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Synthesis of Pyrroles by Nickel-Catalysed Arylative Cyclisations of Alkynamides

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

By

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September 2018

Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the Master degree in September 2017, 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. The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chieh-Hsu Chung

The following thesis contains results reported in the following publication:

Synthesis of Multisubstituted Pyrroles by Nickel-Catalyzed Arylative Cyclizations of *N*-Tosylalkynamides, Gillbard, S. M.; Chung, C.-H.; Karad, S. N.; Panchal, H.; Lewis, W.; Lam, H. W. *Chem. Commun.* **2018**, *54*, 11769-11772.
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Last but not least, thanks my parent, whiteout their supports I could not study in Nottingham, and thanks them for always being supportive and considerate. Congratulations on my brother marriage and having a baby this year.

Thanks everyone who has participated in my amazing journey.

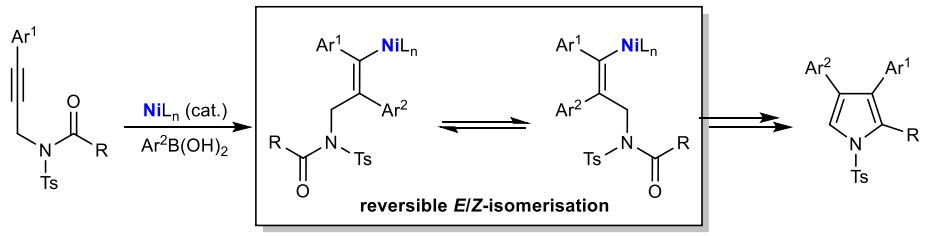
Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
Br	broad
Bu	butyl
cat.	catalyst
cod	1,5-cyclooctadiene
Cy	cyclohexane
d	doublet
DEPT	distortionless enhancement by polarisation transfer
DIPEA	*N*,*N*-diisopropylethylamine
DMF	dimethylformamide
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess(es)
equiv	equivalent
ESI	electrospray ionisation
Et	ethyl
RT	room temperate
g	gram
h	hour
Hex	hexyl
HRMS	high-resolution mass spectrometry
Hz	hertz
i	*iso*
IR	infrared
J	coupling constants
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz

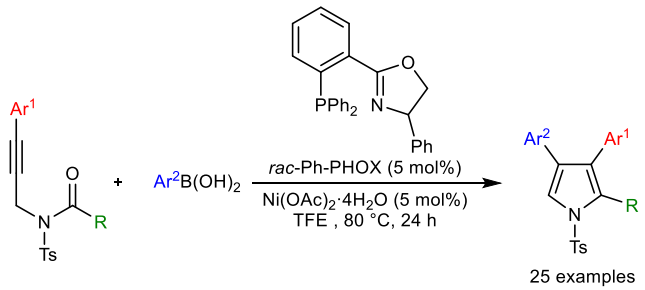
mL	millilitre
mmol	millimol
MOM	chloromethyl methyl
m.p.	melting point
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
N.R.	no reaction
Ph	phenyl
pin	pinacol
Pr	propyl
rac-	racemic
RT	room temperature
R_f	retardation factor
s	singlet
t	triplet
t	tert(iary)
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
UV	ultraviolet

Abstract

A nickel-based catalytic system for the *anti*-carbometallative cyclisations of alkynamides to arylboronic acids is described. The reactions proceed using catalytic nickel and (*rac*)-Ph-PHOX, to provide alkenylnickel species which can undergo reversible *E*/*Z*-isomerisation, followed by cyclisation onto an *N*-tosylamide to give 2,3,4-trisubstituted pyrroles.



Pyrroles are of widespread chemical significance, being present in numerous biologically active natural products. This methodology was used to generate a series of multisubstituted pyrroles and perform concise syntheses of BODIPY derivative and pyrrolyl propionic acid.



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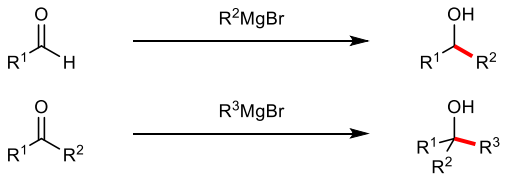
1. Introduction

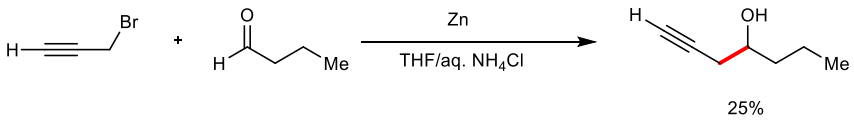
1.1 Nickel-Catalysed Nucleophilic Additions

Using organometallics to perform nucleophilic additions is very common in organic syntheses. The Grignard reaction is a well-known example which utilises organic magnesium halides to react with an aldehyde or ketone to form a secondary or tertiary alcohol (Scheme 1.1). In this reaction, a carbonyl group is attacked by a Grignard reagent as a nucleophile to generate a new carbon-carbon bond.



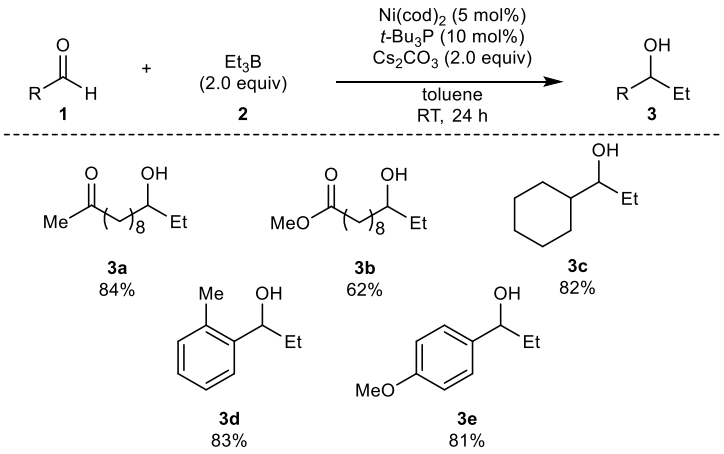
Scheme 1.1: Addition of Grignard Reagents to Carbonyl Groups

The Barbier reaction with an organozinc reagent is another example and has been widely used. Compared to Grignard reaction, the Barbier reaction is a one-pot synthesis, and it is unnecessary to prepare the organometallic reagent separately. Also, milder reaction conditions are often possible. For example, Scheme 1.2 shows that the reagent is able to run the reaction in water at room temperature.[1]



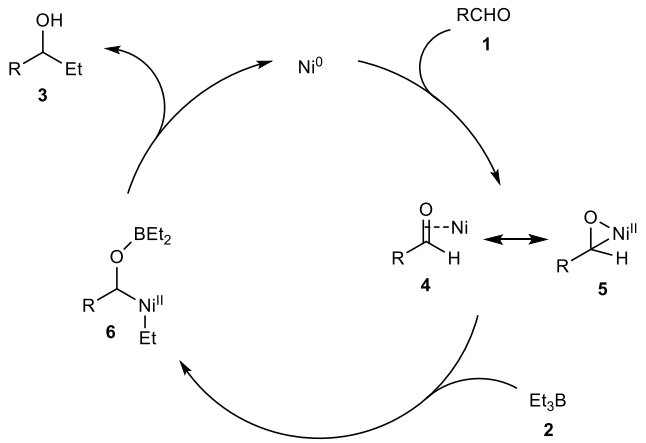
Scheme 1.2: Zinc-Mediated Coupling of Propargylic Bromides

Some first row transition-metal catalysts have also been used in nucleophilic additions, such as cobalt[2] and copper[3]. In 2005, Yorimitsu and co-workers[4] developed a nickel-catalysed alkylation of trialkylboranes **2** to aldehydes **1** to produce various secondary alcohols **3** (Scheme 1.3). The reaction afforded the desired alcohols in generally good yields. The alkylations tolerated aldehydes with cyclohexane, ketone or ester functionalities to form the corresponding alcohols **3a-3c** in 62-82% yields, and some examples of aryl aldehydes are also tolerated, including sterically hindered 2-methylbenzaldehyde and electron-rich 4-anisaldehyde, which underwent alkylation to generate **3d** and **3e** in 83% and 81% yields.



Scheme 1.3: Ni-Catalysed Alkylation of Aldehydes with Trialkylboranes

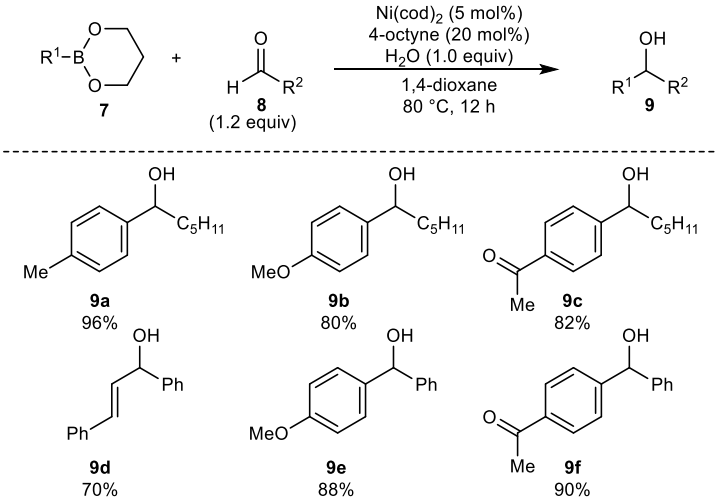
The catalytic cycle for this reaction was proposed (Scheme1.4). First, a nickel(0) species coordinates with the aldehyde **1** to give η^2-coordinated complex **4** or its resonance form **5**, which can undergo a transmetallation of Et_3B **2** to give the intermediate **6**. Then reductive elimination occurs, thus regenerating the nickel(0) species and forming the alcohol **3** which is protonated upon work-up.



Scheme 1.4: Proposed Catalytic Cycle for the Ni-catalysed Alkylation.

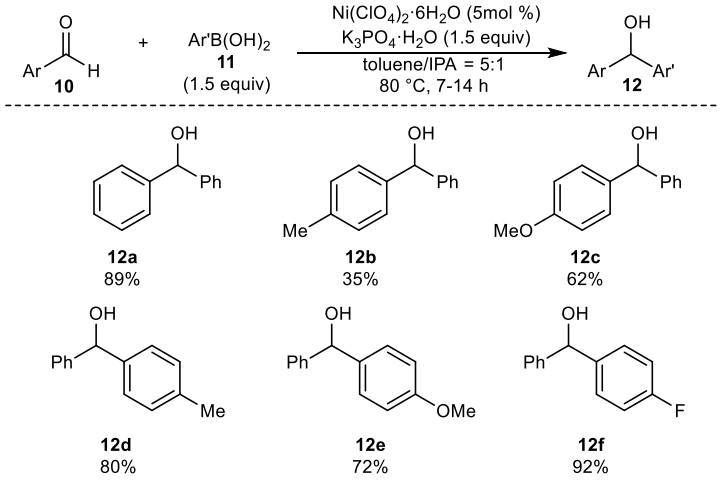
In the same year, Shirakawa and co-workers[5] published a method of nickel-catalysed addition of organoboronates to aldehydes, and the scope was based on various arylboronates **7** reacting with hexanal or benzaldehyde **8** (Scheme 1.5). The addition of arylboronate which contained electron-donating or -withdrawing groups at the *para*-position to hexanal gave in high yields (**9a**-**9c**). Also, it was discovered that the reactions of benzaldehyde to the same arylboronates were

obtained in 88% and 90% yields (**9e** and **9f**). The styryl group was also tested, and the corresponding allylic alcohol **9d** was furnished in good yield. According to the results of compounds **9c** and **9f**, the reaction was chemoselective for aldehydes in the presence of ketones. Furthermore, the compatibility of organoboronates compares favourably to other more nucleophilic organometallics, such as Grignard reagents, for electrophilic functional groups.



Scheme 1.5: Ni-Catalysed Addition of Organoboronates to Aldehydes.

An early study of nickel(II) catalysed addition was published by Bao and co-workers in 2008.[6] In the paper, nickel(II) catalysts was used for addition reactions of arylboronic acids to aryl aldehydes. In contrast to nickel(0) catalysts, nickel(II) are cheap and easy handle. Moreover, it also be the first example that using boronic acids as electrophiles in nickel-catalysed addition to a ketone. Because boronic acids are easily prepared and commercially available, this method is more attractive than using boronate esters.

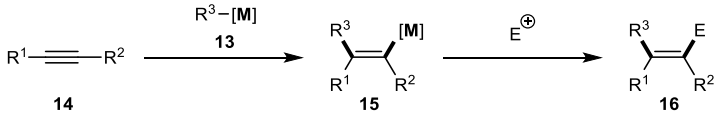


Scheme 1.6: Ni Salt-Catalyzed Arylation of Aryl Aldehydes with Arylboronic Acids

In the substrate scope (Scheme 1.6), the addition of phenylboronic acid to benzaldehyde showed great reactivity to give benzhydrol **12a** in 89% yield, but electron-rich aldehydes showed lower conversions and decreased yields of **12b** and **12c** (35% and 62% respectively), some arylboronic acid variations were also tested, such as electron-donating and -withdrawing groups at the *para*-position of arylboronic acid, and the corresponding diarylmethanols **12d**-**12f** were obtained in good yields.

