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Nickel-Catalysed Synthesis of Multisubstituted Pyrroles by *anti*-Carbometallative Cyclisations

Thesis submitted to the University of Nottingham for the degree of MSc Chemistry (by Research)

by

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Declaration

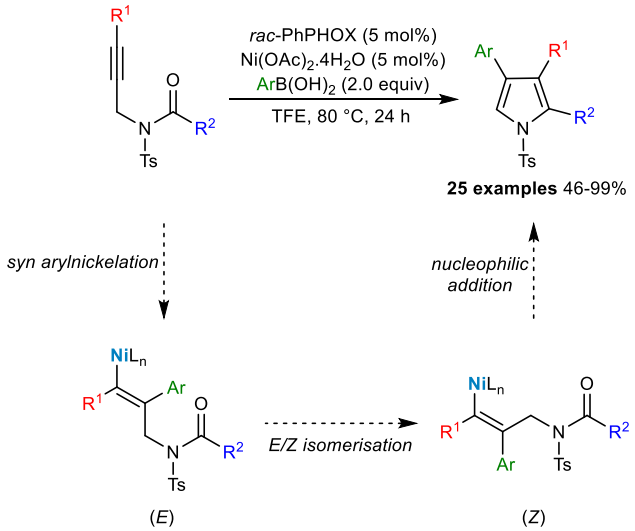
I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification. I confirm that the work submitted is my own, except work which has formed part of jointly-authored publications. The contributions of myself and other authors to this work have been specifically indicated where relevant. I confirm that appropriate credit has been given with the thesis where references has been made to the work of others.

Part of this work contains results reported in the following publication:

Synthesis of multisubstituted pyrroles by nickel-catalyzed arylative cyclizations of *N*-tosyl alkynamides, Gillbard, S. M.; Chung, C.-H.; Karad, S. N.; Panchal, H.; Lewis, W.; Lam, H. W. *Chem. Commun.* **2018**, *54*, In press

Abstract

Herein is presented the first example of nickel-catalysed cyclisation of *N*-tosylalkynamides with arylboronic acids to give 2,3,4-trisubstituted pyrroles. The reaction is initiated by alkyne arylnickelation and proceeds *via* an essential *E/Z* isomerisation step which allows for cyclisation. An investigation of the scope of the reaction and the boronic acid gave rise to 25 examples in 46-99% yield.



Further, the described method was successfully applied to the synthesis of precursors to BODIPY derivatives and it was attempted to apply the method to the synthesis of the group of marine alkaloids, lamellarins.

Acknowledgements

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Abbreviations

Ac	acyl
acac	acetylacetonate
Ar	aryl
atm	atmosphere
Boc	*t*-butyloxycarbonyl
BODIPY	boron dipyrromethene fluorophore
Bn	benzyl
bpy	2,2'-bipyridine
ca.	*circa*
Cat.	catalyst
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*'-dicyclohexylcarbodiimide
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	*enantiomeric excess*
Eqn	equation
Equiv	equivalents
Et	ethyl
g	grams
h	hour(s)
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant
M	metal
M	molar
m	multiplet
Me	methyl

mg	milligram
MHz	mega hertz
min	minute(s)
mL	millilitres
mm	millimetre
mmol	millimole
MOM	methoxymethyl acetal
m.p.	melting point
Ms	methanesulfonyl
nbd	norbornadiene
n-Bu	normal butyl
NMR	nuclear magnetic resonance
N,N'-DMEDA	*N,N*'-dimethylethylenediamine
NR	no reaction
Ph	phenyl
PMP	*para*-methoxyphenyl
p-TSA	*para*-toluenesulfonic acid
rac	racemic
ref.	reference
RT	room temperature
s	singlet
t	triplet
t	time
TBS	*tertiary*-butyldimethylsilyl ether
*t*Bu	tertiary butyl
Temp.	temperature
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl ethers
TLC	thin layer chromatography
Ts	4-toluenesulfonyl

1.0 Introduction

The introduction presented in this thesis will consist of two parts: an introduction to pyrroles and an introduction to *anti*-carbometallative nickel catalysed cyclisations.

1.1 Importance of Pyrroles

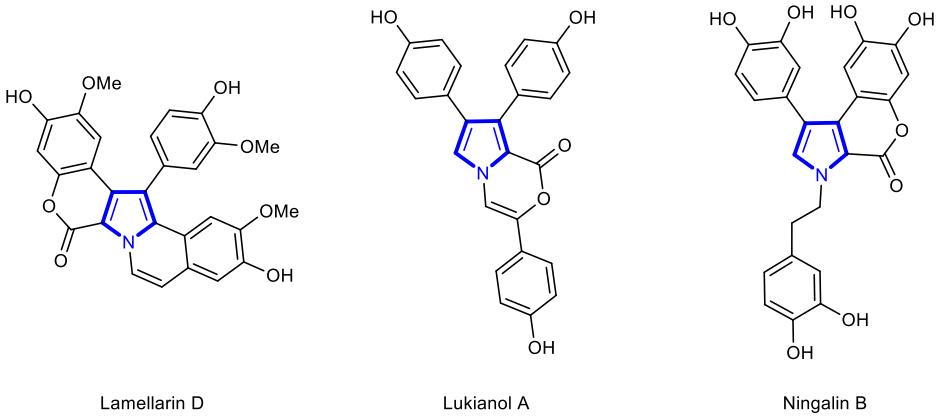
Pyrrole is an aromatic heterocyclic compound which was discovered in the 1830's and was first isolated in 1857 by T. Anderson (Figure 1).[1,2] It consists of four carbon atoms and one nitrogen atom. The lone pair on the nitrogen is in the plane of the ring and is therefore a part of the π-system, which in turn gives the pyrrole its aromatic character.[1] In the years following its discovery, scientists increasingly gained interest in pyrrole and its aromatic properties.



Figure 1: Pyrrole.

Compounds containing a pyrrole scaffold have been identified as important in many areas, such as natural dyes,[3] natural products[4], pharmaceuticals[5] and biologically active compounds.[5]

Lamellarin D, lukianol A and ningalin B are all pyrrole-derived alkaloids isolated from the marine mollusc lamellaria and they all contain aryl groups at the 3- and 4-position of the pyrrole and carbonyl functionality at the 2-position (Figure 2).[4] Lamellarin D has shown to possess powerful cytotoxic activity against multidrug-resistant tumor cell lines.

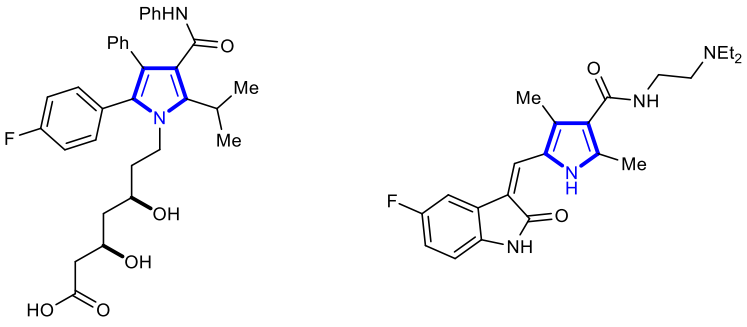


Lamellarin D | Lukianol A | Ningalin B

Figure 2: Examples of pyrrole-containing natural products found in marine organisms.

Due to the limited supply of alkaloids from natural sources and in view of their importance, the total synthesis of these molecules has attracted much interest.[6-8]

From a medicinal perspective, pyrrole scaffolds are very sought after due to the vast amounts of pyrrole-containing compounds that show biological activity. Antiviral, antibacterial, antifungal, anticancer, anti-inflammatory, antipsychotic, reversal of multidrug-resistance and HIV-1 integrase inhibition are some of the biological activities that have been reported for pyrrole and its derivatives (Figure 3).[5]



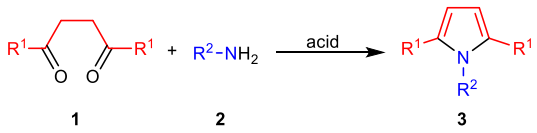
Atorvastatin
Used to lower cholesterol

Sunitinib
Used as an oral treatment of renal cancer

Figure 3: Examples of bioactive compounds.

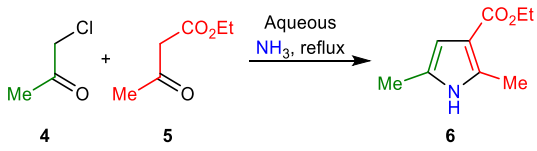
1.2 Traditional Routes for the Synthesis of Pyrrole and its Derivatives

One of the earliest examples of the synthesis of substituted pyrroles was reported by Paal and Knorr independently in 1884.[9,10] The now widely known Paal-Knorr synthesis is the acid-mediated condensation of a primary amine **1** or ammonia with a 1,4-diketone **2** to give a 2,4-disubstituted pyrrole **3** (Scheme 1).[11]



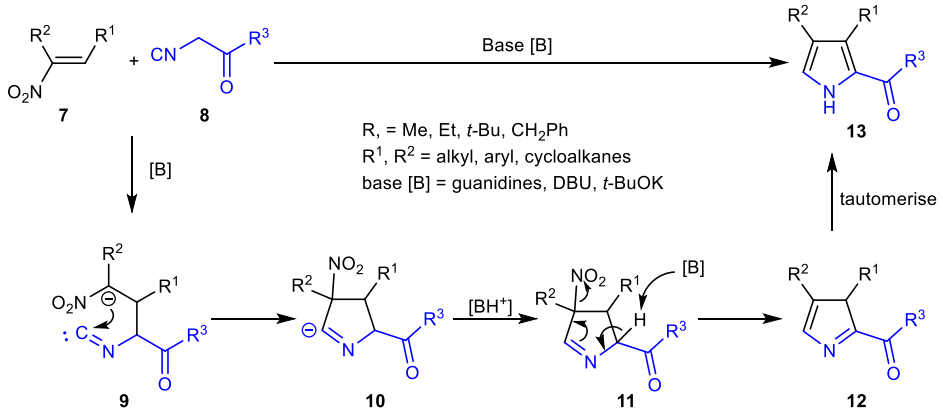
Scheme 1: The Paal-Knorr pyrrole synthesis.

In 1890 the first multicomponent synthesis to give pyrrole derivatives was developed by Hantzsch.[12] The Hantzsch pyrrole synthesis involves the condensation of an α-halocarbonyl **4** with a ketone **5** and a primary amine (Scheme 2) to give 2,4,5-trisubstituted pyrroles **6**.[13] The Hantzsch reaction allows for the synthesis of more complex pyrroles compared to the Paal-Knorr reaction; however, it has received little attention in the literature. Deleterious side reactions such as self-condensation and low yields have hindered its development.[14]



Scheme 2: The Hantzsch pyrrole synthesis.

In contrast to the already mentioned traditional pyrrole synthetic routes, the Barton-Zard reaction allows for various substitution at the 3- and 4-position of the pyrrole.[3] In 1985, Barton and Zard reported the base-catalysed reaction of nitroalkenes **7** (generated from β-nitro acetates) with alkyl isocyanoacetates **8** to give access to the useful 3,4-substituted pyrrole-2-carboxylates **13** (Scheme 3).[15] The reaction proceeds *via* a Michael-type addition followed by cyclisation to give intermediate **10**. Subsequent deprotonation, leading to loss of the nitro group followed by rearrangement gives pyrrole **13**.

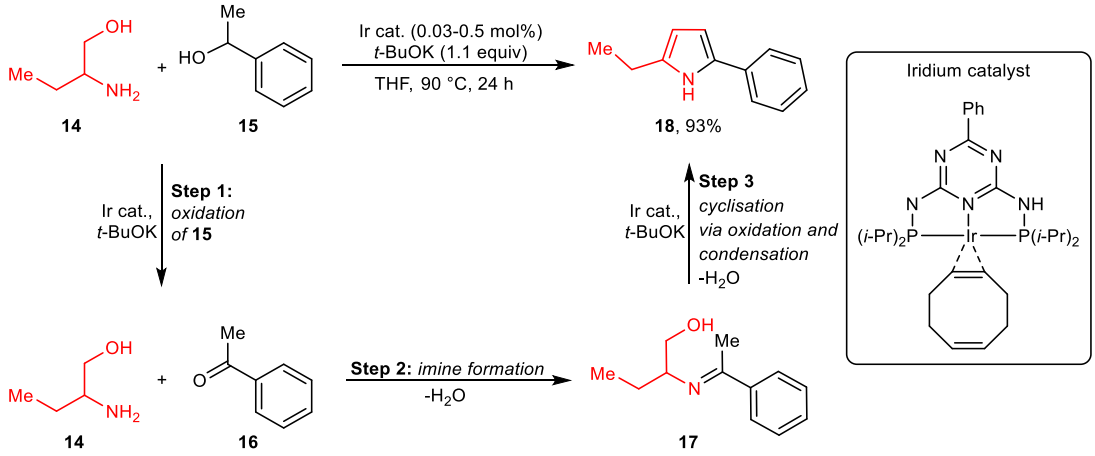


Scheme 3: The Barton-Zard pyrrole synthesis.

1.3 Recent Examples of Catalytic Pyrrole Syntheses

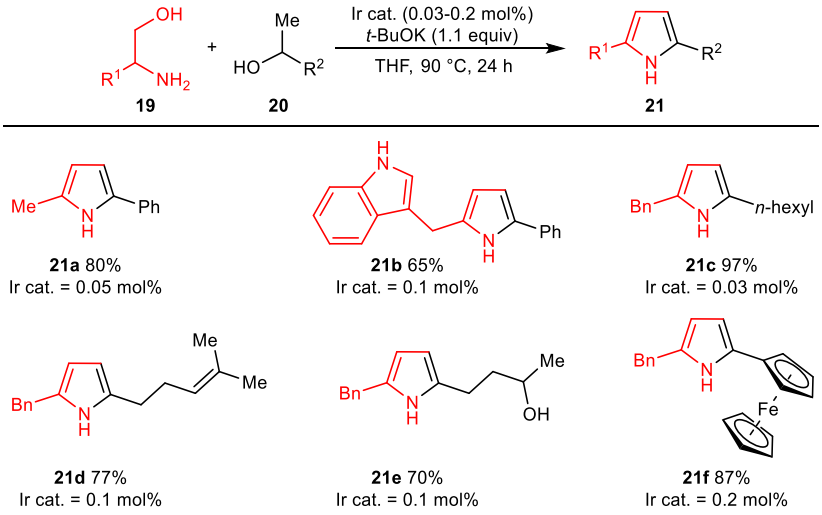
An increase in the reported examples of catalytic procedures for the synthesis of pyrroles shows the vibrant activity in the field.[8,16-25] Selected examples are described in the following section.

In 2013 Kempe and co-workers reported the iridium-catalysed pyrrole synthesis using secondary alcohols **15** and amino alcohols **14** (Scheme 4).[16] The first step of the reaction is an oxidation of the secondary alcohol to give ketone **16** which then undergoes imine formation with the amino alcohol **14** to give compound **17**. From here an iridium-catalysed cyclisation occurs *via* the alcohol dehydrogenation and condensation to give product **18**. Overall, two equivalents of water and hydrogen are eliminated during the reaction.



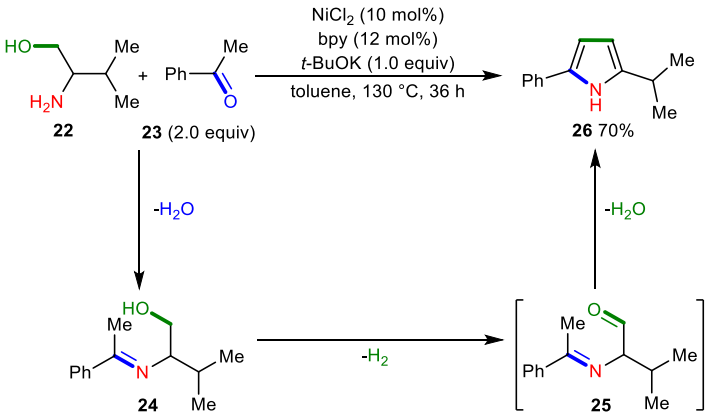
Scheme 4: Iridium-catalysed dehydrogenative condensation to give substituted pyrroles.

The scope of the reaction proved to be broad, with both the amino alcohol and secondary alcohol being varied. The reaction tolerated aryl- and alkyl-groups (**21a-21e**), olefins (**21d**) and hydroxyl-groups (**21e**) (Scheme 5). Having an *n*-hexyl substituent at the alcohol gave a 97% conversion to the corresponding pyrrole with the use of only 0.03 mol% iridium catalyst (**21c**), whereas having an amine containing substituent at the amino alcohol only gave a 65% conversion with 0.1 mol% iridium catalyst (**21b**). Strikingly, with an increased catalyst loading of 0.2 mol%, the reaction tolerated the synthesis of a ferrocene substituted pyrrole in 87% yield (**21f**). The synthesis of 2,3,5-trisubstitued pyrroles were also successful.



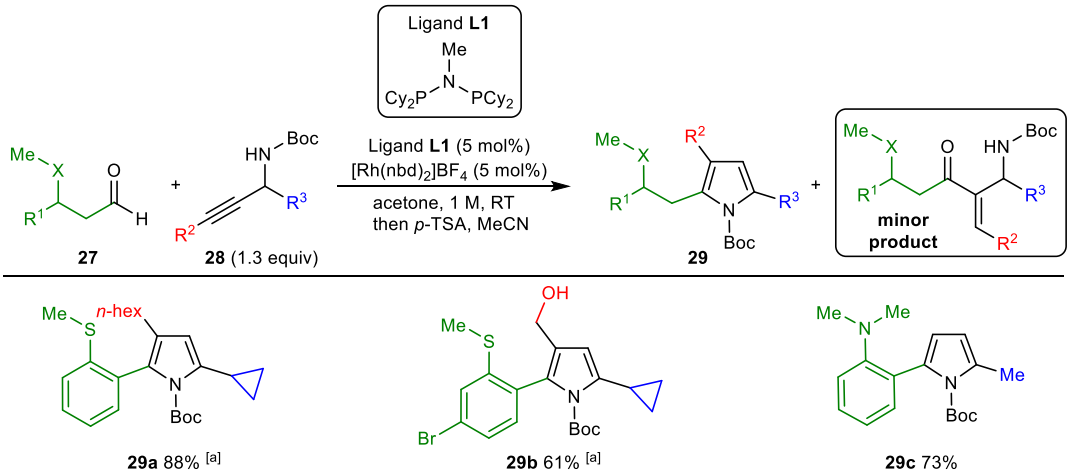
Scheme 5: Dehydrogenative condensation to give substituted pyrroles.

Banerjee and co-workers reported the nickel-catalysed reaction of a ketone **23** with a β-amino alcohol **22** to give 2,5-substituted pyrroles **26** (Scheme 6).[24] The first step is the imine formation to give structure **24**, which then undergoes a nickel-catalysed transformation of imine alcohol **24** to imine aldehyde **25** and subsequently tautomerisation, cyclisation and base-catalysed condensation leads to the product **26**. These reaction conditions also allow for 2,3,5-trisubstituted pyrroles to be formed.



Scheme 6: Nickel-catalysed dehydrogenative coupling of β- and γ-amino alcohols with ketones to give pyrroles.

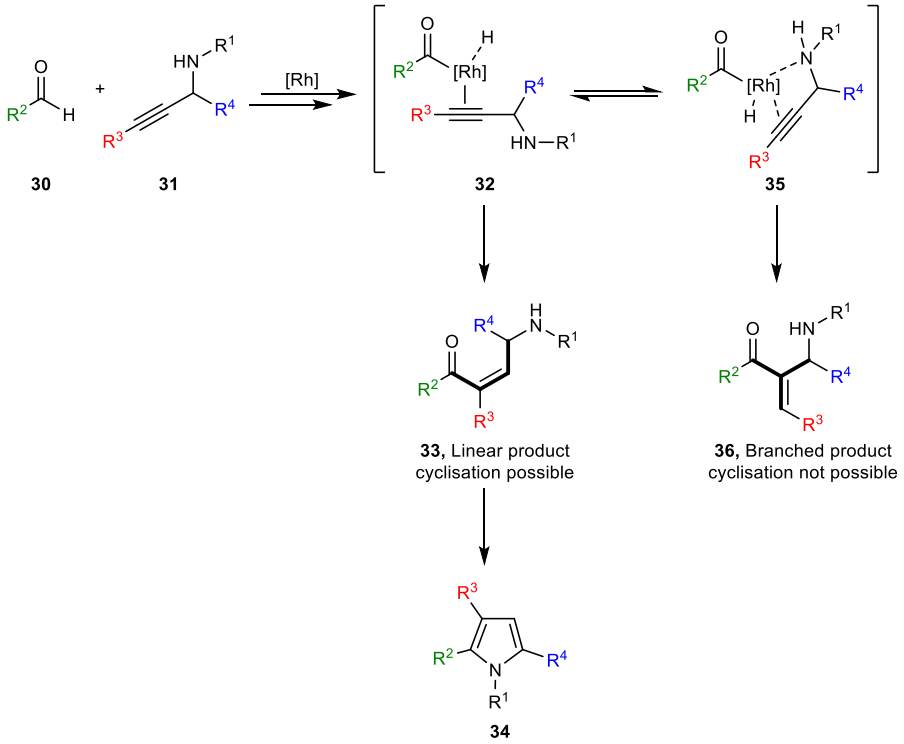
Willis and co-workers described a one-pot direct synthesis of substituted pyrroles **29** from aldehydes **27** and propargylic amines **28** (Scheme 7).[20] The reaction proceeds *via* an intermolecular hydroacylation to give the γ-amino enone compound followed by Brønsted-acid-catalysed cyclisation. The reaction shows good to excellent yields when using substituents such as alkyl- and aryl-groups (**29a-29c**), cyclopropane (**29a-29b**) and alcohol (**29c**).



Scheme 7: Rhodium-catalysed synthesis of pyrroles using linear-selective hydroacylation reaction. [a] dppm (5 mol%) used in place of PNP(Cy).

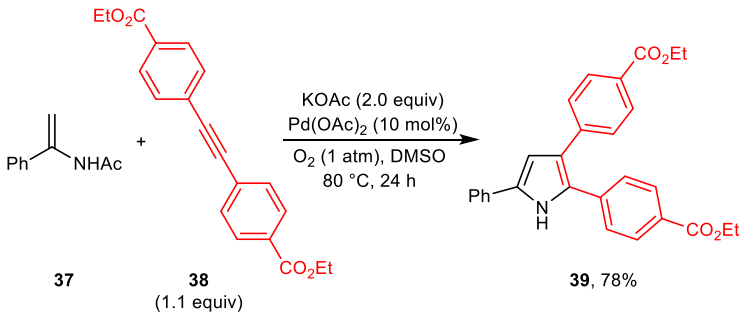
One of the main challenges to overcome was the elimination of the branched regioisomer (minor product) obtained from the hydroacylation reaction, since only the linear product **33** was capable of undergoing cyclisation to give the desired pyrrole (Scheme 8). The use of PNP ligand system, increase in concentration and lower

temperatures allowed for the mixture of linear and branched products to be obtained in a 20:1 ratio respectively.



Scheme 8: Regioisomers obtained from the hydroacylation reaction.

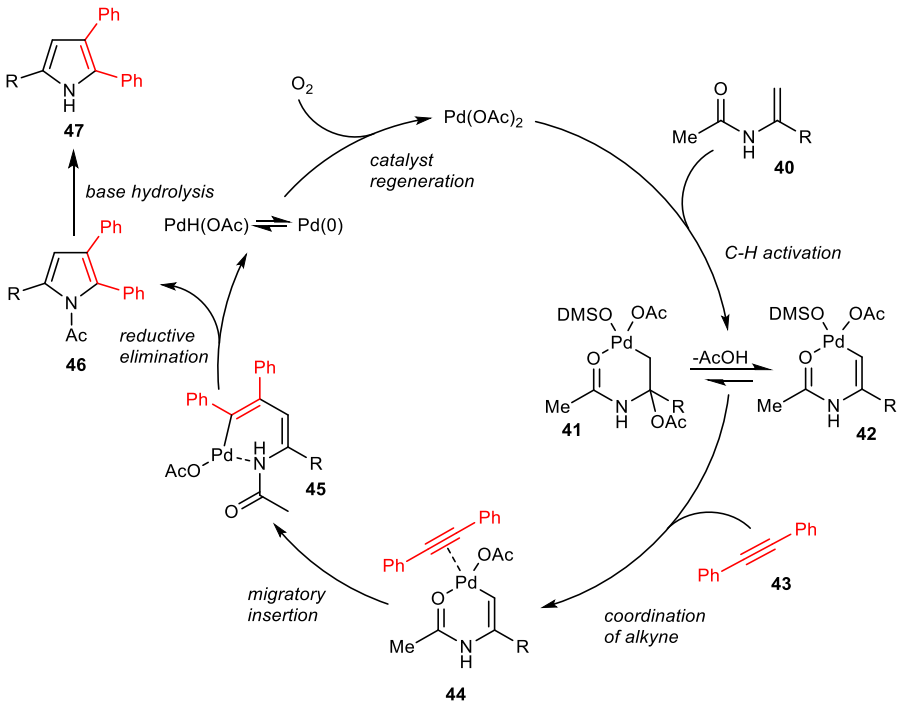
Loh and co-workers reported the palladium-catalysed reaction between enamides **37** and alkynes **38** to give 2,3,5-trisubstituted pyrroles **39** (Scheme 9).[18] The reaction utilised molecular oxygen as an oxidant for the Pd(II)/Pd(0) catalytic cycle. Yields of up to 78% were obtained when using symmetrical alkynes.



Scheme 9: Palladium-catalysed cyclisation of enamides and alkynes.

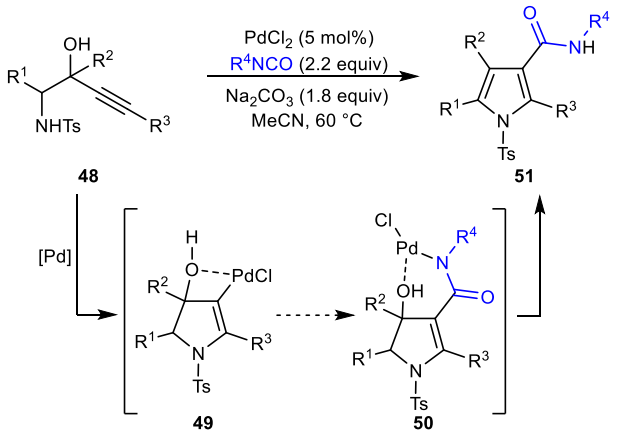
A possible catalytic cycle was proposed for the reaction (Scheme 10). The first step is formation of the alkenyl palladium species **41** from the addition of $Pd(OAc)_2$ to enamide **40**. Secondly, the alkyne coordinates to the palladium and replaces DMSO

followed by migratory insertion to give **45**. Then reductive elimination allows for the cyclisation of **45**, which undergoes basic hydrolysis to give the final product **47** and the addition of molecular oxygen regenerates the Pd(II)-species.



Scheme 10: Proposed catalytic cycle.

Reddy and co-workers reported the synthesis of substituted pyrroles from 1-amino-3-alkyn-2-ols **48** (Scheme 11).[22] The tethered sulfonamide acts as the nucleophile and intramolecularly attacks the alkyne to give **49**. The alkenyl palladium-species couples to an isocyanate electrophile to give **50**, which then dehydrates to give product **51**, a pyrrole 3-carboxamide.

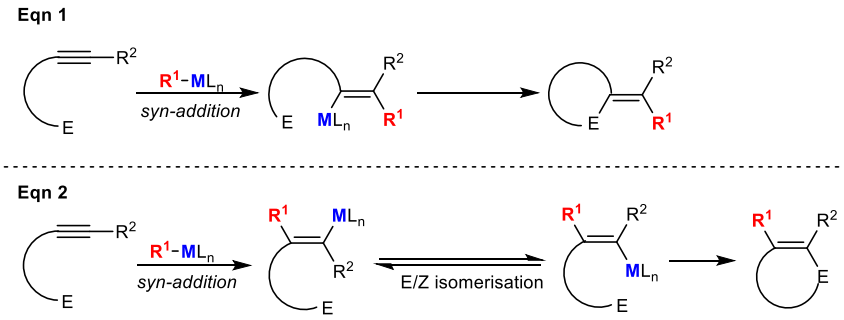


Scheme 11: Nucleo-metallative pyrrole synthesis.

The economic, efficient synthesis of highly substituted pyrroles from simple starting materials and with the tolerance of various functional groups is still a challenge to synthetic chemists. The following section describes the use of nickel catalysis to initiate a cascade-reaction to form multiple bonds in one step, permitted due to the reversible *E/Z* isomerisation.

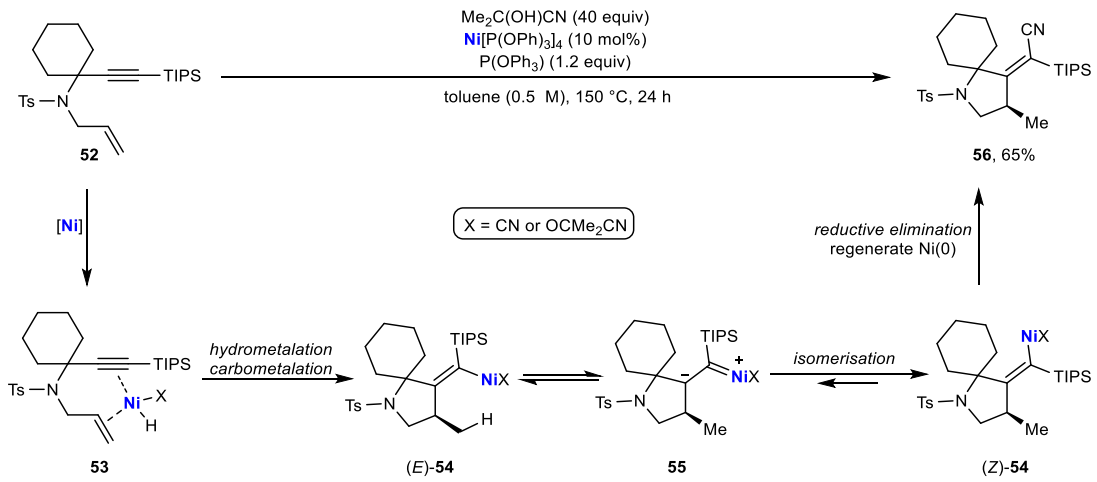
1.4 Nickel-Catalysed *anti*-Carbometallative Cyclisation

There are two ways in which an organometallic species can add across an alkyne (Scheme 12). *Syn*-carbometalation across an alkyne where the metal adds proximal to the electrophile favours direct cyclisation (Scheme 12, **Eqn 1**). With *syn*-carbometalation across the alkyne where the metal adds distal to the electrophile, the generated geometry does not allow for cyclisation to occur, but with an *E/Z* isomerisation interchange the cyclisation is made possible (Scheme 12, **Eqn 2**).



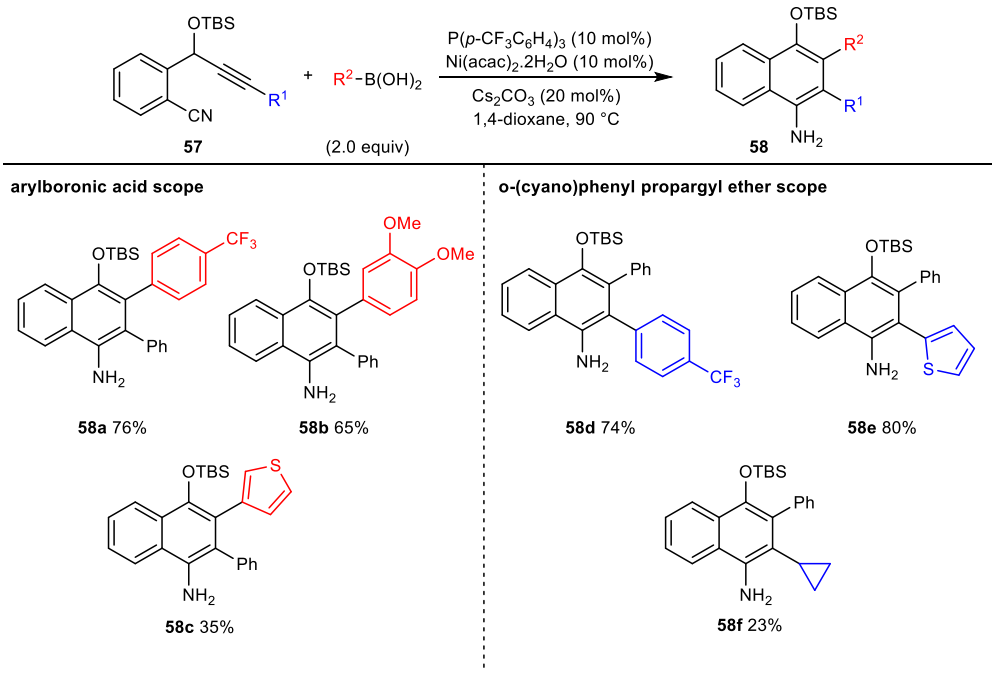
Scheme 12: Proximal and distal addition to alkynes containing a tethered electrophile.

