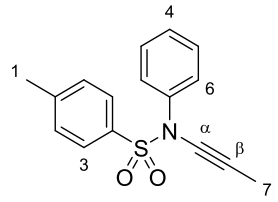
(*E*)-/(*Z*)-*N*-(3-Methylpent-3-en-1-yn-1-yl)-*N*-phenyltosylamide, 60ak



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and 1-methyl-1-propenylmagnesium bromide (3.01 mL of a 0.5 M solution in THF, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (4% Et_2O/40–60 petroleum ether) afforded the title compound (373 mg, 1.15 mmol, 78%) as a colourless oil;

R_f 0.51 (10% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2921, 2227, 1595, 1488, 1372, 1270, 1173, 1090, 1028, 924, 891, 813, 778, 692, 669;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H data for (*E*)-isomer: 7.60–7.54 (2H, m, *H*3), 7.37–7.23 (7H, m, *H*2, *H*4, *H*5, *H*6), 5.66 (1H, qq, *J* = 6.8, 1.5 Hz, *H*8), 2.42 (3H, s, *H*1), 1.82 (3H, quin, *J* = 1.5 Hz, *H*7), 1.76 (3H, dq, *J* = 6.8, 1.5 Hz, *H*9); data for (*Z*)-isomer: 7.60–7.54 (2H, m, *H*3), 7.37–7.23 (7H, m, *H*2, *H*4, *H*5, *H*6), 5.86 (1H, qq, *J* = 7.0, 1.5 Hz, *H*8), 2.42 (3H, s, *H*1), 1.77 (3H, quin, *J* = 1.5 Hz, *H*7), 1.68 (3H, dq, *J* = 7.0, 1.5 Hz, *H*9);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C data for (*E*)-isomer: 144.8, 139.18, 132.94, 131.3, 129.4, 129.0, 128.22, 128.02, 126.1, 117.8, 86.5 (Cα), 70.0 (Cβ), 22.9, 21.7, 16.2; (*Z*)-isomer: 144.7, 139.22, 132.88, 132.3, 129.3, 128.9, 128.25, 127.95, 126.1, 117.6, 79.4 (Cα), 73.4 (Cβ), 21.7, 17.1, 14.1;
HRMS (ES+) calc. for $C_{19}H_{19}NNaO_2S$ $[M+Na]^+$ 348.1029, found 348.1029.

_N_-(Prop-1-yn-1-yl)-_N_-phenyltosylamide, 60al



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and methylmagnesium bromide (0.50 mL of a 3.0 M solution in Et_2O which was further diluted with 1.0 mL anhydrous TBME, added dropwise over 1 minute, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (4% Et_2O/40–60 petroleum ether), followed by recrystallisation from hexane/Et_2O (3:1) afforded the title compound (365 mg, 1.16 mmol, 80%) as colourless needles;

m.p. 103–104 °C;

R_f 0.32 (20% Et_2O/40–60 petroleum ether);

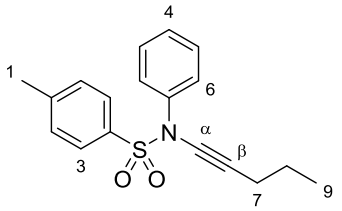
IR (thin film, ν_{max} / cm^{-1}) 2919, 2262, 1594, 1488, 1455, 1368, 1282, 1174, 1090, 1028, 926, 897, 813, 756, 705, 692, 680, 652;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57–7.52 (2H, m, *H*3), 7.33–7.21 (7H, m, *H*2, *H*4, *H*5, *H*6), 2.42 (3H, s, *H*1), 1.91 (3H, s, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 139.2, 133.0, 129.3, 128.9, 128.1, 127.9, 126.1, 72.7 (Cα), 65.7 (Cβ), 21.6, 3.3;

HRMS (ES+) calc. for $C_{16}H_{15}NNaO_2S$ $[M+Na]^+$ 308.0716, found 308.0716.

_N_-(Pent-1-yn-1-yl)-_N_-phenyltosylamide, 60am



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and propylmagnesium bromide (0.75 mL of a 2.0 M solution in Et_2O which was further diluted with 0.75 mL anhydrous TBME, added dropwise over 1 minute, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (4% Et_2O/40–60 petroleum ether) afforded a yellow oil, which was crystallised from hexane/dibutyl ether (1:1) at −20 °C to afford the title compound (365 mg, 1.16 mmol, 80%) as colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 40–41 °C;

R_f 0.24 (4% Et_2O/40–60 petroleum ether);

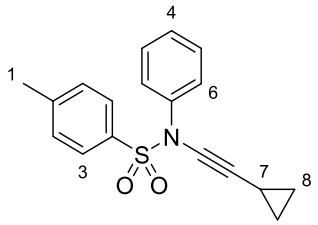
IR (thin film, ν_{max} / cm^{-1}) 2963, 2254, 1595, 1490, 1371, 1266, 1175, 1091, 1028, 925, 893, 813, 692, 653;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.58–7.51 (2H, m, *H*3), 7.34–7.22 (7H, m, *H*2, *H*4, *H*5, *H*6), 2.42 (3H, s, *H*1), 2.27 (2H, t, *J* = 7.1 Hz, *H7*), 1.53 (2H, sxt, *J* = 7.1 Hz, *H8*), 0.95 (3H, t, *J* = 7.1 Hz, *H9*);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 139.4, 133.0, 129.3, 128.9, 128.2, 127.8, 126.1, 74.0 (Cα), 70.2 (Cβ), 22.3, 21.6, 20.5, 13.4;

HRMS (ES+) calc. for $C_{18}H_{19}NNaO_2S$ $[M+Na]^+$ 336.1029, found 336.1029.

***N*-(Cyclopropylethynyl)-*N*-tosylamide, 60an**



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%) and cyclopropylmagnesium bromide (1.75 mL of a 1.0 M solution in THF, added dropwise over 1.5 minutes, 1.75 mmol, 1.2 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (4% Et_2O/40–60 petroleum ether) afforded a pale yellow solid which was recrystallised from hexane:Et_2O (4:1) to give the title compound (405 mg, 1.30 mmol, 89%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 69 °C;

R_f 0.47 (20% Et_2O/40–60 petroleum ether);

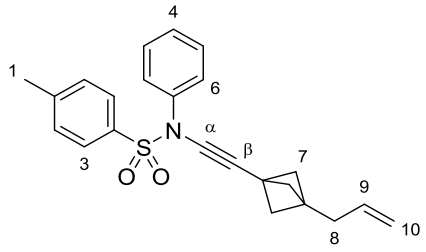
IR (thin film, ν_{max} / cm^{-1}) 3013, 2250, 1595, 1489, 1368, 1271, 1173, 1090, 1028, 924, 892, 812, 773, 692, 675;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.58–7.51 (2H, m, *H*3), 7.34–7.18 (7H, m, *H*2, *H*4, *H*5, *H*6), 2.43 (3H, s, *H*1), 1.32 (1H, tt, *J* = 8.1, 4.9 Hz, *H*7), 0.82–0.75 (2H, m, H8), 0.69–0.62 (2H, m, H8);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 139.3, 133.0, 129.3, 128.9, 128.2, 127.8, 126.0, 74.6 (Cβ), 69.3 (Cα), 21.6, 8.7, -0.7;

HRMS (ES+) calc. for $C_{18}H_{17}NNaO_2S$ $[M+Na]^+$ 334.0872, found 334.0872.

_N_-((3-Allylbicyclo[1.1.1]pentan-1-yl)ethynyl)-_N_-phenyltosylamide, 60ao



The chloroynamide was synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) following example procedure **1.2e**. Complete consumption of the dichloroenamide was verified by TLC. The cooling bath was then removed and the reaction mixture was then allowed to warm to room temperature (approx. 21 °C) whilst stirring.

(3-Allylbicyclo[1.1.1]pentan-1-yl)magnesium bromide solution was prepared and used as followed: ***Safety Note****:* Extreme care should be taken when working with glassware under pressure. This reaction was conducted in a properly equipped fume hood behind a blast shield. To an oven dried, argon flushed Ace pressure vial (20 mL) equipped with a magnetic stirrer bar, was added allylmagnesium bromide (4.0 mL of a 1 M solution in Et_2O, 4.0 mmol, 2.74 equiv.) and [1.1.1]propellane (2.47 mL of a 0.81 M solution in Et_2O, 2.0 mmol, 1.37 equiv.). The vial was sealed with a screw cap and placed in an oil bath preheated to 100 °C. The reaction was stirred at this temperature for 3 hours, and the vial was then removed from the bath and cooled to room temperature (21 °C).

To the previously prepared suspension of chloroynamide in TBME was added $CuCN{\cdot}2P(OMe)_3$ (183 μL of a 0.1 M solution in THF, 18.3 μmol, 1.25 mol%), and the reaction stirred for 5 minutes at room temperature. The solution of (3-allylbicyclo[1.1.1]pentan-1-yl)magnesium bromide was then added dropwise over 1 minute by syringe, and the reaction was stirred for 30 minutes at room temperature. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (3 → 5% Et_2O/40–60 petroleum ether) afforded the title compound (298 mg, 0.788 mmol, 54%) as a white powder. This compound can be recrystallised from hexane to give colourless needles that were suitable for X-ray diffraction;

m.p. 100–101 °C
R_f 0.44 (10% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2971, 2909, 2873, 2245, 1595, 1491, 1374, 1218, 1187, 1174, 1124, 1090, 915, 813, 764, 710, 691, 658;

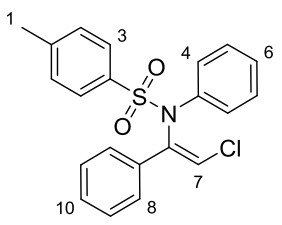
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59–7.51 (2H, m, *H*3), 7.34–7.24 (5H, m, *H*2, *H*4, *H*5), 7.24–7.18 (2H, m, *H*6), 5.74–5.64 (1H, m, *H*9), 5.04–4.95 (2H, m, *H*10), 2.44 (3H, s, *H*1), 2.19 (2H, d, *J* = 7.3 Hz, *H*8), 1.89 (6H, s, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 139.0, 134.8, 132.9, 129.3, 128.9, 128.3, 128.0, 126.2, 116.2, 73.0 (Cα), 69.8 (Cβ), 54.5, 41.4, 36.2, 28.6, 21.7;

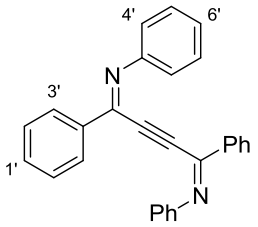
HRMS (ES+) calc. for $C_{23}H_{24}NO_2S$ $[M+H]^+$ 378.1522, found 378.1522.

2.1c *Miscellaneous*.

(*Z*)-*N*-(2-Chloro-1-phenylvinyl)-*N*-phenyltosylamide, 61, & (1*Z*,4*Z*)-N^1,N^4,1,4-Tetraphenylbut-2-yne-1,4-diimine, 63



61



63

Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous THF (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCl_2$ (9.8 mg, 73 μmol, 5 mol%) and phenylmagnesium bromide (1.75 mL of a 1.0 M solution in THF, added dropwise over 1 hour, 1.75 mmol, 1.2 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (6% Et_2O/40–60 petroleum ether) afforded the title compounds alongside the desired *N*-phenyl-*N*-(phenylethynyl)tosylamide **60a**. Recrystallisation of enamide **61** from hexane/Et_2O (3:1) gave (226 mg, 0.588 mmol, 40%) as colourless crystals and recrystallisation of imine **63** from ice-cold hexane gave (5.5 mg, 14.3 μmol, 2%) as lemon yellow plates. Both sets of crystals were suitable for X-ray diffraction;

- Data for enamide **61**:

m.p. 113 °C;

R_f 0.25 (10% Et_2O/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3078, 1735, 1596, 1445, 1352, 1307, 1240, 1220, 1091, 1031, 951, 813, 757, 690, 669, 611;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66–7.59 (2H, m, *H*3), 7.55–7.48 (2H, m, *H*9), 7.44–7.38 (2H, m, *H*5), 7.36–7.29 (3H, m, *H*8, *H*10), 7.27–7.20 (2H, m, *H*4), 7.20–7.13 (3H, m, *H*2, *H*6), 6.67 (1H, s, *H*7), 2.38 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.8, 142.1, 139.5, 137.1, 135.9, 129.09, 129.06, 129.0, 128.6, 128.1, 127.0, 126.7, 125.8, 119.9, 21.5;

HRMS (ES+) calc. for $C_{21}H_{18}{}^{35}ClNNaO_2S$ $[M+Na]^+$ 406.0639, found 406.0639.

- Data for imine **63**:

m.p. >120 °C (dec.);

R_f 0.60 (10% Et_2O/40–60 petroleum ether);

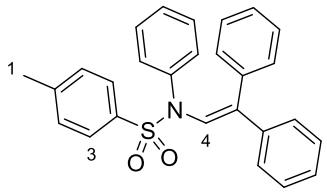
IR (thin film, ν_{max} / cm^{-1}) 3059, 2922, 1726, 1590, 1572, 1481, 1448, 1322, 1297, 1169, 1096, 1071, 1023, 999, 906, 838, 823, 771, 744, 692, 667;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.65–7.58 (2H, m, *H*3′), 7.48–7.40 (3H, m, *H*5′, *H*6′), 7.33–7.27 (3H, m, *H*1′, *H*2′), 7.06–6.97 (2H, m, *H*4′);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 152.0, 149.6, 136.0, 131.4, 129.1, 128.4, 128.2, 125.0, 120.0, 88.0;

HRMS (ES+) calc. for $C_{28}H_{21}N_2$ $[M+H]^+$ 385.1699, found 385.1700.

_N_-(2,2-Diphenylvinyl)-_N_-phenyltosylamide, 62



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), CuCN (6.5 mg, 73 µmol, 5 mol%), $P(OMe)_3$ (17 µL, 0.146 mmol, 10 mol%) and phenylmagnesium bromide (1.75 mL of a 1.0 M solution in THF, added dropwise over 1 minute, 1.75 mmol, 1.2 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**, using EtOAc instead of Et_2O. Column chromatography (2% Et_2O/40–60 petroleum ether) afforded the title compound (49.6 mg, 0.117 mmol, 8%), which was obtained as a pale yellow powder, alongside *N*-phenyl-*N*-(phenylethynyl)tosylamide **60a**. Crystals of **62** that were suitable for X-ray diffraction were grown by recrystallisation from *i*-PrOH to give colourless needles;

m.p. 136–138 °C;

R_f 0.29 (10% Et_2O/40–60 petroleum ether);

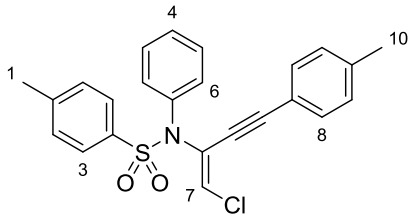
IR (thin film, ν_{max} / cm^{-1}) 3057, 3028, 1619, 1593, 1491, 1444, 1399, 1355, 1289, 1248, 1185, 1166, 1089, 1075, 1027, 1004, 981, 910, 828, 815, 800, 776, 759, 732, 693, 663, 637;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56–7.49 (2H, m, *H*3), 7.31–7.23 (5H, m, *H*2, Ph*H*), 7.18–7.11 (2H, m, Ph*H*), 7.10–7.03 (3H, m, Ph*H*), 7.01 (1H, s, *H*4), 7.01–6.93 (3H, m, Ph*H*), 6.91–6.85 (2H, m, Ph*H*), 6.79–6.72 (2H, m, Ph*H*), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.9, 140.5, 140.3, 137.6, 136.4, 134.7, 130.0, 129.5, 128.17, 128.18, 128.15, 127.73, 127.72, 127.69, 127.5, 127.0, 126.7, 125.9, 21.6;

HRMS (ES+) calc. for $C_{27}H_{24}NO_2S$ $[M+H]^+$ 426.1522, found 426.1522.

(*E*)-*N*-(1-Chloro-4-(*p*-tolyl)but-1-en-3-yn-2-yl)-*N*-phenyltosylamide, 65a



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (1.46 mL of a 0.1 M solution in THF, 146 μmol, 10 mol%) and (*p*-tolylethynyl)magnesium chloride (prepared according to example procedure **1.2c** from 1-ethynyl-4-methylbenzene (0.45 mL, 3.51 mmol, 2.4 equiv.) in anhydrous THF (4 mL), using ethylmagnesium chloride (1.75 mL of a 2.0 M solution in THF, 3.51 mmol, 2.4 equiv.) and stirring at 0 °C for 1 hour). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (2% Et_2O/40–60 petroleum ether) afforded an orange solid that was recrystallised from heptane to give the title compound (329 mg, 0.780 mmol, 53%) as yellow plates. These crystals were suitable for X-ray diffraction;

m.p. 118–119 °C;

R_f 0.19 (5% Et_2O/40–60 petroleum ether);

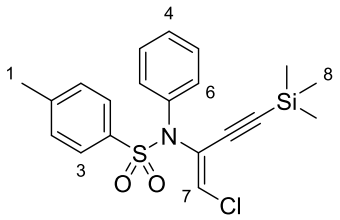
IR (thin film, ν_{max} / cm^{-1}) 3078, 2922, 2205, 1595, 1508, 1490, 1458, 1358, 1240, 1166, 1140, 1091, 969, 844, 815, 738, 695, 665, 609;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.64 (2H, m, *H*3), 7.38–7.29 (5H, m, *H*4, *H*5, *H*6), 7.25–7.20 (2H, m, *H*2), 7.16–7.09 (4H, m, *H*8, *H*9), 6.96 (1H, s, *H*7), 2.40 (3H, s, *H*1), 2.37 (3H, s, *H*10);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.9, 139.9, 139.7, 136.1, 131.5, 130.5, 129.3, 129.2, 129.1, 128.4, 128.3, 128.2, 125.0, 118.6, 98.8, 81.9, 21.56, 21.54;

HRMS (ES+) calc. for $C_{24}H_{21}{}^{35}ClNO_2S$ $[M+H]^+$ 422.0976, found 422.0976.

(*E*)-*N*-(1-Chloro-4-(trimethylsilyl)but-1-en-3-yn-2-yl)-*N*-phenyltosylamide, 65b



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (1.46 mL of a 0.1 M solution in THF, 146 μmol, 10 mol%) and ((trimethylsilyl)ethynyl)magnesium chloride (prepared according to example procedure **1.2c** from trimethylsilylacetylene (0.49 mL, 3.51 mmol, 2.4 equiv.) in anhydrous THF (4 mL), using ethylmagnesium chloride (1.75 mL of a 2.0 M solution in THF, 3.51 mmol, 2.4 equiv.) and stirring at 0 °C for 1 hour). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (2% Et_2O/40–60 petroleum ether) afforded a pale yellow solid which was recrystallised from hexane at −20 °C overnight to give the title compound (303 mg, 0.751 mmol, 51%) as colourless plates. These crystals were suitable for X-ray diffraction;

m.p. 120–121 °C;

R_f 0.42 (10% Et_2O/40–60 petroleum ether);

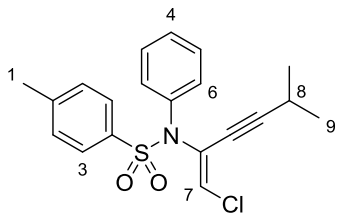
IR (thin film, ν_{max} / cm^{-1}) 3080, 2961, 2153, 1596, 1492, 1361, 1251, 1168, 1091, 980, 860, 846, 816, 695, 666, 613;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (2H, m, *H*3), 7.35–7.23 (7H, m, *H*2, *H*4, *H*5, *H*6), 6.98 (1H, s, *H*7), 2.44 (3H, s, *H*1), 0.11 (9H, s, *H*8);

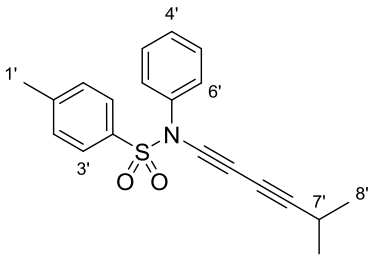
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.9, 139.5, 136.1, 131.6, 129.3, 129.1, 128.41 (2C), 128.37, 124.5, 105.4, 96.8, 21.6, -0.6;

HRMS (ES+) calc. for $C_{20}H_{23}N^{35}ClO_2SSi$ $[M+H]^+$ 404.0902, found 404.0901.

(*E*)-*N*-(1-Chloro-5-methylhex-1-en-3-yn-2-yl)-*N*-phenyltosylamide, 65c & *N*-(5-Methylhexa-1,3-diyn-1-yl)-*N*-phenyltosylamide, 60ap



65c



60ap

Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (1.46 mL of a 0.1 M solution in THF, 146 μmol, 10 mol%) and (3-methylbut-1-yn-1-yl)magnesium chloride (prepared according to example procedure **1.2c** from 3-methylbut-1-yne (0.36 mL, 3.51 mmol, 2.4 equiv.) in anhydrous THF (4 mL), using ethylmagnesium chloride (1.75 mL of a 2.0 M solution in THF, 3.51 mmol, 2.4 equiv.) and stirring at 0 °C for 1 hour). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (2% Et_2O/40–60 petroleum ether) afforded the compounds **65c** and **60ap** as orange solids, which were both recrystallised from hexane at −20 °C overnight. This gave **65c** (76.3 mg, 0.204 mmol, 14%) as colourless plates and **60ap** (15.5 mg, 45.9 μmol, 3%) as colourless needles. Both sets of crystals were suitable for X-ray diffraction;

- Data for enyne **65c**:

m.p. 97–99 °C;

R_f 0.25 (5% Et_2O/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3084, 2972, 2224, 1595, 1492, 1358, 1322, 1238, 1165, 1091, 1013, 949, 894, 832, 814, 695, 665, 610;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (2H, d, *J* = 8.3 Hz, *H*3), 7.35–7.21 (7H, m, *H*2, *H*4, *H*5, *H*6), 6.86 (1H, s, *H*7), 2.58 (1H, spt, *J* = 6.9 Hz, *H*8), 2.42 (3H, s, *H*1), 1.06 (6H, d, *J* = 6.9 Hz, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.8, 139.7, 136.3, 129.4, 129.2, 129.1, 128.34, 128.28, 128.2, 124.9, 105.6, 73.3, 22.1, 21.5, 21.2;

HRMS (ES+) calc. for $C_{20}H_{21}{}^{35}ClNO_2S$ $[M+H]^+$ 374.0976, found 374.0978.

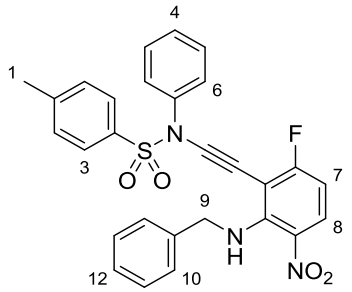
- Data for diyne **60ap**:

R_f 0.30 (5% Et_2O/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2973, 2932, 2871, 2254, 2165, 1594, 1490, 1455, 1376, 1187, 1175, 1090, 990, 922, 891, 813, 762;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61–7.56 (2H, m, *H*3′), 7.34–7.27 (5H, m, *H*2′, *H*4′, *H*5′), 7.24–7.18 (2H, m, *H*6′), 2.67 (1H, spt, *J* = 6.9 Hz, *H*8′), 2.44 (3H, s, *H*1′), 1.19 (6H, d, *J* = 6.9 Hz, *H*7′);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.2, 138.3, 133.2, 129.7, 129.2, 128.5, 128.2, 126.3, 89.3, 68.4, 63.7, 57.9, 22.5, 21.7, 21.3;
HRMS (ES+) calc. for $C_{20}H_{19}NNaO_2S$ $[M+Na]^+$ 360.1029, found 360.1029.

_N_-((2-(Benzylamino)-6-fluoro-3-nitrophenyl)ethynyl)-_N_-phenyltosylamide, 66



To a 3 mL vial, equipped with a magnetic stirrer bar, was added sequentially *N*-((2,6-difluoro-3-nitrophenyl)ethynyl)-*N*-phenyltosylamide (50.0 mg, 117 μmol, 1.0 equiv.), anhydrous toluene (1.0 mL), anhydrous Et_3N (24 μL, 0.18 mmol, 1.5 equiv.) and benzylamine (13 μL, 0.12 mmol, 1.0 equiv.). The vial was sealed with a screw cap and stirred for 3 hours. The resulting orange mixture was then poured into a 25 mL separating funnel containing Et_2O (~5 mL) and aqueous saturated NH_4Cl (~10 mL). The reaction vessel was thoroughly rinsed with Et_2O and water (2×1 mL each, alternately) and these washings were poured into the separating funnel. The organic layer was then separated and the aqueous was further extracted with Et_2O (2×5 mL). The organic extracts were then combined, dried (Na_2SO_4) and concentrated in vacuo afforded a bright orange solid. Recrystallisation from hexane/Et_2O afforded the title compound (57.0 mg, 111 μmol, 95%) as bright orange needles. These crystals were suitable for X-ray diffraction;

m.p. 110 °C;

R_f 0.35 (15% EtOAc/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3327, 3066, 2922, 2236, 1605, 1495, 1455, 1374, 1244, 1187, 1173, 1090, 804, 761, 730, 691, 661;

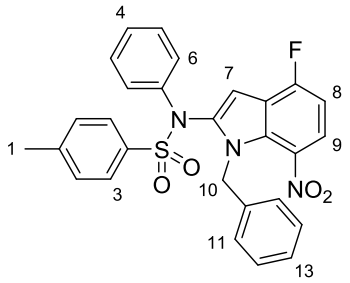
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.59 (1H, br. t, *J* = 5.6 Hz, N*H*), 8.07 (1H, dd, *J* = 9.5, 6.1 Hz, *H*8), 7.47 (2H, d, *J* = 8.6 Hz, *H*3), 7.25–7.10 (12H, m, *H*2, *H*4, *H*5, *H*6, *H*10, *H*11, *H*12), 6.34 (1H, dd, *J* = 9.5, 7.6 Hz, *H*7), 5.00 (2H, d, *J* = 5.6 Hz, *H*9), 2.31 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 168.8 (1C, d, *J* = 259 Hz), 148.2 (1C, d, *J* = 5.6 Hz), 145.2, 138.3 (1C, d, *J* = 3.2 Hz), 133.2, 131.3, 129.6, 129.20, 129.19 (1C, d, *J* = 12.7 Hz), 128.8, 128.4, 128.1, 127.6, 127.3, 126.1, 104.3 (1C, d, *J* = 25.4 Hz), 99.1 (1C, d, *J* = 21.5 Hz), 93.6 (1C, d, *J* = 5.6 Hz, Cα), 61.5 (Cβ), 49.7, 21.7; ***Note***: A single ^{13}C resonance is obscured due to signal overlap

^{19}F NMR (376 MHz, $CDCl_3$) δ_F −93.0 (1F, dd, *J* = 7.6, 6.1 Hz);

HRMS We were unable to obtain an accurate mass (ES+ or CI+) due to decomposition upon ionisation.

_N_-(1-Benzyl-4-fluoro-7-nitro-1_H_-indol-2-yl)-_N_-phenyltosylamide, 67



To a 3 mL vial, equipped with a magnetic stirrer bar, was added sequentially *N*-((2,6-difluoro-3-nitrophenyl)ethynyl)-*N*-phenyltosylamide (50.0 mg, 117 μmol, 1.0 equiv.), anhydrous toluene (1.0 mL), anhydrous Et_3N (24 μL, 0.18 mmol, 1.5 equiv.) and benzylamine (13 μL, 0.12 mmol, 1.0 equiv.). The vial was sealed with a screw cap and stirred for 3 hours. To the resulting orange mixture was added Cs_2CO_3 (76.1 mg, 233 μmol, 2.0 equiv.) and the mixture stirred at 80 °C overnight. The mixture was then allowed to cool to room temperature and was then poured into a 25 mL separating funnel containing Et_2O (~5 mL) and aqueous saturated NH_4Cl (~10 mL). The reaction vessel was thoroughly rinsed with Et_2O and water (2×1 mL each, alternately) and these washings were poured into the separating funnel. The organic layer was then separated and the aqueous was further extracted with Et_2O (2×5 mL). The organic extracts were then combined, dried (Na_2SO_4) and concentrated in vacuo afforded an orange solid. Recrystallisation from EtOH afforded the title compound (43.6 mg, 84.6 μmol, 72%) as golden yellow needles. These crystals were suitable for X-ray diffraction;

m.p. >100 °C (dec.);

R_f 0.35 (15% EtOAc/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3066, 1522, 1495, 1454, 1359, 1319, 1299, 1246, 1208, 1185, 1167, 1090, 956, 910, 815, 730, 695, 669;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.64 (1H, dd, *J* = 8.7, 5.1 Hz, *H*9), 7.58 (2H, d, *J* = 8.4 Hz, *H*3), 7.33 (2H, d, *J* = 8.2 Hz, *H*2), 7.31 (5H, m, *H*11, *H*12, *H*13), 7.16–7.04 (3H, m, *H*4, *H*5), 6.77 (1H, t, *J* = 8.7 Hz, *H*8), 6.69–6.65 (2H, m, *H*6), 6.62 (1H, s, *H*7), 5.68 (2H, br. s, *H*10), 2.49 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.7 (1C, d, *J* = 256 Hz), 144.9, 139.3, 138.4, 136.1, 134.6, 134.1 (1C, d, *J* = 2.9 Hz), 129.7, 129.4, 128.52, 128.49, 128.4, 128.2, 127.8 (1C, d, *J* = 11.4 Hz), 127.4, 126.7, 122.7 (1C, d, *J* = 9.5 Hz), 118.8 (1C, d, *J* = 22.9 Hz), 104.8 (1C, d, *J* = 21.0 Hz), 97.5, 48.6, 21.7;

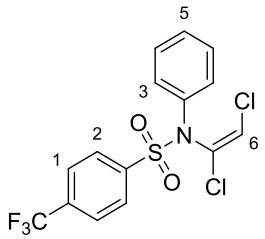
^{19}F NMR (376 MHz, $CDCl_3$) δ_F −111.2 (1F, dd, *J* = 8.7, 5.1 Hz);

HRMS (ES+) calc. for $C_{28}H_{22}FN_3NaO_4S$ $[M+Na]^+$ 538.1207, found 538.1205.

2.2 Sulfonamide Scope.

2.2a *Dichloroenamides*.

(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-phenyl-4-(trifluoromethyl)benzenesulfonamide, 53b



Following example procedure **1.2a**: Synthesised from *N*-phenyl-4-(trifluoromethyl) benzenesulfonamide (1.22 g, 4.05 mmol, 1.0 equiv.) in DMF (3.04 mL) using trichloroethylene (0.40 mL, 4.45 mmol, 1.1 equiv.) and Cs_2CO_3 (1.98 g, 6.07 mmol, 1.5 equiv.). The reaction takes approximately 2 hours to reach completion. Column chromatography (5% EtOAc/pentane) afforded the title compound (1.53 g, 3.86 mmol, 95%) as a cream solid;

m.p. 90–92 °C;

R_f 0.47 (5% EtOAc/pentane);

IR (thin film, ν_{max} / cm^{-1}) 3088, 1608, 1593, 1489, 1454, 1405, 1372, 1322, 1283, 1225, 1172, 1133, 1094, 1062, 1018, 951, 911, 843, 815, 759, 734, 714, 695, 679, 617;

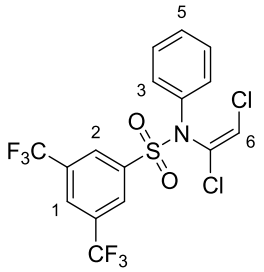
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.90 (2H, d, *J* = 8.2 Hz, *H*1), 7.74 (2H, d, *J* = 8.2 Hz, *H*2), 7.45–7.34 (5H, m, *H*3, *H*4, *H*5), 6.50 (1H, d, *H*6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 142.1, 137.2, 135.1 (2C, q, *J* = 33.1 Hz), 130.1, 129.6, 129.5, 129.1, 128.7, 125.9 (2C, q, *J* = 3.7 Hz), 123.1 (1C, q, *J* = 272.9 Hz), 121.1;

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F −63.2;

HRMS We were unable to obtain an accurate mass (ES+ or CI+) due to decomposition upon ionisation.

(*E*)-*N*-Phenyl-*N*-(1,2-dichlorovinyl)-3,5-bis(trifluoromethyl)benzenesulfonamide, 53c



Following example procedure **1.2a**: Synthesised from *N*-phenyl-3,5-bis(trifluoromethyl) benzenesulfonamide (1.18 g, 3.20 mmol, 1.0 equiv.) in DMF (2.4 mL) using trichloroethylene (0.32 mL, 3.51 mmol, 1.1 equiv.) and Cs_2CO_3 (1.56 g, 4.79 mmol, 1.5 equiv.). The reaction takes approximately 2 hours to reach completion. Column chromatography (10% → 15% Et_2O/pentane) afforded the title compound as a yellow oil, which slowly solidified upon standing to form a yellow powder (1.33 g, 2.87 mmol, 89%);

m.p. 64–66 °C;

R_f 0.65 (4% Et_2O/pentane);

IR (thin film, ν_{max} / cm^{-1}) 3090, 1490, 1382, 1360, 1279, 1172, 1140, 1109, 907, 815, 696, 634;

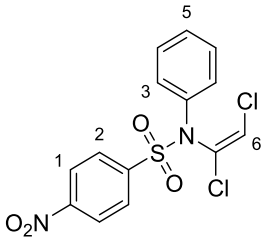
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.16 (2H, s, *H*2), 8.10 (1H, s, *H*1), 7.48–7.42 (1H, m, *H*5), 7.42–7.36 (2H, m, *H*4), 7.35–7.30 (2H, m, *H*3), 6.52 (1H, s, *H*6);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 141.0, 136.7, 132.6 (2C, q, J = 34.7 Hz), 130.1, 129.8, 129.6, 128.8 (2C, q, J = 3.6 Hz), 128.7, 126.9 (1C, spt, J = 3.5 Hz), 122.2 (2C, q, J = 273.4 Hz), 121.5;

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ_F −63.1;

HRMS (APCI+) calc. for $C_{16}H_{10}{}^{35}Cl_2F_6NNaO_2S$ $[M+H]^+$ 463.9708, found 463.9705.

(*E*)-*N*-(1,2-Dichlorovinyl)-4-nitro-*N*-phenylbenzenesulfonamide, 53d



Following example procedure **1.2a**: Synthesised from 4-nitro-*N*-phenylbenzenesulfonamide (850 mg, 3.05 mmol, 1.0 equiv.) in DMF (2.29 mL) using trichloroethylene (0.30 mL, 3.36 mmol, 1.1 equiv.) and Cs_2CO_3 (1.49 g, 4.58 mmol, 1.5 equiv.). ***Note:*** The reaction was incomplete after 2 hours (as analysed by TLC (5% EtOAc/pentane)) and a further 0.5 equiv. of trichloroethylene was added at this time. The reaction was then stirred for another hour. Recrystallisation (acetone/heptane) afforded the title compound (728 mg, 1.95 mmol, 64%) as yellow crystals. These crystals were suitable for X-ray diffraction;

m.p. 162–163 °C;

R_f 0.18 (5% EtOAc/pentane);

IR (thin film, ν_{max} / cm^{-1}) 3103, 1607, 1531, 1489, 1403, 1373, 1350, 1311, 1283, 1224, 1175, 1094, 1014, 952, 913, 855, 816, 739, 686, 616;

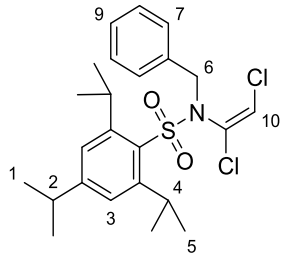
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.34–8.27 (2H, m, *H*2), 7.98–7.90 (2H, m, *H*1), 7.47–7.33 (5H, m, *H*3, *H*4, *H*5), 6.51 (1H, s, *H*6);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 150.5, 144.1, 137.0, 129.81, 129.76, 129.7, 128.7, 124.0, 121.3;

Note: A single ^{13}C resonance is obscured due to signal overlap.

HRMS We were unable to obtain an accurate mass (ES+ or CI+) due to decomposition upon ionisation.

(*E*)-*N*-Benzyl-*N*-(1,2-dichlorovinyl)-2,4,6-tri-*i*-propylbenzenesulfonamide, 53e



Following example procedure **1.2a**: Synthesised from *N*-benzyl-2,4,6-tri-*i*-propyl benzenesulfonamide (430 mg, 1.15 mmol, 1.0 equiv.) in DMF (0.87 mL) using trichloroethylene (114 μL, 1.27 mmol, 1.1 equiv.) and Cs_2CO_3 (563 mg, 1.73 mmol, 1.5 equiv.). The reaction was stirred overnight for ~15 hours arbitrarily. Column chromatography (5% Et_2O/pentane) afforded the title compound (515 mg, 1.10 mmol, 96%) as a white powder;

m.p. 77–78 °C;

R_f 0.63 (10% Et_2O/pentane);

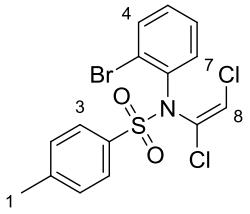
IR (thin film, ν_{max} / cm^{-1}) 2959, 2930, 2870, 1600, 1459, 1426, 1370, 1336, 1168, 1104, 1038, 1006, 940, 819, 792, 702, 663;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41–7.28 (5H, m, *H*7, *H*8, *H*9), 7.21 (2H, s, *H*3), 6.18 (1H, s, *H*10), 4.65 (2H, br. s, *H*6), 4.15 (2H, spt, *J* = 6.8 Hz, *H*4), 2.92 (1H, spt, *J* = 6.8 Hz, *H*1), 1.30 (12H, d, *J* = 6.8 Hz, *H*5), 1.26 (6H, d, *J* = 6.8 Hz, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 154.1, 152.3, 133.8, 131.4, 130.6, 129.6, 128.4, 124.2, 120.7, 51.1, 34.2, 30.2, 25.0, 23.5; ***Note***: A single ^{13}C resonance is obscured due to signal overlap.

HRMS (ES+) calc. for $C_{24}H_{32}{}^{35}Cl_2NNaO_2S$ $[M+H]^+$ 468.1525, found 468.1525.

(*E*)-*N*-(2-Bromophenyl)-*N*-(1,2-dichlorovinyl)tosylamide, 53f



Following example procedure **1.2a**: Synthesised from *N*-(2-bromophenyl)tosylamide (1.00 g, 3.07 mmol, 1.0 equiv.) in DMF (2.3 mL) using trichloroethylene (0.30 mL, 3.37 mmol, 1.1 equiv.) and Cs_2CO_3 (1.50 g, 4.60 mmol, 1.5 equiv.). The reaction was stirred overnight for ~15 hours arbitrarily. Column chromatography (10% Et_2O/pentane) afforded the title compound (1.01 g, 2.40 mmol, 78%) as a white powder. This compound can be recrystallised from Et_2O/hexane (1:5) to give colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 133–135 °C;

R_f 0.37 (10% EtOAc/40–60 petroleum ether);

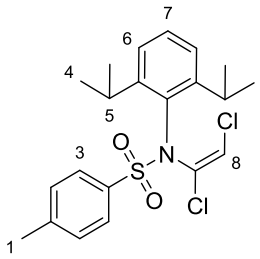
IR (thin film, ν_{max} / cm^{-1}) 3075, 2922, 1597, 1470, 1369, 1289, 1227, 1169, 1088, 1048, 930, 813,757, 707;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72–7.66 (2H, m, *H*3), 7.61 (1H, dd, *J* = 7.8, 1.6 Hz, *H*4), 7.59 (1H, dd, *J* = 7.8, 1.6 Hz, *H*7), 7.31 (1H, td, *J* = 7.8, 1.6 Hz, *H*5), 7.26 (2H, m, *H*2), 7.24 (1H, td, *J* = 7.8, 1.6 Hz, *H*6), 6.43 (1H, s, *H*8), 2.44 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.9, 135.8, 135.4, 134.3, 134.0, 130.7, 129.42, 129.35, 129.0, 127.5, 124.9, 119.4, 21.7;

HRMS (ES+) calc. for $C_{15}H_{12}{}^{79}Br^{35}Cl_2NNaO_2S$ $[M+Na]^+$ 441.9041, found 441.9057.

(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-(2,6-di-*i*-propylphenyl)tosylamide, 53g



Following example procedure **1.2a**: Synthesised from *N*-(2,6-di-*i*-propylphenyl)tosylamide (300 mg, 0.905 mmol, 1.0 equiv.) in DMF (0.70 mL) using trichloroethylene (89 μL, 0.996 mmol, 1.1 equiv.) and Cs_2CO_3 (442 mg, 1.36 mmol, 1.5 equiv.). The reaction takes approximately 3 hours to reach completion. Column chromatography (20% Et_2O/pentane) afforded the title compound (361 mg, 0.847 mmol, 94%) as a white powder. Crystals suitable for X-ray diffraction were grown by slow evaporation of a solution of the title compound in pentane;

m.p. 140 °C;

Rf 0.63 (20% EtOAc/40–60 petroleum ether);

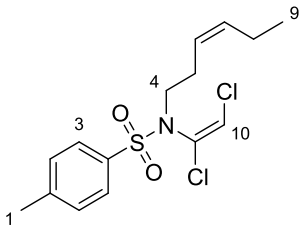
IR (thin film, ν_{max} / cm^{-1}) 2973, 1598, 1466, 1359, 1168, 1075, 932, 809, 666;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67–7.62 (2H, m, *H*3), 7.43–7.37 (1H, m, *H*7), 7.27–7.21 (4H, m, *H*2, *H*6), 6.19 (1H, s, *H*8), 3.37 (2H, spt, *J* = 6.6 Hz, *H*5), 2.41 (3H, s, *H*1), 1.17 (6H, d, *J* = 6.6 Hz, *H*4), 1.12 (6H, d, *J* = 6.6 Hz, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 150.6, 144.4, 136.9, 132.0, 131.7, 130.1, 129.1, 128.9, 125.3, 113.3, 28.9, 25.2, 24.0, 21.6; ***Note***: A single ^{13}C resonance is obscured due to signal overlap.

HRMS (ES+) calc. for $C_{21}H_{25}{}^{35}Cl_2NNaO_2S$ $[M+Na]^+$ 448.0875, found 448.0881.

_N_-((_E_)-1,2-Dichlorovinyl)-_N_-[(_Z_)-hex-3-en-1-yl]tosylamide, 53h



Following example procedure **1.2a**: Synthesised from (*Z*)-*N*-(hex-3-en-1-yl)tosylamide (3.36 g, 13.3 mmol, 1.0 equiv.) in DMF (10 mL) using trichloroethylene (1.31 mL, 14.6 mmol, 1.1 equiv.) and Cs_2CO_3 (6.48 g, 19.9 mmol, 1.5 equiv.). The reaction takes approximately 2 hours to reach completion. Column chromatography (15% Et_2O/pentane) afforded the title compound (4.28 g, 12.3 mmol, 93%) as a colourless oil;

R_f 0.45 (10% Et_2O/pentane);

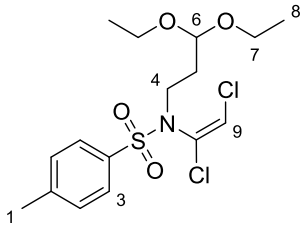
IR (thin film, ν_{max} / cm^{-1}) 2964, 1598, 1456, 1362, 1167, 1090, 815, 661;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.1 Hz, *H*3), 7.32 (2H, d, *J* = 8.1 Hz, *H*2), 6.51 (1H, s, *H*10), 5.46 (1H, dtt, *J* = 10.7, 7.3, 1.6 Hz, *H*7), 5.26 (1H, dtt, 10.7, 7.2, 1.6 Hz, *H*6), 3.22 (2H, br. s, *H*4), 2.44 (3H, s, *H*1), 2.28 (2H, q, *J* = 7.6 Hz, *H*5), 2.00 (2H, quind, *J* = 7.5, 1.6 Hz, *H*8), 0.94 (3H, t, *J* = 7.5 Hz, *H*9);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 135.3, 134.9, 129.8, 129.7, 128.5, 123.7, 121.6, 47.8, 25.8, 21.8, 20.7, 14.3;

HRMS (ES^+) calc. for $C_{15}H_{19}{}^{35}Cl_2NNaO_2S$ $[M+Na]^+$ 370.0406, found 370.0407.

_N_-[(_E_)-1,2-Dichlorovinyl]-_N_-(3,3-diethoxypropyl)tosylamide, 53i



Following example procedure **1.2a**: Synthesised from *N*-(3,3-diethoxypropyl)tosylamide (502 mg, 1.67 mmol, 1.0 equiv.) in DMF (1.3 mL) using trichloroethylene (165 µL, 1.83 mmol, 1.1 equiv.) and Cs_2CO_3 (814 mg, 2.50 mmol, 1.5 equiv.). The reaction takes approximately 2 hours to reach completion. Column chromatography (20 → 30% EtOAc/pentane) afforded the title compound (556 mg, 1.41 mmol, 85%) as a yellow oil which slowly solidified to form a white powder;

m.p. 62–64 °C;

R_f 0.30 (20% Et_2O/pentane);

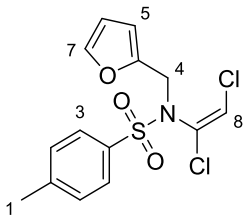
IR (thin film, ν_{max} / cm^{-1}) 2976, 2881, 1598, 1449, 1362, 1167, 1121, 1090, 1059, 964, 815, 707, 672;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.2 Hz, *H*3), 7.32 (2H, d, *J* = 8.2 Hz, *H*2), 6.51 (1H, s, *H*9), 4.62 (1H, t, *J* = 5.6 Hz, *H*6), 3.64 (2H, dq, *J* = 9.3, 7.0 Hz, *H*7), 3.49 (2H, dq, *J* = 9.3, 7.1 Hz, *H*7), 3.32 (2H, br. s, *H*4), 2.44 (3H, s, *H*1), 1.83 (2H, td, *J* = 7.0, 5.6 Hz, *H*5), 1.19 (6H, t, *J* = 7.1 Hz, *H*8);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 135.1, 130.0, 129.8, 128.6, 121.5, 100.6, 62.2, 44.2, 32.2, 21.8, 15.5;

HRMS (APCI+) calc. for $C_{16}H_{23}{}^{35}Cl_2NNaO_4S$ $[M+Na]^+$ 418.0617, found 418.0621.

(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-(furan-2-ylmethyl)tosylamide, 53j



Following example procedure **1.2a**: Synthesised from *N*-(furan-2-ylmethyl)tosylamide (279 mg, 1.11 mmol, 1.0 equiv.) in DMF (0.83 mL) using trichloroethylene (197 μL, 1.22 mmol, 1.1 equiv.) and Cs_2CO_3 (543 mg, 1.67 mmol, 1.5 equiv.). The reaction takes approximately 2 hours to reach completion. Column chromatography (10 → 20% EtOAc/pentane) afforded the title compound (329 mg, 0.950 mmol, 85%) as colourless crystals;

m.p. 96–97 °C;

R_f 0.28 (10% Et_2O/pentane);

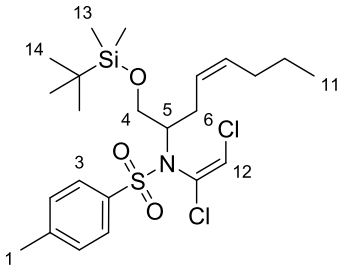
IR (thin film, ν_{max} / cm^{-1}) 3088, 1598, 1501, 1361, 1166, 1090, 1010, 942, 814, 661;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.87–7.81 (2H, m, *H*3), 7.37–7.31 (3H, m, *H*2, *H*7), 6.37 (1H, s, *H*8), 6.31–6.27 (2H, m, *H*5, *H*6), 4.47 (2H, br. s, *H*4), 2.46 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 147.2, 144.7, 143.2, 135.4, 129.7, 129.3, 128.4, 122.0, 110.6, 110.5, 44.4, 21.7;

HRMS (ES+) calc. for $C_{14}H_{13}{}^{35}Cl_2NNaO_3S$ $[M+Na]^+$ 367.9885, found 367.9886.

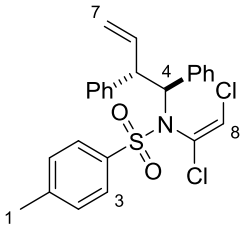
_N_-[(_Z_)-1-{[_t_-Butyl(dimethyl)silyl]oxy}oct-4-en-2-yl]-_N_-[(_E_)-1,2-dichlorovinyl]tosylamide, 53k



Following example procedure **1.2a**: Synthesised from (*Z*)-*N*-(1-((*t*-butyldimethylsilyl)oxy)oct-4-en-2-yl)tosylamide (359 mg, 0.872 mmol) in DMF (1 mL) using trichloroethylene (86 µL, 0.959 mmol, 1.1 equiv.) and Cs_2CO_3 (426 mg, 1.31 mmol, 1.5 equiv.). The reaction takes approximately 3 hours to reach completion. Column chromatography (0 → 10% EtOAc/pentane) afforded the title compound (335 mg, 0.661 mmol, 76%) as a pale yellow oil;

R_f 0.55 (5% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3088, 2957, 2929, 2858, 1599, 1463, 1360, 1254, 1167, 1091, 836, 814, 667;
^{1}H NMR (500 MHz, toluene-d_8, 363 K)* δ_H 7.86 (2H, d, *J* = 8.0 Hz, *H*3), 6.88 (2H, d, *J* = 8.0 Hz, *H*2), 6.14 (1H, s, *H*12), 5.60–5.20 (2H, m, *H*7, *H*8), 4.07–3.94 (1H, m, *H*5), 3.93–3.86 (1H, m, *H*4), 3.85–3.77 (1H, m, *H*4), 2.81–2.69 (1H, m, *H*6), 2.53–2.41 (1H, m, *H*6), 2.06–1.93 (5H, m, *H*1, *H*9), 1.33 (2H, sxt, *J* = 7.2 Hz, *H*10), 0.97–0.84 (12H, m, *H*11, *H*14), 0.07–0.01 (6H, m, *H*13); ***Note***: At room temperature, slow rotation around the C^5–N single bond leads to peak broadening and splitting in the ^{1}H NMR spectrum.
^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ_C 143.8, 138.3, 132.0, 129.9, 129.5, 128.9, 126.4, 122.6, 64.7, 64.4, 29.8, 28.6, 26.0, 22.9, 21.0, 18.4, 13.6, −5.5;
HRMS (ES^+) calc. for $C_{23}H_{37}{}^{35}Cl_2NNaO_3SSi$ $[M+Na]^+$ 528.1533, found 528.1533.

_N_-((_E_)-1,2-Dichlorovinyl)-_N_-((1_s_,2_s_)-1,2-diphenylbut-3-en-1-yl)tosylamide, 53l



To a stirring solution of *N*-benzylidenetosylamide (500 mg, 1.93 mmol, 1.0 equiv.) and cinnamyl bromide (1.14 g, 5.78 mmol, 3.0 equiv.) in THF:H_2O (8 mL each) was added indium powder (664 mg, 5.78 mmol, 3.0 equiv.) and the reaction stirred overnight. The reaction was quenched with 1 M HCl (10 mL) and stirred vigorously for 15 minutes, followed by the addition of Et_2O (15 mL). The organic layer was separated, and the aqueous extracted with Et_2O (3×10 mL). The combined organic extracts were then washed with aqueous saturated $NaHCO_3$ (20 mL) and the organic layer separated, dried (Na_2SO_4) and concentrated in vacuo to afford the crude title product (657 mg, containing ~20% cinnamyl alcohol and 1,2-diphenylbut-3-en-1-ol) as a white solid. This solid was used directly in the next reaction without purification.

To a nitrogen flushed flask equipped with a magnetic stirrer bar and a septum, was added the crude amide, powdered Cs_2CO_3 (777 mg, 2.34 mmol, ~1.7 equiv.) and DMF (1.25 mL). The resulting suspension was then stirred at 50 °C for 10 minutes, followed by the addition of trichloroethylene (0.16 mL, 1.75 mmol, ~1.3 equiv.) dropwise over 10 minutes. The resulting mixture was stirred at 50 ºC until reaction completion, as analysed by TLC (~5 hours). Upon cooling to room temperature, the mixture was partitioned between EtOAc (10 mL) and brine (30 mL), the organic layer was separated and further washed with brine (2×30 mL). The organic layer was then dried (Na_2SO_4), filtered and concentrated in vacuo. Column chromatography (3% Et_2O/40–60 petroleum ether), followed by recrystallisation from *i*-PrOH:H_2O (10:1), afforded the title compound (446 mg, 0.943 mmol, 49%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 99–100 °C;

R_f 0.56 (4% EtOAc/40–60 petroleum ether);

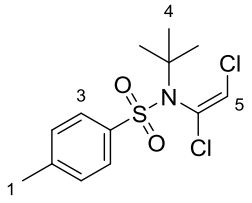
IR (thin film, ν_{max} / cm^{-1}) 3083, 3031, 1598, 1494, 1454, 1353, 1163, 1089, 973, 912, 813, 701, 664;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48–7.05 (12H, br. m, *H*3, Ph*H*), 7.00 (2H, d, *J* = 8.1 Hz, *H*2), 6.51 (1H, s, *H*8), 5.79 (1H, ddd, *J* = 17.1, 10.4, 8.6 Hz, *H*6), 5.47 (1H, br. d, *J* = 7.6 Hz, *H*4), 4.94 (1H, d, *J* = 10.4 Hz, *H*7), 4.90 (1H, br. d, *J* = 17.1 Hz, *H*7), 4.60–4.22 (1H, br. m, *H*5), 2.34 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 143.5, 140.6, 137.4, 136.8, 136.3, 134.7, 130.7, 128.9, 128.2, 128.0, 127.5, 126.7, 124.5, 117.4, 68.6, 52.2, 51.6, 21.4; ***Note***: This compound is rotameric and as a result some ^{13}C resonances are duplicated or obscured due to peak broadening.