1.2 Nickel-Catalysed Carbometallations of Alkynes

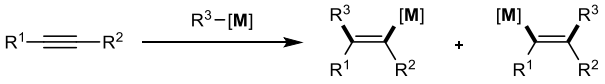
The additions of organometallics to alkynes has been widely used for generating highly substituted alkenes in different methods.[7] In general, the organometallic reagent **13** coordinates with an alkyne **14** and then inserts into the triple bond to form a metal-carbon bond and a carbon-carbon bond, where the two new bonds are formed on the same side of the resulting carbon-carbon double bond **15**. Then the alkenylmetal **16** intermediate can easily react with an electrophile to give tetrasubstituted alkenes (Scheme 1.7).



Scheme 1.7: Additions of Organometallics Across Alkynes

The key step for controlling the geometric chemistry is the migratory insertion. Commonly, a regioisomeric mixture of products is given by the addition of

unsymmetrical alkynes (Scheme 1.8). In order to avoid undesirable products, regiocontrol is needed, and therefore significant research focuses on controlling this issue.

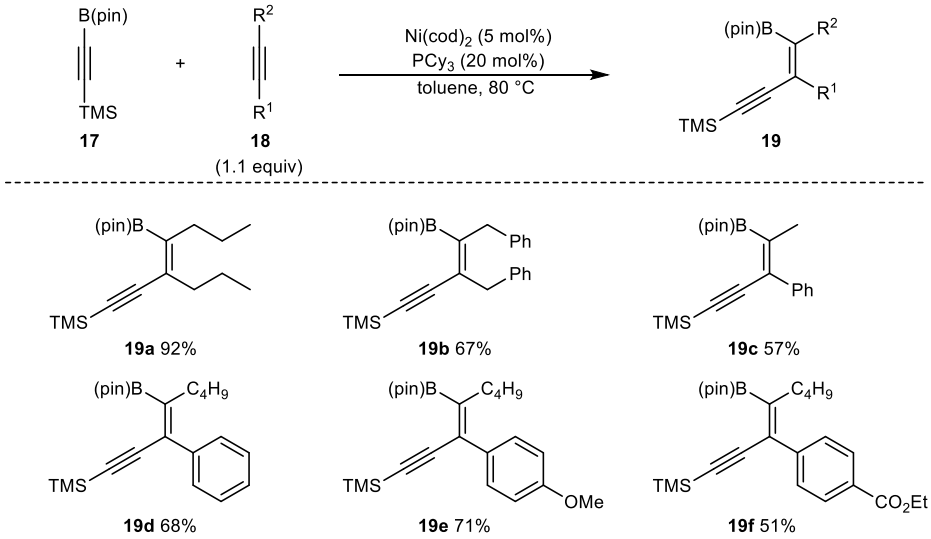


Scheme 1.8: Mixtures of Products from Low Regiocontrol Reaction.

More research has shown that varying the metal reagents can give high regioselectivity. Utilising stoichiometric organometallic reagent, such as Mg, Li or Cu,[8] to undergo these transformations has been well-studied, and a growing number of transition-metal catalyst systems are ever developing.[9]

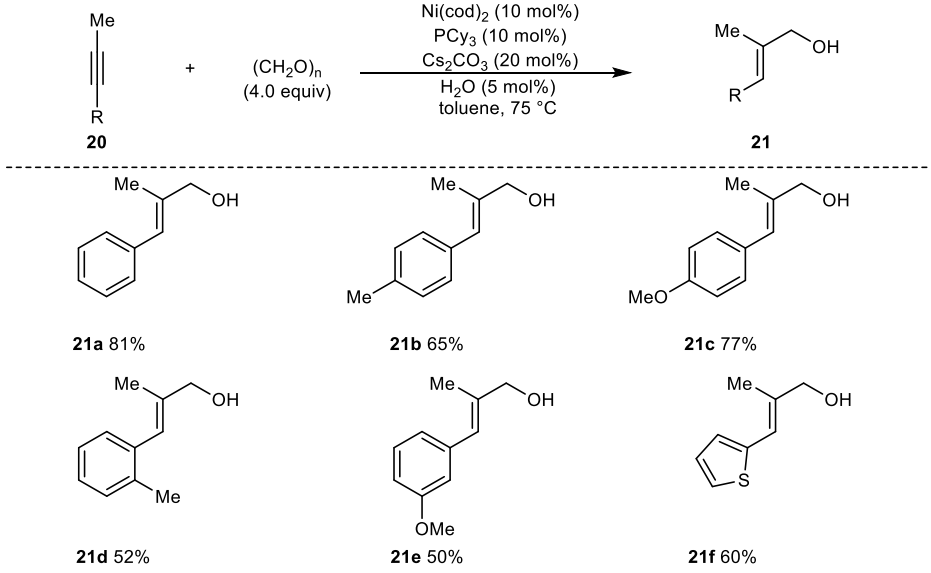
An early example of nickel-catalysed carbometallations of alkynes was reported by Suginome and co-workers.[10] The report showed a range of alkynylboranes react with alkynes to form the corresponding addition product in good yields and high regioselectivity.

The substrate scope (Scheme 1.9) was based on addition of silyl-substituted alkynylborane **17** with aryl or alkyl alkynes **18**. In the first example, reaction of 4-octyne was showed an excellent yield to form the corresponding alkynylboration product **19a** in 92%. Under the same condition, reaction of dibenzylacetylene afforded the compound **19b** in lower yield. Furthermore, different unsymmetrical 1-aryl-1-alkynes showed good reactivity giving rise to the product **19c**-**19f** in 51-71% yields. Most of the entries showed 90% desirable product, and high regioselectivity is achieved in this reaction.



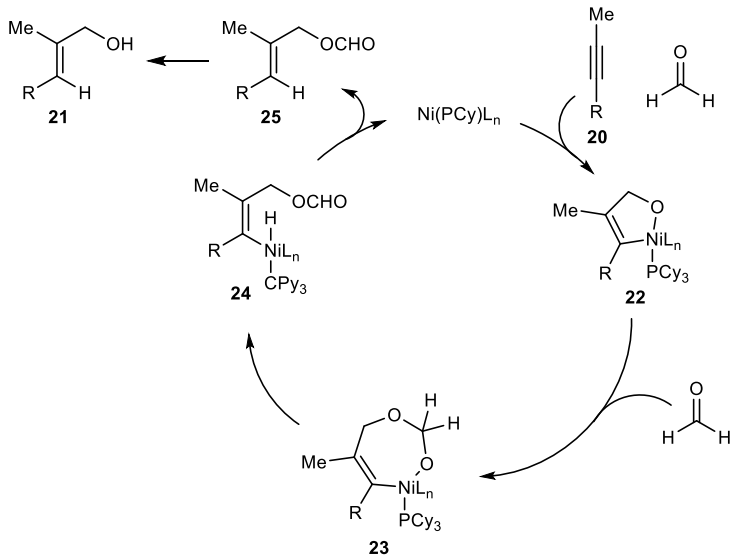
Scheme 1.9: Ni-Catalysed Alkynylboration of Alkynes with **18**

In 2011, Krische and co-workers[11] reported an example of nickel-catalysed hydroxymethylation of alkynes **20** with formaldehyde, and it was a new method for synthesising trisubstituted allylic alcohols (Scheme 1.10). The addition of 1-phenyl-1-butyne to formaldehyde produced alkene **21a** in 81% yield. Then, different electron-donating and -withdrawing group at the *para*-position (**21b** and **21c**) were showed in good yields, but increasing the steric hindrance at the *meta*- or *ortho*-position resulted in lower yields (**21d** and **21e**). Aromatic heterocycles were also able to effectively activate in this reaction (**21f**). In general, the scope of the reaction was good where the desired product was provided with >95% regioselectivity.



Scheme 1.10: Ni-Catalysed Hydrohydroxymethylation of Alkyne **20**

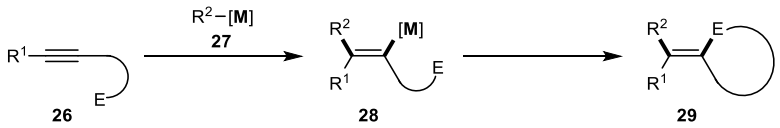
Krische and co-workers exploited the proposed mechanism to illustrate the stoichiometric reaction (Sheme 1.11). First of all, nickel catalysts underwent oxidative coupling to alkyne **20** and formaldehyde to generate nickeladihydrofurans **22**, followed by reacting with excess formaldehyde and forming metallacycles **23**. Then a *β*-hydride elimination occurred to furnish conjugated enones **24**. Finally, formate esters **25** were cleaved upon isolation to give the resulting alkene **21**.



Scheme 1.11: Proposed Catalytic Cycle for Ni-Catalysed Alkyne Hydrohydroxymethylation

1.3 Nickel-Catalysed Carbometallative Cyclisations of Alkynyl Electrophile

Carbometallative cyclisation is a reaction which combines carbometallation and intramolecular cyclisation in a chemical transformation, and the inseparable intermediate is the key intermediate of the reaction. As example showed in Scheme 1.12, after the migratory insertion, alkenylmetal species **28** is formed by addition of organometallics **27** to alkynes **26**. Then, cyclisation occurs spontaneously, so that the alkenylmetal species can cyclise onto the electrophile to generate the cyclic compound **29**.

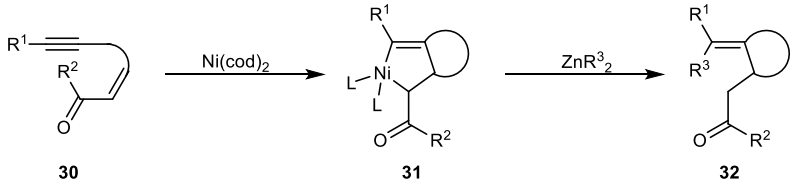


Scheme 1.12: Carbometallative Cyclisation of Alkynyl Electrophile.

Because cyclisation is followed by addition sequentially in the same pot and same process, this reaction is a domino reaction. The main advantages of domino reactions

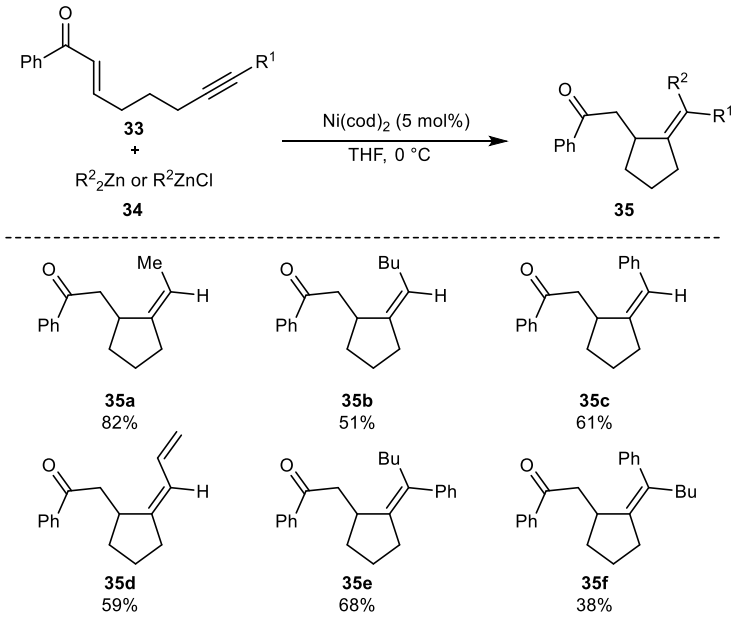
include reduction of reaction time and work required by combining several reactions, as well as the complex products that can be made in the overall sequence.

In 1996, Montgomery and Savchenko[12] published research of nickel-catalysed carbometallative cyclisations of alkynyl enones. First, a cyclisation of alkyne **30** with alkene species form the cyclic alkenylmetal intermediates **31**. The intermediates are trapped by the organozinc reagents to complete transmetallation, and substituted alkenes **32** are produced after reductive elimination (Scheme 1.13).



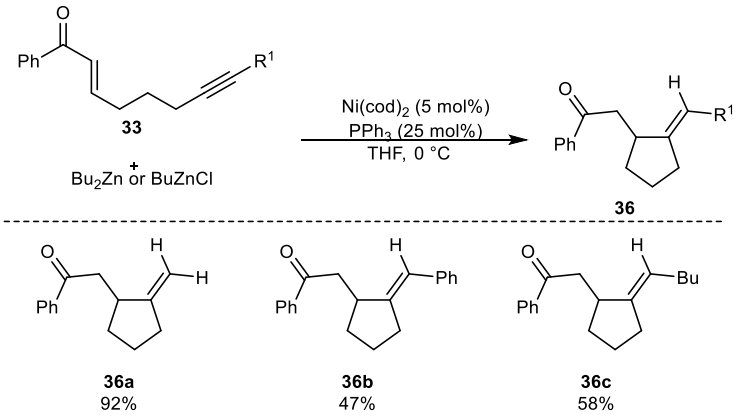
Scheme 1.13: Proposed Mechanism for Ni-Catalysed Carbometallative Cyclisations

The scope of the alkylative cyclisations was extended to include products containing cyclic tri- or tetrasubstituted alkenes (Scheme 1.14). Acyclic non-enolisable enones **33** were tested with aryl-, alkenyl- and alkyl-substituted organozinc reagents **34** to form the corresponding product **35** in 51-82%. Comparing compound **35e** and **35f**, the specific form of diastereomers could be selectively produced by different substrate and organozinc combinations.