In 2013, Nishida and co-workers reported the nickel-catalysed *anti*-carbocyanative cyclisation using 1,6-enynes **52** (Scheme 13), a cyclisation/cyanation cascade reaction.[26] It was suggested that the Ni(0) undergoes oxidative addition to generate the H-Ni-X species which then hydronickelates onto the alkene. The generated organonickel species then carbonickelates onto the alkyne to give (*E*)-**54**, which in the presence of significant steric repulsion isomerises ((*E*)-**54**↔(*Z*)-**54**). This isomerisation was suggested to be promoted by the formation of a nickel-carbene species **55** which allowed for rotation around the C-C bond. Reductive elimination resulted in the formation of **56** and the regeneration of Ni(0).



Scheme 13: A cyclisation/cyanation cascade reaction.

Liu and co-workers reported in 2016 a nickel-catalysed cyclisation using boronic acids and propargyl ether substrates with a tethered nitrile as the electrophile (Scheme 14).[27] The nickel-catalysed addition/cyclisation of *o*-(cyano)phenyl propargyl ethers **57** with arylboronic acids provided 1-naphthylamines with wide structural diversity **58**. The reaction was enabled due to the regioselective addition of the aryl-nickel species to the alkyne and the *E/Z* isomerisation following the carbonickelation of the alkyne.

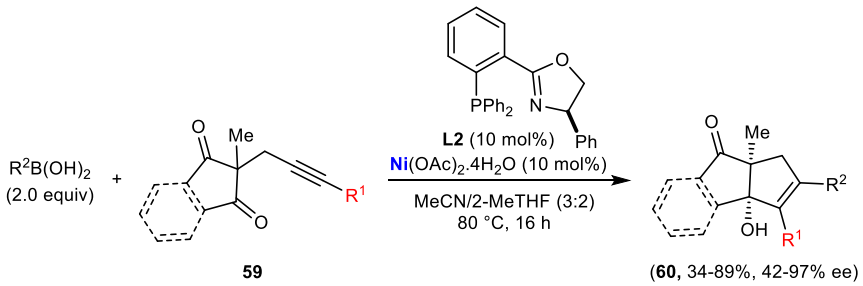


Scheme 14: Nickel-catalysed cyclisation of alkyne-nitriles with arylboronic acids.

The scope of the reaction with respect to the arylboronic acids gave good yields with both electron-withdrawing and -donating substituents (**58a-58b**) but a lower yield of

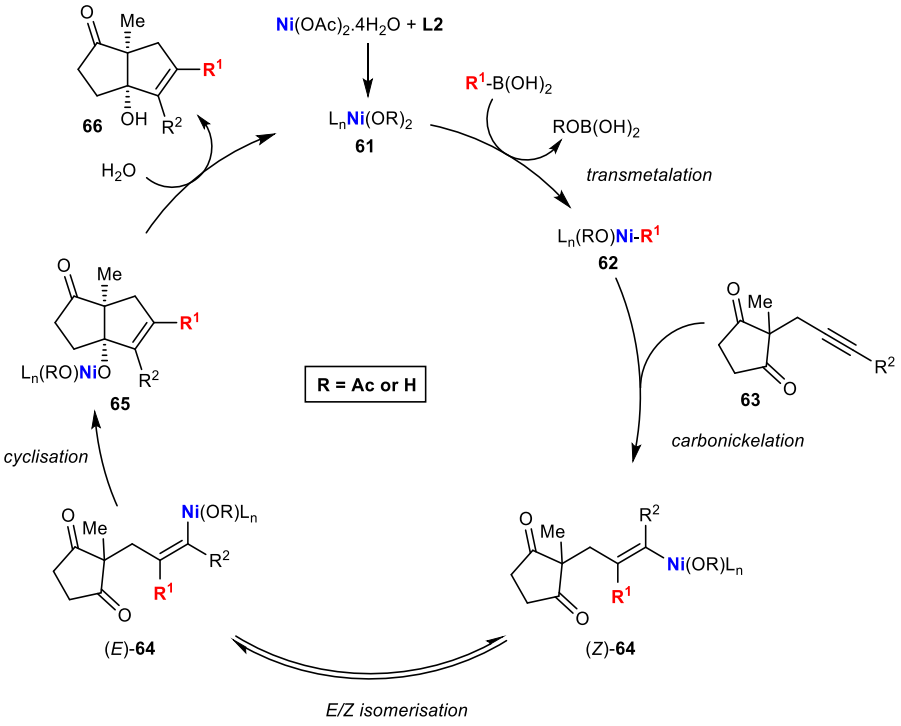
35% was observed when using a 3-thienylboronic acid (**58c**). The scope of the reaction with respect to the alkyne substituent gave good yields with a substituted aryl group (**58d**) and 2-thienyl (**58e**) but gave a low yield of 23% when using a cyclopropane substituent (**58f**). Further, it was suggested that a Ni(I) species was involved in the mechanistic cycle.

In 2016, Lam and co-workers reacted arylboronic acids with alkynes **59** to generate alkenyl nickel species which after *E/Z* isomerisation was in the correct geometry to subsequently add to a tethered ketone in an addition/cyclisation cascade reaction (Scheme 15).[28] The reaction gave yields ranging from 34-89% and with enantioselectivities of up to 97% *ee*.



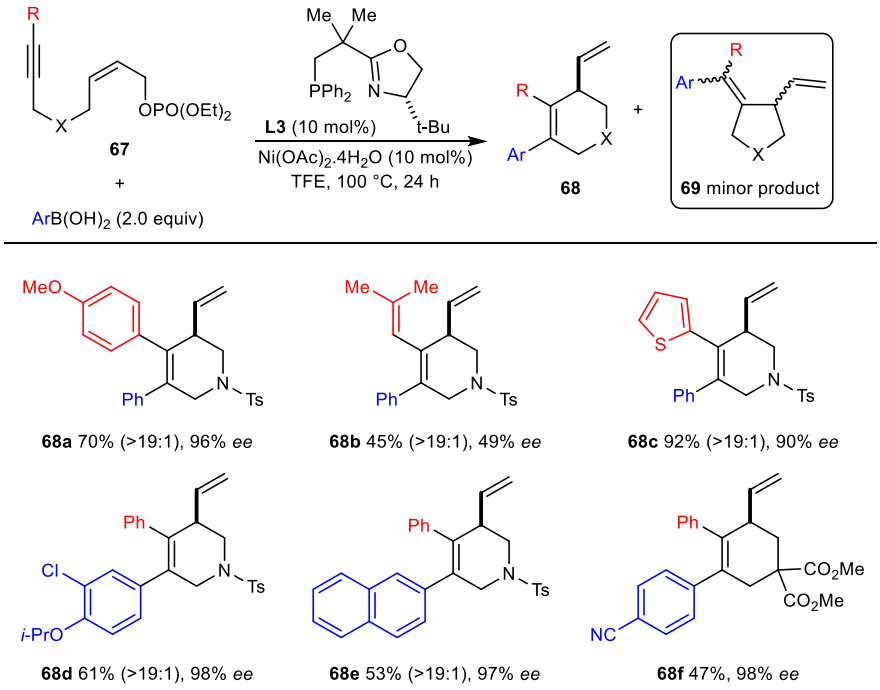
Scheme 15: A addition/cyclisation cascade reaction.

The proposed catalytic cycle starts with the formation of nickel-complex **61** which transmetalates with arylboronic acid to give **62** followed by the *syn*-arylnickelation of **62** with **63** to give the alkenyl-nickel intermediate **(*Z*)-64** (Scheme 16). *E/Z* isomerisation enables the formation of the *E*-isomer **(*E*)-64** which then cyclises onto the ketone and subsequent protonolysis liberates the product **66** and regenerates the nickel complex. It was suggested that the cyclisation pushed the *E/Z* equilibrium to the *E*-isomer.



Scheme 16: Proposed catalytic cycle.

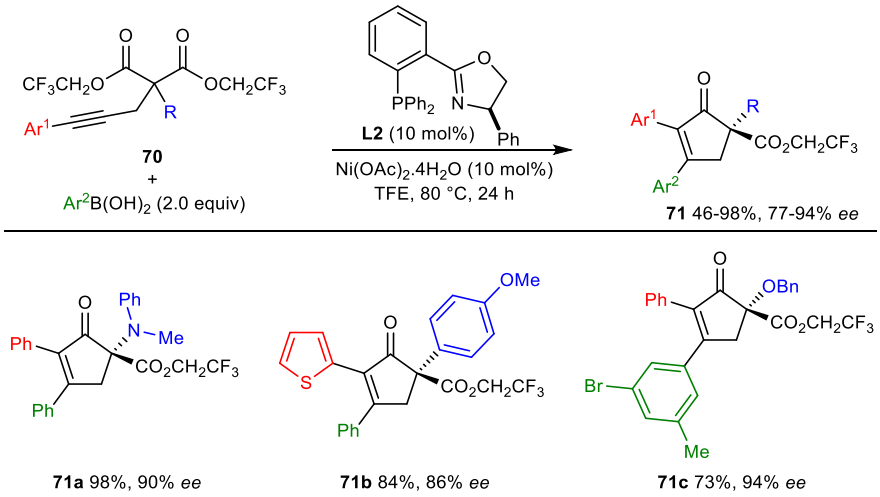
Lam and co-workers extended the addition/cyclisation cascade work to other substrates.[28,29] The use of *Z*-allylic phosphates **67** as the electrophile enabled the synthesis of multisubstituted chiral aza- and carbocycles **68** (Scheme 17).[29] The reaction showed the formation of two products with the major product **68** being the result of the aryl-nickel species adding in a distal fashion across the alkyne and the minor product **69** being the result of the aryl nickel species adding in a proximal fashion across the alkyne.



Scheme 17: Synthesis of carbo- and hetero cyclic compounds.

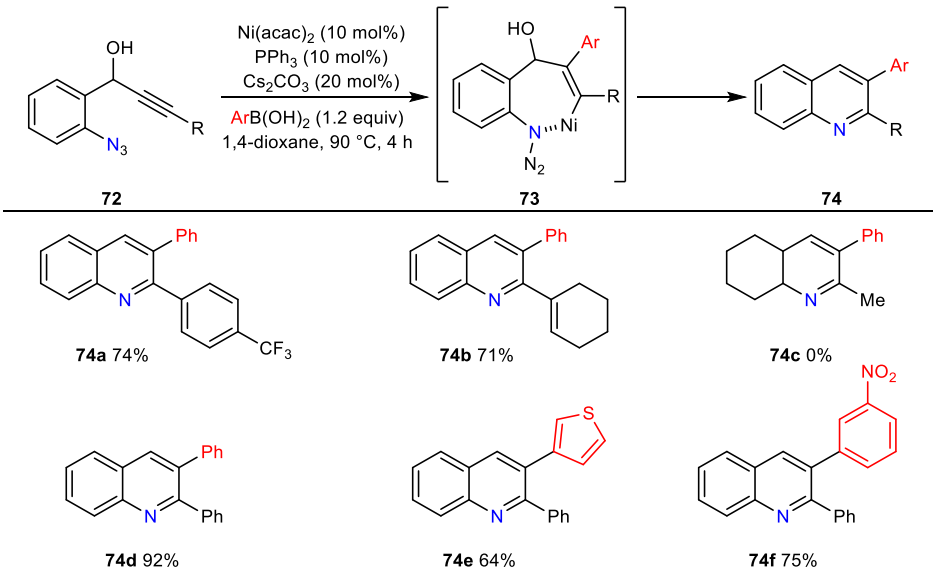
The use of an electron-donating phenyl group substituted at the alkyne gave a good yield and excellent *ee* (**68a**). Having a thienyl group substituted at the alkyne gave excellent yields and *ee*'s (**68c**) and having an alkenyl group substituted at the alkyne gave a poor yield and *ee* (**68b**). The reaction tolerated the use of disubstituted phenylboronic acid (**68d**), naphthylboronic acid (**68e**) and 4-cyanophenylboronic acid (**68f**) with excellent *ee*'s.

The Lam group used malonate esters **70** to enable the synthesis of non-racemic cyclopent-2-enones **71** (Scheme 18). The reaction proceeded in 46-98% yield with 77-94% *ee* and showed to tolerate amines (**71a**), thienyl (**71b**) and substituted aryl groups (**71b-71c**).[30]



Scheme 18: Synthesis of chiral cyclopent-2-enones.

Reddy and co-workers described the synthesis of 2,3-diarylquinolines using nickel-catalysed *anti*-carbometallative cyclisation of alkyne azides with organoboronic acids using the azide as the electrophile (Scheme 19).[31] The reaction gave good to excellent yields up to 92% (**74a**). Substitutions such as trifluoromethyl substituted phenyl (**74a**) and cycloalkene (**74b**) at the alkyne were tolerated. 3-Thienyl (**74e**) and nitro substituted phenyl (**74f**) were tolerated as substituents of the boronic acid. However, with a methyl group at the alkyne-position and a tethered hexane ring (rather than benzene) no product was obtained (**74c**).



Scheme 19: Synthesis of substituted quinolines.

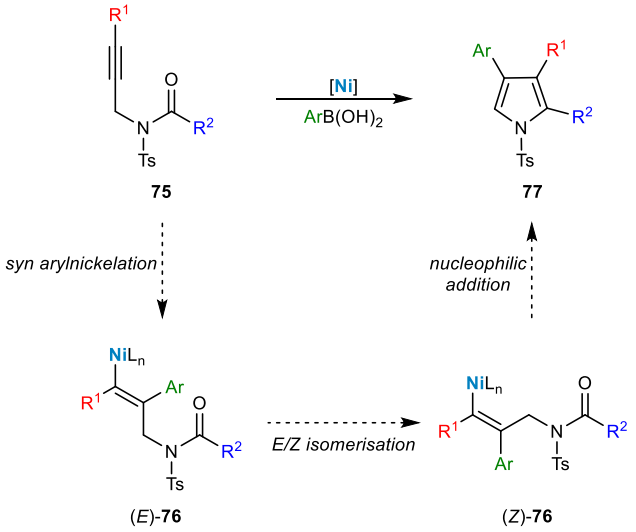
In summary, since its first discovery in the 19th century, pyrrole and its derivatives have been of high interest to synthetic chemists due to its aromatic character and more

recently identified widespread applications. Economic and efficient methods for the synthesis of highly substituted pyrroles from simple starting materials, and with the tolerance of various functional groups, are still the target for many synthetic chemists. Nickel-catalysis to initiate a cascade-reaction, is a method, which satisfy many of these requirements.

2.0 Results and Discussion: Nickel-Catalysed Synthesis of Multisubstituted Pyrroles by *anti*-Carbometallative Cyclisation

2.1 Aims and Objectives

Nickel-catalysed *anti*-carbometallative cyclisation of alkynyl electrophiles has been described by various groups to give both carbo- and heterocyclic products. The Lam group has successfully investigated these types of reactions where ketones, *Z*-allylic phosphates and esters are used as electrophiles.[28-30] Whereas, the groups of Liu and Reddy have researched the use of nitriles and azides respectively.[27,31] However, amide electrophiles are yet to be described which due to their relatively low electrophilicity is not surprising.

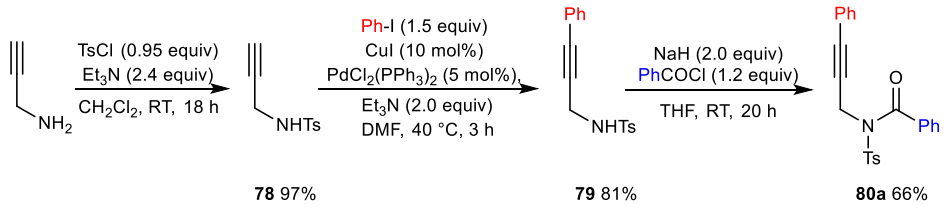


Scheme 20: Nickel-catalysed pyrrole synthesis.

Nickel-catalysed *anti*-carbometallative cyclisation of alkynes using tethered amide electrophiles could open the door to the synthesis of highly substituted pyrroles (Scheme 20). This method would additionally provide an efficient addition/cyclisation cascade reaction using simple starting materials and with the use of the earth abundant metal, nickel.

2.2 Reaction Screening

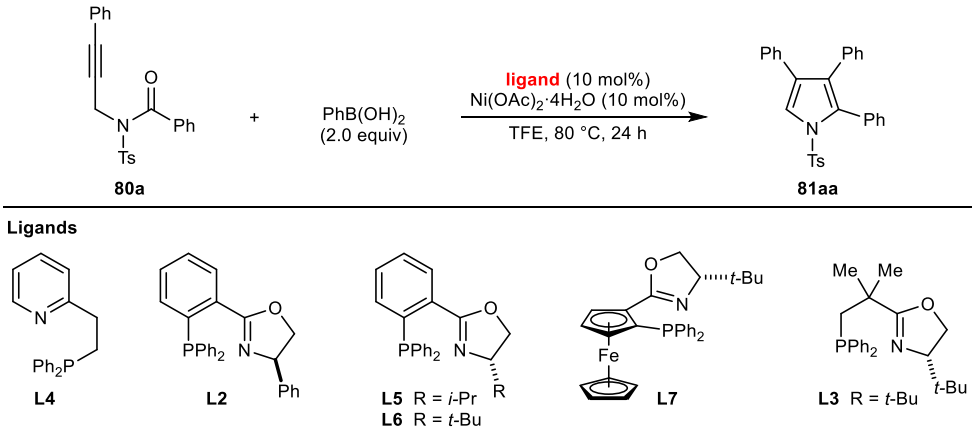
The alkynamide **80** was synthesised by a tosylation reaction followed by a Sonogashira reaction and lastly an acylation reaction (Scheme 21). This substrate was used for screening of the nickel-catalysed cyclisation reaction presented within this thesis.



Scheme 21: Synthesis of substrate **80a**. The acylation reaction to give **80a** was carried out by Chieh-Hsu Chung.

Due to reactions previously carried out by the Lam group, the first chosen reaction conditions were 2.0 equivalents of boronic acid, 10 mol% of ligand and $Ni(OAc)_2.4H_2O$ in TFE at 80 °C for 24 h. Ligand screening was carried out illustrating that Ph-PHOX (**L2**) gave the best yield (Table 1, entry 3).

Table 1: Ligand screening.

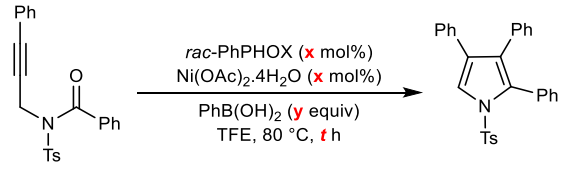


Entry	Ligand	Yield of **80a** [%][a]	Yield of **81aa** [%][a]
1	-	>95	<5
2	**L4**	33	27
3	**L2**	-	90
4	**L5**	18	52
5	**L6**	13	70
6	**L7**	10	63
7	**L3**	11	52

[a] ^{1}H NMR yields. Reactions were carried out at 0.05 mmol scale. 1,4-Dimethoxy benzene was used as an internal standard. Entry 2-7 were carried out by Chieh-Hsu Chung.

The reaction of **80a** with phenylboronic acid gave a 91% yield of **81aa** when using 10 mol% catalyst and running the reaction for 24 h (Table 2, entry 1). When the reaction was performed with 5 mol% catalyst loading, the reaction reached completion after 17 hours (according to TLC) yielding 72% product (Entry 2) and with the use of 7 mol% catalyst loading the reaction yielded 84% (Entry 3). Increasing the reaction time to 24 hours and carrying out the reaction in the presence of 5 mol% catalyst loading improved the reaction, giving the desired product in 93% yield (Entry 4). With these promising results, a further decrease in catalyst loading to 2 mol% was attempted; however, this reaction gave only 53% yield (Entry 5).

Table 2: Further optimisation.



80a **81aa**

Entry	x [mol%]	*t* [h]	y [equiv]	Yield of **81aa** [%][a]	Yield of **80a** [%][a]
1	10	24	2.0	91[b]	-
2	5	17	2.0	72	-
3	7	17	2.0	84	-
4	5	24	2.0	93	-
5	2	24	2.0	53[c]	8[c]
6	5	24	1.2	60	28
7	5	24	1.5	81	21

[a] Isolated yields, unless specified. Reactions were carried out at 0.30 mmol scale [b] (*R*)-Ph-PHOX was used. [c] ^{1}H NMR yield, reaction carried out at 0.05 mmol scale and 1,3,5-trimethoxybenzene was used as an internal standard. Entry 1 was carried out by Chieh-Hsu Chung.

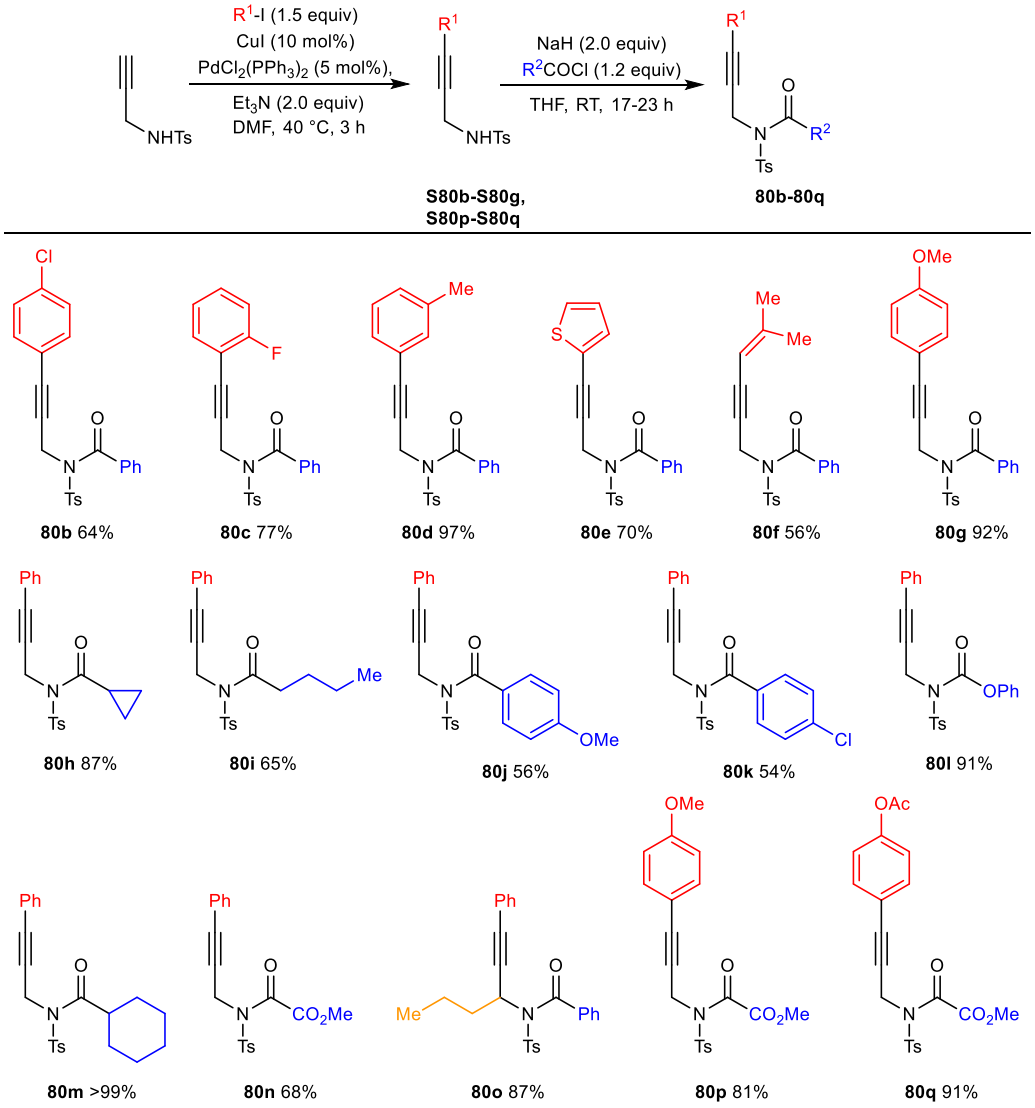
Decreasing the equivalents of boronic acid to 1.5 and 1.2 gave yields of 60 and 81% respectively (Entry 6 and 7), with both the reactions showing starting material remaining. Whereas the use of 2.0 equivalents of boronic acid as mentioned above yielded 93% and full conversion.

In summary, the optimised conditions were 5 mol% $Ni(OAc)_2.4H_2O$ and *rac*-Ph-PHOX, 2.0 equivalents of phenylboronic acid in TFE at 80 °C for 24 h, and these reaction conditions were used as the standard conditions for subsequent reactions.

2.3 Substrate Synthesis

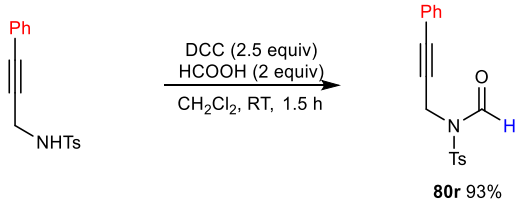
With the optimised conditions for the nickel-catalysed cyclisation of **81aa**, a range of *N*-tosylalkynamide substrates were synthesised with various functionalities (Table 3).

Table 3: Substrate synthesis



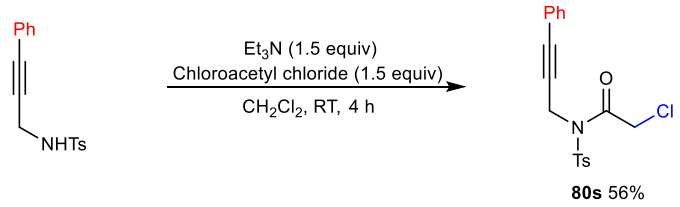
All yields are of isolated acylation products. Reaction conditions for Sonogashira products **S80e**, **S80f** and **S80e** varied slightly, refer to experimental for exact conditions. Reaction conditions for acylation reactions varied slightly, refer to experimental for exact reaction conditions.

The synthesis of formylated propargylic sulphonamide **80r** utilised formic acid and the dehydrating agent *N,N*'-dicyclohexylcarbodiimide (Scheme 22).



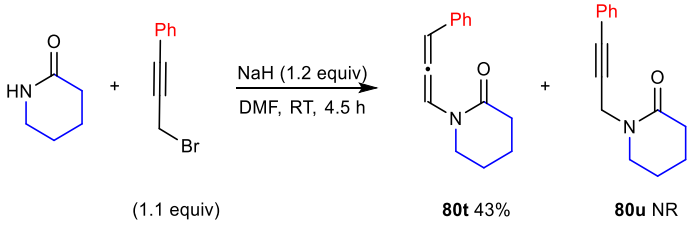
Scheme 22: Synthesis of substrate **80r**.

The synthesis of substrate **80s** utilised triethylamine as the base compared to sodium hydride utilised in the standard conditions (Scheme 23). The reason for the use of a weaker base was to avoid the deprotonation of the chloroacetyl chloride. The increased number of equivalents of chloroacetyl chloride, compared to the general acylation reaction conditions, suggests that some deprotonation of this compound was occurring.



Scheme 23: Synthesis of substrate **80s**.

An alkylation reaction was carried out to obtain propargyl lactam **80u**; however, the allene lactam **80t** was observed in 43% yield (Scheme 24).



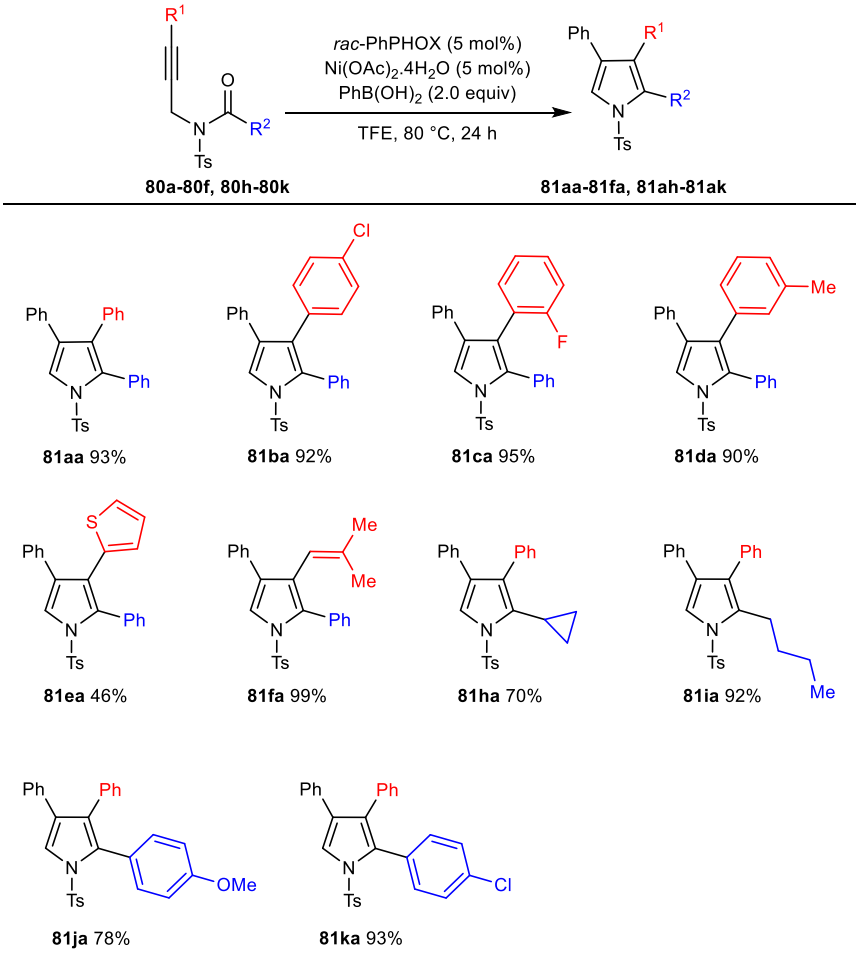
Scheme 24: Synthesis of substrate **80t**.

2.4 Scope of the Reaction

The scope of the reaction was then investigated. *Para*- (**81ba**), *ortho*- (**81ca**) and *meta*-substituted phenyls (**81da**) at the alkyne position were all tolerated, as well as 2-thienyl (**81ea**) (Table 4). The substitution at the alkyne was not limited to just aromatic groups as a simple alkenyl group (**81fa**) could be implemented to achieve a very high yield of

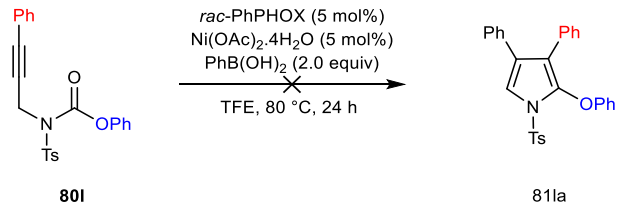
99%. Variation at the amide was tolerated, with electron-withdrawing (**81ka**) and electron-donating phenyl groups (**81ja**) furnishing the desired products in good yields, as well as cyclopropyl (**81ha**) and an *n*-butyl group (**81ia**).

Table 4: Scope of substrate.



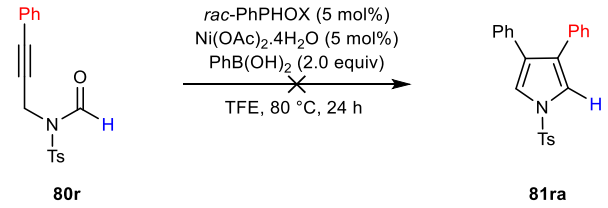
Isolated yields. Reactions were carried out at 0.30 mmol scale.

Installing an OPh group to generate a carbamate was detrimental to the reaction, with no product being observed and complete recovery of starting material (Scheme 25).