HRMS (ES+) calc. for $C_{25}H_{23}{}^{35}Cl_2NNaO_2S$ $[M+Na]^+$ 494.0719, found 494.0717.

(*E*)-*N*-(*t*-Butyl)-*N*-(1,2-dichlorovinyl)tosylamide, 53m

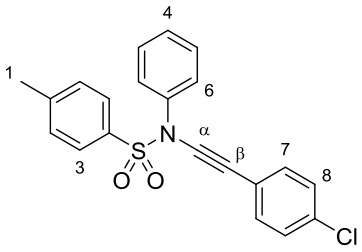


Following example procedure **1.2a**: Synthesised from *N*-(*t*-butyl)tosylamide (1.00 g, 4.40 mmol, 1.0 equiv.) in DMF (3.3 mL) using trichloroethylene (0.44 mL, 4.84 mmol, 1.1 equiv.) and Cs_2CO_3 (2.15 g, 6.60 mmol, 1.5 equiv.). The reaction was stirred overnight for ~15 hours arbitrarily. Column chromatography (10% Et_2O/pentane) afforded the title compound (1.27 g, 3.94 mmol, 90%) as colourless crystals. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of the title compound in toluene;

m.p. 92–93 °C;
R_f 0.75 (20% EtOAc/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3087, 2984, 1598, 1351, 1159, 1107, 1089, 951, 812, 787, 706, 670;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.84 (2H, d, *J* = 8.2 Hz, *H*3), 7.26 (2H, d, *J* = 8.2 Hz, *H*2), 6.39 (1H, s, *H*5), 2.41 (3H, s, *H*1), 1.52 (9H, s, *H*4);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.9, 138.0, 131.5, 129.2, 128.5, 121.6, 64.3, 29.8, 21.5;
HRMS (ES+) calc. for $C_{13}H_{17}{}^{35}Cl_2NNaO_2S$ $[M+Na]^+$ 344.0249, found 344.0243.

2.2b *Ynamides*.

_N_-((4-Chlorophenyl)ethynyl)-_N_-phenyltosylamide, 68a



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.46 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (183 µL of a 0.1 M solution in THF, 18.3 µmol, 1.25 mol%) and 4-chlorophenylmagnesium bromide (1.50 mL of a 1.0 M solution in Et_2O, 1.50 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (2.5% EtOAc/pentane) afforded a pale yellow solid which was recrystallised from *i*-PrOH/heptane to give the title compound (478 mg, 1.25 mmol, 86%) as colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 140–141 °C;

R_f 0.24 (10% Et_2O/pentane);

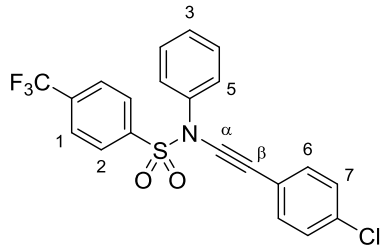
IR (thin film, ν_{max} / cm^{-1}) 3066, 2239, 1594, 1488, 1454, 1398, 1373, 1339, 1295, 1187, 1172, 1089, 1064, 1027, 1014, 922, 891, 827, 814, 790, 752, 705, 689, 657, 610;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 (2H, d, *J* = 8.3 Hz, *H*3), 7.39–7.23 (11H, m, *H2, H*4, *H*5, *H*6, *H*7, *H*8), 2.44 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1, 138.7, 133.9, 132.9, 132.6, 129.5, 129.1, 128.6, 128.4, 128.2, 126.3, 121.1, 83.9 (Cα), 69.5 (Cβ), 21.7;

HRMS (ES+) calc. for $C_{21}H_{16}{}^{35}ClNNaO_2S$ $[M+Na]^+$ 404.0483, found 404.0483.

_N_-((4-Chlorophenyl)ethynyl)-_N_-phenyl-4-(trifluoromethyl)benzenesulfonamide, 68b



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-(1,2-dichlorovinyl)-*N*-phenyl-4-(trifluoromethyl)benzenesulfonamide (500 mg, 1.26 mmol, 1.0 equiv.) in anhydrous TBME (2 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), CuCN·2LiCl (16 µL of a 1.0 M solution in THF, 16 µmol, 1.25 mol%) and 4-chloromagnesium bromide (1.39 mL of a 1.0 M solution in Et_2O, 1.39 mmol, 1.1 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Filtration through a silica pad (eluting with 20% CH_2Cl_2/pentane), followed by recrystallisation from TBME/heptane (1:3) afforded the title compound (457 mg, 1.05 mmol, 83%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 132 °C;

R_f 0.31 (2% Et_2O/pentane);

IR (thin film, ν_{max} / cm^{-1}) 3071, 2242, 1593, 1489, 1405, 1382, 1321, 1174, 1135, 1108, 1091, 1062, 1016, 925, 895, 828, 792, 753, 734, 716, 687;

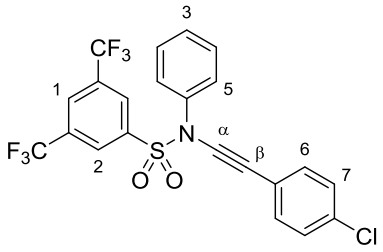
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.86 (2H, d, *J* = 8.3 Hz, *H*1), 7.78 (2H, d, *J* = 8.3 Hz, *H*2), 7.43–7.34 (3H, m, *H*3, *H*4), 7.34–7.26 (6H, m, *H*5, *H*6, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 139.3, 138.3, 135.6 (1C, q, *J* = 33.4 Hz), 134.4, 132.7, 129.4, 128.8, 128.73, 128.70, 126.2, 126.1 (2C, q, *J* = 4.0 Hz), 123.1 (1C, q, *J* = 273 Hz), 120.6, 83.0 (Cα), 69.9 (Cβ);

^{19}F NMR (376 MHz, $CDCl_3$) δ_F −63.2;

HRMS (ES+) calc. for $C_{22}H_{18}{}^{35}ClF_3NO_3S$ $[M+MeOH+H]^+$ 468.0643, found 468.0642.

***N*-((4-Chlorophenyl)ethynyl)-*N*-phenyl-3,5-bis(trifluoromethyl)benzenesulfonamide, 68c**



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)-3,5-bis(trifluoromethyl)benzenesulfonamide (150 mg, 0.323 mmol, 1.0 equiv.) in anhydrous TBME (4 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), CuCN·2LiCl (4 µL of a 1.0 M solution in THF, 4 µmol, 1.25 mol%) and 4-chloromagnesium bromide (0.36 mL of a 1.0 M solution in Et_2O, 0.36 mmol, 1.1 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (0 → 2% Et_2O/pentane) afforded the title compound (127 mg, 0.251 mmol, 78%) as a white powder;

m.p. 108–109 °C;

R_f 0.73 (4% Et_2O/pentane);

IR (thin film, ν_{max} / cm^{-1}) 3087, 2244, 1625, 1593, 1489, 1456, 1391, 1358, 1279, 1179, 1142, 1109, 1092, 1064, 1015, 927, 905, 829, 790, 753, 722, 691, 682, 625;

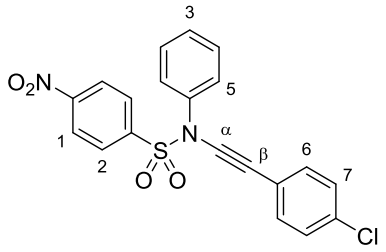
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.16 (1H, s, *H*1), 8.12 (2H, s, *H*2), 7.44–7.36 (3H, m, *H*3, *H*4), 7.30–7.27 (4H, m, *H*6, *H*7), 7.27–7.21 (2H, m, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 137.9, 134.8, 132.89 (2C, q, *J* = 34.2 Hz), 132.88, 129.6, 129.3, 128.8, 128.4 (2C, q, *J* = 3.4 Hz), 127.3 (1C, spt, *J* = 3.5 Hz), 126.2, 122.3 (2C, q, *J* = 273 Hz), 120.0, 82.2 (Cα), 70.5 (Cβ); ****Note***: a single ^{13}C resonance is obscured due to signal overlap.

^{19}F NMR (376 MHz, $CDCl_3$) δ_F −63.0;

HRMS (ES+) calc. for $C_{23}H_{17}{}^{35}ClF_6NO_3S$ $[M+MeOH+H]^+$ 536.0516, found 536.0517.

_N_-((4-Chlorophenyl)ethynyl)-4-nitro-_N_-phenylbenzenesulfonamide, 68d



Following example procedure **1.2f**: Synthesised from finely powdered (*E*)-*N*-phenyl-*N*-(1,2-dichlorovinyl)-4-nitrobenzenesulfonamide (150 mg, 0.402 mmol, 1.0 equiv.) in anhydrous TBME (5 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). ***Note*:** the starting dichloroenamide is poorly soluble in TBME and after the addition of LiHMDS at 0 °C, the reaction was stirred at room temperature (21 °C) for 2 hours. At this time, TLC analysis (10% Et_2O/pentane) indicated incomplete conversion of the starting dichloroenamide, and additional LiHMDS (1.2 equiv.) was added to the reaction at 0 °C. The reaction was then stirred at room temperature for 1 additional hour to achieve complete conversion. The diarylzinc solution was prepared using anhydrous TBME (1.0 mL), 4-chlorophenylmagnesium bromide (0.44 mL of a 1.0 M solution in Et_2O, 0.44 mmol, 1.1 equiv.), zinc(II) chloride (0.22 mL of a 1.0 M solution in Et_2O, 0.22 mmol, 0.55 equiv.), and the reaction conducted using CuCN·2LiCl (5 µL of a 1.0 M solution in THF, 5 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Filtration through a silica pad (eluting with 20% CH_2Cl_2/pentane), followed by recrystallisation from EtOAc/heptane (1:2) afforded the title compound (126 mg, 0.306 mmol, 76%) as yellow needles. These crystals were suitable for X-ray diffraction;

m.p. 169–170 °C;

R_f 0.49 (10% Et_2O/pentane);

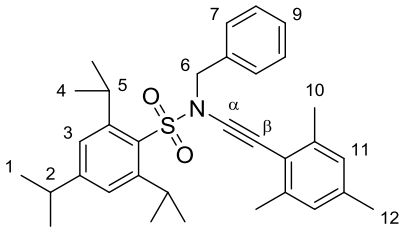
IR (thin film, ν_{max} / cm^{-1}) 3105, 2242, 1606, 1592, 1531, 1488, 1402, 1382, 1347, 1312, 1180, 1089, 1064, 1014, 925, 900, 855, 829, 791, 738, 690;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.39–8.31 (2H, m, *H*1), 7.96–7.86 (2H, m, *H*2), 7.44–7.35 (3H, m, *H*3, *H*4), 7.35–7.25 (6H, m, *H*5, *H*6, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 150.9, 141.1, 138.0, 134.6, 132.8, 129.5, 129.4, 129.0, 128.8, 126.2, 124.2, 120.4, 82.6 (Cα), 70.1 (Cβ);

HRMS (ES+) calc. for $C_{20}H_{17}{}^{35}ClN_3O_4S$ $[M+NH_4]^+$ 430.0623, found 430.0623.

_N_-Benzyl-2,4,6-tri-_i_-propyl-_N_-(mesitylethynyl)benzenesulfonamide, 68e



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-benzyl-*N*-(1,2-dichlorovinyl)-2,4,6-tri-*i*-propylbenzenesulfonamide (200 mg, 0.427 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), CuCN·2LiCl (4 µL of a 1.0 M solution in THF, 4 µmol, 1.25 mol%), and mesitylmagnesium bromide (0.44 mL of a 1.0 M solution in THF, 0.44 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (0 → 3% Et_2O/pentane) afforded an orange oil, which was crystallised using MeOH (~1 mL) to afford the title compound (167 mg, 0.324 mmol, 76%) as colourless plates. These crystals were suitable for X-ray diffraction;

m.p. 89–90 °C;

R_f 0.46 (4% Et_2O/pentane);

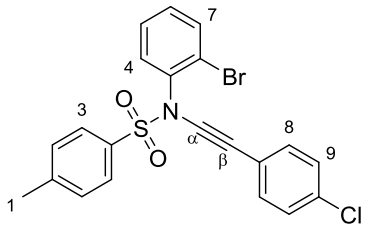
IR (thin film ν_{max} / cm^{-1}) 2960, 2929, 2870, 2231, 1600, 1565, 1497, 1458, 1427, 1370, 1332, 1258, 1168, 1103, 1075, 1060, 1038, 1004, 931, 899, 852, 766, 733, 697, 670, 624;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47–7.37 (2H, m, *H*8), 7.38–7.28 (3H, m, *H*7, *H*9), 7.20 (2H, s, *H*3), 6.72 (2H, s, *H*11), 4.74 (2H, s, *H*8), 4.22 (2H, spt, *J* = 6.8 Hz, *H*5), 2.93 (1H, spt, *J* = 6.9 Hz, *H*2), 2.20 (3H, s, *H*12), 1.90 (6H, s, *H*10), 1.27 (6H, d, *J* = 6.9 Hz, *H*1),1.23 (12H, d, *J* = 6.8 Hz, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.1, 152.1, 140.0, 137.0, 135.0, 130.4, 129.2, 128.5, 128.2, 127.3, 124.0, 119.5, 89.1 (Cα), 70.4 (Cβ), 53.4, 34.3, 29.7, 24.7, 23.6, 21.2, 20.5;

HRMS (ES+) calc. for $C_{33}H_{42}NNaO_2S$ $[M+H]^+$ 516.2931, found 516.2930.

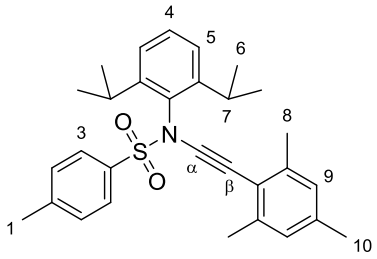
_N_-(2-Bromophenyl)-_N_-((4-chlorophenyl)ethynyl)tosylamide, 68f



Following example procedure **1.2f:** Synthesised from (*E*)-*N*-(2-bromophenyl)-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.19 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), CuCN·2LiCl (15 µL of a 1.0 M solution in THF, 15 µmol, 1.25 mol%), $P(OMe)_3$ (4 µL, 30 µmol, 2.50 mol%) and 4-chlorophenylmagnesium bromide (1.22 mL of a 1.0 M solution in Et_2O, further diluted with 1 mL of anhydrous THF, 1.22 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (10% Et_2O/pentane) afforded a yellow oil, which was crystallised from MeOH/benzene (~2:1) at −20 °C overnight to afford the title compound (452 mg, 0.982 mmol, 83%) as colourless needles;

m.p. 78–79 °C;
R_f 0.26 (10% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3066, 2980, 2240, 1595, 1492, 1469, 1374, 1187, 1173, 1090, 1043, 1014, 918, 828, 814;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73–7.68 (2H, m, *H*3), 7.58–7.53 (1H. m, *H*7), 7.38–7.21 (9H, *H*2, *H*4, *H*5, *H*6, *H*8, *H*9), 2.46 (3H, s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.3, 137.1, 134.4, 134.2, 133.9, 132.7, 130.7, 130.6, 129.7, 128.5 (2C), 128.3, 123.5, 121.2, 82.9 (Cα), 69.7 (Cβ), 21.7;
HRMS (ES+) calc. for $C_{21}H_{16}{}^{79}Br^{35}ClNO_2S$ $[M+H]^+$ 459.9768, found 459.9769.

_N_-(2,6-Di-_i_-propylphenyl)-_N_-(mesitylethynyl)tosylamide, 68g



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-(1,2-dichlorovinyl)-*N*-(2,6-di-*i*-propylphenyl)tosylamide (150 mg, 0.352 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), CuCN·2LiCl (4 µL of a 1.0 M solution in THF, 4 µmol, 1.25 mol%), and mesitylmagnesium bromide (0.36 mL of a 1.0 M solution in THF, 0.363 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (0 → 4% Et_2O/pentane) afforded the title compound (135 mg, 0.285 mmol, 81%) as a white powder. This compound can be recrystallised from TBME/hexane (1:3) to give colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 165 °C;

R_f 0.27 (4% Et_2O/pentane);

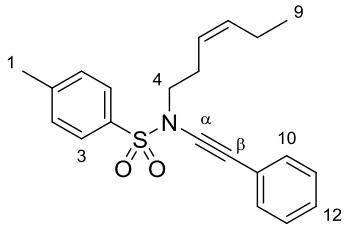
IR (thin film, ν_{max} / cm^{-1}) 2968, 2869, 2231, 1597, 1461, 1443, 1361, 1337, 1186, 1169, 1090, 1060, 1042, 921, 853, 809, 775, 734, 704, 663, 614;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.98–7.89 (2H, m, *H*3), 7.40–7.32 (3H, m, *H*4, *H*5), 7.23–7.17 (2H, m, *H*2), 6.85 (2H, s, *H*9), 3.19 (2H, spt, *J* = 6.7 Hz, *H*7), 2.48 (3H, s, *H*1), 2.31 (6H, s, *H*8), 2.27 (3H, s, *H*10), 1.21 (6H, d, *J* = 6.7 Hz, *H*6), 1.16 (6H, d, *J* = 6.7 Hz, *H*6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 148.5, 144.6, 140.5, 137.4, 135.7, 133.9, 129.9, 129.5, 128.3, 127.5, 124.5, 119.6, 90.6 (Cα), 67.1 (Cβ), 29.0, 25.2, 23.3, 21.7, 21.2, 21.0;

HRMS (ES+) calc. for $C_{30}H_{36}NO_2S$ $[M+H]^+$ 474.2461, found 474.2461.

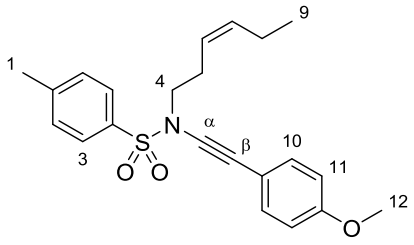
_N_-[(_Z_)-Hex-3-en-1-yl]-_N_-(phenylethynyl)tosylamide, 68h



Following example procedure **1.2e**: Synthesised from _N_-((_E_)-1,2-dichlorovinyl)-_N_-[(_Z_)-hex-3-en-1-yl]tosylamide (492 mg, 1.41 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (176 µL of a 0.1 M solution in THF, 17.6 µmol, 1.25 mol%) and phenylmagnesium bromide (1.45 mL of a 1.0 M solution in THF, 1.45 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (3 → 5% Et_2O/pentane) afforded the title compound (430 mg, 1.22 mmol, 86%) as a yellow oil;

R_f 0.38 (10% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 2963, 2234, 1598, 1494, 1364, 1168, 1090, 813, 754, 691, 676;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.84 (2H, d, _J_ = 8.4 Hz, _H_3), 7.40–7.27 (7H, m, _H_2, _H_10, _H_11, _H_12), 5.48 (1H, dtt, _J_ = 10.7, 7.3, 1.5 Hz, _H_7), 5.27 (1H, dtt, _J_ = 10.7, 7.4, 1.6 Hz, _H_6), 3.42 (2H, t, _J_ = 7.5 Hz, _H_4), 2.47–2.41 (5H, m, _H_1, _H_5), 2.04 (2H, quind, _J_ = 7.5, 1.5 Hz, _H_8), 0.95 (3H, t, _J_ = 7.5 Hz, _H_9);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 135.2, 134.8, 131.4, 129.9, 128.4, 127.9, 127.8, 123.6, 123.0, 82.4 (Cα), 71.0 (Cβ), 51.4, 26.1, 21.8, 20.8, 14.3;
HRMS (ES+) calc. for $C_{21}H_{24}NO_2S$ $[M+H]^+$ 354.1522, found 354.1521.

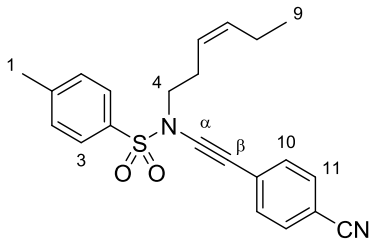
_N_-[(_Z_)-Hex-3-en-1-yl]-_N_-[(4-methoxyphenyl)ethynyl]tosylamide, 68i



Following example procedure **1.2e**: Synthesised from *N*-((*E*)-1,2-dichlorovinyl)-*N*-[(*Z*)-hex-3-en-1-yl]tosylamide (516 mg, 1.49 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (186 µL of a 0.1 M solution in THF, 18.6 µmol, 1.25 mol%) and 4-methoxyphenylmagnesium bromide (1.53 mL of a 1.0 M solution in THF, 1.53 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (3 → 8% Et_2O/pentane) afforded the title compound (473 mg, 1.24 mmol, 83%) as a pale yellow oil;

R_f 0.45 (20% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 2962, 2236, 1605, 1511, 1362, 1247, 1168, 1090, 832, 664;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83 (2H, d, *J* = 8.2 Hz, *H*3), 7.35 (2H, d, *J* = 8.2 Hz, *H*2), 7.32 (2H, d, *J* = 8.8 Hz, *H*10), 6.83 (2H, d, *J* = 8.8 Hz, *H*11), 5.47 (1H, dtt, *J* = 10.8, 7.3, 1.6 Hz, *H*7), 5.26 (1H, dtt, *J* = 10.8, 7.3, 1.6 Hz, *H*6), 3.81 (3H, s, *H*12), 3.39 (2H, t, *J* = 7.5 Hz, *H*4), 2.47–2.38 (5H, m, *H*1, *H*5), 2.03 (2H, quind, *J* = 7.5, 1.6 Hz, *H*8), 0.94 (3H, t, *J* = 7.5 Hz, *H*9);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.6, 144.6, 135.1, 134.9, 133.5, 129.8, 127.8, 123.7, 114.9, 114.0, 80.9 (Cα), 70.6 (Cβ), 55.4, 51.5, 26.1, 21.8, 20.8, 14.3;
HRMS (ES+) calc. for $C_{22}H_{25}NNaO_3S$ $[M+Na]^+$ 406.1447, found 406.1446.

_N_-[(4-Cyanophenyl)ethynyl]-_N_-[(_Z_)-hex-3-en-1-yl]tosylamide, 68j



Following example procedure **1.2e**: Synthesised from _N_-((_E_)-1,2-dichlorovinyl)-_N_-[(_Z_)-hex-3-en-1-yl]tosylamide (507 mg, 1.46 mmol 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (146 µL of a 0.1 M solution in THF, 14.6 µmol, 1.25 mol%) and 4-cyanophenylmagnesium chloride (prepared according to example procedure **1.2c** from 4-iodobenzonitrile (400 mg, 1.75 mmol, 1.2 equiv.) in anhydrous THF (4 mL) using _i_-propylmagnesium chloride (1.02 mL of a 2.0 M solution in THF, 2.04 mmol, 1.4 equiv.)). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (5 → 17% Et_2O in pentane) afforded a viscous yellow oil that solidified on standing, giving the title compound (398 mg, 1.05 mmol, 72%) as a white powder. This compound can be recrystallised from toluene/heptane to give colourless needles;

m.p. 54–55 °C (toluene/heptane);

R_f 0.30 (20% Et_2O/pentane);

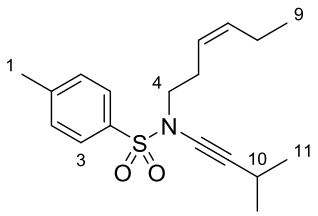
IR (thin film, ν_{max} / cm^{-1}) 2963, 2222, 1603, 1366, 1186, 1169, 1106, 1090, 959, 838, 814, 714, 659;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.82 (2H, d, _J_ = 8.2 Hz, _H_3), 7.57 (2H, d, _J_ = 8.5 Hz, _H_11), 7.40 (2H, d, _J_ = 8.5 Hz, _H_10), 7.36 (2H, d, _J_ = 8.2 Hz, _H_2), 5.48 (1H, dtt, _J_ = 10.8, 7.3, 1.7 Hz, _H_7), 5.25 (1H, dtt, _J_ = 10.8, 7.3, 1.6 Hz, _H_6), 3.44 (2H, t, _J_ = 7.4 Hz, _H_4), 2.49–2.38 (5H, m, _H_1, _H_5), 2.01 (2H, quind, _J_ = 7.5, 1.6 Hz, _H_8), 0.93 (3H, t, _J_ = 7.5 Hz, _H_9);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.2, 135.4, 134.7, 132.1, 131.0, 130.0, 128.4, 127.8, 123.3, 118.7, 110.6, 87.3 (Cα), 70.7 (Cβ), 51.4, 26.2, 21.8, 20.8, 14.3;

HRMS (ES+) calc. for $C_{22}H_{23}N_2O_2S$ $[M+H]^+$ 379.1475, found 379.1474.

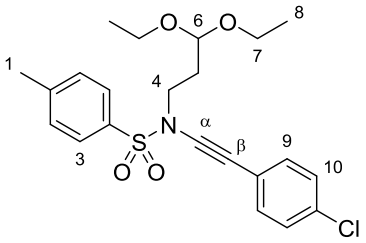
_N_-[(_Z_)-Hex-3-en-1-yl]-_N_-(3-methylbut-1-yn-1-yl)tosylamide, 68k



Following example procedure **1.2e**: Synthesised from *N*-((*E*)-1,2-dichlorovinyl)-*N*-[(*Z*)-hex-3-en-1-yl]tosylamide (139 mg, 0.399 mmol, 1.0 equiv.) in anhydrous TBME (0.6 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (50 µL of a 0.1 M solution in THF, 5.0 µmol, 1.25 mol%) and *i*-propylmagnesium bromide (0.48 mL of a 1.0 M solution in THF, 0.480 mmol, 1.2 equiv.). ***Note:*** The Grignard reagent was added at −5 °C. In this reaction, 1.03 equiv. of *i*-propylmagnesium bromide did not lead to complete consumption of chloroynamide (as analysed by TLC (20% CH_2Cl_2/pentane)) and 1.2 equiv. was required. Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (0 → 4% Et_2O in pentane) afforded the title compound (61 mg, 191 µmol, 48%) as a pale yellow oil;

R_f 0.45 (10% Et_2O in pentane);
IR (thin film, ν_{max} / cm^{-1}) 2967, 2932, 2252, 1598, 1494, 1363, 1168, 1091, 997, 814, 670;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.2 Hz, *H*3), 7.22 (2H, d, *J* = 8.2 Hz, *H*2), 5.35 (1H, dtt, *J* = 10.7, 7.4, 1.6 Hz, *H*7), 5.13 (1H, dtt, *J* = 10.7, 7.4, 1.4 Hz, *H*6), 3.15 (2H, t, *J* = 7.5 Hz, *H*4), 2.54 (1H, spt, *J* = 6.9 Hz, *H*10), 2.34 (3H, s, *H*1), 2.24 (2H, q, *J* = 7.4 Hz, *H*5), 1.91 (2H, quind, *J* = 7.5, 1.4 Hz, *H*8), 1.05 (6H, d, *J* = 6.9 Hz, *H*11), 0.84 (3H, t, *J* = 7.5 Hz, *H*9);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 135.0, 134.9, 129.7, 127.9, 124.0, 76.0, 72.8, 51.4, 26.0, 23.4, 21.8, 20.8, 20.7, 14.4;
HRMS (ES+) calc. for $C_{18}H_{26}NO_2S$ $[M+H]^+$ 320.1679, found 320.1683.

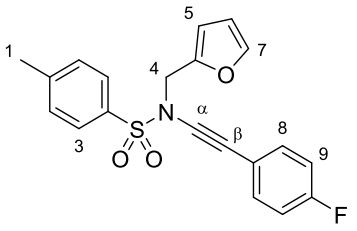
***N*-((4-Chlorophenyl)ethynyl)-*N*-(3,3-diethoxypropyl)tosylamide, 68l**



Following example procedure **1.2e**: Synthesised from *N*-[(*E*)-1,2-dichlorovinyl]-*N*-(3,3-diethoxypropyl)tosylamide (454 mg, 1.15 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (143 μL of a 0.1 M solution in THF, 14.3 μmol, 1.25 mol%), and 4-chlorophenylmagnesium bromide (1.18 mL of a 1.0 M solution in Et_2O, which was further diluted with 1.2 mL of anhydrous THF, 1.18 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (10 → 20% Et_2O/pentane) afforded the title compound (420 mg, 0.964 mmol, 84%) as a yellow oil;

R_f 0.30 (20% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 2975, 2879, 2236, 1596, 1492, 1367, 1294, 1170, 1090, 1059, 876, 827, 815, 707, 657;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.82 (2H, d, *J* = 8.2 Hz, *H*3), 7.35 (2H, d, *J* = 8.2 Hz, *H*2), 7.30–7.23 (4H, m, *H*9, *H*10), 4.60 (1H, t, *J* = 5.6 Hz, *H*6), 3.65 (2H, dq, *J* = 9.3, 7.0 Hz, *H*7), 3.55–3.44 (4H, m, *H*4, *H*7), 2.45 (3H, s, *H*1), 2.00 (2H, dt, *J* = 5.6, 7.1 Hz, *H*5), 1.20 (6H, *J* = 7.0 Hz, *H*8);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8, 134.3, 133.8, 132.5, 129.8, 128.6, 127.7, 121.3, 100.4, 83.2 (Cα), 69.9 (Cβ), 62.8, 47.9, 32.5, 21.6, 15.3;
HRMS (ES+) calc. for $C_{22}H_{26}{}^{35}ClNNaO_4S$ $[M+Na]^+$ 458.1163, found 458.1163.

_N_-((4-Fluorophenyl)ethynyl)-_N_-(furan-2-ylmethyl)tosylamide, 68m



Following example procedure **1.2e**: Synthesised from *N*-[(*E*)-1,2-dichlorovinyl]-*N*-(3,3-diethoxypropyl)tosylamide (103 mg, 0.297 mmol, 1.0 equiv.) in anhydrous TBME (0.8 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (30 μL of a 0.1 M solution in THF, 3.0 μmol, 1 mol%), and 4-fluorophenylmagnesium bromide (0.18 mL of a 2.0 M solution in Et_2O, which was further diluted with 0.16 mL of anhydrous THF, 0.371 mmol, 1.25 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (7.5 → 10% Et_2O/pentane) afforded the title compound (68.8 mg, 0.186 mmol, 63%) as a pale yellow oil;

R_f 0.39 (20% Et_2O/pentane);

IR (thin film, ν_{max} / cm^{-1}) 2997, 2240, 1599, 1509, 1364, 1227, 1169, 1091, 1006, 933, 836, 717, 664;

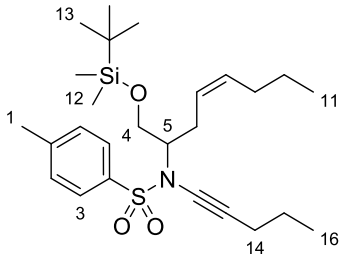
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.3 Hz, *H*3), 7.34–7.29 (3H, m, *H*2, *H*7), 7.29–7.23 (2H, m, *H*8), 6.96 (2H, m, *H*9), 6.31 (1H, d, *J* = 3.2 Hz, *H*5), 6.28 (1H, dd, *J* = 3.2, 1.8 Hz, *H*6), 4.64 (2H, s, *H*4), 2.44 (3H, s, *H*1);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.4 (1C, d, *J* = 249 Hz), 148.0, 144.8, 143.2, 134.7, 133.5 (2C, d, *J* = 8.1 Hz), 129.8, 128.0, 118.9 (1C, d, *J* = 3.2 Hz), 115.6 (2C, d, *J* = 22.3 Hz), 110.7, 110.6, 81.8 (Cα), 70.4 (Cβ), 48.4, 21.8;

^{19}F NMR (470 MHz, $CDCl_3$) δ_F −118.6 (1F, tt, *J* = 8.7, 5.2 Hz);

HRMS (ES+) calc. for $C_{20}H_{16}FNNaO_3S$ $[M+Na]^+$ 392.0727, found 392.0727.

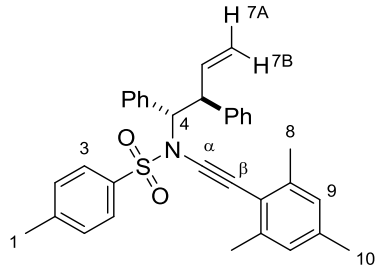
_N_-[(_Z_)-1-{[_t_-Butyl(dimethyl)silyl]oxy}oct-4-en-2-yl-_N_-(pent-1-yn-1-yl)tosylamide, 68n



Following example procedure **1.2e**: Synthesised from *N*-[(*Z*)-1-{[*t*-butyl(dimethyl)silyl]oxy}oct-4-en-2-yl]-*N*-[(*E*)-1,2-dichlorovinyl]tosylamide (314 mg, 0.620 mmol, 1.0 equiv.) in anhydrous TBME (0.8 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), $CuCN{\cdot}2P(OMe)_3$ (78 µL of a 0.1 M solution in THF, 7.8 µmol, 1.25 mol%) and *n*-propylmagnesium bromide (0.32 mL of a 2.0 M solution in Et_2O, further diluted with 0.32 mL of THF, 0.638 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (0 → 4% Et_2O/pentane) afforded the title compound (195 mg, 0.408 mmol, 66%) as a pale yellow oil;

R_f 0.40 (5% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 2958, 2930, 2858, 2250, 1598, 1463, 1292, 1169, 1118, 1092, 837, 778, 669;
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.1 Hz, *H*3), 7.27 (2H, d, *J* = 8.1 Hz, *H*2), 5.30 (1H, dtt, *J* = 10.9, 7.3, 1.6 Hz, *H*8), 5.13 (1H, dtt, *J* = 10.9, 7.3, 1.6 Hz, *H*7), 3.89 (1H, dq, *J* = 8.9, 6.1 Hz, *H*5), 3.62 (1H, dd, *J* = 10.3, 6.2 Hz, *H*4), 3.54 (1H, dd, *J* = 10.3, 6.2 Hz, *H*4), 2.42 (3H, s, *H*1), 2.35 (1H, dddd, *J* = 15.1, 7.3, 5.6, 1.7 Hz, *H*6), 2.25 (2H, t, *J* = 6.9 Hz, *H*14), 2.18 (1H, dddd, *J* = 15.1, 8.1, 6.6, 1.5 Hz, *H*6), 1.93 (2H, qd, *J* = 7.4, 1.6 Hz, *H*9), 1.50 (2H, sxt, *J* = 7.2 Hz, *H*15), 1.31 (2H, sxtd, *J* = 7.4, 1.7 Hz, *H*10), 0.94 (3H, t, *J* = 7.4 Hz, *H*16), 0.88–0.82 (12H, m, *H*11, *H*13), 0.01 (3H, s, *H*12), 0.00 (3H, s, *H*12);
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.0, 136.3, 132.7, 129.4, 127.9, 124.8, 72.0, 70.4, 63.8, 61.8, 29.5, 27.5, 26.0, 22.8, 22.6, 21.7, 20.8, 18.4, 13.9, 13.6, −5.3, −5.4;
HRMS (ES+) calc. for $C_{26}H_{44}NO_3SSi$ $[M+H]^+$ 478.2806, found 478.2805.

_N_-((1_S_,2_S_)-1,2-Diphenylbut-3-en-1-yl)-_N_-(mesitylethynyl)tosylamide, 68o



Following example procedure **1.2e**: Synthesised from (*E*)-*N*-benzyl-*N*-(1,2-dichlorovinyl)-2,4,6-tri-*i*-propylbenzenesulfonamide (200 mg, 0.423 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), CuCN·2LiCl (5 µL, of a 1.0 M solution in THF, 5 µmol, 1.25 mol%), and mesitylmagnesium bromide (0.44 mL of a 1.0 M solution in THF, 0.436 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (0 → 5% Et_2O/pentane) afforded the title compound (186 mg, 0.358 mmol, 84%) as a pale yellow oil that solidified on standing. This compound can be recrystallised by vapour diffusion of pentane into a concentrated solution of the title compound in toluene/CH_2Cl_2 (~5:1), at 0 °C, to give colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 140–141 °C;

R_f 0.29 (5% Et_2O/pentane);

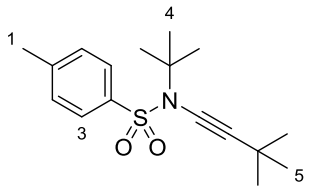
IR (thin film, ν_{max} / cm^{-1}) 3063, 3031, 2978, 2917, 2226, 1599, 1495, 1454, 1363, 1306, 1292, 1185, 1167, 1089, 1032, 1019, 974, 942, 915, 855, 825, 811, 749, 731, 699, 682, 665, 615;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62–7.54 (2H, m, Ph*H*), 7.47–7.41 (2H, m, Ph*H*), 7.37–7.25 (6H, m, Ph*H*), 7.18–7.11 (2H, m, *H*3), 7.67–7.91 (2H, m, *H*2), 6.87 (2H, s, *H*9), 5.75 (1H, ddd, *J* = 17.1, 10.3, 8.0 Hz, *H*6), 5.52 (1H, d, *J* = 11.7 Hz, *H*4), 4.88 (1H, dt, *J* = 10.3, 1.2 Hz, *H*7_A), 4.79 (1H, dt, *J* = 17.1, 1.2 Hz, *H*7_B), 4.25 (1H, dd, *J* = 11.7, 8.0 Hz, *H*5), 2.30 (3H, s, *H*1), 2.29 (3H, s, *H*10), 2.25 (6H, s, *H*8);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.6, 140.63, 140.61, 138.1, 137.8, 137.6, 135.1, 128.9, 128.6, 128.4, 128.33, 128.28, 128.2, 127.8, 127.6, 127.0, 119.7, 117.7, 87.3 (Cα), 71.8 (Cβ), 66.0, 52.8, 21.4, 21.2, 21.1;

HRMS (ES+) calc. for $C_{34}H_{34}NO_2S$ $[M+H]^+$ 520.2305, found 520.2304.

_N_-(_t_-Butyl)-_N_-(3,3-dimethylbut-1-yn-1-yl)tosylamide, 68p



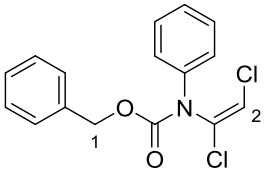
Following example procedure **1.2e**: Synthesised from (*E*)-*N*-(*t*-butyl)-*N*-(1,2-dichlorovinyl)tosylamide (500 mg, 1.55 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), CuCN·2LiCl (19 µL of a 1.0 M solution in THF, 19 µmol, 1.25 mol%), $P(OMe)_3$ (5 µL, 38 µmol, 2.50 mol%) and *t*-butylmagnesium bromide (0.94 mL of a 1.7 M solution in THF, 1.60 mmol, 1.03 equiv.). Upon completion, the reaction was worked up and extracted as for example procedure **1.2e**. Column chromatography (0 → 3% Et_2O/pentane) afforded the title compound (386 mg, 1.26 mmol, 81%) as a yellow oil. ***Note***: This compound is not stable to prolonged storage.

R_f 0.33 (5% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 2970, 2243, 1599, 1476, 1459, 1357, 1250, 1159, 1089, 943, 867, 813, 718, 663;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85–7.80 (2H, m, *H*3), 7.31–7.27 (2H, m, *H*2), 2.43 (3H, s, *H*1), 1.41 (9H, s, *H*5), 1.19 (9H, s, *H*4);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.8, 137.5, 129.1, 127.9, 79.9, 72.4, 63.2, 31.1, 29.2, 27.6, 21.5;
HRMS (ES+) calc. for $C_{17}H_{25}NNaO_2S$ $[M+Na]^+$ 330.1498, found 330.1499.

2.3 Carbamates Scope.

2.3a *Dichloroenamides*.

Benzyl (*E*)-(1,2-dichlorovinyl)(phenyl)carbamate, 69a



To a 100 mL round bottomed flask, equipped with a stirrer bar, was added anhydrous CH_2Cl_2 (25 mL), phenyl isocyanate (4.60 mL, 42.0 mmol, 1.0 equiv.) and then benzyl alcohol (4.35 mL, 42.0 mmol, 1.0 equiv.), and the reaction was stirred overnight at room temperature. Complete conversion was then confirmed by TLC. The solution was then concentrated in vacuo to afford benzyl phenylcarbamate as a pale yellow solid. This solid was further dried under high vacuum for 1 hour to remove residual CH_2Cl_2.

To this solid was added powdered Cs_2CO_3 (20.5 g, 63.0 mmol, 1.5 equiv.), the flask was capped with a septum and evacuated under high vacuum for ~1 minute. After backfilling with nitrogen, DMF (31 mL) was added and the reaction was stirred at 50 °C for 10 minutes. Trichloroethylene (4.15 mL, 46.2 mmol, 1.1 equiv.) was then added dropwise over 10 minutes, and the resulting mixture was stirred at 50 °C for 4 hours. Complete conversion was then confirmed by TLC. Upon cooling to room temperature, the mixture was partitioned between Et_2O (150 mL) and brine (500 mL), the organic layer was separated and further washed with brine (2×200 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated in vacuo.

Column chromatography (10% Et_2O/40–60 petroleum ether) afforded the title compound as a yellow oil, which was further purified by crystallisation from pentane/Et_2O (2:1, 60 mL) at 0 °C overnight. Once crystallisation had ceased, the remaining yellow solution was decanted and the colourless crystals were washed with ice cold pentane (2×20 mL). The crystals were then dried under high vacuum for 1 hour. This afforded 12.0 g (37.4 mmol, 89%) of the title compound. These crystals were suitable for X-ray diffraction;

m.p. 46–48 °C;

R_f 0.64 (30% Et_2O/40–60 petroleum ether);

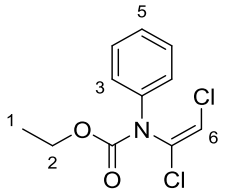
IR (thin film, ν_{max} / cm^{-1}) 3089, 3034, 1730, 1617, 1596, 1495, 1455, 1382, 1304, 1275, 1231, 1151, 1075, 1041, 1020, 887, 821, 749, 693;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55–7.23 (10H, m, Ph*H*), 6.37 (1H, s, *H*2), 5.30 (2H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.5, 138.2, 135.5, 131.3, 129.1, 128.5, 128.2, 127.9, 127.5, 125.8, 116.9, 88.5;

HRMS (ES+) calc. for $C_{16}H_{13}{}^{35}Cl_2NNaO_2$ $[M+Na]^+$ 344.0216, found 344.0217.

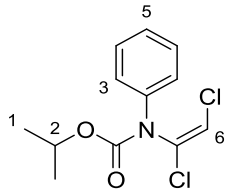
Ethyl (*E*)-(1,2-dichlorovinyl)(phenyl)carbamate, 69b



Following example procedure **1.2a**: Synthesised from ethyl phenylcarbamate (500 mg, 3.03 mmol, 1.0 equiv.) in DMF (2.3 mL) using trichloroethylene (0.30 mL, 3.33 mmol, 1.1 equiv.) and Cs_2CO_3 (1.48 g, 4.54 mmol, 1.5 equiv.). The reaction takes approximately 3 hours to reach completion. Column chromatography (5% Et_2O/40–60 petroleum ether) afforded the title compound (758 mg, 2.91 mmol, 96%) as a pale yellow oil;

R_f 0.67 (30% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3089, 2983, 1731, 1619, 1597, 1494, 1371, 1309, 1235, 1175, 1149, 1052, 1026, 901, 826, 750, 693;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44–7.35 (4H, m, *H*3, *H*4), 7.35–7.27 (1H, m, *H*5), 6.36 (1H, s, *H*6), 4.30 (2H, q, *J* = 7.1 Hz, *H*2), 1.32 (3H, t, *J* = 7.1 Hz, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.6, 138.3, 131.5, 129.0, 127.3, 125.8, 116.6, 63.1, 14.3;
HRMS (ES+) calc. for $C_{11}H_{11}{}^{35}Cl_2NNaO_2$ $[M+Na]^+$ 282.0059, found 282.0060.

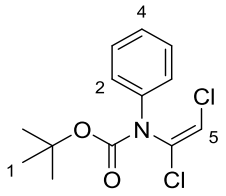
***i*-Propyl (*E*)-(1,2-dichlorovinyl)(phenyl)carbamate, 69c**



Following example procedure **1.2a**: Synthesised from *i*-propyl phenylcarbamate (500 mg, 2.79 mmol, 1.0 equiv.) in DMF (2.1 mL) using trichloroethylene (0.28 mL, 3.07 mmol, 1.1 equiv.) and Cs_2CO_3 (1.36 g, 4.18 mmol, 1.5 equiv.). The reaction takes approximately 3 hours to reach completion. Column chromatography (4% Et_2O/40–60 petroleum ether) afforded the title compound (583 mg, 2.13 mmol, 76%) as a pale yellow oil;

R_f 0.68 (30% EtOAc/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3091, 2982, 1730, 1619, 1598, 1495, 1359, 1307, 1239, 1182, 1156, 1107, 1016, 931, 822, 751, 693;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43–7.34 (4H, m, *H*3, *H*4), 7.34–7.25 (1H, m, *H*5), 6.34 (1H, s, *H*6), 5.07 (1H, spt, *J* = 6.3 Hz, *H*2), 1.31 (6H, d, *J* = 6.3 Hz, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.1, 138.4, 131.6, 129.0, 127.2, 125.7, 116.4, 71.0, 21.8;
HRMS (CI+) calc. for $C_{12}H_{14}{}^{35}Cl_2NO_2$ $[M+H]^+$ 274.0396, found 274.0389.

(*E*)-*t*-Butyl (1,2-dichlorovinyl)(phenyl)carbamate, 69d



Synthesised according to example procedure **1.2b**;

R_f 0.67 (20% EtOAc/40–60 petroleum ether);

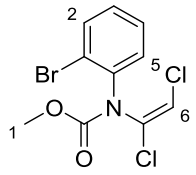
IR (thin film, ν_{max} / cm^{-1}) 3081, 2928, 1730, 1598, 1495, 1369, 1315, 1154, 1014, 900, 826,756, 693;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41–7.34 (4H, m, *H*2*, H*3), 7.31–7.24 (1H, m, *H*4), 6.31 (1H, s, *H*5), 1.52 (9H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 151.3, 138.5, 132.0, 128.9, 127.0, 125.7, 115.9, 82.8, 28.0.

Data are consistent with literature values.[245]

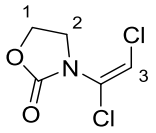
(*E*)-Methyl (2-bromophenyl)(1,2-dichlorovinyl)carbamate, 69e



Following example procedure **1.2a**: Synthesised from methyl (2-bromophenyl)carbamate (1.00 g, 4.35 mmol, 1.0 equiv.) in DMF (3.3 mL) using trichloroethylene (0.59 mL, 4.79 mmol, 1.1 equiv.) and Cs_2CO_3 (2.12 g, 6.53 mmol, 1.5 equiv.). The reaction was stirred overnight for ~15 hours arbitrarily. Recrystallisation from heptane (*plus* a few drops of benzene) afforded the title compound (1.23 g, 3.78 mmol, 87%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 80–81 °C;
R_f 0.31 (10% EtOAc/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3074, 2949, 1740, 1475, 1439, 1309, 1264, 1157, 1070, 1019, 527, 757;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (1H, dd, *J* = 8.0, 1.3 Hz, *H*2), 7.42 (1H, dd, *J* = 8.1, 1.7 Hz, *H*5), 7.36 (1H, ddd, *J* = 8.1, 7.3, 1.3 Hz, *H*4) *H*3, *H*4), 7.23 (1H, ddd, *J* = 8.0, 7.3, 1.7 Hz, *H*3), 6.33 (1H, br. s, *H*6), 3.84 (3H, br. s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.1, 137.3, 133.8, 131.1, 129.8, 128.8, 128.4, 123.5, 115.6, 54.1;
HRMS (ES+) calc. for $C_{10}H_8{}^{79}Br^{35}Cl_2NNaO_2$ $[M+Na]^+$ 345.9008, found 345.9017.

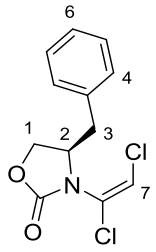
(*E*)-3-(1,2-Dichlorovinyl)oxazolidin-2-one, 69f



Following example procedure **1.2a**: Synthesised from oxazolidin-2-one (500 mg, 5.74 mmol, 1.0 equiv.) in DMF (7.7 mL) using trichloroethylene (0.57 mL, 6.32 mmol, 1.1 equiv.) and Cs_2CO_3 (2.81 g, 8.61 mmol, 1.5 equiv.). The reaction takes approximately 3 hours to reach completion. Column chromatography (25% EtOAc/40–60 petroleum ether) afforded the title compound (855 mg, 4.70 mmol, 82%) as a white powder;

R_f 0.10 (10% EtOAc/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3094, 1757, 1622, 1480, 1395, 1312, 1221, 1100, 1033, 895, 820, 756
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.34 (1H, s, *H*3), 4.54–4.43 (2H, m, *H*1), 3.88–3.78 (2H, m, *H*2);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.7, 127.0, 116.8, 62.8, 44.0;
HRMS (ES+) calc. for $C_5H_5{}^{35}Cl_2NNaO_2$ $[M+Na]^+$ 203.9590, found 203.9591.

(*S*,*E*)-4-Benzyl-3-(1,2-dichlorovinyl)oxazolidin-2-one, 69g



Following example procedure **1.2a**: Synthesised from (*S*)-4-benzyloxazolidin-2-one (500 mg, 2.82 mmol, 1.0 equiv.) in DMF (2.1 mL) using trichloroethylene (0.28 mL, 3.10 mmol, 1.1 equiv.) and Cs_2CO_3 (1.38 g, 4.23 mmol, 1.5 equiv.). The reaction takes approximately 2 hours to reach completion. Column chromatography (20% EtOAc/40–60 petroleum ether) afforded the title compound (709 mg, 2.61 mmol, 92%) as a pale yellow oil;

R_f 0.36 (25% EtOAc/40–60 petroleum ether);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ +1.43 (c 1, $CHCl_3$);

IR (thin film, ν_{max} / cm^{-1}) 3089, 2917, 1770, 1623, 1497, 1479, 1455, 1396, 1371, 1307, 1225, 1183, 1106, 1029, 900, 822, 756, 732, 703, 653;

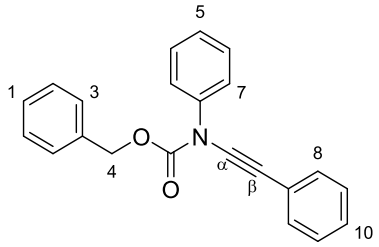
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37–7.25 (3H, m, *H*5, *H*6), 7.23–7.16 (2H, m, *H*4), 6.43 (1H, s, *H*7), 4.42 (1H, dddd, *J* = 9.5, 80, 7.3, 4.4 Hz, *H*1), 4.35 (1H, dd, *J* = 8.6, 8.0 Hz, *H*1), 4.18 (1H, dd, *J* = 8.6, 7.3 Hz, *H*1), 3.18 (1H, dd, *J* = 13.4, 4.4 Hz, *H*3), 2.79 (1H, dd, *J* = 13.4, 9.5 Hz, *H*3);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.3, 134.5, 129.0, 128.9, 127.5, 126.2, 118.2, 68.2, 56.7, 38.8;

HRMS (ES+) calc. for $C_{12}H_{12}{}^{35}Cl_2NO_2$ $[M+H]^+$ 272.0240, found 272.0241.

2.3b *Ynamides.*

Benzyl phenyl(phenylethynyl)carbamate, 71a



Synthesised according to example procedure **1.2f**;

m.p. 75–77 °C;

R_f 0.38 (10% Et_2O/40–60 petroleum ether);

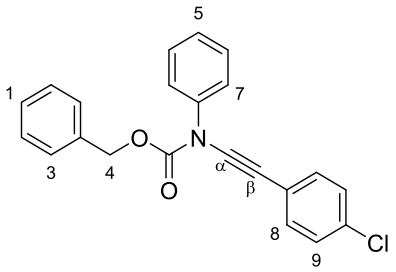
IR (thin film, ν_{max} / cm^{-1}) 3033, 2960, 2251, 1737, 1492, 1383, 1262, 1215, 1017, 947, 910, 753, 692;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62–7.55 (2H, m, *H*7), 7.53–7.35 (9H, m, *H*1, *H*2, *H*3, *H*6, *H*8), 7.35–7.27 (4H, m, *H*5, *H*9, *H*10), 5.36 (2H, s, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.1, 139.4, 135.4, 131.2, 129.0, 128.6, 128.3, 128.2, 127.9, 127.7, 127.0, 124.6, 122.9, 82.8 (Cα), 70.4 (Cβ), 68.9;

HRMS (ES+) calc. for $C_{22}H_{17}NNaO_2$ $[M+Na]^+$ 350.1152, found 350.1152.

Benzyl ((4-chlorophenyl)ethynyl)(phenyl)carbamate, 71b



Following example procedure **1.2f:** Synthesised from benzyl (*E*)-(1,2-dichlorovinyl)(phenyl) carbamate (500 mg, 1.55 mmol, 1.0 equiv.) in anhydrous TBME (13 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous toluene (1.0 mL), 4-chlorophenylmagnesium bromide (1.63 mL of a 1.0 M solution in Et_2O, 1.63 mmol, 1.05 equiv.), zinc(II) chloride (0.82 mL of a 1.0 M solution in Et_2O, 0.823 mmol, 0.53 equiv.), and the reaction conducted using CuCN·2LiCl (20 µL of a 1.0 M solution in THF, 20 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (5% Et_2O/40–60 petroleum ether) afforded a pale yellow solid which was recrystallised from hexane/dibutyl ether (10:1) to give the title compound (410 mg, 1.13 mmol, 73%) as colourless needles;

m.p. 122–123 °C;

R_f 0.22 (5% Et_2O/40–60 petroleum ether);

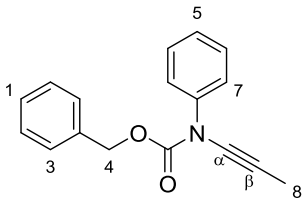
IR (thin film, ν_{max} / cm^{-1}) 3035, 2251, 1734, 1594, 1490, 1456, 1381, 1361, 1271, 1212, 1126, 1089, 1014, 826, 752, 693, 670;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.55–7.48 (2H, m, *H*7), 7.45–7.32 (7H, m, *H*1, *H*2, *H*3, *H*6), 7.32–7.27 (3H, m, *H*5, *H*8), 7.27–7.23 (2H, m, *H*9), 5.32 (2H, s, *H*4);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 154.0, 139.2, 135.3, 133.6, 132.3, 129.0, 128.57, 128.55, 128.4, 127.9, 127.2, 124.6, 121.5, 83.7 (Cα), 69.4 (Cβ), 69.0;

HRMS We were unable to obtain an accurate mass (ES+ or CI+) due to decomposition upon ionisation.