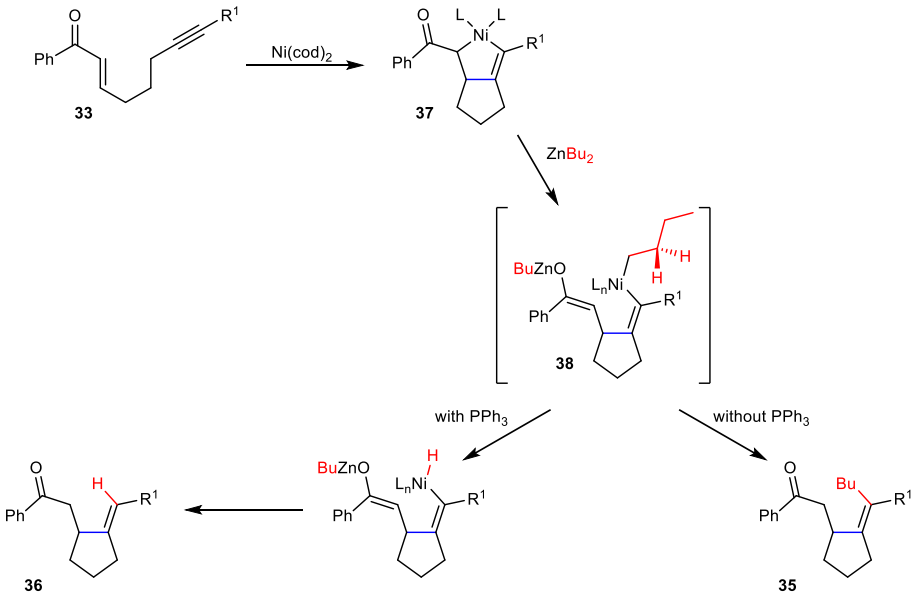
Scheme 1.14: Ni-Catalysed Alkylative Cyclisation

In the same paper, another carbometallative cyclisation pathway was also demonstrated. Instead of alkylative cyclisation, reductive cyclisations occurred in the presence of PPh_3 ligand (Scheme 1.15). The terminal alkyne showed high reactivity in the reductive cyclisation to generate terminal alkene **36**, but lower yields were obtained when internal alkynes were used to form trisubstituted alkenes (**36b** and **36c**).



Scheme 1.15: Ni-Catalysed Reductive Cyclisation

The proposed mechanism of this cyclisation showed that nickelcycle **37** is a common intermediate for both alkylative cyclisation and reductive cyclisation (Scheme1.16). In the absence of PPh_3 ligands, reductive elimination was followed by transmetallation between nickel and zinc to furnish tetrasubstituted alkene products **35**. On the other hand, when the PPh_3 ligands were added, β-hydride elimination occurred before reductive elimination, and trisubstituted alkenes **36** were produced. Montgomery speculated that intermediate **38** was more electron-rich when the excess PPh_3 was present, and therefore β-hydride elimination was favoured. Alternatively, the PPh_3 ligand causes a higher steric hindrance to form alkyl and alkenyl group in opposite orientation in intermediate **38**, thus preventing reductive elimination.

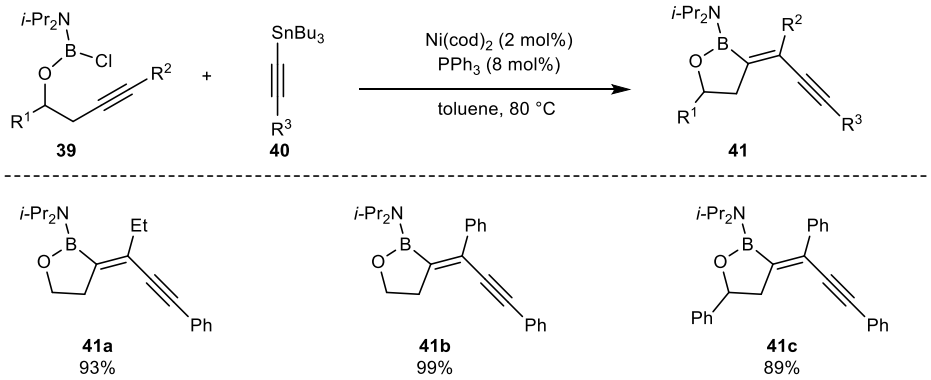


Scheme 1.16: Proposed Two Pathways for Alkylative and Reductive Cyclisations

1.4 Nickel-Catalysed *anti*-Carbometallative Cyclisations of Alkynyl Electrophile

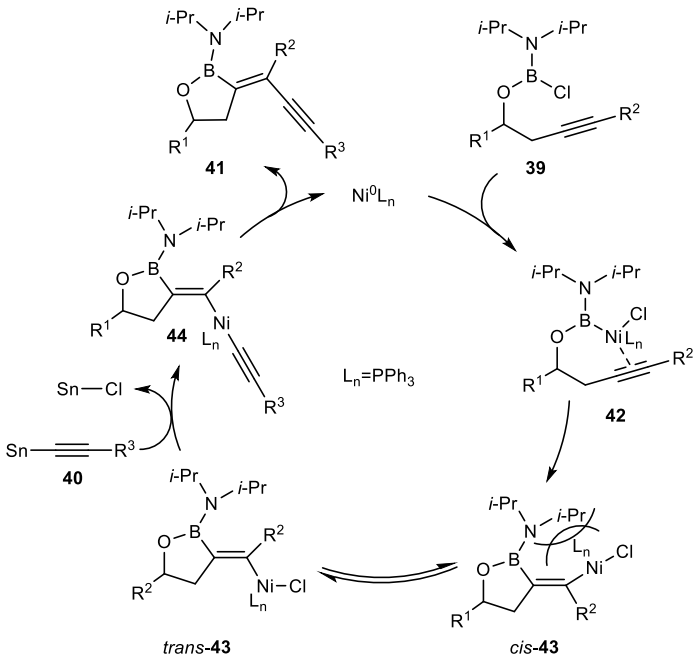
As discussed in the previous section, the additions of organometallics to alkynes undergo the migratory insertion to give substituted alkenes. In this transformation, *syn*-addition products are common because migratory insertion from two new bonds on the same side, but a few examples of *anti*-addition could be found in recent reports. It was proposed that an *E*/*Z*-isomerisation occur to give the *anti*-addition products.

An early example of nickel-catalysed *anti*-carbometallation of alkynes was published by Suginome and Yamamoto.[13] In the paper (Scheme 1.17), chloroboryl homopropargylic ethers **39** underwent *trans*-alkynylboration with a range of alkynes **40** to given the corresponding products **40** in remarkable yields.



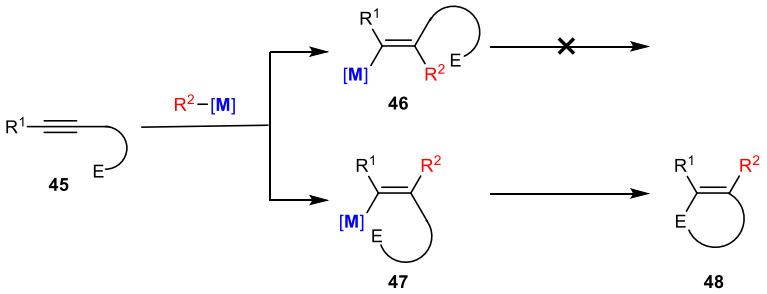
Scheme 1.17: Ni-Catalysed *trans*-Alkynylboration of Alkynes

The proposed mechanism for the *trans*-alkynylboration was presumed as shown in Scheme 1.18. First, nickel coordinates with the alkyne **39**, followed by oxidative addition of the B-Cl bond to form the intermediate **42**. After migratory insertion, a postulated reversible *E/Z*-isomerisation occured which the steric repulsion between PPh_3 ligands and the diisopropylamino group drove *cis*- to *tans*-alkenylnickel species **43**. Finally, the nickel species underwent transmetallation with organotin reagents **40** to generate intermediate **44**, followed by reductive elimination to regenerate nickel catalysts and to give the product **41**.



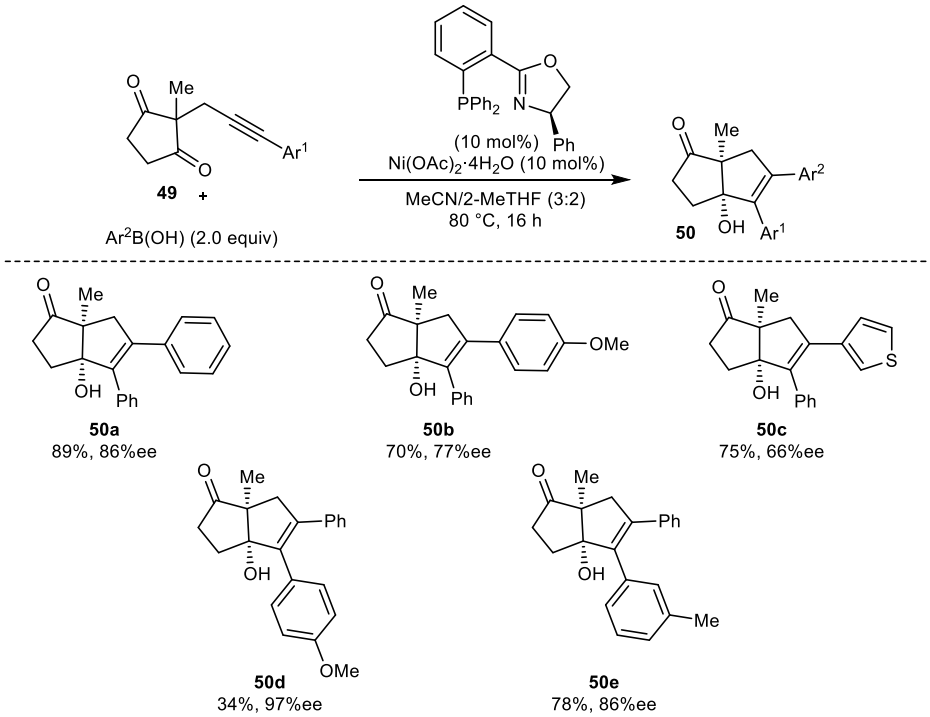
Scheme 1.18: Proposed Catalytic Cycle for Ni-Catalysed *trans*-Alkynylboration

In 2006, Lam group[14] developed the first example of nickel-catalysed *anti*-carbometallative cyclisations of alkynes (Scheme 1.19). After the migratory insertion of the alkynes **45**, a *syn*-carbometallation intermediate **46** is impossible to cyclise due to geometric constraints. On the contrary, After the reversible *E/Z*-isomerisation, an *anti*-carbometallation intermediate **47** shows correct geometry for cyclisation to furnish the cyclic product **48**.



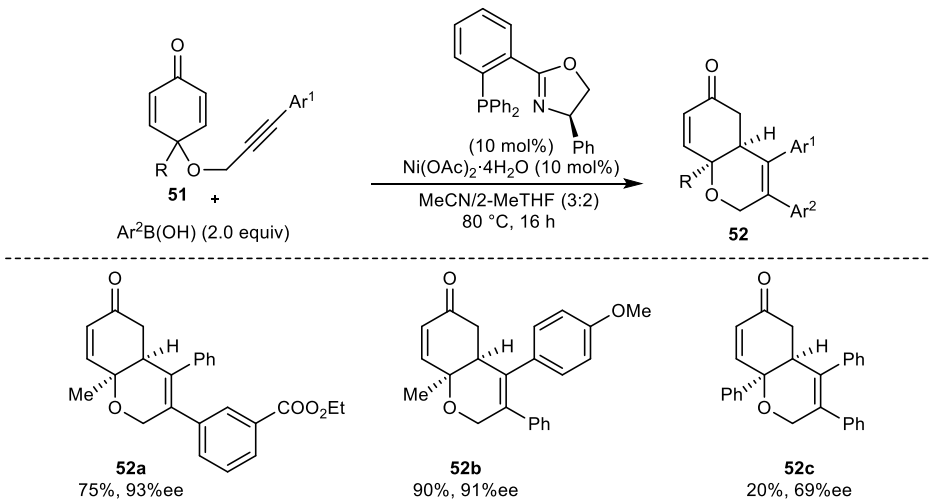
Scheme 1.19: Carbometallative Cyclisation of Alkynyl Electrophiles

In light of these results, the methodology was explored and wildely used in organic synthesis. The first scope showed cyclisations of diverse arylboronic acid to alkynone **49** (Scheme 1.20), and cyclic product **50a**-**50c** were obtained in 70-89% yields and high enantioselectivities. In addition, variation of the alkynones were tested, resulting in the desired product **50d** and **50e**.