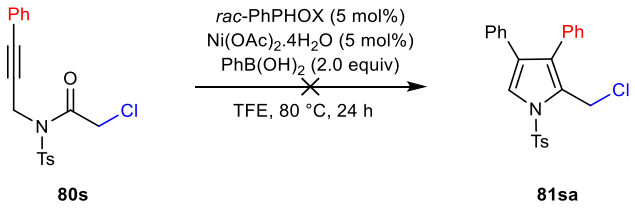
Scheme 25: Scope of substrate.

Cyclisation of the formylated alkynamide to get pyrrole **81ra** showed to be an undesirable reaction and the presence of *p*-toluenesulfonamide in 34% yield was observed (Scheme 26). The reaction was performed with a 20 mol% catalyst loading in otherwise identical conditions. Unfortunately, this reaction was unsuccessful.



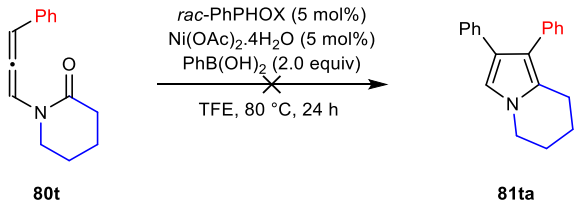
Scheme 26: Scope of substrate.

The instalment of a chloromethyl group at the amide position (**80s**) showed recovery of starting material (**80s**) and decomposition when carrying out the reaction at standard condition and the same was observed at increased conditions of 10 mol% catalyst at 100 °C (Scheme 27).



Scheme 27: Scope of substrate.

Cyclisation of allene lactam (**80t**) proved to be detrimental to the reaction (Scheme 28).

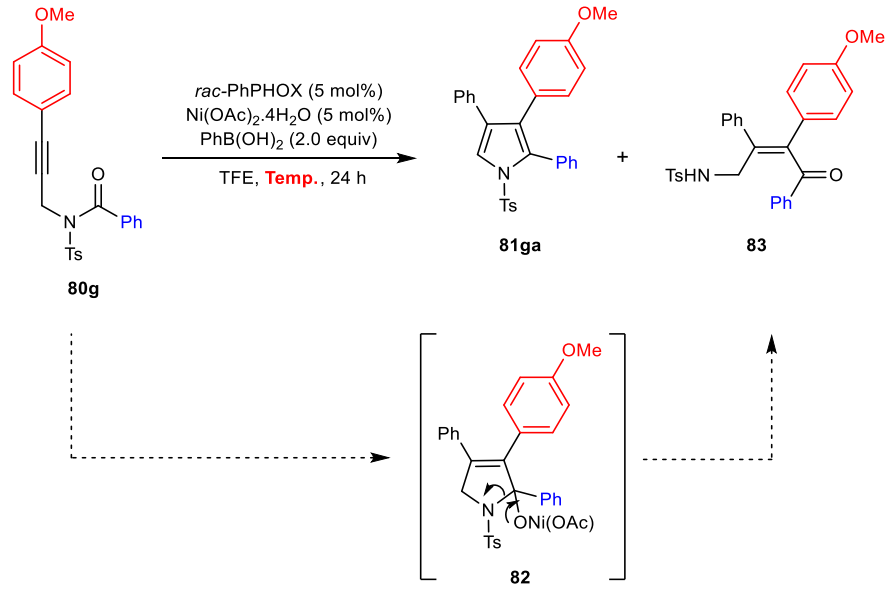


Scheme 28: Scope of substrate.

Two products were obtained when having a *para*-methoxy phenyl at the alkyne, the cyclised product **81ga** and the acyclic tetrasubstituted alkene **83** (Table 5). The cyclised product was isolated in 54% yield and the acyclic tetrasubstituted alkene in

23% yield (Entry 1). The improvement of the ratio of cyclised product to acyclic tetrasubstituted alkene was attempted by performing the reaction at 110 °C, however, yields of 51% and 20% respectively were observed (Entry 2). Product **81ga** is suggested to have been formed after the cyclisation step where the oxygen lone pair is donated back rather than being eliminated as seen in intermediate **82**.

Table 5: Scope of substrate.

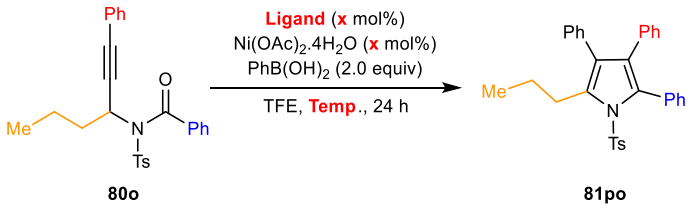


Entry	Temp. [°C]	Yield of **81ga** [%]	Yield of **83** [%]
1	80	54[a]	23[a]
2	110	51[b]	20[b]

[a] Isolated yield, the reaction was carried out at 0.30 mmol scale. [b] ^{1}H NMR yield, the reaction was carried out at 0.05 mmol scale and 1,3,5-trimethoxybenzene was used as an internal standard.

In order to obtain a 2,3,4,5-tetra-substituted pyrrole, substrate **80o** was used (Table 6). Unfortunately, the reaction did not work when tested with various ligands (Entry 1, 2 and 3). The use of *rac*-Ph-PHOX and an increase in temperature was not successful either (Entry 4 and 5).

Table 6: Scope of substrate.



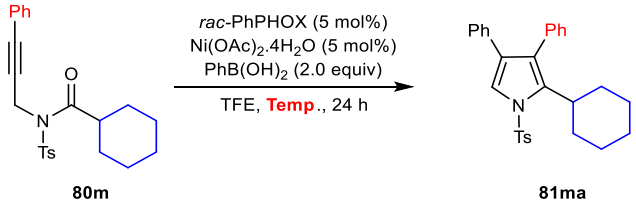
80o **81po**

Entry	Ligand	x [mol%]	Temp. [°C]	Yield of **81po** [%][a]
1	*rac*-Ph-PHOX	5	80	-
2	Py-PHOS	5	80	-
3	Neo-PHOX	5	80	-
4	*rac*-Ph-PHOX	10	100	-
5	*rac*-Ph-PHOX	10	120	-

[a] ^{1}H NMR yield. Reactions were carried out at 0.05 mmol scale.

When having a cyclohexane group at the amide **80m** and performing the reaction at standard conditions, the reaction yielded only 24% (Table 7, entry 1). Pleasingly with an increase in temperature to 120 °C a 54% yield was obtained (Entry 3).

Table 7: Scope of substrate.



80m **81ma**

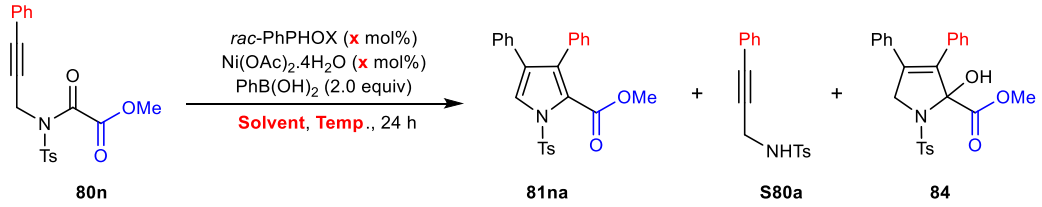
Entry	Temp. [°C]	Yield of **81ma** [%][a]
1	80	24
2	100	40
3	120	54

[a] Isolated yield. Reactions were carried out at 0.30 mmol scale.

Having an ester group at the C2 position along with aryl groups at C3 and C4 of the pyrrole is of high interest due to the appearance of these scaffolds in many lamellarins.[6] Unfortunately, the cyclisation of substrate **80n** using standard conditions gave product **S80a** (Table 8, Entry 1). A solvent screening was carried out with the use of dioxane leading to the recovery of starting material **80n** (Entry 2) and the use of THF lead to a mixture of product **81na** and side product **84** (Entry 3). The side product was cyclised product which had not undergone 1,4-elimination of water. It was expected that an increase in temperature could increase the yield of the reaction.

As expected, an increase in temperature to 120 °C gave a yield of 73% product **81na** (Entry 6).

Table 8: Scope of substrate.

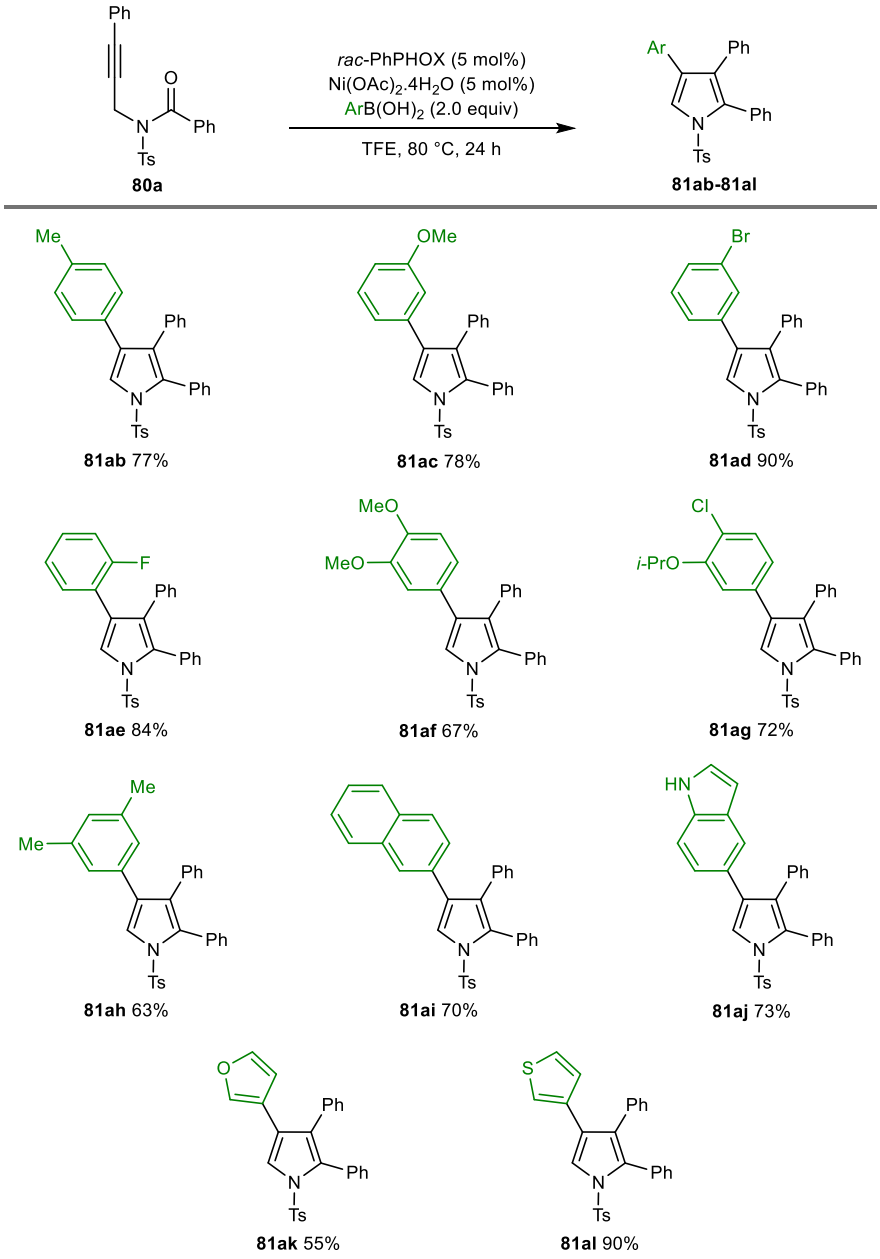


Entry	x [mol%]	Solvent	Temp. [°C]	Yield of **81na** [%][a]	Yield of **S80a** [%][a]	Yield of **84** [%][a]	Yield of **80n** [%][a]
1	5	TFE	80	-	present	-	-
2	20	Dioxane	100	-	-	-	present
3	20	THF	80	30	-	48	-
4	20	THF	100	54[b]	-	-	-
5	20	THF	110	63[b]	-	-	-
6	20	THF	120	73	-	-	

[a] Isolated yield, unless specified, reactions were carried out at 0.30 mmol scale. [b] ^{1}H NMR yield, reactions were carried out at 0.05 mmol scale and 1,3,5-trimethoxybenzene was used as an internal standard.

The scope of the boronic acid was investigated showing that various aryl groups were tolerated in yields ranging from 55-90% (Table 9). The reaction was compatible with *para*- (**81ab**), *meta*- (**81ac-81ad**) and *ortho*- (**81ae**) substituted phenylboronic acids as well as disubstituted phenylboronic acids (**81af-81ah**) with methyl (**81ah**), halide (**81g**) or alkoxy groups (**81af-81ag**). Further, 2-naphthylboronic acid (**81ai**) was tolerated as well as heteroarylboronic acids such as 5-indolyl- (**81aj**), 3-furanyl- (**81ak**) and 3-thienylboronic acids (**81al**).

Table 9: Scope of arylboronic acid.

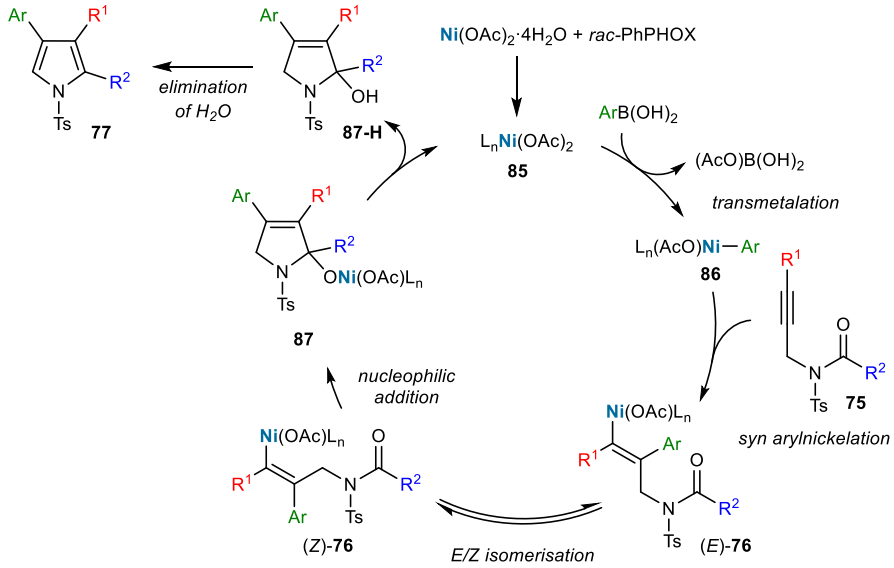


Isolated yields. The reactions were carried out at 0.30 mmol scale. Entry **81ab-81ai** and **81ak-81al** were carried out by Chieh-Hsu Chung

2.5 Postulated Catalytic Cycle and Mechanistic Insight

A proposed catalytic cycle is shown in scheme 29. The ligand coordinates to the nickel acetate to give catalyst **85** followed by a transmetalation of an arylboronic acid to give nickel-species **86** which then *syn*-arylnickelates onto the alkyne to give **(*E*)-76** with nickel distal to the electrophile. *E/Z* Isomerisation allows access to **(*Z*)-76** and the

alkenyl nickel species, acting as a nucleophile, attacks the amide to give the cyclised structure **87**. Protonation of the nickel alkoxide followed by dehydration leads to the re-aromatised product **77** and the regeneration of nickel catalyst **85**.

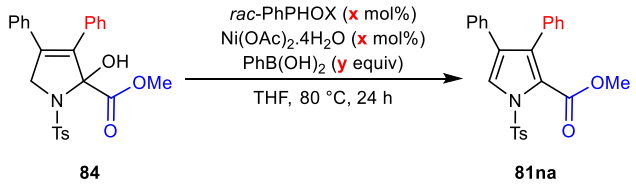


Scheme 29: Postulated catalytic cycle.

As seen in the reaction of **80n** in Table 8 in the previous section a 3-pyrroline side product is obtained. This side product is good evidence of the proposed catalytic cycle going *via* intermediate **87**.

For mechanistic insight, the side product **84** was resubmitted to the reaction conditions (Table 10). First, the side product was resubmitted using just solvent and no conversion was observed (Entry 1). Secondly, the side product was resubmitted using solvent and 20 mol% catalyst and still no conversion was observed (Entry 2). Lastly, the side product was resubmitted using solvent, 20 mol% catalyst and 2.0 equivalents of phenylboronic acid and a mixture of product **81na** and side product **84** was observed in a ratio of 38:41 (Entry 3). This observation suggested that the boronic acid is not only involved in the transmetalation of the alkyne but is also important for the elimination of the water.

Table 10: Resubmitting side product **84** to the reaction conditions.



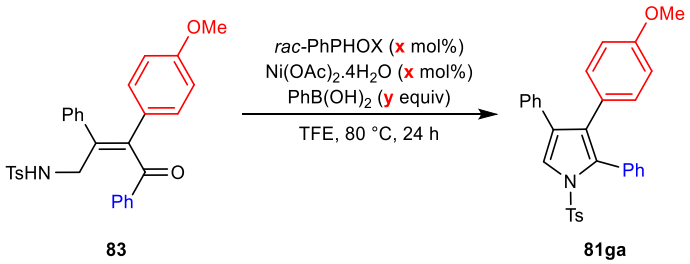
84 **81na**

Entry	x [mol%]	y [equiv]	Yield of **81na** [%][a]	Yield of **84** [%][a]
1	0	0	-	55
2	20	0	-	80
3	20	2.0	38	41

[a] ^{1}H NMR yields. Reactions were carried out at 0.05 mmol scale and 1,3,5-trimethoxybenzene was used as an internal standard.

The acyclic tetrasubstituted alkene obtained from the reaction seen in table 5 was similarly to above, resubmitted to the reaction conditions (Table 11). In all three cases no conversion was observed which suggested that the side product was obtained irreversibly (Entry 1, 2 and 3).

Table 11: Resubmitting side product to the reaction conditions.



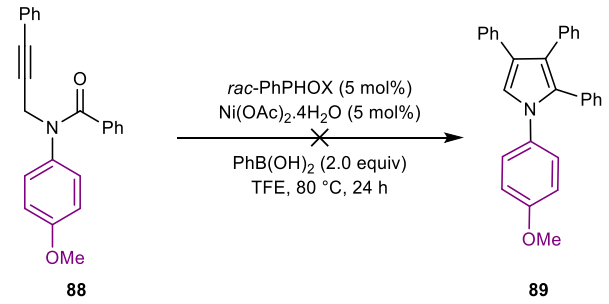
83 **81ga**

Entry	x [mol%]	y [equiv]	Yield of **81ga** [%][a]	Yield of **83** [%][a]
1	0	0	-	36
2	5	0	-	70
3	5	2.0	-	51

[a] ^{1}H NMR yields. Reactions were carried out at 0.05 mmol scale and 1,3,5-trimethoxybenzene was used as an internal standard.

To extend the scope and utility of the reaction a cyclisation reaction was done using substrate **88**, which has a PMP protecting group rather than a tosyl protecting group (Scheme 30). Unfortunately, the reaction was unsuccessful, suggesting that electron-donating groups at the amide are not compatible with this reaction. This could suggest

that an electron-withdrawing tosyl at the amide is essential to increase the electrophilicity of the amide.

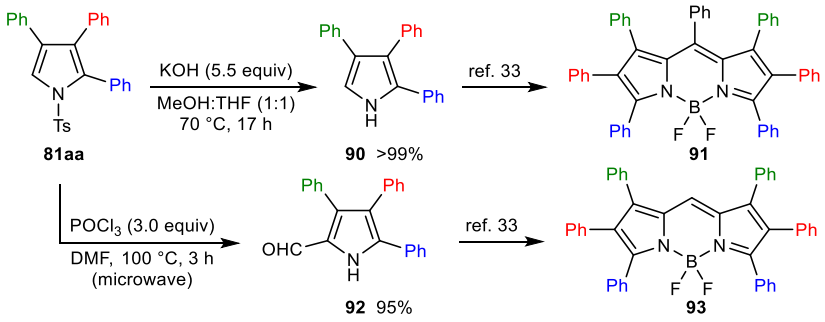


Scheme 30: Cyclisation with PMP protecting group.

2.6 Synthesis of Precursors to BODIPY Derivatives

BODIPY dyes are used as labelling agents, for example of proteins and DNA. [32] BODIPY dyes are also used as fluorescent switches, chemosensors and laser dyes.

From structure **81aa** two reaction were done to give precursors to BODIPY derivatives (Scheme 31).[33] The first reaction was a tosyl deprotection to give precursor **90** in >99% yield, and the second reaction was the combined tosyl deprotection and C4 formylation to give precursor **92** in 95% yield. The combined deprotection/formylation reaction is a novel reaction discovered in a serendipitous fashion during this project.



Scheme 31: Synthesis of precursors to BODIPY derivatives. Reaction to synthesise **90** was carried out by Chieh-Hsu Chung.

2.7 Attempts Towards the Total Synthesis of Lamellarins

Lamellarins are a group of more than 50 pyrrole-derived alkaloids (Figure 4).[6] One type of lamellarins has the pyrrole as a part of a fused pentacyclic skeleton which contain an either partially saturated (Type 1a) or fully unsaturated (Type 1b) isoquinoline moiety. Another type of lamellarins are the 3,4-diaryl-2-ester substituted pyrrole (Type 2). As mentioned previously, natural products often have interesting bioactive abilities and are therefore a popular target for synthetic chemists.

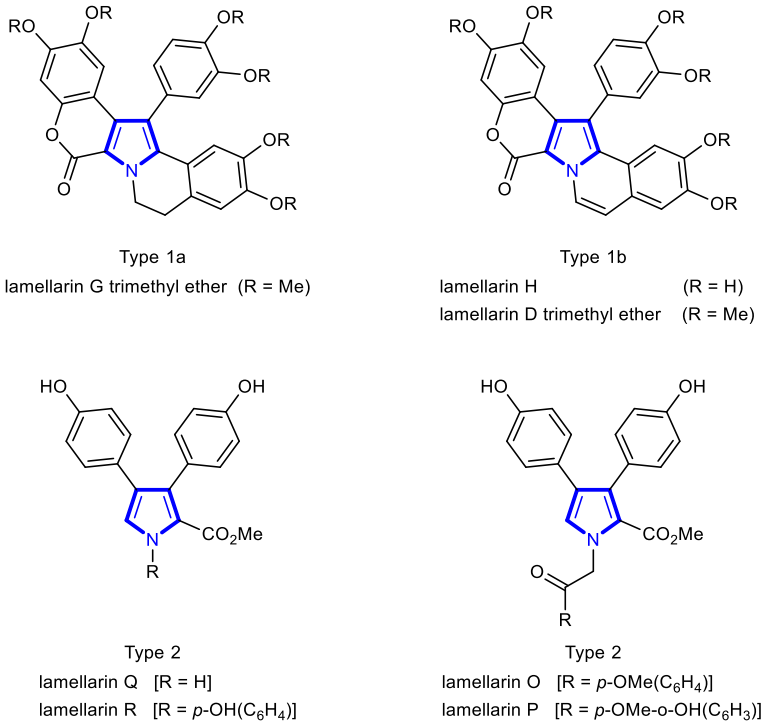


Figure 4: Types of lamellarins.

2.7.1 Attempts Towards the Synthesis of Lamellarin D Trimethyl Ether

Many strategies for synthesising lamellarin D trimethyl ether are known.[6] Commonly, the isoquinoline moiety is established *via* a Pomeranz-Fritsch-type cyclisation following a lactonization (Figure 5).

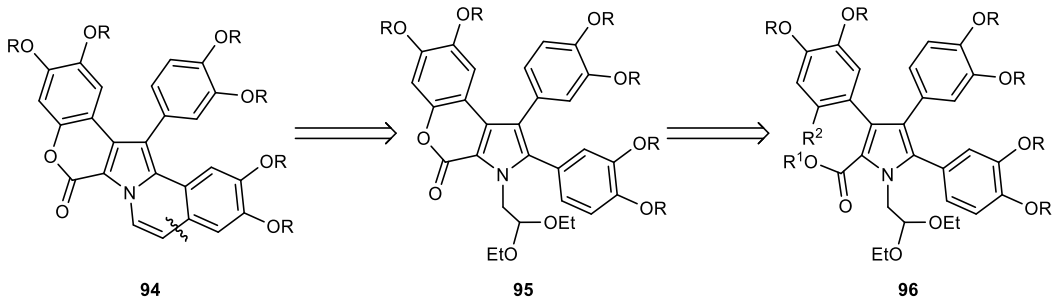
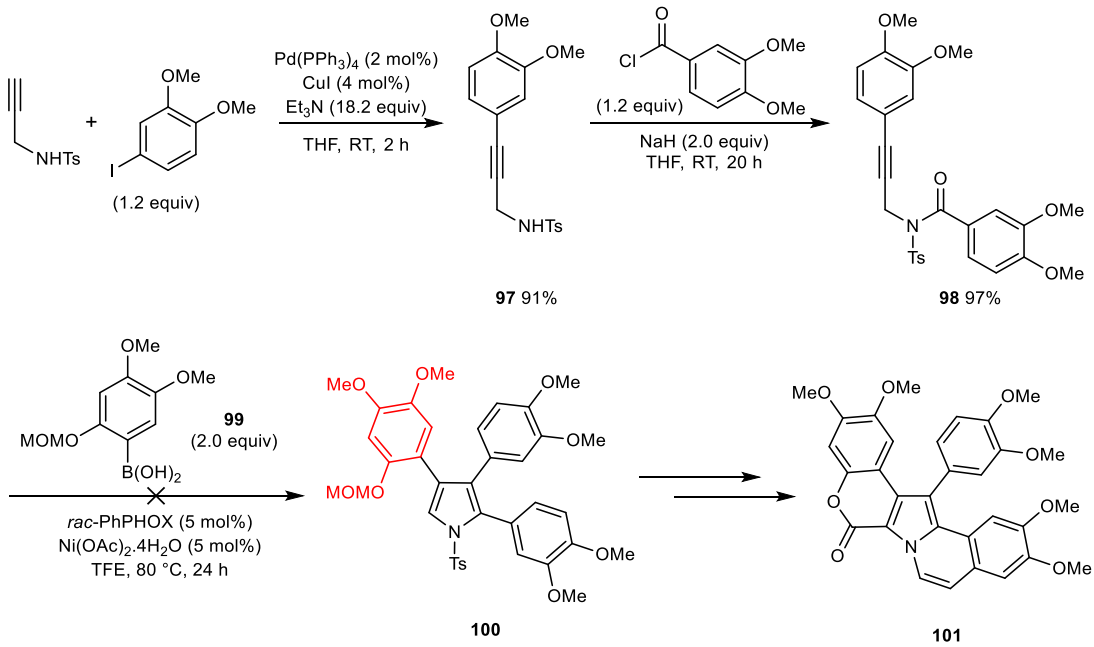


Figure 5: Retrosynthetic analysis of Lamellarin D trimethyl ether.

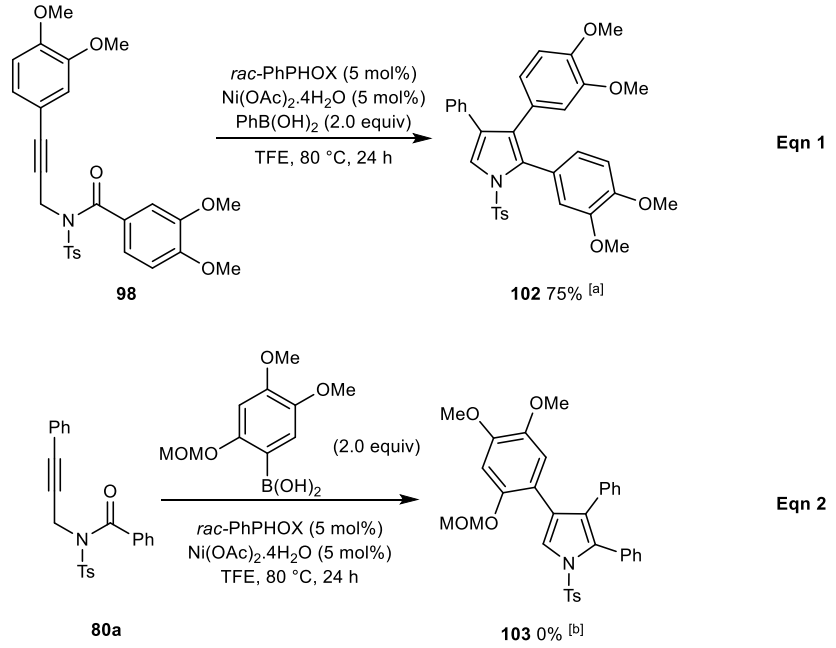
The use of an *ortho*-OMOM aryl group at the C3 position of pyrrole to cyclise onto an ester at the C2 position has previously been reported in the synthesis of lamellarins.[7] Therefore, it was attempted to synthesise compound **100** using *ortho*-OMOM-boronic acid **99** (Scheme 32). Firstly, a Sonogashira reaction followed by an acylation reaction afforded compound **98**. Unfortunately, the cyclisation reaction to give **101** did not afford any product and cleaving of the amide to give amine **97** was observed.



Scheme 32: Attempted total synthesis of lamellarin D trimethyl ether. The boronic acid **99** was synthesised by Chieh-Hsu Chung and the cyclisation to give **100** was tested by Chieh-Hsu Chung.

Two test reactions were carried out to locate the problematic step of the cyclisation (Scheme 33). Firstly, substrate **98** was cyclised using the standard phenylboronic acid and product **102** was obtained in 75% yield and therefore it was concluded that the substrate was not the problem. Secondly, the simple substrate **80a** was cyclised using

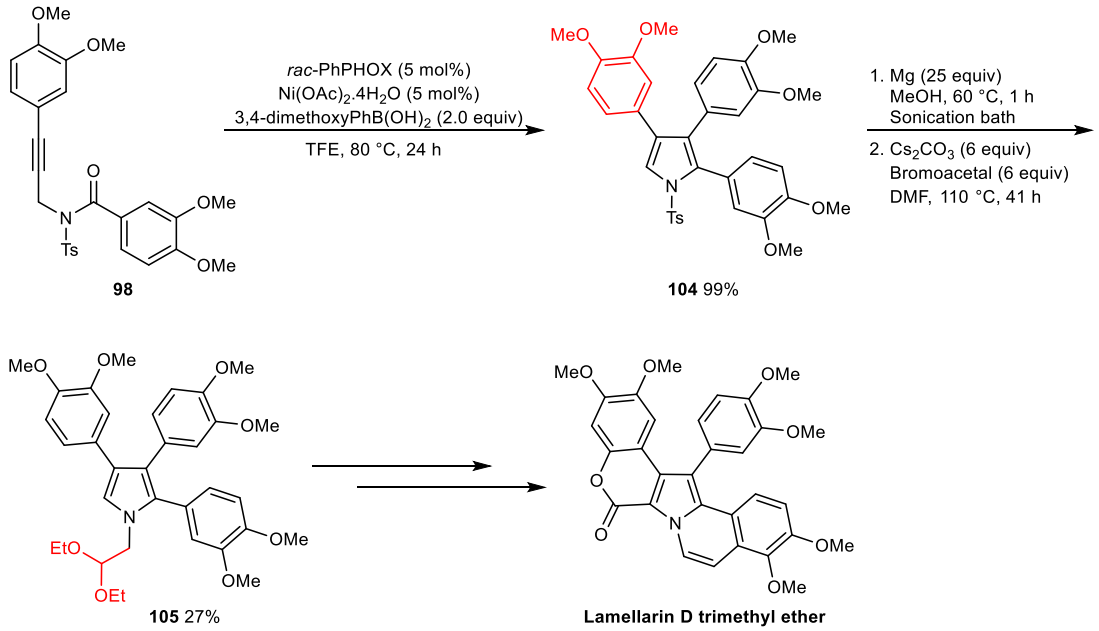
the 4,5-dimethoxy-2-OMOM-boronic acid and conversion to give **103** was not observed which concluded that it was due to the boronic acid that the cyclisation in scheme 32 was unsuccessful. Further, it was expected that the size of the OMOM group was reason for the unsuccessful reaction.



Scheme 33: Test reactions. [a] Isolated yield. [b] ^{1}H NMR yield.

Steglich and co-workers reported a lactonization having a hydrogen at R^1 and R^2 (Figure 5).[34] With the knowledge of this known reactivity attained, a new strategy was established. The idea was to use the herein presented nickel chemistry to do a cyclisation using 3,4-dimethoxyboronic acid followed by the Pomeranz-Fritsch-type cyclisation and then the generation of the cyclic ester.