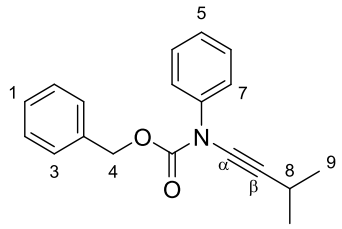
Benzyl phenyl(prop-1-yn-1-yl)carbamate, 71c



Following example procedure **1.2f**: Synthesised from benzyl (*E*)-(1,2-dichlorovinyl)(phenyl) carbamate (500 mg, 1.55 mmol, 1.0 equiv.) in anhydrous TBME (13 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The dimethylzinc solution was prepared using anhydrous toluene (1.0 mL), methylmagnesium iodide (1.09 mL of a 3.0 M solution in Et_2O, diluted to 1.0 M with anhydrous Et_2O, 3.26 mmol, 2.1 equiv.), zinc(II) chloride (1.63 mL of a 1.0 M solution in Et_2O, 1.63 mmol, 1.05 equiv.), and the reaction conducted using CuCN·2LiCl (20 µL of a 1.0 M solution in THF, 20 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (5% Et_2O/40–60 petroleum ether) afforded the title compound (234 mg, 0.881 mmol, 57%) as a pale yellow oil;

R_f 0.22 (5% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3034, 2918, 2271, 1728, 1595, 1492, 1455, 1387, 1340, 1270, 1199, 1044, 1023, 750, 691, 659;
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.50–7.45 (2H, m, *H*7), 7.43–7.31 (7H, m, *H*1, *H*2, *H*3, *H*6), 7.26 (1H, tt, *J* = 7.3, 1.3 Hz, *H*5), 5.29 (2H, s, *H*4), 1.96 (3H, s, *H*8);
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 154.8, 139.9, 135.6, 128.8, 128.5, 128.2, 127.9, 126.7, 124.6, 72.7 (Cα), 68.6, 65.2 (Cβ), 3.24;
HRMS (ES+) calc. for $C_{17}H_{15}NNaO_2$ $[M+Na]^+$ 288.0995, found 288.0996.

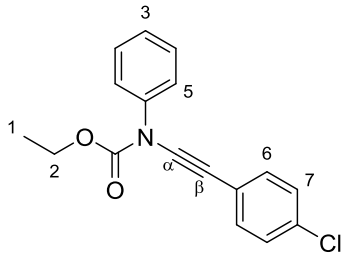
Benzyl (3-methylbut-1-yn-1-yl)(phenyl)carbamate, 71d



Following example procedure **1.2f**: Synthesised from benzyl (*E*)-(1,2-dichlorovinyl)(phenyl) carbamate (500 mg, 1.55 mmol, 1.0 equiv.) in anhydrous TBME (13 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The di-*i*-propylzinc solution was prepared using anhydrous toluene (1.0 mL), *i*-propylmagnesium chloride (1.63 mL of a 2.0 M solution in Et_2O, diluted to 1.0 M with anhydrous Et_2O, 3.26 mmol, 2.1 equiv.), zinc(II) chloride (1.63 mL of a 1.0 M solution in Et_2O, 1.63 mmol, 1.05 equiv.), and the reaction conducted using CuCN·2LiCl (20 µL of a 1.0 M solution in THF, 20 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (5% Et_2O/40–60 petroleum ether) afforded the title compound (336.5 mg, 1.15 mmol, 74%) as a pale yellow oil;

R_f 0.33 (5% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2968, 2262, 1731, 1595, 1493, 1456, 1382, 1264, 1202, 1155, 1095, 1043, 1021, 755, 736, 691, 659;
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.54–7.49 (2H, m, *H*7), 7.45–7.31 (7H, m, *H*1, *H*2, *H*3, *H*6), 7.25 (1H, tt, *J* = 7.3, 1.3 Hz, *H*5), 5.30 (2H, s, *H*4), 2.73 (1H, spt, *J* = 6.9 Hz, *H*8), 1.22 (6H, d, *J* = 6.9 Hz, *H*9);
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 154.6, 139.9, 135.6, 128.7, 128.4, 128.1, 127.7, 126.5, 124.2, 75.2 (Cβ), 73.2 (Cα), 68.5, 23.1, 20.4;
HRMS (ES+) calc. for $C_{19}H_{19}NNaO_2$ $[M+Na]^+$ 316.1308, found 316.1309.

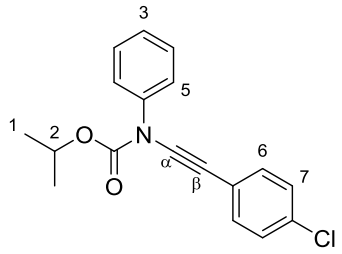
Ethyl ((4-chlorophenyl)ethynyl)(phenyl)carbamate, 71e



Following example procedure **1.2f:** Synthesised from ethyl (*E*)-(1,2-dichlorovinyl)(phenyl) carbamate (500 mg, 1.92 mmol, 1.0 equiv.) in anhydrous TBME (19 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous TBME (2.0 mL), 4-chlorophenylmagnesium bromide (2.11 mL of a 1.0 M solution in Et_2O, 2.11 mmol, 1.1 equiv.), zinc(II) chloride (1.06 mL of a 1.0 M solution in Et_2O, 2.11 mmol, 0.55 equiv.), and the reaction conducted using CuCN·2LiCl (24 μL of a 1.0 M solution in THF, 24 μmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (0 → 3% Et_2O/pentane) afforded the title compound (441 mg, 1.47 mmol, 77%) as a colourless oil that solidifies on standing in the freezer at -20 °C. Crystals suitable for X-ray diffraction were grown by cooling a concentrated solution of the title compound in pentane to -20 °C for 3 months;

R_f 0.26 (5% Et_2O/40–60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2981, 2253, 1733, 1594, 1490, 1396, 1370, 1268, 1240, 1214, 1173, 1125, 1088, 1049, 1025, 1013, 825, 757, 747, 692, 670;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.58–7.52 (2H, m, *H*5), 7.46–7.39 (2H, m, *H*4), 7.39–7.33 (2H, m, *H*6), 7.31–7.26 (2H, m, *H*7), 7.28 (1H, tt, *J* = 7.4, 1.1 Hz, *H*3), 4.36 (2H, q, *J* = 7.2 Hz, *H*2), 1.39 (3H, t, *J* = 7.2 Hz, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.0, 139.3, 133.5, 132.3, 128.9, 128.5, 126.9, 124.6, 121.5, 83.9 (Cα), 69.1 (Cβ), 63.7, 14.3;
HRMS (ES+) calc. for $C_{17}H_{14}{}^{35}ClNNaO_2$ $[M+Na]^+$ 322.0605, found 322.0607.

_i_-Propyl ((4-chlorophenyl)ethynyl)(phenyl)carbamate, 71f



Following example procedure **1.2f:** Synthesised from *i*-propyl (*E*)-(1,2-dichlorovinyl)(phenyl) carbamate (150 mg, 0.547 mmol, 1.0 equiv.) in anhydrous TBME (5.5 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous TBME (1.0 mL), 4-chlorophenylmagnesium bromide (0.60 mL of a 1.0 M solution in Et_2O, 0.602 mmol, 1.1 equiv.), zinc(II) chloride (0.30 mL of a 1.0 M solution in Et_2O, 0.300 mmol, 0.55 equiv.), and the reaction conducted using CuCN·2LiCl (7 µL of a 1.0 M solution in THF, 7 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (0 → 3% Et_2O/pentane) afforded the title compound (135 mg, 0.430 mmol, 79%) as a white powder. Crystals suitable for X-ray diffraction were grown by cooling a concentrated solution of the title compound in pentane/dibutyl ether (4:1) to −20 °C overnight to give colourless crystals.

m.p. 165 °C;

R_f 0.35 (5% Et_2O/40–60 petroleum ether);

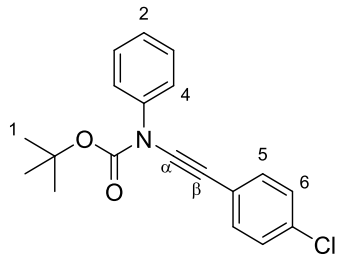
IR (thin film, ν_{max} / cm^{-1}) 2981, 2252, 1731, 1490, 1364, 1268, 1219, 1181, 1126, 1103, 1089, 1012, 826, 758, 749, 692;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57–7.51 (2H, m, *H*5), 7.45–7.38 (2H, m, *H*4), 7.37–7.32 (2H, m, *H*6), 7.30–7.25 (2H, m, *H*7), 7.29 (1H, tt, *J* = 7.4, 1.2 Hz, *H*3), 5.10 (1H, spt, *J* = 6.3 Hz, *H*2), 1.38 (6H, d, *J* = 6.3 Hz, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.6, 139.4, 133.4, 132.2, 128.9, 128.5, 126.9, 124.6, 121.7, 84.1 (Cα), 71.9, 69.2 (Cβ), 21.8;

HRMS (ES+) calc. for $C_{18}H_{16}{}^{35}ClNNaO_2$ $[M+Na]^+$ 336.0762, found 336.0763.

_t_-Butyl ((4-chlorophenyl)ethynyl)(phenyl)carbamate, 71g



Following example procedure **1.2f:** Synthesised from *i*-propyl (*E*)-(1,2-dichlorovinyl)(phenyl) carbamate (150 mg, 0.521 mmol, 1.0 equiv.) in anhydrous TBME (5.2 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous TBME (1.0 mL), 4-chlorophenylmagnesium bromide (0.57 mL of a 1.0 M solution in Et_2O, 0.573 mmol, 1.1 equiv.), zinc(II) chloride (0.29 mL of a 1.0 M solution in Et_2O, 0.287 mmol, 0.55 equiv.), and the reaction conducted using CuCN·2LiCl (7 µL of a 1.0 M solution in THF, 7 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (0 → 2% Et_2O/pentane) afforded the title compound (125 mg, 0.381 mmol, 73%) as a colourless oil that solidified on standing. This compound can be recrystallised by cooling a concentrated solution of the title compound in pentane to ~2 °C in a fridge for 1 week to give colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 71 °C;

R_f 0.36 (2.5% Et_2O/40–60 petroleum ether);

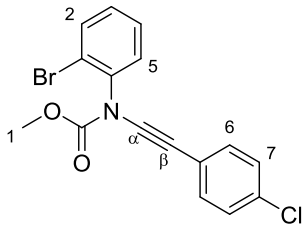
IR (thin film, ν_{max} / cm^{-1}) 2980, 2252, 1731, 1594, 1491, 1394, 1367, 1279, 1252, 1149, 1126, 1088, 1012, 859, 825, 758, 742, 692, 677;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55–7.50 (2H, m, *H*4), 7.43–7.36 (2H, m, *H*3), 7.34–7.29 (2H, m, *H*5), 7.28–7.24 (2H, m, *H*6), 7.26 (1H, tt, *J* = 7.4, 1.2 Hz, *H*2), 1.57 (9H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.7, 139.5, 133.2, 132.0, 128.8, 128.5, 126.7, 124.7, 121.9, 84.6 (Cα), 83.5, 69.1 (Cβ), 27.9;

HRMS (ES+) calc. for $C_{19}H_{18}{}^{35}ClNNaO_2$ $[M+Na]^+$ 350.0918, found 350.0919.

Methyl (2-bromophenyl)((4-chlorophenyl)ethynyl)carbamate, 71h



Following example procedure **1.2f**: Synthesised from methyl (*E*)-(1,2-dichlorovinyl)(2-bromophenyl) carbamate (500 mg, 1.54 mmol, 1.0 equiv.) in anhydrous TBME (15 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous TBME (2.0 mL), 4-chlorophenylmagnesium bromide (3.23 mL of a 1.0 M solution in Et_2O, 3.23 mmol, 2.1 equiv.), zinc(II) chloride (1.62 mL of a 1.0 M solution in Et_2O, 1.62 mmol, 1.05 equiv.), and the reaction conducted using CuCN·2LiCl (19 µL of a 1.0 M solution in THF, 19 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (10% Et_2O/pentane) afforded a pale yellow oil, which was crystallised from heptane (~2 mL) *plus* a couple of drops of *i*-PrOH to give the title compound (421 mg, 1.15 mmol, 75%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 103–104 °C;

R_f 0.28 (10% Et_2O/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2955, 2253, 1740, 1493, 1474, 1438, 1366, 1293, 1258, 1229, 1090, 1069, 1029, 1012, 828, 752;

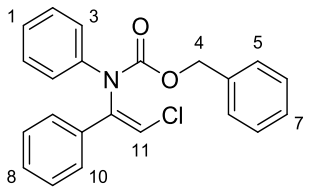
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (1H, dd, *J* = 7.8, 1.5 Hz, *H*2), 7.48 (1H, dd, *J* = 7.8, 1.6 Hz, *H*5), 7.39 (1H, td, *J* = 7.8, 1.6 Hz, *H*4), 7.36–7.30 (2H, m, *H*6), 7.26 (1H, td, J = 7.8, 1.5 Hz, *H*3), 7.26–7.21 (2H, m, *H*7), 3.88 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.3, 138.1, 133.8, 132.7, 130.2, 129.2, 128.6, 128.5 (2C), 122.4, 121.3, 83.0 (Cα), 68.8 (Cβ), 54.7;

HRMS (ES+) calc. for $C_{16}H_{11}{}^{79}B^{35}ClNNaO_2$ $[M+Na]^+$ 385.9554, found 385.9554.

2.3c *Miscellaneous*.

Benzyl (*Z*)-(2-chloro-1-phenylvinyl)(phenyl)carbamate, (*Z*)-72



Following example procedure **1.2e**: Synthesised from benzyl (*E*)-(1,2-dichlorovinyl)(phenyl) carbamate (500 mg, 1.55 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.), phenylmagnesium bromide (1.60 mL of a 1.0 M solution in THF, 1.60 mmol, 1.03 equiv.), CuCN·2LiCl (19 µL of a 1.0 M solution in THF, 19 µmol, 1.25 mol%) and $P(OMe)_3$ (5 µL, 40 µmol, 2.5 mol%) at 21 °C. The reaction was stirred for 2 h at 21 °C and was quenched with aqueous saturated NH_4Cl (15 mL), followed by the addition of EtOAc (10 mL), and the layers separated. The aqueous was further extracted with EtOAc (2×10 mL), the organic extracts combined, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (5 → 10% Et_2O/40–60 petroleum ether) afforded ynamide **71a** (125 mg, 0.382 mmol, 25%), an inseparable mixture of (*Z*)-**72** and (*E*)-**72** (198 mg, 0.544 mmol, 35%), (*E*)-ester **73** (48.8 mg, 0.134 mmol, 9%) and oxazolone **74** (~5 mg, ~20 µmol, 1%).

- See before for ynamide **71a** data;

- Data for carbamate (*Z*)-**72**:

R_f 0.21 (10% Et_2O/40–60 petroleum ether);

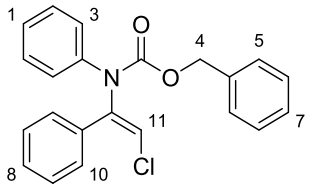
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37–7.47 (5H, m, Ph*H*), 7.36–7.24 (8H, m, PhH), 7.24–7.18 (2H, br. m, Ph*H*), 7.13–7.08 (1H, m, Ph*H*), 6.64 (1H, s, *H*11), 5.22(2H, br. s, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.0, 140.0, 135.8, 135.4, 128.9, 128.8, 128.7 (2C), 128.3, 127.9 (2C), 125.9, 125.6, 124.3, 117.1, 68.0;

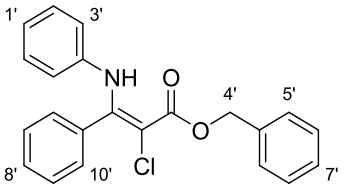
HRMS (ES+) calc. for $C_{22}H_{19}{}^{35}ClNO_2$ $[M+H]^+$ 364.1099, found 364.1100.

- See next for carbamate (*E*)-**72**, (*E*)-ester **73** and oxazolone **74** data.

Benzyl (*E*)-(2-chloro-1-phenylvinyl)(phenyl)carbamate, (*E*)-72 & Benzyl (*E*)-2-chloro-3-phenyl-3-(phenylamino)acrylate, 73



(*E*)-**72**



73

Following example procedure **1.2e**: Synthesised from benzyl (*E*)-(1,2-dichlorovinyl)(phenyl) carbamate (250 mg, 0.776 mmol, 1.0 equiv.) in anhydrous TBME (2.0 mL) using LiHMDS (freshly prepared according to example procedure **1.2e**, 1.2 equiv.) and phenylmagnesium bromide (1.75 mL of a 1.0 M solution in THF, 1.75 mmol, 1.2 equiv.) at 0 °C (***Note**:* no CuCN was added). The reaction was stirred for 2 h at 21 °C and was quenched with aqueous saturated NH_4Cl (15 mL), followed by the addition of EtOAc (10 mL), and the layers separated. The aqueous was further extracted with EtOAc (2×10 mL), the organic extracts combined, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (5 → 10% Et_2O/40–60 petroleum ether) afforded the title compounds as yellow oils. Carbamate (*E*)-**72** was crystallised from benzene/hexane (1:5) to afford (88.2 mg, 0.242 mmol, 31%) as colourless crystals, and ester **73** was crystallised from hexane to give (63.0 mg, 0.173 mmol, 22%) as colourless crystals. Both sets of crystals were suitable for X-ray diffraction;

- Data for carbamate (*E*)-**72**:

m.p. 96–97 °C;

R_f 0.21 (10% Et_2O/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3067, 1714, 1597, 1493, 1382, 1295, 1250, 1202, 1139, 1045, 1020, 762, 733, 696;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66–7.53 (2H, m, *H*10′), 7.43–7.22 (10H, m, *H2′*, *H5′*, *H6′*, *H7′*, *H8′*, *H9′*), 7.22–7.09 (3H, m, *H1′*, *H3′*), 6.42 (1H, s, *H*11′), 5.15 (2H, s, *H*4′);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.5, 141.6, 141.1, 135.7, 134.1, 128.9, 128.8, 128.6, 128.4, 128.2, 128.0, 127.9, 126.0, 125.2, 119.1, 67.9;

HRMS (ES+) calc. for $C_{22}H_{19}{}^{35}ClNO_2$ $[M+H]^+$ 364.1099, found 364.1100.

- Data for ester **73**:

m.p. 78–80 °C;

R_f 0.46 (10% Et_2O/40–60 petroleum ether);

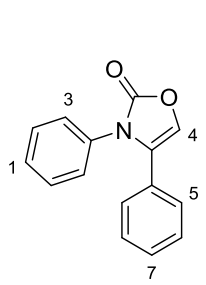
IR (thin film, ν_{max} / cm^{-1}) 3232, 3064, 3034, 1650, 1594, 1567, 1499, 1421, 1254, 1225, 1132, 1049, 781, 765, 754, 696;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.8 (1H, s, N*H*), 7.52–7.44 (2H, m, *H*10′), 7.44–7.38 (2H, m, *H*9′), 7.38–7.29 (6H, m, *H*5′, *H*6′, *H*7′, *H*8′), 7.09–7.00 (2H, m, *H*2′), 6.94–6.88 (1H, m, *H*1′), 6.64–6.58 (2H, m, *H*3′), 5.34 (2H, s, *H*4′);

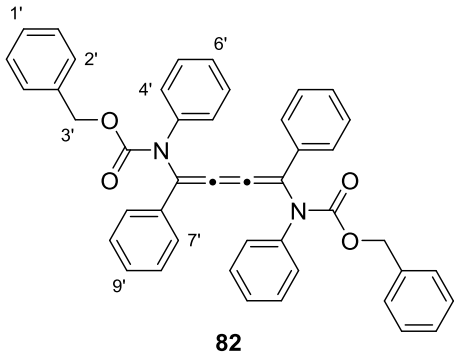
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 167.5, 157.4, 139.6, 136.2, 133.6, 129.5, 129.3, 128.6, 128.5, 128.3, 128.0, 127.8, 123.7, 122.7, 93.5, 66.5;

HRMS (ES+) calc. for $C_{22}H_{19}{}^{35}ClNO_2$ $[M+H]^+$ 364.1099, found 364.1100.

3,4-Diphenyloxazol-2(3*H*)-one, 74 & Dibenzyl (1,4-diphenylbuta-1,2,3-triene-1,4-diyl)(*E*/*Z*)-bis(phenylcarbamate), 82



74



82

Following example procedure **1.2f:** Synthesised from benzyl (*E*)-(1,2-dichlorovinyl)(phenyl) carbamate (500 mg, 1.55 mmol, 1.0 equiv.) in anhydrous toluene (4 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv. using anhydrous toluene (1.5 mL) and anhydrous Et_3N (2.60 mL, 15.5 mmol, 10 equiv.)). The diarylzinc solution was prepared using anhydrous toluene (1.0 mL), phenylmagnesium bromide (0.57 mL of a 2.8 M solution in Et_2O, 1.63 mmol, 1.05 equiv.), zinc(II) chloride (0.43 mL of a 1.9 M solution in 2-MeTHF, 0.823 mmol, 0.53 equiv.), and the reaction conducted using CuCN·2LiCl (20 μL of a 1.0 M solution in THF, 20 μmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (5% → 50% Et_2O/40–60 petroleum ether) afforded the desired ynamide **71a** (254 mg, 0.775 mmol, 50%) as a pale yellow powder, and a mixed fraction containing both title compounds (71.6 mg) as a brown foam. Crystallisation of the foam (MeOH/benzene) afforded the cumulene **82** (~5 mg, 8 μmol, 1%) as lemon yellow microcrystals, and the oxazolone **74** remained in solution. The microcrystals were too small for X-ray diffraction studies. The remaining solution was concentrated and recolumned (10% EtOAc/pentane) to afford the oxazolone as an off-white powder, which was recrystallised from heptane *plus* 2 drops each of benzene and ethanol to give **74** (43.1 mg, 0.182 mmol, 12%) as colourless plates. These plates were suitable for X-ray diffraction.

- Data for oxazolone **74**:

m.p. 129–130 °C;

R_f 0.08 (10% Et_2O/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3063, 2919, 1757, 1597, 1499, 1448, 1381, 1308, 1261, 1176, 1081, 975, 761, 729, 694, 656;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37–7.23 (6H, m, *H*1, *H*2, *H*6, *H*7), 7.21–7.16 (2H, m, *H*3), 7.09–7.04 (2H, m, *H*5), 7.01 (1H, s, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.9, 133.9, 129.5, 129.1, 129.0, 128.7, 127.9, 127.5, 126.6, 126.4, 124.8;

HRMS (ES+) calc. for $C_{15}H_{12}NO_2$ $[M+H]^+$ 238.0863, found 238.0864.

- Data for cumulene **82**:

R_f 0.08 (10% Et_2O/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3059, 2953, 1765, 1718, 1595, 1490, 1446, 1382, 1318, 1273, 1225, 1082, 1045, 1021, 761, 693;

^{1}H NMR (400 MHz, $CDCl_3$)* δ_H 7.41–7.33 (5H, m, Ph*H′*), 7.25–7.11 (6H, m, Ph*H′*), 7.10–7.05 (2H, m, *H*7′), 7.04–6.98 (2H, m, *H*4′), 5.10 (2H, s, *H*3′);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 154.9 (m), 154.4, 149.2 (m), 148.4, 141.7, 141.5 (m), 136.3 (m), 136.2, 135.7 (m), 135.5, 133.9, 129.2, 129.0, 128.8, 128.73, 128.71, 128.6, 128.5, 128.3, 127.94, 127.90, 127.8, 127.5, 126.6, 126.5, 126.4, 126.0, 125.9, 125.7, 124.8, 121.7, 68.1, 67.9 (m);

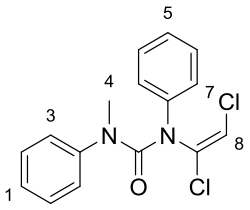
HRMS (ES+) calc. for $C_{44}H_{34}N_2NaO_4$ $[M+Na]^+$ 677.2411, found 677.2409.

****Note*:** The data includes peaks for both (*E*)- and (*Z*)- isomers, which for the most part were indistinguishable. The label (m) indicates peaks that clearly belong to the minor isomer. This compound was found to undergo slow isomerisation whilst in $CDCl_3$ solution.

2.4 Urea Scope.

2.4a *Dichloroenamides*.

(*E*)-1-(1,2-Dichlorovinyl)-3-methyl-1,3-diphenylurea, 83a



Following example procedure **1.2b**: Synthesised from 1-methyl-1,3-diphenylurea (1.00 g, 4.42 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (375 mg, 1.11 mmol, 0.25 equiv.) in toluene (44 mL) using 50% w/v aqueous solution of KOH (20 mL) and trichloroethylene (1.19 mL, 13.3 mmol, 3.0 equiv.) added dropwise over 2 minutes at 60 °C. The reaction takes approximately 2 hours to reach completion. Recrystallisation from heptane (a hot filtration was required to remove tarry residues) afforded the title compound (1.24 g, 3.85 mmol, 87%) as colourless crystals. These crystals were suitable for X-ray diffraction. ****Note***: This compound is found to be unstable upon prolonged storage and should be used within a couple of days.

m.p. 113–114 °C;

R_f 0.25 (10% EtOAc/pentane);

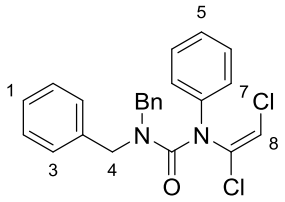
IR (thin film, ν_{max} / cm^{-1}) 3090, 1675, 1595, 1493, 1420, 1354, 1294, 1274, 1174, 1126, 906, 831, 798, 754, 731, 692, 664;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.24–7.16 (4H, m, *H*2, *H*6), 7.15–7.06 (4H, m, *H*3, *H*7), 7.05–6.99 (2H, m, *H*1, *H*5), 6.01 (1H, s, *H*8), 3.34 (3H, s, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.4, 143.6, 140.1, 133.0, 129.0, 128.8, 126.3, 126.19, 126.17, 125.6, 113.4, 39.7;

HRMS (ES+) calc. for $C_{16}H_{15}{}^{35}Cl_2N_2O$ $[M+H]^+$ 321.0556, found 321.0557.

(*E*)-1,1-Dibenzyl-3-(1,2-dichlorovinyl)-3-phenylurea, 83b



Following example procedure **1.2b**: Synthesised from *N*,*N*-dibenzyl-*N'*-phenylurea (1.00 g, 3.16 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (268 mg, 0.790 mmol, 0.25 equiv.) in toluene (30 mL) using 50% w/v aqueous solution of KOH (15 mL) and trichloroethylene (0.85 mL, 9.48 mmol, 3.0 equiv.) added dropwise over 2 minutes at 60 °C. The reaction takes approximately 2 hours to reach completion. Recrystallisation from heptane (a hot filtration was required to remove tarry residues) afforded the title compound (1.23 g, 2.98 mmol, 94%) as pale yellow needles. These crystals were suitable for X-ray diffraction. ***Note***: This compound is found to be unstable upon prolonged storage and should be used within a couple of days.

m.p. 104–105 °C;

R_f 0.65(20% EtOAc/40–60 petroleum ether);

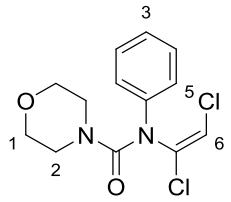
IR (thin film, ν_{max} / cm^{-1}) 2909, 1669, 1595, 1494, 1455, 1404, 1227, 1142, 1079, 908, 814, 731, 694;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36–7.26 (8H, m, *H*1, *H*2, *H*6), 7.21 (1H, tt, *J* = 7.3, 1.2 Hz, *H*5), 7.20–7.15 (4H, m, *H*3), 7.13–7.07 (2H, m, *H*7), 6.29 (1H, s, *H*8), 4.35 (4H, s, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 157.9, 140.7, 136.1, 133.6, 129.5, 128.5, 128.4, 127.6, 126.2, 124.1, 113.9, 50.4;

HRMS (ES+) calc. for $C_{23}H_{20}{}^{35}Cl_2N_2NaO$ $[M+Na]^+$ 433.0845, found 433.0842.

(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-phenylmorpholine-4-carboxamide, 83c



Following example procedure **1.2b**: Synthesised from *N*-phenylmorpholine-4-carboxamide (1.00 g, 4.85 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (412 mg, 1.21 mmol, 0.25 equiv.) in toluene (50 mL) using 50% w/v aqueous solution of KOH (25 mL) and trichloroethylene (1.31 mL, 14.6 mmol, 3.0 equiv.) added dropwise over 2 minutes at 60 °C. The reaction takes approximately 1.5 hours to reach completion. Recrystallisation from heptane (a hot filtration was required to remove tarry residues) afforded the title compound (1.26 g, 4.18 mmol, 86%) as pale yellow crystals. These crystals were suitable for X-ray diffraction. ****Note***: This compound is found to be unstable upon prolonged storage and should be used within a couple of days;

m.p. 116–118 °C;

R_f 0.44 (50% EtOAc/pentane);

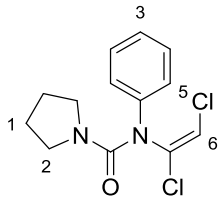
IR (thin film, ν_{max} / cm^{-1}) 2967, 2922, 2858, 1677, 1594, 1492, 1452, 1421, 1338, 1300, 1270, 1236, 1114, 754, 696;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42–7.34 (2H, m, *H*4), 7.25–7.19 (1H, m, *H*3), 7.14–7.07 (2H, m, *H*5), 6.28 (1H, s, *H*6), 3.64–3.55 (4H, m, *H*1), 3.43–3.35 (4H, m, *H*2);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.9, 140.2, 133.0, 129.6, 126.2, 123.5, 113.6, 66.4, 46.0;

HRMS (ES+) calc. for $C_{13}H_{14}{}^{35}Cl_2N_2NaO_2$ $[M+Na]^+$ 323.0325, found 323.0325.

(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-phenylpyrrolidine-1-carboxamide, 83d



Following example procedure **1.2b**: Synthesised from *N*-phenylpyrrolidine-1-carboxamide (1.00 g, 5.26 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (446 mg, 1.32 mmol, 0.25 equiv.) in toluene (50 mL) using 50% w/v aqueous solution of KOH (25 mL) and trichloroethylene (1.42 mL, 15.8 mmol, 3.0 equiv.) added dropwise over 2 minutes at 60 °C. The reaction takes approximately 2 hours to reach completion. Recrystallisation from heptane (a hot filtration was required to remove tarry residues) afforded the title compound (1.31 g, 4.72 mmol, 87%) as pale yellow needles. These crystals were suitable for X-ray diffraction. ***Note***: This compound is found to be unstable upon prolonged storage and should be used within a couple of days;

m.p. 74–76 °C;

R_f 0.44 (30% EtOAc/40–60 petroleum ether);

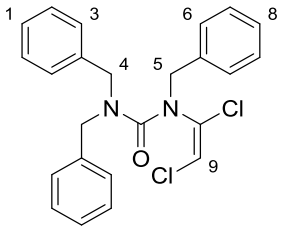
IR (thin film, ν_{max} / cm^{-1}) 3066, 2974, 2880, 1672, 1594, 1491, 1395, 1342, 1261, 1228, 1192, 755, 698;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40–7.31 (2H, m, *H*4), 7.24–7.18 (1H, m, *H*3), 7.17–7.11 (2H, m, *H*5), 6.26 (1H, s, *H*6), 3.56–3.06 (4H, br. m, *H*2), 1.90–1.75 (4H, m, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.8, 140.0, 132.8, 129.3, 125.9, 124.4, 113.3, 47.7, 25.3;

HRMS (ES+) calc. for $C_{13}H_{15}{}^{35}Cl_2N_2O$ $[M+H]^+$ 285.0556, found 285.0557.

(*E*)-1,1,3-Tribenzyl-3-(1,2-dichlorovinyl)urea, 83e



Following example procedure **1.2b**: Synthesised from 1,1,3-tribenzylurea (500 mg, 1.51 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (128 mg, 0.378 mmol, 0.25 equiv.) in toluene (15 mL) using 50% w/v aqueous solution of KOH (7.5 mL) and trichloroethylene (0.41 mL, 4.54 mmol, 3.0 equiv.) added dropwise over 2 minutes at 60 °C. The reaction was halted after 48 hours. Column chromatography (4% Et_2O/pentane) gave a yellow oil which was crystallised from heptane (~1 mL) *plus* 2 drops of benzene. This afforded the title compound (126 mg, 0.296 mmol, 20%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 73–75 °C;

R_f 0.64 (10% EtOAc/pentane);

IR (thin film, ν_{max} / cm^{-1}) 3088, 3030, 2927, 1667, 1495, 1454, 1407, 1363, 1313, 1275, 1223, 1134, 1076, 1029, 948, 815, 736, 698, 670;

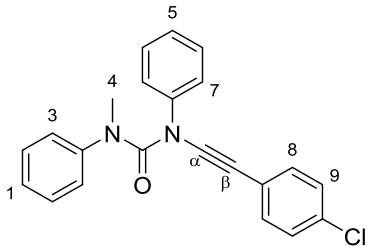
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55–7.47 (2H, m, *H*6), 7.36–7.28 (3H, m, *H*7, *H*8), 7.28–7.18 (6H, m, *H*1, *H*2), 7.13–7.00 (4H, m, *H*3), 5.86 (1H, s, *H*9), 4.65 (2H, s, *H*5), 4.40 (4H, s, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.3, 136.3, 136.2, 134.1, 129.4, 128.4, 128.2, 128.0, 127.7, 127.3, 112.4, 52.7, 50.1;

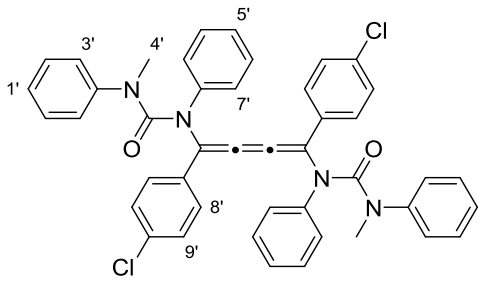
HRMS (ES+) calc. for $C_{24}H_{23}{}^{35}Cl_2N_2O$ $[M+H]^+$ 425.1182, found 425.1181.

2.4b *Ynamides.*

1-((4-Chlorophenyl)ethynyl)-3-methyl-1,3-diphenylurea, 85a & (*E*)-1,1′-(1,4-Bis(4-chloro phenyl) buta-1,2,3-triene-1,4-diyl)bis(3-methyl-1,3-diphenylurea), (*E*)-88



85a



(*E*)-**88**

Following example procedure **1.2f:** Synthesised from (*E*)-1-(1,2-dichlorovinyl)-3-methyl-1,3-diphenylurea (500 mg, 1.56 mmol, 1.0 equiv.) in anhydrous TBME (16 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous toluene (5 mL), 4-chlorophenylmagnesium bromide (4.67 mL of a 1.0 M solution in Et_2O, 4.67 mmol, 3.0 equiv.), zinc(II) chloride (1.23 mL of a 1.9 M solution in 2-MeTHF, 2.33 mmol, 1.5 equiv.) and tmeda (2.33 mL, 15.6 mmol, 10.0 equiv.), and the reaction conducted using CuCN·2LiCl (20 µL of a 1.0 M solution in THF, 20 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (0 → 40% EtOAc/pentane) afforded yne-urea **85a** as a pale yellow solid and the cumulene (*E*)-**88** as an intense yellow solid. Recrystallisation of the yne-urea from heptane/Et_2O (~4:1) afforded 395 mg (1.09 mmol, 70%) as colourless needles. Recrystallisation of the cumulene from heptane/Et_2O (~4:1) afforded 31 mg (42 µmol, 5%) as golden yellow crystals. These crystals were suitable for X ray diffraction;

- Data for yne-urea **85a**:

m.p. 96–97 °C;

R_f 0.35 (10% EtOAc/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3065, 2243, 1686, 1595, 1492, 1420, 1351, 1274, 1239, 1141, 1115, 1090, 1014, 908, 827, 741, 693, 659;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40–7.27 (6H, m, Ph*H*), 7.24–7.14 (6H, m, Ph*H*(×4), *H*8), 7.02–6.96 (2H, m, *H*9), 3.43 (3H, m, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.8, 144.2, 140.9, 133.2, 132.4, 129.3, 128.9, 128.3, 126.3, 125.7, 125.4, 122.8, 121.6, 84.8 (Cα), 70.5 (Cβ), 39.9;

HRMS (ES+) calc. for $C_{22}H_{18}{}^{35}ClN_2O$ $[M+H]^+$ 361.1102, found 361.1103.

- Data for cumulene (*E*)-**88**:

m.p. >150 °C (dec.);

R_f 0.07 (10% EtOAc/40–60 petroleum ether);

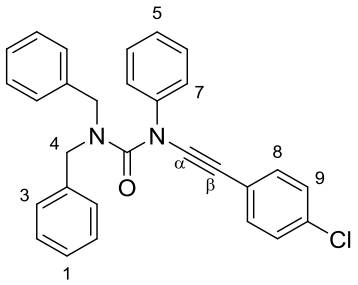
IR (thin film, ν_{max} / cm^{-1}) 3063, 2938, 1669, 1595, 1494, 1486, 1455, 1419, 1352, 1273, 1159, 1108, 1090, 1010, 830, 750, 731, 695;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33–7.26 (2H, m, *H*6′), 7.22–7.15 (1H, m, *H*5′), 7.08–7.04 (2H, m, *H*8′), 7.04–7.96 (5H, m, *H*1′, *H*2′, *H*3′), 6.83–6.78 (2H, m, *H*7′), 6.69–6.63 (2H, m, *H*9′), 3.14 (3H, m, *H*4′);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.3, 145.3, 143.5, 143.4, 134.6, 133.8, 129.1, 128.8, 128.3, 126.9, 126.0, 125.8, 125.3, 125.1, 121.4, 39.1;

HRMS (ES+) calc. for $C_{44}H_{35}{}^{35}Cl_2N_4O_2$ $[M+H]^+$ 721.2132, found 721.2132.

1,1-Dibenzyl-3-((4-chlorophenyl)ethynyl)-3-phenylurea, 85b

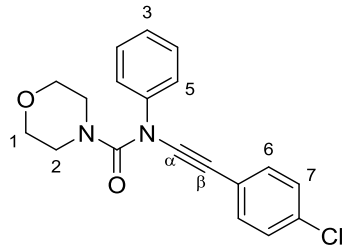


Following example procedure **1.2f:** Synthesised from (*E*)-1,1-dibenzyl-3-(1,2-dichlorovinyl)-3-phenylurea (500 mg, 1.22 mmol, 1.0 equiv.) in anhydrous TBME (12 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous toluene (4 mL), 4-chlorophenylmagnesium bromide (3.65 mL of a 1.0 M solution in Et_2O, 3.65 mmol, 3.0 equiv.), zinc(II) chloride (0.96 mL of a 1.9 M solution in 2-MeTHF, 1.82 mmol, 1.5 equiv.) and anhydrous tmeda (1.82 mL, 12.2 mmol, 10.0 equiv.), and the reaction conducted using CuCN·2LiCl (15 µL of a 1.0 M solution in THF, 15 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (10% CH_2Cl_2/2% EtOAc/pentane → 10% CH_2Cl_2/4% EtOAc/pentane) afforded the title compound (397 mg, 0.880 mmol, 72%) as a thick, pale yellow oil.

Crystallisation was accomplished using the following procedure: This material was dissolved in ethanol (~2 mL) with a couple of drops of benzene, and the solution was flash frozen at −78 °C. After allowing the frozen mixture to warm gradually to room temperature (~21 °C), this was repeated twice more to initiate seed formation. Once a seed had grown, the solution was left at room temperature for 1 week to afford 444 mg (0.839 mmol, 69%) of the title compound as colourless crystals. These crystals were suitable for X-ray diffraction. ***Note***: An equimolar amount of benzene co-crystallised with the compound;

m.p. 60–63 °C;
R_f 0.48 (10% EtOAc/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3031, 2240, 1687, 1596, 1492, 1454, 1407, 1359, 1234, 1119, 1089, 961, 826, 752, 693, 661, 607;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41–7.23 (14H, m, *H*1, *H*2, *H*3, *H*6, *H*7), 7.22–7.13 (3H, m, *H*5, *H*8), 7.11–7.05 (2H, m, *H*9), 4.65 (4H, s, *H*4);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 157.9, 140.9, 136.4, 133.3, 132.0, 129.0, 128.7, 128.5, 128.0, 127.7, 125.2, 121.5, 84.8 (Cα), 71.1 (Cβ), 50.7;
HRMS (ES+) calc. for $C_{29}H_{23}{}^{35}ClN_2NaO$ $[M+Na]^+$ 473.1391, found 473.1392.

_N_-((4-Chlorophenyl)ethynyl)-_N_-phenylmorpholine-4-carboxamide, 85c



Following example procedure **1.2f:** Synthesised from (*E*)-*N*-(1,2-dichlorovinyl)-*N*-phenylmorpholine-1-carboxamide (300 mg, 0.996 mmol, 1.0 equiv.) in anhydrous TBME (10 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous toluene (3 mL), 4-chlorophenylmagnesium bromide (2.99 mL of a 1.0 M solution in Et_2O, 2.99 mmol, 3.0 equiv.), zinc(II) chloride (0.79 mL of a 1.9 M solution in 2-MeTHF, 1.49 mmol, 1.5 equiv.) and anhydrous tmeda (1.49 mL, 4.86 mmol, 10.0 equiv.), and the reaction conducted using CuCN·2LiCl (12 µL of a 1.0 M solution in THF, 12 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (20% CH_2Cl_2/10% EtOAc/pentane → 20% CH_2Cl_2/15% EtOAc/pentane) afforded the title compound (163 mg, 0.501 mmol, 71%) as a colourless solid. This compound can be recrystallised from heptane (~1 mL) *plus* a few drops of toluene to give colourless crystals that were suitable for X-ray diffraction;

m.p. 122–123 °C;

R_f 0.35 (30% EtOAc/pentane);

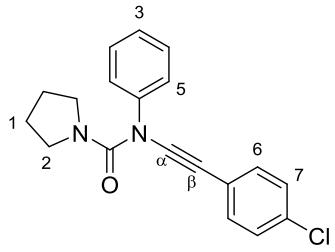
IR (thin film, ν_{max} / cm^{-1}) 2965, 2919, 2856, 2240, 1686, 1596, 1491, 1451, 1413, 1360, 1300, 1271, 1237, 1114, 1089, 1071, 1056, 1013, 984, 828, 752, 691, 647;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43–7.35 (4H, m, *H*4, *H*5), 7.35–7.31 (2H, m, *H*6), 7.31–7.27 (2H, m, *H*7), 7.20 (1H, tt, *J* = 6.4, 2.2 Hz, *H*3), 4.79–4.71 (4H, m, *H*2), 4.71–4.64 (4H, m, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.6, 140.7, 133.6, 132.2, 129.1, 128.7, 125.4, 121.6, 121.5, 84.8 (Cα), 70.3 (Cβ), 66.6, 46.5;

HRMS (ES+) calc. for $C_{19}H_{18}{}^{35}ClN_2O_2$ $[M+H]^+$ 341.1051, found 341.1052.

_N_-((4-Chlorophenyl)ethynyl)-_N_-phenylpyrrolidine-1-carboxamide, 85d



Following example procedure **1.2f:** Synthesised from (*E*)-*N*-(1,2-dichlorovinyl)-*N*-phenylpyrrolidine-1-carboxamide (200 mg, 0.701 mmol, 1.0 equiv.) in anhydrous TBME (7 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous toluene (2 mL), 4-chlorophenylmagnesium bromide (2.10 mL of a 1.0 M solution in Et_2O, 2.10 mmol, 3.0 equiv.), zinc(II) chloride (0.55 mL of a 1.9 M solution in 2-MeTHF, 1.05 mmol, 1.5 equiv.) and anhydrous tmeda (1.05 mL, 7.01 mmol, 10.0 equiv.), and the reaction conducted using CuCN·2LiCl (9 µL of a 1.0 M solution in THF, 9 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (20% CH_2Cl_2/10% EtOAc/pentane → 20% CH_2Cl_2/15% EtOAc/pentane) afforded a pale yellow oil that was crystallised by flash freezing a concentrated solution of the title compound in heptane (~1 mL), *plus* two drops of toluene, at −78 °C, and allowing the frozen mixture to warm gradually to −20 °C in a freezer overnight. This afforded the title compound (163 mg, 0.501 mmol, 71%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 46–47 °C;

R_f 0.28 (20% EtOAc/pentane);

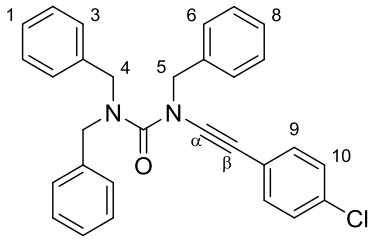
IR (thin film, ν_{max} / cm^{-1}) 2973, 2881, 2237, 1681, 1595, 1490, 1377, 1230, 1189, 1123, 1089, 1013, 827, 753, 692;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43–7.36 (4H, m, *H*4, *H*5), 7.36–7.32 (2H, m, *H*6), 7.31–7.25 (2H, m, *H*7), 7.18 (1H, tt, *J* = 6.7, 1.9 Hz, *H*3), 4.67–4.65 (4H, m, *H*2), 1.98–1.88 (4H, m, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.0, 140.8, 133.3, 132.2, 129.0, 128.6, 125.2, 122.2, 122.0, 85.2 (Cα), 70.1 (Cβ), 48.3, 25.5;

HRMS (ES+) calc. for $C_{19}H_{18}{}^{35}ClN_2O$ $[M+H]^+$ 325.1102, found 325.1103.

1,1,3-Tribenzyl-3-((4-chlorophenyl)ethynyl)urea, 85e



Following example procedure **1.2f**: Synthesised from (*E*)-1,1,3-tribenzyl-3-(1,2-dichlorovinyl)urea (100 mg, 0.235 mmol, 1.0 equiv.) in anhydrous TBME (4 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous toluene (2 mL), 4-chlorophenylmagnesium bromide (0.71 mL of a 1.0 M solution in Et_2O, 0.705 mmol, 3.0 equiv.), zinc(II) chloride (0.19 mL of a 1.0 M solution in Et_2O, 0.35 mmol, 1.5 equiv.) and anhydrous tmeda (0.35 mL, 2.35 mmol, 10.0 equiv.), and the reaction conducted using CuCN·2LiCl (3 µL of a 1.0 M solution in THF, 3 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (2% → 5% Et_2O/pentane) afforded the title compound (60.9 mg, 0.131 mmol, 56%) as a pale yellow oil. Crystallisation by slow evaporation of a solution of the title compound in heptane (~1 mL) *plus* 3 drops of ethanol gave the title compound as colourless crystals. These crystals were suitable for X-ray diffraction.

m.p. 45–48 °C;

R_f 0.40 (10% Et_2O/ pentane);

IR (thin film, ν_{max} / cm^{-1}) 3064, 3031, 2928, 2236, 1666, 1494, 1453, 1433, 1410, 1263, 1224, 1116, 1089, 1076, 826, 733, 698;

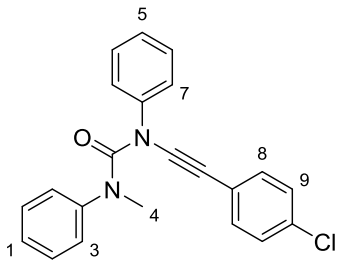
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45–7.37 (2H, m, Ph*H*), 7.37–7.15 (13H, m, Ph*H*), 7.09–7.03 (2H, m, *H*9), 6.69–6.63 (2H, m, *H*10), 4.76 (2H, s, *H*5), 4.61 (4H, s, *H*4);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.9, 136.7, 136.4, 132.7, 131.3, 129.0, 128.6, 128.4, 128.3, 127.9, 127.8, 127.4, 121.8, 86.8 (Cα), 71.2 (Cβ), 55.1, 50.8;

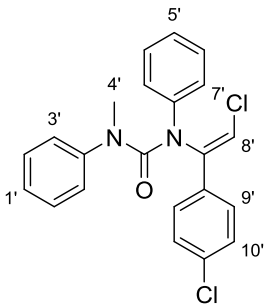
HRMS (ES+) calc. for $C_{30}H_{26}{}^{35}ClN_2O$ $[M+H]^+$ 465.1728, found 465.1730.

2.4c *Miscellaneous*.

1-((4-Chlorophenyl)ethynyl)-3-methyl-1,3-diphenylurea, 85a & (*Z*)-1-(2-Chloro-1-(4-chloro phenyl)vinyl)-3-methyl-1,3-diphenylurea, (*Z*)**-87**



85a



(*Z*)-**87**

Following example procedure **1.2f:** Synthesised from (*E*)-1-(1,2-dichlorovinyl)-3-methyl-1,3-diphenylurea (300 mg, 0.934 mmol, 1.0 equiv.) in anhydrous TBME (10 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). The diarylzinc solution was prepared using anhydrous toluene (4.0 mL), 4-chlorophenylmagnesium bromide (2.80 mL of a 1.0 M solution in Et_2O, 2.80 mmol, 3.0 equiv.), zinc(II) chloride (0.74 mL of a 1.9 M solution in 2-MeTHF, 1.40 mmol, 1.5 equiv.), and the reaction conducted using CuCN·2LiCl (12 µL of a 1.0 M solution in THF, 12 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (0 → 10% EtOAc/pentane) afforded yne-urea **85a** as a yellow solid and chloroenamide (*Z*)-**87** as a colourless oil. Recrystallisation of yne-urea **85a** from heptane/Et_2O (~4:1) afforded 244 mg (0.650 mmol, 70%) as colourless needles. Crystallisation of chloroenamide (*Z*)-**87** from heptane *plus* a couple of drops of Et_2O afforded 58.8 mg (0.148 mmol, 16%) as colourless crystals;

- Data for yne-urea **85a** as before.

- Data for chloroenamide (*Z*)-**87**:

m.p. 118–120 °C;

R_f 0.28 (10% EtOAc/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3080, 1666, 1596, 1493, 1456, 1420, 1400, 1357, 1297, 1278, 1164, 1112, 1092, 1012, 909, 851, 816, 753, 731, 695;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.27–7.18 (6H, m, *H*9′, Ph*H*′(×4)), 7.16–7.11 (2H, m, *H*10′), 7.11–7.02 (6H, m, Ph*H*′), 5.87 (1H, s, *H*8′), 3.13 (3H, s, *H*4′);

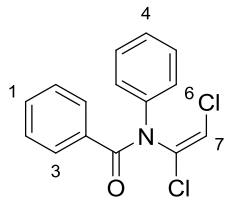
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.3, 143.7, 142.2, 141.7, 135.0, 134.6, 128.9, 128.8, 128.7, 127.6, 125.7, 125.4, 124.9, 124.4, 113.7, 39.3;

HRMS (ES+) calc. for $C_{22}H_{19}{}^{35}Cl_2N_2O$ $[M+H]^+$ 397.0869, found 397.0868.

2.5 Amide Scope.

2.5a *Dichloroenamides*.

(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-phenylbenzamide, 89a



Following example procedure **1.2b**: Synthesised from *N*-phenylbenzamide (1.00 g, 5.07 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (430 mg, 1.27 mmol, 0.25 equiv.) in toluene (50 mL) using 50% w/v aqueous solution of KOH (20 mL) and trichloroethylene (1.37 mL, 15.2 mmol, 3.0 equiv.) added dropwise over 2 minutes at 21 °C. The reaction takes approximately 2 hours to reach completion. After extraction/concentration in vacuo, the resulting brown solid was recrystallised from ethanol, and once the mixture had cooled to room temperature and crystals had grown, the suspension was further cooled to −20 °C for ~2 hours to enable further crystallisation. This afforded the title compound (1.31 g, 4.48 mmol, 88%) as pale yellow crystals. These crystals were suitable for X-ray diffraction;

m.p. 107–108 °C;

R_f 0.37 (10% Et_2O/pentane);

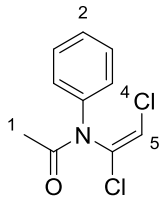
IR (thin film, ν_{max} / cm^{-1}) 3086, 1681, 1595, 1491, 1448, 1317, 1277, 1151, 1075, 889, 851, 817, 782, 758, 717, 696, 666, 645;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 7.3 Hz, *H*3), 7.44 (1H, t, *J* = 7.3, 1.2 Hz, *H*1), 7.41–7.22 (7H, m, *H*2, *H*4, *H*5, *H*6), 6.27 (1H, s, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.4, 139.0, 134.4, 132.9, 131.4, 129.3, 128.5, 128.0, 127.7, 126.4, 116.2;

HRMS (ES+) calc. for $C_{15}H_{12}{}^{35}Cl_2NO$ $[M+H]^+$ 292.0291, found 292.0292.