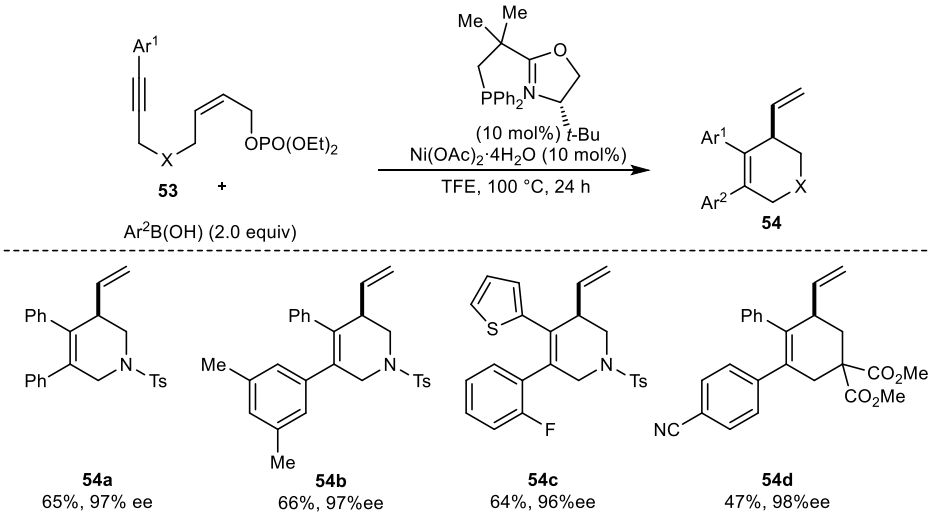
Scheme 1.20: Ni-Catalysed *anti*-Carbometallative Cyclisation of Cyclic 1,3-Diketones

Moreover, substrates containing alkynes tethered to a cyclohexa-1,3-dienone **51** were also highly effective to form the corresponding product (**52a** and **52b**) in outstanding yields and enantioselectivities (Scheme 1.21). Finally, changing the substituent at the quaternary centre to alkyne **52c** was also possible.



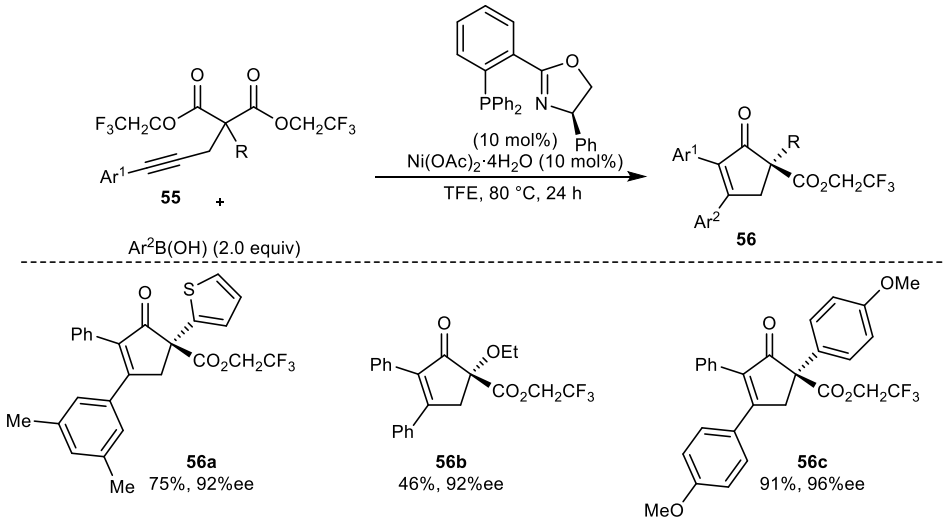
Scheme 1.21: Ni-Catalysed *anti*-Carbometallative Cyclisation of Alkynyl Cyclohexa-1,3-dienones

Some other useful reports form the Lam group, such as nickel-catalysed intramolecular allylic alkenylations[15] and nickel-catalysed desymmetrisations[16]. In Scheme 1.22, a range of allylic phosphates **53** underwent allylic alkenylations with various arylboronic acid to give six-membered ring products **54a-54d** in acceptable yields and excellent enantioselectivities.



Scheme 1.22: Ni-Catalysed *anti*-Carbometallative Cyclisation of 1,6-enynes

Also, malonate esters were investigated to synthesise chiral cyclopent-2-enone, and the scope of this reaction with respect to the alkynyl malonate **55** was then explored in desymmetrisations with arylboronic acid (Scheme 1.23). This gave cyclopent-2-enones **56** in generally good yields (73–92%) and remarkable enantioselectivities.



Scheme 1.23: Ni-Catalysed *anti*-Carbometallative Cyclisation of Alkynyl Malonate

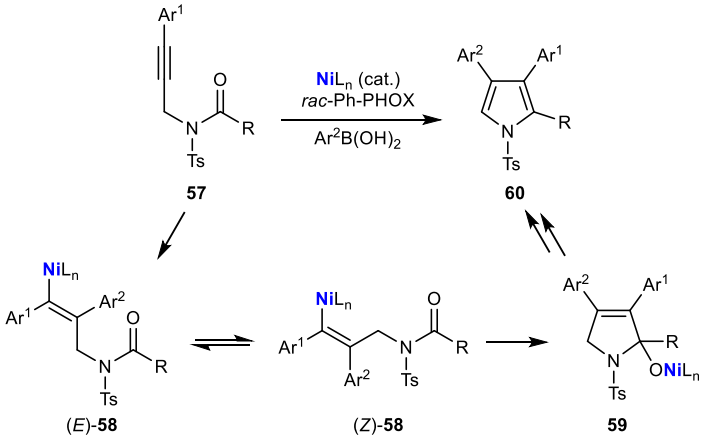
Overall, while nickel-catalysed *anti*-carbometallative cyclisation have been used in a few of synthesises, it has not been well explored. This methodology would achieve a wide range of alkynyl electrophiles to form important cyclic structural in a single transformation.

2. Result and Discussion

2.1 Synthesis of Pyrroles by Nickel-Catalysed Arylative Cyclisations of Alkynamides

2.1.1 Aims and Objective

Based on the examples discussed in the previous section, some reports[14–16] of nickel-catalysed *anti*-carbometallative cyclisations have been published, and a few types of alkynyl electrophiles have been developed to form various carbo- and heterocyclic products. However, amides have not yet been investigated in this reaction. Amides are rarely used in common nucleophilic additions due to their low electrophilicity and reactivity. Nevertheless, the successful utilisation of amides could provide a range of multisubstituted pyrroles (Scheme 2.1).



Scheme 2.1: Proposed Synthesis of Pyrroles

Pyrroles are common heterocycles which have been found from much of the World's flora and fauna.[17] Due to their characteristic planar and electron rich properties, pyrroles have showed high reactivity in many biological contexts and as a result scientists have increased their research into biological or synthetic studies. Many useful products containing pyrrole have been isolated and identified from natural sources, moreover a growing number of total syntheses have been explored. Some examples as shown in Figure 2.1, storniamide A was isolated in 1996, and it was confirmed to have antibiotic activity against Gram-positive bacteria.[18] Also, the first total synthesis was reported in 1999 by the Boger group.[19] Lycogarubin C was another representative example which was found in 1994, and it was classified as chromopyrrolic acid (CPA) and exhibited inhibition of protein kinases as well as topoisomerase I.[20] Furthermore, rigidin E is active inhibitor of against calmodulin brain phosphodiesterase,[21] and atorvastatin has been used as inhibition of HMG-CoA reductase (HMGR).[22]

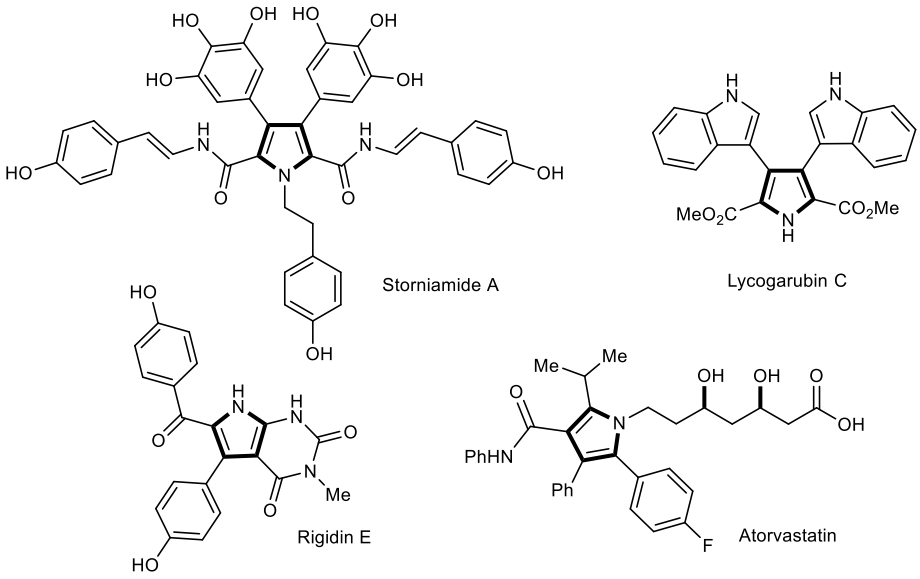
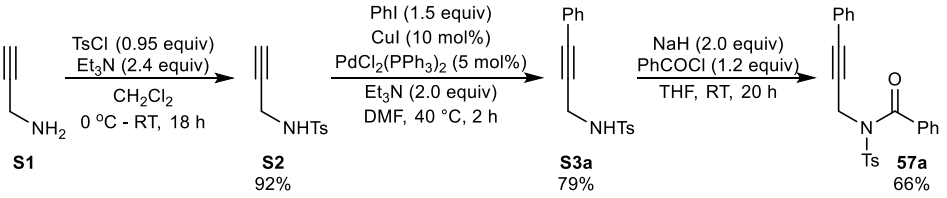


Figure 2.1: Natural Products Containing Multisubstituted Pyrroles

2.1.2 Preparation of Substrates

It was decided to use the propynylamide **57a** for the reaction optimisation and substrates was synthesised according to literature procedures[23–25]. The method for the synthesis of substrate **57a** began with the commercially available propynylamine **S1** which underwent tosylation to form protected propynylamine **S2**. Through a Sonogashira coupling reaction, the phenylpropynyl amine **S3a** was successfully generated. Then acetylation formed the alkynamides **57a** in good yields. A range of substrates could be made undergoing same pathway by manipulation of Sonogashira coupling reactions and acetylation to give a selection of alternative alkynamides[23,25].



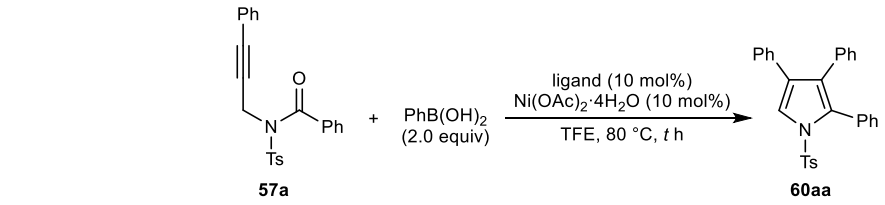
Scheme 2.2: Substrates **57a** Synthesis

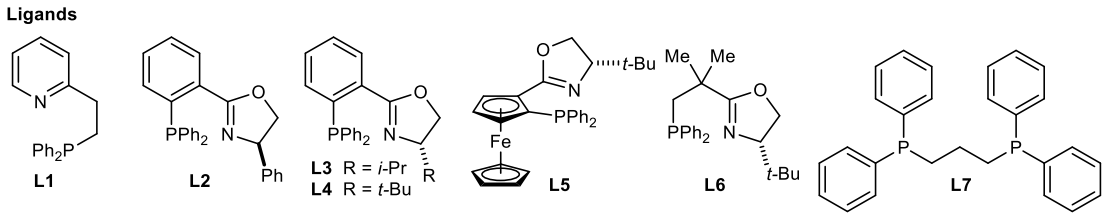
2.1.3 Optimisation

Based on the previous report from the Lam group,[14] which had resulted in the development of a nickel-catalysed system for the arylative cyclisations, it was decided to use similar conditions in this reaction (Table 2.1). The investigations began with reaction of alkynamide **57a** to $PhB(OH)_2$ giving pyrrole **60aa**, which was conducted

in the presence of $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) in 2,2,2-trifluoroethanol (TFE) at 80 °C. However, these reactions were unsuccessful at producing the desired product **60aa**. Then, a screen of P,N-ligands (10 mol%) was undertaken (entries 2-13). Entries 2-7 showed that the reactions were not completed in after 16 h. Therefore, the reaction time was increased to 24 h with achiral ligand **L1**, which gave **60aa** in 27% yield as determined by ^{1}H NMR analysis, but the starting material **57a** still remained (entry 8). Pleasingly, chiral phosphinooxazolines **L2**–**L6** were examined (entries 9-13), and (*R*)-Ph-PHOX (**L2**) gave **60aa** in 90% NMR yield with no starting material remaining (entry 9). Finally, diphosphine ligand dppp (**L7**) was also tested, but no better result was found.