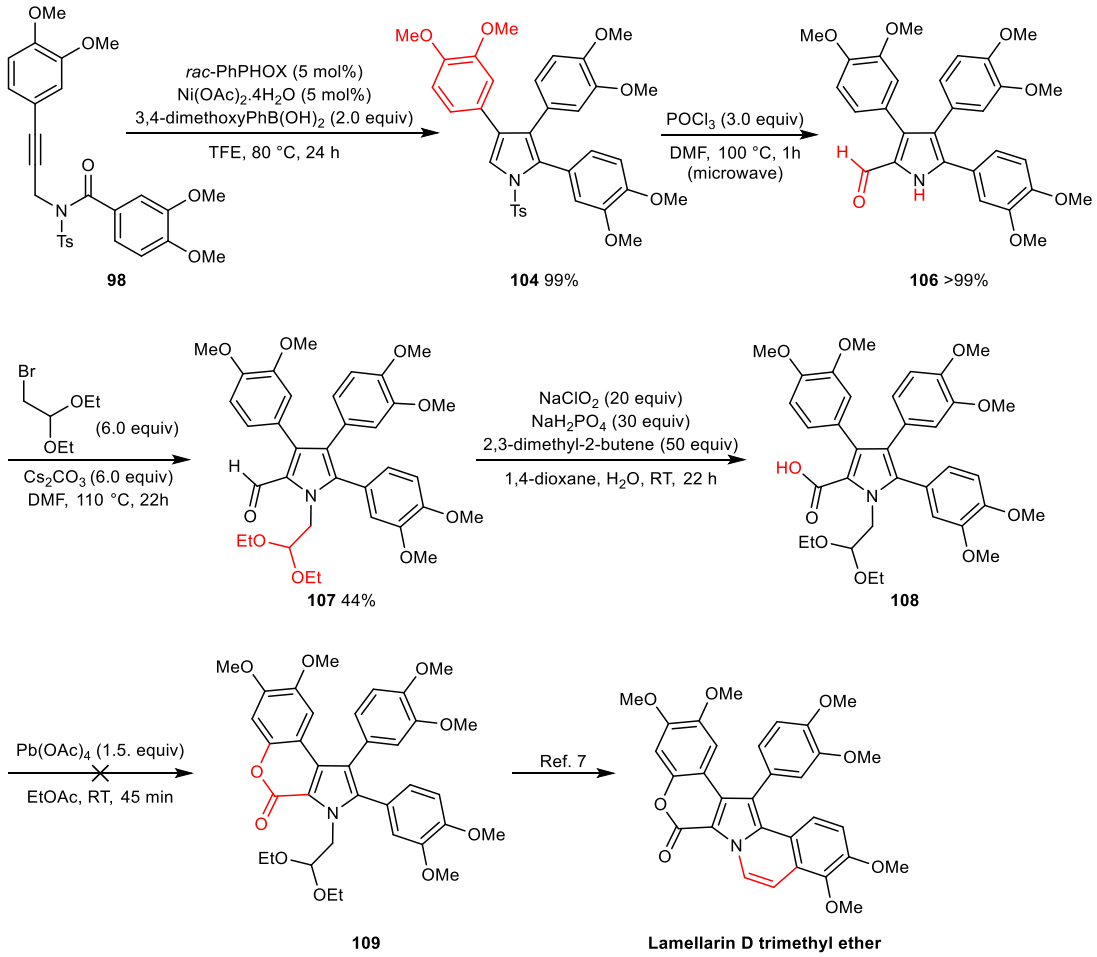
The first nickel-catalysed cyclisation step gave 99% yield under standard conditions (Scheme 34). The next step was a tosyl deprotection of the pyrrole which gave a mixture of tosylated and de-tosylated **104** as an inseparable mixture and therefore the following alkylation reaction was done using the mixture. The overall yield from the tosyl deprotection and alkylation was 27 % (only proton NMR spectroscopy and mass spectrometry were carried out). Due to the ineffectiveness of the described method, another strategy for the synthesis of lamellarin D was created.



Scheme 34: Attempted total synthesis of lamellarin D trimethyl ether

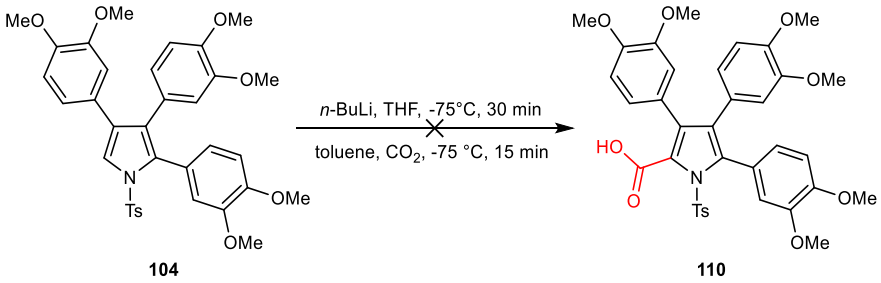
Another possible synthesis route was to reverse the order of the Pomeranz-Fritsch-type cyclisation and the generation of the cyclic ester. The first step would be to add an aldehyde at the free site of the pyrrole, followed by conversion into the corresponding acid. Cyclisation followed by tosyl-deprotection, alkylation and lastly the Pomeranz-Fritsch-type cyclisation would furnish the desired product.

For this natural synthesis route the first step was a formylation of compound **104** (Scheme 35). Unexpectedly, tosyl-deprotection was also observed leading to compound **106** in >99% yield. This result intervened with the initial strategy. It was thought that a free pyrrole would be very reactive and therefore the obvious next step was the alkylation of the pyrrole which yielded 44% of **107**. From here a Pinnick-type oxidation was performed. It was impossible to purify the acid **108**. However, with data showing the disappearance of the aldehyde peak in ^{1}H NMR, a clean spot at a higher R_f on the TLC plate and strong appearance in negative targeted mass spectrometry [M-H] as well as positive targeted mass spectrometry [M+H], the crude was used in the following cyclisation which unfortunately was unsuccessful. The common intermediate **109** would have been reached if this cyclisation had been successful.[7]



Scheme 35: Attempt of total synthesis of lamellarin D trimethyl ether

Pyrrole **110** with a carboxylic acid at the C4 position was obtained. A method using *n*-BuLi to deprotonate the free site of the pyrrole followed by purging of CO_2 gas had been reported.[35] This method was applied to our substrate **104**, but unfortunately was not successful.



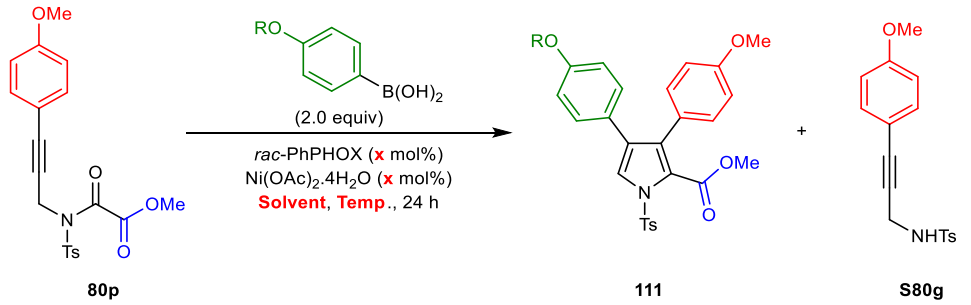
Scheme 36: Direct carboxylic acidification.

2.7.2 Attempts Towards the Synthesis of Type 2 Lamellarins

To generate type 2 lamellarins using the nickel-catalysed pyrrole synthesis described within, it would be necessary to cyclise a substrate with a *para*-substituted phenyl at the alkyne and a methyl-oxo-acetate at the amide using a *para*-substituted boronic acid. The success of this cyclisation followed by a tosyl deprotection and deprotection to give *para*-alcohols at the 2 aryl groups would give lamellarin Q and from here a simple alkylation would lead to various type 2 lamellarins (Figure 4).

The synthesis of a pyrrole with ester functionality at the 2-position and phenyl at the 3- and 4-position yielded 73% when using THF and 20 mol% catalyst at 120 °C (Table 9). The same reaction conditions were applied to substrate **80p** to obtain a 3,4-di-*para*-methoxyphenyl substituted pyrrole with an ester at the 2-position **111** (Table 12, entry 1). Unfortunately, the reaction was unsuccessful. A solvent screen revealed that solvents containing an alcohol group such as isopropanol and TFE cleaved the methyl-oxo-acetate to give **S80g** and most other solvents lead to the recovery of starting material **80p** (Entry 2-4, 6, 8-9). The use of MeCN as a solvent gave 11% yield (Entry 10).

Table 12: Synthesis of type 2 lamellarins.



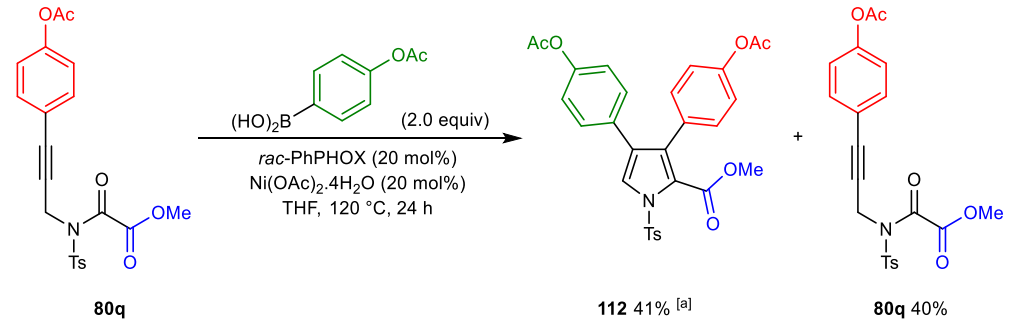
80p **111** **S80g**

Entry	R	x [mol%]	Temp. [°C]	Solvent	Yield of **111** [%][a]	Yield of **S80g** [%][a]	Yield of **80p** [%][a]
1	Me	20	120	THF	-	-	53
2	Me	5	80	DME	-	-	79
3	Me	5	80	isopropanol	-	65	-
4	Me	5	120	TFE	-	55	-
5	Me	5	120	1,4-dioxane	-	-	-
6	Me	5	120	toluene	-	-	75
7	Me	5	120	DMF	-	-	-
8	Me	5	100	chlorobenzene	-	-	86
9	Me	5	100	EtOAc	-	-	65
10	Me	5	100	MeCN	11[b]	-	34
11	Ac	20	120	THF	19[c]	-	16[c]
12[c]	Ac	20	120	THF	34	-	-

[a] ^{1}H NMR yield unless specified, reactions were carried out at 0.05 mmol scale and 1,3,5-trimethoxybenzene was used as an internal standard. [b] Yield based on the presence of the characteristic aromatic pyrrole singlet (7.56 ppm). [c] Isolated yield, reaction was carried out at 0.10 mmol scale. [c] 4.0 equiv of the boronic acid was used.

The boronic acid was varied using an electron-withdrawing acetoxy group rather than the electron-donating methoxy group. This reaction resulted in a 19% isolated yield (Entry 11). It was previously suggested that the boronic acid has an impact on the elimination of water as well as the carbonickelation (Table 12). Therefore, the reaction was carried out using 4.0 equivalents of boronic acid which gave a yield of 34% (Entry 12).

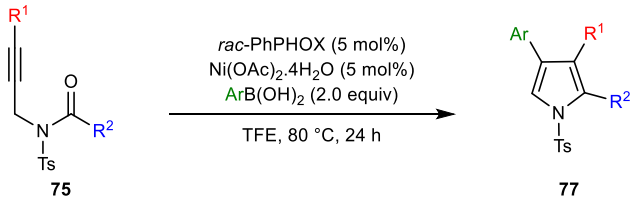
With these results in hand, substrate **80q** was synthesised having a *para*-acetoxy phenyl at the alkyne (Scheme 37). The cyclisation reaction was incomplete after 24 h and gave a mixture of product **112** and starting material **80q** of 41:40 respectively.



Scheme 37: Synthesis of type 2 lamellarins. NMR yield. 1,3,5-Trimethoxybenzene was used as an internal standard. [a] Yield based on the presence of the characteristic aromatic pyrrole singlet (7.62 ppm).

2.8 Conclusion

This project has resulted in the development of a nickel-catalysed addition/cyclisation/elimination cascade reaction to give substituted pyrroles *via* an essential *E/Z* isomerisation step (Scheme 38). The reaction demonstrated a wide reaction scope at the alkyne and amide, presenting both aryl and alkyl groups in good yields, as well as a wide reaction scope of the boronic acid. With the success of this reaction a natural extension of this work would be to extend the chain on either the alkyne of the amide side to obtain 6-membered heterocycles.



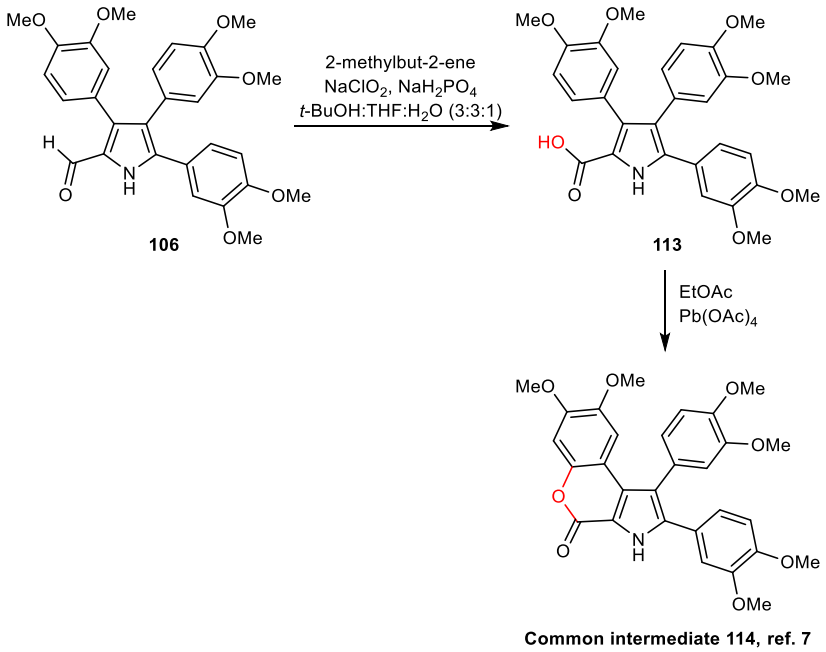
Scheme 38: Nickel-catalysed pyrrole synthesis

2,3,4-Triphenyl-1-tosyl-1*H*-pyrrole was synthesised in 93% yield utilising the method described within. Subsequent reactions lead to the synthesis of two precursors to BODIPY derivatives yielding >99 and 95%.

Currently, the total synthesis of lamellarin D was unsuccessful when employing the nickel-catalysed cyclisation as the pyrrole synthesising step, but various additional strategies are described in the following section.

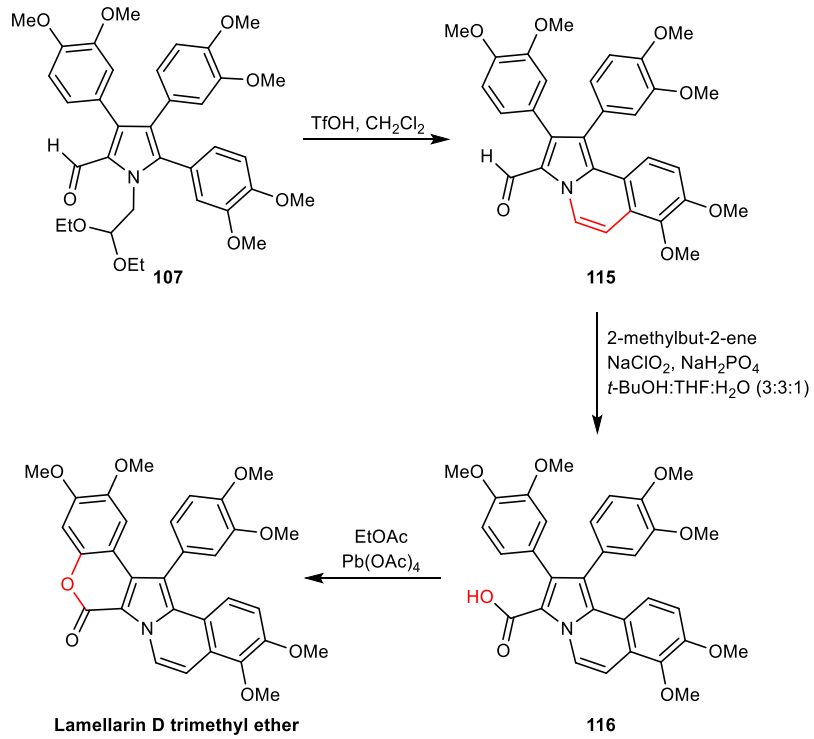
2.9 Future Work

As mentioned in the previous section, the cyclic ester formation of the acetaldehyde diethylacetal containing compound **108** proved to be problematic (Scheme 35). It is a possibility that the large group on the nitrogen was the reason for this reaction not working. With the free pyrrole proving to be stable when handled, converting the aldehyde to the acid[36] and generating the cyclic ester[34] before alkylating the nitrogen (Scheme 39) would be a possibility and would lead to the common intermediate **114**.[7]



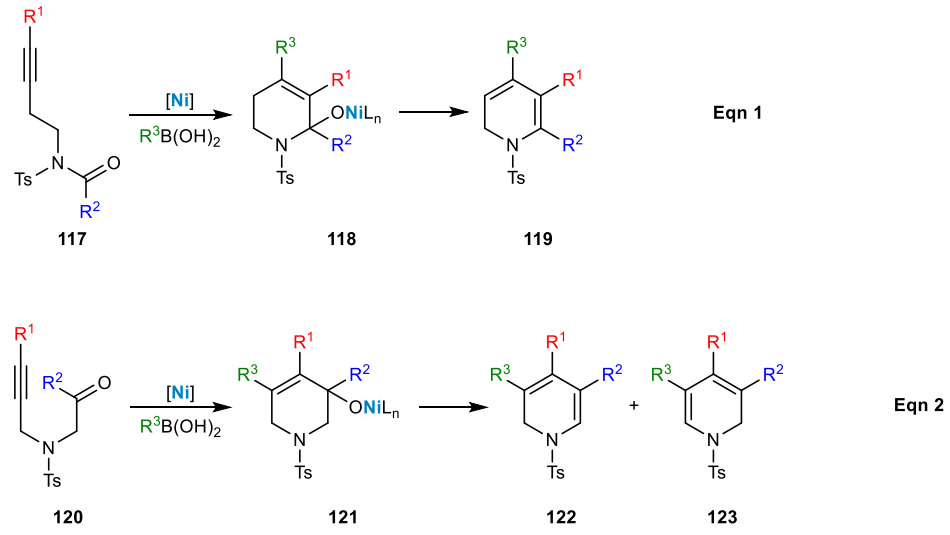
Scheme 39: Strategy for the synthesis of common intermediate of lamellarin D trimethyl ether synthesis.

Similarly, to above, if the reason for the unsuccessful lactonisation (Scheme 35) was the large group on the nitrogen, then performing the Pomeranz-Fritsch-type cyclisation of compound **107** to give iso-quinoline **115** prior to the cyclic ester formation could lead to lamellarin D trimethyl ether (Scheme 40)[7].



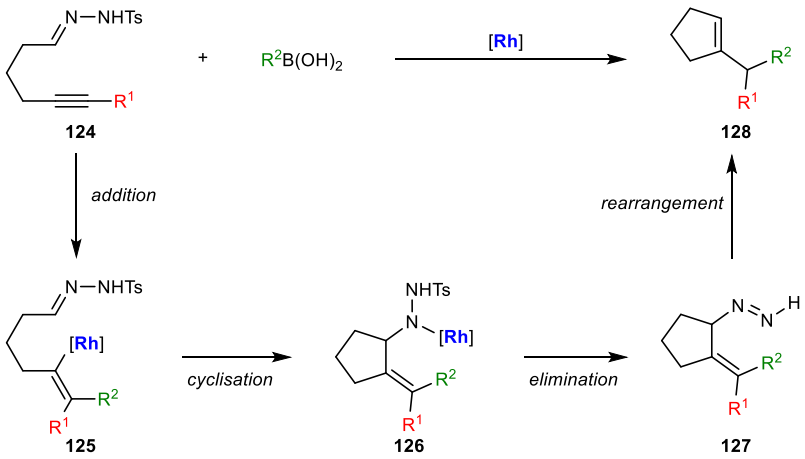
Scheme 40: Strategy for the synthesis of lamellarin D trimethyl ether.

The nickel-catalysed cyclisation onto an amide using boronic acids employed in the chemistry within could be used for chain-extended substrates (Scheme 41). One method would be to extend the chain on the alkyne side which would result in 2,3,4-substituted nitrogen cycle **119**, followed by a possible tosyl elimination to give 2,3,4-substituted pyridine (Eqn 1). Similarly, an extension of the chain on the amide side could lead to nitrogen cycle/pyridine but with a 3,4,5-substitution pattern (Eqn 2).



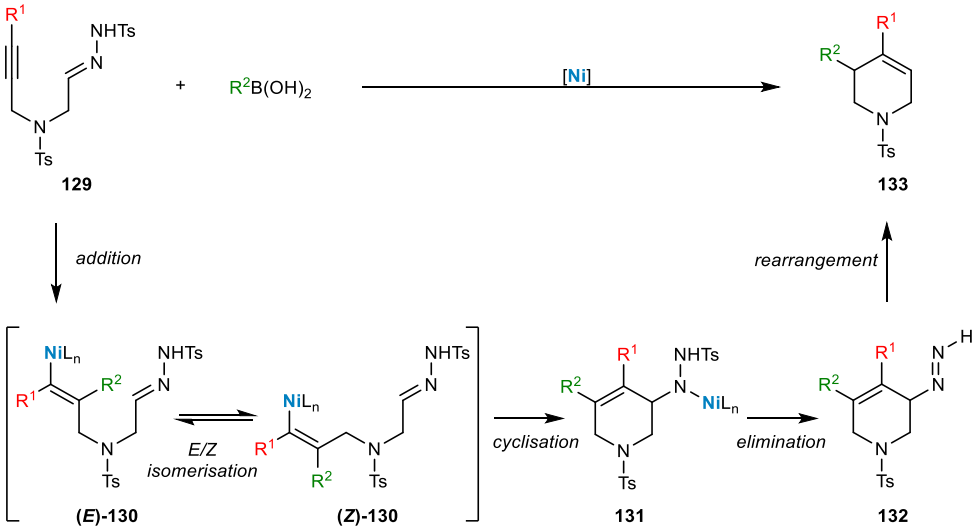
Scheme 41: Extending the chain of the substrate.

Lee and co-workers reported the rhodium-catalysed tandem addition-cyclisation-rearrangement of alkynylhydrazones using organoboronic acids (Scheme 42).[37] The boronic acid adds proximal to the electrophile across the alkyne followed by cyclisation, elimination and rearrangement to give product **128**.



Scheme 42: Rhodium-catalysed addition-cyclisation-rearrangement.

Applying a nickel catalyst to this reaction rather than rhodium would place the nickel distal to the electrophile and then *E/Z* isomerisation would allow for cyclisation (Scheme 43). The cyclised compound **131** could then undergo elimination and rearrangement, similarly to the rhodium-catalysed reaction, would give product **133**.



Scheme 43: An addition-cyclisation-rearrangement cascade reaction. Suggested by a member of the Lam group.

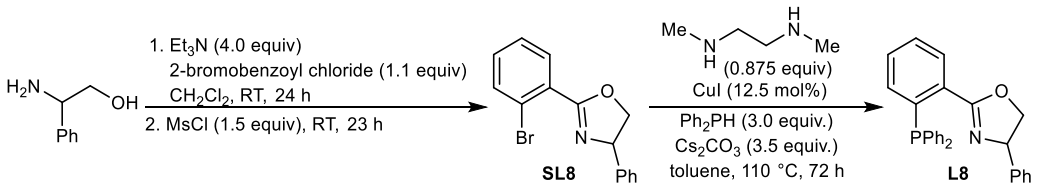
As a result of this project, numerous new strategies for synthesising compounds containing a pyrrole scaffold have unfolded. Future work should include the utility of this method to synthesise lamellarin D. Further, this project has also encouraged extensions to the nickel-catalysed cyclisation reaction presented within such as chain-extending on the alkyne side or the amide side.

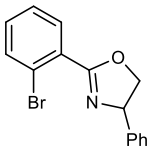
3.0 Experimental

3.1 General Information

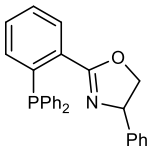
All air-sensitive reactions were carried out under an inert atmosphere using oven-dried apparatus. 2,2,2-Trifluoroethanol (TFE) was purchased from Alfa Aesar and degassed before use using a stream of argon gas (20 min). All commercially available reagents were used as received unless otherwise stated. Petroleum ether refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40-60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Compounds were visualized by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron or Fluorochem 60 Å particle size 40-63 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallization is reported in parentheses. Infrared (IR) spectra were recorded on Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total reflectance technique. NMR spectra were acquired on Bruker Ascend 400 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane via the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. For DMSO-d_6, the shifts are referenced to 2.50 ppm for ^{1}H NMR spectroscopy and 39.52 ppm for ^{13}C NMR spectroscopy. Coupling constants (J) are quoted to the nearest 0.1 Hz. Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High-resolution mass spectra were recorded using electrospray ionization (ESI) techniques. X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation.

3.2 Preparation of *rac*-Ph-PHOX





2-(2-Bromophenyl)-4-phenyl-4,5-dihydrooxazole (SL8). The compound **SL8** was prepared by modification of a previously reported procedure.[38] Et_3N (20.3 mL, 146 mmol) was added to a flask containing DL-2-phenylglycinol (5.00 g, 36.4 mmol) in CH_2Cl_2 (150 mL) and the solution was cooled to 0 °C before 2-bromobenzoyl chloride (5.2 mL, 40 mmol) was added dropwise. The mixture was gradually warmed to room temperature and stirred for 24 h. The reaction was recooled to 0 °C and MsCl (4.2 mL, 54 mmol) was added dropwise. The reaction was gradually warmed to room temperature, stirred for 23 h, quenched with saturated aqueous NH_4Cl solution (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (10% EtOAc/petroleum ether) to give the title compound **SL8** as a yellow oil (7.34 g, 67%). The analytical data were consistent with those reported previously.[39] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, dd, *J* = 7.6, 1.9 Hz, Ar**H**), 7.68 (1H, dd, *J* = 7.9, 1.3 Hz, Ar**H**), 7.42-7.34 (5H, m, Ar**H**), 7.34-7.28 (2H, m, Ar**H**), 5.45 (1H, dd, *J* = 10.2, 8.4 Hz, C**H**$_2$), 4.83 (1H, dd, *J* = 10.2, 8.4 Hz, C**H**$_2$), 4.30 (1H, t, *J* = 8.4 Hz, C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4 (C), 142.2 (C), 134.0 (CH), 131.9 (CH), 131.6 (CH), 129.8 (C), 128.9 (2 × CH), 127.8 (CH), 127.2 (CH), 126.9 (2 × CH), 122.1 (C), 75.1 (CH_2), 70.6 (CH).

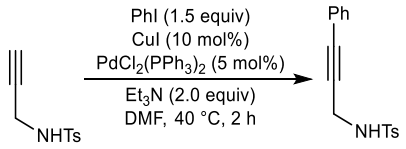


2-[2-(Diphenylphosphanyl)phenyl]-4-phenyl-4,5-dihydrooxazole (L8). The Ligand **L8** was prepared by modification of a previously reported procedure.[38] *N*,*N*'-DMEDA (0.31 mL, 2.9 mmol), CuI (79.0 mg, 0.415 mmol) and PPh_2H (1.7 mL, 9.8 mmol) were placed in a Schlenk flask and the contents were evacuated and refilled with N_2 gas (× 3 cycles). Toluene (25 mL) which had been freshly degassed (using a stream of argon gas for 15 min) was added and the mixture was stirred at room temperature for 20 min. A solution of oxazole **SL8**[36,37] (1.00 g, 3.31 mmol) in freshly degassed toluene (5 mL) was added, followed

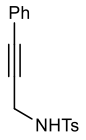
by Cs_2CO_3 (3.77 g, 11.6 mmol). The Schlenk flask was sealed and the contents were stirred at 110 °C for 72 h. The reaction was cooled to room temperature, filtered through celite and concentrated in *vacuo*. The residue was purified by column chromatography (10% EtOAc/petroleum ether) to give the title compound **L8** as a white solid (713 mg, 53%). The analytical data were consistent with those reported previously.[40] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-7.97 (1H, m, Ar**H**), 7.45-7.28 (12H, m, Ar**H**), 7.24-7.14 (3H, m, Ar**H**), 7.03-6.84 (3H, m, Ar**H**), 5.25 (1H, t, *J* = 9.6 Hz, C**H**), 4.57 (1H, dd, *J* = 10.2, 8.3 Hz, C**H**$_2$), 3.96 (1H, t, *J* = 8.9 Hz, C**H**$_2$); HRMS (ESI) Exact mass calculated for $[C_{27}H_{22}NOPNa]^+$ $[M+Na]^+$: 430.1331, found 430.1315.

3.3 Preparation of Substrates

Preparation of Substrate 80a



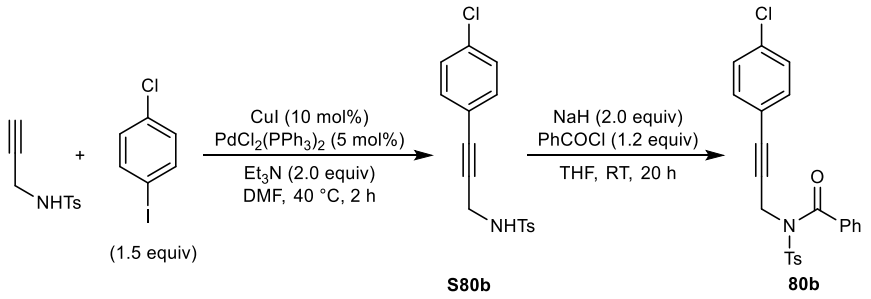
S80a

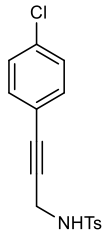


4-Methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (S80a).[41] To a stirred solution of $PdCl_2(PPh_3)_2$ (842 mg, 1.20 mmol) and CuI (457 mg, 2.40 mmol) in DMF (30 mL) was added freshly degassed Et_3N (6.7 mL, 48 mmol) and iodobenzene (4.0 mL, 36 mmol) under a nitrogen atmosphere. A solution of 4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (5.00 g, 23.9 mmol) in DMF (20 mL) was added and the resulting solution was stirred at 40 °C for 3 h. The reaction was quenched with 50% brine (500 mL) and extracted with EtOAc (3 x 250 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 x 500 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (10% to 20% EtOAc/petroleum ether) to give the title compound **S80a** as a brown solid (5.54 g, 81%). The analytical data were consistent with those reported previously.[41] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.77 (2H, m, Ar**H**), 7.34-7.20 (5H, m, Ar**H**), 7.18-7.10 (2H, m, Ar**H**), 4.61 (1H, t, *J* = 6.2 Hz, N**H**), 4.08 (2H, d, *J* = 6.2 Hz, C**H**$_2$), 2.36 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ

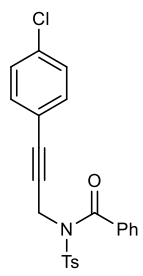
143.9 (C), 137.0 (C), 131.7 (2 × CH), 129.9 (2 × CH), 128.7 (CH), 128.3 (2 × CH), 127.6 (2 × CH), 122.2 (C), 84.9 (C), 83.3 (C), 34.0 (CH_2), 21.6 (CH_3).