(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-phenylacetamide, 89b

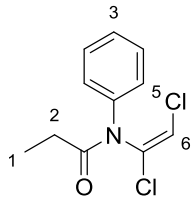


Synthesised from *N*-phenylacetamide (500 mg, 3.70 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (314 mg, 0.925 mmol, 0.25 equiv.) in toluene (40 mL) using 50% w/v aqueous solution of KOH (20 mL) and trichloroethylene (0.50 mL, 5.55 mmol, 1.5 equiv.) added dropwise over 2 minutes at 40 °C, following example procedure **1.2b**. The reaction takes approximately 2 hours to reach completion. Column chromatography (0 → 5% Et_2O/pentane) afforded the title compound (431 mg, 1.87 mmol, 51%) as a yellow solid;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.69–7.14 (5H, m, *H*2, *H*3, *H*4), 6.42 (1H, br. s, *H*5), 2.79–1.75 (3H, br. m, *H*1);
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 169.3, 139.4, 138.1, 133.2, 131.1, 129.4, 128.0, 126.7, 117.4, 116.4, 22.1. ***Note*:** This compound is rotameric and as a result some ^{13}C resonances are duplicated and/or broadened.

Data are consistent with literature values.[245]

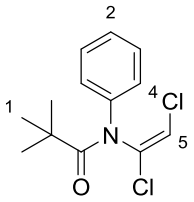
(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-phenylpropionamide, 89c



Synthesised from *N*-phenylpropionamide (1.00 g, 6.70 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (569 mg, 1.68 mmol, 0.25 equiv.) in toluene (60 mL) using 50% w/v aqueous solution of KOH (30 mL) and trichloroethylene (0.90 mL, 10.1 mmol, 1.5 equiv.) added dropwise over 2 minutes at 40 °C, following example procedure **1.2b**. The reaction takes approximately 1 hour to reach completion. Column chromatography (0 → 4% Et_2O/pentane) afforded the title compound (859 mg, 3.52 mmol, 53%) as a yellow oil;

R_f 0.29 (4% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3083, 2940, 1699, 1613, 1595, 1492, 1460, 1362, 1290, 1257, 1220, 1198, 1127, 1074, 1049, 882, 811, 760, 717, 694, 659;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.52–7.29 (5H, m, *H*3, *H*4, *H*5), 6.40 (1H, br. s, *H*6), 2.43 (2H, br. s, *H*2), 1.17 (3H, br. t, *J* = 6.8 Hz, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.7, 138.7, 132.4, 129.5, 128.4, 127.4, 116.9, 27.4, 9.02;
HRMS (ES+) calc. for $C_{11}H_{12}{}^{35}Cl_2NO$ $[M+H]^+$ 244.0291, found 244.0292.

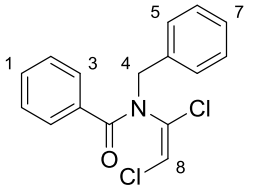
(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-phenylpivalamide, 89d



Synthesised from *N*-phenylpivalamide (1.00 g, 5.64 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (479 mg, 1.41 mmol, 0.25 equiv.) in toluene (50 mL) using 50% w/v aqueous solution of KOH (20 mL) and trichloroethylene (1.52 mL, 16.9 mmol, 3.0 equiv.) added dropwise over 5 minutes at 60 °C, following example procedure **1.2b**. The reaction was stirred overnight to reach completion. Column chromatography (5% Et_2O/pentane) afforded the title compound (1.10 g, 4.04 mmol, 72%) as a pale yellow wax. This compound can be recrystallised from MeOH/H_2O to give colourless crystals suitable for X-ray diffraction;

m.p. 65–67 °C (MeOH/H_2O);
R_f 0.50 (10% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3088, 2968, 1677, 1594, 1492, 1480, 1397, 1366, 1274, 1220, 1179, 1063, 1028, 852, 821, 797, 760, 701;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48–7.35 (5H, m, *H*2, *H*3, *H*4), 6.25 (1H, s, *H*5), 1.17 (9H, s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 177.9, 139.9, 133.9, 129.2, 129.0, 128.8, 115.1, 41.8, 28.9;
HRMS (ES+) calc. for $C_{13}H_{16}{}^{35}Cl_2NO$ $[M+H]^+$ 272.0604, found 272.0605.

(*E*)-*N*-Benzyl-*N*-(1,2-dichlorovinyl)benzamide, 89e



Preparation using KOH in toluene:

Following example procedure **1.2b**: Synthesised from *N*-benzylbenzamide (500 mg, 2.37 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (201 mg, 0.593 mmol, 0.25 equiv.) in toluene (24 mL) using 50% w/v aqueous solution of KOH (12 mL) and trichloroethylene (0.64 mL, 7.11 mmol, 3.0 equiv.) added dropwise over 2 minutes at 60 °C, following example procedure **1.2b**. The reaction takes approximately 2 hours to reach completion. Column chromatography (5 → 10% Et_2O/pentane) afforded the title compound (553 mg, 1.81 mmol, 76%) as a colourless oil that solidifies on standing at −20 °C in the freezer. Recrystallisation can be achieved from heptane *plus* a few drops of toluene at −20 °C for 4 days, but the mass recovery was poor owing to facile dissolution upon slight warming above −20 °C. These crystals were suitable for X-ray diffraction.

Preparation using NaH in 2-MeTHF:

To an oven dried, nitrogen-flushed 25 mL two-necked round bottomed flask, equipped with a magnetic stirrer bar, a reflux condenser and two septa, was added sodium hydride (240 mg of a 60% dispersion in mineral oil, 5.9 mmol, 2.5 equiv.). The flask was then evacuated under high vacuum for 30 seconds to remove air and backfilled with nitrogen (this vacuum cycle was repeated twice more – see ***Safety Note*** in procedure **1.2a**). After backfilling with nitrogen, anhydrous 2-MeTHF (2.4 mL) was added and the resulting grey suspension was heated to 75 °C whilst stirring. Next, a solution of *N*-benzylbenzamide (500 mg, 2.37 mmol, 1.0 equiv.) in anhydrous 2-MeTHF (2.4 mL) was added dropwise over 5 minutes and the resulting mixture was stirred at 75 °C for 1.5 hours. During this time the reaction solution gained a yellow hue.

Next a solution of trichloroethylene (0.32 mL, 3.55 mmol, 1.5 equiv.) in anhydrous 2-MeTHF (1 mL) was added dropwise over 4 minutes, and the mixture was stirred at 75 °C for 1 hour. Complete conversion was then confirmed by TLC (10% Et_2O/petroleum ether). Upon cooling to room temperature, the reaction was quenched by the slow addition of "wet" 2-MeTHF (5 mL), followed by NH_4Cl (20 mL) and the mixture stirred for 30 minutes. The mixture was poured into a 250 mL separating funnel and the organic layer was separated. The aqueous layer was then extracted with Et_2O (3×40 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated in vacuo to afford a brown oil. Column chromatography (5 → 10% Et_2O/pentane) afforded 498 mg (1.63 mmol, 69%) of the title compound.

m.p. 55 °C;

R_f 0.67 (20% Et_2O/pentane);

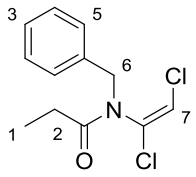
IR (thin film, ν_{max} / cm^{-1}) 3087, 3032, 1668, 1615, 1447, 1357, 1317, 1295, 1243, 1139, 1075, 1028, 944, 816, 785, 759, 718, 698, 652;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.79–7.69 (2H, m, *H*3), 7.54–7.44 (3H, m, *H*1, *H*6), 7.43–7.28 (5H, m, *H*2, *H*5, *H*7), 5.84 (1H, s, *H*8), 5.22 (1H, br. d, *J* = 14.2 Hz, *H*4), 4.61 (1H, br. d, *J* = 14.2 Hz, *H*4);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 169.9, 135.3, 134.8, 132.7, 131.1, 129.5, 128.3, 127.9, 127.8, 127.5, 116.2, 49.3;

HRMS (ES+) calc. for $C_{16}H_{14}{}^{35}Cl_2NO$ $[M+H]^+$ 306.0447, found 306.0448.

(*E*)-*N*-Benzyl-*N*-(1,2-dichlorovinyl)propionamide, 89f



Following example procedure **1.2b**: Synthesised from *N*-benzylpropionamide (200 mg, 1.22 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (104 mg, 0.306 mmol, 0.25 equiv.) in toluene (12 mL) using 50% w/v aqueous solution of KOH (6 mL) and trichloroethylene (0.33 mL, 3.63 mmol, 3.0 equiv.) added dropwise over 10 minutes at 60 °C. The reaction was halted after 48 hours. Column chromatography (4% Et_2O/pentane) afforded the title compound (153 mg, 0.593 mmol, 48%) as a colourless solid;

m.p. 74 °C;

R_f 0.72 (20% EtOAc/pentane);

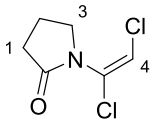
IR (thin film, ν_{max} / cm^{-1}) 3081, 3032, 2983, 2929, 2880, 1672, 1638, 1495, 1456, 1412, 1372, 1274, 1203, 1159, 1074, 1016, 966, 947, 860, 813, 764, 705, 677;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40–7.33 (2H, m, *H*4), 7.33–7.27 (3H, m, *H*3, *H*5), 6.25 (1H, s, *H*7), 5.02 (1H, AB d, J_{AB} = 14.3 Hz, *H*6), 4.42 (1H, AB d, J_{BA} = 14.3 Hz, *H*6), 2.47 (2H, q, *J* = 7.4 Hz, *H*2), 1.19 (3H, t, *J* = 7.4 Hz, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.9, 135.4, 132.5, 129.5, 128.3, 127.9, 117.6, 48.9, 26.7, 9.0;

HRMS (ES+) calc. for $C_{12}H_{13}{}^{35}Cl_2NNaO$ $[M+Na]^+$ 280.0266, found 280.0268.

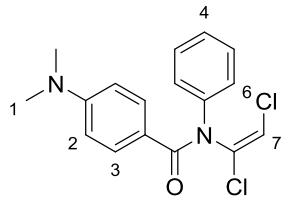
(*E*)-1-(1,2-Dichlorovinyl)pyrrolidin-2-one, 89g



Following example procedure **1.2b**: Synthesised from anhydrous pyrrolidinone (1.00 g, 11.8 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (997 mg, 2.94 mmol, 0.25 equiv.) in toluene (20 mL) using 50% w/v aqueous solution of KOH (20 mL) and trichloroethylene (3.17 mL, 35.3 mmol, 3.0 equiv.) added dropwise over 1 hour at 40 °C. The reaction was halted after 48 hours. Column chromatography (30% EtOAc/pentane) afforded the title compound (193 mg, 1.07 mmol, 9%) as pale yellow oil;

R_f 0.44 (30% EtOAc/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3084, 2892, 1717, 1624, 1379, 1301, 1244, 1200, 813, 652;
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.27 (1H, s, *H*4), 3.60 (2H, t, *J* = 7.1 Hz, *H*3), 2.44 (2H, t, *J* = 7.9 Hz, *H*1), 2.15 (2H, tt, *J* = 7.9, 7.1 Hz, *H*2);
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 173.1, 127.7, 115.3, 46.7, 30.4, 18.6;
HRMS (ES+) calc. for $C_6H_7{}^{35}Cl_2NNaO$ $[M+Na]^+$ 201.9797, found 201.9799.

(*E*)-*N*-(1,2-Dichlorovinyl)-4-(dimethylamino)-*N*-phenylbenzamide, 89h



Following example procedure **1.2b**: Synthesised from 4-(dimethylamino)-*N*-phenylbenzamide (720 mg, 3.00 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (254 mg, 0.75 mmol, 0.25 equiv.) in toluene (30 mL) using 50% w/v aqueous solution of KOH (15 mL) and trichloroethylene (0.81 mL, 9.00 mmol, 3.0 equiv.) added dropwise over 2 minutes at 60 °C. The reaction takes approximately 2 hours to reach completion. After extraction/concentration in vacuo, the resulting brown solid was recrystallised from methanol, and once the mixture had cooled to room temperature and crystals had grown, the suspension was further cooled to −20 °C for ~2 hours to enable further crystallisation. This afforded the title compound (818 mg, 2.54 mmol, 82%) as pale yellow needles. These crystals were suitable for X-ray diffraction;

m.p. 168–170 °C;

R_f 0.39 (20% EtOAc/pentane);

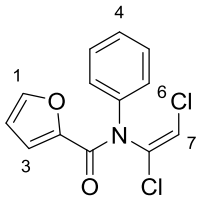
IR (thin film, ν_{max} / cm^{-1}) 3086, 2900, 1666, 1602, 1528, 1492, 1368, 1316, 1274, 1231, 1190, 1172, 946, 811, 756, 695;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63–7.54 (2H, m, *H*3), 7.39–7.31 (2H, m, *H*5), 7.29–7.20 (3H, m, *H*4, *H*6), 6.59–6.51 (2H, m, *H*2), 6.26 (1H, s, *H*7), 3.00 (6H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.3, 152.4, 140.1, 133.4, 131.0, 129.2, 127.0, 126.1, 120.4, 115.2, 110.4, 39.9;

HRMS (ES+) calc. for $C_{17}H_{17}{}^{35}Cl_2N_2O$ $[M+H]^+$ 335.0713, found 335.0711.

(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-phenylfuran-2-carboxamide, 89i



Following example procedure **1.2b**: Synthesised from *N*-phenylfuran-2-carboxamide (500 mg, 2.67 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (227 mg, 0.668 mmol, 0.25 equiv.) in toluene (27 mL) using 50% w/v aqueous solution of KOH (13 mL) and trichloroethylene (0.72 mL, 8.01 mmol, 3.0 equiv.) added dropwise over 2 minutes at 21 °C. The reaction takes approximately 2 hours to reach completion. Column chromatography (6% Et_2O/pentane) afforded the title compound (457 mg, 1.62 mmol, 61%) as a yellow solid;

m.p. 60–63 °C;

R_f 0.73 (20% EtOAc/pentane);

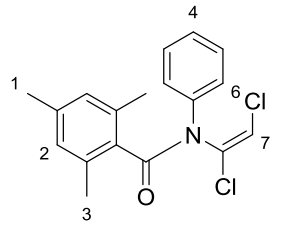
IR (thin film, ν_{max} / cm^{-1}) 3086, 1670, 1615, 1594, 1572, 1492, 1468, 1388, 1320, 1231, 1187, 1149, 1092, 1014, 886, 827, 756, 695, 660;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.51–7.46 (1H, m, *H*3), 7.46–7.34 (5H, m, *H*4, *H*5, *H*6), 6.62 (1H, br. s, *H*1), 6.40 (1H, s, *H*7), 6.39 (1H, dd, *J* = 3.7, 1.7 Hz, *H*2);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 157.7, 146.1, 145.6, 138.7, 131.8, 129.5, 128.4, 127.1, 118.4, 116.5, 111.6;

HRMS (ES+) calc. for $C_{13}H_9{}^{35}Cl_2NNaO_2$ $[M+Na]^+$ 303.9903, found 303.9904.

(*E*)-*N*-(1,2-Dichlorovinyl)-2,4,6-trimethyl-*N*-phenylbenzamide, 89j



Following example procedure **1.2b**: Synthesised from 2,4,6-trimethyl-*N*-phenylbenzamide (1.00 g, 4.18 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (355 mg, 1.05 mmol, 0.25 equiv.) in toluene (30 mL) using 25% w/v aqueous solution of KOH (15 mL) and trichloroethylene (1.13 mL, 12.5 mmol, 3.0 equiv.) added dropwise over 2 minutes at 21 °C. The reaction takes approximately 3 hours to reach completion. Recrystallisation from heptane afforded the title compound (1.16 g, 3.47 mmol, 83%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 142–144 °C;

R_f 0.54 (10% EtOAc/pentane);

IR (thin film, ν_{max} / cm^{-1}) 3085, 2952, 2921, 2860, 1682, 1611, 1595, 1493, 1454, 1318, 1274, 1178, 1123, 853, 834, 811, 756, 696, 614;

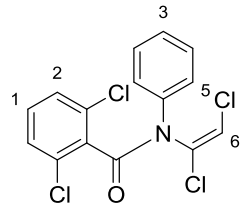
^{1}H NMR (400 MHz, $CDCl_3$) δ_H data for major rotamer: 7.25–7.11 (5H, m, *H*4, *H*5, *H*6), 6.67 (2H, s, *H*2), 6.48 (1H, s, *H*7), 2.29 (6H, br. s, *H*3), 2.17 (3H, s, *H*1); data for minor rotamer: 7.58–7.51 (2H, m, *H*6), 7.50–7.43 (2H, m, *H*5), 7.38–7.33 (1H, m, *H*4), 6.87 (2H, s, *H*2), 6.10 (1H, s, *H*7), 2.42 (6H, s, *H*3), 2.30 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C combined data: 169.8, 138.89, 138.86, 135.4, 134.3, 131.8, 131.6, 129.1*, 128.7, 128.2*, 128.1, 127.8, 127.7*, 126.5*, 126.1, 117.1, 116.5*, 21.2*, 21.0, 20.1*, 19.6;

***Note*:** Those ^{13}C resonances indicated by * belong to the minor rotamer, but due to signal overlap, not all of these resonances can be discerned.

HRMS (ES+) calc. for $C_{18}H_{18}{}^{35}Cl_2NO$ $[M+H]^+$ 334.0760, found 334.0760.

(*E*)-2,6-Dichloro-*N*-(1,2-dichlorovinyl)-*N*-phenylbenzamide, 89k



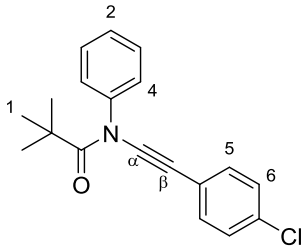
Following example procedure **1.2b**: Synthesised from 2,6-dichloro-*N*-phenylbenzamide (1.00 g, 3.76 mmol, 1.0 equiv.) and tetrabutylammonium hydrogensulfate (319 mg, 0.940 mmol, 0.25 equiv.) in toluene (30 mL) using 25% w/v aqueous solution of KOH (15 mL) and trichloroethylene (1.01 mL, 11.3 mmol, 3.0 equiv.) added dropwise over 2 minutes at 21 °C. The reaction takes approximately 3 hours to reach completion. Recrystallisation from heptane (a hot filtration was required to remove tarry residues) afforded the title compound (1.08 g, 2.99 mmol, 80%) as colourless crystals. These crystals were suitable for X-ray diffraction;

m.p. 135–137 °C;
R_f 0.41 (10% EtOAc/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3085, 1691, 1594, 1562, 1492, 1432, 1323, 1304, 1281, 1262, 1196, 1166, 1071, 842, 818, 797, 781, 761, 748, 731, 697, 681;
^{1}H NMR (400 MHz, $CDCl_3$)* δ_H 7.65–7.50 (2H, m, *H*5), 7.31–19 (3H, m, *H*1, *H*4), 7.18–6.95 (3H, m, *H*2, *H*3), 6.49 (1H, s, *H*6); ***Note*:** The compound is rotameric with many overlapping peaks.
^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 163.5, 138.0, 136.2, 134.1, 132.1, 130.8, 130.2, 129.8, 129.2, 129.1, 129.0, 128.9, 128.1, 128.0, 127.9, 127.8, 127.6, 127.0, 126.6, 118.4, 117.8;
HRMS (ES+) calc. for $C_{15}H_{10}{}^{35}Cl_4NO$ $[M+H]^+$ 359.9511, found 359.9513.

***Note*:** It was not possible to categorically assign peaks to each rotamer (^{1}H & ^{13}C)

2.5b *Ynamides*.

N-((4-Chlorophenyl)ethynyl)-*N*-phenylpivalamide, 90d



Following example procedure **1.2f:** Synthesised from (*E*)-*N*-(1,2-dichlorovinyl)-*N*-phenylpivalamide (200 mg, 0.735 mmol, 1.0 equiv.) in anhydrous TBME (7.4 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). ***Note*:** The elimination step was conducted at 0 °C. The diarylzinc solution was prepared using anhydrous toluene (2 mL), 4-chlorophenylmagnesium bromide (2.20 mL of a 1.0 M solution in Et_2O, 2.20 mmol, 3.0 equiv.), zinc(II) chloride (0.58 mL of a 1.9 M solution in 2-MeTHF, 1.10 mmol, 1.5 equiv.) and anhydrous tmeda (1.10 mL, 7.35 mmol, 10.0 equiv.), and the reaction conducted using CuCN·2LiCl (9 µL of a 1.0 M solution in THF, 9 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (5% Et_2O/pentane) afforded the title compound (165 mg, 0.528 mmol, 72%) as a colourless solid. This compound can be recrystallised from heptane (~1 mL) to give colourless crystals that were suitable for X-ray diffraction. ***Note*:** This compound begins to decompose within hours in $CDCl_3$ and C_6D_6, but the crystals were found to be stable for at least a week on the bench.

m.p. 104–105°C;

R_f 0.27 (5% Et_2O/pentane);

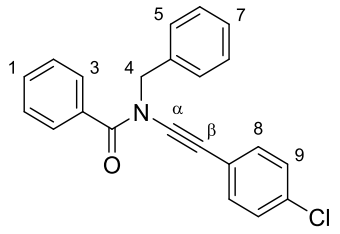
IR (thin film, ν_{max} / cm^{-1}) 2977, 2243, 1696, 1594, 1490, 1398, 1359, 1272, 1213, 1143, 1087, 1013, 826, 753, 695;

^{1}H NMR (400 MHz, C_6D_6) δ_H 7.40–7.30 (2H, m, *H*4), 7.12–7.05 (2H, m, *H*3), 6.99–6.94 (1H, m, *H*2), 6.92 (4H, s, *H*5, *H*6), 1.50 (9H, s, *H*1);

^{13}C NMR (101 MHz, C_6D_6) δ_C 177.5, 141.9, 133.9, 132.1, 129.3, 129.0, 127.6, 126.6, 122.0, 87.5 (Cα), 72.5 (Cβ), 41.1, 27.2;

HRMS (ES+) calc. for $C_{19}H_{19}{}^{35}ClNO$ $[M+H]^+$ 312.1150, found 312.1150.

***N*-Benzyl-*N*-((4-chlorophenyl)ethynyl)benzamide, 90e**



Following example procedure **1.2f**: Synthesised from (*E*)-*N*-benzyl-*N*-(1,2-dichlorovinyl)benzamide (250 mg, 0.817 mmol, 1.0 equiv.) in anhydrous TBME (8.2 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). ***Note*:** This elimination reaction was conducted at room temperature (~21 °C). The diarylzinc solution was prepared using anhydrous toluene (2.5 mL), 4-chlorophenylmagnesium bromide (2.45 mL of a 1.0 M solution in Et_2O, 2.45 mmol, 3.0 equiv.), zinc(II) chloride (0.65 mL of a 1.9 M solution in 2-MeTHF, 1.22 mmol, 1.5 equiv.) and anhydrous tmeda (1.22 mL, 8.17 mmol, 10.0 equiv.), and the reaction conducted using CuCN·2LiCl (10 µL of a 1.0 M solution in THF, 10 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (5% Et_2O/pentane) afforded a pale yellow oil, which was crystallised at −20 °C overnight from heptane (~2 mL) *plus* a couple of drops of benzene to give the title compound (193 mg, 0.558 mmol, 68%) as colourless crystals. ***Note*:** This compound begins to decompose within hours in C_6D_6, but the crystals were found to be stable for at least a week in the fridge (2 °C).

m.p. 53–54 °C;

R_f 0.49 (10% Et_2O/pentane);

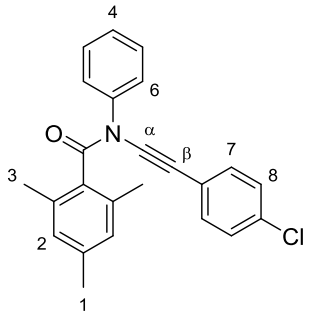
IR (thin film, ν_{max} / cm^{-1}) 3064, 3032, 2242, 1672, 1493, 1447, 1389, 1356, 1289, 1244, 1123, 1089, 1075, 1014, 962, 826, 700;

^{1}H NMR (400 MHz, C_6D_6) δ_H 7.84–7.77 (2H, m, *H*3), 7.45–7.37 (2H, *H*5), 7.16–7.11 (2H, m, *H*6), 7.11–7.06 (1H, m, *H*7), 7.06–7.02 (1H, m, *H*1), 7.02–6.96 (2H, m, *H*2), 6.87–6.81 (2H, m, *H*8), 6.77–6.72 (2H, m, *H*9), 4.79 (2H, s, *H*4);

^{13}C NMR (101 MHz, C_6D_6) δ_C 169.9, 136.6, 134.2, 133.5, 131.8, 131.5, 129.2 (2C), 128.9, 128.8, 128.3, 127.9, 122.0, 87.2 (Cα), 72.8 (Cβ), 52.9;

HRMS We were unable to obtain an accurate mass (ES+ or CI+) due to decomposition upon ionisation.

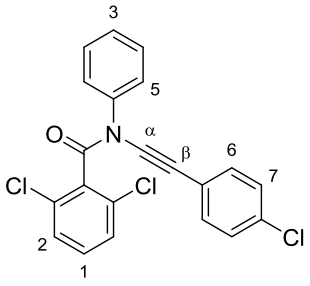
_N_-((4-Chlorophenyl)ethynyl)-2,4,6-trimethyl-_N_-phenylbenzamide, 90j



Following example procedure **1.2f:** Synthesised from (*E*)-*N*-(1,2-dichlorovinyl)-2,4,6-trimethyl-*N*-phenylbenzamide (500 mg, 1.50 mmol, 1.0 equiv.) in anhydrous TBME (15 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). ***Note*:** The elimination step was conducted at room temperature (~21 °C). The diarylzinc solution was prepared using anhydrous toluene (4.5 mL), 4-chlorophenylmagnesium bromide (4.49 mL of a 1.0 M solution in Et_2O, 4.49 mmol, 3.0 equiv.), zinc(II) chloride (1.18 mL of a 1.9 M solution in 2-MeTHF, 2.24 mmol, 1.5 equiv.) and anhydrous tmeda (2.24 mL, 15.0 mmol, 10.0 equiv.), and the reaction conducted using CuCN·2LiCl (19 µL of a 1.0 M solution in THF, 19 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (5% Et_2O/pentane) afforded the title compound (386 mg, 1.03 mmol, 69%) as a colourless oil that yellows on standing. ***Note*:** This compound was stored as a frozen matrix in benzene.

R_f 0.45 (10% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3038, 2951, 2919, 2859, 2247, 1700, 1612, 1594, 1489, 1456, 1357, 1266, 1214, 1162, 1121, 1088, 1054, 1014, 854, 826, 755, 694, 686, 634, 607;
^{1}H NMR (400 MHz, C_6D_6) δ_H 7.72 (2H, d, *J* = 7.8 Hz, *H*6), 7.12–7.18 (2H, dd, *J* = 7.8, 7.4 Hz, *H*5), 7.03 (1H, t, *J* = 7.4 Hz, *H*4), 6.80 (2H, d, *J* = 8.3 Hz, *H*7), 6.68 (2H, s, *H*2) 6.61 (2H, d, *J* = 8.3 Hz, *H*8), 2.37 (6H, s, *H*3), 2.09 (3H, s, *H*1);
^{13}C NMR (101 MHz, C_6D_6) δ_C 171.6, 139.3, 139.1, 134.7, 134.1, 133.5, 131.8, 129.4, 128.7, 128.3, 128.1, 127.8, 127.5, 125.1, 121.7, 85.6 (Cα), 71.4 (Cβ), 21.2, 19.1;
HRMS (ES+) calc. for $C_{24}H_{21}{}^{35}Cl$ NO $[M+H]^+$ 374.1306, found 374.1309.

2,6-Dichloro-*N*-((4-chlorophenyl)ethynyl)-*N*-phenylbenzamide, 90k

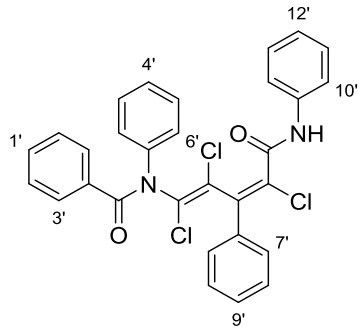


Following example procedure **1.2f**: Synthesised from (*E*)-2,6-dichloro-*N*-(1,2-dichlorovinyl)-*N*-phenylbenzamide (500 mg, 1.38 mmol, 1.0 equiv.) in anhydrous TBME (14 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). ***Note*:** The elimination step was conducted at room temperature (~21 °C). The diarylzinc solution was prepared using anhydrous toluene (4 mL), 4-chlorophenylmagnesium bromide (4.15 mL of a 1.0 M solution in Et_2O, 4.15 mmol, 3.0 equiv.), zinc(II) chloride (1.09 mL of a 1.9 M solution in 2-MeTHF, 2.08 mmol, 1.5 equiv.) and anhydrous tmeda (2.08 mL, 13.9 mmol, 10.0 equiv.), and the reaction conducted using CuCN·2LiCl (17 µL of a 1.0 M solution in THF, 17 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (5% Et_2O/pentane) afforded the title compound (361 mg, 0.901 mmol, 65%) as a colourless oil. ***Note*:** This compound was stored as a frozen matrix in benzene;

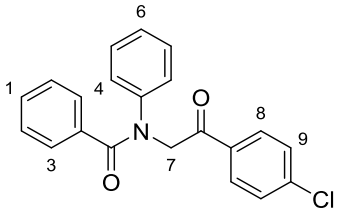
R_f 0.46 (10% Et_2O/pentane);
IR (thin film, ν_{max} / cm^{-1}) 3069, 2249, 1709, 1593, 1577, 1562, 1490, 1433, 1356, 1282, 1196, 1143, 1106, 1089, 1076, 1014, 850, 826, 796, 779, 755, 724, 706, 692, 626;
^{1}H NMR (400 MHz, C_6D_6) δ_H data for major rotamer: 7.80–7.70 (2H, m, *H*5), 7.19–7.10 (2H, m, *H*4), 7.03–6.97 (1H, m, *H*3), 6.83 (2H, d, *J* = 8.1 Hz, *H*2), 6.82–6.78 (2H, m, *H*6), 6.70–6.64 (2H, m, *H*7), 6.50 (1H, t, *J* = 8.1 Hz, *H*1); data for minor rotamer: 7.52–7.46 (2H, m, *H*5), 7.13–7.08 (2H, m, *H*6), 6.90–6.85 (2H, m, *H*7), 6.83–6.79 (2H, m, *H*4), 6.78–6.72 (1H, m, *H*3), 6.51 (2H, d, *J* = 8.1 Hz, *H*2), 6.21 (1H, t, *J* = 8.1 Hz, *H*1);
^{13}C NMR (101 MHz, C_6DC_6) δ_C data for major rotamer: 165.5, 138.6, 135.7, 134.1, 133.0, 132.4, 132.3, 131.1, 129.5, 128.8, 127.8, 125.2, 121.1, 84.5(Cα), 71.6 (Cβ); minor rotamer: 165.4, 139.6, 134.7, 134.2, 132.2, 131.0, 129.3, 129.0, 128.9, 128.0, 127.8, 126.4, 121.6, 84.7 (Cα), 72.2 (Cβ);
HRMS (ES+) calc. for $C_{21}H_{13}{}^{35}Cl_3NO$ $[M+H]^+$ 400.0057, found 400.0057.

2.5c *Miscellaneous*.

_N_-Phenyl-_N_-((1_E_,3_E_)-1,2,4-trichloro-5-oxo-3-phenyl-5-(phenylamino)penta-1,3-dien-1-yl)benzamide, 92 & _N_-(2-(4-Chlorophenyl)-2-oxoethyl)-_N_-phenylbenzamide, 93a



92



93a

Following example procedure **1.2f:** Synthesised from (*E*)-*N*-(1,2-dichlorovinyl)-*N*-phenylbenzamide (200 mg, 0.685 mmol, 1.0 equiv.) in anhydrous TBME (6.9 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.) at 0 °C. The diarylzinc solution was prepared using anhydrous toluene (2.0 mL), 4-chlorophenylmagnesium bromide (2.05 mL of a 1.0 M solution in Et_2O, 2.05 mmol, 3.0 equiv.), zinc(II) chloride (0.54 mL of a 1.9 M solution in 2-MeTHF, 1.03 mmol, 1.5 equiv.) and anhydrous tmeda (1.03 mL, 8.56 mmol, 10 equiv.), and the reaction conducted using CuCN·2LiCl (9 µL of a 1.0 M solution in THF, 9 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (20% → 30% EtOAc/pentane) afforded trichloroenamide **92** as a yellow oil and δ-ketoamide **93a** as a white powder and. Crystallisation of trichloroenamide **92** from heptane *plus* a couple of drops of Et_2O afforded 40.2 mg (73.4 µmol, 21%) as colourless crystals. Recrystallisation of δ-ketoamide **93a** from MeOH/H_2O (~5:1) afforded 117 mg (0.334 mmol, 49%) as colourless needles. Both sets of crystals were suitable for X-ray diffraction;

- Data for trichloroenamide **92**:

m.p. 138–140 °C;

R_f 0.29 (30% EtOAc/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3305, 2981, 2888, 1668, 1599, 1533, 1492, 1443, 1383, 1319, 1270, 1157, 1075, 953, 909, 817, 782, 755, 732, 694, 644;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.00 (1H, s, N*H*), 7.58 (2H, br. d, *J* = 7.5 Hz, *H*3′), 7.54 (2H, d, *J* = 7.8 Hz, *H*10′), 7.41–7.31 (3H, m, *H*1′, *H*11′), 7.25–7.15 (3H, m, *H*2′, *H*12′), 7.89–6.89 (10H, br. m, *H*4′, *H*5′, *H*6′, *H*7′, *H*8′, *H*9′);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 169.8, 159.8, 139.6, 136.9, 133.7, 131.3, 129.4, 129.3, 129.10, 129.06, 128.8, 128.5, 126.6, 128.1, 127.9, 126.2, 125.2, 120.2. ***Note*:** Due to significant broadening of peaks, four ^{13}C resonances are obscured;

HRMS (ES+) calc. for $C_{30}H_{22}{}^{35}Cl_3N_2O_2$ $[M+H]^+$ 547.0741, found 547.0739.

- Data for δ-ketoamide **93a**:

m.p. 184 °C;

R_f 0.20 (30% EtOAc/40–60 petroleum ether);

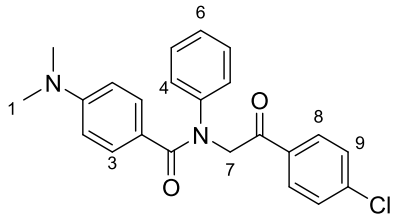
IR (thin film, ν_{max} / cm^{-1}) 2980, 1698, 1643, 1591, 1493, 1447, 1402, 1379, 1322, 1307, 1284, 1222, 1163, 1091, 995, 976, 821, 791, 730, 698;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.99–7.89 (2H, m, *H*8), 7.50–7.42 (2H, m, *H*9), 7.42–7.33 (2H, m, *H*3), 7.28–7.23 (1H, m, *H*1), 7.23–7.10 (7H, m, *H*2, *H*4, *H*5, *H*6), 5.29 (2H, s, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 192.5, 170.3, 143.9, 140.1, 135.1, 133.6, 129.9, 129.4, 129.12, 129.09, 128.9, 127.7, 127.5, 126.9, 57.0;

HRMS (ES+) calc. for $C_{21}H_{16}{}^{35}ClNNaO_2$ $[M+Na]^+$ 372.0762, found 372.0763.

_N_-(2-(4-Chlorophenyl)-2-oxoethyl)-4-(dimethylamino)-_N_-phenylbenzamide, 93h



Following example procedure **1.2f:** Synthesised from (*E*)-*N*-(1,2-dichlorovinyl)-4-(dimethylamino)-*N*-phenylbenzamide (100 mg, 0.298 mmol, 1.0 equiv.) in anhydrous TBME (3 mL) using LiHMDS (freshly prepared according to example procedure **1.2f**, 1.2 equiv.). ***Note*:** This elimination reaction was conducted at room temperature (~21 °C). The diarylzinc solution was prepared using anhydrous toluene (1.0 mL), 4-chlorophenylmagnesium bromide (0.89 mL of a 1.0 M solution in Et_2O, 0.894 mmol, 3.0 equiv.), zinc(II) chloride (0.24 mL of a 1.9 M solution in 2-MeTHF, 0.447 mmol, 1.5 equiv.) and anhydrous tmeda (0.45 mL, 2.98 mmol, 10 equiv.), and the reaction conducted using CuCN·2LiCl (4 µL of a 1.0 M solution in THF, 4 µmol, 1.25 mol%). Upon completion, the reaction was worked up and extracted as for example procedure **1.2f**. Column chromatography (20% → 30% EtOAc/pentane) afforded the title compound as a yellow solid. Vapour diffusion of pentane into a concentrated solution of this material in toluene/EtOAc (1:1) afforded the title compound (32.4 mg, 86.4 µmol, 29%) as colourless needles. These crystals were suitable for X-ray diffraction;

m.p. 175–177 °C;

R_f 0.13 (20% EtOAc/40–60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3062, 2924, 2811, 1699, 1631, 1603, 1525, 1494, 1405, 1362, 1322, 1306, 1283, 1221, 1196, 1176, 1091, 977, 910, 823, 759, 728, 698;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.99–7.89 (2H, m, *H*8), 7.48–7.39 (2H, m, *H*9), 7.33–7.27 (2H, m, *H*3), 7.27–7.18 (4H, m, *H*4, *H*5), 7.17–7.11 (1H, m, *H*6), 6.47–6.38 (2H, m, *H*2), 5.26 (2H, s, *H*7), 2.91 (6H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 193.1, 170.3, 151.3, 145.0, 139.8, 133.7, 131.3, 131.2, 129.4, 129.1, 129.0, 127.4, 126.3, 121.2, 110.3, 110.2, 57.3, 40.0, 39.9;

HRMS (ES+) calc. for $C_{23}H_{22}{}^{35}ClN_2O_2$ $[M+H]^+$ 393.1364, found 393.1366.

Supporting Information

Chapter 2 - Synthesis and Application of Yndiamides

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1 General.

1.1 General information.

Reagents, solvents and techniques: All reagents, obtained from Acros, Alfa and TCI (Fisher Scientific), Fluorochem, Sigma-Aldrich and Strem fine chemical suppliers, were used directly as supplied. Anhydrous powdered caesium carbonate was obtained from Fluorochem and copper(I) iodide (99.999% trace metals basis) was obtained from Sigma Aldrich. These were both stored and dispensed in a N_2 filled glovebox. Solvents were either used as commercially supplied, or as purified by standard techniques. Anhydrous dichloromethane, THF and toluene were each obtained from solvent dispenser units having been passed through an activated alumina column under argon, and had a water content of <10 ppm. Degassed solvents were obtained by freeze-pump-thawing; the cycle was repeated 5 times. Unless otherwise stated, all non-aqueous reactions were performed in oven-dried apparatus under a nitrogen atmosphere at room temperature.

Chromatography: Reactions were monitored by thin layer chromatography on pre-coated aluminium-backed plates (Merck Kieselgel 60 with fluorescent indicator UV254). Spots were visualised by quenching of UV fluorescence or by staining with potassium permanganate or vanillin, and retention factors are reported with the solvent system in parentheses. Flash column chromatography was performed on silica gel obtained from Macherey Nagel (MN 60, 230–400 mesh) under a positive pressure of nitrogen, using the stated solvent system.

Melting Points: Melting points were obtained using a Griffin melting point apparatus and are uncorrected.

Infrared Spectroscopy: Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer equipped with a diamond ATR module, with the sample being prepared as a thin film. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

NMR Spectroscopy: ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on Bruker AV400 or Bruker AVII500 spectrometers using TOPSPIN software, with the deuterated solvent acting as the internal deuterium lock. ^{1}H NMR spectra were recorded at 400 or 500 MHz, ^{13}C NMR spectra were recorded at 101 or 126 MHz with ^{1}H decoupling, ^{19}F NMR spectra were recorded at 376 MHz and ^{31}P NMR spectra were recorded at 162 MHz.

The residual protic solvent signal(s) acted as the internal reference for ^{1}H NMR spectra [$CDCl_3$ (δ 7.26) or toluene-d_8 (δ 7.09)], and the deuterated solvent signal acted as the internal reference for ^{13}C NMR spectra [$CDCl_3$ (δ 77.0) or toluene-d_8 (δ 137.5)]. ^{19}F and ^{31}P NMR spectra were not externally referenced.

Chemical shifts (δ) are quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and ^{19}F NMR spectra, and 0.1 ppm for ^{13}C NMR spectra. Only those signals in the ^{13}C NMR spectra that are within 0.1 ppm are reported to the nearest 0.01 ppm. Peak multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, spt = septet, m = multiplet, br. = broad, app. = apparent. Coupling constants (*J*) are reported to the nearest 0.1 Hz. Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HSQC, HMBC, and/or NOESY experiments.

High-Resolution Mass Spectrometry: Electrospray ionisation (ESI) HRMS were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using water:methanol:formic acid (10:89.9:0.1) as eluent. The system uses a heated electrospray ionisation (HESI-II) probe and has a resolution of 50,000 FWHM under conditions for maximum sensitivity. The mass reported is that containing the most abundant isotopes, with all values reported to 4 decimal places and within a 5 ppm tolerance.

Chemical ionisation (CI) HRMS was performed on an Agilent 7200 Q-ToF instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software, and the reagent gas used was ammonia. All values are reported to 4 decimal places and are within a 5 ppm tolerance.

1.2 General procedures.

1.2a Example procedure for the synthesis of 1,1-dibromoenamides.

Step 1: To an oven dried, 250 mL round bottomed flask. equipped with a magnetic stirrer bar. was added *N*-benzyltosylamide (5.00 g, 19.1 mmol, 1.0 equiv.) and the flask was capped with a septum. The flask was then evacuated under high vacuum for 30 seconds to remove air and carefully backfilled with nitrogen (this vacuum cycle was repeated twice more). Next was added anhydrous THF (115 mL, 6 mL $mmol^{-1}$ of amide substrate) and the resulting solution was cooled to 0 °C whilst stirring. A solution of *n*-butyllithium (8.42 mL of a 2.5 M solution in hexanes, 21.1 mmol, 1.1 equiv.) was then added dropwise over 5 minutes, and left to stir at 0 °C for 10 minutes. ***Note***: The solution turned a pale yellow upon the addition of *n*-butyllithium, but when nearing the reaction end point, the solution will begin to turn deep orange, which upon stirring will return to pale yellow. Slow the rate of addition at this point and cease the addition of *n*-butyllithium when the reaction remains deep orange.

To a second oven dried, 100 mL round bottomed flask. equipped with a magnetic stirrer bar. was added 1*H*-benzotriazole-1-carbaldehyde (BtCHO)[381] (3.38 g, 23.0 mmol, 1.2 equiv.) and the flask was capped with a septum. The flask was then evacuated under high vacuum for 30 seconds to remove air and carefully backfilled with nitrogen (this vacuum cycle was repeated twice more). Anhydrous THF (40 mL, 2 mL $mmol^{-1}$ of amide substrate) was added and the mixture stirred until full dissolution of the material. This solution was then added dropwise, either by syringe or using an oven dried cannula, to previously prepared solution of *N*-lithiated sulfonamide at 0 °C. The flask which contained BtCHO was rinsed with a further 10 mL of anhydrous THF and this was added to the reaction. The cooling bath was removed at this point and the reaction mixture was then stirred at room temperature until reaction completion (~20 minutes), as analysed by TLC (20% EtOAc/petroleum ether). ***Note***: There is sometimes a white precipitate (lithium benzotriazolide) formed during this reaction. The reaction mixture was poured into a 500 mL separating funnel containing Et_2O (~80 mL) and a 2 M aqueous solution of K_2CO_3 (150 mL). The reaction vessel was thoroughly rinsed with Et_2O and water (3×20 mL each, alternately) and these washings were poured into the separating funnel. The organic layer was then separated and further washed with 2 M aqueous K_2CO_3 (2×200 mL). At this point, TLC analysis (20% EtOAc/petroleum ether) of both the organic and aqueous layers was conducted to confirm complete separation of the product from the remaining BtCHO and benzotriazole (stained with vanillin to visualise). ***Note***: If the separation is not complete, continue extraction as necessary. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to afford crude *N*-benzyl-*N*-tosyl formamide **158** (5.48 g) as a pale yellow solid. This was used in the next step without purification.

Step 2: To an oven dried 250 mL round bottomed flask equipped with a magnetic stirrer bar was added triphenylphosphine (20.1 g, 76.5 mmol, 4.0 equiv.) and the flask was capped with a septum. The flask was then evacuated under high vacuum for 30 seconds to remove air and carefully backfilled with nitrogen (this vacuum cycle was repeated twice more). Next was added anhydrous CH_2Cl_2 (115 mL, 6 mL $mmol^{-1}$ of amide substrate) and the resulting solution was cooled to -10 °C whilst stirring. A solution of tetrabromomethane (12.7 g, 38.3 mmol, 2.0 equiv.) in anhydrous CH_2Cl_2 (20 mL, 1 mL $mmol^{-1}$ of amide substrate), which was prepared in the same manner as the solution of BtCHO previously, was next added dropwise, either by syringe or using an oven dried cannula, to the solution of triphenylphosphine and the mixture was stirred at -10 °C for 30 minutes. The resulting yellow/orange solution was cooled to -30 °C and a solution of crude formamide (5.48 g, 18.9 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (60 mL, 3 mL $mmol^{-1}$ of amide substrate) was added dropwise over 20 minutes (at a maximum rate of 1 mmol min^{-1}) at -30 °C. The stirring reaction mixture was then allowed to warm gradually to room temperature over a period of 4 hours and was stirred until reaction completion (~4–5 hours). ***Note***: The reaction mixture turns a dark orange or red upon completion. Complete consumption of the formamide was verified at this point by TLC (20% Et_2O/petroleum ether, visualise under UV and/or stain with $KMnO_4$).

The resulting dark red mixture was then concentrated in vacuo to roughly 50% volume and was poured onto a silica gel column (dimensions ~8×10 cm) that was pre-soaked with 10% EtOAc/petroleum ether. ***Note***: The solid phosphonium/phosphine oxide byproducts are insoluble in 10% EtOAc/petroleum ether and sonication may be required to break up this solid into a fine powder to facilitate product isolation. The reaction vessel was rinsed with 10% EtOAc/petroleum ether (2×10 mL) and the washings were added to the column. The compound was eluted from the silica using 10% EtOAc/petroleum ether and concentration of the filtrate afforded *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide **156a** (8.17 g, 18.4 mmol, 96%) as a white solid. This wa usually of sufficient purity for use in subsequent couplings, however further purification can be achieved by recrystallisation from either heptane or ethanol. This gives the compound as hair-like colourless needles. It is also highly recommended that all dibromoenamides be stored in a freezer (-20 °C) under inert atmosphere.

1.2b Example procedure for the synthesis of yndiamides.

To an oven dried, 100 mL round bottomed flask, equipped with a magnetic stirrer bar was added *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide **156a** (5.00 g, 11.2 mmol, 1.1 equiv.) and *N*-(but-3-en-1-yl)tosylamide (2.30 g, 10.2 mmol, 1.0 equiv.), and the flask was capped with a septum. The flask was then evacuated under high vacuum for 10 minutes to remove air and carefully backfilled with nitrogen (this vacuum cycle was repeated twice more, but at 1 minute intervals). This flask was taken to a nitrogen filled glovebox and copper(I) iodide (389 mg, 2.03 mmol, 0.2 equiv.), anhydrous

1,10-phenanthroline (736 mg, 4.08 mmol, 0.4 equiv.) and powdered anhydrous caesium carbonate (9.98 g, 30.6 mmol, 3.0 equiv.) were added. ***Note***: The caesium carbonate should be finely powdered and dispensing under inert atmosphere is crucial to prevent absorption of atmospheric moisture. Furthermore, for most reactions 2.5 equiv. of anhydrous caesium carbonate is sufficient to achieve full conversion, but 3.0 equiv. can be used without detriment. The flask was then removed from the glovebox and was equipped with a reflux condenser topped with a septum. This was connected to a Schlenk line with a needle through the septum, and the vessel was purged under high vacuum for 10 minutes, followed by the careful addition of nitrogen (this vacuum cycle was repeated twice more, but at 1 minute intervals). Anhydrous THF (33 mL, 3 $mmol^{-1}$ of amide substrate) was added through the condenser, and the mixture was sonicated for 10 minutes to dissolve the soluble reactants. The resulting dark blue suspension was then stirred vigorously under a nitrogen atmosphere at 60 °C until reaction completion (30 hours), as analysed by TLC (4% Et_2O/toluene or 10% CH_2Cl_2/2% EtOAc/40-60 petroleum ether, visualise under UV and stain with $KMnO_4$ or vanillin). In general, these reactions typically take 18–36 hours to reach completion. ***Note***: After sonication, the suspension is usually dark blue, but depending on the nature of the substrates used, can also be dark green or dark brown. Within 30 minutes at 60 °C, these reactions change colour to give a beige/brown mixture, before turning dark blue/brown upon reaction completion. ***Note***: The reagents and reactions must be kept strictly anhydrous to minimise the formation of byproducts. If the reaction mixture becomes pale blue, it is very likely it was contaminated with water and there will be increased amounts of bromoketene aminal or diyne formed. The reactions of phosphoramidates are more sensitive to moisture and often turn pale blue, which results in lower yields of the desired product.

Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL), and the resultant mixture was poured onto a Celite® pad (dimensions ~5×5 cm) that was pre-soaked with EtOAc. The reaction vessel was rinsed with EtOAc (2×10 mL) and the washings added onto the Celite®. The compound was eluted using EtOAc and the brown filtrate was concentrated in vacuo. Column chromatography (10% CH_2Cl_2/2% EtOAc/40-60 petroleum ether) afforded the yndiamide, *N*-benzyl-*N*-(((*N*′-but-3-en-1-yl)tosylamido)ethynyl)-tosylamide **148k** (3.18 g, 6.88 mmol, 61%), as a white powder. ***Note***: The yndiamides and starting sulfonamides often have very similar R_f values, and this solvent mixture is very effective at providing separation. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of yndiamide in toluene.

1.2c General procedure for palladium-catalysed cycloisomerisation of enyndiamides.[33]

To a solution of yndiamide (1.0 equiv.) in anhydrous toluene (6 mL $mmol^{-1}$) was added *N*,*N*′-bis(benzylidene)ethylenediamine (bbeda) (10 mol%) and $Pd(OAc)_2$ (10 mol%). The resulting orange

solution was stirred at 60 °C until reaction completion (as indicated by TLC analysis). ***Note***: These reactions typically turn black upon completion. The reaction mixture was then cooled to room temperature and was concentrated in vacuo. Purification was performed as described for each compound.

1.2d General procedure for thermal [4+2] cycloadditions of enyndiamides.

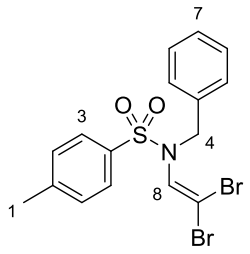
To a solution of 1,3-diene (1.0 equiv.) in toluene (5 mL $mmol^{-1}$) was added dienophile (1.0 equiv.). The mixture was stirred at the stated temperature until reaction completion (as indicated by TLC analysis). Upon completion, the reaction mixture was cooled to room temperature, and was concentrated in vacuo. Purification was performed as described for each compound.

2 Characterisation data.

2.1 Synthesis of Yndiamides.

2.1a *Dibromoenamides*.

_N_-Benzyl-_N_-(2,2-dibromovinyl)tosylamide, 156a

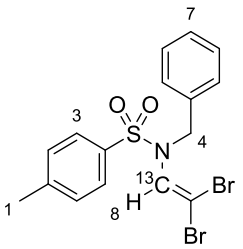


Synthesis according to example procedure **1.2a**;

m.p. 122–123 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 8.3 Hz, *H*3), 7.38–7.23 (7H, m, *H*2, *H*5, *H*6, *H*7), 6.61 (1H, s, *H*8), 4.53 (2H, s, *H*4), 2.45 (3H, s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 135.7, 135.0, 131.3, 129.9, 128.6, 128.5, 128.1, 127.4, 97.2, 52.7, 21.6.

Data are consistent with literature values.[211]

_N_-Benzyl-_N_-(2,2-dibromovinyl-1-^{13}C)tosylamide, 156a*



To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar and a septum was added anhydrous ^{13}C-sodium formate (50.0 mg, 0.726 mmol, 1.0 equiv.), *N*-benzyltosylamide (189 mg, 0.726 mmol, 1.0 equiv.), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride salt (EDCI·HCl) (278 mg, 1.45 mmol, 2.0 equiv.) and 4-(dimethylamino) pyridine (DMAP) (195 mg, 1.59 mmol, 2.2 equiv.). Anhydrous CH_2Cl_2 (2.5 mL) was added and the mixture was stirred at room temperature until reaction completion (~5 hours as analysed by TLC (20% EtOAc/petroleum ether)). The resulting mixture was diluted with EtOAc (10 mL) and extracted with 1 M aqueous HCl (3×10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to afford the crude ^{13}C-formamide. Trituration with ice-cold Et_2O afforded the ^{13}C-formamide (199 mg, 0.684 mmol, 94%) as a white powder.

Following *step 2* of example procedure **1.2a**: To an oven dried, nitrogen flushed flask was added triphenylphosphine (542 mg, 2.08 mmol, 4.0 equiv.) and anhydrous CH_2Cl_2 (3 mL), and cooled to –10 °C whilst stirring. A solution of tetrabromomethane (343 mg, 1.04 mmol, 2.0 equiv.) in anhydrous CH_2Cl_2 (1 mL) was next added and the mixture was stirred at –10 °C for 30 minutes. The resulting yellow/orange solution was cooled to –30 °C and a solution of ^{13}C-formamide (150 mg, 0.520 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (2 mL) was added dropwise over 10 minutes. The stirring reaction mixture was then allowed to warm gradually to room temperature and stirred overnight. The resulting dark red mixture was concentrated in vacuo to roughly 50% volume and then filtered through a silica gel column (eluting with 10% EtOAc/petrol) to afford the crude dibromoenamide. Recrystallisation from heptane afforded the title compound (121 mg, 0.272 mmol, 53%) as colourless needles;

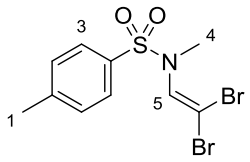
m.p. 122 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 8.3 Hz, *H*3), 7.38–7.23 (7H, m, *H*2, *H*5, *H*6, *H*7), 6.61 (1H, d, *J* = 186 *Hz*, *H*8), 4.53 (2H, d, *J* = 3.7 Hz, *H*4), 2.45 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 135.7, 135.0, 131.3* (1C, s and d, *J* = 94.2 Hz), 129.9, 128.6, 128.5, 128.1, 127.4, 97.1 (1C, d, *J* = 94.2 Hz), 52.7, 21.6; *The indicated signal corresponds to the ^{13}C labelled carbon.