Table 2.1: Evaluation of reaction conditions[a]



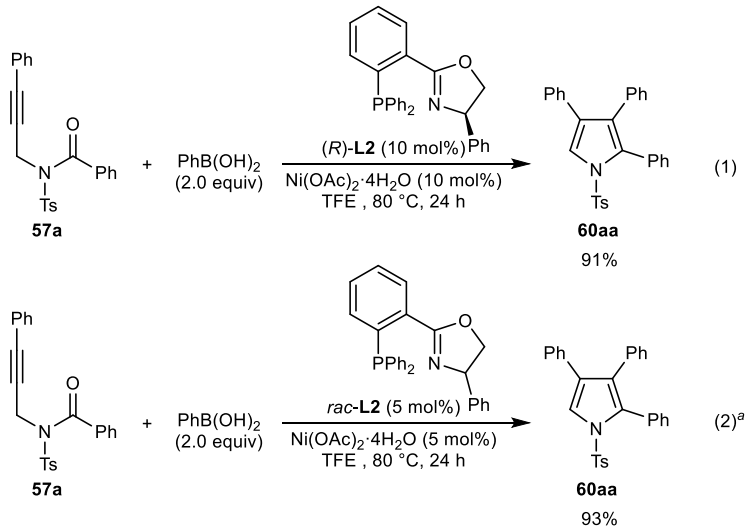


Entry	Ligand	Time	Yield of **57a** [%][b]	Yield of **60aa** [%][b]
1	–	24	>95	<5
2	**L1**	16	85	<5
3	**L2**	16	39	32
4	**L3**	16	19	52
5	**L4**	16	9	60
6	**L5**	16	86	<5
7	**L6**	16	20	54
8	**L1**	24	33	27
9	**L2**	24	–	90
10	**L3**	24	18	52
11	**L4**	24	13	70
12	**L5**	24	10	63

13	**L6**	24	11	52
14	**L7**	24	19	29

[a] Reactions were conducted with 0.05 mmol of **57aa**. [b] Determined by ^{1}H NMR analysis using 1,4-dimethoxybenzene as an internal standard.

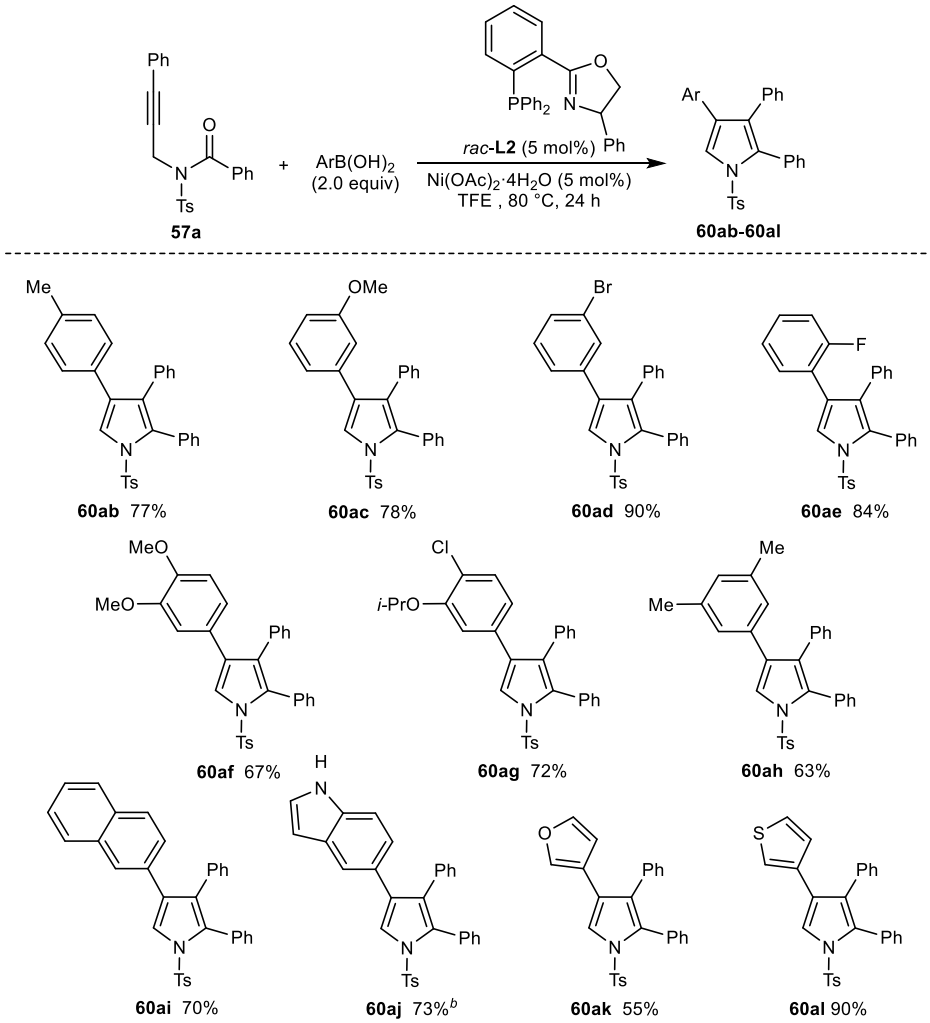
With optimised conditions in hand, the reaction was extended on a 0.3 mmole scale, and resulting pyrrole **60aa** was generated in 91% yield [Scheme 2.3, Eq. (1)]. Instead of using (*R*)-Ph-PHOX ligand, the racemic version was used which showed an excellent yield (93%) and the catalyst loading could be lowered to 5 mol% [Eq. (2)].



Scheme 2.3: Reaction Scale-up and Decrease of Catalyst Loading
[a] Reaction carried out by S. M. Gillbard.

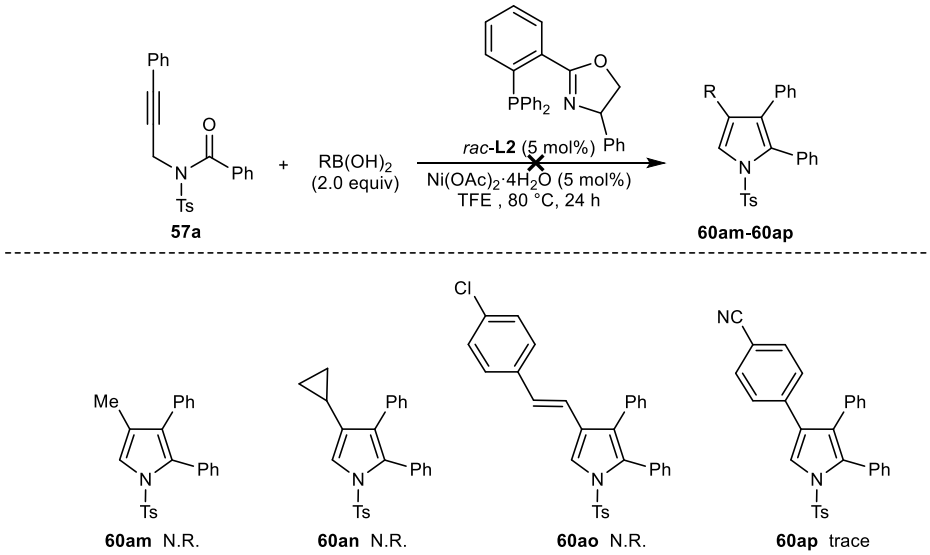
2.1.4 Variation of Boronic Acid

With the optimised reaction conditions in hand, we turned our attention to investigating the scope of boronic acid, and pyrroles **60ab**-**60al** were obtained in generally good yields from alkynyamide **57a** (Scheme 2.4). The scope included *para*-(**60ab**), *meta*- (**60ac** and **60ad**), and *ortho*-substituted (**60ae**) phenylboronic acids with different electron-donating group. Also, disubstituted phenylboronic acids with methyl (**60ah**), halide (**60ag**), or alkoxy groups (**60af** and **60ag**) were tolerated. Furthermore, 2-naphthylboronic acid (**60ai**) and various heteroarylboronic acids were possible, including 5-indolylboronic acid (**60aj**), 3-furanylboronic acid (**60ak**), and 3-thienylboronic acid (**60al**).



Scheme 2.4: Scope of Boronic Acids[a]
[a] Reactions were conducted with 0.30 mmol of **57a** in TFE (3 mL). Yields are of isolated products. [b] Reaction carried out by S. M. Gillbard.

Unfortunately, no reaction occurred using alkylboronic acids or alkenylboronic acid (Scheme 2.5), such as methyl (**60am**), cyclopropyl (**60an**), and styryl boronic acids (**60ao**). 4-Cyanophenylboronic acid, which contains a strong electron-withdrawing group at the *para*-position, was also tested, but only trace of pyrrole **60ap** was detected by ^{1}H NMR analysis.



Scheme 2.5: Scope of Boronic Acids Not Work[a]
[a] Reactions were conducted with 0.30 mmol of **57a** in TFE (3 mL).

By growing crystals of pyrrole **60af** that were suitable for X-ray analysis, the structures of the pyrroles were confirmed (figure 2.2).

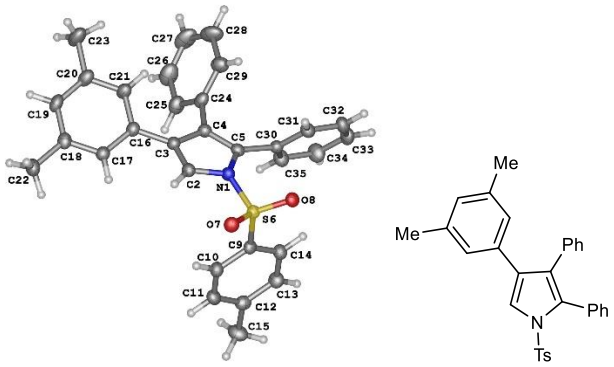
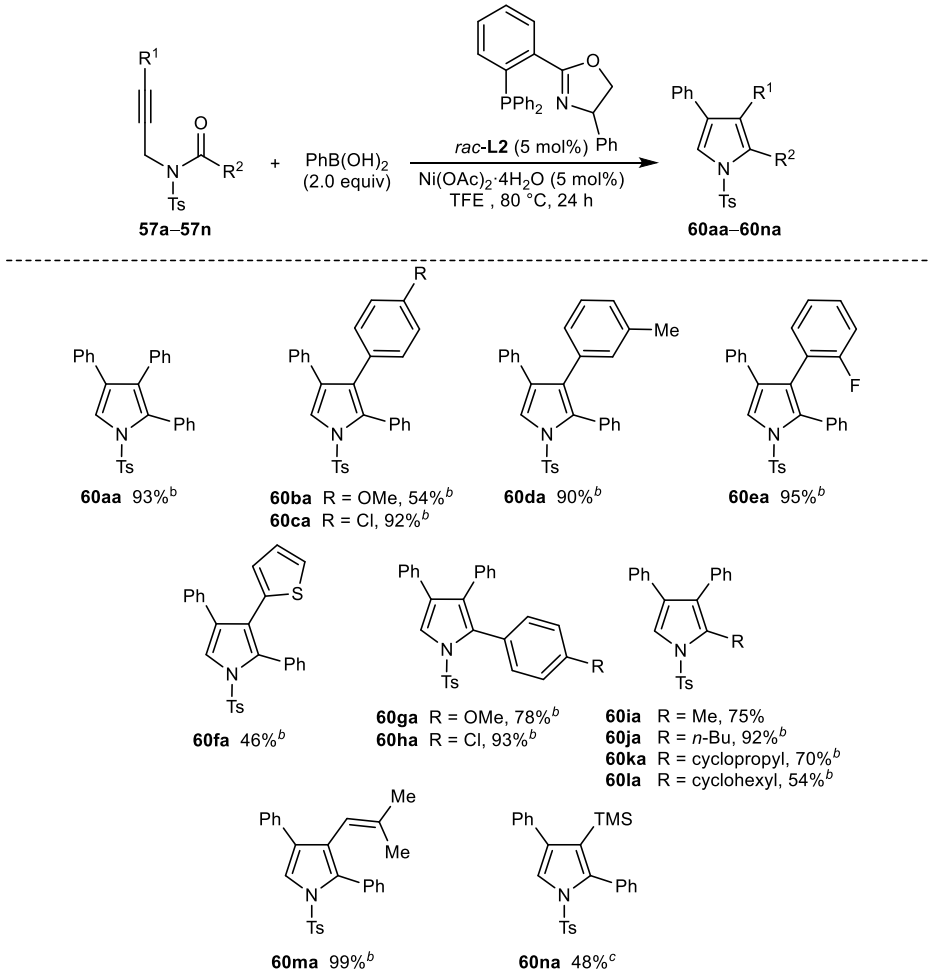


Figure 2.2: X-Ray Structures of **60af**[a]
[a] X-ray crystallography carried out by Dr W. Lewis

2.1.5 Substrate Scope

The investigations of substrate scope carried out by Simone Gillbard, and the research was based on a range of alkynamides **57a**-**57n** with $PhB(OH)_2$ to give trisubstituted pyrroles **60aa**-**60na**. The reaction is compatible with alkyne substituent containing phenyl group (**60aa**), different electron-donating (**60ba** and **60da**) or halide (**60ca** and **60ea**) substituted benzenes, and a 2-thienyl group (**60fa**). Instead of the benzoyl group of the amide, *para*-substituted benzenes (**60ga** and **60ha**) were tried in good yield. *N*-Acyl groups with alkyl substituents are also possible, such as methyl (**60ia**), *n*-butyl (**60ja**), cyclopropyl (**60ka**), or cyclohexyl (**60la**) group. Pleasingly, the reaction was

not only effective with aromatic groups at the alkyne, the conversion of 1,3-enyne group gave pyrrole **60ma** in 99% yield, and the TMS group (**60na**) was also tolerated.