Preparation of Substrate 80b





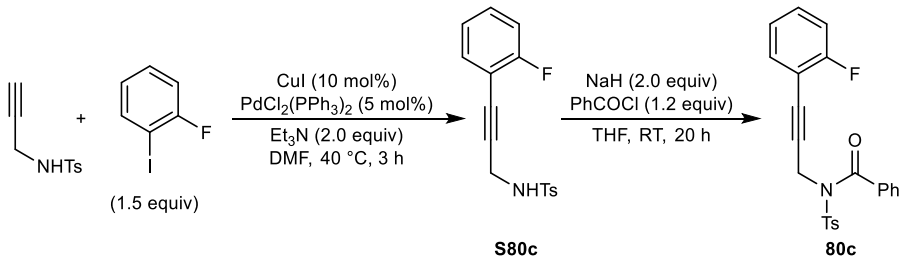
***N*-[3-(4-Chlorophenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (S80b).**[42] To a stirred solution of $PdCl_2(PPh_3)_2$ (168 mg, 0.240 mmol) and CuI (91.4 mg, 0.480 mmol) in DMF (6 mL) was added freshly degassed Et_3N (1.3 mL, 9.3 mmol) and 1-chloro-4-iodobenzene (1.71 g, 7.17 mmol) under a nitrogen atmosphere. 4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1.00 g, 4.80 mmol) in DMF (4 mL) was added and the resulting solution was stirred at 40 °C for 2 h. The reaction was quenched with 50% brine (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (20% EtOAc/petroleum ether) to give the title compound **S80b** as a reddish-brown solid (1.01 g, 66%). The analytical data were consistent with those reported previously.[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.76 (2H, m, Ar**H**), 7.31-7.27 (2H, m, Ar**H**), 7.25-7.18 (2H, m, Ar**H**), 7.10-7.00 (2H, m, Ar**H**), 4.61 (1H, t, *J* = 6.2 Hz, N**H**), 4.07 (2H, d, *J* = 6.2 Hz, C$\mathbf{H}_2$), 2.37 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 143.9 (C), 137.0 (C), 134.8 (C), 132.9 (2 × CH), 129.9 (2 × CH), 128.7 (2 × CH), 127.7 (2 × CH), 120.6 (C), 84.4 (C), 83.8 (C), 33.9 (CH_2), 21.6 (CH_3).

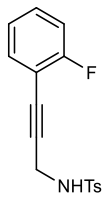


***N*-[3-(4-Chlorophenyl)prop-2-yn-1-yl]-*N*-tosylbenzamide (80b).** A solution of the *N*-tosyl propargyl amine **S80b** (500 mg, 1.56 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 74.8 g, 3.12 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h.

Benzoyl chloride (0.22 mL, 1.9 mmol) was added dropwise and the resulting solution was stirred at room temperature for 20 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (5% to 30% EtOAc/petroleum ether) to give the title compound **80b** as a white solid (425 mg, 64%). R_f = 0.49 (40% EtOAc/petroleum ether); m.p. 145-147 °C (Et_2O); IR 1689 (C=O), 1489, 1352, 1309, 1244, 1165, 1071, 945, 714, 570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98-7.90 (2H, m, Ar**H**), 7.58-7.54 (2H, m, Ar**H**), 7.54-7.48 (1H, m, Ar**H**), 7.43-7.37 (2H, m, Ar**H**), 7.31-7.22 (6H, m, Ar**H**), 4.80 (2H, s, C**H**$_2$), 2.41 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C), 145.2 (C), 135.9 (C), 135.0 (C), 134.2 (C), 133.1 (2 × CH), 132.0 (CH), 129.5 (2 × CH), 129.1 (2 × CH), 128.8 (2 × CH), 128.5 (2 × CH), 128.1 (2 × CH), 120.7 (C), 84.9 (C), 84.0 (C), 38.8 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{18}ClNO_3SNa]^+$ $[M+Na]^+$: 446.0588, found 446.0597.

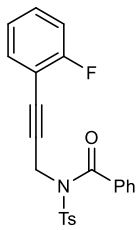
Preparation of Substrate 80c





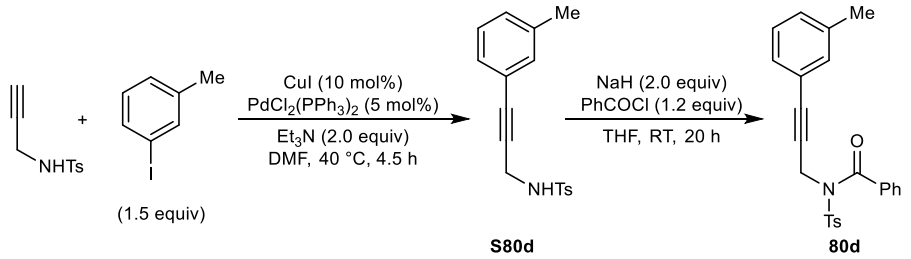
***N*-[3-(2-Fluorophenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (S80c).** To a stirred solution of $PdCl_2(PPh_3)_2$ (168 mg, 0.240 mmol) and CuI (91.4 mg, 0.480 mmol) in DMF (6 mL) was added freshly degassed Et_3N (1.3 mL, 9.3 mmol) and 2-fluoroiodobenzene (0.84 mL, 7.2 mmol) under a nitrogen atmosphere. A solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1.00 g, 4.80 mmol) in DMF (4 mL) was added and the resulting solution was stirred at 40 °C for 3 h. The reaction was quenched with 50% brine (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (20% to 30% EtOAc/petroleum ether) to give the title compound S**80c** as a pale brown solid (778 mg, 53%). R_f = 0.35 (40% EtOAc/petroleum ether); m.p. 125-126 °C (Et_2O); IR 3283

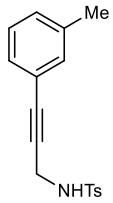
(NH), 1597, 1490, 1428, 1326, 1255, 1213, 1150, 813, 763 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17-8.14 (1H, m, N**H**), 7.73 (2H, d, J = 8.3 Hz, Ar**H**), 7.43-7.37 (1H, m, Ar**H**), 7.34-7.31 (2H, m, Ar**H**), 7.25-7.08 (3H, m, Ar**H**), 4.00 (2H, d, J = 5.3 Hz, C**H**$_2$), 2.28 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8 (d, $J_{C\text{-}F}$ = 249.6 Hz, C), 142.8 (C), 137.8 (C), 133.4 (CH), 130.8 (d, $J_{C\text{-}F}$ = 8.1 Hz, CH), 129.4 (2 × CH), 126.8 (2 × CH), 124.5 (d, $J_{C\text{-}F}$ = 3.5 Hz, CH), 115.6 (d, $J_{C\text{-}F}$ = 20.6 Hz, CH), 110.1 (d, $J_{C\text{-}F}$ = 15.4 Hz, C), 90.4 (d, $J_{C\text{-}F}$ = 3.2 Hz, C), 76.6 (C), 32.6 (CH_2), 20.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –110.1 (s); HRMS (ESI) Exact mass calculated for $[C_{16}H_{14}FNO_2SNa]^+$ $[M+Na]^+$: 326.0621, found 326.0620.



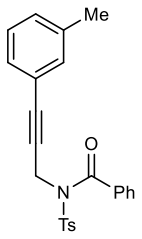
***N*-[3-(2-Fluorophenyl)prop-2-yn-1-yl]-*N*-tosylbenzamide (80c).** A solution of the *N*-tosyl propargyl amine **S80c** (500 mg, 1.65 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 79.2 mg, 3.30 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Benzoyl chloride (0.23 mL, 2.0 mmol) was added dropwise and the resulting solution was stirred at room temperature for 20 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (10% to 35% EtOAc/petroleum ether) to give the title compound **80c** as an orange solid (514 mg, 77%). R_f = 0.49 (40% EtOAc/petroleum ether); m.p. 100-101 °C (Et_2O); IR 1692 (C=O), 1492, 1350, 1314, 1245, 1185, 1162, 1072, 781, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (2H, d, J = 8.5 Hz, Ar**H**), 7.60-7.57 (2H, m, Ar**H**), 7.52-7.47 (1H, m, Ar**H**), 7.42-7.26 (6H, m, Ar**H**), 7.12-7.06 (2H, m, Ar**H**), 4.84 (2H, s, C**H**$_2$), 2.40 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C), 163.1 (d, $J_{C\text{-}F}$ = 252.0 Hz, C), 145.1 (C), 135.7 (C), 134.2 (C), 133.7 (CH), 131.9 (CH), 130.7 (d, $J_{C\text{-}F}$ = 8.1 Hz, CH), 129.5 (2 × CH), 129.1 (2 × CH), 128.5 (2 × CH), 127.9 (2 × CH), 124.1 (d, $J_{C\text{-}F}$ = 3.7 Hz, CH), 115.7 (d, $J_{C\text{-}F}$ = 20.64 Hz, CH), 110.8 (d, $J_{C\text{-}F}$ = 15.4 Hz, C), 89.2 (d, $J_{C\text{-}F}$ = 3.3 Hz, C), 78.6 (C), 38.8 (CH_2), 21.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –110.0 (s); HRMS (ESI) Exact mass calculated for $[C_{23}H_{18}FNO_3SNa]^+$ $[M+Na]^+$: 430.0884, found 430.0885.

Preparation of Substrate 80d





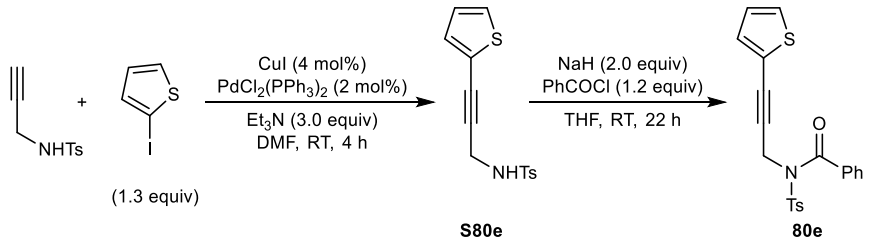
4-Methyl-*N*-[3-(3-methylphenyl)prop-2-yn-1-yl]benzenesulfonamide (S80d). To a stirred solution of $PdCl_2(PPh_3)_2$ (168 mg, 0.240 mmol) and CuI (91.4 mg, 0.480 mmol) in DMF (6 mL) was added freshly degassed Et_3N (1.3 mL, 9.3 mmol) and 3-iodotoluene (0.92 mL, 7.2 mmol) under a nitrogen atmosphere. A solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1.00 g, 4.78 mmol) in DMF (4 mL) was added and the resulting solution was stirred at 40 °C for 4.5 h. The reaction was quenched with 50% brine (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (20% EtOAc/petroleum ether) to give the title compound **S80d** as a white solid (861 mg, 60%). $R_f = 0.41$ (40% EtOAc/petroleum ether); m.p. 108-109 °C (Et_2O); IR 3275 (NH), 2923, 1597, 1484, 1431, 1324, 1153, 1090, 1057, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.77 (2H, m, Ar**H**), 7.31-7.27 (2H, m, Ar**H**), 7.17-7.04 (2H, m, Ar**H**), 7.01-6.86 (2H, m, Ar**H**), 4.64 (1H, t, $J = 6.2$ Hz, N**H**), 4.07 (2H, d, $J = 6.2$ Hz, C$\mathbf{H}_2$), 2.37 (3H, s, ArC$\mathbf{H}_3$), 2.29 (3H, s, ArC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 138.0 (C), 137.0 (C), 132.3 (CH), 129.8 (2 × CH), 129.6 (CH), 128.8 (CH), 128.2 (CH), 127.7 (2 × CH), 122.0 (C), 85.1 (C), 82.9 (C), 34.0 (CH_2), 21.6 (CH_3), 21.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{17}H_{17}NO_2SNa]^+$ $[M+Na]^+$: 322.0872, found 322.0875.

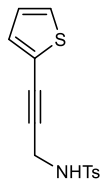


***N*-[3-(3-Methylphenyl)prop-2-yn-1-yl]-*N*-tosylbenzamide (80d).** A solution of the *N*-tosyl propargyl amine **S80d** (500 mg, 1.67 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 80.1 mg, 3.33 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Benzoyl chloride (0.23 mL, 2.0 mmol) was added dropwise and the resulting solution was stirred at room temperature for 20 h. The reaction was quenched with

brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (2% to 14% EtOAc/petroleum ether) to give the title compound **80d** as a yellow oil (655 mg, 97%). R_f = 0.46 (40% EtOAc/petroleum ether); IR 2921, 1687 (C=O), 1598, 1485, 1355, 1239, 1165, 1069, 948, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-7.98 (2H, m, Ar**H**), 7.60-7.57 (2H, m, Ar**H**), 7.53-7.48 (1H, m, Ar**H**), 7.43-7.38 (2H, m, Ar**H**), 7.29-7.26 (2H, m, Ar**H**), 7.22-7.11 (4H, m, Ar**H**), 4.80 (2H, s, C**H**$_2$), 2.41 (3H, s, ArC**H**$_3$), 2.33 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C), 145.0 (C), 138.2 (C), 135.9 (C), 134.3 (C), 132.4 (CH), 131.9 (CH), 129.8 (CH), 129.5 (2 × CH), 129.2 (2 × CH), 128.9 (CH), 128.6 (2 × CH), 128.4 (CH), 128.0 (2 × CH), 122.0 (C), 85.4 (C), 83.5 (C), 39.0 (CH_2), 21.8 (CH_3), 21.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{21}NO_3SNa]^+$ $[M+Na]^+$: 426.1134, found 426.1149.

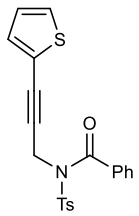
Preparation of Substrate 80e





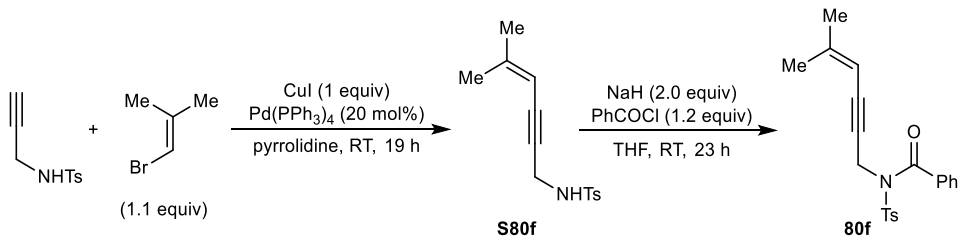
4-Methyl-*N*-[3-(2-thienyl)prop-2-yn-1-yl]benzenesulfonamide (S80e). To a stirred solution of $PdCl_2(PPh_3)_2$ (67.4 mg, 0.096 mmol), CuI (36.6 mg, 0.192 mmol) and *N*-tosyl propargyl amine (1.00 g, 4.80 mmol) in THF (0.2 M) was added degassed Et_3N (2.0 mL, 14 mmol) and 2-iodothiophene (0.69 mL, 6.2 mmol) under a nitrogen atmosphere and the resulting solution was stirred at room temperature for 4 h. The reaction was filtered through celite and concentrated in *vacuo*. The residue was purified by column chromatography (30% EtOAc/petroleum ether) to give the title compound **S80e** as a brown solid (860 mg, 62%). R_f = 0.59 (40% EtOAc/petroleum ether); m.p. 137-138 °C (Et_2O); IR 3268 (NH), 1596, 1492, 1417, 1337, 1319, 1156, 1038, 813, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.77 (2H, m, Ar**H**), 7.31-7.27 (2H, m, Ar**H**), 7.21 (1H, dd, *J* = 5.1, 1.2 Hz, Ar**H**), 6.97 (1H, dd, *J* = 3.6, 1.2 Hz, Ar**H**), 6.91 (1H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 4.68 (1H, t, *J* = 6.2 Hz, N**H**), 4.09 (2H, d, *J* = 6.2 Hz, C**H**$_2$), 2.38 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

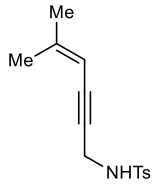
δ 144.0 (C), 136.8 (C), 132.5 (CH), 129.9 (2 × CH), 127.59 (2 × CH), 127.57 (CH), 127.0 (CH), 122.1 (C), 87.2 (C), 78.2 (C), 34.1 (CH_2), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{13}NO_2S_2Na]^+$ $[M+Na]^+$: 314.0280, found 314.0278.



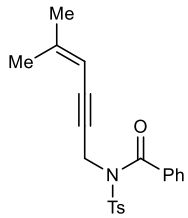
***N*-[3-(2-Thienyl)prop-2-yn-1-yl]-*N*-tosylbenzamide (80e).** A solution of the *N*-tosyl propargyl amine **S80e** (500 mg, 1.72 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 82.5 mg, 3.44 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Benzoyl chloride (0.24 mL, 2.1 mmol) was added dropwise and the resulting solution was stirred at room temperature for 22 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (5% to 30% EtOAc/petroleum ether) to give the title compound **80e** as a yellow solid (482 mg, 70%). R_f = 0.42 (40% EtOAc/petroleum ether); m.p. 103-104 °C (Et_2O); IR 3090, 2924, 2229 (C≡C), 1688 (C=O), 1595, 1352, 1312, 1243, 1159, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.94 (2H, m, Ar**H**), 7.57-7.49 (3H, m, Ar**H**), 7.43-7.38 (2H, m, Ar**H**), 7.30-7.27 (3H, m, Ar**H**), 7.14 (1H, dd, *J* = 3.6, 1.2 Hz, Ar**H**), 6.98 (1H, dd, *J* = 5.2, 3.6 Hz, Ar**H**), 4.82 (2H, s, C**H**$_2$), 2.42 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C), 145.2 (C), 135.8 (C), 134.3 (C), 132.9 (CH), 131.9 (CH), 129.6 (2 × CH), 129.1 (2 × CH), 128.6 (2 × CH), 128.0 (2 × CH), 127.8 (CH), 127.1 (CH), 122.1 (C), 87.8 (C), 78.5 (C), 39.0 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{17}NO_3S_2Na]^+$ $[M+Na]^+$: 418.0542, found 418.0541.

Preparation of Substrate 80f





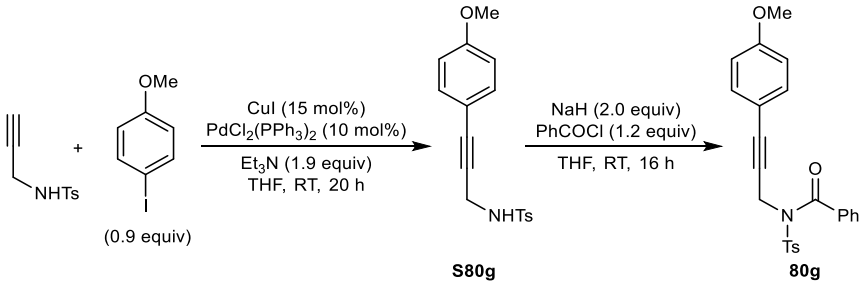
4-Methyl-*N*-(5-methylhex-4-en-2-yn-1-yl)benzenesulfonamide (S80f). $Pd(PPh_3)_4$ (1.11 g, 0.96 mmol) and CuI (914 mg, 4.80 mmol) were added to a flask which was sealed and purged with N_2. Degassed pyrrolidine (24 mL) was added and the resulting solution was purged with N_2 for 10 min. *N*-Tosyl propargyl amine (1.00 g, 4.80 mmol) and 1-bromo-2-methyl-1-propene (0.54 mL, 5.3 mmol) were added, and the mixture was stirred at room temperature for 19 h. The reaction was quenched with distilled water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (1% to 17% EtOAc/petroleum ether) to give the title compound **S80f** as a dark brown solid (277 mg, 22%). R_f = 0.46 (40% EtOAc/petroleum ether); m.p. 63-65 °C (Et_2O); IR 3280 (NH), 2920, 1597, 1432, 1323, 1153, 1090, 1036, 812, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.72 (2H, m, Ar**H**), 7.34-7.28 (2H, m, Ar**H**), 5.01-4.99 (1H, m, $(CH_3)_2C$=C**H**), 4.93 (1H, br s, N**H**), 3.95 (2H, d, *J* = 2.1 Hz, NC$\mathbf{H}_2$), 2.39 (3H, s, ArC$\mathbf{H}_3$), 1.72 (3H, s, =C(C$\mathbf{H}_3$)$_2$), 1.68 (3H, s, =C(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6 (C), 143.6 (C), 136.8 (C), 129.7 (2 × CH), 127.5 (2 × CH), 104.2 (CH), 85.1 (C), 82.8 (C), 34.0 (CH_2), 24.8 (CH_3), 21.6 (CH_3), 20.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{17}NO_2SNa]^+$ $[M+Na]^+$: 286.0872, found 286.0872.

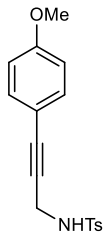


***N*-(5-Methylhex-4-en-2-yn-1-yl)-*N*-tosylbenzamide (80f).** A solution of the *N*-tosyl propargyl amine **S80f** (200 mg, 0.759 mmol) in THF (3 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 36.5 mg, 1.52 mmol) in THF (4 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Benzoyl chloride (0.11 mL, 0.95 mmol) was added dropwise and the resulting solution was stirred at room temperature for 23 h. The reaction was quenched with brine (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (5% to 20% EtOAc/petroleum ether) to give the title compound **80f** as a pale yellow solid (156 mg, 56%). R_f = 0.33 (30% EtOAc/petroleum ether); m.p. 90-91 °C (Et_2O); IR 2933, 1695 (C=O), 1438, 1352, 1292, 1238, 1165, 1064, 811, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.93 (2H, m, Ar**H**), 7.57-7.55 (2H, m, Ar**H**), 7.51-7.47 (1H, m, Ar**H**),

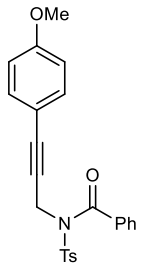
7.40-7.36 (2H, m, Ar**H**), 7.31-7.27 (2H, m, Ar**H**), 5.22-5.19 (1H, m, $(CH_3)_2C$=C**H**), 4.72 (2H, d, *J* = 2.1 Hz, C**H**$_2$), 2.43 (3H, s, ArC**H**$_3$), 1.81 (3H, s, =C(C**H**$_3$)$_2$), 1.80 (3H, s, =C(C**H**$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C), 150.5 (C), 144.9 (C), 136.0 (C), 134.3 (C), 131.8 (CH), 129.4 (2 × CH), 129.2 (2 × CH), 128.5 (2 × CH), 128.0 (2 × CH), 104.4 (CH), 85.6 (C), 83.3(C), 39.2 (CH_2), 25.0 (CH_3), 21.8 (CH_3), 21.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{21}NO_3SNa]^+$ [M+Na]$^+$: 368.1315, found 368.1316.

Preparation of Substrate 80g



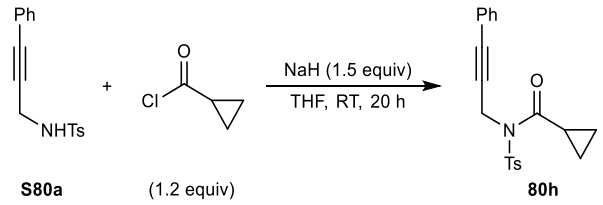


***N*-[3-(4-Chlorophenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (S80g).**[43] To a stirred solution of $PdCl_2(PPh_3)_2$ (562 mg, 0.801 mmol) and CuI (228 mg, 1.20 mmol) in THF (6 mL) was added freshly degassed Et_3N (2.4 mL, 17 mmol) and iodobenzene (1.79 g, 7.65 mmol) under a nitrogen atmosphere. A solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1.85 g, 8.84 mmol) in THF (3.5 mL) was added and the resulting solution was stirred at room temperature for 20 h. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (5% to 20% EtOAc/petroleum ether) to give the title compound **S80g** as a pale brown solid (1.67 g, 72%). The analytical data were consistent with those reported previously.[43] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.70 (2H, m, Ar**H**), 7.31-7.27 (2H, m, Ar**H**), 7.17-7.03 (2H, m, Ar**H**), 6.88-6.66 (2H, m, Ar**H**), 4.56 (1H, t, *J* = 6.2 Hz, N**H**), 4.06 (2H, d, *J* = 6.2 Hz, C**H**$_2$), 3.79 (3H, s, C**H**$_3$), 2.38 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (C), 143.8 (C), 137.0 (C), 133.2 (2 × CH), 129.8 (2 × CH), 127.6 (2 × CH), 114.2 (C), 113.9 (2 × CH), 84.8 (C), 81.9 (C), 55.4 (CH_3), 34.1 (CH_2), 21.7 (CH_3).



***N*-[3-(4-Methoxyphenyl)prop-2-yn-1-yl]-*N*-tosylbenzamide (80g).** NaH (60% dispersion in mineral oil, 75.8 mg, 3.16 mmol) was added portionwise to a solution of the *N*-tosyl propargyl amine **S80g** (500 mg, 1.59 mmol) in THF (15 mL). The resulting solution was stirred for 1 h. The mixture was cooled to 0 °C, and benzoyl chloride (0.22 mL, 1.9 mmol) was added dropwise. The resulting solution was gradually warmed to room temperature and stirred for 16 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (20% EtOAc/petroleum ether) to give the title compound **80g** as a pale yellow solid (345 mg, 52%). R_f = 0.41 (40% EtOAc/petroleum ether); m.p. 122-123 °C (Et_2O); IR 2919, 2839, 2213 (C≡C), 1683 (C=O), 1604, 1509, 1363, 1295, 1183, 572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05-7.93 (2H, m, Ar**H**), 7.62-7.54 (2H, m, Ar**H**), 7.53-7.47 (1H, m, Ar**H**), 7.43-7.36 (2H, m, Ar**H**), 7.29-7.26 (2H, m, Ar**H**), 7.26-7.23 (2H, m, Ar**H**), 6.88-6.79 (2H, m, Ar**H**), 4.79 (2H, s, C$\mathbf{H}_2$), 3.82 (3H, s, OC$\mathbf{H}_3$), 2.40 (3H, s, ArC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C), 160.1 (C), 145.0 (C), 135.9 (C), 134.3 (C), 133.3 (2 × CH), 131.8 (CH), 129.4 (2 × CH), 129.2 (2 × CH), 128.5 (2 × CH), 128.0 (2 × CH), 114.2 (C), 114.1 (2 × CH), 85.1 (C), 82.5 (C), 55.5 (CH_3), 39.1 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{21}NO_4SNa]^+$ $[M+Na]^+$: 442.1083, found 442.1083.

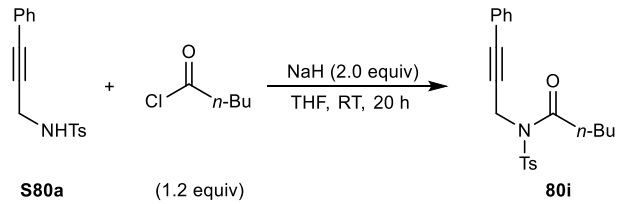
***N*-(3-Phenylprop-2-yn-1-yl)-*N*-tosylpentanamide (80h)**



A solution of the *N*-tosyl propargyl amine **S80a** (500 mg, 1.75 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 140 mg, 3.50 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Cyclopropanecarbonyl chloride (0.19 mL, 2.1 mmol) was added dropwise and the resulting solution was stirred at room temperature for 17 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$),

filtered and concentrated in *vacuo*. The residue was purified by column chromatography (15% EtOAc/petroleum ether) to give the title compound **80h** as a pale yellow solid (539 mg, 87%). R_f = 0.50 (40% EtOAc/petroleum ether); m.p. 106-108 °C (Et_2O); IR 2919, 2242 (C≡C), 1683 (C=O), 1596, 1490, 1355, 1156, 1043, 711, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04-7.89 (2H, m, Ar**H**), 7.40-7.26 (7H, m, Ar**H**), 4.97 (2H, s, C**H**$_2$), 2.41 (3H, s, ArC**H**$_3$), 2.35 (1H, tt, *J* = 7.8, 4.6 Hz, C**H**C=O), 1.08-0.99 (2H, m, cyclopropyl**H**), 0.89-0.79 (2H, m, cyclopropyl**H**).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C), 144.9 (C), 136.8 (C), 131.8 (2 × CH), 129.7 (2 × CH), 128.7 (CH), 128.4 (2 × CH), 128.1 (2 × CH), 122.4 (C), 84.3 (C), 84.1 (C), 36.4 (CH_2), 21.7 (CH_3), 14.4 (CH), 10.6 (2 × CH_2); HRMS (ESI) Exact mass calculated for $[C_{20}H_{19}NO_3SNa]^+$ $[M+Na]^+$: 376.0978, found 376.0979.

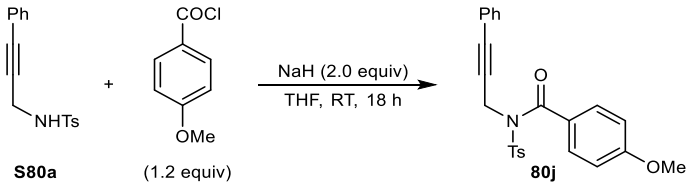
_N_-(3-Phenylprop-2-yn-1-yl)-_N_-tosylpentanamide (80i)



A solution of the *N*-tosyl propargyl amine **S80a** (500 mg, 1.75 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 84.0 mg, 3.50 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Valeroyl chloride (0.25 mL, 2.1 mmol) was added dropwise and the resulting solution was stirred at room temperature for 20 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (2% to 14% EtOAc/petroleum ether) to give the title compound **80i** as a yellow solid (420 mg, 65%). R_f = 0.51 (40% EtOAc/petroleum ether); m.p. 53-54 °C (Et_2O); IR 2934, 2875, 1703 (C=O), 1343, 1173, 1147, 1087, 1052, 860, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05-7.87 (2H, m, Ar**H**), 7.40-7.27 (7H, m, Ar**H**), 4.91 (2H, s, C**H**$_2$), 2.66-2.61 (2H, m, C**H**$_2$), 2.41 (3H, s, ArC**H**$_3$), 1.65-1.50 (2H, m, C**H**$_2$), 1.37-1.16 (2H, m, C**H**$_2$), 0.84 (3H, t, *J* = 7.4 Hz, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C), 145.0 (C), 136.6 (C), 131.8 (2 × CH), 129.7 (2 × CH), 128.8 (CH), 128.4 (2 × CH),

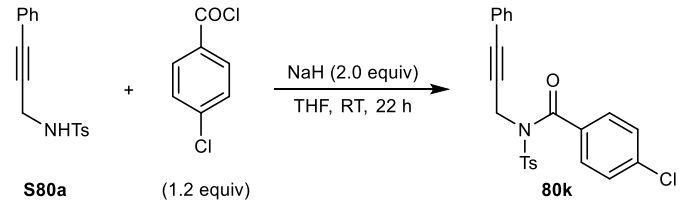
128.3 (2 × CH), 122.3 (C), 84.4 (C), 84.0 (C), 36.3 (CH_2), 35.8 (CH_2), 26.5 (CH_2), 22.2 (CH_2), 21.7 (CH_3), 13.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{23}NO_3SNa]^+$ $[M+Na]^+$: 392.1291, measured 392.1302.

4-Methoxy-*N*-(3-phenylprop-2-yn-1-yl)-*N*-tosylbenzamide (80j)



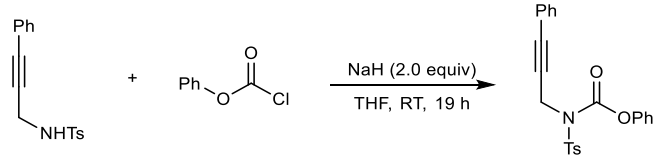
A solution of the *N*-tosyl propargyl amine **S80a** (500 mg, 1.75 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 84.0 mg, 3.50 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. 4-Methoxybenzoyl chloride (0.28 mL, 2.1 mmol) was added dropwise and the resulting solution was stirred at room temperature for 18 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (20% EtOAc/petroleum ether) to give the title compound **80j** as a white solid (415 mg, 56%). R_f = 0.59 (40% EtOAc/petroleum ether); m.p. 94-95 °C (Et_2O); IR 2928, 2835, 1789, 1682 (C=O), 1602, 1357, 1305, 1243, 1166, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03-7.93 (2H, m, Ar**H**), 7.70-7.62 (2H, m, Ar**H**), 7.36-7.25 (7H, m, Ar**H**), 6.94-6.87 (2H, m, Ar**H**), 4.79 (2H, s, C**H**$_2$), 3.85 (3H, s, OC**H**$_3$), 2.39 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C), 162.9 (C), 144.9 (C), 136.0 (C), 131.8 (2 × CH), 130.9 (2 × CH), 129.5 (2 × CH), 129.1 (2 × CH), 128.8 (CH), 128.4 (2 × CH), 126.2 (C), 122.2 (C), 113.9 (2 × CH), 85.1 (C), 83.8 (C), 55.6 (CH_3), 39.3 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{22}NO_4SNa]^+$ $[M+Na]^+$: 442.1083, found 442.1075.