HRMS (ES+) calc. for $C_{15}{}^{13}CH_{15}{}^{79}Br_2NNaO_2S$ $[M+Na]^+$ 466.9116, found 466.9116.

_N_-Methyl-_N_-(2,2-dibromovinyl)tosylamide, 156b

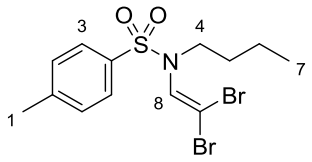


Following *step 1* of example procedure **1.2a**: *N*-methyl-*N*-tosylformamide (828 mg, 3.88 mmol, 72%) was prepared from *N*-methyltosylamide (1.00 g, 5.40 mmol, 1.0 equiv.) in anhydrous THF (32 mL) with *n*-butyllithium (2.38 mL of a 2.5 M solution in hexanes, 5.94 mmol, 1.1 equiv.) and BtCHO (953 mg, 6.48 mmol, 1.2 equiv.).

Following *step 2* of example procedure **1.2a**: The dibromoenamide was synthesised using *N*-methyl-*N*-formyltosylamide (500 mg, 2.34 mmol, 1.0 equiv.), triphenylphosphine (2.46 g, 9.36 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (30 mL) and tetrabromomethane (1.56 g, 4.68 mmol, 2.0 equiv.). This afforded the title compound (812 mg, 2.20 mmol, 94%) as a white powder. ***Note***: This compound is very sensitive to hydrolysis in air and must be stored under inert atmosphere;

m.p. 68–70 °C;
R_f 0.56 (20% EtOAc/40-60 petroleum ether);
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.3 Hz, *H*3), 7.35 (2H, d, *J* = 8.3 Hz, *H*2), 6.96 (1H, s, *H*8), 3.05 (3H, s, *H*4), 2.44 (3H, s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 134.2, 132.9, 129.9, 127.4, 89.5, 36.0, 21.6;
HRMS (ES+) calc. for $C_{10}H_{12}{}^{79}Br_2NO_2S$ $[M+H]^+$ 367.8950, found 367.8951.

_N_-_n_-Butyl-_N_-(2,2-dibromovinyl)tosylamide, 156c



Following example procedure **1.2a**: Synthesised from *N*-*n*-butyltosylamide (2.50 g, 11.0 mmol, 1.0 equiv.) in anhydrous THF (66 mL) with *n*-butyllithium (4.84 mL of a 2.5 M solution in hexanes, 12.1 mmol, 1.1 equiv.), BtCHO (1.94 mg, 13.2 mmol, 1.2 equiv.) in anhydrous THF (33 mL), triphenylphosphine (11.6 g, 44.0 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (99 mL) and tetrabromomethane (7.30 g, 22.0 mmol, 2.0 equiv.). This afforded the title compound (4.04 g, 9.79 mmol, 89%) as a cream powder;

m.p. 83–85 °C;

R_f 0.33 (5% EtOAc/pentane);

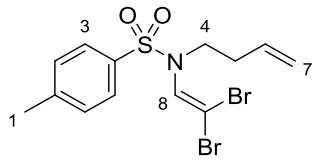
IR (thin film, ν_{max} / cm^{-1}) 2957, 2928, 2871, 1599 1493, 1467. 1387, 1353, 1327, 1293, 1240, 1182, 1164, 1122, 1089, 1059, 1036, 997, 933, 860, 832 814, 801, 739, 654;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.2 Hz, *H*3), 7.32 (2H, d, *J* = 8.2 Hz, *H*2), 6.64 (1H, s, *H*8), 3.30 (2H, t, *J* = 7.6 Hz, *H*4), 2.43 (3H, s, *H*1), 1.50 (2H, quin, *J* = 7.6 Hz, *H*5), 1.33 (2H, sxt, *J* = 7.6 Hz, *H*6), 0.90 (3H, t, *J* = 7.6 Hz, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 135.5, 131.5, 129.8, 127.3, 95.6, 49.0, 30.4, 21.6, 19.8, 13.6;

HRMS (ES+) calc. for $C_{13}H_{18}{}^{79}Br_2NO_2S$ $[M+H]^+$ 409.9420, found 409.9419.

***N*-(But-3-en-1-yl)-*N*-(2,2-dibromovinyl)tosylamide, 156d**



Following example procedure **1.2a**: Synthesised from *N*-(but-3-en-1-yl)tosylamide (1.00 g, 4.44 mmol, 1.0 equiv.) in anhydrous THF (25 mL) with *n*-butyllithium (1.95 mL of a 2.5 M solution in hexanes, 4.88 mmol, 1.1 equiv.), BtCHO (784 mg, 5.33 mmol, 1.2 equiv.) in anhydrous THF (12 mL), triphenylphosphine (4.66 g, 17.8 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (25 mL) and tetrabromomethane (2.94 g, 8.88 mmol, 2.0 equiv.). This afforded the title compound (1.65 g, 4.04 mmol, 91%) as a white powder;

m.p. 61–63 °C;

R_f 0.44 (4% EtOAc/10% CH_2Cl_2/40-60 petroleum ether);

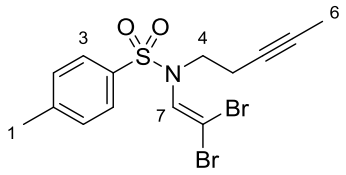
IR (thin film, ν_{max} / cm^{-1}) 2922, 1641, 1597, 1493, 1352, 1043, 1090, 860, 814, 723, 660;

^{1}H NMR (400 MHz, $CDCl_3$) 7.72–7.65 (2H, m, *H*3), 7.32 (2H, d, *J* = 8.1 Hz, *H*2), 6.70 (1H, s, *H*8), 5.71 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, *H*6), 5.13–4.99 (2H, m, *H*7), 3.41 (2H, t, *J* = 7.3 Hz, *H*4), 2.43 (3H, s, *H*1), 2.32–2.25 (2H, m, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 135.5, 134.1, 131.4, 129.8, 127.3, 117.5, 95.4, 48.6, 32.9, 21.6;

HRMS (ES+) calc. for $C_{13}H_{16}{}^{79}Br_2NO_2S$ $[M+H]^+$ 407.9263, found 407.9264.

_N_-(2,2-Dibromovinyl)-_N_-(pent-3-yn-1-yl)tosylamide, 156e



Following example procedure **1.2a**: Synthesised from *N*-(pent-3-yn-1-yl)tosylamide (1.00 g, 4.21 mmol, 1.0 equiv.) in anhydrous THF (25 mL) with *n*-butyllithium (1.85 mL of a 2.5 M solution in hexanes, 4.64 mmol, 1.1 equiv.), BtCHO (744 mg, 5.06 mmol, 1.2 equiv.) in anhydrous THF (12 mL), triphenylphosphine (4.42 g, 16.9 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (25 mL) and tetrabromomethane (2.79 g, 8.43 mmol, 2.0 equiv.). This afforded the title compound (1.62 g, 3.85 mmol, 91%) as a white powder;

m.p. 104 °C;

R_f 0.49 (5% EtOAc/10% CH_2Cl_2/40-60 petroleum ether);

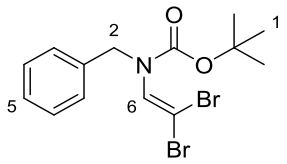
IR (thin film, ν_{max} / cm^{-1}) 2918, 1597, 1437, 1354, 1164, 1092, 814, 719;

^{1}H NMR (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.3 Hz, *H*3), 7.33 (2H, d, *J* = 8.3 Hz, *H*2), 6.79 (1H, s, *H*7), 3.49 (2H, t, *J* = 7.6 Hz, *H*4), 2.44 (3H, s, *H*1), 2.45–2.36 (2H, m, *H*5), 1.75 (3H, t, *J* = 2.6 Hz, *H*6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 135.8, 131.3, 129.9, 127.3, 95.8, 78.2, 75.1, 48.4, 21.6, 19.6, 3.5;

HRMS (ES+) calc. for $C_{14}H_{16}{}^{79}Br_2NO_2S$ $[M+H]^+$ 419.9263, found 419.9265.

_t_-Butyl benzyl(2,2-dibromovinyl)carbamate, 156k

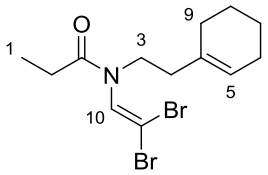


Following example procedure **1.2a**: Synthesised from *t*-butyl benzylcarbamate (200 mg, 0.965 mmol, 1.0 equiv.) in anhydrous THF (5 mL) with *n*-butyllithium (0.42 mL, 2.5 M in hexanes, 1.06 mmol, 1.1 equiv.), BtCHO (170 mg, 1.16 mmol, 1.2 equiv.) in anhydrous THF (2.5 mL), triphenylphosphine (1.01 g, 3.86 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (5 mL) and tetrabromomethane (640 mg, 1.93 mmol, 2.0 equiv.). This afforded the title compound (359 mg, 0.918 mmol, 95%) as a colourless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34–7.14 (5H, m, *H*3, *H*4, *H*5), 6.97 (1H, br. s, *H*6), 4.73 (2H, s, *H*2), 1.45 (9H, br. s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.2, 133.6, 129.0, 128.5, 128.2, 128.1, 127.4, 126.7, 126.6, 125.3, 81.9, 50.1, 28.1; ***Note***: This spectrum has multiple peaks attributed to rotamers.

Data are consistent with literature values.[537]

_N_-(3-(Cyclohex-1-en-1-yl)ethyl)-_N_-(2,2-dibromovinyl)propionamide, 156n



To an oven dried flask cooled to 0 °C was added ethyl formate (12.9 mL, 160 mmol, 10 equiv.) followed by 2-(cyclohex-1-en-1-yl)ethylamine (2.00 g, 16.0 mmol, 1.0 equiv.) dropwise over 10 minutes. The reaction was stirred for 1 hour and then concentrated in vacuo to afford the crude formamide. The flask was purged with nitrogen, followed by addition of anhydrous CH_2Cl_2 (40 mL), and was cooled to 0 °C. 4-(*N*,*N*-Dimethylamino)pyridine (195 mg, 1.60 mmol, 0.1 equiv.) and triethylamine (4.45 mL, 32.0 mmol, 2.0 equiv.) were added, followed by propionyl chloride (1.67 mL, 19.2 mmol, 1.2 equiv.) dropwise. The reaction was allowed to warm to room temperature and was stirred for 2 hours. The reaction was carefully quenched with water (50 mL), and the organic layer separated. The organic layer was washed with 2 M aqueous HCl (2×20 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the imide (2.54 g, 12.1 mmol, 76%) as a colourless oil. The compound was used in the next step without further purification.

Following *step 2* of example procedure **1.2a**: To an oven dried, nitrogen flushed flask was added triphenylphosphine (2.51 g, 9.56 mmol, 4.0 equiv.) and anhydrous CH_2Cl_2 (15 mL), and cooled to –10 °C whilst stirring. Tetrabromomethane (1.58 g, 4.78 mmol, 2.0 equiv.) was next added and the mixture was stirred at –10 °C for 30 minutes. The resulting yellow/orange solution was cooled to –30 °C and a solution of imide (500 mg, 2.39 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (8 mL) was added dropwise over 15–20 minutes. The stirred reaction mixture was then allowed to warm gradually to room temperature and stirred until reaction completion (~4 hours). The resulting dark red mixture was concentrated in vacuo to roughly 50% volume and then filtered through a silica gel column (eluting with 10% EtOAc/40-60 petroleum ether) to afford the title compound (501 mg, 1.37 mmol, 57%) as a white powder;

m.p. 65–67 °C;

R_f 0.78 (20% EtOAc/40-60 petroleum ether);

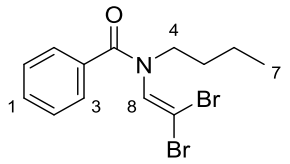
IR (thin film, ν_{max} / cm^{-1}) 2931, 1740, 1674, 1595, 1373, 136, 1045, 866;

^{1}H NMR (400 MHz, $CDCl_3$) 6.97 (1H, s, *H*10), 5.41 (1H, s, *H*5), 3.63 (2H, t, *J* = 7.1 Hz, *H*3), 2.25 (2H, q, *J* = 7.3 Hz, *H*2), 2.14 (2H, t, *J* = 7.2 Hz, *H*4), 2.02–1.84 (4H, m, *H*6, *H*9), 1.66–1.46 (4H, m, *H*7, *H*8), 0.95 (3H, t, *J* = 7.2 Hz, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 172.6, 134.9, 134.8, 123.5, 96.1, 44.9, 36.3, 27.9 (2C), 25.3, 22.8, 22.3, 9.1;

HRMS (ES+) calc. for $C_{13}H_{20}{}^{79}Br_2NO$ $[M+H]^+$ 363.9906, found 363.9908.

_N_-Butyl-_N_-(2,2-dibromovinyl)benzamide, 156p

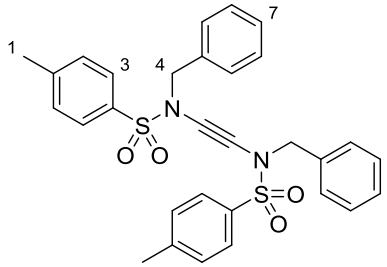


Following example procedure **1.2a**: Synthesised from *N*-butylbenzamide (200 mg, 1.13 mmol, 1.0 equiv.) in anhydrous THF (6 mL) with *n*-butyllithium (0.50 mL of a 2.5 M solution in hexanes, 1.24 mmol, 1.1 equiv.), BtCHO (199 mg, 1.35 mmol, 1.2 equiv.) in anhydrous THF (3 mL), triphenylphosphine (1.18 g, 4.51 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (6 mL) and tetrabromomethane (748 mg, 2.26 mmol, 2.0 equiv.). This afforded the title compound (277 mg, 0.768 mmol, 68%) as a colourless oil;

R_f 0.71 (20% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2959, 2932, 2872, 1649, 1600, 1447, 1400, 106, 1275, 860, 791, 711;
^{1}H NMR (400 MHz, $CDCl_3$) 7.55–7.48 (2H, m, *H*3), 7.48–7.41 (1H, m, *H*1), 7.41–7.35 (2H, m, *H*2), 7.01 (1H, s, *H*8), 3.67 (2H, t, *J* = 7.8 Hz, *H*4), 1.69–1.47 (2H, m, *H*5), 1.37 (2H, sxt, *J* = 7.4 Hz, *H*6), 0.95 (3H, t, *J* = 7.4 Hz, *H*7);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.0, 135.5, 135.2, 130.7, 128.1, 128.0, 92.9, 47.1, 29.9, 20.2, 13.8;
HRMS (ES+) calc. for $C_{13}H_{16}{}^{79}Br_2NO$ $[M+H]^+$ 359.9593, found 359.9598.

2.1b *Yndiamides*.

_N_,_N_'-(Ethyne-1,2-diyl)bis(_N_-benzyltosylamide), 148b



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (187 mg, 0.421 mmol, 1.1 equiv.), *N*-benzyltosylamide (100 mg, 0.383 mmol, 1.0 equiv.), CuI (14.6 mg, 76.5 μmol, 0.2 equiv.), 1,10-phenantholine (27.6 mg, 0.153 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (312 mg, 0.957 mmol, 2.5 equiv.) in anhydrous THF (1.2 mL). Trituration with Et_2O/40-60 petroleum ether (roughly 2:1) afforded the title compound (172 mg, 0.316 mmol, 83%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of the title compound in toluene;

m.p. 141–143 °C;

R_f 0.50 (4% Et_2O/toluene);

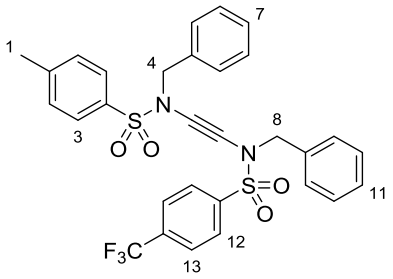
IR (thin film, ν_{max} / cm^{-1}) 3032, 2926, 1597, 1496, 1361, 1167, 1089;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54 (4H, d, *J* = 8.3Hz, H3), 7.30–7.15 (10H, m, *H*2, *H*6, *H*7), 7.07–6.98 (4H, m, *H*5), 4.39 (4H, s, *H*4), 2.43 (6H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 134.8, 134.5, 129.5, 128.6, 128.4, 128.0, 127.6, 69.9, 55.9, 21.6;

HRMS (ES+) calc. for $C_{30}H_{29}N_2O_4S_2$ $[M+H]^+$ 545.1563, found 545.1557.

_N_-Benzyl-_N_-(((_N_-benzyl-4-(trifluoromethyl)phenyl)sulfonamido)ethynyl)tosylamide, 148c



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (200 mg, 0.449 mmol, 1.1 equiv.), *N*-benzyl-4-(trifluoromethyl)phenylsulfonamide (129 mg, 0.408 mmol, 1.0 equiv.), CuI (15.6 mg, 81.6 μmol, 0.2 equiv.), 1,10-phenantholine (29.4 mg, 0.163 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (333 mg, 1.02 mmol, 2.5 equiv.) in anhydrous THF (1.4 mL). Column chromatography (10% Et_2O/40-60 petroleum ether), followed by recrystallisation from Et_2O/hexane, afforded the title compound (163 mg, 0.272 mmol, 67%) as colourless needles. These crystals were also suitable for X-ray diffraction;

m.p. 140–141 °C;

R_f 0.69 (20% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2981, 1407, 1365, 1322, 1168, 1134, 1062, 712;

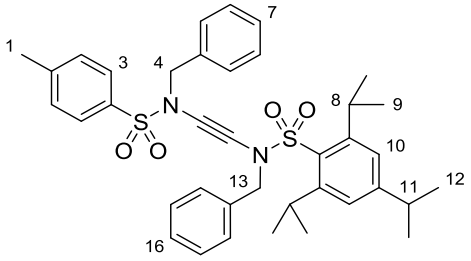
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (2H, d, *J* = 8.6 Hz, *H*13), 7.61–7.54 (4H, m, *H*3, *H*12), 7.31–7.12 (8H, m, *H*2, *H*6, *H*7, *H*10, *H*11), 7.09–7.03 (2H, m, *H*9), 7.00–6.95 (2H, m, *H*5), 4.45 (2H, s, *H*8), 4.43 (2H, s, *H*4), 2.43 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 141.1, 134.73 (1C, q, *J* = 33 Hz), 134.72, 134.4, 134.0, 129.7, 128.59, 128.56, 128.47, 128.45, 128.3, 128.2, 128.0, 127.6, 125.9 (2C, q, *J* = 3.7 Hz), 123.1 (1C, q, *J* = 273 Hz), 70.1, 69.6, 56.5, 55.8, 21.6;

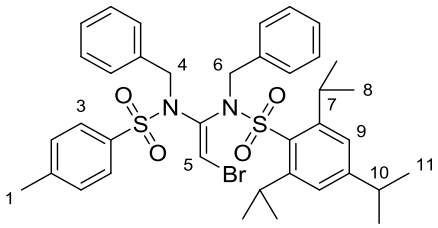
^{19}F NMR (376 MHz, $CDCl_3$) δ_P -63.2;

HRMS (ES+) calc. for $C_{30}H_{26}N_2O_4S_2F_3$ $[M+H]^+$ 599.1281 found 599.1279.

_N_-Benzyl-_N_-(((_N_-benzyltosylamido)ethynyl)-2,4,6-triisopropylbenzenesulfonamide, 148e & (_Z_)-_N_-benzyl-_N_-(1-((_N_-benzyltosylamido)-2-bromovinyl)-2,4,6-tri-_i_-propylbenzenesulfonamide 155d



148e



155d

Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.225 mmol, 1.1 equiv.), *N*-benzyl-2,4,6-triisopropylbenzenesulfonamide (76.3 mg, 0.204 mmol, 1.0 equiv.), CuI (7.8 mg, 40.8 µmol, 0.2 equiv.), 1,10-phenantholine (14.7 mg, 81.6 µmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (166 mg, 0.511 mmol, 2.5 equiv.) in anhydrous THF (0.6 mL). Column chromatography (2.5% CH_2Cl_2/1.25% EtOAc → 5% CH_2Cl_2/2.5% EtOAc/40-60 petroleum ether) afforded the yndiamide **148e** (64.3 mg, 97.9 µmol, 48%) as a yellow foam and the bromoketene aminal **155d** as a yellow oil**. 155d** was crystallised from hexane at room temperature to afford 43.0 mg (58.1 µmol, 28%) as colourless crystals. These crystals were also suitable for X-ray diffraction;

- Data for yndiamide **148e**:

R_f 0.42 (10% CH_2Cl_2/5% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2961, 1598, 1365, 1166, 1089, 724, 695, 622;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.51–7.45 (2H, m, *H*3), 7.31–7.10 (12H, m, *H*2, *H*6, *H*7, *H*10, *H*14, *H*15, *H*16), 6.98–6.92 (2H, m, *H*5), 4.51 (2H, s, *H*4), 4.28 (2H, s, *H*13), 3.92 (2H, spt, *J* = 6.7 Hz, *H*8), 2.92 (1H, spt, *J* = 7.0 Hz, *H*11), 2.40 (3H, s, *H*1), 1.26 (6H, d, *J* = 7.0 Hz, *H*12), 1.10 (12H, d, *J* = 6.7 Hz, *H*9);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.8, 151.8, 144.1, 134.9, 134.8, 134.4, 130.3, 129.5, 128.9, 128.6, 128.4, 128.3, 128.0, 127.9, 127.6, 123.8, 71.9, 69.4, 55.9, 54.1, 34.2, 29.7, 24.6, 23.5, 21.6;

HRMS (ES+) calc. for $C_{38}H_{45}N_2O_4S_2$ $[M+H]^+$ 657.2815 found 657.2813.

- Data for bromoketene aminal **155d**:

m.p. 61–63 °C;

R_f 0.48 (10% CH_2Cl_2/5% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2960, 1599, 1496, 1456, 1330, 1164, 666;

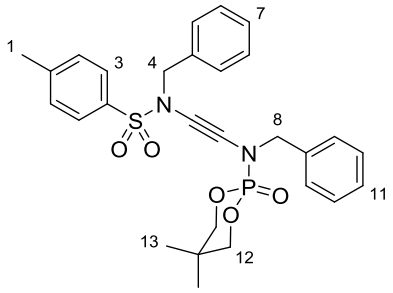
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 (2H, d, *J* = 8.3 Hz, *H*3), 7.25–7.19 (5H, m, Ph*H*), 7.19–7.14 (5H, m, Ph*H*), 7.13 (2H, d, *J* = 8.3 Hz, *H*2), 7.10 (2H, s, *H*9), 6.19 (1H, s, *H*5), 4.89 (2H, s, *H*6),

4.69 (2H, s, *H*4), 3.83 (2H, spt, *J* = 6.6 Hz, *H*7), 2.88 (1H, spt, *J* = 6.9 Hz, *H*10), 2.35 (3H, s, *H*1), 1.23 (6H, d, *J* = 6.9 Hz, *H*11), 1.10 (12H, d, *J* = 6.6 Hz, *H*8);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.8, 152.1, 144.0, 136.5, 136.4, 136.2, 136.0, 133.1, 129.5, 129.0, 128.5, 128.2, 128.12, 128.06, 127.6, 127.3, 124.1, 107.5, 50.8, 50.7, 34.1, 30.2, 24.9, 23.5, 21.5;

HRMS (ES+) calc. for $C_{38}H_{46}{}^{79}BrN_2O_4S_2$ $[M+H]^+$ 737.2077 found 737.2075.

_N_-Benzyl-_N_-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl)tosyl amide, 148g



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.225 mmol, 1.1 equiv.), 2-(benzylamino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (52.1 mg, 0.204 mmol, 1.0 equiv.), CuI (7.8 mg, 40.8 μmol, 0.2 equiv.), 1,10-phenantholine (14.7 mg, 81.6 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (166 mg, 0.511 mmol, 2.5 equiv.) in anhydrous THF (0.7 mL). Column chromatography (30% EtOAc → 50% EtOAc/40-60 petroleum ether) afforded a brown solid which was recrystallised (EtOAc/hexane) to give the title compound (88.8 mg, 0.165 mmol, 81%) as colourless crystals. These crystals were also suitable for X-ray diffraction;

m.p. 114 °C;

R_f 0.32 (50% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3032, 2970, 1597, 1497, 1456, 1409, 1360, 1290, 1169, 1059, 1009, 813, 725, 702, 596;

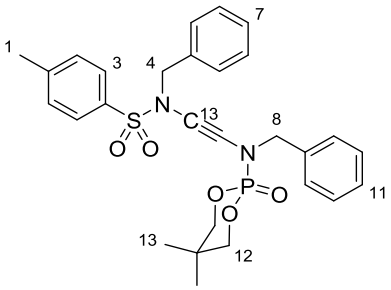
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61–7.54 (2H, m, *H*3), 7.35–7.29 (3H, m, *H*10, *H*11), 7.29–7.18 (7H, m, *H*2, *H*6, *H*7, *H*9), 7.17–7.09 (2H, m, *H*5), 4.36 (2H, s, *H*4), 4.36 (2H, d, *J* = 8.6 Hz, *H*8), 3.92 (2H, dd, *J* =10.8, 7.1 Hz, *H*12), 3.84 (2H, dd, *J* = 15.4, 10.8 Hz, *H*12), 2.44 (3H, s, *H*1), 1.11 (3H, s, *H*13), 0.69 (3H, s, *H*13);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 136.6 (1C, d, *J* = 1.5 Hz), 135.0, 134.8, 129.6, 129.2, 128.5 (2C), 128.4, 128.2, 127.8, 127.6, 79.2 (2C, d, *J* = 7.3 Hz), 72.9 (1C, d, *J* = 5.1 Hz), 64.7 (1C, d, *J* = 5.1 Hz), 55.72, 55.65 (1C, d, *J* = 7.3 Hz), 31.7 (1C, d, *J* = 7.3 Hz), 21.7, 21.6, 20.4;

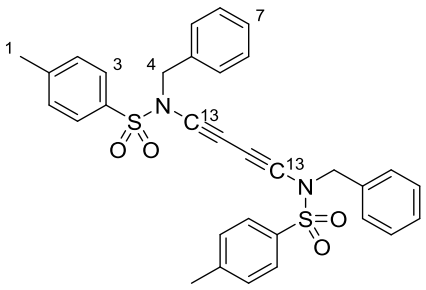
^{31}P NMR (162 MHz, $CDCl_3$) δ_P -4.96;

HRMS (ES+) calc. for $C_{28}H_{32}N_2O_5PS$ $[M+H]^+$ 539.1764, found 539.1760.

N*-Benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl-1-^{13}C) tosylamide, 148g* & *N*,*N'*-(buta-1,3-diyne-1,4-diyl-1,4-$^{13}C_2$)bis(*N*-benzyltosylamide), 159



148g*



159*

Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl-1-^{13}C)tosylamide (50.0 mg, 0.112 mmol, 1.1 equiv.), 2-(benzylamino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (26.0 mg, 0.101 mmol, 1.0 equiv.), CuI (3.9 mg, 20.3 μmol, 0.2 equiv.), 1,10-phenantholine (7.3 mg, 40.7 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (83.0 mg, 0.254 mmol, 2.5 equiv.) in anhydrous THF (0.33 mL). Column chromatography (30% EtOAc → 50% EtOAc/40-60 petroleum ether) afforded **159*** (5.8 mg, 10.2 μmol, 18%) as a white powder and **148g*** (30.2 mg, 55.9 μmol, 55%) as a pale yellow powder;

- Data for ^{13}C-labelled yndiamide **148g***:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61–7.54 (2H, m, *H*3), 7.35–7.29 (3H, m, *H*10, *H*11), 7.29–7.18 (7H, m, *H*2, *H*6, *H*7, *H*9), 7.17–7.09 (2H, m, *H*5), 4.36 (2H, d, *J* = 4.6 Hz, *H*4), 4.35 (2H, d, *J* = 8.6 Hz, *H*8), 3.92 (2H, dd, *J* = 10.8, 7.1 Hz, *H*12), 3.84 (2H, dd, *J* = 15.4, 10.8 Hz, *H*12), 2.44 (3H, s, *H*1), 1.10 (3H, s, *H*13), 0.69 (3H, s, *H*13);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 144.3, 136.6 (1C, d, *J* = 1.5 Hz), 134.9, 134.7, 129.6, 129.2, 128.5 (2C), 128.4, 128.3, 127.7, 127.6, 79.2 (2C, d, *J* = 7.2 Hz), 64.7* (1C, d, *J* = 5.6 Hz), 55.71, 55.65 (1C, d, *J* = 7.2 Hz), 31.7 (1C, d, *J* = 7.2 Hz), 21.7, 21.6, 20.4; ****Note***: The unlabelled alkyne carbon was not observed. **This signal corresponds to the ^{13}C labelled carbon.

^{31}P NMR (162 MHz, $CDCl_3$) δ_P -4.96;

HRMS (ES+) calc. for $C_{27}{}^{13}CH_{32}N_2O_5PS$ $[M+H]^+$ 540.1798, found 540.1796.

- Data for ^{13}C-labelled diyne **159***:

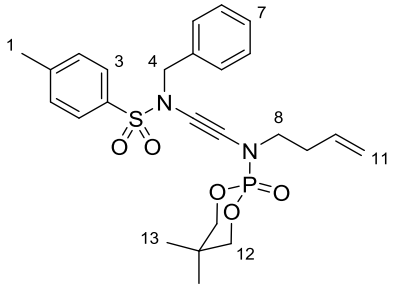
R_f 0.62 (4% Et_2O/toluene)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (4H, d, *J* = 8.3 Hz, *H*3), 7.35–7.19 (14H, m, *H*2, *H*5, *H*6, *H*7), 4.52 (4H, t, *J* = 2.2 Hz, *H*4), 2.44 (6H, s, *H*1);

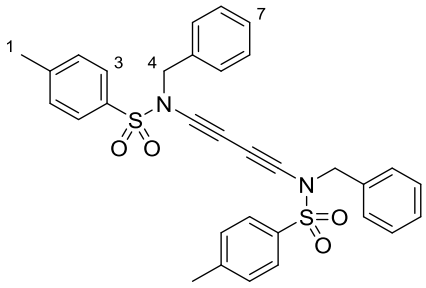
^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 144.9, 134.7, 134.1, 129.8, 128.60, 128.58, 128.4, 127.6, 75.9** (1C, s), 55.8, 21.7; ****Note***: The unlabelled alkyne carbon was not observed. **This signal corresponds to the ^{13}C labelled carbon.

HRMS (ES+) calc. for $C_{30}{}^{13}C_2H_{29}N_2O_4S_2$ $[M+H]^+$ 571.1630, found 571.1629.

_N_-Benzyl-_N_-((but-3-en-1-yl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide, 148h & _N,N'_-(buta-1,3-diyne-1,4-diyl)bis(_N_-benzyltosylamide), 159



148h



159

Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (450 mg, 1.01 mmol, 1.1 equiv.), 2-(but-3-en-1-ylamino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (201 mg, 0.919 mmol, 1.0 equiv.), CuI (35.0 mg, 0.184 mmol, 0.2 equiv.), 1,10-phenantholine (66.2 mg, 0.368 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (749 mg, 2.30 mmol, 2.5 equiv.) in anhydrous THF (3.1 mL). Column chromatography (50% EtOAc/40-60 petroleum ether → 100% EtOAc) afforded recovered 2-(but-3-en-1-ylamino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (143.1 mg, 0.654 mmol), the diyne **159** and the yndiamide **148h** as brown solids. Both were further purified by recrystallisation (EtOAc/hexane) to give **159** (49.6 mg, 87.2 μmol, 17%) and **148h** (95.5 mg, 0.190 mmol, 21% (72% brsm)), both as colourless needles. The yndiamide crystals were also suitable for X-ray diffraction, but suitable crystals of the diyne were grown by vapour diffusion of pentane into a concentrated solution of **159** in toluene;

- Data for yndiamide **148h**:

m.p. 72 °C;

R_f 0.24 (50% EtOAc/petrol);

IR (thin film, ν_{max} / cm^{-1}) 2971, 1641, 1597, 1409, 1358, 1290, 1167, 1059, 1004;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.3 Hz, *H*3), 7.35–7.25 (7H, m, *H*2, *H*5, *H*6, *H*7), 5.66 (1H, ddt, *J* = 17.9, 9.5, 6.8 Hz, *H*10), 5.08–4.95 (2H, m, *H*11), 4.52 (2H, s, *H*4), 3.98–3.76 (4H, m, *H*12), 3.21 (2H, q, *J* = 7.7 Hz, *H*8), 2.42 (3H, s, *H*1), 2.19 (2H, q, *J* = 7.0 Hz, *H*9), 1.06 (3H, s, *H*13), 0.69 (3H, s, *H*13);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 135.1, 134.8, 134.1, 129.6, 129.0, 128.5, 128.2, 127.6, 117.2, 78.7 (2C, d, *J* = 7.2 Hz), 72.7 (1C, d, *J* = 4.8 Hz), 63.8 (1C, d, *J* = 4.8 Hz), 55.7, 51.0 (1C, d, *J* = 7.2 Hz), 32.7, 31.7 (1C, d, *J* = 7.2 Hz), 21.5 (2C), 20.3;

^{31}P NMR (162 MHz, $CDCl_3$) δ_P -4.52;

HRMS (ES+) calc. for $C_{25}H_{32}N_2O_5PS$ $[M+H]^+$ 503.1764, found 503.1762.

- Data for diyne **159**:

m.p. 148 °C;

R_f 0.62 (4% Et_2O/toluene);

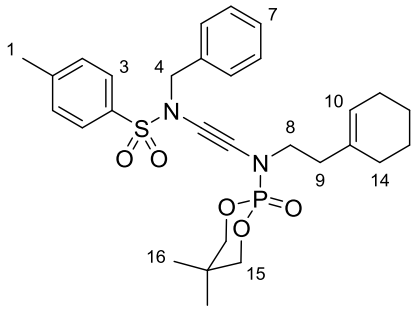
IR (thin film, ν_{max} / cm^{-1}) 2981, 2169, 1596, 1495, 1367, 1168, 1089;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (4H, d, *J* = 8.3 Hz, *H*3), 7.35–7.19 (14H, m, *H*2, *H*5, *H*6, *H*7), 4.52 (4H, s, *H*4), 2.44 (6H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.9, 134.7, 134.1, 129.8, 128.59, 128.58, 128.4, 127.6, 75.9, 60.0, 55.8, 21.7;

HRMS We were unable to obtain an accurate mass (ES+ or CI+) due to decomposition upon ionisation.

_N_-Benzyl-_N_-(((2-(cyclohex-1-en-1-yl)ethyl)(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl) amino)ethynyl)tosylamide, 148i



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (200 mg, 0.449 mmol, 1.1 equiv.), 2-((2-(cyclohex-1-en-1-yl)ethyl)amino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (112 mg, 0.408 mmol, 1.0 equiv.), CuI (15.6 mg, 81.7 μmol, 0.2 equiv.), 1,10-phenantholine (29.4 mg, 0.163 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (399 mg, 1.22 mmol, 3.0 equiv.) in anhydrous THF (1.5 mL). Column chromatography (35% EtOAc→40% EtOAc/40-60 petroleum ether), followed by crystallisation from Et_2O, afforded the title compound (148 mg, 0.265 mmol, 65%) as colourless needles. These crystals were also suitable for X-ray diffraction;

m.p. 106–107 °C;

R_f 0.24 (35% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2928, 1597, 1456, 1408, 1358, 1288, 1165, 1057, 991, 918, 814, 698, 658, 594;

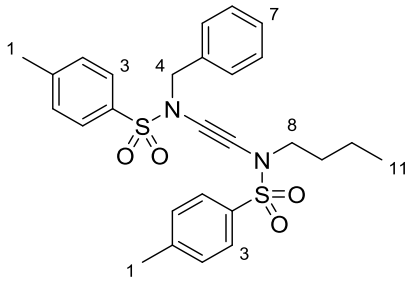
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.3 Hz, *H*3), 7.34–7.27 (7H, m, *H*2, *H*5, *H*6, *H*7), 5.36–5.31 (1H, m, *H*10), 4.53 (2H, s, *H*4), 3.93 (2H, dd, *J* = 10.9, 7.8 Hz, *H*15), 3.83 (2H, dd, *J* = 15.2, 10.9 Hz, *H*15), 3.22 (2H, td, *J* = 8.3, 6.8 Hz, *H*8), 2.43 (3H, s, *H*1), 2.06 (2H, br. t, *J* = 7.5 Hz, *H*9), 1.99–1.90 (2H, br. m, *H*11), 1.86–1.79 (2H, br. m, *H*14), 1.62–1.54 (2H, m, *H*13), 1.54–1.46 (2H, m, *H*12), 1.07 (3H, s, *H*16), 0.70 (3H, s, *H*16);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 135.2, 134.9, 133.8, 129.6, 129.1, 128.5, 128.2, 127.7, 123.6, 78.7 (2C, d, *J* = 7.2 Hz), 72.9 (1C, d, *J* = 5.6 Hz), 63.9 (1C, d, *J* = 5.6 Hz), 55.8, 50.2 (1C, d, *J* = 6.4 Hz), 36.6, 31.8 (1C, d, *J* = 7.2 Hz), 28.0, 25.2, 22.8, 22.2, 21.61, 21.56, 20.4;

^{31}P NMR (162 MHz, $CDCl_3$) δ_P -4.33;

HRMS (ES+) calc. for $C_{29}H_{38}N_2O_5PS$ $[M+H]^+$ 557.2234, found 557.2231.

_N_-Benzyl-_N_-(((_N_'-_n_-butyltosylamido)ethynyl)tosylamide, 148j



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.225 mmol, 1.1 equiv.), *N*-*n*-butyltosylamide (46.4 mg, 0.204 mmol, 1.0 equiv.), CuI (7.8 mg, 40.8 μmol, 0.2 equiv.), 1,10-phenantholine (14.7 mg, 81.7 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (166 mg, 0.511 mmol, 2.5 equiv.) in anhydrous THF (0.7 mL). Column chromatography (2% Et_2O/toluene) afforded the title compound (67.9 mg, 0.133 mmol, 65%) as a colourless oil that solidifies on standing. Crystals suitable for X-ray diffraction were grown by slow evaporation of a solution of **148j** in CH_2Cl_2/hexane (1:5);

m.p. 80–81 °C;

R_f 0.60 (4% Et_2O/toluene);

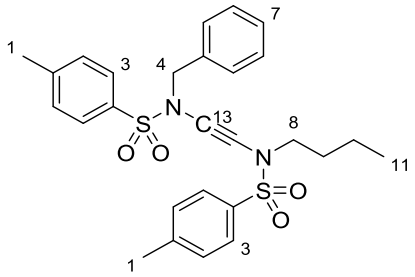
IR (thin film, ν_{max} / cm^{-1}) 2959, 2930, 1597, 1495, 1361, 1166, 1088;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.64 (2H, m, *H*2), 7.63–7.57 (2H, m, *H*2), 7.32–7.21 (7H, m, *H*3, *H*6, *H*7), 7.20–7.14 (2H, m, *H*5), 4.49 (2H, s, *H*4), 3.17 (2H, t, *J* = 7.2 Hz, *H*8), 2.43 (6H, s, *H*1), 1.34–1.22 (2H, m, *H*9), 1.18–1.07 (2H, m, *H*10), 0.77 (3H, t, *J* = 7.3 Hz, *H*11);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.3, 134.8 (2C), 134.6, 129.59, 129.58, 128.7, 128.4, 128.1, 127.6, 127.5, 69.7, 69.0, 55.9, 51.3, 29.5, 21.6 (2C), 19.2, 13.5;

HRMS (ES+) calc. for $C_{27}H_{31}N_2O_4S_2$ $[M+H]^+$ 511.1720, found 511.1719.

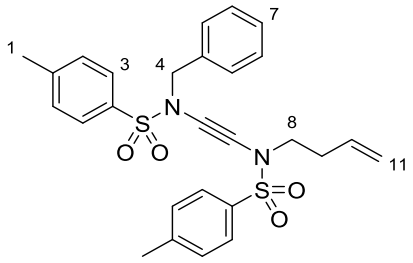
N*-Benzyl-*N*-(((*N*-butyltosylamido)ethynyl-1-^{13}C)tosylamide, 148j



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl-1-^{13}C)tosylamide (50.0 mg, 0.112 mmol, 1.1 equiv.), *N*-butyltosylamide (23.2 mg, 0.101 mmol, 1.0 equiv.), CuI (3.9 mg, 20.3 µmol, 0.2 equiv.), 1,10-phenantholine (7.3 mg, 40.7 µmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (83.0 mg, 0.254 mmol, 2.5 equiv.) in anhydrous THF (0.3 mL). Column chromatography (5% CH_2Cl_2/2.5% EtOAc/40-60 petroleum ether) afforded the title compound (36.5 mg, 71.3 µmol, 70%) as a white powder;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.64 (2H, m, *H*2), 7.63–7.57 (2H, m, *H*2), 7.32–7.21 (7H, m, *H*3, *H*6, *H*7), 7.20–7.14 (2H, m, *H*5), 4.49 (2H, d, *J* = 4.6 Hz, *H*4), 3.17 (2H, t, *J* = 7.2 Hz, *H*8), 2.44 (6H, s, *H*1), 1.34–1.22 (2H, m, *H*9), 1.18–1.07 (2H, m, *H*10), 0.77 (3H, t, *J* = 7.3 Hz, *H*11);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.3, 134.8, 134.6, 129.61, 129.58, 128.8, 128.4, 128.1, 127.7, 127.5, 69.3 (1C, d, *J* = 8.7 Hz), 69.0* (1C, s), 55.9, 51.3, 29.6, 21.6 (2C), 19.2, 13.5; *This signal corresponds to the ^{13}C labelled carbon.
HRMS (ES+) calc. for $C_{26}{}^{13}CH_{31}N_2O_4S_2$ $[M+H]^+$ 512.1753, found 512.1752.

_N_-Benzyl-_N_-(((_N_'-(but-3-en-1-yl)tosylamido)ethynyl)tosylamide, 148k

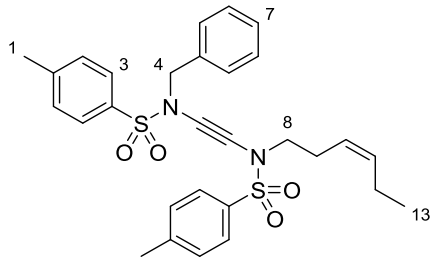


Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (500 mg, 1.12 mmol, 1.1 equiv.), *N*-(but-3-en-1-yl)tosylamide (230 mg, 1.02 mmol, 1.0 equiv.), CuI (38.9 mg, 0.204 mmol, 0.2 equiv.), 1,10-phenantholine (73.6 mg, 0.408 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (998 mg, 3.06 mmol, 3.0 equiv.) in anhydrous THF (3.3 mL). Column chromatography (10% CH_2Cl_2/2% EtOAc/40-60 petroleum ether) afforded the title compound (406 mg, 0.798 mmol, 78%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **148k** in toluene;

Also synthesised from *N*-(but-3-en-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (500 mg, 1.22 mmol, 1.1 equiv.), *N*-benzyltosylamide (290 mg, 1.11 mmol, 1.0 equiv.), CuI (42.3 mg, 0.222 mmol, 0.2 equiv.), 1,10-phenantholine (80.1 mg, 0.444 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (1.09 g, 3.33 mmol, 3.0 equiv.) in anhydrous THF (3.6 mL). Column chromatography (10% CH_2Cl_2/2% EtOAc/40-60 petroleum ether) afforded the title compound (456 mg, 0.876 mmol, 79%) as a white powder;

m.p. 86–87 °C;
R_f 0.33 (20% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2980, 1597, 1495, 1410, 1361, 1166, 1089, 813;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (2H, d, *J* = 8.3 Hz, *H*2), 7.63 (2H, d, *J* = 8.3 Hz, *H*2), 7.37–7.25 (7H, m, *H*3, *H*6, *H*7), 7.25–7.17 (2H, m, H5), 5.55 (1H, ddt, *J* = 17.0, 10.3, 6.8 Hz, *H*10), 5.01–4.89 (2H, m, *H*11), 4.53 (2H, s, *H*4), 3.29 (2H, t, *J* = 7.3 Hz, *H*8), 2.47 (6H, s, *H*1), 2.13–2.03 (2H, m, *H*9);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.4, 134.88, 134.85, 134.6, 133.6, 129.63, 129.61, 128.7, 128.41, 128.1, 127.7, 127.5, 117.5, 69.52, 69.46, 55.9, 51.0, 31.9, 21.6 (2C);
HRMS (ES+) calc. for $C_{27}H_{29}N_2O_4S_2$ $[M+H]^+$ 509.1563, found 509.1563.

(*Z*)-*N*-Benzyl-*N*-(((*N*'-(hex-3-en-1-yl)tosylamido)ethynyl)tosylamide, 148l



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (550 mg, 1.24 mmol, 1.1 equiv.), *N*-(hex-3-en-1-yl)tosylamide (285 mg, 1.12 mmol, 1.0 equiv.), CuI (42.8 mg, 0.225 mmol, 0.2 equiv.), 1,10-phenantholine (81.0 mg, 0.449 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (1.10 g, 3.37 mmol, 3.0 equiv.) in anhydrous THF (3.6 mL). Column chromatography (10% CH_2Cl_2/2% EtOAc/40-60 petroleum ether) afforded the title compound (406 mg, 0.757 mmol, 67%) as a colourless oil that solidifies on standing, affording crystals that were used for X-ray diffraction;

m.p. 45–46 °C;

R_f 0.42 (20% EtOAc/40-60 petroleum ether);

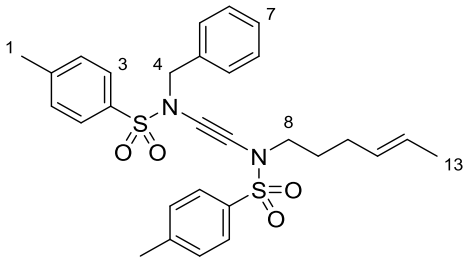
IR (thin film, ν_{max} / cm^{-1}) 2963, 1597, 1495, 1361, 1166, 1088;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.3 Hz, *H*3), 7.60 (2H, d, *J* = 8.3 Hz, *H*3), 7.31–7.20 (7H, m, *H*2, *H*6, *H*7), 7.20–7.13 (2H, m, *H*5), 5.42–5.32 (1H, m, *H*11), 5.12–5.01 (1H, m, *H*10), 4.50 (2H, s, *H*4), 3.19 (2H, t, *J* = 7.6 Hz, *H*8), 2.43 (6H, s, *H*1), 2.05 (2H, q, *J* = 7.6 Hz, *H*9), 1.86 (2H, quind, *J* = 7.5, 1.5 Hz, *H*12), 0.89 (3H, t, *J* = 7.6 Hz, *H*13);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.4, 134.9, 134.8, 134.7, 134.6, 129.6 (2C), 128.7, 128.4, 128.1, 127.6, 127.5, 123.3, 69.6, 69.3, 55.9, 51.4, 25.7, 21.6 (2C), 20.4, 14.1;

HRMS (CI+) calc. for $C_{29}H_{33}N_2NaO_4S_2$ $[M+H]^+$ 537.1876, found 537.1882.

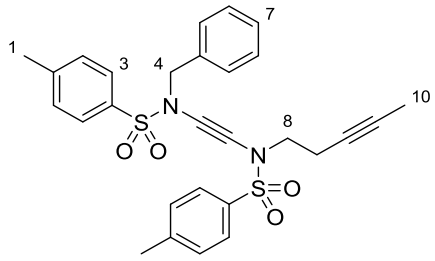
(*E*)-*N*-Benzyl-*N*-(((*N*'-(hex-4-en-1-yl)tosylamido)ethynyl)tosylamide, 148m



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (500 mg, 1.12 mmol, 1.1 equiv.), (*E*)-*N*-(hex-4-en-1-yl)tosylamide (259 mg, 1.02 mmol, 1.0 equiv.), CuI (38.9 mg, 0.204 mmol, 0.2 equiv.), 1,10-phenantholine (73.6 mg, 0.408 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (998 mg, 3.06 mmol, 3.0 equiv.) in anhydrous THF (3.3 mL). Column chromatography (10% CH_2Cl_2/2% EtOAc/40-60 petroleum ether) afforded the title compound (460 mg, 0.857 mmol, 84%) as a pale yellow semi solid;

R_f 0.44 (20% EtOAc/petrol);
IR (thin film, ν_{max} / cm^{-1}) 2931, 1597, 1495, 1411, 1361, 1166, 813;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.1 Hz, *H*3), 7.60 (2H, d, *J* = 8.1 Hz, *H*3), 7.33–7.21 (7H, m, *H*2, *H*6, *H*7), 7.21–7.13 (2H, m, *H*5), 5.38–5.27 (1H, m, *H*11), 5.27–5.15 (1H, m, *H*12), 4.49 (2H, s, *H*4), 3.17 (2H, t, *J* = 7.2 Hz, *H*8), 2.44 (6H, s, *H*1), 1.80 (2H, q, *J* = 6.9 Hz, *H*10), 1.62 (3H, dd, *J* = 6.1, 1.2 Hz, *H*13), 1.37 (2H, quin, *J* = 7.2 Hz, *H*9);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.3, 134.8 (2C), 134.6, 129.61, 129.59, 129.5, 128.7, 128.4, 128.1, 127.7, 127.5, 125.9, 69.7, 69.1, 55.9, 51.0, 28.9, 27.4, 21.6 (2C), 17.9;
HRMS (ES+) calc. for $C_{29}H_{33}N_2O_4S_2$ $[M+H]^+$ 537.1876, found 537.1876.

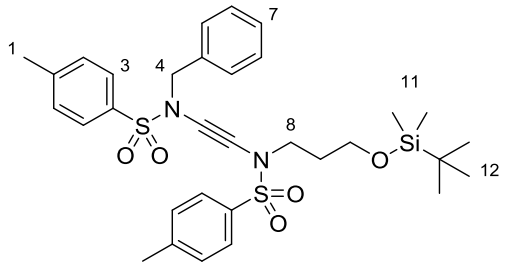
_N_-Benzyl-_N_-(((_N′_-(pent-3-yn-1-yl)tosylamido)ethynyl)tosylamide, 148n



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (30 mg, 67.4 μmol, 1.0 equiv.), *N*-(pent-3-yn-1-yl)tosylamide (16.0 mg, 67.4 μmol, 1.0 equiv.), CuI (2.6 mg, 13.5 μmol, 0.2 equiv.), 1,10-phenantholine (4.9 mg, 27.0 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (65.9 mg, 0.202 mmol, 3.0 equiv.) in anhydrous THF (0.2 mL). Column chromatography (2% Et_2O/toluene) afforded the title compound (26.0 mg, 49.9 μmol, 74%) as a viscous, pale yellow oil;

R_f 0.53 (4% Et_2O/toluene);
IR (thin film, ν_{max} / cm^{-1}) 2924, 1597, 1491, 1412, 1363, 1165, 1091, 989, 811, 710, 678;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.3 Hz, *H*3), 7.62 (2H, d, *J* = 8.3 Hz, *H*3), 7.33–7.22 (7H, m, *H*2, *H*6, *H*7), 7.20–7.15 (2H, m, *H*5), 4.50 (2H, s, *H*4), 3.38–3.29 (2H, m, *H*8), 2.45 (3H, s, *H*1), 2.44 (3H, s, *H*1), 2.15–2.06 (2H, m, *H*9), 1.70 (3H, t, *J* = 2.4 Hz, *H*10);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 144.5, 134.9, 134.8, 134.6, 129.7, 128.8, 128.5, 128.2, 127.68, 127.65, 127.56, 77.7, 75.4, 69.8, 69.3, 56.0, 50.7, 21.7, 18.2, 3.4;
HRMS (ES+) calc. for $C_{28}H_{29}N_2O_4S_2$ $[M+H]^+$ 521.1563, found 521.1567.

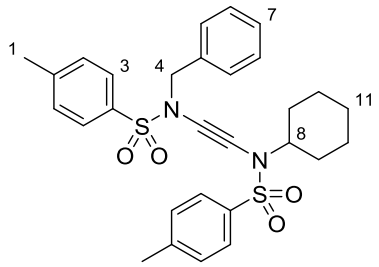
_N_-Benzyl-_N_-(((_N_-(3-((_t_-butyldimethylsilyl)oxy)propyl)tosylamido)ethynyl)tosylamide, 148o



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (185 mg, 0.416 mmol, 1.2 equiv.), *N*-(3-((*t*-butyldimethylsilyl)oxy)propyl)tosylamide (119 mg, 0.346 mmol, 1.0 equiv.), CuI (13.2 mg, 69.3 μmol, 0.2 equiv.), 1,10-phenantholine (25.0 mg, 0.139 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (339 mg, 1.04 mmol, 3.0 equiv.) in anhydrous THF (1.2 mL). Column chromatography (14% Et_2O/40-60 petroleum ether) afforded the title compound (137 mg, 0.219 mmol, 63%) as a colourless oil;

R_f 0.13 (14% Et_2O/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2924, 1598, 1494, 1350, 1163, 1093, 904, 746, 658;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73–7.65 (2H, m, *H*3), 7.64–7.58 (2H, m, *H*3), 7.34–7.22 (7H, m, *H*2 (×2), *H*6, *H*7), 7.19–7.14 (2H, m, *H*5), 4.49 (2H, s, *H*4), 3.42 (2H, t, *J* = 5.9 Hz, *H*10), 3.31 (2H, t, *J* = 7.2 Hz, *H*8), 2.44 (3H, s, *H*1), 2.44 (3H, s, *H*1), 1.51 (2H, tt, *J* = 7.2, 5.9 Hz, *H*9), 0.87 (9H, s, *H*12), 0.01 (6H, s, *H*11);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 144.3, 134.8, 134.7, 134.6, 129.6, 129.5, 128.7, 128.3, 128.0, 127.6, 127.5, 69.5, 69.2, 59.4, 55.8, 48.5, 30.6, 25.8, 21.6 (2C), 18.1, -5.5;
HRMS (ES+) calc. for $C_{32}H_{43}N_2O_5S_2Si$ $[M+H]^+$ 627.2377, found 627.2376.