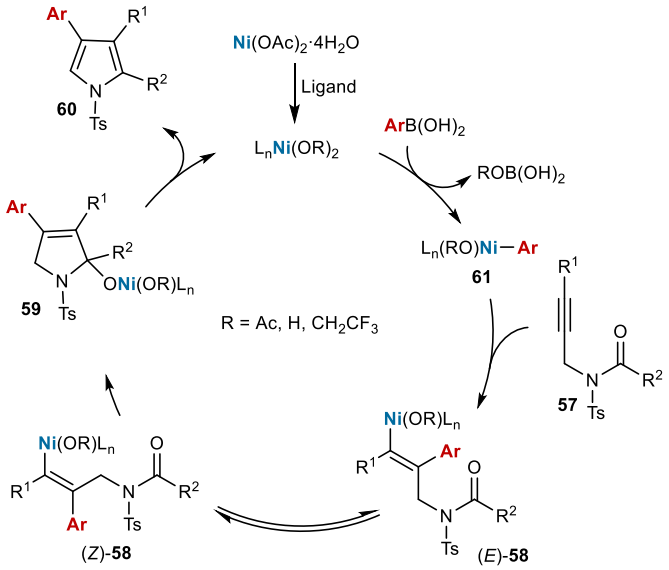
Scheme 2.6: Scope of alkynamides[a]

[a] Reactions were conducted with 0.30 mmol of **57a**–**57n** in TFE (3 mL). Yields are of isolated products. [b] Reaction carried out by S. M. Gillbard. [c] Determined by ^{1}H NMR analysis using 1,4-dimethoxybenzene as an internal standard.

2.1.6 Proposed Mechanism

The proposed catalytic cycle of *anti*-carbometallative cyclisation of alkynamide is shown in Scheme 2.7. Transmetallation of $ArB(OH)_2$ with the nickel complex formed an arylnickel species **61**, which was followed by carbonickelation of the alkyne **57** and forming (*E*)-**58**. Although (*E*)-**58** cannot cyclise onto the amide because of geometric constraints, after the reversible *E*/*Z*-isomerisation, (*Z*)-**58** shows correct geometry for attacking carboxyl group to furnish nickel alkoxide **60**. Incorporating a tosyl group into alkynamide was expected to increase the reactivity of this nucleophilic addition

due to electron-withdrawing property of tosyl group. Finally, dehygration of **59** regenerates the nickel species and provides the 2,3,4-trisubstituted pyrrole **60**.



Scheme 2.7: Proposed Catalytic Cycle of Ni-Catalysed Arylative Cyclisations of Alkynamides

2.2 Application

Pyrroles are useful building blocks in many synthetic applications. To illustrate the synthetic utility of this reaction, the methodology was applied to the preparation of natural products or useful materials.

2.2.1 Towards the Synthesis of Lamellarin D Trimethyl Ether

The earliest attempt to apply this methodology was in the synthesis of lamellarins, which exhibit a wide range of useful biological activities, and more than 50 lamellarins have been invented.[26] One of the most prominent member in lamellarins family is lamellarin α 20-Sulfate, which was investigated to use for HIV-1 integrase inhibitor[27]. Because most lamellarins contain a tri- or tetra-substituted pyrrole core (Scheme 2.3), it gave us high interest and intention for synthesis lamellarins by *anti*-carbometallative cyclisation. We start the first strategy with lamellarin D. According to some studies, lamellarin D is highly effective against multidrug resistance (MDR) cancer cell[28], and its first total synthesis was published by Iwao and co-workers in 1997[29].

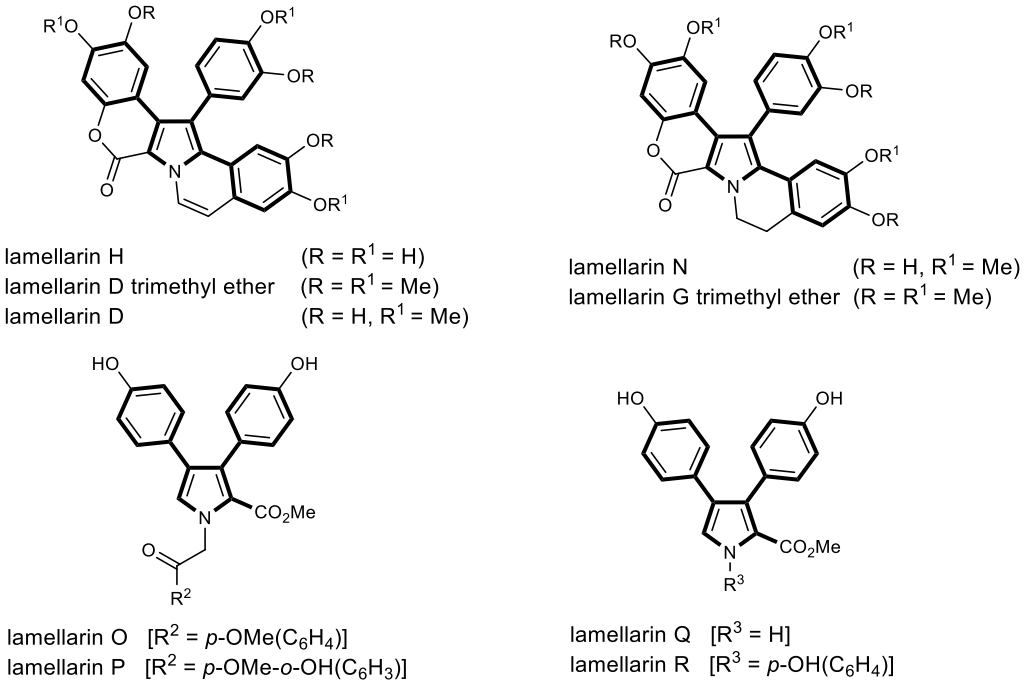
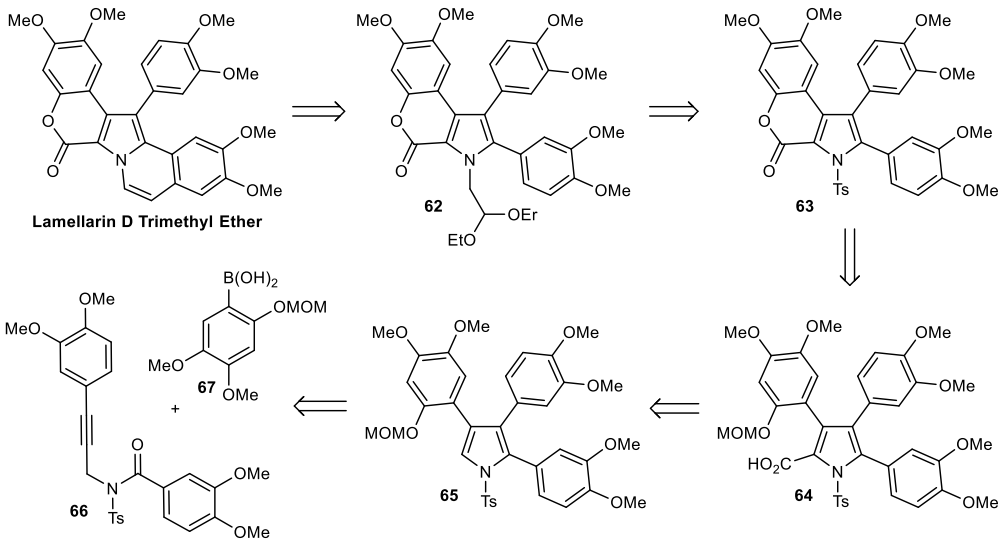


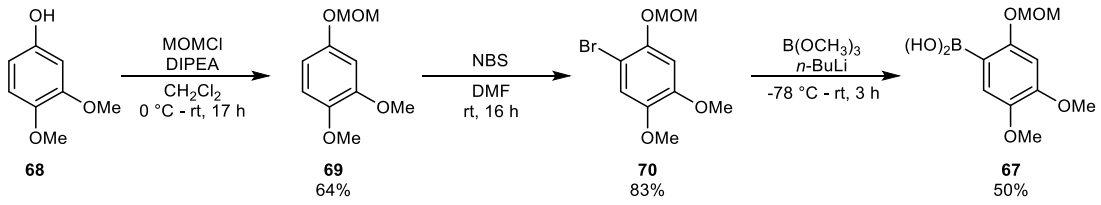
Figure 2.3: Representative Members in Lamellarin Family

Retrosynthetically, we envisioned intermediate **62** could be converted into lamellarin D trimethyl ether by Friedel–Crafts cyclisation onto the diethyl acetal. Intermediate **62** is formed by deprotection and alkylation of lactone **63**, which could be obtained from carboxylic acid **64**. We proposed accessing the carboxylic group of **64** by a Vilsmeier-Haack reaction of pyrrole **65** and a subsequent oxidation. Pyrrole **65** would be generated through an *anti*-carbometallative cyclisation of alkynamide **66** with boronic acid **67**.



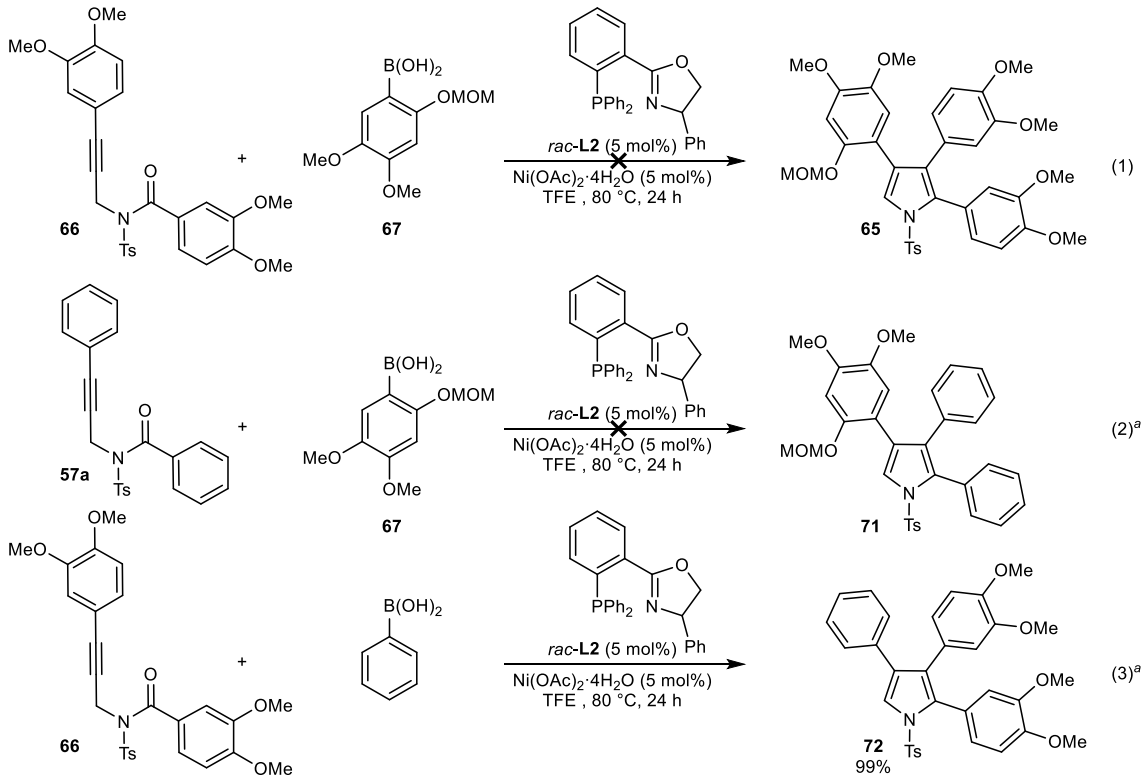
Scheme 2.8: Retrosynthetic Analysis for the Synthesis of Lamellarin D Trimethyl Ether

The preparation of boronic acid **67** was synthesised according to a literature procedure (Scheme 2.9).[30] The synthesis started from commercially available 3,4-dimethoxyphenol **68** which underwent MOM-protection to form the protecting phenol **69**, followed by bromination with NBS to give bromobenzene **70**. Finally, boronic acid **67** was made by borylation of the aryl lithium reagent.