4-Chloro-*N*-(3-phenylprop-2-yn-1-yl)-*N*-tosylbenzamide (80k)



A solution of the *N*-tosyl propargyl amine **S80a** (500 mg, 1.75 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 84.0 mg, 3.50 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. 4-Chlorobenzoyl chloride (0.27 mL, 2.1 mmol) was added dropwise and the resulting solution was stirred at room temperature for 22 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (10% EtOAc/petroleum ether) to give the title compound **80k** as a pale yellow solid (482 mg, 70%). R_f = 0.61 (40% EtOAc/petroleum ether); m.p. 110-111 °C (Et_2O); IR 2917, 1787, 1698 (C=O), 1590, 1488, 1422, 1365, 1312, 1235, 940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.92 (2H, m, Ar**H**), 7.55-7.52 (2H, m, Ar**H**), 7.40-7.27 (9H, m, Ar**H**), 4.78 (2H, s, C**H**$_2$), 2.41 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (C), 145.3 (C), 138.3 (C), 135.7 (C), 132.8 (C), 131.8 (2 × CH), 129.62 (2 × CH), 129.60 (2 × CH), 129.1 (2 × CH), 129.0 (CH), 128.9 (2 × CH), 128.5 (2 × CH), 122.1 (C), 85.3 (C), 83.6 (C), 38.8 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{18}ClNO_3SNa]^+$ $[M+Na]^+$: 446.0588, found 446.0604.

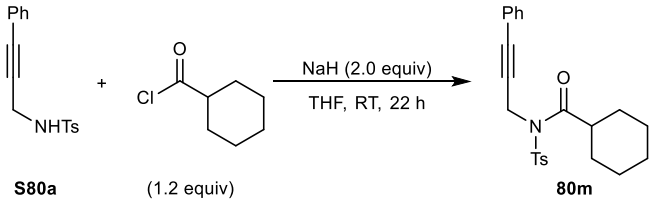
Phenyl (3-phenylprop-2-yn-1-yl)(tosyl)carbamate (80l)



A solution of *N*-tosyl propargyl amine **S80a** (500 mg, 1.75 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 84.0 mg, 3.50 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Phenyl chloroformate (0.26 mL, 2.1 mmol) was added dropwise and the resulting solution was stirred at room temperature for 19 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (20% EtOAc/petroleum ether) to give the title compound **80l** as an off white solid (643 g, 91%). R_f = 0.50 (40% EtOAc/petroleum ether); IR 3262, 3073, 2974, 1757, 1591,

1490, 1360, 1319, 1168, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12-7.97 (2H, m, Ar**H**), 7.47-7.38 (2H, m, Ar**H**), 7.38-7.26 (7H, m, Ar**H**), 7.24-7.19 (1H, m, Ar**H**), 7.06-6.94 (2H, m, Ar**H**), 5.03 (2H, s, C**H**$_2$), 2.42 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5 (C), 150.1 (C), 145.2 (C), 135.9 (C), 131.9 (2 × CH), 129.6 (2 × CH), 129.5 (2 × CH), 129.0 (2 × CH), 128.8 (CH), 128.5 (2 × CH), 126.5 (CH), 122.3 (2 × CH), 121.4 (C), 84.6 (C), 83.8 (C), 37.5 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{19}NO_4SNa]^+$ $[M+Na]^+$: 428.0927, found: 428.0919.

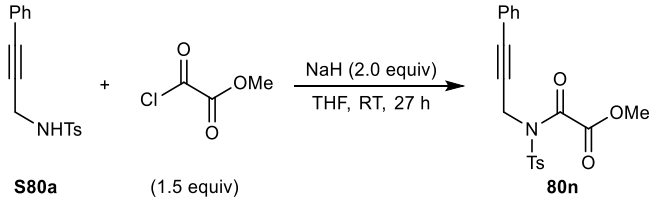
***N*-(3-Phenylprop-2-yn-1-yl)-*N*-tosylcyclohexanecarboxamide (80m)**



A solution of the *N*-tosyl propargyl amine **S80a** (500 mg, 1.75 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 84.0 mg, 3.50 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Cyclohexanecarbonyl chloride (0.28 mL, 2.1 mmol) was added dropwise and the resulting solution was stirred at room temperature for 22 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (10% EtOAc/petroleum ether) to give the title compound **80m** as a yellow solid (692 mg, >99%). R_f = 0.57 (40% EtOAc/petroleum ether); m.p. 94-95 °C (Et_2O); IR 2935, 1697 (C=O), 1596, 1511, 1353, 1294, 1163, 1134, 1085, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03-7.90 (2H, m, Ar**H**), 7.39-7.27 (7H, m, Ar**H**), 4.92 (2H, s, C**H**$_2$), 2.91 (1H, tt, *J* = 11.4, 3.3 Hz, C**H**C=O) 2.41 (3H, s, ArC**H**$_3$), 1.78-1.67 (2H, m, cyclohexyl**H**), 1.67-1.58 (3H, m, cyclohexyl**H**), 1.46-1.32 (2H, m, cyclohexyl**H**), 1.23-1.09 (3H, m, cyclohexyl**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1 (C), 144.9 (C), 137.0 (C), 131.8 (2 × CH), 129.7 (2 × CH), 128.8 (CH), 128.5 (2 ×

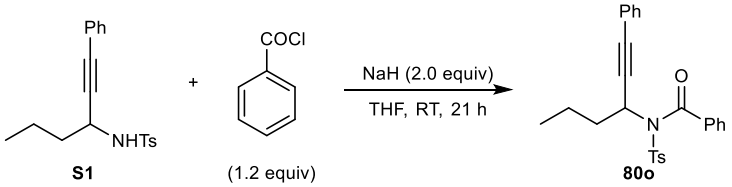
CH), 128.1 (2 × CH), 122.4 (C), 84.4 (C), 84.3 (C), 44.2 (CH), 36.1 (CH_2), 29.4 (2 × CH_2), 25.63 (CH_2), 25.60 (2 × CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{25}NO_3SNa]^+$ $[M+Na]^+$: 418.1444, found 418.1447.

Methyl 2-{[4-methyl-*N*-(3-phenylprop-2-yn-1-yl)phenyl]sulfonamido}-2-oxoacetate (80n)



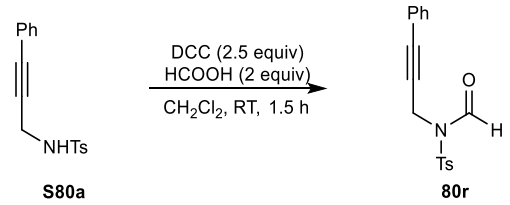
A solution of the *N*-tosyl propargyl amine **S80a** (500 mg, 1.75 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 84.0 mg, 3.50 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Methyl oxalyl chloride (0.24 mL, 2.6 mmol) was added dropwise and the resulting solution was stirred at room temperature for 27 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (3% to 10% EtOAc/petroleum ether) to give the title compound **80n** as a pale yellow solid (440 mg, 68%). R_f = 0.45 (40% EtOAc/petroleum ether); m.p. 101-103 °C (Et_2O); IR 2958, 1758, 1682 (C=O), 1373, 1325, 1155, 866, 803, 669, 583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08-7.92 (2H, m, Ar**H**), 7.34-7.26 (3H, m, Ar**H**), 7.26-7.20 (2H, m, Ar**H**), 7.16-7.04 (2H, m, Ar**H**), 4.72 (2H, s, C**H**$_2$), 3.98 (3H, s, OC**H**$_3$), 2.35 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8 (C), 160.3 (C), 146.2 (C), 134.7 (C), 131.8 (2 × CH), 130.1 (2 × CH), 128.8 (2 × CH), 128.7 (CH), 128.2 (2 × CH), 122.0 (C), 84.7 (C), 81.3 (C), 53.5 (CH_3), 34.8 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{17}NO_5SNa]^+$ $[M+Na]^+$: 394.0720, found 394.0715.

***N*-(1-Phenylhex-1-yn-3-yl)-*N*-tosylbenzamide (80o)**



A solution of *N*-tosyl propargyl amine **S1** (380 mg, 1.16 mmol) in THF (6 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 55.7 mg, 2.32 mmol) in THF (6 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Benzoyl chloride (0.16 mL, 1.4 mmol) was added dropwise and the resulting solution was stirred at room temperature for 21 h. The reaction was quenched with brine (15 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (5% to 20% EtOAc/petroleum ether) to give the title compound **80o** as a clear oil (435 g, 87%). R_f = 0.53 (40% EtOAc/petroleum ether); IR 2960, 1685, 1597, 1353, 1264, 1164, 1085, 1020, 812, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.78 (2H, m, Ar**H**), 7.59-7.52 (2H, m, Ar**H**), 7.52-7.46 (1H, m, Ar**H**), 7.41-7.34 (4H, m, Ar**H**), 7.34-7.27 (3H, m, Ar**H**), 7.23 (2H, d, *J* = 8.2 Hz, Ar**H**), 5.10 (1H, t, *J* = 7.7 Hz, C**H**), 2.37 (3H, s, C$\mathbf{H}_3$), 2.26-2.10 (2H, m, C$\mathbf{H}_2$), 1.59-1.43 (2H, m, C$\mathbf{H}_2$), 0.94 (3H, t, *J* = 7.4 Hz, C$\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C), 144.8 (C), 136.5 (C), 135.5 (C), 131.9 (CH), 131.9 (2 × CH), 129.5 (2 × CH), 128.9 (2 × CH), 128.5 (CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 122.8 (C), 87.0 (C), 84.8 (C), 52.7 (CH), 37.3 (CH_2), 21.7 (CH_3), 20.2 (CH_2), 13.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{25}NO_3SNa]^+$ $[M+Na]^+$: 454.1447, found 454.1443.

***N*-(3-Phenylprop-2-yn-1-yl)-*N*-tosylformamide (80r)**.

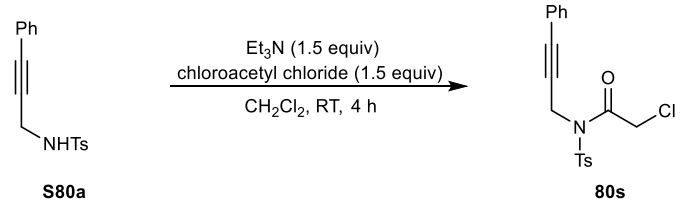


S80a **80r**

To a solution of *N*-tosyl propargyl amine **S80a** (500 mg, 1.75 mmol) in CH_2Cl_2 (1.75 mL) was added formic acid (0.13 mL, 3.5 mmol) followed by DCC (904 mg, 4.38 mmol) and the resulting mixture was stirred for 1 h 30 min. The reaction was diluted with CH_2Cl_2 (10 mL), filtered over celite and concentrated in *vacuo*. The residue was purified by column chromatography (10 to 20% EtOAc/petroleum ether) to give the title compound **80r** as a brown solid (511 mg, 93%). R_f= 0.36 (40% EtOAc/petroleum ether); IR 3267, 1703, 1595, 1488, 1360, 1157, 1087, 1056, 898, 666 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) δ 9.11 (1H, s, C**H**O), 7.90-7.70 (2H, m, Ar**H**), 7.32-7.18 (5H, m, Ar**H**), 7.09-7.01 (2H, m, Ar**H**), 4.62 (2H, s, C**H**$_2$), 2.32 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4 (CHO), 145.8 (C), 135.3 (C), 131.7 (2 × CH), 130.2 (2 × CH), 128.6 (CH), 128.2 (2 × CH), 128.0 (2 × CH), 122.0 (C), 84.2 (C), 81.6 (C), 32.1 (CH_2), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{17}H_{15}NO_3SNa]^+$ $[M+Na]^+$: 336.0665, found: 336.0665.

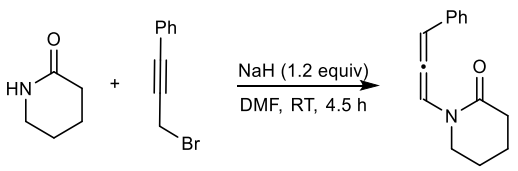
2-Chloro-*N*-(3-phenylprop-2-yn-1-yl)-*N*-tosylacetamide (80s)



S80a **80s**

To an ice-cooled suspension of *N*-tosyl propargyl amine **S80a** (500 mg, 1.75 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.37 mL, 2.6 mmol) and the resulting mixture was stirred for 15 min. A solution of chloroacetyl chloride (0.21 mL, 2.6 mmol) in CH_2Cl_2 (5 mL) was added and the resulting solution was warmed to room temperature and stirred for 3 h. The reaction was quenched with water (20 mL) and extracted with DCM (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (30% EtOAc/petroleum ether) to give the title compound **80s** as an off white solid (353 mg, 56%). R_f = 0.51 (40% EtOAc/petroleum ether); IR 3056, 1718, 1598, 1490, 1355, 1155, 1087, 1058, 921, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.87 (2H, m, Ar**H**), 7.43-7.26 (7H, m, Ar**H**), 4.89 (2H, s, C**H**$_2$), 4.55 (2H, s, C**H**$_2$), 2.41 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (C), 145.9 (C), 135.5 (C), 131.9 (2 × CH), 130.1 (2 × CH), 128.9 (CH), 128.41 (2 × CH), 128.38 (2 × CH), 122.0 (C), 84.9 (C), 82.8 (C), 44.1 (CH_2), 37.0 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{16}ClNO_3SNa]^+$ $[M+Na]^+$: 384.0432, found: 384.0431.

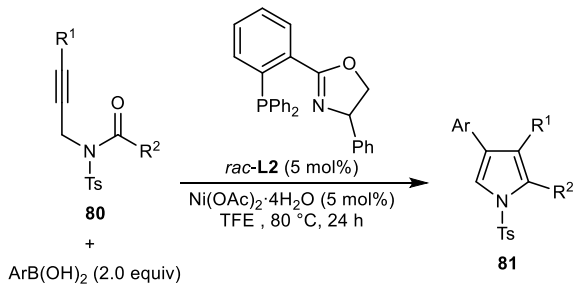
1-(3-Phenylpropa-1,2-dien-1-yl)piperidin-2-one (80t).



(1.1 equiv) **80t**

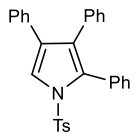
A solution of the δ-valerolactam (297 mg, 3.00 mmol) in DMF (3 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 86.4 mg, 3.60 mmol) in THF (4 mL) and the resulting solution was stirred for 30 min. Propargyl bromide (0.22 mL, 3.3 mmol) was added dropwise and the resulting solution was stirred at room temperature for 4 h. The reaction was quenched with water (15 mL) and extracted with EtOAc (5 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (60% EtOAc/petroleum ether) to give the title compound **80t** as a brown oil (273 mg, 43%). R_f = 0.25 (40% EtOAc/petroleum ether); IR 2948, 1634, 1482, 1434, 1412, 1346, 1329, 1292, 1229, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (1H, d, *J* = 6.2 Hz, C**H**), 7.40-7.31 (4H, m, Ar**H**), 7.28-7.23 (1H, m, Ar**H**), 6.77 (1H, d, *J* = 6.2 Hz, C**H**), 3.48-3.19 (2H, m, C$\mathbf{H}_2$), 2.59-2.45 (2H, m, C$\mathbf{H}_2$), 1.93-1.76 (4H, m, 2 × C$\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ197.7 (C), 168.4(C), 134.5(C), 128.8 (2 × CH), 127.9 (CH), 127.2 (2 × CH), 105.6 (CH), 102.4 (CH), 46.3 (CH_2), 32.9 (CH_2), 22.7 (CH_2), 21.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{14}H_{15}NONa]^+$ $[M+Na]^+$: 236.1046, found 236.1047.

3.4 Nickel-Catalysed Synthesis of Pyrroles: General Procedure A

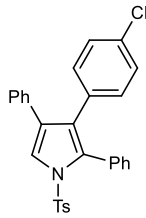


An oven-dried microwave vial fitted with a stirrer bar was charged with the appropriate substrate **80** (0.30 mmol), arylboronic acid (0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (3.7 mg, 0.015 mmol) and *rac*-**L2** (6.1 mg, 0.015 mmol). The vial was capped with a crimp cap PTFE seal and evacuated and back filled with argon (3 cycles). TFE (3 mL) which had been freshly degassed (using a stream of argon for 20 min) was added, the septum was sealed with PTFE tape, and the contents were stirred at room temperature for 10 min and then at 80 °C for 24 h. The reaction was cooled to room temperature, quenched with 50% brine (10 mL) and extracted with EtOAc (5 × 10 mL). (Extraction of the aqueous layer 5 times using EtOAc is essential for high yields.) The combined organic layers were dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue

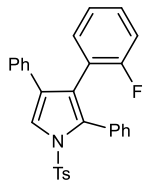
was purified by column chromatography using EtOAc/petroleum ether to give the pyrrole **81**.



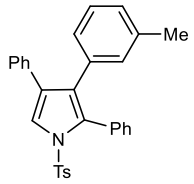
2,3,4-Triphenyl-1-tosyl-1*H*-pyrrole (81aa).[44] The title compound was prepared according to General Procedure A, using propargyl amide **80a** (117 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (125 mg, 93%). R_f = 0.57 (40% EtOAc/petroleum ether); m.p. 193-194 °C (Et_2O); IR 3138, 3059, 2922, 1597, 1365, 1192, 1168, 1101, 1071, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (1H, s, Ar**H**), 7.32-7.28 (2H, m, Ar**H**), 7.26-7.19 (4H, m, Ar**H**), 7.19-7.11 (6H, m, Ar**H**), 7.09-6.99 (5H, m, Ar**H**), 6.90-6.83 (2H, m, Ar**H**), 2.38 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 135.9 (C), 133.9 (C), 133.5 (C), 132.8 (2 × CH), 132.3 (C), 130.6 (2 × CH), 130.3 (C), 129.6 (2 × CH), 128.6 (2 × CH), 128.4 (3 × CH), 127.84 (C), 127.79 (2 × CH), 127.7 (2 × CH), 127.3 (2 × CH), 127.1 (C), 126.8 (CH), 126.5 (CH), 120.0 (CH), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{29}H_{23}NO_2SNa]^+$ $[M+Na]^+$: 472.1374, found: 472.1335. These data are consistent with those reported previously.[44]



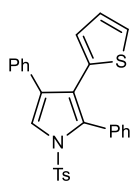
3-(4-Chlorophenyl)-2,4-diphenyl-1-tosyl-1*H*-pyrrole (81ba). The title compound was prepared according to General Procedure A, using propargyl amide **80b** (127 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (15% EtOAc/petroleum ether) to give a white solid (134 mg, 92%). R_f = 0.56 (40% EtOAc/petroleum ether); m.p. 194-196 °C (Et_2O); IR 2921, 1595, 1534, 1488, 1361, 1167, 1088, 1029, 592, 541 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, s, Ar**H**), 7.32-7.27 (3H, m, Ar**H**), 7.26-7.22 (3H, m, Ar**H**), 7.20-7.11 (6H, m, Ar**H**), 7.03-6.96 (4H, m, Ar**H**), 6.78 (2H, d, J = 8.5 Hz, Ar**H**), 2.38 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 135.7 (C), 133.5 (C), 132.7 (2 × CH), 132.4 (C), 132.3 (C), 132.0 (C), 131.8 (2 × CH), 130.0 (C), 129.6 (2 × CH), 128.58 (2 × CH), 128.55 (CH), 128.5 (2 × CH), 128.1 (2 × CH), 127.7 (2 × CH), 127.5 (2 × CH), 127.0 (CH), 126.8 (C), 126.5 (C), 120.1 (CH), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{29}H_{22}ClNO_2SNa]^+$ $[M+Na]^+$: 506.0952, found 506.0952.



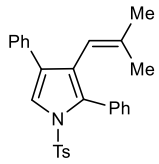
3-(2-Fluorophenyl)-2,4-diphenyl-1-tosyl-1*H*-pyrrole (81ca). The title compound was prepared according to General Procedure A, using propargyl amide **80c** (122 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (15% EtOAc/petroleum ether) to give a pale yellow solid (133 mg, 95%). R_f = 0.59 (40% EtOAc/petroleum ether); m.p. 152-153 °C (Et_2O); IR 3034, 1597, 1488, 1445, 1365, 1191, 1167, 699, 670, 589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, s, Ar**H**), 7.32-7.27 (2H, m, Ar**H**), 7.25-7.06 (11H, m, Ar**H**), 7.03 (2H, d, J = 7.1 Hz, Ar**H**), 6.91 (1H, td, J = 7.4, 2.0 Hz, Ar**H**), 6.88-6.79 (2H, m, Ar**H**), 2.38 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6 (C), 159.2 (C), 145.0 (C), 135.7 (C), 133.8 (C), 133.5 (C), 132.8 (d, $J_{C\text{-}F}$ = 3.3 Hz, CH), 132.2 (2 × CH), 130.0 (C), 129.6 (2 × CH), 129.2 (d, $J_{C\text{-}F}$ = 8.0 Hz, CH), 128.4 (2 × CH), 127.60 (2 × CH), 127.56 (2 × CH), 127.5 (CH), 127.2 (2 × CH), 126.9 (CH), 123.7 (d, $J_{C\text{-}F}$ = 3.6 Hz, CH), 121.9 (C), 121.7 (d, $J_{C\text{-}F}$ = 16.1 Hz, C), 119.7 (CH), 115.4 (d, $J_{C\text{-}F}$ = 22.1 Hz, CH), 21.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –112.8 (s); HRMS (ESI) Exact mass calculated for $[C_{29}H_{22}FNO_2SNa]^+$ $[M+Na]^+$: 490.1247, found 490.1238.



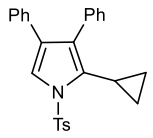
2,4-Diphenyl-3-(3-methylphenyl)-1-tosyl-1*H*-pyrrole (81da). The title compound was prepared according to General Procedure A, using propargyl amide **80d** (121 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (20% EtOAc/ petroleum ether) to give a yellow solid (125 mg, 90%). R_f = 0.62 (40% EtOAc/petroleum ether); m.p. 153-155 °C (Et_2O); IR 2922, 1597, 1492, 1444, 1362, 1166, 1092, 776, 671, 591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (1H, s, Ar**H**), 7.32-7.28 (2H, m, Ar**H**), 7.26-7.10 (10H, m, Ar**H**), 7.04-6.99 (2H, m, Ar**H**), 6.95-6.83 (2H, m, Ar**H**), 6.68-6.63 (2H, m, Ar**H**), 2.38 (3H, s, C**H**$_3$), 2.06 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 137.1 (C), 135.9 (C), 133.9 (C), 133.3 (C), 132.7 (2 × CH), 132.2 (C), 131.3 (CH), 130.4 (C), 129.6 (2 × CH), 128.5 (2 × CH), 128.28 (3 × CH), 127.9 (C), 127.64 (3 × CH), 127.58 (CH), 127.23 (3 × CH), 127.1 (C), 126.8 (CH), 119.9 (CH), 21.7 (CH_3), 21.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{30}H_{25}NO_2SNa]^+$ $[M+Na]^+$: 486.1498, found 486.1477.



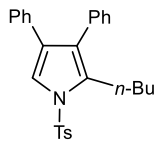
2,4-Diphenyl-3-(2-thienyl)-1-tosyl-1*H*-pyrrole (81ea). The title compound was prepared according to General Procedure A, using propargyl amide **80e** (119 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/petroleum ether) to give a white solid (62.7 mg, 46%). R_f = 0.56 (40% EtOAc/petroleum ether); m.p. 142-143 °C (Et_2O); IR 3071, 1728, 1595, 1446, 1165, 1094, 775, 693, 667, 591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar**H**), 7.37-7.26 (8H, m, Ar**H**), 7.25-7.19 (2H, m, Ar**H**), 7.22 -7.13 (2H, m, Ar**H**), 7.15-7.07 (2H, m, Ar**H**), 7.04 (1H, dd, *J* = 5.1, 1.2 Hz, Ar**H**), 6.74 (1H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 6.50 (1H, dd, *J* = 3.6, 1.2 Hz, Ar**H**), 2.42 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (C), 135.7 (C), 134.6 (C), 133.6 (C), 132.8 (2 × CH), 132.5 (C), 130.0 (C), 129.7 (2 × CH), 128.9 (2 × CH), 128.8 (CH), 128.4 (2 × CH), 127.79 (3 × CH), 127.4 (2 × CH), 127.21 (C), 127.18 (CH), 126.5 (CH), 125.4 (CH), 121.0 (C), 120.0 (CH), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{21}NO_2S_2Na]^+$ $[M+Na]^+$: 478.0906, found 478.0903.



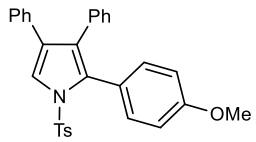
3-(2-Methylprop-1-en-1-yl)-2,4-diphenyl-1-tosyl-1*H*-pyrrole (81fa). The title compound was prepared according to General Procedure A, using propargyl amide **80f** (110 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/petroleum ether) to give a white solid (127 mg, 99%). R_f = 0.53 (40% EtOAc/petroleum ether); m.p. 153-154 °C (Et_2O); IR 3144, 3053, 2962, 2927, 1597, 1356, 1155, 695, 617, 592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, s, Ar**H**), 7.51-7.43 (2H, m, Ar**H**), 7.38-7.26 (5H, m, Ar**H**), 7.26-7.21 (3H, m, Ar**H**), 7.15-7.05 (4H, m, Ar**H**), 5.75-5.69 (1H, m, $(CH_3)_2C$=C**H**), 2.36 (3H, s, ArC**H**$_3$), 1.58 (3H, d, *J* = 1.4 Hz, =C(C**H**$_3$)$_2$), 1.07 (3H, d, *J* = 1.2 Hz, =C(C**H**$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 138.1 (C), 135.8 (C), 134.6 (C), 132.8 (C), 132.1 (2 × CH), 131.2 (C), 129.5 (2 × CH), 128.5 (2 × CH), 128.2 (C), 128.0 (CH), 127.8 (2 × CH), 127.4 (2 × CH), 127.3 (2 × CH), 126.8 (CH), 125.1 (C), 120.1 (CH), 116.1 (CH), 25.4 (CH_3), 21.7 (CH_3), 19.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{25}NO_2SNa]^+$ $[M+Na]^+$: 450.1498, found 450.1495.



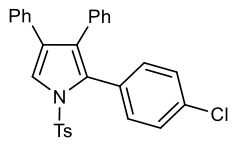
2-Cyclopropyl-3,4-diphenyl-1-tosyl-1*H*-pyrrole (81ha). The title compound was prepared according to General Procedure A, using propargyl amide **80h** (106 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (5% EtOAc/petroleum ether) to give a white solid (86.8 mg, 70%). R_f = 0.64 (40% EtOAc/petroleum ether); m.p. 107-108 °C (Et_2O); IR 3145, 3056, 2923, 1597, 1350, 1170, 746, 699, 670, 580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.78 (2H, m, Ar**H**), 7.50 (1H, d, *J* = 0.7 Hz, Ar**H**), 7.38-7.32 (2H, m, Ar**H**), 7.26-7.21 (3H, m, Ar**H**), 7.21-7.15 (3H, m, Ar**H**), 7.11-7.04 (4H, m, Ar**H**), 2.45 (3H, s, C**H**$_3$), 1.90-1.78 (1H, m, cyclopropyl**H**), 0.64-0.52 (2H, m, cyclopropyl**H**), 0.04-(–0.06) (2H, m, cyclopropyl**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 136.7 (C), 134.3 (C), 133.9 (C), 132.6 (C), 130.9 (2 × CH), 130.0 (2 × CH), 128.5 (2 × CH), 128.2 (2 × CH), 127.8 (2 × CH), 127.6 (2 × CH), 127.2 (C), 126.8 (CH), 126.6 (CH), 119.7 (CH), 21.8 (CH_3), 8.7 (2 × CH_2), 7.2 (CH) (one carbon signal merged with others); HRMS (ESI) Exact mass calculated for $[C_{26}H_{23}NO_2SNa]^+$ $[M+Na]^+$: 436.1342, found 436.1333.



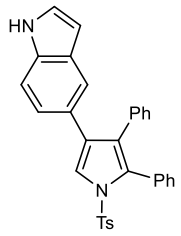
2-Butyl-3,4-diphenyl-1-tosyl-1*H*-pyrrole (81ia). The title compound was prepared according to General Procedure A, using propargyl amide **80i** (111 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (8% EtOAc/petroleum ether) to give a colorless oil (118 mg, 92%). R_f = 0.68 (40% EtOAc/petroleum ether); IR 3031, 2957, 2929, 2870, 1734, 1597, 1365, 1171, 669, 590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.72 (2H, m, Ar**H**), 7.48 (1H, s, Ar**H**), 7.34-7.30 (2H, m, Ar**H**), 7.30-7.22 (3H, m, Ar**H**), 7.20-7.14 (3H, m, Ar**H**), 7.12-7.06 (4H, m, Ar**H**), 2.71-2.62 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.42 (3H, s, ArC**H**$_3$), 1.47-1.35 (2H, m, C**H**$_2$CH$_2$CH$_3$), 1.22-1.10 (2H, m, C**H**$_2$CH$_3$), 0.74 (3H, t, *J* = 7.3 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 136.7 (C), 134.5 (C), 133.8 (C), 133.7 (C), 130.5 (2 × CH), 130.1 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.6 (C), 127.04 (C), 126.96 (CH), 126.9 (2 × CH), 126.6 (CH), 119.3 (CH), 33.1 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 21.7 (CH_3), 13.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{27}NO_2S]^+$ $[M+H]^+$: 430.1835, found 430.1828.



2-(4-Methoxyphenyl)-3,4-diphenyl-1-tosyl-1*H*-pyrrole (81ja). The title compound was prepared according to General Procedure A, using propargyl amide **80j** (126 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (10% to 15% EtOAc/petroleum ether) to give a white solid (112 mg, 78%). R_f = 0.49 (40% EtOAc/petroleum ether); m.p. 169-171 °C (Et_2O); IR 2922, 1603, 1490, 1363, 1293, 1249, 1166, 1096, 669, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar**H**), 7.34-7.29 (2H, m, Ar**H**), 7.25-7.19 (3H, m, Ar**H**), 7.18-7.12 (4H, m, Ar**H**), 7.08-7.01 (3H, m, Ar**H**), 6.96-6.90 (2H, m, Ar**H**), 6.90-6.83 (2H, m, Ar**H**), 6.72-6.66 (2H, m, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 2.38 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (C), 144.8 (C), 135.9 (C), 134.0 (C), 133.9 (2 × CH), 133.7 (C), 132.1 (C), 130.6 (2 × CH), 129.6 (2 × CH), 128.6 (2 × CH), 128.3 (2 × CH), 127.79 (C), 127.76 (2 × CH), 127.7 (2 × CH), 127.1 (C), 126.8 (CH), 126.4 (CH), 122.5 (C), 119.9 (CH), 112.8 (2 × CH), 55.3 (CH_3), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{30}H_{25}NO_3SNa]^+$ $[M+Na]^+$: 502.1447, found 502.1447.

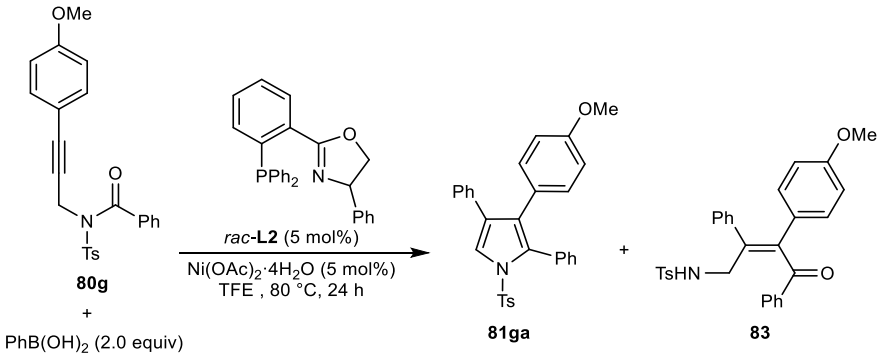


2-(4-Chlorophenyl)-3,4-diphenyl-1-tosyl-1*H*-pyrrole (81ka). The title compound was prepared according to General Procedure A, using propargyl amide **80k** (127 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (5% to 10% EtOAc/petroleum ether) to give a pale orange solid (135 mg, 93%). R_f = 0.69 (40% EtOAc/petroleum ether); m.p. 205-206 °C (Et_2O); IR 3136, 3064, 2922, 1597, 1490, 1365, 1169, 1092, 671, 594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (1H, s, Ar**H**), 7.36-7.30 (2H, m, Ar**H**), 7.25-7.19 (3H, m, Ar**H**), 7.19-7.12 (6H, m, Ar**H**), 7.10-7.01 (3H, m, Ar**H**), 6.98-6.92 (2H, m, Ar**H**), 6.87-6.81 (2H, m, Ar**H**), 2.39 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (C), 135.8 (C), 134.5 (C), 134.0 (2 × CH), 133.6 (C), 133.2 (C), 130.9 (C), 130.5 (2 × CH), 129.7 (2 × CH), 128.9 (C), 128.5 (2 × CH), 128.4 (2 × CH), 128.0 (2 × CH), 127.7 (2 × CH), 127.6 (2 × CH), 127.3 (C), 127.0 (CH), 126.8 (CH), 120.4 (CH), 21.8 (CH_3) (one carbon signal overlapped with others); HRMS (ESI) Exact mass calculated for $[C_{29}H_{22}ClNO_2SNa]^+$ $[M+Na]^+$: 506.0952, found 506.0955.