_N_-Benzyl-_N_-(((_N_-cyclohexyltosylamido)ethynyl)tosylamide, 148q



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (200 mg, 0.449 mmol, 1.1 equiv.), *N*-cyclohexyltosylamide (114 mg, 0.408 mmol, 1.0 equiv.), CuI (15.6 mg, 81.7 μmol, 0.2 equiv.), 1,10-phenantholine (29.4 mg, 0.163 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (399 mg, 1.22 mmol, 3.0 equiv.) in anhydrous THF (1.5 mL). Column chromatography (15% Et_2O/40-60 petroleum ether) afforded the title compound (132 mg, 0.250 mmol, 61%) as a white powder. Crystals suitable for X-ray diffraction were grown by slow cooling of a solution of the title compound in $Et_2O/CHCl_3$/hexane (~2:1:10) from 70 °C to room temperature;

m.p. 113–114 °C;

R_f 0.68 (35% Et_2O/petrol);

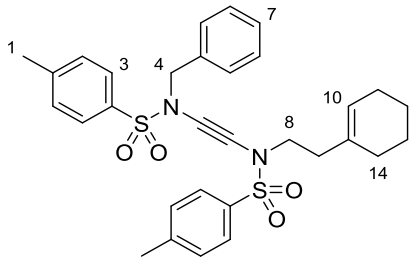
IR (thin film, ν_{max} / cm^{-1}) 2934, 2857, 1597, 1495, 1416, 1362, 1167, 1090, 814, 702, 662;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.3 Hz, *H*3), 7.61 (2H, d, *J* = 8.3 Hz, *H*3), 7.32–7.22 (7H, m, *H*2 (×2), *H*6, *H*7), 7.22–7.16 (2H, m, *H*5), 4.53 (2H, s, *H*4), 3.64 (1H, tt, *J* = 11.6, 4.1 Hz, *H*8), 2.44 (3H, s, *H*1), 2.44 (3H, s, *H*1), 1.63–1.53 (2H, br. m, *H*10), 1.53–1.45 (1H, br. m, *H*11), 1.42–1.32 (2H, br. m, *H*9), 1.16 (2H, qt, *J* = 13.2, 3.2 Hz, *H*10), 0.96 (2H, qd, *J* = 12.2, 3.4 Hz, *H*9), 0.80 (1H, qt, *J* = 13.0, 3.7 Hz, *H*11);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 144.1, 136.3, 134.9, 134.8, 129.59, 129.57, 128.9, 128.4, 128.1, 127.8, 127.3, 70.4, 67.5, 59.2, 55.9, 30.6, 25.2, 24.7, 21.6 (2C);

HRMS (ES+) calc. for $C_{29}H_{33}N_2O_4S_2$ $[M+H]^+$ 537.1876, found 537.1879.

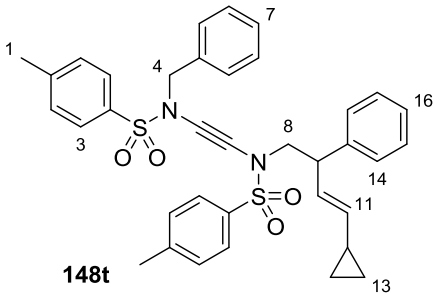
_N_-Benzyl-_N_-(((_N_'-(2-(cyclohex-1-en-1-yl)ethyl)tosylamide)ethynyl)tosylamide, 148s

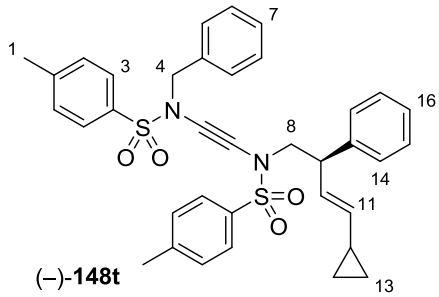


Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (250 mg, 0.562 mmol, 1.1 equiv.), *N*-(2-(cyclohex-1-en-1-yl)ethyl)tosylamide (143 mg, 0.511 mmol, 1.0 equiv.), CuI (19.5 mg, 0.102 mmol, 0.2 equiv.), 1,10-phenantholine (36.8 mg, 0.204 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (499 mg, 1.53 mmol, 3.0 equiv.) in anhydrous THF (1.7 mL). Column chromatography (10% CH_2Cl_2/2% EtOAc/40-60 petroleum ether) afforded the title compound (193 mg, 0.343 mmol, 67%) as a viscous pale yellow oil that solidifies on standing. Crystals suitable for X-ray analysis were grown by very slow evaporation of a solution of **148s** in hexane;

R_f 0.42 (20% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2926, 1597, 1495, 1410, 1362, 1166, 1089, 729;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (2H, d, *J* = 8.3 Hz, *H*3), 7.60 (2H, d, *J* = 8.3 Hz, *H*3), 7.33–7.20 (7H, m, *H*2, *H*6, *H*7), 7.20–7.12 (2H, m, *H*5), 5.22 (1H, br. m, *H*10), 4.50 (2H, s, *H*4), 3.29–3.20 (2H, m, *H*8), 2.43 (6H, s, *H*1), 1.99–1.84 (4H, m, *H*9, *H*11), 1.79–1.69 (2H, m, *H*14), 1.63–1.38 (4H, *H*12, *H*13);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.3, 135.0, 134.8, 134.7, 133.2, 129.59, 129.57, 128.7, 128.4, 128.1, 127.7, 127.5, 123.8, 69.6, 69.3, 55.9, 50.3, 35.9, 28.0, 25.1, 22.7, 22.2, 21.6 (2C);
HRMS (ES+) calc. for $C_{31}H_{35}N_2O_4S_2$ $[M+H]^+$ 563.2033, found 563.2032.

(*E*)-*N*-Benzyl-*N*-(((*N*'-(4-cyclopropyl-2-phenylbut-3-en-1-yl)tosylamido)ethynyl)tosylamide, (±)-**148t** **& (*R*,*E*)-*N*-Benzyl-*N*-(((*N*'-(4-cyclopropyl-2-phenylbut-3-en-1-yl)tosylamido)ethynyl)-tosylamide,** (–)-1**48t**





Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (330 mg, 0.741 mmol, 1.1 equiv.), (*E*)-*N*-(4-cyclopropyl-2-phenylbut-3-en-1-yl)tosylamide (230 mg, 0.674 mmol, 1.0 equiv.), CuI (25.7 mg, 0.135 mmol, 0.2 equiv.), 1,10-phenantholine (48.6 mg, 0.270 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (659 mg, 2.02 mmol, 3.0 equiv.) in anhydrous THF (3.6 mL). Column chromatography (10% CH_2Cl_2/2% EtOAc/40-60 petroleum ether) afforded the title compound (305 mg, 0.488 mmol, 72%) as a viscous, yellow oil;

(–)-**148t** was synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (750 mg, 1.68 mmol, 1.1 equiv.), (*R*,*E*)-*N*-(4-cyclopropyl-2-phenylbut-3-en-1-yl)tosylamide (523 mg, 1.53 mmol, 1.0 equiv.), CuI (56.3 mg, 0.305 mmol, 0.2 equiv.), 1,10-phenantholine (110.4 mg, 0.611 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (1.50 g, 4.59 mmol, 3.0 equiv.) in anhydrous THF (4.5 mL). Column chromatography (10% CH_2Cl_2/2% EtOAc/40-60 petroleum ether) afforded the title compound (513 mg, 0.801 mmol, 54%) as a yellow oil;

- Data for yndiamide (±)-**148t**:

R_f 0.44 (20% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3030, 2925, 1597, 1494, 1362, 1166, 1089, 909, 729;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63 (2H, d, *J* = 8.3 Hz, *H*3), 7.41 (2H, d, *J* = 8.3 Hz, *H*3), 7.31–7.08 (12H, m, *H*2, *H*6, *H*7, *H*14, *H*15, *H*16), 7.04–6.94 (2H, m, *H*5), 5.48 (1H, dd, *J* = 15.3, 7.2 Hz, *H*10), 4.86 (1H, dd, *J* = 15.3, 8.8 Hz, *H*11), 4.49 & 4.45 (2H, AB q, J_{AB} = 14.4 Hz, *H*4), 3.56–3.46 (1H, m, *H*8), 3.45–3.34 (2H, m, *H*8, *H*9), 2.40 (3H, s, *H*1), 2.38 (3H, s, *H*1), 1.31–1.19 (1H, m, *H*12), 0.65–0.54 (2H, m, *H*13), 0.33–0.19 (2H, m, *H*13);

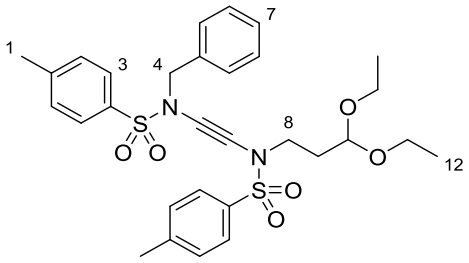
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 144.1, 140.9, 136.8, 134.8, 134.7, 129.53, 129.4, 128.41, 128.37 (3C), 128.0, 127.8, 127.6, 127.5, 126.6, 126.5, 70.0, 69.3, 55.92, 55.88, 46.7, 21.53, 21.51, 13.7, 6.6, 6.5;

HRMS (CI+) calc. for $C_{36}H_{37}N_2NaO_4S_2$ $[M+H]^+$ 625.1189, found 625.2207.

- Data for yndiamide (–)-**148t** were identical to those above:

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –24.1 (c 1, $CHCl_3$).

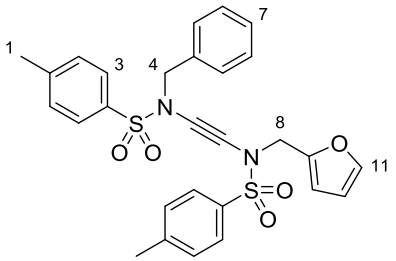
_N_-Benzyl-_N_-(((_N_-(3,3-diethoxypropyl)tosylamido)ethynyl)tosylamide, 148u



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (500 mg, 1.12 mmol, 1.2 equiv.), *N*-(3,3-diethoxypropyl)tosylamide (282 mg, 0.934 mmol, 1.0 equiv.), CuI (35.7 mg, 0.187 mmol, 0.2 equiv.), 1,10-phenantholine (67.5 mg, 0.374 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (915 mg, 2.81 mmol, 3.0 equiv.) in anhydrous THF (3.3 mL). Column chromatography (10% CH_2Cl_2/5% EtOAc/40-60 petroleum ether) afforded the title compound (461 mg, 0.788 mmol, 84%) as a colourless oil;

R_f 0.18 (10% CH_2Cl_2/5% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2975, 2929, 1597, 1494, 1455, 1410, 1166, 1122, 1089, 1058, 1019, 813, 656;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.3 Hz, *H*3), 7.60 (2H, d, *J* = 8.3 Hz, *H*3), 7.28 (2H, d, *J* = 8.3 Hz, *H*2), 7.27–7.21 (5H, m, *H*2, *H*6, *H*7), 7.20–7.12 (2H, m, *H*5), 4.48 (2H, s, *H*4), 4.40 (1H, t, *J* = 5.5 Hz, *H*10), 3.54 (2H, dq, *J* = 9.3, 7.1 Hz, *H*11), 3.38 (2H, dq, *J* = 9.3, 7.1 Hz, *H*11), 3.29 (2H, t, *J* = 7.2 Hz, *H*8), 2.43 (3H, s , *H*1), 2.43 (3H, s , *H*1), 1.72–1.64 (2H, m, *H*9), 1.15 (6H, t, *J* = 7.1 Hz, *H*12);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.4, 134.8, 134.64, 134.56, 129.6 (2C), 128.6, 128.4, 128.1, 127.6, 127.5, 100.2, 69.6, 69.2, 61.8, 55.9, 47.8, 32.1, 21.6 (2C), 15.2;
HRMS (ES+) calc. for $C_{30}H_{37}N_2O_6S_2$ $[M+H]^+$ 585.2088, found 585.2082.

_N_-Benzyl-_N_-(((_N_-(furan-2-ylmethyl)tosylamido)ethynyl)tosylamide, 148v



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.225 mmol, 1.2 equiv.), *N*-(furan-2-ylmethyl)tosylamide (47.0 mg, 0.187 mmol, 1.0 equiv.), CuI (7.1 mg, 37.4 μmol, 0.2 equiv.), 1,10-phenantholine (13.5 mg, 74.9 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (183 mg, 0.562 mmol, 3.0 equiv.) in anhydrous THF (0.7 mL). Column chromatography (10% CH_2Cl_2/3% EtOAc/40-60 petroleum ether) afforded the title compound (58.5 mg, 0.109 mmol, 58%) as a white powder;

m.p. 121–122 °C;

R_f 0.21 (10% CH_2Cl_2/5% EtOAc/40-60 petroleum ether);

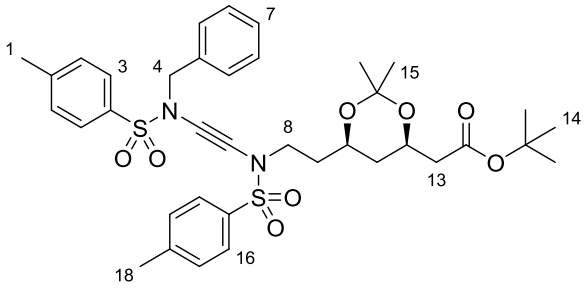
IR (thin film, ν_{max} / cm^{-1}) 3032, 2924, 1671, 1596, 1377, 1347, 1190, 1163, 1090, 1062, 813, 733, 702, 672;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.64–7.58 (2H, m, *H*3), 7.58–7.52 (2H, m, *H*3), 7.28–7.20 (7H, m, *H*2 (×2), *H*6, *H*7), 7.19 (1H, dd, *J* = 2.0, 0.7 Hz, *H*9), 7.12–7.05 (2H, m, *H*5), 6.18 (1H, dd, *J* = 3.3, 2.0 Hz, *H*10), 5.97 (1H, dd, *J* = 3.3, 0.7 Hz, *H*11), 4.47 (2H, s, *H*4), 4.42 (2H, s, *H*8), 2.44 (3H, s, *H*1), 2.43 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 148.0, 144.4, 144.3, 142.7, 134.9, 134.7, 134.6, 129.6, 129.4, 128.7, 128.4, 128.0, 127.70, 127.66, 110.4, 110.2, 70.1, 69.4, 56.0, 48.6, 21.7 (2C);

HRMS (ES+) calc. for $C_{28}H_{26}N_2NaO_5S_2$ $[M+Na]^+$ 557.1175, found 557.1175.

***t*-Butyl 2-((4*R*,6*R*)-6-(2-((*N*-(((*N*-benzyltosylamido)ethynyltosylamido)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate, 148w**



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (200 mg, 0.449 mmol, 1.1 equiv.), *t*-butyl 2-((4*R*,6*R*)-2,2-dimethyl-6-(2-(tosylamido)ethyl)-1,3-dioxan-4-yl)acetate (175 mg, 0.408 mmol, 1.0 equiv.), CuI (15.6 mg, 81.7 μmol, 0.2 equiv.), 1,10-phenantholine (29.4 mg, 0.163 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (333 mg, 1.02 mmol, 2.5 equiv.) in anhydrous THF (1.2 mL). Column chromatography (20% Et_2O → 25% Et_2O/40-60 petroleum ether) afforded the title compound (210 mg, 0.296 mmol, 72%) as a pale yellow foam. Crystals suitable for X-ray diffraction were grown by very slow evaporation of a solution of **148w** in dibutyl ether. ***Note***: This compound was very reluctant to crystallise and tended to oil out in most cases;

R_f 0.51 (30% EtOAc/40-60 petroleum ether);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +36.9 (c 1, $CHCl_3$);

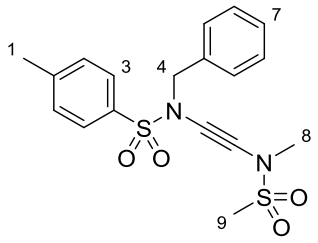
IR (thin film, ν_{max} / cm^{-1}) 2977, 2925, 1728, 1597, 1365, 1166, 1089, 814, 729;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.3 Hz, *H*16), 7.53 (2H, d, *J* = 8.3 Hz, *H*3), 7.28 (2H, d, *J* = 8.3 Hz, *H*17), 7.27–7.19 (5H, m, *H*2, *H*6, *H*7), 7.18–7.09 (2H, m, *H*5), 4.48 & 4.44 (2H, AB q, J_{AB} = 13.9 Hz, *H*4), 4.17 (1H, dddd, *J* = 11.5, 7.3, 5.9, 1.9 Hz, *H*12), 3.75 (1H, dtd, *J* = 11.2, 6.1, 2.0 Hz, *H*10), 3.35 (1H, dt, *J* = 12.9, 7.3 Hz, *H*8), 3.20 (1H, dt, *J* = 12.9, 6.4 Hz, *H*8), 2.42 (3H, s, *H*18), 2.41 (3H, s, *H*1), 2.37 (1H, dd, *J* = 15.1, 5.9 Hz, *H*13), 2.26 (1H, dd, *J* = 15.1, 7.3 Hz, *H*13), 1.47–1.40 (2H, m, *H*9), 1.44 (9H, s, *H*14), 1.39–1.32 (1H, m, *H*11), 1.35 (3H, s, *H*15), 1.30 (3H, s, *H*15), 1.02 (1H, dt, *J* = 12.5, 11.5 Hz, *H*11);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.9, 144.4, 144.3, 134.7, 134.5, 134.4, 129.6, 129.5, 128.5, 128.3, 128.0, 127.5, 127.3, 98.6, 80.4, 69.4, 69.1, 65.8, 65.3, 55.7, 47.5, 42.5, 36.0, 34.0, 29.8, 27.9, 21.49, 21.46, 19.4;

HRMS (ES+) calc. for $C_{37}H_{46}N_2NaO_8S_2$ $[M+Na]^+$ 733.2588, found 733.2580.

_N_-Benzyl-_N_-((_N_-methylmethylsulfonamido)ethynyl)tosylamide, 148x



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.225 mmol, 1.1 equiv.), *N*-methyl methylsulfonamide (22.3 mg, 0.204 mmol, 1.0 equiv.), CuI (7.8 mg, 40.8 μmol, 0.2 equiv.), 1,10-phenantholine (14.7 mg, 81.7 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (166 mg, 0.511 mmol, 2.5 equiv.) in anhydrous THF (0.7 mL). Column chromatography (25% Et_2O→50% Et_2O/40-60 petroleum ether) afforded the title compound (48.5 mg, 0.123 mmol, 61%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of the title compound in toluene;

m.p. 121–122 °C;

R_f 0.18 (20% EtOAc/40-60 petroleum ether);

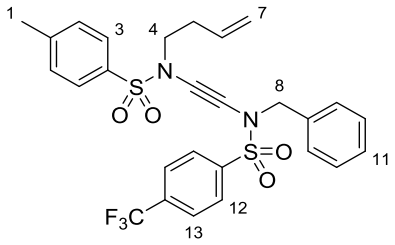
IR (thin film, ν_{max} / cm^{-1}) 3032, 2932, 1715, 1597, 1497, 1398, 1358, 1167, 1090, 961, 773, 715, 660;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.3 Hz, *H*3), 7.33–7.27 (5H, m, *H*2, *H*6, *H*7), 7.25–7.19 (2H, m, *H*5), 4.55 (2H, s, *H*4), 3.11 (3H, s, *H*9), 2.79 (3H, s, *H*8), 2.44 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 134.9, 134.6, 129.8, 128.7, 128.5, 128.3, 127.6, 71.1, 68.7, 55.8, 39.7, 36.6, 21.6;

HRMS (ES+) calc. for $C_{18}H_{20}N_2NaO_4S_2$ $[M+Na]^+$ 415.0757, found 415.0755.

_N_-Benzyl-_N_-(((_N_-(but-3-en-1-yl)tosylamido)ethynyl)-4-(trifluoromethyl)benzenesulfonamide, 160a



Following example procedure **1.2b**: Synthesised from *N*-(but-3-en-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (200 mg, 0.489 mmol, 1.1 equiv.), *N*-benzyl-4-(trifluoromethyl)phenylsulfonamide (140 mg, 0.444 mmol, 1.0 equiv.), CuI (16.9 mg, 88.9 μmol, 0.2 equiv.), 1,10-phenantholine (32.0 mg, 0.178 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (362 mg, 1.11 mmol, 2.5 equiv.) in anhydrous THF (1.4 mL). Column chromatography (7% EtOAc/40-60 petroleum ether) afforded the title compound (109 mg, 0.194 mmol, 44%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **160a** in toluene;

m.p. 85–86 °C;

R_f 0.36 (20% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2980, 1406, 1367, 1322, 1168, 1134, 1062, 710, 611;

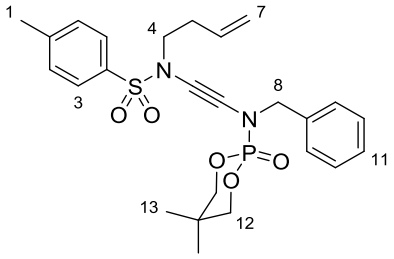
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.86 (2H, d, *J* = 8.3 Hz, *H*13), 7.70 (2H, d, *J* = 8.3 Hz, *H*12), 7.58 (2H, d, *J* = 8.6 Hz, *H*3), 7.32–7.18 (5H, m, *H*2, *H*10, *H*11), 7.18–7.10 (2H, m, *H*9), 5.55 (1H, ddt, *J* = 16.8, 10.4, 6.8 Hz, *H*6), 5.02–4.88 (2H, m, *H*7), 4.54 (2H, s, *H*8), 3.32 (2H, t, *J* = 7.2 Hz, *H*4), 2.43 (3H, s, *H*1), 2.12 (2H, tdt, *J* = 7.2, 6.8, 1.0 Hz, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 141.1, 134.9 (1C, q, *J* = 33.4 Hz), 134.8, 134.0, 133.4, 129.7, 128.7, 128.5, 128.4, 128.1, 127.4, 126.1 (2C, q, *J* = 3.7 Hz), 123.1 (1C, q, *J* = 273 Hz), 117.7, 69.8, 69.1, 56.4, 50.9, 32.0, 21.6;

^{19}F NMR (376 MHz, $CDCl_3$) δ_P -63.1;

HRMS (ES+) calc. for $C_{27}H_{26}N_2O_4S_2F_3$ $[M+H]^+$ 563.1281 found 563.1278.

***N*-((Benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl)-*N*-(but-3-en-1-yl) tosylamide, 160b**



Following example procedure **1.2b**: Synthesised from *N*-(but-3-en-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.244 mmol, 1.1 equiv.), 2-(benzylamino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (56.7 mg, 0.222 mmol, 1.0 equiv.), CuI (8.5 mg, 44.4 μmol, 0.2 equiv.), 1,10-phenantholine (16.0 mg, 88.8 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (217 mg, 0.666 mmol, 3.0 equiv.) in anhydrous THF (0.8 mL). Column chromatography (35% EtOAc → 50% EtOAc/40-60 petroleum ether) afforded a brown solid which was recrystallised (EtOAc/hexane) to give the title compound (90.6 mg, 0.180 mmol, 81%) as colourless needles. These crystals were also suitable for X-ray diffraction;

m.p. 75–76 °C;

R_f 0.28 (50% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2970, 1597, 1455, 1408, 1358, 1289, 1169, 1089, 1053, 1007, 917, 814, 728, 670, 627;

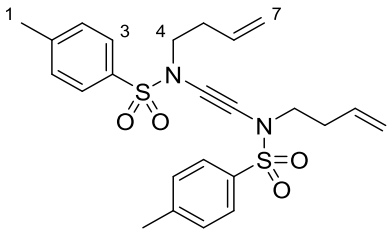
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59 (2H, d, *J* = 8.3 Hz, *H*3), 7.36–7.25 (5H, m, *H*9, *H*10, *H*11), 7.23 (2H, d, *J* = 8.3 Hz, *H*2), 5.59 (1H, ddt, *J* = 17.1, 10.2, 6.8 Hz, *H*6), 5.02–4.92 (2H, m, *H*7), 4.41 (2H, d, *J* = 8.3 Hz, *H*8), 3.93 (2H, dd, *J* = 11.0, 9.5 Hz, *H*12), 4.09 (2H, dd, *J* = 14.2, 11 Hz, *H*12), 3.28 (2H, t, *J* = 7.2 Hz, *H*4), 2.42 (3H, s, *H*1), 2.19–2.02 (2H, m, *H*5), 1.15 (3H, s, *H*13), 0.93 (3H, s, *H*13);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 136.3 (1C, d, *J* = 1.6 Hz), 134.6, 133.6, 129.5, 128.4, 128.3, 127.7, 127.4, 117.4, 78.7 (2C, d, *J* = 7.2 Hz), 71.8 (1C, d, *J* = 5.6 Hz), 64.0 (1C, d, *J* = 5.6 Hz), 55.4 (1C, d, *J* = 7.9 Hz), 50.7, 32.0 (1C, d, *J* = 7.2 Hz), 31.9, 21.5 (2C), 20.6;

^{31}P NMR (162 MHz, $CDCl_3$) δ_P -3.51;

HRMS (ES+) calc. for $C_{25}H_{32}N_2O_5PS$ $[M+H]^+$ 503.1764, found 503.1749.

_N_,_N'_-(Ethyne-1,2-diyl)bis(_N_-(but-3-en-1-yl)tosylamide), 160c



Following example procedure **1.2b**: Synthesised from *N*-(but-3-en-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (500 mg, 1.22 mmol, 1.1 equiv.), *N*-(but-3-en-1-yl)tosylamide (250 mg, 1.11 mmol, 1.0 equiv.), CuI (42.3 mg, 0.222 mmol, 0.2 equiv.), 1,10-phenantholine (80.1 mg, 0.444 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (1.09 g, 3.33 mmol, 3.0 equiv.) in anhydrous THF (3.6 mL). Column chromatography (10% CH_2Cl_2/3% EtOAc/40-60 petroleum ether) afforded the title compound (460 mg, 0.950 mmol, 86%) as a white powder. Crystals suitable for X-ray diffraction were grown by slow evaporation of a solution of **160c** in pentane;

m.p. 58–60 °C;

R_f 0.18 (10% CH_2Cl_2/4% EtOAc/40-60 petroleum ether);

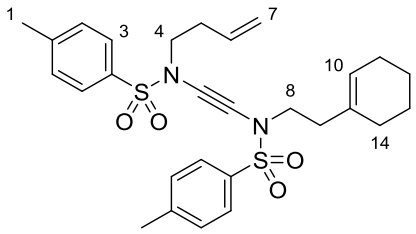
IR (thin film, ν_{max} / cm^{-1}) 2980, 2928, 1641, 1597, 1412, 1364, 1170, 1090, 912, 714, 677, 658;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (4H, d, *J* = 8.1 Hz, *H*3), 7.31 (4H, d, *J* = 8.1 Hz, *H*2), 5.65 (2H, ddt, *J* = 17.1, 10.3, 6.8 Hz, *H*6), 5.08–4.98 (4H, m, *H7*), 3.39 (4H, t, *J* = 7.3 Hz, *H*4), 2.44 (6H, s, *H*1), 2.33–2.24 (4H, m, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 134.9, 133.6, 129.7, 127.6, 117.6, 69.0, 51.0, 32.2, 21.6;

HRMS (ES+) calc. for $C_{24}H_{29}N_2O_4S_2$ $[M+H]^+$ 473.1563, found 473.1568.

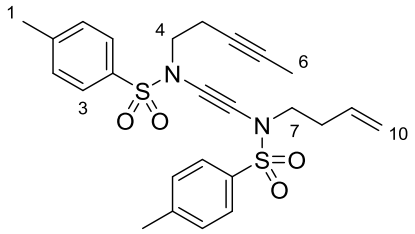
_N_-(But-3-en-1-yl)-_N_-(((_N'_-(2-(cyclohex-1-en-1-yl)ethyl)tosylamido)ethynyl)tosylamide, 160d



Following example procedure **1.2b**: Synthesised from *N*-(but-3-en-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (200 mg, 0.489 mmol, 1.2 equiv.), *N*-(2-(cyclohex-1-en-1-yl)ethyl)tosylamide (114 mg, 0.407 mmol, 1.0 equiv.), CuI (15.5 mg, 81.5 μmol, 0.2 equiv.), 1,10-phenantholine (29.4 mg, 0.163 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (398 mg, 1.22 mmol, 3.0 equiv.) in anhydrous THF (1.5 mL). Column chromatography (10% CH_2Cl_2/3% EtOAc/40-60 petroleum ether) afforded the title compound (165 mg, 0.313 mmol, 77%) as a pale yellow oil;

R_f 0.24 (10% CH_2Cl_2/4% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2927, 1597, 1410, 1362, 1166, 1089, 913, 729, 659;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.64 (4H, m, *H*3), 7.33–7.26 (4H, m, *H*2), 5.64 (1H, ddt, *J* = 17.1, 10.2, 6.8 Hz, *H*6), 5.40–5.33 (1H, br. m, *H*10), 5.07–4.95 (2H, m, *H*7), 3.42–3.32 (4H, m, *H*4, *H*8), 2.42 (6H, s, *H*1), 2.31–2.21 (2H, m, *H*5), 2.11 (2H, t, *J* = 7.5 Hz, *H*9), 1.96–1.87 (2H, br. m, *H*11), 1.87–1.79 (2H, br. m, *H*14), 1.61–1.52 (2H, m, *H*13), 1.52–1.44 (2H, m, *H*12);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.42, 144.36, 134.9, 134.7, 133.5, 133.2, 129.6 (2C), 127.5, 127.4, 123.9, 117.5, 69.1, 68.8, 51.0, 50.2, 36.1, 32.1, 28.0, 25.1, 22.6, 22.0, 21.5 (2C);
HRMS (ES+) calc. for $C_{28}H_{35}N_2O_4S_2$ $[M+H]^+$ 527.2033, found 527.2040.

_N_-(But-3-en-1-yl) _N_-(((_N′_-(pent-3-yn-1-yl)phenyl)tosylamido)ethynyl)tosylamide, 160e

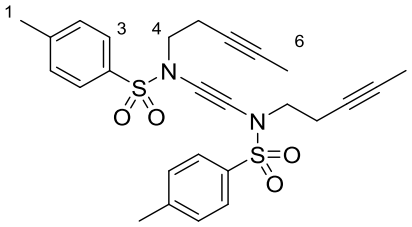


Following example procedure **1.2b**: Synthesised from *N*-(but-3-en-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (200 mg, 0.489 mmol, 1.1 equiv.), *N*-(pent-3-yn-1-yl) tosylamide (106 mg, 0.444 mmol, 1.0 equiv.), CuI (16.9 mg, 88.9 μmol, 0.2 equiv.), 1,10-phenantholine (32.0 mg, 0.178 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (434 mg, 1.33 mmol, 3.0 equiv.) in anhydrous THF (1.5 mL). Column chromatography (10% EtOAc/40-60 petroleum ether) afforded the title compound (169.9 mg, 0.350 mmol, 79%) as a pale yellow oil. Crystals suitable for X-ray diffraction were grown by allowing a concentrated solution of the title compound in hexane (*plus* 2 drops of dibutyl ether) to stand at room temperature for 2 months. ***Note***: This compound was very reluctant to crystallise and tended to oil out in most cases;

Also synthesised from *N*-(pent-3-yn-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.237 mmol, 1.2 equiv.), *N*-(but-3-en-1-yl)tosylamide (44.6 mg, 0.198 mmol, 1.0 equiv.), CuI (7.5 mg, 39.6 μmol, 0.2 equiv.), 1,10-phenantholine (14.3 mg, 79.2 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (193 mg, 0.594 mmol, 3.0 equiv.) in anhydrous THF (0.7 mL). Column chromatography (10% CH_2Cl_2/4% EtOAc/40-60 petroleum ether) afforded the title compound (68.9 mg, 0.142 mmol, 72%) as a pale yellow oil;

R_f 0.15 (10% CH_2Cl_2/4% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2920, 1597, 1495, 1410, 1362, 1167, 1090, 907, 814, 675;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76–7.68 (4H, m, *H*3), 7.35–7.28 (4H, m, *H*2), 5.65 (1H, ddt, *J* = 17.1, 10.2, 6.8 Hz, *H*9), 5.09–4.98 (2H, m, *H*10), 3.50–3.42 (2H, m, *H*4), 3.39 (2H, t, *J* = 7.5 Hz, *H*7), 2.45 (3H, s, *H*1), 2.44 (3H, s, *H*1), 2.34 (2H, tq, *J* = 7.6, 2.5 Hz, *H*5), 2.32–2.24 (2H, m, *H*8), 1.71 (3H, t, *J* = 2.5 Hz, *H*6);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6 (2C), 134.9, 134.8, 133.6, 129.7 (2C), 127.63, 127.60, 117.7, 77.8, 74.5, 69.3, 68.8, 51.0, 50.8, 32.2, 21.7 (2C), 18.5, 3.4;
HRMS (ES+) calc. for $C_{25}H_{29}N_2O_4S_2$ $[M+H]^+$ 485.1563, found 485.1563.

_N_,_N_′-(Ethyne-1,2-diyl)bis(_N_-(pent-3-yn-1-yl)tosylamide), 160f



Following example procedure **1.2b**: Synthesised from *N*-(pent-3-yn-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (75 mg, 0.178 mmol, 1.1 equiv.), *N*-(pent-3-yn-1-yl)tosylamide (38.4 mg, 0.162 mmol, 1.0 equiv.), CuI (6.2 mg, 32.4 μmol, 0.2 equiv.), 1,10-phenantholine (11.7 mg, 64.8 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (158 mg, 0.486 mmol, 3.0 equiv.) in anhydrous THF (0.6 mL). Column chromatography (10% CH_2Cl_2/3% EtOAc/40-60 petroleum ether) afforded the title compound (58.6 mg, 0.118 mmol, 73%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **160f** in CH_2Cl_2;

m.p. 130–132 °C;

R_f 0.44 (30% EtOAc/40-60 petroleum ether);

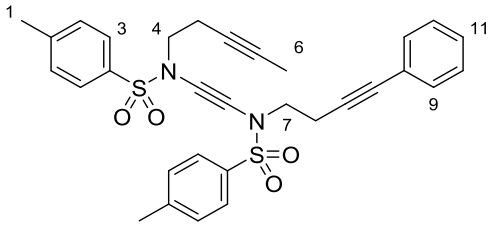
IR (thin film, ν_{max} / cm^{-1}) 2920, 1597, 1493, 1412, 1364, 1164, 1090, 991, 814, 710, 675;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (4H, d, *J* = 8.3 Hz, *H*3), 7.32 (4H, d, *J* = 8.3 Hz, *H*2), 3.17 (4H, t, *J* = 7.6 Hz, *H*4), 2.45 (6H, s, *H*1), 2.34 (4H, tq, *J* = 7.6, 2.4 Hz, *H*5), 1.71 (6H, t, *J* = 2.4 Hz, *H*6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 134.8, 129.7, 127.6, 77.9, 74.5, 69.0, 50.8, 21.6, 18.5, 3.4;

HRMS (ES+) calc. for $C_{26}H_{28}N_2NaO_4S_2$ $[M+Na]^+$ 519.1383, found 519.1374.

_N_-(((_N′_-(4-Phenylbut-3-yn-1-yl)tosylamido)ethynyl)-_N_-(pent-3-yn-1-yl)tosylamide, 160g



Following example procedure **1.2b**: Synthesised from *N*-(pent-3-yn-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.237 mmol, 1.1 equiv.), *N*-(pent-3-yn-1-yl)tosylamide (64.6 mg, 0.216 mmol, 1.0 equiv.), CuI (8.2 mg, 43.1 μmol, 0.2 equiv.), 1,10-phenantholine (15.6 mg, 86.3 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (211 mg, 0.648 mmol, 3.0 equiv.) in anhydrous THF (0.7 mL). Column chromatography (10% CH_2Cl_2/3% EtOAc/40-60 petroleum ether) afforded the title compound (63.2 mg, 0.113 mmol, 52%) as a tan solid. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **160g** in benzene;

m.p. 95 °C;

R_f 0.70 (50% EtOAc/40-60 petroleum ether);

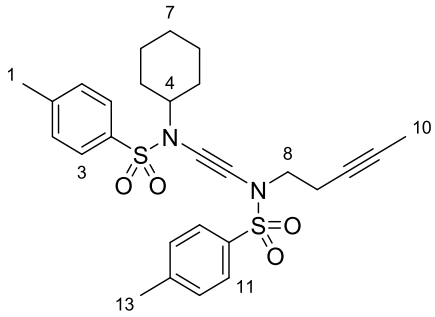
IR (thin film, ν_{max} / cm^{-1}) 2920, 1597, 1491, 1412, 1366, 1168, 1092, 675;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.4 Hz, *H*3), 7.73 (2H, d, *J* = 8.4 Hz, *H*3), 7.37–7.22 (9H, m, *H*2, *H*9, *H*10, *H*11), 3.60 (2H, t, *J* = 7.5 Hz, *H*7), 3.45 (2H, t, *J* = 7.6 Hz, *H*4), 2.64 (2H, t, *J* = 7.5 Hz, *H*8), 2.43 (3H, s, *H*1), 2.39 (3H, s, *H*1), 2.34 (2H, tq, *J* = 7.6, 2.5 Hz, *H*5), 1.71 (3H, t, *J* = 2.5 Hz, *H*6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.69, 144.65, 134.8, 134.7, 131.6, 129.74, 129.73, 128.2, 128.0, 127.62, 127.61, 123.1, 85.2, 82.5, 77.8, 74.5, 69.3, 68.9, 50.8, 50.4, 21.63, 21.61, 19.1, 18.5, 3.4.

HRMS (ES+) calc. for $C_{31}H_{30}N_2NaO_4S_2$ $[M+Na]^+$ 581.1539, found 581.1528.

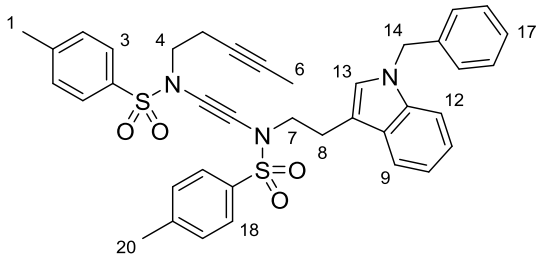
_N_-Cyclohexyl-_N_-(((_N_-(pent-3-yn-1-yl)tosylamido)ethynyl)tosylamide, 160h



Following example procedure **1.2b**: Synthesised from *N*-(pent-3-yn-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (30 mg, 71.2 μmol, 1.2 equiv.), *N*-cyclohexyltosylamide (15.0 mg, 59.4 μmol, 1.0 equiv.), CuI (2.3 mg, 11.9 μmol, 0.2 equiv.), 1,10-phenantholine (4.3 mg, 23.7 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (58.0 mg, 0.178 mmol, 3.0 equiv.) in anhydrous THF (0.2 mL). Column chromatography (10% CH_2Cl_2/3% EtOAc/40-60 petroleum ether) afforded the title compound (19.9 mg, 38.8 μmol, 65%) as a pale yellow oil which solidified on standing. Crystals suitable for X-ray diffraction were grown by slow cooling of a concentrated solution of **160h** in hexane from 70 °C to room temperature;

R_f 0.23 (10% CH_2Cl_2/5% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2932, 2857, 1597, 1417, 1362, 1167, 1090, 761, 662;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77–7.69 (4H, m, *H*3, *H*11), 7.30 (4H, d, *J* = 8.3 Hz, *H*2), 3.84–3.67 (1H, br. m, *H*4), 3.50 (2H, t, *J* = 7.6 Hz, *H*8), 2.45 (3H, s, *H*1), 2.44 (3H, s, *H*13), 2.40–2.32 (2H, m, *H*9), 1.71 (3H, t, *J* = 2.6 Hz, *H*10), 1.75–1.63 (2H, m, *H*5), 1.61–1.49 (3H, m, *H*5, *H*7), 1.34–1.17 (4H, m, *H*6), 1.08–1.82 (1H, m, *H*7);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.3, 136.2, 135.0, 129.66, 129.65, 127.8, 127.4, 77.8, 74.7, 69.8, 67.3, 59.2, 50.7, 31.0, 25.3, 24.8, 21.64, 21.63, 18.6, 3.4;
HRMS (ES+) calc. for $C_{27}H_{33}N_2O_4S_2$ $[M+H]^+$ 513.1876, found 513.1874.

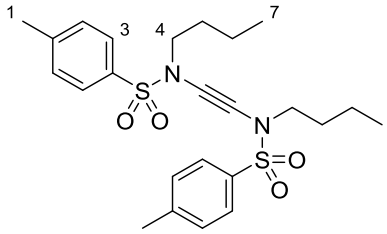
_N_-(2-(1-Benzyl-1_H_-indol-3-yl)ethyl)-_N_-(((_N_-(pent-3-yn-1-yl)tosylamido)ethynyl)tosylamide, 160i



Following example procedure **1.2b**: Synthesised from *N*-(pent-3-yn-1-yl)-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.237 mmol, 1.2 equiv.), *N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)tosylamide (80.0 mg, 0.198 mmol, 1.0 equiv.), CuI (7.5 mg, 39.6 μmol, 0.2 equiv.), 1,10-phenantholine (14.3 mg, 79.2 μmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (193 mg, 0.594 mmol, 3.0 equiv.) in anhydrous THF (0.7 mL). Column chromatography (10% CH_2Cl_2/5% EtOAc/40-60 petroleum ether) afforded the title compound (116 mg, 0.174 mmol, 88%) as a tan oil;

R_f 0.12 (10% CH_2Cl_2/5% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2920, 1597, 1495, 1467, 1412, 1363, 1166, 1090, 907, 706, 674;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 8.3 Hz, *H*18), 7.60 (2H, d, *J* = 8.1 Hz, *H*3), 7.45 (1H, d, *J* = 7.8 Hz, *H*9), 7.31–7.02 (12H, m, *H*2, *H*10, *H*11, *H*12, *H*15, *H*16, *H*17, *H*19), 6.95 (1H, s, *H*13), 5.21 (2H, s, *H*14), 3.63 (2H, t, *J* = 7.6 Hz, *H*7), 3.44 (2H, t, *J* = 7.7 Hz, *H*4), 3.00 (2H, t, *J* = 7.6 Hz, *H*8), 2.39 (3H, s, *H*1), 2.36 (3H, s, *H*20), 2.35–2.28 (2H, m, *H*5), 1.69 (3H, t, *J* = 2.4 Hz, *H*6);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 144.3, 137.5, 136.5, 134.9, 134.8, 129.7, 129.5, 129.0, 128.7, 127.8, 127.6, 127.4, 126.8, 126.7, 121.7, 119.1, 118.6, 110.5, 109.7, 77.8, 74.6, 69.3, 68.9, 52.0, 50.8, 49.9, 24.0, 21.61, 21.57, 18.5, 3.42;
HRMS (ES+) calc. for $C_{38}H_{38}N_3O_4S_2$ $[M+H]^+$ 664.2298, found 664.2295.

_N,N′_-(Ethyne-1,2-diyl)bis(_N_-_n_-butyl-tosylamide), 160l



Following example procedure **1.2b**: Synthesised from *N*-*n*-butyl-*N*-(2,2-dibromovinyl)tosylamide (500 mg, 1.22 mmol, 1.1 equiv.), *N*-*n*-butyltosylamide (251 mg, 1.11 mmol, 1.0 equiv.), CuI (42.1 mg, 0.22 mmol, 0.2 equiv.), 1,10-phenantholine (79.7 mg, 0.44 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (1.08 g, 3.32 mmol, 2.5 equiv.) in anhydrous THF (3.7 mL). Column chromatography (5% EtOAc/hexane) afforded the title compound (347 mg, 0.728 mmol, 66%) as a tan powder. If necessary, this compound can be recrystallised from CH_2Cl_2/pentane. Crystals suitable for X-ray crystallography were grown from a saturated solution of CH_2Cl_2/pentane;

m.p. 63–65 °C;

R_f 0.19 (5% EtOAc/hexane);

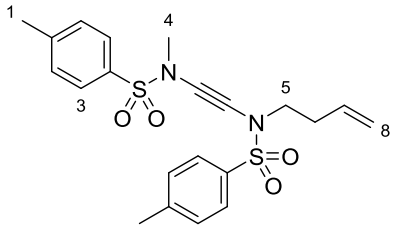
IR (thin film, ν_{max} / cm^{-1}) 2960, 2874, 1598, 1459, 1412, 1365, 1171, 1090, 1027, 889, 814, 709, 675, 655;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (4H, d, *J* = 7.4 Hz, *H*3), 7.31 (4H, d, *J* = 7.4 Hz, *H*2), 3.32 (4H, t, *J* = 6.8 Hz, *H*4), 2.42 (6H, s, *H*1), 1.52 (4H, quin, *J* = 6.8 Hz, *H5*), 1.29 (4H, sxt, *J* = 6.8 Hz, *H*6), 0.87 (6H, t, *J* = 6.8 Hz, *H*7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 134.9, 129.6, 127.5, 68.7, 51.3, 29.8, 21.6, 19.3, 13.5;

HRMS (ES+) calc. for $C_{24}H_{32}N_2NaO_4S_2$ $[M+Na]^+$ 499.1696, found 499.1696.

_N_-(But-3-en-1-yl)-_N_-(((_N_-methyltosylamido)ethynyl)tosylamide, 160m



Following example procedure **1.2b**: Synthesised from *N*-methyl-*N*-(2,2-dibromovinyl)tosylamide (300 mg, 0.813 mmol, 1.1 equiv.), *N*-(but-3-en-1-yl)tosylamide (166 mg, 0.739 mmol, 1.0 equiv.), CuI (28.2 mg, 0.148 mmol, 0.2 equiv.), 1,10-phenantholine (53.3 mg, 0.296 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (602 mg, 1.85 mmol, 2.5 equiv.) in anhydrous THF (2.4 mL). Column chromatography (5% Et_2O/40-60 petroleum ether) afforded the title compound (238 mg, 0.551 mmol, 75%) as a pale yellow solid. Crystals suitable for X-ray analysis were grown by cooling a concentrated solution of the title compound in hexane to –20 °C;

m.p. 38–40 °C;

R_f 0.36 (20% EtOAc/petrol);

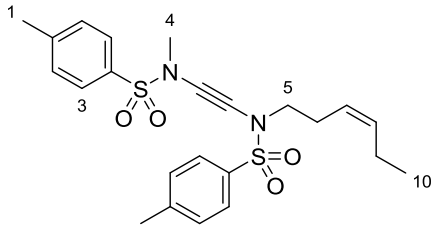
IR (thin film, ν_{max} / cm^{-1}) 2931, 1597, 1493, 1397, 1361, 1164, 993, 911, 813, 713, 674, 656;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (4H, d, *J* = 8.3 Hz, *H*3), 7.31 (2H, d, *J* = 8.3 Hz, *H*2), 7.30 (2H, d, *J* = 8.3 Hz, *H*2), 5.60 (1H, ddt, *J* = 17.1, 10.2, 6.8, *H*7), 5.05–4.93 (2H, m, *H*8), 3.34 (2H, t, *J* = 7.2 Hz, *H*5), 3.05 (3H, s, *H*4), 2.41 (6H, s, *H*1), 2.23 (2H, q, *J* = 7.2 Hz, *H*6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 144.5, 134.6, 133.4, 133.3, 129.6, 129.5, 127.5, 127.4, 117.4, 70.8, 67.0, 50.9, 39.7, 31.9, 21.4 (2C);

HRMS (ES+) calc. for $C_{21}H_{25}N_2O_4S_2$ $[M+H]^+$ 433.1250, found 433.1252.

(*Z*)-*N*-(((*N*-Methyltosylamido)ethynyl)-*N*-(hex-3-en-1-yl)tosylamide, 160n



Following example procedure **1.2b**: Synthesised from *N*-methyl-*N*-(2,2-dibromovinyl)tosylamide (300 mg, 0.813 mmol, 1.1 equiv.), (*E*)-*N*-(hex-4-en-1-yl)tosylamide (187 mg, 0.739 mmol, 1.0 equiv.), CuI (28.2 mg, 0.148 mmol, 0.2 equiv.), 1,10-phenantholine (53.3 mg, 0.296 mmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (602 mg, 1.85 mmol, 2.5 equiv.) in anhydrous THF (2.4 mL). Column chromatography (5% Et_2O/40-60 petroleum ether) afforded the title compound (273 mg, 0.593 mmol, 80%) as a pale yellow oil;

R_f 0.42 (20% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2962, 1597, 1493, 1456, 1397, 1362, 1163, 1088, 1018, 903, 813, 711, 673, 652;

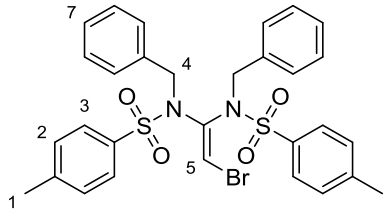
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (4H, d, *J* = 8.6 Hz, *H*3), 7.31 (2H, d, *J* = 8.3 Hz, *H*2), 7.30 (2H, d, *J* = 8.3 Hz, *H*2), 5.44–5.36 (1H, m, *H*7), 5.19–5.09 (1H, m, *H*8), 3.28 (2H, t, *J* = 7.3 Hz, *H*5), 3.05 (3H, s, H4), 2.41 (6H, s, *H*1), 2.23 (2H, q, *J* = 7.2 Hz, *H*6), 1.93 (2H, quind, *J* = 7.5, 1.5 Hz, *H*9), 0.89 (3H, t, *J* = 7.5 Hz, *H*10);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 144.4, 134.71, 134.66, 133.4, 129.6, 129.5, 127.5, 127.4, 123.3, 70.6, 67.1, 51.3, 39.7, 25.7, 21.4 (2C), 20.4, 14.0;

HRMS (ES+) calc. for $C_{23}H_{29}N_2O_4S_2$ $[M+H]^+$ 461.1563, found 461.1563.

2.1c *Miscellaneous*.

_N_,_N_'-(2-Bromoethene-1,1-diyl)bis(_N_-benzyltosylamide), 155b



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.225 mmol, 1.1 equiv.), *N*-benzyltosylamide (53.4 mg, 0.202 mmol, 1.0 equiv.) and powdered anhydrous Cs_2CO_3 (166 mg, 0.511 mmol, 2.5 equiv.) in anhydrous THF (0.7 mL) without copper additives. Column chromatography (5% Et_2O/40-60 petroleum ether) afforded the title compound (117.9 mg, 0.188 mmol, 92%) as a white solid. Crystals suitable for X-ray diffraction were grown by very slow cooling (over ~5 hours) of a *i*-PrOH/toluene/hexane (~1:1:5) solution of **155b** from 80 °C to room temperature. ***Note***: It was extremely difficult to grow sufficiently good single-crystals for X-ray analysis. This compound tended to afford an amorphous mass or crystals containing multiple twin components.

m.p. 95 °C;

R_f 0.58 (4% Et_2O/toluene);

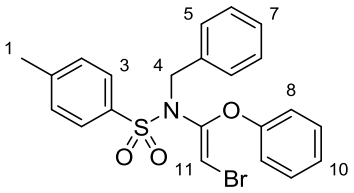
IR (thin film, ν_{max} / cm^{-1}) 3033, 1597, 1495, 1345, 1161, 1087, 811, 702, 674;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.3 Hz, *H*3), 7.48 (2H, d, *J* = 8.3 Hz, *H*2), 7.25–7.03 (14H, m, *H*3, *H*5, *H*6, *H*7), 6.12 (1H, s, *H*8), 4.66 (2H, br. s, *H*4), 4.64 (2H, s, *H*4), 2.39 (3H, s, *H*1), 2.34 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 144.0, 136.4, 136.3, 136.2, 136.1, 135.2, 129.4 (2C), 128.9, 128.4, 128.3, 128.2 (2C), 128.1, 127.7, 127.5, 106.4, 51.6, 50.8, 21.54, 21.47;

HRMS (ES+) calc. for $C_{30}H_{29}{}^{79}BrN_2NaO_4S_2$ $[M+Na]^+$ 647.0644, found 647.0643.