Scheme 2.9: Boronic Acid **67** Synthesis

Unfortunately, *anti*-carbometallative cyclisation as the key step in the total synthesis of lamellarins did not occur in the reaction of alkynamide **66** with boronic acid **67** (Scheme 2.10 Eq. 1). In an attempt to understand the reactivity of boronic acid **67**, an effort was made to verify that once the desired pyrrole **71** was obtained, the *anti*-carbometallative cyclisation of alkynamide **57a** could be conducted (Eq. 2). However, the reaction did not afford the pyrrole **71**, and the alkynamide **57a** was decomposed. In addition, the cyclisation of phenylboronic acid to alkynamide **66** was also tested, and the resulting pyrrole **72** was obtained in 99 % yield. Based on these results, the boronic acid with sterically hindering *ortho*-substitution affect the reaction, and did not generate the desirable product. Further studies towards the synthesis of lamellarin D trimethyl ether were concluded by Simone Gillbard, and will not be described here.

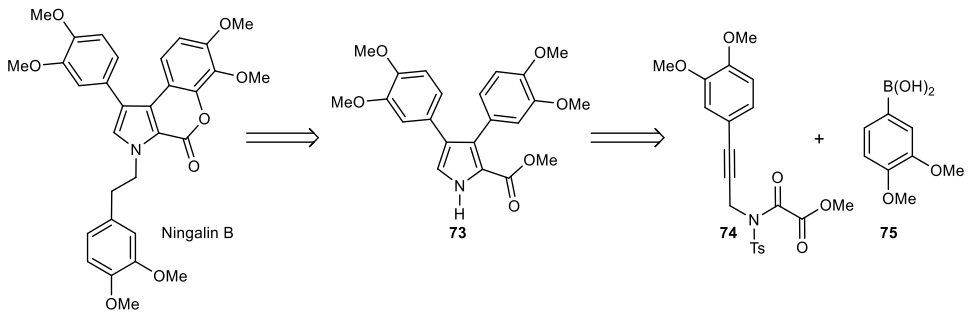


Scheme 2.10: Attempted Cyclisation of Alkynamide **66** to Boronic Acid **67**
[a] Reaction carried out by S. M. Gillbard.

2.2.2 Towards the Synthesis of Ningalin B

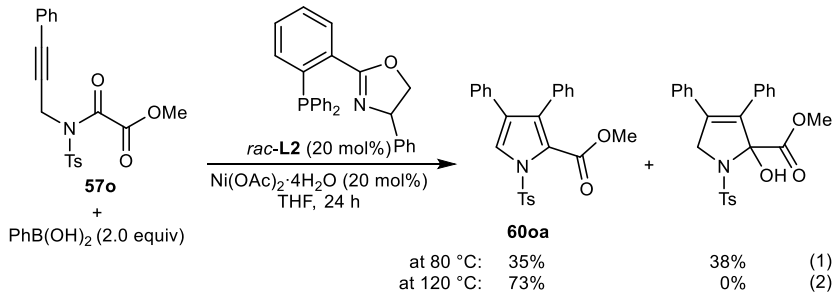
Some ningalins were discovered and showed bioactive characteristic, and ningalin B has been used as nontoxic MDR modulators[31]. Also, ningalin derivative were developed to be used for cancer chemotherapy[32]. Due to the bioactive utilities, ningalin B analogues have been particularly attractive target molecules for many research groups.

The retrosynthetic analysis showed in Scheme 2.11. The intermediate **73** was previously converted into ningalin B[33]. The pyrrole **73** might be made through *anti*-carbometallative cyclisation of alkynamide **74** with boronic acid **75** and followed by detosylation.



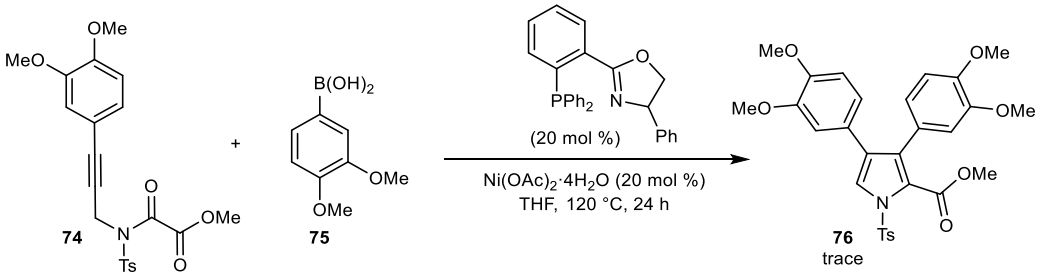
Scheme 2.11: Retrosynthetic Analysis for the Synthesis of Ningalin B

The motivation of the synthesis of ningalin B came from examples like those depicted in Scheme 2.12. The cyclisation of substrate **57o** failed under the standard conditions because the methyl oxalyl group was cleaved during the reaction. Changing the solvent to THF and increasing the catalyst loading to 20 mol% successfully gave pyrrole **60oa** in 35% yield (Eq.1). Furthermore, increasing the temperature to 120 °C gave a higher yield, and none of side product was obtained (Eq.2).



Scheme 2.12: *anti*-Carbometallative Cyclisation of the Alkynamid **57o**[a]
[a] Reaction carried out by S. M. Gillbard.

Regrettably, the *anti*-carbometallative cyclisation of alkynamide **74** to boronic acid **75** was unsuccessful, with only a trace of pyrrole **76** was detected by ^{1}H NMR analysis, and the starting material **74** was decomposed (Scheme 2.13). This problem might result from the high temperature used, but no further optimisation in this reaction was carried out.

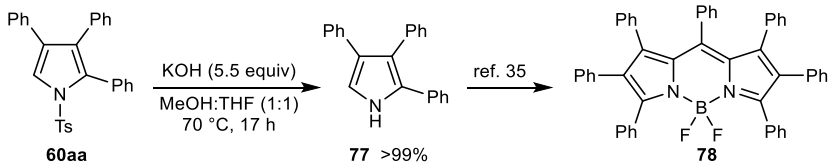


Scheme 2.13: Attempted Cyclisation of Alkynamide **74** to Boronic Acid **75**

2.2.3 Towards the Synthesis of BODIPY Derivatives

Boron-dipyrromethene (BODIPY) is a type of fluorescent dyes which has been reported using in bioanalytical and diagnostic applications[34]. Because of their favourable physical and chemical characteristics, the synthetic access to BODIPY dyes are attractive.

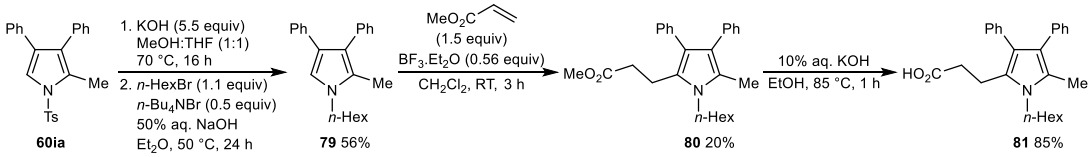
In the previous synthesis (See Section 2.1.3), pyrrole **60aa** was successfully made in 93% yield, which could undergo detosylation with KOH in MeOH/THF (1:1) at 70 °C to give pyrrole **77** in >99% yield. Pyrrole **77** has previously been converted into BODIPY derivative **78**[35] (Scheme 2.14).



Scheme 2.14: Synthesis of Precursors to BODIPY Derivatives

2.2.4 Synthesis of *N*-Alkyl Diphenyl Pyrrolyl Propionic Acid

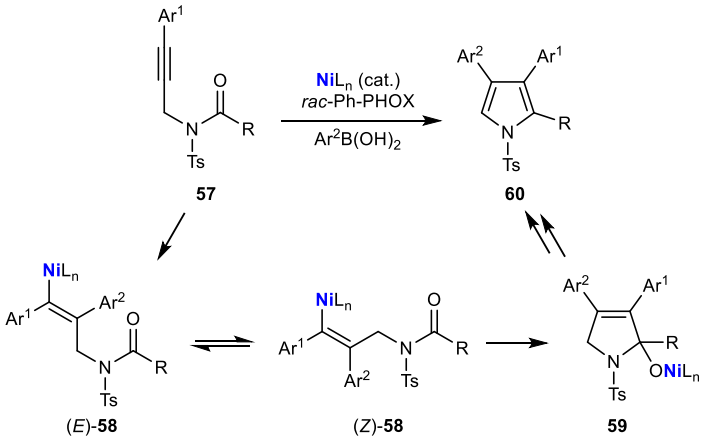
Nonsteroidal antiinflammatory drugs (NSAID) are widely used agents, which have received a lot of attention in recent years. Dannhardt and Lehr [36] published a report showed that *N*-alkyl diphenyl pyrrolyl acetic and propionic acids were strong inhibitor of in vitro of cyclooxygenase (COX) and 5-lipoxygenase. We attempted to start this synthesis from pyrrole **60ia** which could be efficiently made by the methodology that has discussed previously (See Section 2.1.5). *N*-Deprotection of pyrrole **60ia** formed the free NH-pyrrole without purification which was alkylated to give pyrrole **79** in 56% yield over two steps. Then, a 1,4-addition with methyl acrylate gave ester **80** in modest yield. Finally, the ester **80** was hydrolysed by KOH to give propionic acid **81** in 85% yield (Scheme 2.15).



Scheme 2.15: Formal Synthesis of *N*-Alkyl Diphenyl Pyrrolyl Propionic Acid

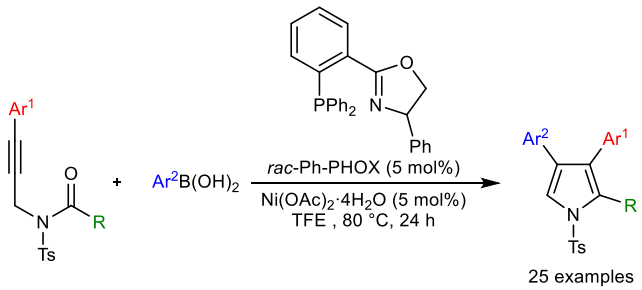
2.3 Conclusion

In summary, an extensive evaluation of the *anti*-carbometallative cyclisation of *N*-tosyl alkynamides has been described, and the reversible *E*/*Z* isomerisation of alkenylnickel species as a key step enable cyclisation to take place. This reaction was the first example of nickel-catalysed arylative cyclisations of amides to form pyrroles (Scheme 2.16).



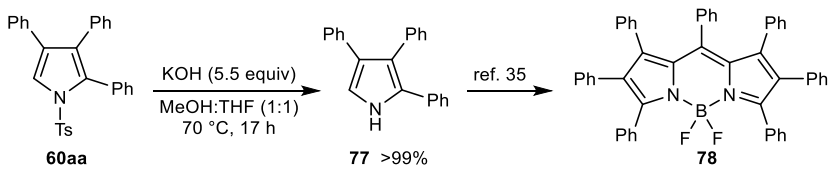
Scheme 2.16: Proposed Synthesis of Pyrroles

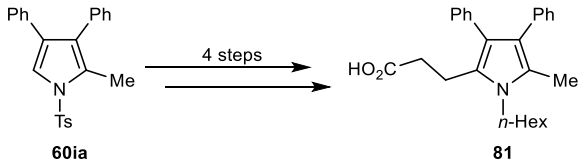
As the result, a new method of synthesis 2,3,4-trisubstituted pyrroles was developed. A wide range of alkynamides and various arylboronic acids were employed to form the corresponding pyrroles in 46-99% yield (Scheme 2.17).



Scheme 2.17: Ni-Catalysed Arylative Cyclisations of Alkynamides

Finally, to illustrate the synthetic utility of this reaction, the methodology was applied to the synthesis of precursors to BODIPY derivatives and biologically active pyrroles.





60ia 81

Scheme 2.18: Applications of Ni-Catalysed Arylative Cyclisations

2.4 Future Work

While many useful compounds have been successful made by the *anti*-carbometallative cyclisation, there is still no conclusive knowledge about the reversible *E*/*Z* isomerisation as a key step in this reaction. In order to improve the understanding, further experimental and theoretical studies are necessary. For example, detailed analysis of stoichiometric reactions of alkynes with well-defined arylnickel complexes could shed some light on the key steps of this reaction.

Also, development of formal synthesis of useful compounds is a key goal for the project. The retrosynthesis to making lamellarin D needs to be redesigned which should avoid using a sterically hindering boronic acid, and further optimisations for the cyclisation of making precursors to ningalin B are required. Other applications of natural products containing 2,3,4-trisubstituted pyrroles structure would be of great interest.

3. Experimental

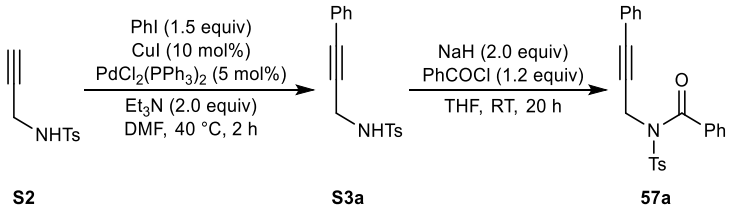
3.1 General Information

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.

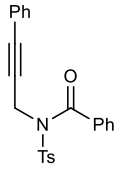
The solvent of recrystallisation is reported in parentheses. Infrared (IR) spectra were recorded on Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total refraction technique. NMR spectra were acquired on Bruker Ascend 400 spectrometers. ^{1}H and ^{13}C NMR spectra 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 1H NMR spectroscopy and 77.16 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 the electrospray ionisation (ESI) technique. X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuK_{α} radiation.