5-(4,5-Diphenyl-1-tosyl-1*H*-pyrrole-3-yl)-1*H*-indole (81aj). The title compound was prepared according to General Procedure A, using propargyl amide **80a** (117 mg, 0.30 mmol) and 5-indolylboronic acid (96.6 mg, 0.60 mmol), and purified by column chromatography (30% EtOAc/petroleum ether) to give a pale green solid (107 mg, 73%). R_f = 0.19 (30% EtOAc/petroleum ether); m.p. 213-214 °C (Et_2O); IR 3409 (NH), 1596, 1365, 1188, 1168, 1098, 1087, 1066, 701, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, br s, NH), 7.64 (1H, s, Ar**H**), 7.53-7.50 (1H, m, Ar**H**), 7.35-7.27 (3H, m, Ar**H**), 7.24-7.21 (1H, m, Ar**H**), 7.19-7.12 (5H, m, Ar**H**), 7.06-6.98 (5H, m, Ar**H**), 6.94 (1H, dd, *J* = 8.4, 1.7 Hz, Ar**H**), 6.90-6.86 (2H, m, Ar**H**), 6.50-6.46 (1H, m, Ar**H**) 2.38 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 136.0 (C), 135.0 (C), 133.8 (C), 132.8 (2 × CH), 132.1 (C), 130.7 (2 × CH), 129.6 (2 × CH), 128.5 (C), 128.2 (CH), 128.24 (C), 128.18 (C), 127.7 (2 × CH), 127.6 (2 × CH), 127.3 (2 × CH), 126.3 (CH), 125.6 (C), 124.6 (CH), 123.5 (CH), 120.7 (CH), 119.8 (CH), 110.8 (CH), 103.0 (CH), 21.8 (CH_3) (one carbon signal merged with another); HRMS (ESI) Exact mass calculated for $[C_{31}H_{24}N_2O_2SNa]^+$ $[M+Na]^+$: 511.1451, found: 511.1446.

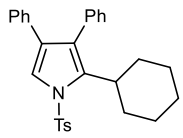
3-(4-Methoxyphenyl)-2,4-diphenyl-1-tosyl-1*H*-pyrrole (81ga) and (*Z*)-*N*-(3-(4-methoxyphenyl)-4-oxo-2,4-diphenylbut-2-en-1-yl)-4-methylbenzenesulfonamide (83)



General Procedure A was followed using propargyl amide **80g** (126 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Purification by column chromatography (20% to 40% EtOAc/ petroleum ether) gave pyrrole **81ga** a white solid (78.1 mg, 54%) followed by alkene **83** as a pale yellow solid that had small traces of inseparable, unidentified impurities (33.0 mg, *ca.* 23%).

Data for **81ga**: R_f = 0.54 (40% EtOAc/petroleum ether); m.p. 167-169 °C (Et_2O); IR 2920, 1598, 1509, 1375, 1241, 1170, 1097, 1029, 698, 584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar**H**), 7.32-7.28 (2H, m, Ar**H**), 7.26-7.10 (10H, m, Ar**H**), 7.04-6.99 (2H, m, Ar**H**), 6.82-6.72 (2H, m, Ar**H**), 6.66-6.52 (2H, m, Ar**H**), 3.68 (3H, s, OC**H**$_3$), 2.38 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (C), 144.8 (C), 135.9 (C), 134.0 (C), 132.8 (2 × CH), 132.0 (C), 131.6 (2 × CH), 130.5 (C), 129.6 (2 × CH), 128.6 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 127.7 (2 × CH), 127.5 (C), 127.3 (2 × CH), 127.1 (C), 126.8 (CH), 125.7 (C), 120.0 (CH), 113.3 (2 × CH), 55.1 (CH_3), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{30}H_{25}NO_3SNa]^+$ $[M+Na]^+$: 502.1447, found 502.1438.

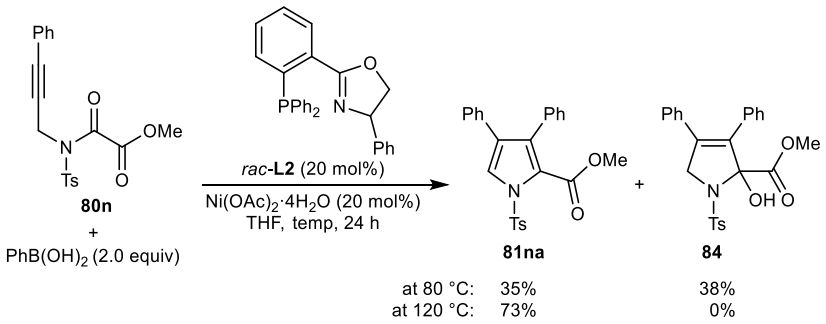
Data for **83**: R_f = 0.27 (40% EtOAc/petroleum ether); IR 3357 (NH), 1671, 1607, 1509, 1476, 1287, 1249, 1131, 1029, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.14 (1H, s, N**H**), 8.12-8.04 (2H, m, Ar**H**), 7.60-7.50 (5H, m, Ar**H**), 7.09-7.05 (4H, m, Ar**H**), 6.96-6.89 (3H, m, Ar**H**), 6.72-6.67 (2H, m, Ar**H**), 6.64-6.59 (2H, m, Ar**H**), 4.54 (2H, s, C**H**$_2$), 3.70 (3H, s, |OC**H**$_3$), 2.31 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6 (C), 159.3 (C), 145.1 (C), 141.0 (C), 139.3 (C), 135.3 (C), 133.4 (C), 132.4 (CH), 130.9 (2 × CH), 129.8 (2 × CH), 129.7 (2 × CH), 128.9 (2 × CH), 128.3 (C), 128.2 (2 × CH), 128.0 (2 × CH), 127.8 (2 × CH), 126.4 (CH), 117.9 (C), 113.5 (2 × CH), 62.7 (CH_2), 55.2 (CH_3), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{30}H_{27}NO_4SNa]^+$ $[M+Na]^+$: 520.1553, found 520.1553.



2-Cyclohexyl-3,4-diphenyl-1-tosyl-1*H*-pyrrole (81ma). The title compound was prepared according to a modification of General Procedure A (in that the temperature was 120 °C rather than 80 °C), using propargyl amide **80m** (119 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (1% to 5% EtOAc/petroleum ether) to give a pale orange solid (73.7 mg, 54%). R_f = 0.64 (40% EtOAc/petroleum ether); m.p. 93-95 °C (Et_2O); IR 3155, 3056, 2924, 2853, 1598, 1446, 1167, 1092, 670, 591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.73 (2H, m, Ar**H**), 7.57-7.50 (1H, m, Ar**H**), 7.36 (2H, d, J = 8.1 Hz, Ar**H**), 7.29-7.25 (3H, m, Ar**H**), 7.21-7.10 (5H, m, Ar**H**), 7.10-7.02 (2H, m, Ar**H**), 3.21-3.00 (1H, m, C**H**), 2.46 (3H, s, ArC**H**$_3$), 1.59-1.47 (3H, m, cyclohexyl**H**), 1.45-1.33 (2H, m, cyclohexyl**H**), 1.19-1.01 (4H, m, cyclohexyl**H**), 0.91-0.74 (1H, m, cyclohexyl**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0

(C), 137.0 (C), 136.7 (C), 135.7 (C), 134.0 (C), 131.5 (2 × CH), 130.1 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.8 (2 × CH), 127.6 (C), 127.20 (CH), 127.17 (2 × CH), 126.6 (C), 126.4 (CH), 118.2 (CH), 37.5 (CH), 32.9 (2 × CH_2), 27.3 (2 × CH_2), 25.8 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{29}H_{29}NO_2SNa]^+$ $[M+Na]^+$: 478.1811, found 478.1807.

Methyl 3,4-diphenyl-1-tosyl-1*H*-pyrrole-2-carboxylate (81na) and methyl 3,4-diphenyl-1-tosyl-1*H*-pyrrole-2-carboxylate (84)



At 80 °C: An oven-dried microwave vial fitted with a stirrer bar was charged with propargyl amide **80n** (186 mg, 0.50 mmol), phenylboronic acid (122 mg, 1.00 mmol), $Ni(OAc)_2·4H_2O$ (24.9 mg, 0.10 mmol) and *rac*-**L2** (40.7 mg, 0.10 mmol). The vial was capped with a crimp cap PTFE seal and evacuated and back filled with argon (3 cycles). THF (5 mL) which had been freshly degassed (using stream of argon for 20 min) was added, the septum was resealed with PTFE tape, and the contents were stirred at RT for 10 min followed by 80 °C for 24 h. The reaction was cooled to room temperature and diluted with 50% brine (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/ petroleum ether) to give pyrrole **81na** as a pale yellow solid (76.4 mg, 35%) followed by pyrroline **84** as a yellow oil that had small traces of inseparable, unidentified impurities (85.6 mg, *ca.* 38%).

Data for **81na**: R_f = 0.53 (40% EtOAc/petroleum ether); m.p. 201-202 °C (Et_2O); IR 3028, 2947, 1723 (C=O), 1596, 1338, 1230, 1118, 816, 759, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02-7.90 (2H, m, Ar**H**), 7.63 (1H, s, Ar**H**), 7.41-7.35 (2H, m, Ar**H**), 7.29-7.26 (2H, m, Ar**H**), 7.25-7.15 (4H, m, Ar**H**), 7.15-7.04 (4H, m, Ar**H**), 3.60 (3H, s, OC**H**$_3$), 2.46 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (C), 145.4 (C),

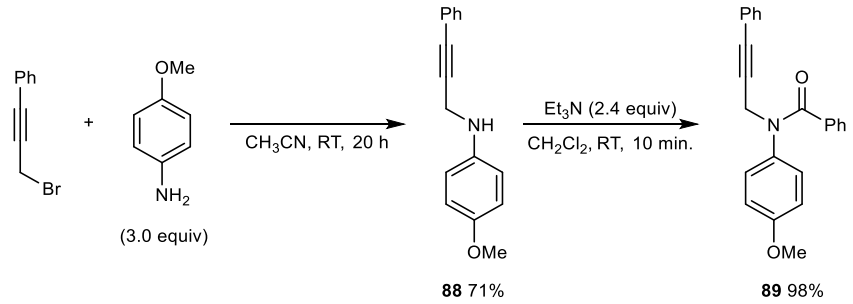
136.1 (C), 132.9 (C), 132.8 (C), 132.7 (C), 130.1 (2 × CH), 129.8 (2 × CH), 128.6 (2 × CH), 128.4 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 127.7 (CH), 127.5 (C), 127.2 (CH), 123.2 (C), 123.1 (CH), 52.2 (CH_3), 21.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{25}H_{21}NO_4SNa]^+$ $[M+Na]^+$: 454.1087, found 454.1083.

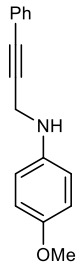
Data for **84**: R_f = 0.45 (40% EtOAc/petroleum ether); IR 3472 (OH), 3026, 1742, 1339, 1258, 1155, 752, 696, 667, 575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.88 (2H, m, Ar**H**), 7.34-7.31 (2H, m, Ar**H**), 7.29-7.27 (2H, m, Ar**H**), 7.25-7.14 (6H, m, Ar**H**), 7.09-7.06 (2H, m, Ar**H**) 5.12 (1H, s, O**H**), 4.85 (1H, d, *J* = 13.5 Hz, C**H**$_2$), 4.32 (1H, d, *J* = 13.5 Hz, C**H**$_2$), 3.78 (3H, s, OC**H**$_3$), 2.42 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C), 143.9 (C), 136.8 (2 × C), 134.1 (C), 132.23 (C), 132.19 (C), 129.7 (2 × CH), 129.5 (2 × CH), 128.78 (CH), 128.75 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 128.1 (2 × CH), 127.9 (2 × CH), 96.2 (C), 54.6 (CH_2), 54.2 (CH_3), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{25}H_{23}NO_5SNa]^+$ $[M+Na]^+$: 472.1189, found 472.1190.

At 120 °C: A modification of General Procedure A (in that a 20 mol% catalyst loading was employed, the temperature was 120 °C rather than 80 °C, and THF was used as the solvent) was followed using propargyl amide **80n** (111 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (14.9 mg, 0.06 mmol) and *rac*-**L2** (24.4 mg, 0.06 mmol) in THF (3 mL) at 120 °C. Purification by column chromatography (15% EtOAc/petroleum ether) give pyrrole **81na** as a pale yellow solid (93.7 mg, 73%).

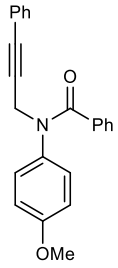
3.5 Further Transformations

Preparation of Substrate 89





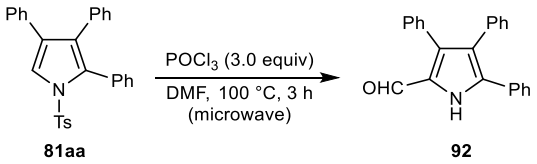
4-Methoxy-*N*-(3-phenylprop-2-yn-1-yl)aniline (88). The alkynamine **88** was prepared by modification of a previously reported procedure.[45] To a stirred solution of *p*-anisidine (1.89 g, 15.4 mmol) in freshly degassed CH_3CN (8.8 mL) was added a solution of phenyl propargyl bromide (1.00 g, 5.12 mmol) in CH_3CN (1 mL) and the contents were stirred at room temperature for 20 h. The reaction was quenched with NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (10% EtOAc/petroleum ether) to give the title compound **88** as an orange solid (858 g, 71%). The analytical data were consistent with those reported previously.[46] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (2H, m, Ar**H**), 7.34-7.26 (3H, m, Ar**H**), 6.88-6.78 (2H, m, Ar**H**), 6.77-6.69 (2H, m, Ar**H**), 4.11 (2H, s, C**H**$_2$), 3.77 (3H, s, C**H**$_3$), 3.71 (1H, s, N**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (C), 141.4 (C), 131.8 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 123.1 (C), 115.3 (2 × CH), 114.9 (2 × CH), 86.8 (C), 83.4 (C), 55.9 (CH_3), 35.7 (CH_2).



***N*-(4-Methoxyphenyl)-*N*-(3-phenylprop-2-yn-1-yl)benzamide (89**). The alkynamide **89** was prepared by modification of a previously reported procedure.[47] To a solution of the *N*-tosyl propargyl amine **88** (498 mg, 2.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added benzoyl chloride (0.29 mL, 2.52 mmol) followed by Et_3N (0.70 mL, 5.0 mmol). The resulting solution was warmed to room temperature and stirred for 10 min. The reaction was quenched with water (120 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with 0.1 M HCl solution (120 mL), saturated $NaHCO_3$ solution (120 mL) and brine (120 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The

residue was purified by column chromatography (35% EtOAc/petroleum ether) to give the title compound **89** as a yellow oil (701 mg, 98%). R_f = 0.35 (40% EtOAc/petroleum ether); IR 3058, 2837, 1716, 1642, 1509, 1423, 1378, 1287, 1025, 788 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.32 (4H, m, Ar**H**), 7.31-7.27 (3H, m, Ar**H**), 7.25-7.07 (5H, m, Ar**H**), 6.81-6.73 (2H, m, Ar**H**), 4.87 (2H, s, C**H**$_2$), 3.75 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C), 158.6 (C), 135.73 (C), 135.68 (C) 131.8 (2 × CH), 129.8 (CH), 129.4 (2 × CH), 128.8 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 127.9 (2 × CH), 123.0 (C), 114.4 (2 × CH), 84.8 (C), 84.4 (C), 55.5 (CH_3), 40.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{23}H_{19}NO_2Na]^+$ $[M+Na]^+$: 364.1308, found 364.1313.

3,4,5-Triphenyl-1*H*-pyrrole-2-carbaldehyde (92)[33]

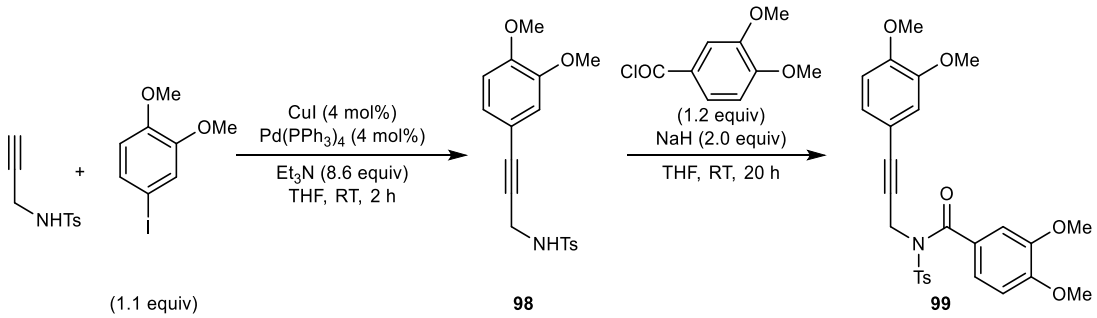


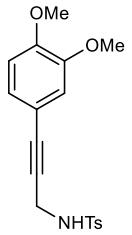
To an oven-dried microwave vial fitted with a stirrer bar was added pyrrole **81aa** (67.4 mg, 0.15 mmol). The vial was capped with a crimp cap PTFE seal and evacuated and back filled with argon (3 cycles). DMF (0.5 mL) which had been freshly degassed (using a stream of argon for 20 min) was added. To a second vial was added DMF (1.3 mL) and the vial was cooled to 0 °C. $POCl_3$ (40 μL, 0.45 mmol) was added dropwise and the solution was stirred at 0 °C for 45 min. The resulting solution of the Vilsmeier reagent was added to the first vial *via* syringe, and the mixture was heated at 100 °C in a microwave reactor for 3 h. The reaction was cooled to room temperature and diluted with saturated aqueous NaOAc solution (15 mL). The mixture was cooled in an ice bath, diluted with distilled water (10 mL), and the solids was collected by filtration. To the solids was added brine (50%, 7 mL) and the suspension was extracted with $CHCl_3$ (3 × 7 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was dissolved in EtOAc, and the solution was filtered through a plug of silica gel and concentrated *in vacuo* to leave the title compound **92** as a brown solid (46 mg, 95%). R_f = 0.42 (40% EtOAC/petroleum ether); IR 3273, 1624 (C=O), 1599, 1431, 1382, 1237, 823, 716, 688, 538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (1H, br s, N**H**), 9.51 (1H, s, C**H**O), 7.32-7.28 (8H,

m, Ar**H**), 7.24-7.18 (5H, m, Ar**H**), 7.07-7.03 (2H, m, Ar**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1 (C), 136.4 (C), 136.1 (C), 133.6 (C), 132.3 (C), 131.1 (C), 131.0 (2 × CH), 130.8 (2 × CH), 129.3 (C), 128.9 (2 × CH), 128.6 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 127.6 (CH), 126.9 (CH), 124.1 (C); HRMS (ESI) Exact mass calculated for $[C_{23}H_{17}NONa]^+$ $[M+Na]^+$: 346.1202, found 346.1194.

This compound has been described previously but in that work, the ^{1}H NMR spectrum was obtained in CD_2Cl_2 as the solvent.[33] Our ^{13}C NMR data are consistent with those reported previously.[33]

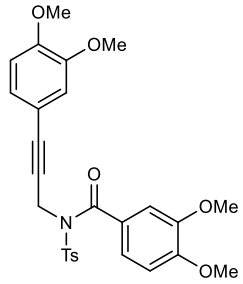
Preparation of Substrate 99



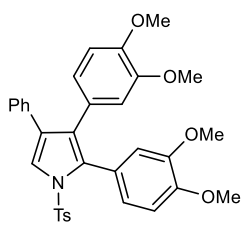


***N*-[3-(3,4-Dimethoxyphenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (98).** To a stirred solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (523 mg, 2.50 mmol) and 3,4-dimethoxyiodobenzene (792 mg, 3.00 mmol) in degassed THF (7 mL, using stream of Ar gas for 30 min) was added $Pd(PPh_3)_4$ (57.8 mg, 0.050 mmol), CuI (19.0 mg, 0.100 mmol), degassed Et_3N (3.0 mL, 22 mmol, using stream of Ar gas for 15 min). The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with distilled water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (40% EtOAc/petroleum ether) to give the title compound **98** as a pale brown solid (789 mg, 91%). R_f = 0.21 (40% EtOAc/petroleum ether); m.p. 123-125 °C (Et_2O); IR 3266 (NH), 2965, 2839, 1598, 1517, 1442, 1362, 1155, 1020, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.76 (2H, m, Ar**H**), 7.30-7.26 (2H, m, Ar**H**), 6.79-6.68 (3H, m, Ar**H**), 4.73 (1H, t, *J* = 6.0 Hz, N**H**), 4.05 (2H, d, *J* = 6.0 Hz, C**H**$_2$), 3.86 (3H, s, OC**H**$_3$), 3.83 (3H, s, OC**H**$_3$), 2.37 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 149.8 (C), 148.6 (C), 143.8 (C), 137.0 (C), 129.8 (2 × CH), 127.6 (2 × CH), 125.1 (CH), 114.4 (CH), 114.3 (C), 110.9 (CH), 84.9 (C), 81.8 (C), 56.0 (2 × CH_3), 34.0 (CH_2), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{19}NO_4SNa]^+$ $[M+Na]^+$: 368.0927, found 368.0926.

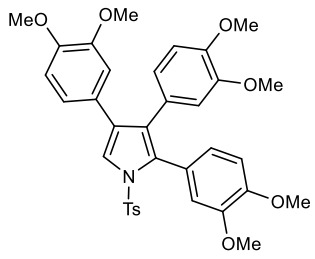


***N*-[3-(3,4-Dimethoxyphenyl)prop-2-yn-1-yl]-3,4-dimethoxy-*N*-tosylbenzamide (99).** A solution of the *N*-tosyl propargyl amine **98** (518 mg, 1.50 mmol) in THF (4 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 72.0 mg, 3.00 mmol) in THF (6 mL). The resulting solution was warmed to room temperature and stirred for 1 h. 3-4-Dimethoxybenzoyl chloride (361 mg, 1.80 mmol) was added in one portion and the resulting solution was stirred at room temperature for 20 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (65% EtOAc/petroleum ether) to give the title compound **99** as a pale yellow solid (744 mg, 97%). R_f = 0.22 (60% EtOAc/petroleum ether); m.p. 164-165 °C (Et_2O); IR 2935, 2837, 1680 (C=O), 1597, 1511, 1352, 1265, 1163, 1134, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02-7.97 (2H, m, Ar**H**), 7.34 (1H, dd, *J* = 8.4, 2.0 Hz, Ar**H**), 7.31-7.26 (2H, m, Ar**H**), 7.19 (1H, d, *J* = 2.0 Hz, Ar**H**), 6.93 (1H, dd, *J* = 8.3, 1.9 Hz, Ar**H**), 6.87 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.83 (1H, d, *J* = 1.9 Hz, Ar**H**), 6.78 (1H, d, *J* = 8.3 Hz, Ar**H**), 4.79 (2H, s, C**H**$_2$), 3.92 (3H, s, OC**H**$_3$), 3.89 (3H, s, OC**H**$_3$), 3.86 (3H, s, OC**H**$_3$), 3.83 (3H, s, OC**H**$_3$), 2.40 (3H, s, ArC**H**$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C), 152.5 (C), 150.0 (C), 148.8 (C), 148.7 (C), 144.9 (C), 136.0 (C), 129.4 (2 × CH), 129.2 (2 × CH), 126.2 (C), 125.2 (CH), 122.7 (CH), 114.5 (CH), 114.3 (C), 111.5 (CH), 111.1 (CH), 110.4 (CH), 85.2 (C), 82.7 (C), 56.2 (CH_3), 56.14 (CH_3), 56.07 (CH_3), 56.0 (CH_3), 39.5 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{27}NO_7SNa]^+$ $[M+Na]^+$: 532.1400, found 532.1393.



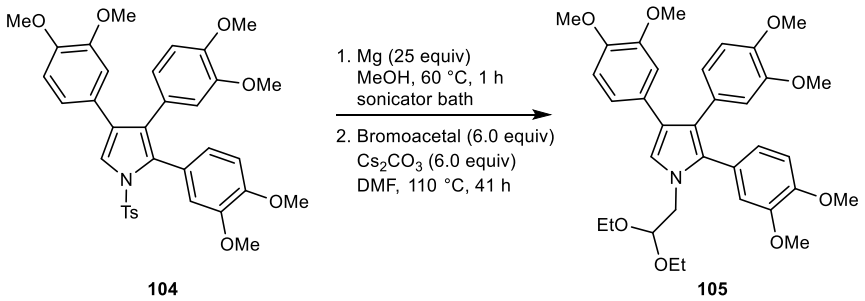
2,3-Bis(3,4-dimethoxyphenyl)-4-phenyl-1-tosyl-1*H*-pyrrole (102). The title compound was prepared according to General Procedure A, using propargyl amide **99** (153 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by

column chromatography (5% to 10% EtOAc/petroleum ether) to give a yellow solid (128 mg, 75%). R_f = 0.20 (40% EtOAc/petroleum ether); m.p. 164-165 °C (Et_2O); IR 2934, 2834, 1582, 1462, 1367, 1171, 1098, 1024, 754, 589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar**H**), 7.35-7.30 (2H, m, Ar**H**), 7.26-7.18 (5H, m, Ar**H**), 7.17-7.11 (2H, m, Ar**H**), 6.70 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.63 (1H, dd, *J* = 8.3, 1.9 Hz, Ar**H**), 6.55 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.49 (1H, d, *J* = 1.9 Hz, Ar**H**), 6.42 (1H, dd, *J* = 8.3, 2.0 Hz, Ar**H**), 6.38 (1H, d, *J* = 2.0 Hz, Ar**H**), 3.88 (3H, s, OC**H**$_3$), 3.76 (3H, s, OC**H**$_3$), 3.62 (3H, s, OC**H**$_3$), 3.42 (3H, s, OC**H**$_3$), 2.37 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1 (C), 148.0 (C), 147.7 (C), 147.4 (C), 144.8 (C), 136.0 (C), 134.0 (C), 131.5 (C), 129.5 (2 × CH_2), 128.7 (2 × CH_2), 128.3 (2 × CH_2), 127.8 (2 × CH_2), 127.3 (C), 126.81 (CH), 126.76 (C), 126.0 (C), 125.7 (CH), 122.83 (C), 122.76 (CH), 119.7 (CH), 115.9 (CH), 113.8 (CH), 110.5 (CH), 110.0 (CH), 55.9 (CH_3), 55.73 (CH_3), 55.69 (CH_3), 55.5 (CH_3), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{33}H_{31}NO_6SNa]^+$ [M+Na]+: 592.1764, found 592.1754.



2,3,4-Tris(3,4-dimethoxyphenyl)-1-tosyl-1H-pyrrole (104). The title compound was prepared according to General Procedure A, using propargyl amide **99** (1.00 g, 1.96 mmol), 3,4-dimethoxyphenylboronic acid (713 mg, 3.92 mmol) and purified by column chromatography (20% to 70% EtOAc/petroleum ether) to give a green solid (1.223 g, 99%). R_f = 0.29 (70% EtOAc/petroleum ether); m.p. 115-116 °C (Et_2O); IR 2934, 2833, 1507, 1462, 1368, 1251, 1096, 1023, 676, 587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, s, Ar**H**), 7.38-7.29 (2H, m, Ar**H**), 7.19-7.11 (2H, m, Ar**H**), 6.84-6.74 (2H, m, Ar**H**), 6.72-6.65 (2H, m, Ar**H**), 6.66-6.58 (1H, m, Ar**H**), 6.61-6.54 (1H, m, Ar**H**), 6.51-6.45 (1H, m, Ar**H**), 6.49-6.40 (2H, m, Ar**H**), 3.88 (3H, s, OC**H**$_3$), 3.86 (3H, s, OC**H**$_3$), 3.76 (3H, s, OC**H**$_3$), 3.64 (3H, s, OC**H**$_3$), 3.62 (3H, s, OC**H**$_3$), 3.46 (3H, s, OC**H**$_3$), 2.37 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1 (C), 148.6 (C), 148.1 (C), 148.0 (C), 147.7 (C), 147.5 (C), 144.8 (C), 136.0 (C), 131.6 (C), 129.5 (2 × CH), 127.8 (2 × CH), 127.3 (C), 126.7 (C), 126.4 (C), 126.2 (C), 125.6 (CH), 123.0 (CH), 122.8 (C), 120.8 (CH), 119.0 (CH), 115.8 (CH), 113.9 (CH), 112.0 (CH), 111.1 (CH), 110.6 (CH), 110.0 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.8 (CH_3), 55.74 (CH_3), 55.72 (CH_3), 55.6 (CH_3), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{35}H_{35}NO_8SNa]^+$ $[M+Na]^+$: 652.1976, found 652.1971.

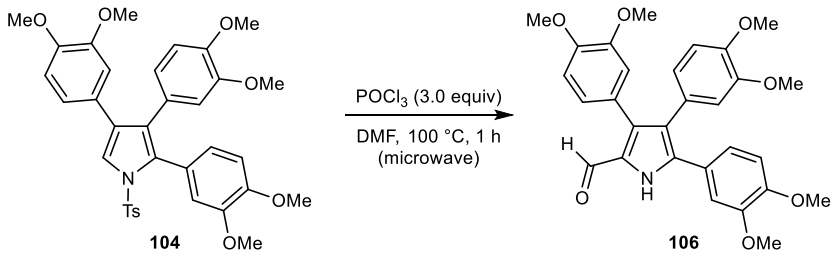
1-(2,2-Diethoxyethyl)-2,3,4-tris(3,4-dimethoxyphenyl)-1*H*-pyrrole (105).



104 105

The pyrrole **105** was prepared by modification of previously reported procedures.[47,7] A solution of activated magnesium turnings (579 mg, 23.8 mmol) and pyrrole **104** (600 mg, 0.95 mmol) in methanol (13.5 mL) was stirred under reflux at 60 °C for 1 h in a sonicator bath. The reaction mixture was left to cool to room temperature, filtered over celite and washed with methanol (30 mL). The solution was washed with NH_4Cl solution (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organics were dried ($MgSO_2$), filtered and concentrated *in vacuo.* No further purification was carried out and the resulting compound was used directly for the second step. The deprotected pyrrole (47.6 mg, 0.10 mmol), Cs_2CO_3 (195 mg, 0.60 mmol) and bromoacetal (0.09 mL, 0.6 mmol) in DMF (10 mL) was stirred at 110 °C for 22 h. The reaction was quenched with water (10 mL), extracted with EtOAc (3 × 10 mL), dried ($MgSO_2$), filtered and concentrated *in vacuo* to give the title compound **105** as a dark green oil that had small traces of inseparable, unidentified impurities (34 mg, 27% over 2 steps). R_f = 0.33 (60% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, s, Ar**H**) 6.83-6.71 (6H, m, Ar**H**), 6.66-6.60 (1H, m, Ar**H**), 6.58-6.52 (2H, m, Ar**H**), 4.57 (1H, t, *J* = 5.3 Hz, C**H**), 3.97 (2H, d, *J* = 5.3 Hz, C**H**$_2$), 3.87 (3H, s, OC**H**$_3$), 3.85 (4H, s, OC**H**$_3$), 3.79 (3H, s, OC**H**$_3$), 3.70 (3H, s, OC**H**$_3$), 3.62 (3H, s, OC**H**$_3$), 3.61-3.55 (2H, m, C**H**$_2$), 3.49 (3H, s, OC**H**$_3$), 3.43-3.35 (2H, m, C**H**$_2$), 1.25 (3H, t, *J* = 7.1 Hz, C**H**$_3$), 1.17 (3H, t, *J* = 7.0 Hz, C**H**$_3$); HRMS (ESI) Exact mass calculated for $[C_{34}H_{41}NO_8Na]^+$ $[M+Na]^+$: 614.2724, found 614.2723. (it was intended to obtain cleaner data when carrying out the reaction on a larger scale and therefore IR and ^{13}C NMR were not obtained for this compound)

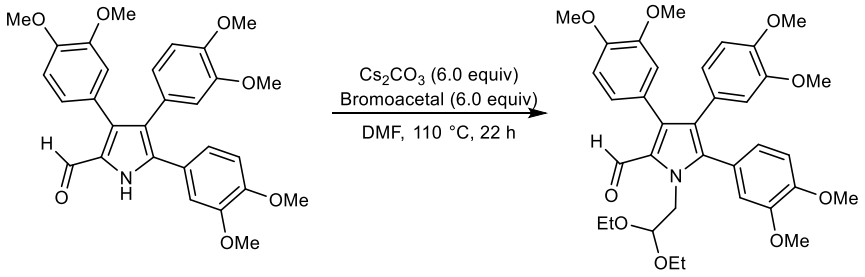
3,4,5-Tris(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carbaldehyde (106).