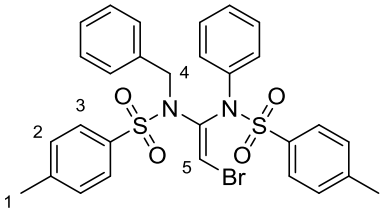
(*Z*)-*N*-Benzyl-*N*-(2-bromo-1-phenoxyvinyl)tosylamide 155c



Following example procedure **1.2b**: Synthesised from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (100 mg, 0.225 mmol, 1.1 equiv.), phenol (19.3 mg, 0.204 mmol, 1.0 equiv.), CuI (7.8 mg, 40.8 µmol, 0.2 equiv.), 1,10-phenantholine (14.7 mg, 81.7 µmol, 0.4 equiv.) and powdered anhydrous Cs_2CO_3 (200 mg, 0.511 mmol, 2.5 equiv.) in anhydrous THF (0.7 mL). Column chromatography (5% CH_2Cl_2/2% EtOAc/40-60 petroleum ether) afforded the title compound (79.5 mg, 0.173 mmol, 85%) as a pale yellow oil that solidified on standing in the freezer (-20 °C). This compound was dissolved in methanol (1 mL) and crystals suitable for X-ray diffraction were grown from this solution at 2 °C (fridge);

R_f 0.37 (10% CH_2Cl_2/4% EtOAc/petrol);
IR (thin film, ν_{max} / cm^{-1}) 3032, 2923, 1640, 1592, 1489, 1352, 1201, 1157, 731, 659;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65–7.58 (2H, m, *H*3), 7.32–7.25 (3H, m, *H*6, *H*7), 7.25–7.18, (4H, m, *H*2, *H*5), 7.17–7.11 (2H, m, *H*10), 7.05–6.97 (1H, m, *H*11), 6.76–6.68 (2H, m, *H*9), 5.96 (1H, s, *H*8), 4.45 (2H, s, *H*4), 2.40 (3H, s, *H*1);
^{13}C NMR (101 MHz, $CDCl_3$) δ_c 154.1, 144.1, 143.6, 135.7, 135.1, 129.6, 129.3, 128.6, 128.5, 128.0, 127.9, 123.4, 117.1, 94.4, 51.4, 21.5;
HRMS (CI+) calc. for $C_{22}H_{21}{}^{79}BrNO_3S$ $[M+H]^+$ 458.0420, found 458.0421.

(*Z*)-*N*-Benzyl-*N*-(2-bromo-1-(*N*-phenyltosylamido)vinyl)tosylamide, 155e



Following example procedure **1.2b**: To a mixture of *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (75.0 mg, 0.168 mmol, 1.0 equiv.), *N*-tosyl aniline (41.7 mg, 0.168 mmol, 1.0 equiv.) and Cs_2CO_3 (220 mg, 0.672 mmol, 4.0 equiv.) was added DMF (1.0 mL), and the mixture was stirred at 60 °C until reaction completion, as analysed by TLC (~3 hours). The reaction mixture was cooled to room temperature and quenched with EtOAc and saturated aqueous NH_4Cl (5 mL each). The organic layer was separated and washed once more with saturated aqueous NH_4Cl, dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (10% CH_2Cl_2 /4% EtOAc/40-60 petroleum ether) afforded the title compound as a yellow oil. The oil was dissolved in toluene/*i*-PrOH/hexane (1:1:8, ~4 ml total volume) at 70 °C and the solution was allowed to slowly cool to room temperature to afford the title compound (75.2 mg, 0.123 mmol, 73%, (*Z*)-/(*E*)- 92:8) as colourless crystals. These crystals were also suitable for X-ray diffraction;

m.p. 124–125 °C;

R_f 0.16 (10% CH_2Cl_2/4% EtOAc/40-60 petroleum ether);

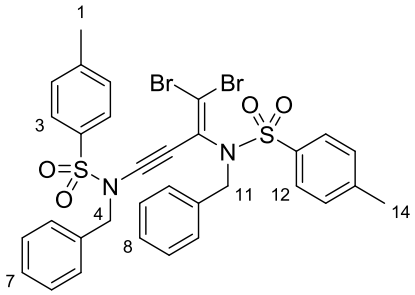
IR (thin film, ν_{max} / cm^{-1}) 3065, 1597, 1490, 1454, 1349, 1164, 1086, 910, 812, 729, 694, 673, 617;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 (4H, m, Ar*H*), 7.27–7.19 (4H, m, Ar*H*), 7.14 (2H, d, *J* = 8.3 Hz, *H*3), 7.113–7.05 (4H, m, Ar*H*), 7.01 (2H, d, *J* = 8.3 Hz, *H*2), 6.90 (2H, d, *J* = 8.3 Hz, *H*2), 6.34 (1H, s, *H*5), 4.65 (2H, s, *H*4), 2.26 (6H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_c 144.0, 143.5, 136.5, 135.7, 135.3, 135.13, 135.09, 130.3, 129.3, 129.2, 129.0, 128.72, 128.68, 128.4, 128.1, 127.8, 128.7, 108.9, 51.1, 21.52, 21.47;

HRMS (ES+) calc. for $C_{29}H_{28}{}^{79}BrN_2NaO_4S_2$ $[M+H]^+$ 611.0668, found $]^+$ 611.0668.

_N_,_N_'-(4,4-Dibromobut-3-en-1-yne-1,3-diyl)bis(_N_-benzyltosylamide), 162



To an oven dried, nitrogen flushed flask was added *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide (200 mg, 0.449 mmol, 1.0 equiv.) and anhydrous THF (5 mL), and the mixture was stirred at –40 °C. To this was added a solution of LiHMDS (0.54 mL of a 1.0 M solution in toluene, 0.54 mmol, 1.2 equiv.) dropwise, and the reaction was allowed to warm gradually to room temperature. ***Note***: TLC analysis during the course of the reaction showed an initial and rapid formation of a single compound (R_f 0.65 (15% Et_2O/40-60 petroleum ether), likely to be the bromoynamide, which over 30–40 minutes at room temperature underwent conversion to the title compound. We were unable to isolate this initially-formed compound due to spontaneous dimerisation upon concentration in vacuo or gentle heating.

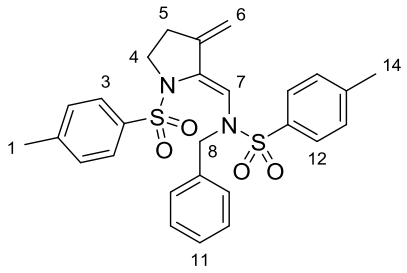
Upon reaction completion, the mixture was quenched with water, followed by extraction with Et_2O (×2). The organic extracts were combined and dried (Na_2SO_4), filtered and concentrated in vacuo. Column chromatography (15% Et_2O/40-60 petroleum ether) afforded the title compound (124.9 mg, 0.225 mmol, 76%) as colourless crystals. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **162** in toluene;

m.p. 116–117 °C;
R_f 0.14 (15% Et_2O/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2922, 2218, 1597, 1495, 1456, 1357, 1166, 1089, 1050, 814, 733, 696, 661;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77–7.69 (4H, m, *H*3, *H*12), 7.34 (2H, d, *J* = 7.8 Hz, *H*13), 7.31–7.15 (8H, m, *H*6, *H*7, *H*8, *H*9, *H*13), 7.11–6.98 (4H, m, *H*5, *H*10), 4.55 (1H, d, *J* = 15.0 Hz, *H*11), 4.47 (1H, d, *J* = 13.9 Hz, *H*4), 4.13 (1H, d, *J* = 13.9 Hz, *H*4), 3.42 (1H, d, *J* = 15.0 Hz, *H*11), 2.47 (3H, s, *H*1), 2.42 (3H, s, *H*14);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.2, 144.1, 134.7, 134.3, 133.7 (2C), 129.9, 129.5, 129.4, 128.60, 128.59 (2C), 128.5, 128.1, 128.1, 127.7, 124.2, 108.3, 91.6, 66.2, 55.0, 52.5, 21.6, 21.5;
HRMS (ES+) calc. for $C_{32}H_{29}{}^{79}Br_2N_2O_4S_2$ $[M+H]^+$ 726.9930, found 726.9929.

2.2 Yndiamide applications.

2.2a *Transition metal-catalysed*.

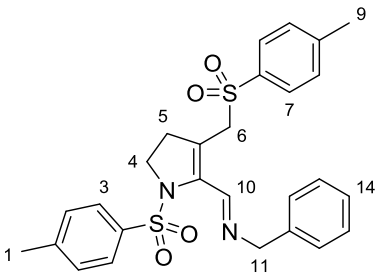
(*Z*)-*N*-Benzyl-*N*-((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide, 170



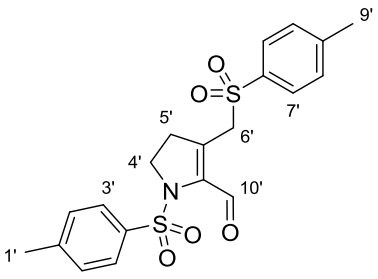
Following general procedure **1.2c**: Synthesised from *N*-benzyl-*N*-(((*N*'-(but-3-en-1-yl)tosylamido)ethynyl)-tosylamide (100 mg, 0.197 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.4 mg, 19.7 μmol, 0.1 equiv.), bbeda (4.7 mg, 19.7 μmol, 0.1 equiv.) in anhydrous toluene (1.2 mL). The reaction takes approximately 30–40 minutes to reach completion. Column chromatography (20% Et_2O/40-60 petroleum ether) afforded the title compound (73.2 mg, 0.144 mmol, 73%) as a pale yellow foam;

R_f 0.29 (20% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3032, 2921, 1656, 1626, 1597, 1495, 1455, 1348, 1162, 1091, 673;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.91–7.84 (2H, m, *H*12), 7.45–7.39 (2H, m, *H*3), 7.38–7.29 (4H, m, *H*2, *H*10) 7.29–7.21 (2H, m, *H*9), 7.21–7.13 (3H, m, *H*2, *H*11), 7.12 (1H, s, *H*7), 5.17 (2H, s, *H*8), 5.03 (1H, t, *J* = 2.3 Hz, *H*6), 4.47 (1H, t, *J* = 2.2 Hz, *H*6), 3.08 (2H, t, *J* = 7.2 Hz, *H*4), 2.39 (6H, s, H1), 1.50 (2H, t, *J* = 7.2 Hz, *H*5);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 143.8, 142.7, 137.0, 136.6, 135.2, 129.5, 129.4, 128.0, 127.94, 127.85, 127.7, 127.1, 121.5, 115.0, 102.3, 48.80, 48.79, 28.5, 21.6 (2C);
HRMS (ES+) calc. for $C_{27}H_{29}N_2O_4S_2$ $[M+H]^+$ 509.1563, found 509.1562.

_N_-Benzyl-1-(1-tosyl-3-(tosylmethyl)-4,5-dihydro-1_H_-pyrrol-2-yl)methanimine, 173 & 1-tosyl-3-(tosylmethyl)-4,5-dihydro-1_H_-pyrrole-2-carbaldehyde, 174



173



174

Following general procedure **1.2c**: Synthesised from *N*-benzyl-*N*-(((*N*'-(but-3-en-1-yl)tosylamido)ethynyl) tosylamide (40.0 mg, 78.6 μmol, 1.0 equiv.), $Pd(OAc)_2$ (1.8 mg, 7.9 μmol, 0.1 equiv.) in anhydrous toluene-d_8 (0.5 mL). This afforded *N*-benzylimine **173** (52% yield, as determined by ^{1}H NMR spectroscopic analysis). Column chromatography (20% Et_2O/40-60 petroleum ether) hydrolysed **173** and afforded aldehyde **174** (16.2 mg, 38.7 μmol, 49%) as a white foam;

- Data for **173**;

R_f 0.10 (20% EtOAc/40-60 petroleum ether);

^{1}H NMR (500 MHz, toluene-d_8) δ_H 7.89 (1H, s, *H*10), 7.53 (2H, d, *J* = 8.1 Hz, *H*3), 7.49 (2H, d, *J* = 8.0 Hz, *H*7), 7.23–7.14 (3H, m, *H*13, *H*14), 7.02–6.97 (2H, m, *H*12), 6.80 (2H, d, *J* = 8.1 Hz, *H*2), 6.75 (2H, d, *J* = 8.0 Hz, *H*7), 4.32 (2H, s, *H*6), 4.13 (2H, s, *H*11), 3.49 (2H, t, *J* = 8.9 Hz, *H*4), 2.17 (2H, t, *J* = 8.9 Hz, *H*5), 1.97 (3H, s, *H*1), 1.94 (3H, s, *H*9);

LRMS (ES+) calc. for $C_{27}H_{29}N_2O_4S_2$ $[M+H]^+$ 509.2, found 509.2. The fragment $[C_{20}H_{21}N_2O_2S]^+$ at m/z 353.2 was also observed, which corresponds to loss of one tosyl group.

- Data for **174**;

R_f 0.07 (20% EtOAc/40-60 petroleum ether);

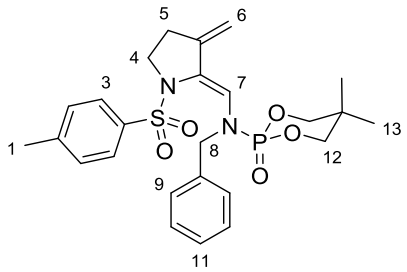
IR (thin film, ν_{max} / cm^{-1}) 2984, 2924, 1736, 1698, 1620, 1596, 1320, 1304, 1235, 1132, 1020, 673;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.38 (1H, s, *H*10′), 7.71–7.67 (2H, m, *H*3′), 7.61–7.56 (2H, m, *H*7′), 7.38–7.31 (4H, m, *H*2, *H*8′), 4.27 (2H, s, *H*6′), 3.77 (2H, t, *J* = 8.8 Hz, *H*4′), 2.46 (3H, s, *H*1′), 2.46 (2H, t, *J* = 8.8 Hz, *H*5′), 2.44 (3H, s, *H*9′);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 185.2, 145.4, 145.0, 139.7, 135.2, 132.5, 130.1, 129.9, 129.32, 129.28, 127.9, 54.7, 48.8, 32.6, 21.72, 21.69;

HRMS (ES+) calc. for $C_{20}H_{22}NO_5S_2$ $[M+H]^+$ 420.0934, found 420.0934.

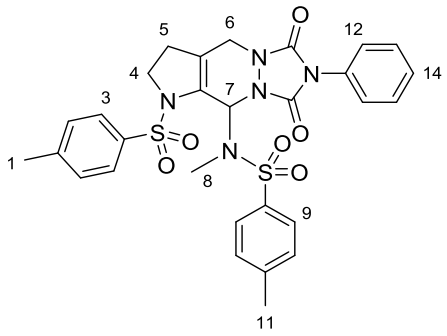
(*Z*)-2-(Benzyl((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)amino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide, 180



Following general procedure **1.2c**: Synthesised from *N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl)-*N*-(but-3-en-1-yl) tosylamide (20.0 mg, 39.8 μmol, 1.0 equiv.), $Pd(OAc)_2$ (0.9 mg, 4.0 μmol, 0.1 equiv.), bbeda (0.9 mg, 4.0 μmol, 0.1 equiv.) in anhydrous toluene (0.3 mL). The reaction takes approximately 20 minutes to reach completion. ***Note***: This compound is extremely unstable, and decomposes on standing in toluene or upon silica gel. In situ reaction with DMAD was unsuccessful;

R_f 0.33 (50% EtOAc/40-60 petroleum ether);
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.3 Hz, *H*3), 7.44 (2H, d, *J* = 7.3 Hz, *H*10), 7.27–7.21 (4H, m, *H*2, *H*9), 7.16 (1H, tt, *J* = 7.3, 1.2 Hz, *H*11), 6.80 (1H, d, *J* = 7.1 Hz, *H*7), 5.00 (2H, d, *J* = 11.2 Hz, *H*8), 4.96 (1H, t, *J* = 2.1 Hz, *H*6), 4.41 (1H, d, *J* = 2.1 Hz, *H*6), 4.29 (2H, t, *J* = 10.9 Hz, *H*12), 4.17 (2H, dd, *J* = 13.4, 10.9 Hz, *H*12), 2.99 (2H, br. t, *J* = 7.1 Hz, *H*4), 2.41 (3H, s, *H*1), 1.43 (2H, br. t, *J* = 7.1 Hz, *H*5), 1.17 (3H, s, *H*13), 1.08 (3H, s, *H*13).

_N_-(6,8-Dioxo-7-phenyl-1-tosyl-2,3,4,7,8,10-hexahydro-1_H_,6_H_-pyrrolo[2,3-d][1,2,4]triazolo[1,2-a]pyridazin-10-yl)-_N_,4-dimethylbenzenesulfonamide, 182

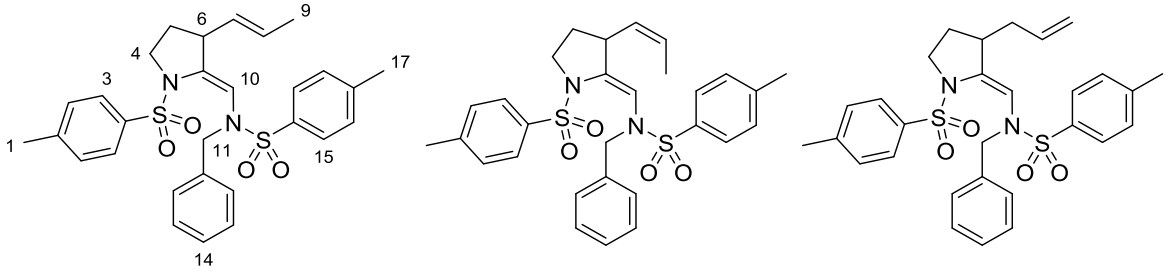


Following general procedure **1.2c**: Synthesised from *N*-(but-3-en-1-yl)-*N*-(((*N*-methyltosylamido)ethynyl) tosylamide (30.0 mg, 69.4 µmol, 1.0 equiv.), $Pd(OAc)_2$ (1.6 mg, 6.9 µmol, 0.1 equiv.), bbeda (1.6 mg, 6.9 µmol, 0.1 equiv.) in anhydrous toluene (0.3 mL). The reaction takes approximately 10 minutes to reach completion. ***Note***: The cycloisomerisation product was quite unstable and decomposed rapidly during silica gel chromatography. It is recommended to use this compound immediately from the crude reaction mixture.

The mixture was subsequently cooled to room temperature, PTAD (12.2 mg, 69.4 µmol, 1.0 equiv.) was added and the resulting mixture was stirred for 5 minutes. The mixture was transferred directly onto a silica gel column, and column chromatography (70% CH_2Cl_2/40-60 petroleum ether) afforded the title compound (21.5 mg, 35.4 µmol, 51%) as a white foam. Crystals suitable for X-ray diffraction were grown by recrystallisation from EtOAc;

R_f 0.06 (60% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3066, 2922, 1783, 1725, 1597, 1503, 1419, 1345, 1288, 1164, 1088, 1026, 929, 816, 766, 727, 707, 688, 657;
^{1}H NMR (500 MHz, $CHCl_3$) δ_H 7.83 (2H, d, *J* = 8.2 Hz, *H*9), 7.74 (2H, d, *J* = 8.4 Hz, *H*3), 7.48–7.43 (2H, m, *H*13), 7.42–7.34 (5H, m, *H*2, *H*12, *H*14), 7.26 (2H, d, *J* = 8.2 Hz, *H*10), 6.82 (1H, t, *J* = 1.2 Hz, *H*7), 4.44 (1H, dq, *J* = 16.3, 1.2 Hz, *H*6), 3.98 (1H, dq, *J* = 16.3, 1.2 Hz, *H*6), 3.94 (1H, ddd, *J* = 12.5, 9.0, 3.6 Hz, *H*4), 3.83 (1H, app. dt, *J* = 12.5, 10.4 Hz, *H*4), 3.19 (3H, s, *H*8), 2.46 (3H, s, H11), 2.35 (3H, s, *H*1), 2.25–2.08 (2H, m, *H*5);
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 151.7, 149.9, 144.7, 143.7, 136.8, 133.4, 131.8, 130.9, 130.0, 129.5, 129.0, 128.2, 127.72, 127.71, 125.9, 125.1, 65.7, 50.6, 44.0, 37.1, 29.7, 21.7, 21.5,
HRMS (ES+) calc. for $C_{29}H_{29}N_5NaO_6S_2$ $[M+Na]^+$ 630.1452, found 630.1447.

_N_-Benzyl-_N_-((_Z_)-(3-((_E_)-prop-1-en-1-yl)-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide, (_E_)-183

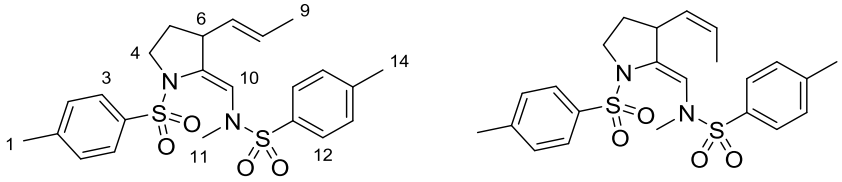


Following general procedure **1.2c**: Synthesised from (*Z*)-*N*-benzyl-*N*-(((*N*'-(hex-3-en-1-yl)tosylamido) ethynyl)tosylamide (100 mg, 0.186 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.2 mg, 18.6 µmol, 0.1 equiv.), bbeda (4.4 mg, 18.6 µmol, 0.1 equiv.) in anhydrous toluene (1.1 mL). The reaction takes approximately 30 minutes to reach completion. Column chromatography (20% Et_2O/40-60 petroleum ether) afforded an inseparable mixture of (*E*)-**183**, (*Z*)-**183** and **183′** (82.9 mg, 0.154\mmol, 83%) as a white foam. Crystals suitable for X-ray diffraction were grown by very slow evaporation of the title compound in heptane (*plus* a few drops of toluene to solubilise);

R_f 0.42 (20% EtOAc/petrol);
IR (thin film, ν_{max} / cm^{-1}) 3030, 2923, 1597, 1495, 1454, 1351, 1162, 1091, 815, 674;
HRMS (CI+) calc. for $C_{29}H_{33}N_2O_4S_2$ $[M+H]^+$ 537.1876, found 537.1875.

- Specific data for major compound, (*E*)-**183**:
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83–7.75 (2H, m, *H*15), 7.43–7.13 (11H, m, *H*2, *H*3, *H*12, *H*13, *H*14), 6.08 (1H, d, *J* = 1.5 Hz, *H*10), 5.23–5.02 (2H, m, *H*11), 5.10 (1H, dqd, *J* = 15.2, 6.6, 0.5 Hz, *H*8), 4.54 (1H, ddq, *J* = 15.2, 8.3, 1.5 Hz, *H*7), 3.22–3.05 (2H, m, *H*4), 2.42 (3H, s, *H*1), 2.40 (3H, s, *H*1), 2.11–1.87 (1H, m, *H*6), 1.54 (3H, dd, *J* = 6.6, 1.5 Hz, *H*9), 1.38–1.28 (1H, m, *H*5), 0.59–0.45 (1H, m, *H*5);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 143.5, 137.0, 133.8, 129.31 (2C), 128.27, 128.14, 128.10, 128.0, 127.93, 127.91, 127.8, 127.7, 127.0, 115.2, 49.5, 48.9, 45.1, 29.0, 21.6 (2C), 17.8.

_N_-Methyl-_N_-((_Z_)-(3-((_E_)-prop-1-en-1-yl)-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide, (_E_)-184



Following general procedure **1.2c**: Synthesised from (*Z*)-*N*-methyl-*N*-(((*N*'-(hex-3-en-1-yl)tosylamido) ethynyl)tosylamide (200 mg, 0.434 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.8 mg, 43.4 μmol, 0.1 equiv.), bbeda (10.3 mg, 43.4 μmol, 0.1 equiv.) in anhydrous toluene (2.6 mL). The reaction takes <10 minutes to reach completion. Column chromatography (25% Et_2O/40-60 petroleum ether) afforded an inseparable mixture of (*E*)-**184** and (Z)-**184** (124 mg, 0.269 mmol, 62%) as a white foam. Crystals suitable for X-ray diffraction were grown by slow evaporation of a solution of the title compound in dibutylether;

m.p. 86–88°C;

R_f 0.24 (40% Et_2O/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2921, 1711, 1597, 1451, 1348, 1160, 1120, 1019, 993, 815, 772, 731, 672, 658;

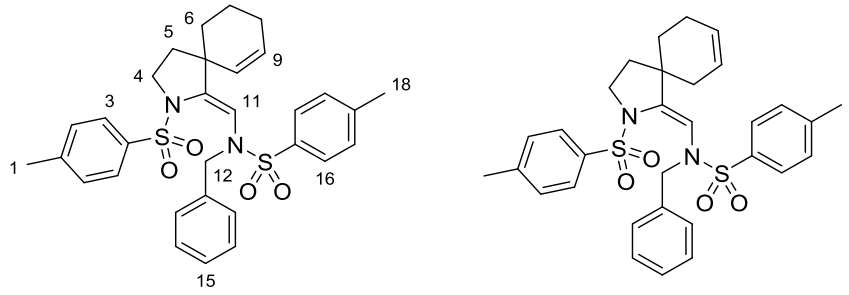
HRMS (ES+) calc. for $C_{23}H_{29}N_2O_4S_2$ $[M+H]^+$ 461.1563, found 461.1564.

- Specific data for major compound, (*E*)-**184**:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.73–7.69 (2H, m, *H*12), 7.61–7.57 (2H, m, *H*3), 7.33–7.26 (4H, m, *H*2, *H*13), 5.78 (1H, d, *J* = 2.0 Hz, *H*10), 5.31 (1H, dq, *J* = 15.1, 6.5 Hz, *H*8), 4.96 (1H, ddq, *J* = 15.1, 8.3, 1.5 Hz, *H*7), 3.57 (1H, ddd, *J* = 11.3, 8.0, 3.4 Hz, *H*4), 3.48 (1H, m, *H*4), 3.12 (3H, s, *H*11), 2.45–2.37 (1H, m, *H*6), 2.44 (3H, s, *H*14), 2.40 (3H, s, *H*1), 1.74 (1H, dddd, *J* = 11.3, 8.0, 7.5, 3.4 Hz, *H*5), 1.63 (3H, dd, *J* = 6.5, 1.5 Hz, *H*9), 1.32 (1H, m, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.0, 143.4, 135.0, 134.9, 131.0, 129.6, 129.4, 129.3, 128.4, 127.8, 127.8, 116.3, 49.8, 45.6, 34.8, 29.3, 21.6, 21.5, 17.8;

(*Z*)-*N*-Benzyl-*N*-((2-tosyl-2-azaspiro[4.5]dec-6-en-1-ylidene)methyl)tosylamide, 185



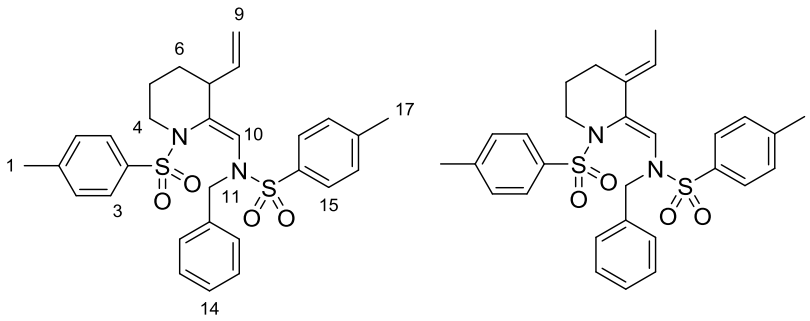
185 85:15 **185'**

Following general procedure **1.2c**: Synthesised from *N*-benzyl-*N*-(((*N*'-(2-(cyclohex-1-en-1-yl)ethyl)tosyl amide)ethynyl)tosylamide (100 mg, 0.178 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.0 mg, 17.8 μmol, 0.1 equiv.), bbeda (4.2 mg, 17.8 μmol, 0.1 equiv.) in anhydrous toluene (1.1 mL). The reaction takes approximately 30 minutes to reach completion. Column chromatography (20% Et_2O/40-60 petroleum ether) afforded an inseparable mixture of **185** and **185′** (72.7 mg, 0.129 mmol, 73%) as a pale yellow oil. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **185** and **185'** in Et_2O/toluene (1:1);

m.p. 149–150 °C;
R_f 0.56 (20% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2926, 1597, 1495, 1351, 1160, 1091, 812, 735, 660;
HRMS (CI+) calc. for $C_{31}H_{35}N_2O_4S_2$ $[M+H]^+$ 563.2033, found 563.2034.

- Specific data for major compound, **185**:
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.87–7.82 (2H, m, *H*16), 7.36–7.14 (11H, m, *H*2, *H*3, *H*13, *H*14, *H*15, *H*17), 5.84 (1H, s, *H*11), 5.59 (1H, dt, *J* = 10.0, 3.7 Hz, *H*9), 5.14 (1H, d, *J* = 15.7 Hz, *H*12), 5.08 (1H, d, *J* = 15.7 Hz, *H*4), 4.56 (1H, dt, *J* = 10.0, 1.4 Hz, *H*10), 3.46–3.38 (1H, br. m, *H*4), 3.14 (1H, td, *J* = 11.5, 6.4 Hz, *H*4), 2.41 (3H, s, *H*18), 2.40 (3H, s, *H*1), 1.94–1.79 (1H, m, *H*8), 1.79–1.66 (1H, m, *H*8), 1.22–1.14 (1H, m, *H*5), 1.15–1.06 (1H, m, *H*7), 1.06–0.93 (1H, m, *H*7), 0.74 (1H, td, *J* = 11.5, 8.4 Hz, *H*5), 0.51 (1H, br. t, *J* = 10.8 Hz, *H*6), 0.27–0.13 (1H, m, *H*6);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 143.3, 137.3, 137.2, 134.3, 133.2, 131.5, 129.2, 128.9, 128.5, 128.04, 127.96, 127.91, 127.85, 127.1, 115.0, 49.3, 48.7, 46.6, 36.1, 31.5, 24.6, 21.57, 21.55, 19.2.

(*Z*)-*N*-Benzyl-*N*-((1-tosyl-3-vinylpiperidin-2-ylidene)methyl)tosylamide, 186



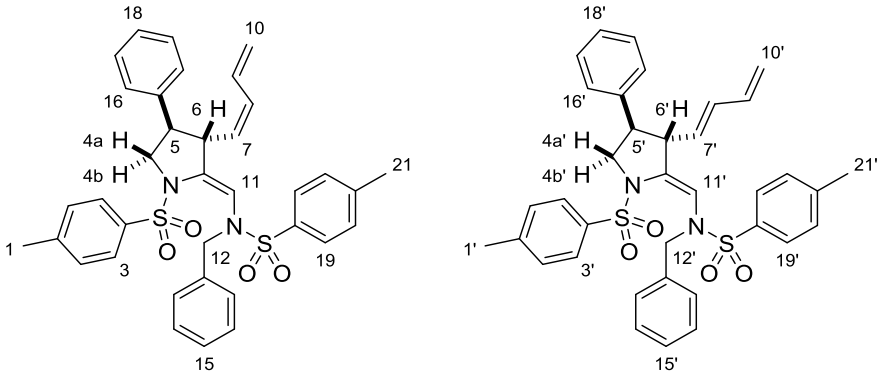
186 85:15 **186'**

Following general procedure **1.2c**: Synthesised from (*E*)-*N*-benzyl-*N*-(((*N*'-(hex-4-en-1-yl)tosylamido) ethynyl)tosylamide (100 mg, 0.186 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.2 mg, 18.6 μmol, 0.1 equiv.), bbeda (4.4 mg, 18.6 μmol, 0.1 equiv.) in anhydrous toluene (1.1 mL). The reaction takes approximately 1.5 hours to reach completion. Column chromatography (20% Et_2O/40-60 petroleum ether) afforded an inseparable mixture of **186** and **186′** (87.8 mg, 0.164 mmol, 89%) as a white foam. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **186** and **186′** in Et_2O/toluene (1:1);

R_f 0.61 (20% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3033, 2921, 1496, 1458, 1352, 1160, 1091, 815, 735, 660;
HRMS (ES+) calc. for $C_{29}H_{32}N_2NaO_4S_2$ $[M+Na]^+$ 559.1696, found 559.1696.

- Specific data for major compound, **186**:
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.81 (2H, *J* = 8.3 Hz, *H*15), 7.57 (2H, d, *J* = 8.3 Hz, *H*3), 7.33 (2H, d, *J* = 8.3 Hz, *H*16), 7.32–7.13 (7H, m, H2, H12, H13, H14), 6.58 (1H, br. s, *H*10), 5.61 (1H, ddd, *J* = 17.2, 9.8, 8.1 Hz, *H*8), 5.22–5.00 (3H, m, *H*9, *H*11), 4.86 (1H, d, *J* = 17.2 Hz, *H*9), 3.75–3.41 (1H, br. m, *H*4), 2.42 (6H, s, *H*1, *H*17), 2.16–1.96 (1H, br. m, *H*7), 1.72–1.51 (1H, br. m, *H*4), 1.45–1.35 (1H, br. m, *H*5), 1.07–0.81 (3H, br. m, *H*5, *H*6);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.69, 143.67, 138.1, 137.9, 136.6, 136.5, 129.6, 129.5, 128.2, 127.7, 127.5, 127.4, 127.01, 126.95, 126.9, 121.2, 49.3, 48.0, 43.3, 31.8, 22.4, 21.59, 21.56.

_N_-Benzyl-_N_-((_Z_)-((3_S_*,4_R_*)-3-(buta-1,3-dien-1-yl)-4-phenyl-1-tosylpyrrolidin-2-ylidene) methyl)tosylamide, 187



(_Z_)-**187** 57:43 (_E_)-**187**

Following general procedure **1.2c**: Synthesised from (_E_)-_N_-benzyl-_N_-(((_N_'-(4-cyclopropyl-2-phenylbut-3-en-1-yl)tosylamido)ethynyl)tosyl amide (100 mg, 0.160 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.6 mg, 16.0 μmol, 0.1 equiv.), bbeda (3.8 mg, 16.0 μmol, 0.1 equiv.) in anhydrous toluene (1.0 mL). The reaction takes approximately 60 minutes to reach completion. Column chromatography (20% Et_2O/40-60 petroleum ether) afforded an inseparable mixture of (_E_)-**187** and (_Z_)-**187** (65.7 mg, 0.105 mmol, 66%) as a white foam. Crystals suitable for X-ray diffraction were grown by crystallisation from methanol/water;

R_f 0.42 (20% EtOAc/40-60 petroleum ether);

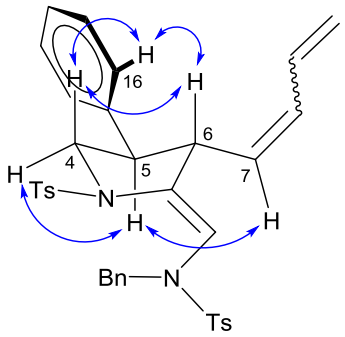
IR (thin film, ν_{max} / cm^{-1}) 3032, 2921, 1597, 1495, 1454, 1351, 1162, 1092, 815, 666;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H Data for (_Z_)-isomer: 7.88 (2H, d, _J_ = 8.3 Hz, _H_19), 7.44 (2H, d, _J_ = 8.3 Hz, _H_3), 7.39–7.24 (9H, m, _H_2, _H_12, _H_13, _H_14, _H_15, _H_20), 7.16–7.06 (3H, m, _H_17, _H_18), 6.56–6.50 (2H, m, _H_16), 6.08 (1H, d, _J_ = 1.2 Hz, _H_11), 5.91 (1H, app. t, _J_ = 11.0 Hz, _H_8), 5.61 (1H, dt, _J_ = 16.9, 11.0 Hz, _H_9), 5.30–5.21 (2H, m, _H_12), 5.09 (1H, d, _J_ = 16.9 Hz, _H_10), 4.99 (1H, d, _J_ = 11.0 Hz, _H_10), 4.58 (1H, app. t, _J_ = 9.7 Hz, _H_7), 3.55–3.49 (1H, m, _H_4b), 3.14 (1H, t, _J_ = 11.0 Hz, _H_4a), 2.50 (3H, s, _H_1), 2.43 (3H, s, _H_21), 2.36 (1H, app. br. t, _J_ = 10.0 Hz, _H_6), 1.71 (1H, app. q, _J_ = 11.2 Hz, _H_5); - Data for (_E_)-isomer: 7.88 (2H, d, _J_ = 8.3 Hz, _H_19′), 7.48 (2H, d, _J_ = 8.3 Hz, _H_3′), 7.39–7.24 (9H, m, _H_2′, _H_12′, _H_13′, _H_14′, _H_15′, _H_20′), 7.16–7.06 (3H, m, _H_17′, _H_18′), 6.55–6.45 (2H, m, _H_16′), 6.13 (1H, d, _J_ = 1.2 Hz, _H_11′), 6.15–6.04 (1H, m, _H_9′), 5.47 (1H, dd, _J_ = 15.2, 10.5 Hz, _H_8′), 5.21–5.12 (2H, m, _H_12′), 4.99–4.92 (2H, m, _H_10′), 4.75 (1H, dd, _J_ = 15.2, 8.6 Hz, _H_7′), 3.49–3.45 (1H, m, _H_4b′), 3.07 (1H, t, _J_ = 11.0 Hz, _H_4a′), 2.50 (3H, s, _H_1′), 2.42 (3H, s, _H_21′), 2.13 (1H, dd, _J_ = 11.2, 8.6 Hz, _H_6′), 1.73 (1H, ddd, _J_ = 11.2, 11.0, 8.8 Hz, _H_5′);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C Data for (_E_)/(_Z_)-isomers: 144.61, 144.56, 143.64, 143.62, 137.8, 137.5, 137.01, 136.98, 136.94, 136.90, 136.0, 134.6, 133.6, 133.4, 133.3, 131.0, 129.9, 129.5, 129.44, 129.41 (2C), 128.53, 128.49, 128.33, 128.30, 128.27, 128.2, 127.92 (2C), 127.85, 127.8,

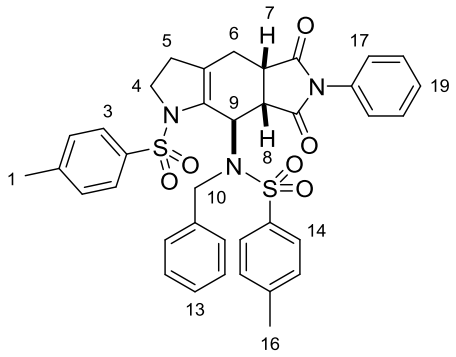
127.5, 127.4, 127.22, 127.18, 127.14, 127.13, 127.09, 127.0 (2C), 126.9, 119.4, 117.2, 115.9, 56.7 (2C), 52.3, 49.2 (2C), 48.3, 48.8, 46.6, 21.71, 21.66, 21.6 (2C);

HRMS (CI+) calc. for $C_{36}H_{37}N_2O_4S_2$ $[M+H]^+$ 625.2189, found 625.2203.



The relative stereochemistry was determined by 2D ^{1}H NOESY data. Correlations between *H*4a, *H*6 and *H*16 are observed on the "top face" of the pyrrolidine ring, as well as complementary correlations between *H*4b, *H*5 and *H*7 on the "bottom face" (depicted above).

_N_-Benzyl-_N_-((4_aS_*,7_aS_*,8_R_*)-5,7-dioxo-6-phenyl-1-tosyl-1,2,3,4,4a,5,6,7,7a,8-decahydro pyrrolo[3,4-f]indol-8-yl)tosylamide, 188



Following general procedure **1.2d**: Synthesised from (*Z*)-*N*-benzyl-*N*-((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide (50.0 mg, 98.3 μmol, 1.0 equiv.) and *N*-phenyl maleimide (17.0 mg, 98.3 μmol, 1.0 equiv.) in toluene (0.5 mL) at 60 °C. Column chromatography (30% EtOAc/40-60 petroleum ether) afforded the title compound (42.3 mg, 62.0 μmol, 63%) as a white solid. Crystals suitable for X-ray diffraction were grown by allowing a concentrated solution of the title compound in methanol/water to stand for 1 month. ***Note***: It was very difficult to grow suitable crystals of this compound from most organic solvents, as it had a tendency to grow hair-like needles that were too fine for crystallographic studies.

m.p. 154–156 °C;

R_f 0.07 (20% EtOAc/40-60 petroleum ether);

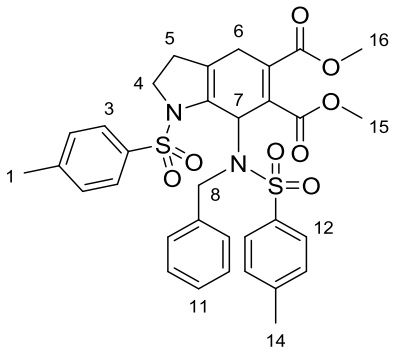
IR (thin film, ν_{max} / cm^{-1}) 3065, 2924, 1713, 1598, 1496, 1385, 1341, 1161, 1091, 690;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.80 (2H, d, *J* = 8.3 Hz, *H*14), 7.67 (2H, d, *J* = 7.1 Hz, *H*11), 7.49 (2H, d, *J* = 8.3 Hz, *H*3), 7.47–7.42 (2H, m, *H*18), 7.42–7.36 (3H, m, *H*12, *H*19), 7.34 (2H, d, *J* = 8.3 Hz, *H*15), 7.34–7.29 (1H, m, *H*13), 7.18–7.11 (2H, m, *H*17), 7.03 (2H, d, *J* = 8.3 Hz, *H*2), 5.65 (1H, s, *H*9), 5.09 (1H, d, *J* = 15.2 Hz, *H*10), 4.86 (1H, d, *J* = 15.2 Hz, *H*10), 3.52 (1H, dd, *J* = 9.5, 0.9 Hz, *H*8), 3.48–3.41 (1H, m, *H*7), 3.40 (1H, ddd, *J* = 12.5, 9.8, 3.6 Hz, *H*4), 2.69 (1H, dd, *J* = 19.0, 10.5 Hz, *H*6), 2.51–2.38 (1H, m, *H*4), 2.45 (3H, s, *H*16), 2.32 (3H, s, *H*1), 2.17 (1H, d, *J* = *1*9.0 Hz, *H*6), 1.79–1.65 (1H, m, *H*5), 1.58–1.47 (1H, m, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 179.0, 175.9, 143.9, 143.3, 138.6, 136.9, 132.8, 131.7, 131.3, 130.3, 129.7, 129.4, 129.1, 129.0, 128.64, 128.61, 128.0, 127.7, 126.7, 126.0, 54.8, 50.5, 47.89, 47.87, 36.5, 30.8, 25.7, 21.6, 21.5;

HRMS (ES+) calc. for $C_{37}H_{35}N_3NaO_6S_2$ $[M+Na]^+$ 704.1860, found 704.1856.

Dimethyl 7-((*N*-benzyltosylamido)-1-tosyl-2,3,4,7-tetrahydro-1*H*-indole-5,6-dicarboxylate, 189



Following general procedure **1.2d**: Synthesised from (*Z*)-*N*-benzyl-*N*-((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide (50.0 mg, 98.3 μmol, 1.0 equiv.) and DMAD (12 μL, 98.3 μmol, 1.0 equiv.) in toluene (0.5 mL), at 60 °C. Column chromatography (30% EtOAc/40-60 petroleum ether) afforded the title compound (43.9 mg, 67.5 μmol, 69%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **189** in CH_2Cl_2;

m.p. 152–154 °C;

R_f 0.02 (20% EtOAc/40-60 petroleum ether);

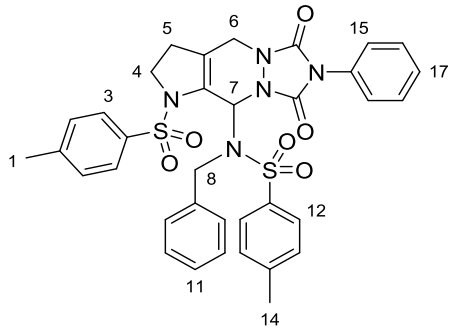
IR (thin film, ν_{max} / cm^{-1}) 2952, 1727, 1597, 1495, 1435, 1333, 1259, 1207, 1159, 1089, 916, 873, 815, 728, 688, 658;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.90 (2H, d, *J* = 8.3 Hz, *H*12), 7.60 (2H, d, *J* = 8.1 Hz, *H*3), 7.30–7.21 (4H, m, *H*2, *H*13), 7.18–7.08 (3H, m, *H*10, *H*11), 7.08–6.98 (2H, m, *H*9), 6.25 (1H, br. s, *H*7), 4.58 (1H, d, *J* = 15.9 Hz, *H*8), 4.28 (1H, d, *J* = 15.9 Hz, *H*8), 3.77 (6H, s, *H*15, *H*16), 3.61 (1H, ddd, *J* = 13.0, 8.8, 1.5 Hz, *H*4), 2.99–2.79 (2H, m, *H*4, *H*6), 2.59 (1H, dd, *J* = 24.0, 5.1 Hz, *H*6), 2.42 (3H, s, *H*14), 2.41 (3H, s, *H*1), 1.58–1.45 (1H, m, *H*5), 1.45–1.30 (1H, m, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 167.3, 165.8, 144.3, 143.2, 138.1, 137.8, 136.6, 133.6, 132.7, 132.1, 131.3, 129.6, 129.2, 128.3, 128.2, 128.0, 127.9, 127.2, 53.5, 52.6, 52.5, 49.9, 49.5, 30.4, 26.2, 21.6, 21.5;

HRMS (ES+) calc. for $C_{33}H_{34}N_2NaO_8S_2$ $[M+Na]^+$ 673.1649, found 673.1639.

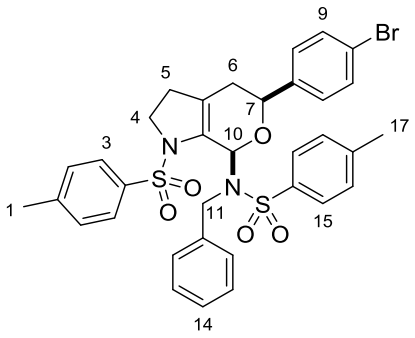
_N_-Benzyl-_N_-(6,8-dioxo-7-phenyl-1-tosyl-2,3,4,7,8,10-hexahydro-1_H_,6_H_-pyrrolo[2,3-d][1,2,4] triazolo[1,2-a]pyridazin-10-yl)tosylamide, 190



Following general procedure **1.2d**: Synthesised from (*Z*)-*N*-benzyl-*N*-((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide (30.0 mg, 59.0 μmol, 1.0 equiv.) and PTAD (10.3 mg, 59.0 μmol, 1.0 equiv.) in toluene (0.3 mL), at room temperature. Column chromatography (70% CH_2Cl_2/40-60 petroleum ether) afforded the title compound (34.3 mg, 50.3 μmol, 85%) as a white foam;

R_f 0.05 (50% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2980, 1777, 1715, 1598, 1420, 1337, 1163, 1089, 911, 726, 688, 656;
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 8.02 (2H, d, *J* = 8.3 Hz, *H*12), 7.69 (2H, d, *J* = 8.3 Hz, *H*3), 7.55–7.42 (5H, m, *H*7, *H*9, *H*10), 7.42–7.36 (1H, m, *H*11), 7.32 (2H, t, *J* = 8.3 Hz, *H*2), 7.30 (2H, t, *J* = 8.3 Hz, *H*13), 7.22–7.17 (3H, m, *H*16, *H*17), 7.17–7.11 (2H, m, *H*15), 4.60 (1H, d, *J* = 16.4 Hz, *H*8), 4.35 (1H, d, *J* = 16.4 Hz, *H*8), 4.07 (1H, d, *J* = 16.4 Hz, *H*6), 3.81–3.69 (2H, m, *H*4, *H*6), 3.32–3.19 (1H, m, *H*4), 2.43 (3H, s, *H*14), 2.41 (3H, s, *H*1), 1.79–1.63 (2H, m, *H*5);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 151.7, 149.1, 144.8, 143.8, 136.8, 136.7, 133.1, 131.7, 131.1, 129.9, 129.5, 129.0, 128.9, 128.7, 128.3, 128.1, 127.9, 127.7, 127.4, 125.1, 63.1, 50.4, 50.0, 44.1, 29.6, 21.6, 21.5;
HRMS We were unable to obtain an accurate mass (ES+ or CI+) due to decomposition upon ionisation. However, fragments at m/z 262.0891 ($[C_{14}H_{16}NO_2S]^+$) and 377.9762 were observed which correspond to cleavage of the exocyclic sulfonamide.

_N_-Benzyl-_N_-((5_S_*,7_R_*)-5-(4-bromophenyl)-1-tosyl-1,2,3,4,5,7-hexahydropyrano[3,4-b]pyrrol-7-yl)tosylamide, 191



To a solution of (*Z*)-*N*-benzyl-*N*-((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide (50.0 mg, 98.3 μmol, 1.0 equiv.) and 4-bromobenzaldehyde (20.0 mg, 0.108 μmol, 1.1 equiv.) in anhydrous CH_2Cl_2 (1.0 mL) at –78 °C was added dropwise $BF_3{\cdot}OEt_2$ (6 μL, 49.2 μmol, 0.5 equiv.), and the reaction was stirred at –78 °C until complete consumption of starting material was observed (as analysed by TLC, ~20 minutes). The reaction was quenched with aqueous saturated $NaHCO_3$ (1 mL) and the mixture was warmed to room temperature. Water and CH_2Cl_2 (4 mL each) was added, the organic layer was separated and the aqueous was extracted with CH_2Cl_2 (×2). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (20% EtOAc/40-60 petroleum ether) afforded the title compound (52.2 mg, 75.2 μmol, 77%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **191** in toluene;

m.p. ~140 °C (dec.);

R_f 0.20 (20% EtOAc/40-60 petroleum ether);

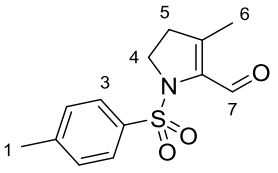
IR (thin film, ν_{max} / cm^{-1}) 2923, 1597, 1491, 1455, 1348, 1164, 1092, 1039, 1010, 929, 814.4, 762, 663;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.85 (2H, d, *J* = 8.1 Hz, *H*15), 7.76 (2H, d, *J* = 8.2 Hz, *H*3), 7.47–7.43 (2H, m, *H*9), 7.33 (2H, d, *J* = 8.2 Hz, *H*2), 7.29–7.23 (2H, m, *H*12), 7.16 (2H, d, *J* = 8.1 Hz, *H*16), 7.16–7.08 (3H, m, *H*13, *H*14), 6.98 (2H, d, *J* = 8.3 Hz, *H*8), 6.85 (1H, br. s, *H*10), 4.62 (1H, dd, *J* = 9.8, 3.4 Hz, *H*7), 4.41 (1H, d, *J* = 16.1 Hz, *H*11), 4.17 (1H, d, *J* = 16.1 Hz, *H*11), 3.52 (1H, ddd, *J* = 12.2, 8.9, 2.3 Hz, *H*4), 2.45 (3H, s, *H*1), 2.40 (3H, s, *H*17), 2.43–2.31 (1H, m, *H*4), 2.22–1.99 (2H, m, *H*6), 1.92–1.77 (1H, m, *H*5), 1.71 (1H, dd, *J* = 15.7, 9.8 Hz, *H*5);

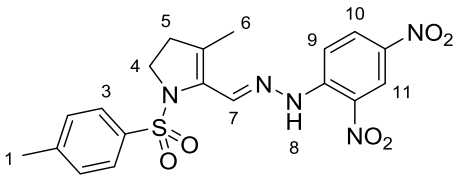
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.0, 143.2, 139.5, 137.2, 136.7, 134.4, 133.0, 132.7, 131.2, 129.6, 129.1, 128.6, 128.3, 127.7, 127.6, 127.1, 127.0, 121.4, 82.7, 73.8, 48.6, 47.3, 33.3, 31.3, 21.6, 21.5;

HRMS We were unable to obtain an accurate mass (ES+ or EI+) due to decomposition upon ionisation.

3-Methyl-1-tosyl-4,5-dihydro-1*H*-pyrrole-2-carbaldehyde, 192 & (*E*)-5-((2-(2,4-dinitrophenyl) hydrazineylidene)methyl)-4-methyl-1-tosyl-2,3-dihydro-1*H*-pyrrole, 192'



192



192'

To a vigorously stirring solution of (*Z*)-*N*-benzyl-*N*-((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)-tosylamide (50.0 mg, 98.3 μmol, 1.0 equiv.) in CH_2Cl_2 (1 mL), at –60 °C, was added trifluoroacetic acid (12 μL, 0.197 mmol, 2.0 equiv.). The reaction was stirred for 15 minutes at –60 °C and quenched with 1 M aqueous NaOH (1 mL). The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (×2). The combined organic layers were then dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (20% EtOAc/40-60 petroleum ether) afforded the title compound (21.4 mg, 80.7 μmol, 82%) as a pale yellow wax;

- Data for aldehyde **192**:

R_f 0.18 (20%EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2922, 2851, 1695, 1620, 1597, 1495, 1348, 1161, 1088, 1026, 816, 673;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 9.75 (1H, s, *H*7), 7.61 (2H, d, *J* = 8.3 Hz, *H*3), 7.31 (2H, d, *J* = 8.3 Hz, *H*2), 3.80–3.69 (2H, m, *H*4), 2.44 (3H, s, *H*1), 2.06–1.95 (5H, m, *H*5, *H*6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 186.3, 144.5, 144.4, 135.2, 132.7, 129.7, 128.0, 48.6, 35.7, 21.6, 14.2;

HRMS (ES+) calc. for $C_{13}H_{15}NNaO_3S$ $[M+Na]^+$ 288.0665, found 288.0665.

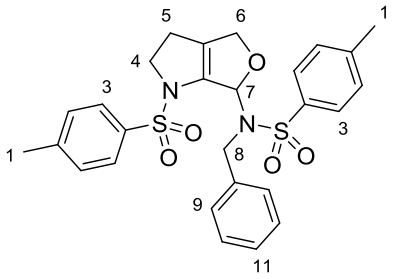
Treatment of a sample of **192** with 2,4-DNP solution, followed by extraction with CH_2Cl_2, afforded compound **192'**. Recrystallisation from methanol gave crystals suitable for X-ray diffraction.

- Data for hydrazone **192'**:

^{1}H NMR (500 MHz, $CHCl_3$) δ_H 11.3 (1H, s, *H*8), 9.17 (1H, d, *J* = 2.7 Hz, *H*11), 8.35 (1H, ddd, *J* = 9.7, 2.7, 0.6 Hz, *H*10), 8.03 (1H, s, *H*7), 7.88 (1H, d, *J* = 9.7 Hz, *H*9), 7.65–7.61 (2H, m, *H*3), 7.34–7.30 (2H, m, *H*2), 3.78 (2H, t, *J* = 8.2 Hz, *H*4), 2.45 (3H, s, *H*1), 2.11–2.04 (2H, m, *H*5), 2.05 (3H, s, *H*6);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.6, 144.3, 142.4, 138.3, 136.0, 133.2, 130.6, 130.0, 129.7, 129.5, 127.8, 123.5, 116.4, 48.8, 35.4, 21.7, 15.1;

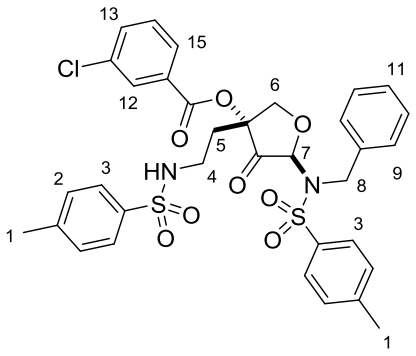
_N_-Benzyl-_N_-(1-tosyl-2,3,4,6-tetrahydro-1_H_-furo[3,4-b]pyrrol-6-yl)tosylamide, 193



To a solution of (*Z*)-*N*-benzyl-*N*-((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide (50.0 mg, 98.3 μmol, 1.0 equiv.) in CH_2Cl_2 (2 mL), at –78 °C, was added dropwise a solution of *m*CPBA (36.4 mg (70–75% w/w balanced with *m*-chlorobenzoic acid and water), 147 μmol, 1.5 equiv.) in CH_2Cl_2 (1 mL). The reaction was stirred for 1 hour at –78 °C and quenched with aqueous saturated Na_2SO_3 (3 mL). The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (×2). The combined organic layers were then dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (15% EtOAc/40-60 petroleum ether) afforded the title compound (22.4 mg, 42.7 μmol, 43%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **193** in EtOAc/toluene (2:1);

R_f 0.20 (30% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2925, 1641, 1598, 1495, 1454, 1334, 1159, 1092, 815, 665;
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.90 (2H, d, *J* = 8.3 Hz, *H*3), 7.67 (2H, d, *J* = 8.3 Hz, *H*3), 7.35–7.26 (6H, m, *H*2, *H*10), 7.24–7.18 (3H, m, *H*9, *H*11), 6.90–6.83 (1H, m, *H*7), 4.41 (1H, d, *J* = 16.1 Hz, *H*8), 4.23 (1H, dq, *J* = 13.2, 1.5 Hz, *H*6), 4.08 (1H, d, *J* = 16.1 Hz, *H*8), 4.04 (1H, ddt, *J* = 13.2, 5.4, 1.5 Hz, *H*6), 3.74 (1H, ddd, *J* = 11.3, 9.9, 5.7 Hz, *H*4), 3.74 (1H, td, *J* = 11.3, 7.6 Hz, *H*4), 2.44 (3H, s, *H*1), 2.42 (3H, s, *H*1), 2.10–1.98 (1H, m, *H*5) , 1.91–1.80 (1H, m, *H*5);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 143.4, 140.8, 137.0, 136.6, 135.0, 133.3, 129.8, 129.5, 128.1, 127.91, 127.86, 127.8, 127.2, 86.8, 69.9, 56.1, 47.4, 25.1, 21.61, 21.56;
HRMS (ES+) calc. for $C_{27}H_{29}N_2O_5S_2$ $[M+H]^+$ 525.1512, found 525.1517.

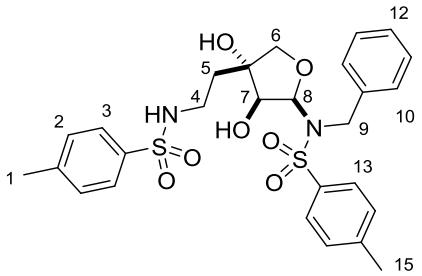
(3*R,5*R**)-5-((*N*-Benzyltosylamido)-3-(2-((tosylamido)ethyl)-4-oxotetrahydrofuran-3-yl 3-chlorobenzoate, 194**



To a vigorously stirring solution of (*Z*)-*N*-benzyl-*N*-((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)-tosylamide (100 mg, 197 μmol, 1.0 equiv.) in CH_2Cl_2 (4 mL), at –78 °C, was added dropwise a solution of *m*CPBA (242 mg (70–75% w/w balanced with *m*-chlorobenzoic acid and water), 0.983 mmol, 5.0 equiv.) in CH_2Cl_2 (2 mL). The reaction was stirred for 1 hour at –78 °C and quenched with aqueous saturated Na_2SO_3 (6 mL). The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (×2). The combined organic layers were then dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (15% CH_2Cl_2/7.5% EtOAc/40-60 petroleum ether) afforded the title compound (128 mg, 184 μmol, 94%) as a white foam;

R_f 0.30 (30% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 3292, 2924, 1782, 1718, 1598, 1496, 1332, 1292, 1264, 1157, 1091, 908, 814, 729, 660;
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.86 (1H, s, *H*12), 7.80 (1H, d, *J* = 7.8 Hz, *H*15), 7.79 (2H, d, *J* = 8.3Hz, *H*3), 7.70 (2H, d, *J* = 8.3 Hz, *H*3), 7.53 (1H, d, *J* = 7.8 Hz, *H*13), 7.35 (1H, t, *J* = 7.8 Hz, *H*14), 7.28 (2H, d, *J* = 8.3 Hz, *H*2), 7.26–7.16 (7H, m, *H*2, *H*9, *H*10, *H*11), 5.44–5.38 (1H, m, *H*7), 4.91–4.81 (1H, m, N*H*), 4.40 (1H, d, *J* = 15.8 Hz, *H*8), 4.26 (1H, d, *J* = 15.8 Hz, *H*8), 4.26 & 4.21 (2H, AB q, J_{AB} = 10.8 Hz, *H*6), 4.21 (1H, AB d, J_{BA} = 10.8 Hz, *H*6***B***), 3.24 (1H, dq, *J* = 13.9, 7.4 Hz, *H*4), 3.14 (1H, ddt, *J* = 13.9, 7.4, 5.6 Hz, *H*4), 2.50–2.38 (4H, m, *H*1, *H*5), 2.38–2.27 (4H, m, *H*1, *H*5);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 204.3, 164.0, 144.1, 143.3, 136.6, 135.8, 134.9, 134.7, 133.9 (2C), 129.9, 129.8, 129.65, 129.62, 128.6, 128.1, 128.04, 127.95, 127.9, 127.0, 86.0, 78.5, 70.9, 51.3, 37.9, 35.6, 21.5, 21.4;
HRMS (ES+) calc. for $C_{34}H_{33}{}^{35}ClN_2NaO_8S_2$ $[M+Na]^+$ 719.1259, found 719.1256.

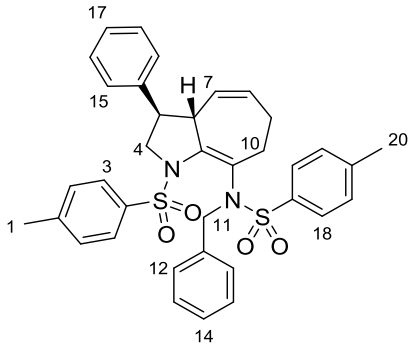
_N_-Benzyl-_N_-((2_R_*,3_S_*,4_R_*)-3,4-dihydroxy-4-(2-(tosylamido)ethyl)tetrahydrofuran-2-yl)tosyl amide, 195



To a solution of (*Z*)-*N*-benzyl-*N*-((3-methylene-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide (50.0 mg, 98.3 μmol, 1.0 equiv.) in CH_2Cl_2 (2 mL), at –78 °C, was added dropwise a solution of *m*CPBA (121 mg (70–75% w/w balanced with *m*-chlorobenzoic acid and water), 492 μmol, 5.0 equiv.) in CH_2Cl_2 (1 mL). The reaction was stirred for 1 hour at –78 °C and quenched with aqueous saturated Na_2SO_3 (3 mL). The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (×2). The combined organic layers were then dried (Na_2SO_4), and concentrated in vacuo. To this crude residue was added MeOH:CH_2Cl_2 (3 mL (5:1)), followed by sodium borohydride (18.6 mg, 492 μmol, 5.0 equiv.) and the reaction was stirred for 30 minutes. Next was added 15% aqueous NaOH solution (3 mL) and the reaction stirred vigorously for 4 hours at room temperature. The reaction mixture was quenched with Et_2O and H_2O (5 mL each) and the organic layer separated. The aqueous was further extracted with Et_2O (×3), the combined organic layers were then dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (50% EtOAc/40-60 petroleum ether) afforded the title compound (39.9 mg, 71.2 μmol, 72%) as a white powder. Crystals suitable for X-ray diffraction were grown by slow cooling of a EtOH/toluene/hexane (~1:2:10) solution of **195** from 80 °C to room temperature;

R_f 0.08 (30% EtOAc/40-60 petroleum ether);
m.p. 144 °C;
IR (thin film, ν_{max} / cm^{-1}) 3487, 3285, 3032, 2952, 1598, 1495, 1327, 1211, 1155, 1092, 1056, 814, 733, 664;
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.74 (2H, d, *J* = 8.1 Hz, *H*3), 7.56 (2H, d, *J* = 8.1 Hz, *H*13), 7.38–7.28 (4H, m, *H*2, *H*11), 7.28–7.21 (3H, m, *H*9, *H*12), 7.19 (2H, d, *J* = 8.3 Hz, *H*14), 5.77 (1H, d, *J* = 3.7 Hz, *H*8), 5.25 (1H, t, *J* = 6.2 Hz, N*H*), 4.53 & 4.42 (2H, AB q, J_{AB} = 15.9 Hz, *H*9), 3.93 (1H, dd, *J* = 4.4, 3.7 Hz, *H*7), 3.80 & 3.71 (2H, AB q, J_{AB} = 9.3 Hz, *H*6), 3.19–3.00 (2H, m, *H*4), 2.97 (1H, d, *J* = 4.4 Hz, O*H*), 2.84 (1H, s, O*H*), 2.42 (3H, s, *H*1), 2.38 (3H, s, *H*15), 1.97 (1H, ddd, *J* = 14.9, 8.1, 5.3 Hz, *H*5), 1.97 (1H, ddd, *J* = 14.9, 6.5, 5.3 Hz, *H*5);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 143.6, 137.4, 136.3, 136.1, 129.8, 129.5, 128.4, 128.2, 127.5, 127.3, 127.1, 91.7, 81.9, 77.5, 76.5, 49.2, 39.0, 30.7, 21.53, 21.50;
HRMS (ES+) calc. for $C_{27}H_{32}N_2NaO_7S_2$ $[M+Na]^+$ 583.1543, found 583.1543.

_N_-Benzyl-_N_-((3_R_,3a_S_)-3-phenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[b]pyrrol-8-yl)tosyl amide, (–)-197



To an oven dried, argon flushed vial with a magnetic stirrer bar was added (*R*,*E*)-*N*-benzyl-*N*-(((*N*'-(4-cyclopropyl-2-phenylbut-3-en-1-yl)tosylamido)ethynyl)tosylamide (20.0 mg, 32.0 μmol, 1.0 equiv.) and a solution of $[(C_{10}H_8)Rh(cod)]SbF_6$ (0.9 mg, 1.6 μmol, 0.05 equiv.) in degassed, anhydrous 1,2-dichloroethane (0.6 mL). The reaction mixture was stirred at 80 °C under argon until reaction completion (as analysed by TLC, ~16 hours). The reaction mixture was allowed to cool to room temperature and concentrated in vacuo. Column chromatography (10% ethyl acetate/40-60 petroleum ether), followed by trituration with ice cold Et_2O, afforded the title compound (11.6 mg, 18.6 μmol, 58%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of (–)-**197** in toluene;

m.p. 190 °C;

R_f 0.42 (22% EtOAc/40-60 petroleum ether);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –30.6 (c 1, $CHCl_3$);

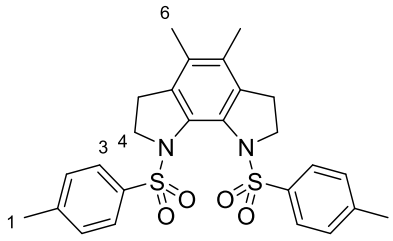
IR (thin film, ν_{max} / cm^{-1}) 2980, 1598, 1495, 1455, 1354, 1166, 1091, 815, 736, 690;

^{1}H NMR (400 MHz, $CHCl_3$)* δ_H 8.01–7.91 (4H, m, *H*3, *H*18), 7.34 (2H, br. d, *J* = 8.1 Hz, *H*19), 7.29 (2H, br. d, *J* = 7.8 Hz, *H*2), 7.26–7.22 (3H, br. m, *H*13, *H*14), 7.21–7.13 (3H, br. m, *H*16, *H*17), 7.12–7.03 (2H, br. m, *H*12), 6.68–6.57 (2H, br. m, *H*15), 5.35–5.26 (1H, br. m, *H*8), 5.16 & 4.98 (2H, AB q, J_{AB} = 15.3 Hz, *H*11), 4.61 (1H, br. d, *J* = 10.8 Hz, *H*7), 4.06 (1H, dd, *J* = 13.0 Hz, 7.6 Hz, *H*4), 2.93–2.78 (2H, br. m, *H*6, *H*10), 2.74 (1H, app. t, *J* = 12.6 Hz, *H*4), 2.54–2.40 (1H, br. m, *H*9), 2.46 (3H, s, *H*20), 2.45 (3H, s, *H*1), 2.40–2.29 (1H, br. m, *H*9), 2.19–2.06 (1H, br. m, *H*10), 1.86 (1H, td, *J* = 11.0, 8.1 Hz, *H*5). ***Note***: This spectrum shows multiple, broad peaks that could indicate the presence of rotamers.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.0, 143.3, 139.2, 138.7, 137.1, 135.9, 134.1, 129.8, 129.7, 129.6, 129.5, 128.7, 128.6, 128.12, 128.07, 127.7, 127.32 (2C), 127.27, 126.3, 56.8, 51.2, 49.6, 48.6, 32.5, 26.0, 21.7, 21.6;

HRMS We were unable to obtain an accurate mass due to decomposition upon ionisation. However, fragments at m/z 262.0890 ($[C_{14}H_{16}NO_2S]^+$) and 364.1346 ($[C_{22}H_{22}NO_2S]^+$) were observed which correspond to cleavage of the exocyclic sulfonamide.

4,5-Dimethyl-1,8-ditosyl-1,2,3,6,7,8-hexahydropyrrolo[3,2-g]indole, 198



To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar was added *N*,*N*′-(ethyne-1,2-diyl)bis(*N*-(pent-3-yn-1-yl)tosylamide (10.0 mg, 20.1 μmol, 1.0 equiv.) and $RhCl(PPh_3)_3$ (1.9 mg, 2.01 μmol, 0.1 equiv.), followed by anhydrous toluene (1 mL). The resulting orange solution was stirred at 50 °C until completion (as indicated by TLC analysis, 2 hours). The reaction mixture was then cooled to room temperature and was concentrated in vacuo. Column chromatography (30% EtOAc/40-60 petroleum ether) afforded the title compound (9.6 mg, 19 μmol, 96%) as a white powder. Crystals suitable for X-ray diffraction were grown by slow cooling of a solution of **198** in hexane from 60 °C to room temperature;

m.p. >152 °C (dec.);

R_f 0.13 (30% EtOAc/petrol);

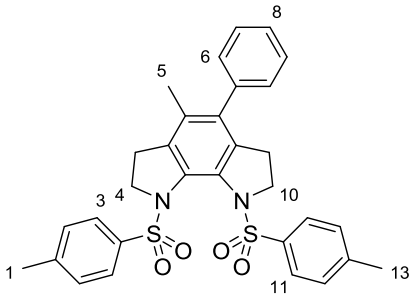
IR (thin film, ν_{max} / cm^{-1}) 2921, 1598, 1494, 1357, 1113, 1090, 916, 731, 672;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.63 (4H, d, *J* = 8.1 Hz, *H*3), 7.19 (4H, d, *J* = 8.1 Hz, *H*2), 4.14 (2H, br. s, *H*4), 3.82 (2H, br. s, *H*4), 2.62–2.32 (4H, br. m, *H*5), 2.39 (6H, s, *H*1), 2.01 (6H, s, *H*6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.5, 136.7, 135.6, 131.7, 130.7, 129.2, 128.0, 51.7, 29.2, 21.6, 15.9;

HRMS (ES+) calc. for $C_{26}H_{28}N_2NaO_4S_2$ $[M+Na]^+$ 519.1383, found 519.1381.

4-Methyl-5-phenyl-1,8-ditosyl-1,2,3,6,7,8-hexahydropyrrolo[3,2-g]indole, 199



To an oven dried, nitrogen flushed flask with a magnetic stirrer bar was added *N*-(((*N*′-(4-phenylbut-3-yn-1-yl)tosylamido)ethynyl)-*N*-(pent-3-yn-1-yl)tosylamide (15.0 mg, 26.7 μmol, 1.0 equiv.) and $RhCl(PPh_3)_3$ (2.5 mg, 2.67 μmol, 0.1 equiv.), followed by anhydrous toluene (1 mL). The resulting orange solution was stirred at 50 °C until completion (as indicated by TLC analysis, 8 hours). The reaction mixture was then cooled to room temperature and was concentrated in vacuo. Column chromatography (30% EtOAc/40-60 petroleum ether) afforded the title compound (13.7 mg, 24.5 μmol, 91%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **199** in toluene;

m.p. >155 °C (dec.);

R_f 0.56 (50% EtOAc/40-60 petroleum ether);

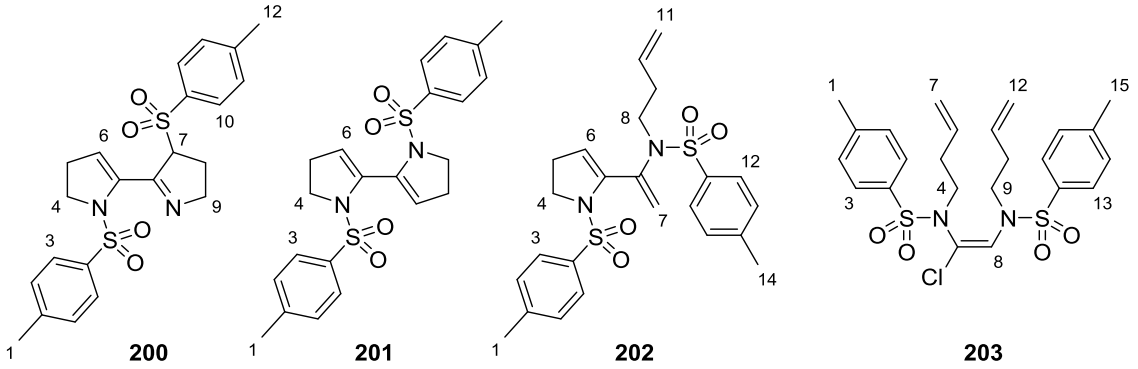
IR (thin film, ν_{max} / cm^{-1}) 2981, 1597, 1358, 1243, 1167, 1090, 677;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.78 (2H, d, *J* = 8.3 Hz, *H*3), 7.56 (2H, d, *J* = 8.2 Hz, *H*11), 7.45–7.28 (3H, br. m, *H*7, *H*8), 7.26 (2H, d, *J* = 8.3 Hz, *H*2), 7.21 (2H, d, *J* = 8.2 Hz, *H*12), 7.09 (1H, br. s, *H*6), 6.76 (1H, br. s, *H*6), 4.26 (1H, br. s, *H*4), 4.01 (1H, br. s, *H*10), 3.88 (1H, br. s, *H*4), 3.78 (1H, br. s, *H*10), 2.71–2.55 (2H, br. m, *H*5), 2.42 (6H, s, *H*1, *H*13), 2.12–1.98 (2H, br. m, *H*9), 1.88 (3H, s, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.73, 143.69, 139.0, 137.13, 137.08, 136.8, 135.8, 135.2, 133.3, 131.7, 130.5, 129.3, 129.2, 128.4, 128.1, 127.9, 127.1, 51.9, 51.7, 29.44, 29.43, 21.62, 21.55, 16.8;

HRMS (ES+) calc. for $C_{31}H_{30}N_2NaO_4S_2$ $[M+Na]^+$ 581.1539, found 581.1538.

1,3′-Ditosyl-4,4′,5,5′-tetrahydro-1*H*,3′*H*-2,2′-bipyrrole, 200 & 1,1′-ditosyl-4,4′,5,5′-tetrahydro-1*H*,1′*H*-2,2′-bipyrrole, 201 & *N*-(but-3-en-1-yl)-*N*-(1-(1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl) vinyl)tosylamide, 202 & (*E*)-*N*,*N*′-(1-Chloroethene-1,2-diyl)bis(*N*-(but-3-en-1-yl)tosylamide), 203



To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar was added yndiamide (100 mg, 197 μmol, 1.0 equiv.) and degassed, anhydrous toluene (1 mL). Next was added a solution of Grubb's 2nd Generation catalyst (8.35 mg, 9.8 μmol, 5 mol %) in degassed, anhydrous toluene (1 mL), and the resulting solution was stirred at 80 °C overnight. The reaction mixture turned from deep red to dark brown during the course of the reaction. Upon cooling, the reaction mixture was loaded directly onto a silica gel column, and column chromatography (10% EtOAc/40-60 petroleum ether → 60% EtOAc/40-60 petroleum ether) afforded the title products **200** (34.7 mg, 78.1 μmol, 37%) and **203** (10.1 mg, 19.8 μmol, 9%), as pale pink solids. Recrystallisation of **200** and **203** from hexane or EtOAc/hexane (1:1), respectively, gave colourless crystals that were suitable for X-ray diffraction. ***Note***: The fractions that contained bipyrrole **201** and pyrrole **202** were contaminated with *N*-but-3-en-1-yltosylamide. The bipyrrole **201** also underwent facile rearrangement to the isomer **200** at ambient conditions. The fraction containing pyrrole **202** was also contaminated with a second compound, the structure of which could not be identified unambiguously but is possibly the imine that would result from an N to C tosyl migration of the exocyclic enamide;

- Data for 1*H*,3′*H*-bipyrrole **200**;

R_f 0.06 (40% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2925, 1596, 1494, 1441, 1350, 1316, 1226, 1161, 1144, 1088, 1019, 973, 916, 815, 731, 709, 678, 612;

^{1}H NMR (500 MHz, $CHCl_3$) δ_H 7.80 (2H, d, *J* = 8.0 Hz, *H*10), 7.59 (2H, d, *J* = 8.2 Hz, *H*3), 7.35 (2H, d, *J* = 8.0 Hz, *H*9), 7.27 (2H, d, *J* = 8.1 Hz, *H*2), 5.94 (1H, br. t, *J* = 2.7 Hz, *H*6), 5.16 (1H, dt, *J* = 10.1, 1.7 Hz, *H*7), 4.17 (1H, dd, *J* = 16.5, 7.9 Hz, *H*9), 3.84 (1H, dt, *J* = 16.5, 7.9 Hz, *H*9), 3.63 (1H, ddd, *J* = 12.4, 9.5, 2.6 Hz, *H*4), 3.24 (1H, dt, *J* = 12.4, 10.7 Hz, *H*4), 2.63 (1H, ddt, *J* = 14.5,

7.3, 1.7 Hz, *H*8), 2.49–2.40 (1H, m, *H*8), 2.44 (3H, s, *H*1), 2.39 (3H, s, *H*12), 1.97 (1H, ddt, *J* = 17.2, 10.3, 3.1 Hz, *H*5), 1.71 (1H, ddt, *J* = 17.2, 10.3 Hz, *H*5);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 161.4, 144.9, 144.3, 138.9, 135.6, 132.3, 129.62, 129.55, 129.0, 128.0, 124.3, 72.5, 60.3, 50.1, 28.3, 26.5, 21.60, 21.58,

HRMS (ES+) calc. for $C_{22}H_{25}N_2O_4S_2$ $[M+H]^+$ 445.1250, found 445.1247.

- Data for 1*H*,1′*H*-bipyrrole **201**;

R_f 0.37 (40% EtOAc/40-60 petroleum ether);

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.92 (4H, d, *J* = 8.1 Hz, *H*3), 7.32 (4H, d, *J* = 8.1 Hz, *H*2), 5.87 (2H, t, *J* = 2.7 Hz, *H*6), 3.82 (4H, t, *J* = 7.7 Hz, *H*4), 2.42 (6H, s, *H*1), 1.89 (4H, td, *J* = 7.7, 2.7 Hz, *H*5);

HRMS (ES+) calc. for $C_{22}H_{25}N_2O_4S_2$ $[M+H]^+$ 445.1250, found 445.1248.

- Data for pyrrole **202**;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.99 (2H, d, *J* = 8.1 Hz, *H*3), 7.81 (2H, d, *J* = 8.1 Hz, *H*12), 7.37–7.28 (4H, m, *H*2, *H*13), 6.00 (1H, t, *J* = 2.5 Hz, *H*6), 5.95 (1H, s, *H*7), 5.74 (1H, ddt, *J* = 17.1, 10.3, 6.6 Hz, *H*10), 5.05–4.95 (2H, m, *H*11), 4.78 (1H, s, *H*7), 3.84 (2H, t, *J* = 7.6 Hz, *H*4), 3.40 (2H, t, *J* = 7.6 Hz, *H*8), 2.43 (6H, s, *H*1, *H*14), 2.36–2.29 (2H, m, *H*9), 1.68 (2H, dt, *J* = 7.6, 2.5 Hz, *H*5);

^{13}H NMR (101 MHz, $CDCl_3$) δ_C 134.6, 129.6, 129.4, 128.6, 128.4, 123.6, 117.9, 117.1, 53.0, 50.6, 32.4, 28.1, 21.62, 21.58; ***Note***: These peaks were identified using HSQC analysis, peaks corresponding to quaternary ^{13}C environments were not identified.

HRMS (ES+) calc. for $C_{24}H_{29}N_2O_4S_2$ $[M+H]^+$ 473.1563, found 473.1563.

- Data for chloroendiamide **203**;

R_f 0.26 (10% EtOAc/40-60 petroleum ether);

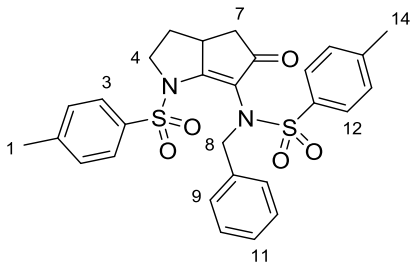
IR (thin film, ν_{max} / cm^{-1}) 3079, 2925, 1642, 1598, 1493, 1455, 1354, 1307, 1259, 1166, 1088, 1019, 995, 966, 923, 814, 745, 660;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.76 (2H, d, *J* = 8.1 Hz, *H*3), 7.68 (2H, d, *J* = 8.1 Hz, *H*13), 7.34 (2H, d, *J* = 8.1 Hz, *H*2), 7.30 (2H, d, *J* = 8.1 Hz, *H*14), 6.95 (1H, s, *H*8), 5.78 (1H, ddt, *J* = 17.0, 10.5, 6.6 Hz, *H*11), 5.57 (1H, ddt, *J* = 17.0, 10.5, 6.7 Hz, *H*6), 5.17–4.91 (4H, m, *H*7, *H*12), 3.82 (2H, br. t, *J* = 7.5 Hz, *H*9), 3.18 (2H, br. s, *H*4), 2.62–2.28 (2H, br. m, *H*10), 2.43 (3H, s, *H*1), 2.42 (3H, s, *H*15), 2.11 (2H, br. q, *J* = 7.6 Hz, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8, 144.3, 135.9, 134.2, 134.1, 133.6, 129.9, 129.6, 128.9, 127.8, 127.4, 117.6, 117.4, 115.1, 48.0, 46.2, 33.6, 31.6, 21.7, 21.6;

HRMS (ES+) calc. for $C_{24}H_{29}N_2O_4S_2$ $[M-Cl]^+$ 473.1563, found 473.1564.

_N_-Benzyl-_N_-(5-oxo-1-tosyl-1,2,3,3a,4,5-hexahydrocyclopenta[b]pyrrol-6-yl)tosylamide, 205



To an oven dried, argon flushed flask equipped with a magnetic stirrer bar was added $Co_2(CO)_8$ (moistened with 1–10% hexane, 74.7 mg, 0.216 mmol, 1.0–1.1 equiv.) and anhydrous toluene (1 mL). To the resultant stirring suspension was added a solution of *N*-benzyl-*N*-(((*N*'-(but-3-en-1-yl)tosylamido)ethynyl)tosylamide (100 mg, 0.197 mmol, 1.0 equiv.) in anhydrous toluene (2 mL) and the reaction heated to 110 °C until completion (as analysed by TLC, 5 hours). The mixture was allowed to cool to room temperature and filtered over Celite®. After concentration in vacuo, column chromatography (50% EtOAc/40-60 petroleum ether) afforded the title compound (92.8 mg, 0.173 mmol, 88%) as a white foam. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **205** in toluene;

m.p. 156 °C;

R_f 0.17 (50% EtOAc/40-60 petroleum ether);

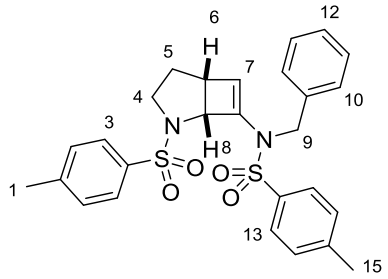
IR (thin film, ν_{max} / cm^{-1}) 2923, 1707, 1619, 1598, 1374, 1342, 1159, 1068, 959, 878, 723, 660;

^{1}H NMR (400 MHz, $CHCl_3$)* δ_H 8.10–7.57 (4H, br. m, *H*3, *H*12), 7.47–7.06 (9H, m, *H*2, *H*9, *H*10, *H*11, *H*13), 4.96–4.78 (1H, m, $H8_A$), 4.78–4.31 (1H, m, $H8_B$), 3.82 (1H, br. t, *J* = 8.9 Hz, $H4_A$), 3.68–3.23 (1H, br. m, $H4_B$), 2.73–2.55 (1H, br. m, *H*6), 2.43 (3H, s, *H*14), 2.40 (3H, s, *H*1), 2.33 (1H, dd, *J* = 17.4, 6.4 Hz, $H7_A$), 2.18–1.84 (1H, br. m, $H5_A$), 1.53 (1H, br. dd, *J* = 17.4, 3.9 Hz, $H7_B$), 1.01–0.79 (1H, br. m, $H5_B$). ***Note***: This spectrum shows multiple, broad peaks that would indicate the presence of rotamers.

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 202.3, 170.6, 144.9, 143.1, 137.3, 134.7, 134.1, 130.5, 130.0, 129.9, 129.0, 128.5, 128.0, 127.7, 118.7, 54.7, 51.5, 42.2, 38.1, 27.9, 21.6, 21.5;

HRMS (ES+) calc. for $C_{28}H_{29}N_2O_5S_2$ $[M+H]^+$ 537.1512, found 537.1503.

_N_-Benzyl-_N_-((1_R_*,5_R_*)-2-tosyl-2-azabicyclo[3.2.0]hept-6-en-7-yl)tosylamide, 206



To an oven dried, argon flushed flask equipped with a magnetic stirrer bar was added $Au(PPh_3)Cl$ (11.7 mg, 23.6 μmol, 0.3 equiv.) and $AgSbF_6$ (8.1 mg, 23.6 μmol, 0.3 equiv.), followed by CH_2Cl_2 (0.3 mL). The mixture was stirred for 10 minutes, followed by the addition of a solution of *N*-benzyl-*N*-(((*N*'-(but-3-en-1-yl)tosylamido)ethynyl)tosylamide (40.0 mg, 78.6 μmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (0.7 mL). The mixture was stirred at room temperature until reaction completion (as analysed by TLC, 8 hours). After concentration in vacuo, column chromatography (10% EtOAc/40-60 petroleum ether) afforded the title compound (20.2 mg, 39.7 μmol, 51%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **206** in EtOAc. ***Note***: It was extremely difficult to grow sufficiently good single-crystals for X-ray analysis as the compound tended to afford crystals containing multiple twin components.

m.p. 135 °C;

R_f 0.28 (20% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 2981, 2889, 1622, 1455, 1347, 1161, 1090, 954, 815, 777, 666;

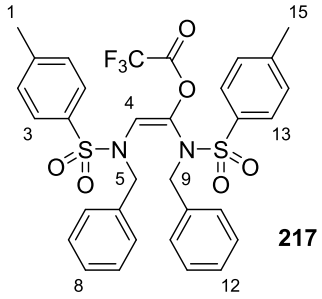
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.73 (2H, d, *J* = 7.8 Hz, *H*13), 7.59 (2H, d, *J* = 7.8 Hz, *H*3), 7.47 (2H, d, *J* = 7.5 Hz, *H*10), 7.37 (2H, t, *J* = 7.5 Hz, *H*11), 7.33–7.27 (1H, m, *H*12), 7.31 (2H, d, *J* = 7.8 Hz, *H*14), 7.28 (2H, d, *J* = 7.8 Hz, *H*2), 5.28 (1H, s, *H*7), 4.99 (2H, d, *J* = 16.1 Hz, *H*9), 4.86 (1H, d, *J* = 2.5 Hz, *H*8), 4.78 (1H, d, *J* = 16.1Hz, *H*9), 3.52 (1H, dd, *J* = 13.2, 7.6 Hz, *H*4), 2.87 (1H, dd, *J* = 7.6, 2.5 Hz, *H*6), 2.54 (1H, td, *J* = 12.6, 5.8 Hz, *H*4), 2.45 (3H, s, *H*15), 2.39 (3H, s, *H*1), 1.14 (1H, dd, *J* = 13.2, 5.8 Hz, *H*5), 0.59 (1H, tt, *J* = 12.6, 7.6 Hz, *H*5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 143.7, 137.2, 136.9, 136.1, 134.8, 129.8, 129.6, 128.6, 127.6, 127.5, 127.3, 127.0, 115.7, 65.0, 50.0, 46.7, 43.1, 26.7, 21.6, 21.5;

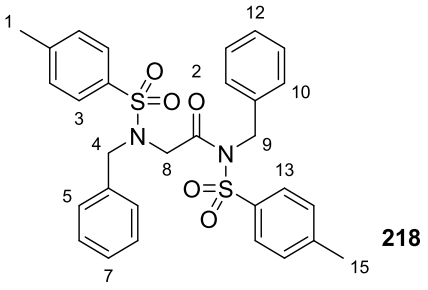
HRMS (ES+) calc. for $C_{27}H_{28}N_2O_4NaS_2$ $[M+Na]^+$ 531.1383, found 531.1382.

2.2b *Brønsted acid-catalysed.*

(*E*)-1,2-Bis((*N*-benzyltosylamido)vinyl 2,2,2-trifluoroacetate, 217 & *N*-Benzyl-2-((*N*-benzyl tosylamido)-*N*-tosylacetamide, 218



217



218

To an oven dried, argon flushed flask equipped with a magnetic stirrer bar was added *N*,*N*'-(ethyne-1,2-diyl)bis(*N*-benzyltosylamide) (50.0 mg, 91.8 μmol, 1.0 equiv.) and anhydrous CH_2Cl_2 (0.4 mL), and the solution was cooled to –60 °C. To the vigorously stirring solution was added trifluoroacetic acid (18 μL, 0.229 mmol, 2.5 equiv.) and stirred for 5 minutes at –60 °C. The mixture was quenched with 1 M aqueous NaOH (0.5 mL) and was immediately warmed to room temperature. The organic layer was separated, and the aqueous was extracted with CH_2Cl_2 (×2). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. At this point, ^{1}H NMR spectroscopic analysis ($CDCl_3$) of the crude material showed that it contained the enol trifluoroacetate **217**. Column chromatography (20% EtOAc/40-60 petroleum ether) hydrolysed this to **218**, and recrystallisation from Et_2O afforded only **218** (44.5 mg, 79.1 μmol, 86%) as colourless crystals. These crystals were also suitable for X-ray analysis;

- Data for enol trifluoroacetate **217**;

IR (thin film, ν_{max} / cm^{-1}) 2981, 1795, 1597, 1496, 1455, 1351, 1224, 1164, 1089, 814, 703, 670;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.72–7.67 (2H, m, *H*13), 7.56–7.51 (2H, m, *H*3), 7.34–7.15 (9H, m, Ar*H*), 7.11 (1H, tt, *J* = 7.3, 1.2 Hz, Ar*H*), 7.11 (1H, s, *H*4), 7.03–6.97 (2H, m, Ar*H*), 6.83–6.78 (2H, m, Ar*H*), 4.79 (2H, s, *H*5), 4.07 (2H, s, *H*9), 2.44 (3H, s, *H*15), 2.42 (3H, s, *H*1)

- Data for amide **218**;

m.p. 137 °C;

R$_f$ 0.18 (20% EtOAc/40-60 petroleum ether);

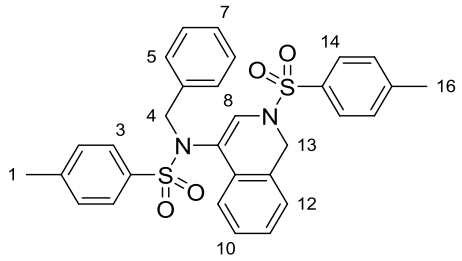
IR (thin film, ν_{max} / cm^{-1}) 3032, 1711, 1597, 1496, 1402, 1338, 1157, 1092, 931, 867, 729;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.54 (2H, d, *J* = 8.3 Hz, *H*13), 7.45 (2H, d, *J* = 8.3 Hz, *H*3), 7.31–7.14 (12H, m, *H*2, *H*6, *H*7, *H*10, *H*11, *H*12, *H*14), 7.05–6.98 (2H, m, *H*5), 4.85 (2H, s, *H*8), 4.41 (2H, s, *H*9), 4.34 (2H, s, *H*4), 2.43 (3H, s, *H*15), 2.41 (3H, s, *H*1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 168.5, 145.1, 143.2, 137.0, 135.9, 135.8, 134.8, 129.9, 129.4, 128.7, 128.6, 128.5, 128.0 (2C), 127.7, 127.42, 127.37, 50.9, 49.4, 49.3, 21.7, 21.6;

HRMS (ES+) calc. for $C_{30}H_{30}N_2NaO_5S_2$ $[M+Na]^+$ 585.1488, found 585.1487.

_N_-Benzyl-_N_-(2-tosyl-1,2-dihydroisoquinolin-4-yl)tosylamide,[238] 219



To an oven dried, argon flushed flask equipped with a magnetic stirrer bar was added *N*,*N*'-(ethyne-1,2-diyl)bis(*N*-benzyltosylamide) (50.0 mg, 91.8 μmol, 1.0 equiv.) and anhydrous CH_2Cl_2 (0.4 mL), and the solution was cooled to –60 °C. To the vigorously stirring solution was added triflic acid (20 μL, 0.229 mmol, 2.5 equiv.) and the mixture was stirred for 5 minutes at –60 °C. The mixture was quenched with 1 M aqueous NaOH (0.5 mL) and warmed to room temperature. The organic layer was separated, and the aqueous was extracted with CH_2Cl_2 (×2). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (20% EtOAc/40-60 petroleum ether) afforded the title compound (39.1 mg, 71.8 μmol, 78%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **219** in toluene;

m.p. 135 °C;

R_f 0.18 (20% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3066, 2922, 1597, 1494, 1454, 1305, 1163, 1090, 1037, 969, 764, 668;

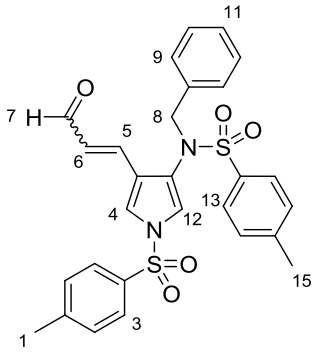
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.70 (2H, d, *J* = 8.1 Hz, *H*3), 7.38 (2H, d, *J* = 8.3 Hz, *H*14), 7.30 (2H, d, *J* = 8.1 Hz, *H*2), 7.25–7.18 (5H, m, *H*5, *H*6, *H*7), 7.17 (2H, d, *J* = 8.3 Hz, *H*15), 7.09–6.98 (3H. m, *H*9, *H*10, *H*11), 6.87–6.79 (1H, m, *H*12), 6.40 (1H, s, *H*8), 4.68–4.53 (2H, br. m, *H*4), 4.53–4.33 (2H, br. m, *H*13), 2.47 (3H, s, *H*1), 2.38 (3H, s, *H*16);

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C 144.2, 143.8, 135.8, 135.5, 134.6, 129.8, 129.7, 129.2, 128.6, 128.4, 127.92, 127.87, 127.8, 127.7, 127.02, 126.95, 125.2, 122.2, 121.9, 54.1, 47.1, 21.6, 21.5.

****Note***: A single ^{13}C resonance is obscured due to signal overlap.

HRMS (ES+) calc. for $C_{30}H_{28}N_2NaO_4S_2$ $[M+Na]^+$ 567.1383, found 567.1382.

_N_-(Benzyl)-_N_-(4-(3-oxoprop-1-en-1-yl)-1-tosyl-1_H_-pyrrol-3-yl)tosylamide, 222



This compound was formed during attempts to grow single crystals of *N*-benzyl-*N*-(((*N*-(furan-2-ylmethyl)tosylamido)ethynyl)tosylamide. A sample (~10 mg) was dissolved in toluene (1.5 mL) in a 2 mL vial and treated with a small amount of activated charcoal to remove coloured residues. This was shaken for 30 seconds, the charcoal was then removed by filtration and the solution was concentrated to ~0.2 mL. Vapour diffusion with pentane afforded crystals of the title compound that were suitable for X-ray diffraction. The crystals contained a 3:1 (*E*)-/(*Z*)-**222** mixture but ^{1}H NMR spectroscopic analysis of the bulk indicated ~1.2:1 mixture

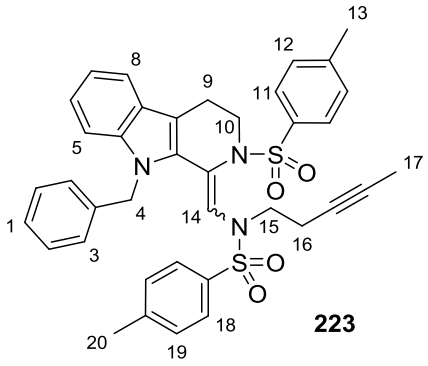
- Data for (*E*)-**222**;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 9.33 (1H, d, *J* = 7.8 Hz, *H*7), 7.64–7.58 (2H, m, *H*3), 7.53–7.48 (2H, m, *H*13), 7.37–7.32 (2H, m, *H*2), 7.29–7.21 (3H, m, *H*4, *H*14), 7.21–7.02 (5H, m, *H*9, *H*10, *H*11), 6.82 (1H, d, *J* = 16.3 Hz, *H*5), 6.64 (1H, d, *J* = 2.4 Hz, *H*12), 6.27 (1H, dd, *J* = 16.3, 7.8 Hz, *H*6), 4.54 (2H, s, *H*8), 2.48 (3H, s, *H*1), 2.36 (3H, s, *H*15)

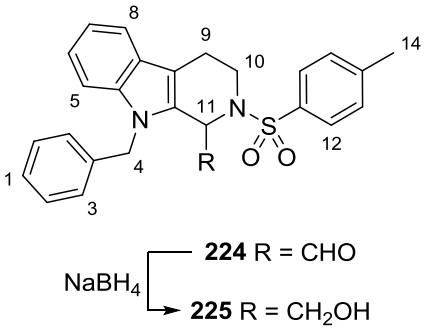
- Data for (*Z*)-**222**;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 9.51 (1H, d, *J* = 7.6 Hz, *H*7), 7.64–7.58 (2H, m, *H*3), 7.53–7.48 (2H, m, *H*13), 7.37–7.32 (2H, m, *H*2), 7.29–7.21 (3H, m, *H*4, *H*14), 7.21–7.02 (5H, m, *H*9, *H*10, *H*11), 6.89 (1H, dd, *J* = 11.5, 1.0 Hz, *H*5), 6.68 (1H, d, *J* = 2.4 Hz, *H*12), 5.89 (1H, dd, *J* = 11.5, 7.6 Hz, *H*6), 4.51 (2H, s, *H*8), 2.47 (3H, s, *H*1), 2.46 (3H, s, *H*15)

_N_-((9-Benzyl-2-tosyl-2,3,4,9-tetrahydro-1_H_-pyrido[3,4-b]indol-1-ylidene)methyl)-_N_-(pent-3-yn-1-yl)tosylamide, 223 & 9-benzyl-2-tosyl-2,3,4,9-tetrahydro-1_H_-pyrido[3,4-b]indole-1-carbaldehyde, 224 & (9-benzyl-2-tosyl-2,3,4,9-tetrahydro-1_H_-pyrido[3,4-b]indol-1-yl)methanol, 225



223



To an oven dried, nitrogen flushed flask equipped with a magnetic stirrer bar was added *N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)-*N*-(((*N*-(pent-3-yn-1-yl)tosylamido)ethynyl)tosylamide (30.0 mg, 45.2 μmol, 1.0 equiv.) and anhydrous CH_2Cl_2 (0.4 mL), and the solution was cooled to –60 °C. To the vigorously stirring solution was added HCl (28 μL, 0.11 mmol, 2.5 equiv.) and stirred for 5 minutes at –60 °C. The mixture was quenched with water (0.5 mL) and was immediately warmed to room temperature. The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (×2). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. At this point, ^{1}H NMR spectroscopic analysis showed that the crude material contained a mixture of *N*-(pent-3-yn-1-yl)tosylamide, enamide **223** and aldehyde **224**. Column chromatography (2% Et_2O/toluene) gave enamide **223** and aldehyde **224** but with insufficient purity. Hydrolysis of the mixture (silica gel) gave ~14 mg of **224** (~90% purity, ~29 μmol of **224**, ~63%).

This material was treated with sodium borohydride (10 mg, 260 μmol, ~9 equiv.) in methanol (0.5 mL) at room temperature. The reaction was quenched with water and CH_2Cl_2 (2 mL each), the organic layer was separated and the aqueous further extracted with CH_2Cl_2 (2×0.5 mL). The combined organic layers were combined, dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (50% Et_2O/40-60 petroleum ether) afforded the alcohol **225** (12.0 mg, 26.9 μmol, 95% (59% overall yield)) as a white powder.

- Data for enamide **223**;

R_f 0.48 (4% Et_2O/toluene);

IR (thin film, ν_{max} / cm^{-1}) 3031, 2921, 2853, 1650, 1597, 1495, 1454, 1349, 1315, 1248, 1214, 1183, 1162, 1091, 1019, 976, 915, 815, 738, 710, 697, 677, 659, 617;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.45–7.31 (7H, m, *H*11, *H*18, Ar*H*), 7.22–7.08 (7H, m, *H*19, Ar*H*), 7.03 (1H, ddd, *J* = 7.9, 6.1, 2.0 Hz, *H*7), 6.83 (2H, d, *J* = 7.8 Hz, *H*12), 6.67 (1H, s, *H*14), 5.46 &

5.35 (2H, AB q, J_{AB} = 17.6 Hz, *H*4), 4.42 (1H, dd, *J* = 14.4, 6.8 Hz, *H*15), 4.33 (1H, ddd, *J* = 14.7, 9.5, 5.3 Hz, *H*10), 3.81 (1H, ddd, *J* = 14.7, 8.9, 6.1 Hz, *H*10), 3.57 (1H, ddd, *J* = 14.4, 13.0, 6.4 Hz, *H*15), 2.71 (1H, ddd, *J* = 16.1, 13.0, 6.8 Hz, *H*9), 2.57 (1H, dd, *J* = 16.1, 6.4 Hz, *H*9), 2.38 (3H, s, *H*20), 2.25–2.14 (1H, m, *H*16), 2.14–2.05 (1H, m, *H*16), 2.03 (3H, s, *H*13), 1.65 (3H, t, *J* = 2.4 Hz, *H*17);

HRMS (ES+) calc. for $C_{38}H_{38}N_3O_4S_2$ $[M+H]^+$ 664.2309, found 664.2300.

- Data for aldehyde **224**;

R_f 0.25 (4% Et_2O/toluene);

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 9.58 (1H, d, *J* = 1.0 Hz, *H*R), 7.44–7.38 (3H, m, *H*8, *H*12), 7.30–7.22 (4H, m, *H*1, *H*2, *H*5), 7.19 (1H, ddd, *J* = 8.3, 7.1, 1.2 Hz, *H*6), 7.10 (2H, d, *J* = 8.1 Hz, *H*13), 7.10 (1H, ddd, *J* = 7.8, 7.1, 0.8 Hz, *H*7), 6.93–6.85 (2H, m, *H*3), 5.45 & 5.34 (2H, AB q, J_{AB} = 16.9 Hz, *H*4), 5.19 (1H, br. s, *H*11), 3.95 (1H, ddd, *J* = 13.9, 5.4, 4.0 Hz, *H*10), 3.54 (1H, ddd, *J* = 13.9, 9.5, 4.4 Hz, *H*10), 2.74 (1H, ddd, 15.9, 4.4, 4.0 Hz, *H*9), 2.62 (1H, dddd, *J* = 15.9, 9.5, 5.4, 1.0 Hz, *H*9), 2.32 (3H, s, *H*14);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 195.8, 143.8, 137.7, 137.1, 136.0, 129.7, 128.9, 127.6, 126.9, 126.3, 125.9, 125.3, 122.8, 119.7, 118.5, 110.5, 109.8, 60.4, 47.2, 42.1, 21.5, 20.3.

- Data for alcohol **225**;

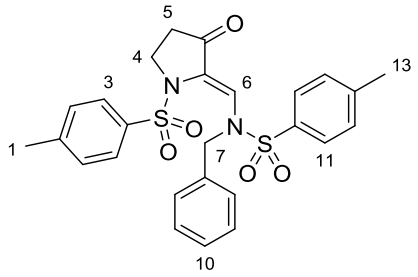
R_f 0.57 (50% EtOAc/40-60 petroleum ether);

IR (thin film, ν_{max} / cm^{-1}) 3504, 3031, 2920, 1598, 1496, 1464, 1454, 1382, 1340, 1306, 1202, 1181, 1157, 1100, 1065, 1040, 994, 911, 862, 814, 721, 699, 650, 617;

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.44 (2H, d, *J* = 8.3 Hz, *H*12), 7.38 (1H, d, *J* = 7.8 Hz, *H*8), 7.30–7.22 (3H, m, *H*1, *H*2), 7.18 (1H, d, *J* = 7.6 Hz, *H*5), 7.14 (1H, td, *J* = 7.6, 0.7 Hz, *H*6), 7.07 (1H, ddd, *J* = 7.8, 6.6, 1.2 Hz, *H*7), 7.03 (2H, d, *J* = 8.3 Hz, *H*13), 6.91–6.82 (2H, m, *H*3), 5.38 & 5.24 (2H, AB q, J_{AB} = 17.1 Hz, *H*4), 5.07 (1H, dd, *J* = 6.8, 5.1 Hz, *H*11), 4.28 (1H, dd, *J* = 14.9, 5.7 Hz, *H*10), 3.85–3.74 (2H, m, *H*R), 3.54 (1H, ddd, *J* = 14.9, 11.9, 4.6 Hz, *H*10), 2.64 (1H, dd, *J* = 15.9, 4.6 Hz, *H*9), 2.52 (1H, ddd, *J* = 15.9, 11.9, 5.7 Hz, *H*9), 2.45 (1H, br. s, O*H*), 2.28 (3H, s, *H*14);**^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.4, 137.2, 137.0, 129.8, 129.6, 128.9, 127.7, 126.7, 126.4, 126.0, 122.4, 119.6, 118.4, 109.8, 109.3, 63.8, 54.8, 47.0, 39.2, 30.3, 21.5, 19.9;

HRMS (ES+) calc. for $C_{26}H_{27}N_2O_3S$ $[M+H]^+$ 447.1748, found 447.1734.

(*Z*)-*N*-Benzyl-*N*-((3-oxo-1-tosylpyrrolidin-2-ylidene)methyl)tosylamide, 229



To a vigorously stirring solution of *N*-benzyl-*N*-(((*N*-(3,3-diethoxypropyl)tosylamido)ethynyl) tosylamide (22.1 mg, 37.8 μmol, 1.0 equiv.) in $CDCl_3$ (0.7 mL), at room temperature, was added HCl (20 μL of a 3–4 M solution in dioxane, ~68 μmol, ~1.8 equiv.) dropwise over 1 hour. Upon reaction completion (as analysed by TLC), the reaction was quenched with water (1 mL) and the organic layer separated. The aqueous was extracted with CH_2Cl_2 (×2) and the combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (20% EtOAc/40-60 petroleum ether) afforded the title compound (12.1 mg, 23.7 μmol, 63%) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of **229** in CH_2Cl_2;

m.p. >160 °C (dec.);
R_f 0.17 (20% EtOAc/40-60 petroleum ether);
IR (thin film, ν_{max} / cm^{-1}) 2961, 2922, 1728, 1621, 1598, 1354, 1164, 1089, 815, 766, 663, 662;
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.87 (1H, s, *H*6), 7.85 (2H, d, *J* = 8.3 Hz, *H*11), 7.49 (2H, d, *J* = 8.3 Hz, *H*3), 7.36 (2H, d, *J* = 8.1 Hz, *H*12), 7.32–7.22 (6H, m, *H*2, *H*8, *H*9), 7.22–7.17 (1H, m, *H*10), 5.23 (2H, s, *H*7), 3.23 (2H, br. s, *H*4), 2.43 (3H, s, *H*13), 2.41 (3H, s, *H*1), 1.31 (2H, br. s, *H*5);
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 199.7, 145.1, 144.9, 135.9, 135.5, 134.0, 130.1, 130.0, 128.3, 127.8, 127.73, 127.69, 127.5, 127.4, 115.7, 49.4, 46.0, 32.7, 21.7, 21.6;
HRMS (ES+) calc. for $C_{26}H_{26}N_2NaO_5S_2$ $[M+Na]^+$ 533.1175, found 533.1175.

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"*When enough people make false promises, words stop meaning anything. Then there are no more answers, only better and better lies.*"

– Jon Snow, *Game of Thrones*