The pyrrole **106** was prepared by modification of a previously reported procedure.[49] To an oven-dried microwave vial fitted with a stirrer bar was added DMF (7 mL) which had been freshly degassed (using a stream of Ar gas for 20 min) and $POCl_3$ (0.22 mL, 2.4) and the contents were stirred in an ice bath for 45 min. To the resulting solution of the Vilsmeier reagent was added pyrrole **104** (500 mg, 0.79 mmol) dissolved in DMF (2.5 mL) *via* syringe. The contents were heated to 100 °C in a microwave for 1 h. The reaction mixture was left to cool to room temperature, diluted with saturated aqueous sodium acetate (150 mL) and heated to boiling in an unsealed volumetric flask. The resulting mixture was cooled in an ice bath, diluted with distilled water (30 mL) and the solids were collected. To the solids was added brine (50%, 20 mL) and the aqueous layer was extracted with chloroform (3 × 40 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title compound **106** as a brown solid (401 mg, 100%). R_f = 0.31 (80% EtOAc/petroleum ether); m.p. 205-206 °C (Et_2O); IR 3283, 3022, 2838, 1627, 1511, 1430, 1237, 1137, 1022, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (1H, s, N**H**), 9.52 (1H, s, C**H**O), 6.97 (1H, dd, *J* = 8.4, 2.1 Hz, Ar**H**), 6.86-6.80 (4H, m, Ar**H**), 6.75 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.69 (1H, d, *J* = 1.8 Hz, Ar**H**), 6.65 (1H, dd, *J* = 8.2, 2.0 Hz, Ar**H**), 6.61 (1H, d, *J* = 2.0 Hz, Ar**H**), 3.88 (3H, s, OC**H**$_3$), 3.88 (3H, s, OC**H**$_3$), 3.84 (3H, s, OC**H**$_3$), 3.64 (6H, s, OC**H**$_3$), 3.58 (3H, s, OC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7 (CHO), 149.4 (C), 148.9 (C), 148.8 (C), 148.7 (C), 148.6 (C), 148.0 (C), 136.6 (C), 136.3 (C), 128.8 (C), 126.6 (C), 125.0 (C), 123.6 (C), 123.4 (CH), 123.3 (CH), 120.4 (CH), 114.3 (CH), 113.9 (CH), 111.3 (CH), 111.2 (CH), 111.1 (CH), 111.0 (CH), 56.02 (CH_3), 55.99 (2 × CH_3), 55.9 (CH_3), 55.84 (CH_3), 55.80 (CH_3) (one carbon signal overlapped

with others); HRMS (ESI) Exact mass calculated for $[C_{29}H_{30}NO_7Na]^+$ $[M+Na]^+$: 526.1836, found 526.1826.

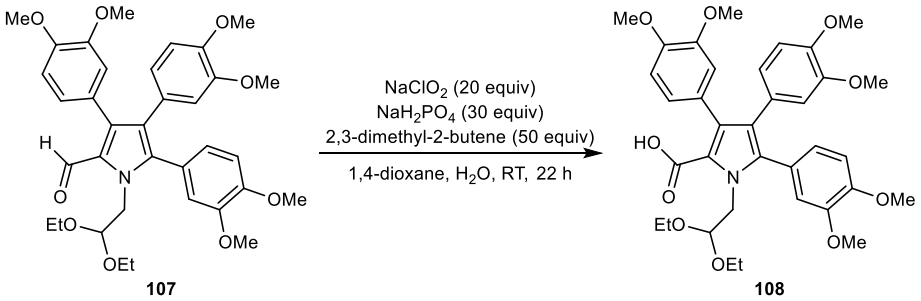
1-(2,2-Diethoxyethyl)-3,4,5-tris(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carbaldehyde (107).



106 **107**

The pyrrole **107** was prepared by modification of previously reported procedure.[7] A solution of deprotected pyrrole **106** (151 mg, 0.30 mmol), Cs_2CO_3 (587 mg, 1.80 mmol) and bromoacetal (0.27 mL, 1.8 mmol) in DMF (25 mL) was stirred at 110 °C for 22 h. The reaction was quenched with water (20 mL), extracted with EtOAc (3 × 40 mL), dried ($MgSO_2$), filtered and concentrated *in vacuo* to give the title compound **107** as a yellow oil (84 mg, 45%). R_f = 0.51 (80% EtOAc/petroleum ether); IR 2972, 2835, 1644 (C=O), 1522, 1463, 1411, 1253, 1234, 1137, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (1H, s, C**H**O), 6.91-6.79 (5H, m, Ar**H**), 6.73-6.66 (1H, m, Ar**H**), 6.59-6.52 (1H, m, Ar**H**), 6.41-6.30 (2H, m, Ar**H**), 4.84 (1H, t, *J* = 5.5 Hz, C**H**), 4.45 (2H, d, *J*=5.5 Hz, C**H**$_2$), 3.88 (3H, s, OC**H**$_3$), 3.87 (3H, s, OC**H**$_3$), 3.76 (3H, s, OC**H**$_3$), 3.72 (3H, s, OC**H**$_3$), 3.66 (3H, s, OC**H**$_3$), 3.65-3.58 (2H, m, C**H**$_2$), 3.51-3.44 (2H, m, C**H**$_2$), 3.42 (3H, s, OC**H**$_3$), 1.13 (6H, t, *J* = 7.0 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.7 (CHO), 149.2 (C), 148.7 (C), 148.6 (C), 148.5 (C), 148.1 (C), 147.2 (C), 141.7 (C), 138.4 (C), 127.5 (C), 126.5 (C), 125.5 (C), 124.4 (CH), 124.0 (C), 123.9 (CH), 122.93 (C), 122.91 (CH), 114.7 (CH), 114.4 (CH), 114.0 (CH), 111.0 (CH), 110.8 (CH), 110.7 (CH), 102.3 (CH), 63.8 (2 × CH_2), 56.03 (CH_3), 55.99 (CH_3), 55.96 (CH_3), 55.9 (CH_3), 55.8 (CH_3), 55.6 (CH_3), 48.7 (CH_2), 15.5 (2 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{35}H_{41}NO_9Na]^+$ $[M+Na]^+$: 642.2674, found 642.2644.

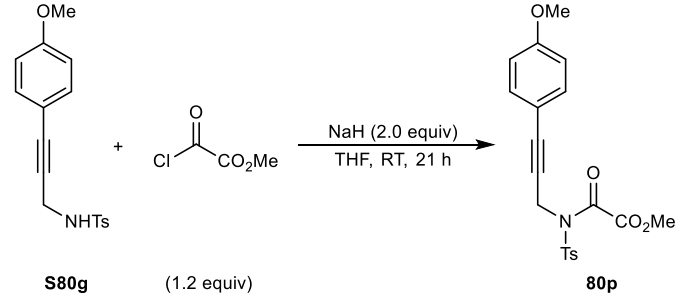
1-(2,2-Diethoxyethyl)-3,4,5-tris(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carboxylic acid (108).



107 108

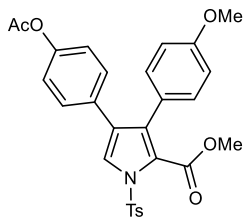
The pyrrole **108** was prepared by modification of previously reported procedure.[36] To a stirred solution of pyrrole **107** (130 mg, 0.21 mmol) in 1,4-dioxane (25 mL) was added 2,3-dimethyl-2-butene (1.25 mL, 10.5 mmol) in one portion. A solution of $NaClO_2$ (380 mg, 4.20 mmol) and NaH_2PO_4 (755 mg, 6.29 mmol) in water (5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 22 h and monitored by mass spectroscopy. The reaction was diluted with CH_2Cl_2 (25 mL) and washed with NH_4Cl solution (10 mL), water (2 × 20 mL) and brine (10 mL). The organic layer was dried ($MgSO_2$), filtered and concentrated *in vacuo* to give the title compound **108** as an orange oil. R_f = 0.48 (80% EtOAc/petroleum ether); HRMS (ESI) Exact mass calculated for $[C_{35}H_{41}NO_{10}Na]^+$ $[M+Na]^+$: 658.2623, found 658.2619. HRMS (ESI) Exact mass calculated for $[C_{35}H_{40}NO_{10}]^-$ $[M-H]^-$: 635.2736, found 635.2701. (The disappearance of the aldehyde peak in ^1H NMR was key reason to conclude that the reaction was successful. However, due to it being impossible to purify compound **108**, no further data analysis was done).

Methyl 2-({*N*-[3-(4-methoxyphenyl)prop-2-yn-1-yl]-4-methylphenyl}sulfonamido)-2-oxoacetate (80p)



S80g (1.2 equiv) 80p

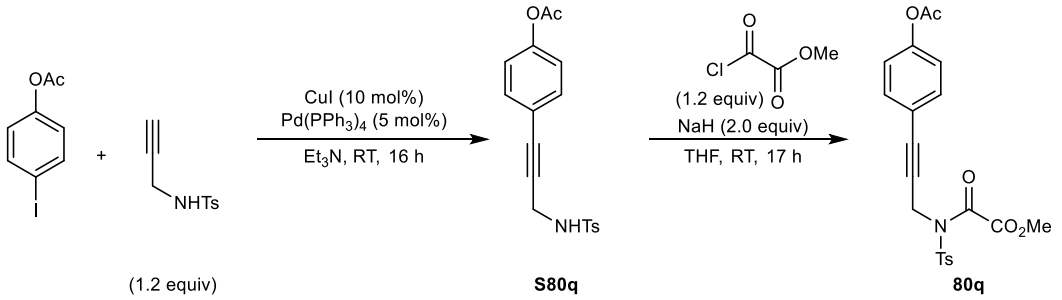
A solution of the *N*-tosyl propargyl amine **S80g** (500 mg, 1.59 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 76.3 mg, 3.18 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. The methyl oxalyl chloride (0.18 mL, 1.9 mmol) was added dropwise and the resulting solution was stirred at room temperature for 21 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography using a normal phase column (PuriFlash column 50 STD-silica 50µ (25.0g), Interchim). The sample was eluted with an ethyl acetate/petroleum ether mixture of increasing polarity (50 min), and a flowrate of 15ml/min to give the title compound **80p** as a light brown solid (518 mg, 81%). R_f = 0.35 (40% EtOAc/petroleum ether); m.p. 80-81 °C (Et_2O); IR 2960, 2924, 1750, 1688, 1607, 1372, 1293, 1252, 1173, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04-7.92 (2H, m, Ar**H**), 7.35-7.28 (2H, m, Ar**H**), 7.09-7.00 (2H, m, Ar**H**), 6.79-6.72 (2H, m, Ar**H**), 4.70 (2H, s, C**H**$_2$), 3.97 (3H, s, OC**H**$_3$), 3.79 (3H, s, OC**H**$_3$), 2.37 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8 (C), 160.3 (C), 159.9 (C), 146.1 (C), 134.8 (C), 133.3 (2 × CH), 130.1 (2 × CH), 128.8 (2 × CH), 114.0 (C), 113.8 (2 × CH), 84.7 (C), 80.0 (C), 55.4 (CH_3), 53.5 (CH_3), 35.0 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{19}NO_6SNa]^+$ $[M+Na]^+$: 424.0825, found 424.0829.

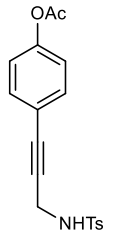


Methyl 4-(4-acetoxyphenyl)-3-(4-methoxyphenyl)-1-tosyl-1*H*-pyrrole-2-carboxylate (111). The title compound was prepared according to General Procedure A, using propargyl amide **80p** (40.1 mg, 0.10 mmol) and 4-acetoxyphenylboronic acid (36.0 mg, 0.20 mmol), 20 mol% $Ni(OAC)_2.4H_2O$ and *rac*-Ph-PHOX, THF and 120 °C. The residue was purified by preparative TLC to give a yellow oil (9.9 mg, 19%). R_f = 0.29 (40% EtOAc/petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.00-7.92 (2H, m, Ar**H**), 7.60 (1H, s, Ar**H**), 7.43-7.36 (2H, m, Ar**H**), 7.14-7.04 (4H, m, Ar**H**), 7.00-6.93 (2H, m, Ar**H**), 6.86-6.77 (2H, m, Ar**H**), 3.81 (3H, s, C**H**$_3$), 3.65 (3H, s, C**H**$_3$), 2.48 (3H, s, ArC**H**$_3$), 2.30 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5 (C), 161.6(C), 159.2 (C), 149.9 (C), 145.4 (C), 136.1 (C), 132.6 (C), 131.3 (2 × CH), 130.5 (C), 129.8 (2 × CH), 129.5 (2 × CH), 128.1 (2 × CH), 126.7 (C), 124.6 (C), 123.1 (CH), 122.2 (C) 121.6 (2 × CH), 113.5 (2 × CH), 55.3 (CH_3),

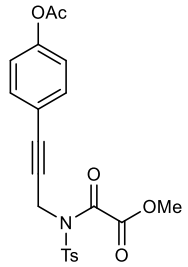
52.2 (CH_3), 21.9 (CH_3), 21.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{28}H_{25}NO_7SNa]^+$ [M+Na]+: 542.1244, found 542.1234. (IR was not obtained for this compound)

Preparation of Substrate 80q





4-{3-[(4-Methylphenyl)sulfonamido]prop-1-yn-1-yl}phenyl acetate (S80q). The *N*-tosyl propargyl amine (S80q) was prepared by modification of a previously reported procedure.[50] To a round bottom flask was added 4-iodophenol (960 mg, 3.66 mmol), 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (921 mg, 4.40 mmol), $PdCl_2(PPh_3)_2$ (128 mg, 0.183 mmol), CuI (69.7 mg, 0.366 mmol) and degassed Et_3N (7.3 mL, 52 mmol) and the contents were stirred for 5 min at room temperature followed by 3 h 15 min at 40 °C. The reaction was quenched with NH_4Cl solution (50 mL) and extracted with EtOAc (3 × 70 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (40 to 50% EtOAc/petroleum ether) to give the title compound **S80q** as a brown solid (1.150 g, 91%). R_f = 0.21 (40% EtOAc/petroleum ether); m.p. 143-144 °C (Et_2O); IR 3269 (NH), 2923, 2851, 1748, 1598, 1504, 1434, 1326, 1155, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.75 (2H, m, Ar**H**), 7.34-7.23 (2H, m, Ar**H**), 7.16-7.10 (2H, m, Ar**H**), 7.04-6.92 (2H, m, Ar**H**), 4.75 (1H, t, *J* = 6.2 Hz, N**H**), 4.06 (2H, d, *J* = 6.2 Hz, C$\mathbf{H}_2$), 2.35 (3H, s, ArC$\mathbf{H}_3$), 2.29 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (C), 150.7 (C), 143.9 (C), 137.0 (C), 132.8 (2 × CH), 129.8 (2 × CH), 127.6 (2 × CH), 121.7 (2 × CH), 119.8 (C), 84.0 (C), 83.5 (C), 33.9 (CH_2), 21.6 (CH_3), 21.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{17}NO_4SNa]^+$ $[M+Na]^+$: 366.0770, found 366.0766.



Methyl-2-{[*N*-(3-(4-acetoxyphenyl)prop-2-yn-1-yl]-4-methylphenyl)sulfonamido}-2-oxoacetate (80q). A solution of the *N*-tosyl propargyl amine **S80q** (500 mg, 1.46 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 69.8 mg, 2.91 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for 1 h. Methyl oxalyl chloride (0.16 mL, 1.8 mmol) was added dropwise and the resulting solution was stirred at room temperature for 17 h. The reaction was quenched with brine (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (30% EtOAc/petroleum ether) to give the title compound **80q** as a brown oil (466 mg, 74%). R_f = 0.39 (40% EtOAc/petroleum ether); IR 2956, 1751, 1693 (C=O), 1597, 1504, 1370, 1191, 1176, 1159, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04-7.92 (2H, m, Ar**H**), 7.35-7.28 (2H, m, Ar**H**), 7.16-7.06 (2H, m, Ar**H**), 7.03-6.89 (2H, m, Ar**H**), 4.70 (2H, s, C**H**$_2$), 3.98 (3H, s, C**H**$_3$), 2.35 (3H, s, ArC**H**$_3$), 2.28 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (C), 161.8 (C), 160.3 (C), 150.8 (C), 146.3 (C), 134.7 (C), 133.0 (2 × CH), 130.1 (2 × CH), 128.8 (2 × CH), 121.6 (2 × CH), 119.6 (C), 83.9 (C), 81.5 (C), 53.5 (CH_3), 34.8 (CH_2), 21.8 (CH_3), 21.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{19}NO_7SNa]^+$ $[M+Na]^+$: 452.0774, found 452.0780.

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5.0 Appendix: Publication

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Synthesis of multisubstituted pyrroles by nickel-catalyzed arylative cyclizations of *N*-tosyl alkynamides†

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The synthesis of multisubstituted pyrroles by the nickel-catalyzed reaction of *N*-tosyl alkynamides with arylboronic acids is reported. These reactions are triggered by alkyne arylnickelation, followed by cyclization of the resulting alkenylnickel species onto the amide. The reversible *E*/*Z* isomerization of the alkenylnickel species is critical for cyclization. This method was applied to the synthesis of pyrroles that are precursors to BODIPY derivatives and a biologically active compound.

Pyrroles are common heterocycles that appear in natural products,[1] pharmaceuticals,[2] dyes,[3] and organic materials.[4] Representative pyrrole-containing natural products include lamellarin D[5,6] and lycogarubin C,[7] whereas drugs that contain a pyrrole include sunitinib[8] and atorvastatin[9] (Fig. 1). In view of their importance, numerous strategies to prepare pyrroles have been developed.[10,11]

We[12] and others[13] have recently described nickel-catalyzed *anti*-carbometallative cyclizations of alkynyl electrophiles that give various carbo- and heterocyclic products. Although these reactions utilized several types of electrophiles,[12,13] amides have yet to be described, which is perhaps unsurprising given their relatively low electrophilicity. Nevertheless, the successful use of amides could provide a versatile synthesis of multisubstituted pyrroles, as shown in Scheme 1. Nickel-catalyzed addition of an arylboronic acid to the alkynamide **1** would give alkenylnickel species (*E*)-**2**. Although the alkenylnickel moiety of (*E*)-**2** cannot cyclize onto the amide because of geometric constraints, reversible *E*/*Z* isomerization of (*E*)-**2** would provide (*Z*)-**2**, the alkenylnickel moiety of which can now attack the amide to give nickel alkoxide **4**. Incorporating an electron-withdrawing *N*-tosyl group into **1** was expected to increase the reactivity of the amide carbonyl to favor this nucleophilic addition. Protonation of **4**, followed by elimination of water, would then provide a 2,3,4-trisubstituted pyrrole **3**.

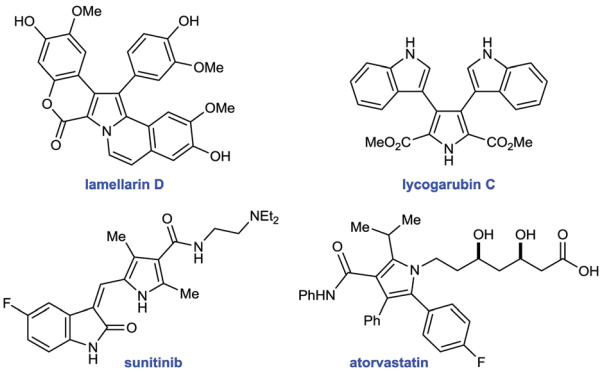
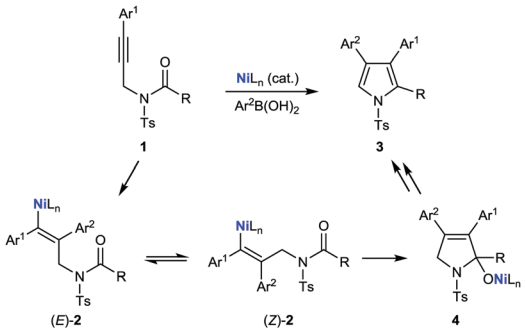


Fig. 1 Representative pyrrole-containing natural products and drugs.



Scheme 1 Proposed synthesis of pyrroles.

Our investigations began with the reaction of alkynamide **1a** with $PhB(OH)_2$ to give pyrrole **3aa**, which was conducted in the presence of $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%) in 2,2,2-trifluoroethanol (TFE) at 80 °C for 24 h (Table 1, entry 1). However, **3aa** was not detected in this reaction. Next, various P,N-ligands (10 mol%)

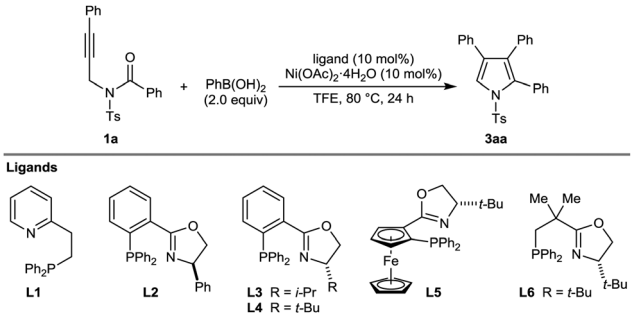
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† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data for **3ah**. CCDC 1861043. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc06649c

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Table 1 Evaluation of reaction conditions[a]



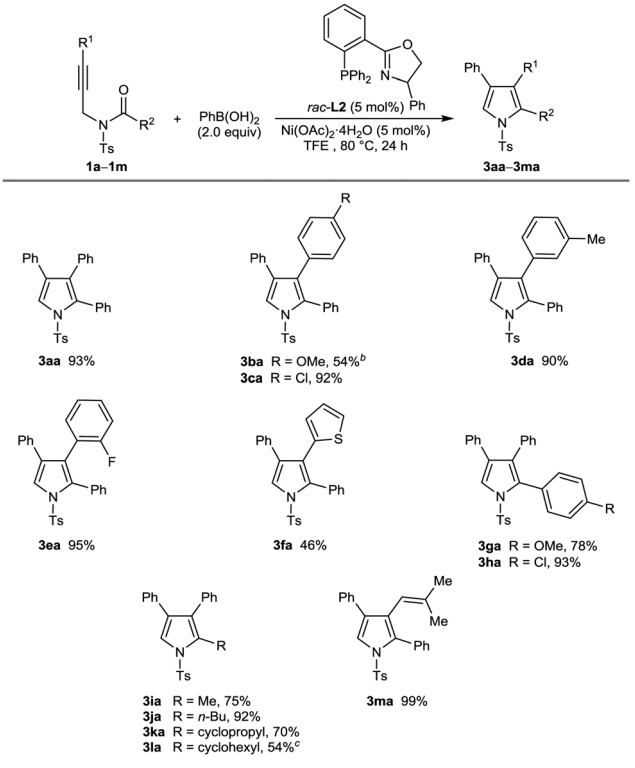
Entry	Ligand	Yield of **1a**[b] [%]	Yield of **3aa**[b] [%]
1	—	>95	<5
2	**L1**	33	27
3	**L2**	—	90
4	**L3**	18	52
5	**L4**	13	70
6	**L5**	10	63
7	**L6**	11	52

[a] Reactions were conducted with 0.05 mmol of **1a**. [b] Determined by ^{1}H NMR analysis using 1,4-dimethoxybenzene as an internal standard.

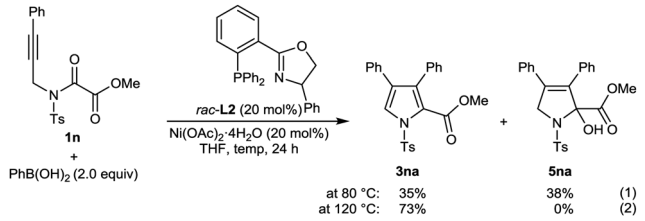
were added (entries 2–7). The achiral ligand **L1** gave **3aa** in 27% yield as determined by ^{1}H NMR analysis, but significant quantities of **1a** remained (entry 2). Chiral phosphinooxazolines **L2–L6** were then examined (entries 3–7) and of these, (*R*)-Ph-PHOX (**L2**) gave **3aa** in 90% NMR yield with no starting material remaining (entry 3).

With an effective ligand identified, the scope of the alkynamide was surveyed in reactions with $PhB(OH)_2$ (Table 2). Here, racemic **L2** was used and satisfactory results were obtained using a reduced catalyst loading of 5 mol%. These experiments gave pyrroles **3aa–3ma** in 46–99% yield.[14] Regarding the alkyne substituent, the reaction is compatible with a phenyl group (**3aa**), various *para*- (**3ba** and **3ca**), *meta*- (**3da**), and *ortho*-substituted phenyl groups (**3ea**), and a 2-thienyl group (**3fa**). Replacement of the benzoyl group of the amide with various *para*-substituted benzoyl groups is also possible (**3ga** and **3ha**[15]). *N*-Acyl groups with alkyl substituents are also tolerated. For example, pyrroles containing methyl (**3ia**), *n*-butyl (**3ja**), cyclopropyl (**3ka**), or cyclohexyl (**3la**) groups were formed in 54–92% yield, although for **3la**, increasing the temperature to 120 °C was required for high conversion. The process is not limited to aromatic groups at the alkyne, as shown by the reaction of 1,3-enyne **1m** to give pyrrole **3ma** in 99% yield. However, a substrate containing a methyl group on the alkyne only gave a complex mixture of products. Furthermore, the *N*-tosyl group is important for reactivity, as *N*-aryl alkynamides failed to cyclize.

Table 2 Scope of alkynamides[a]



[a] Reactions were conducted with 0.30 mmol of **1a–1m** in TFE (3 mL). Yields are of isolated products. [b] An acyclic tetrasubstituted alkene was also isolated in 23% yield (see ESI). [c] Conducted at 120 °C.



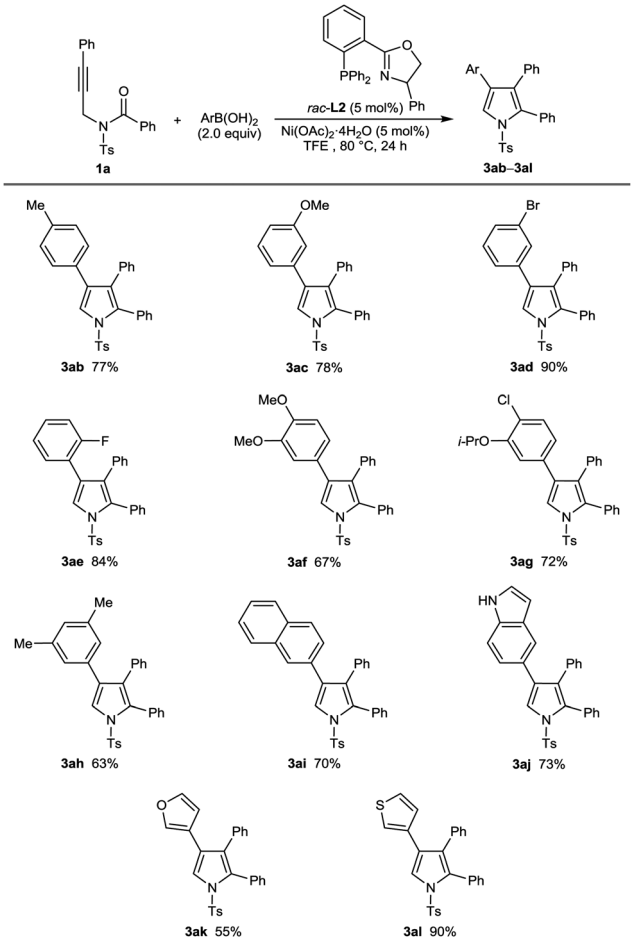
The cyclization of carbomethoxy-containing substrate **1n** failed under the standard conditions, and led only to decomposition by cleavage of the methyl oxalyl group. However, changing the solvent to THF and increasing the catalyst loading to 20 mol% successfully gave pyrrole **3na** in 35% yield, along with 3-pyrroline **5na** in 38% yield (eqn (1)). Increasing the temperature to 120 °C improved the yield of **3na** to 73%, and none of **5na** was observed (eqn (2)).

Pleasingly, this process is compatible with various(hetero)-arylboronic acids, and pyrroles **3ab–3aj** were obtained in 63–90% yield from alkynyamide **1a** (Table 3). The scope includes *para*- (**3ab**), *meta*- (**3ac** and **3ad**), *ortho*- (**3ae**), and disubstituted phenylboronic acids (**3af–3ah**) with methyl (**3ab** and **3ah**), halide (**3ad**, **3ae**, and **3ag**), or alkoxy groups (**3ac**, **3af**, and **3ag**). 2-Naphthylboronic acid (**3ai**) and various heteroarylboronic acids that include 5-indolylboronic acid (**3aj**), 3-furanylboronic acid (**3ak**), and 3-thienylboronic acid (**3al**) are also tolerated. No reaction was observed when 4-pyridinylboronic acid, methylboronic acid, or cyclopropylboronic acid were used.

To illustrate its utility, this methodology was applied to the preparation of pyrroles that have been used in the synthesis of 4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene (BODIPY) derivatives (Scheme 2).[3a,b,d] Removal of the tosyl group from **3aa** with KOH in MeOH/TFH (1:1) at 70 °C gave pyrrole **6** in >99% yield, which has previously been converted into BODIPY derivative **7**.[16] Alternatively, treatment of **3aa** with $POCl_3$ in DMF at 100 °C

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Table 3 Scope of boronic acids[a]

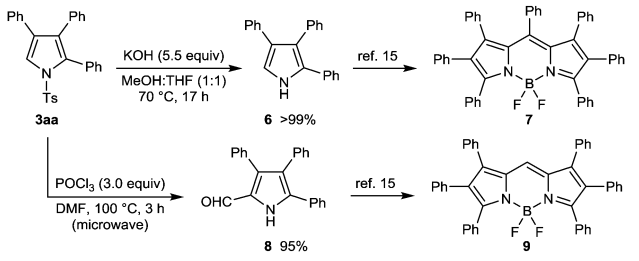


[a] Reactions were conducted with 0.30 mmol of **1a** in TFE (3 mL). Yields are of isolated products.

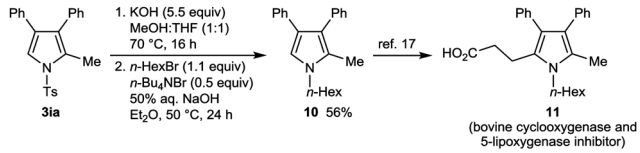
in a microwave reactor resulted in formylation with concomitant removal of the tosyl group to give pyrrole **8**, which has been used in the synthesis of BODIPY derivative **9**.[16]

In a further application, removal of the tosyl group of **3ia** with KOH was followed by immediate alkylation with *n*-hexyl bromide as described previously to give pyrrole **10** in 56% yield over two steps (Scheme 3).[17] Pyrrole **10** was previously converted in two steps into **11**, a known inhibitor of bovine cyclooxygenase and 5-lipoxygenase.[17]

In conclusion, we have developed a synthesis of diverse 2,3,4-trisubstituted pyrroles by the nickel-catalyzed reaction of *N*-tosyl alkynamides with arylboronic acids. These reactions rely upon



Scheme 2 Synthesis of precursors to BODIPY derivatives.



Scheme 3 Formal synthesis of bovine cyclooxygenase and 5-lipoxygenase inhibitor **11**.

the reversible *E*/*Z* isomerization of alkenylnickel species as a key step to enable cyclization to take place. This method was applied to the synthesis of pyrroles that are precursors to BODIPY derivatives, as well as an inhibitor of bovine cyclooxygenase and 5-lipoxygenase.[18]

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Conflicts of interest

There are no conflicts to declare.

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14 The reaction of alkynamide **1a** with 1.5 equivalents of $PhB(OH)_2$ under otherwise identical conditions to those shown in Table 2 gave pyrrole **3aa** in 81% yield, with the mass balance being unreacted starting material.

15 The structure of **3ah** was further confirmed by X-ray crystallography. CCDC 1861043†.

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18 The research data associated with this publication can be found at DOI: 10.17639/nott.372.

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