3.2 Preparation of Substrates

Preparation of Substrate **57a**

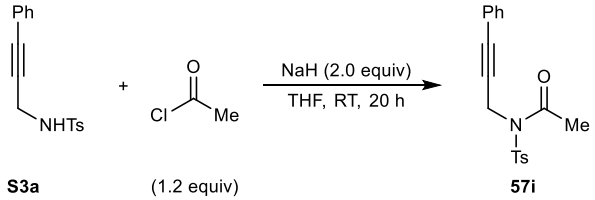


4-Methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (S3a).[24] To a stirred solution of $PdCl_2(PPh_3)_2$ (842 mg, 1.20 mmol) and CuI (457 mg, 2.40 mmol) in DMF (30 mL) was added freshly degassed Et_3N (6.7 mL, 48.1 mmol) and iodobenzene (4.0 mL, 35.9 mmol) under a nitrogen atmosphere. A solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide[23] (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 × 250 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 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 as a brown solid (5.54 g, 81%). The analytical data were consistent with those reported previously.[24]



***N*-(3-Phenylprop-2-yn-1-yl)-*N*-tosylbenzamide (57a).**[25] A solution of *N*-tosyl propargyl amine **S3a**[24] (1.50 g, 5.26 mmol) in THF (20 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 250 mg, 10.4 mmol) in THF (25 mL). The resulting solution was warmed to room temperature and stirred for *ca.* 1 h. Benzoyl chloride (0.73 mL, 6.28 mmol) was added dropwise and the resulting solution was stirred at room temperature for 20 h. The reaction was quenched with brine (60 mL) and extracted with EtOAc (2 × 120 mL). The combined organic layers were washed with brine (60 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 as a dark brown solid (1.34 g, 66%). The analytical data were consistent with those reported previously.[25]

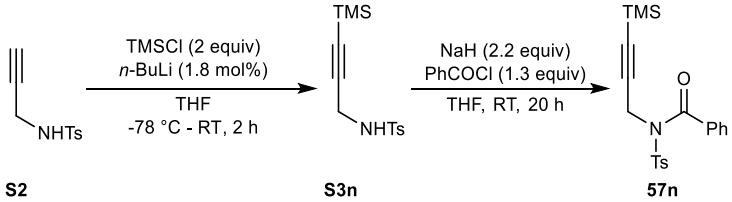
***N*-(3-Phenylprop-2-yn-1-yl)-*N*-tosylacetamide (57i)**

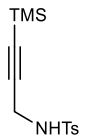


A solution of the *N*-tosyl propargyl amine **S3a** (500 mg, 1.75 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 84.0 mg, 3.50 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for *ca.* 1 h. Acetyl chloride (0.15 mL, 2.10 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 20% EtOAc/petroleum ether) to give the title compound as a pale yellow solid (529 mg, 92). R_f = 0.43 (35% EtOAc/petroleum ether); m.p. 94-96 °C (Et_2O); IR 2989, 1706 (C=O), 1345, 1243, 1158, 1085, 1043 864, 813, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-7.94 (2H, m, Ar**H**), 7.37-7.29 (7H, m, Ar**H**), 4.90 (2H, s, C**H**$_2$), 2.41 (3H, s, ArC**H**$_3$), 2.37 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 (C), 145.2 (C), 136.4 (C), 131.9 (2 × CH), 129.9 (2 × CH), 128.8 (CH), 128.4 (2 × CH), 128.3 (2 ×

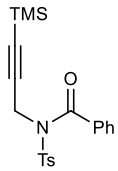
CH), 122.3 (C), 84.3 (C), 83.8 (C), 36.5 (CH_2), 24.8 (CH_3), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{17}NO_3SNa]^+$ $[M+Na]^+$: 350.0821, measured 350.0818.

Preparation of Substrate **57a**





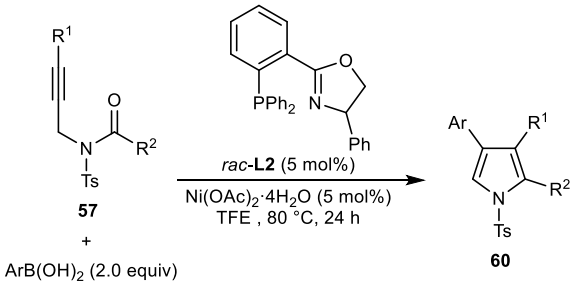
4-Methyl-*N*-(3-(trimethylsilyl)prop-2-yn-1-yl)benzenesulfonamide (S3n). To stirred a solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide[23] (1.0 g, 4.80 mmol) in THF (10 mL) was added dropwise *n*-BuLi (3.5 mL, 8.64 mmol) under a nitrogen atmosphere at -78 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h. TMSCl (1.2ml, 9.60 mmol) was added and the resulting solution was warmed to room temperature and stirred for 1 h. The reaction was quenched with water (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (100 mL) and water (100 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (10% to 30% EtOAc/petroleum ether) to give the title compound as a white solid (474 mg, 35%). The analytical data were consistent with those reported previously.[37]



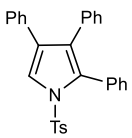
***N*-tosyl-*N*-(3-(trimethylsilyl)prop-2-yn-1-yl)benzamide (57n).** A solution of *N*-tosyl propargyl amine **S3n** (450 mg, 1.60 mmol) in THF (7 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 142 mg, 3.56 mmol) in THF (8 mL). The resulting solution was warmed to room temperature and stirred for *ca.* 1 h. Benzoyl chloride (0.25 mL, 2.13 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 20% EtOAc/petroleum ether) to give the title compound as a white solid (479 mg, 78%). R_f = 0.42 (35% EtOAc/petroleum ether); m.p. 101-102 °C (Et_2O); IR 2952, 1693 (C=O), 1342, 1319, 1248, 1167, 1145, 1070, 1013, 838, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02-7.90 (2H, m, Ar**H**), 7.55-7.44 (3H, m, Ar**H**), 7.36 (2H, ddd, *J* = 8.5, 6.7, 1.5 Hz, Ar**H**), 7.29 (2H, d, *J* =

8.1 Hz, Ar**H**), 4.58 (2H, s, C**H**$_2$), 2.42 (3H, s, ArC**H**$_3$), 0.14 (9H, s, SiC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5 (C), 145.0 (C), 135.7 (C), 134.1(C), 131.7 (CH_2), 129.3 (2 × CH), 129.1 (2 × CH), 128.4 (2 × CH), 127.7 (2 × CH), 100.0 (C), 90.4 (C), 38.8 (CH_2), 21.7 (CH_3), -0.3 (3 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{23}NNaO_3SSi]^+$ $[M+Na]^+$: 408.1060, found 408.1063.

3.3 Nickel-Catalyzed Synthesis of Pyrroles: General Procedure A

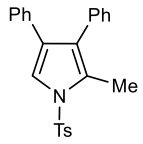


An oven-dried microwave vial fitted with a stirrer bar was charged with the appropriate substrate **57** (0.30 mmol), arylboronic acid (0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (3.7 mg, 0.015 mmol) and *rac*-**L2** (6.1 mg, 0.015 mmol). The vial was capped with a crimp cap PTFE seal and evacuated and back 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 **60**.

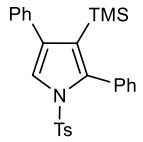


2,3,4-Triphenyl-1-tosyl-1*H*-pyrrole (60aa). The title compound was prepared according to General Procedure A, using propargyl amide **57a** (117 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (125 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}; ^{1}H 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

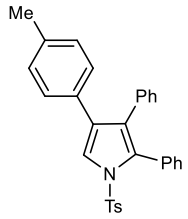
(3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 135.9 (C), 133.9 (C), 133.5 (C), 132.8 (2 × CH), 132.3 (C), 130.6 (2 × CH), 130.3 (C), 129.6 (2 × CH), 128.6 (2 × CH), 128.4 (3 × CH), 127.84 (C), 127.79 (2 × CH), 127.7 (2 × CH), 127.3 (2 × CH), 127.1 (C), 126.8 (CH), 126.5 (CH), 120.0 (CH), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{29}H_{23}NO_2SNa]^+$ $[M+Na]^+$: 472.1374, found: 472.1335.



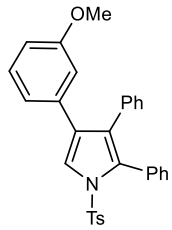
2-Methyl-3,4-diphenyl-1-tosyl-1*H*-pyrrole (60ia). The title compound was prepared according to General Procedure A, using propargyl amide **57i** (98.2 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (87.5 mg, 75%). R_f = 0.66 (35% EtOAc/petroleum ether); IR 3057, 2921, 1597, 1359, 1308, 1173, 1158, 1092, 784, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.79 (2H, m, Ar**H**), 7.52 (1H, s, Ar**H**), 7.39-7.28 (5H, m, Ar**H**), 7.24-7.18 (3H, m, Ar**H**), 7.15-7.06 (4H, m, Ar**H**), 2.46 (3H, s, C**H**$_3$), 2.31 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (C), 136.3 (C), 134.2 (C), 133.8 (C), 130.6 (2 × CH), 130.2 (2 × CH), 128.28 (4 × CH), 128.2 (2 × CH), 128.1 (C), 127.3 (2 × CH), 127.2 (C), 126.9 (CH), 126.7 (CH), 126.5 (C), 118.8 (CH), 21.8 (CH_3), 11.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{21}NO_2SNa]^+$ $[M+Na]^+$: 410.1185, found 410.1180.



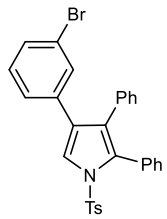
2,4-Diphenyl-1-tosyl-3-(trimethylsilyl)-1*H*-pyrrole (60na). The title compound was prepared according to General Procedure A, using propargyl amide **57n** (115.7 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid. R_f = 0.76 (35% EtOAc/petroleum ether); IR 3213, 2925, 1441, 1351, 1169, 1089, 838, 758, 695, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, s, Ar**H**), 7.43-7.40 (4H, m, Ar**H**), 7.33-7.24 (5H, m, Ar**H**), 7.18-7.13 (5H, m, Ar**H**), 2.42 (3H, s, ArC**H**$_3$), -0.31 (9H, s, SiC**H**$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 140.4 (C), 136.9 (C), 136.0 (C), 133.3 (C), 132.8 (2 × CH), 132.6 (C), 129.6 (2 × CH), 129.51 (2 × CH), 128.8 (CH), 128.1 (2 × CH), 127.7 (2 × CH), 127.2 (CH), 127.1 (2 × CH), 123.0 (C), 120.9 (C), 21.8 (CH_3), 0.8 (3 × CH_3). HRMS (ESI) Exact mass calculated for $[C_{26}H_{27}NNaO_2SSi]^+$ $[M+Na]^+$: 468.1424, found 468.1417.



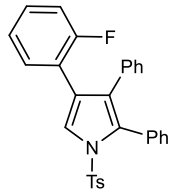
2,3-Diphenyl-4-(4-methylphenyl)-1-tosyl-1*H*-pyrrole (60ab). The title compound was prepared according to General Procedure A, using propargyl amide **1a** (117 mg, 0.30 mmol) and 4-methylphenylboronic acid (81.6 mg, 0.60 mmol), and purified by column chromatography (15% EtOAc/petroleum ether) to give a white solid (106 mg, 77%). R_f = 0.42 (35% EtOAc/petroleum ether); m.p. 185-187 °C (Et_2O); IR 3066, 2920, 1368, 1186, 1169, 1099, 1075, 772, 698, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar**H**), 7.32-7.26 (3H, m, Ar**H**), 7.18-7.12 (5H, m, Ar**H**), 7.86-7.00 (8H, m, Ar**H**), 6.91-6.84 (2H, m, Ar**H**), 2.38 (3H, s, C**H**$_3$), 2.32 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 136.5 (C), 135.9 (C), 133.6 (C), 132.8 (2 × CH), 132.2 (C), 130.9 (C), 130.6 (2 × CH), 130.4 (C), 129.6 (2 × CH), 129.1 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 127.9 (C), 127.8 (2 × CH), 127.7 (2 × CH), 127.3 (2 × CH), 127.1 (C), 126.5 (CH), 119.8 (CH), 21.8 (CH_3), 21.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{30}H_{25}NO_2SNa]^+$ $[M+Na]^+$: 486.1498, found: 486.1493.



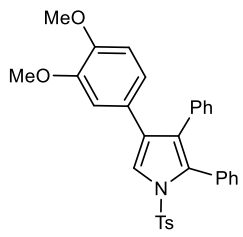
4-(3-Methoxyphenyl)-2,3-diphenyl-1-tosyl-1*H*-pyrrole (60ac). The title compound was prepared according to General Procedure A, using propargyl amide **1a** (117 mg, 0.30 mmol) and 3-methoxyphenylboronic acid (91.2 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (112 mg, 78%). R_f = 0.42 (35% EtOAc/petroleum ether); m.p. 144-146 °C (Et_2O); IR 3135, 3063, 3011, 2949, 1599, 1375, 1171, 1094, 1067, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, s, Ar**H**), 7.34-7.26 (3H, m, Ar**H**), 7.20-7.12 (5H, m, Ar**H**), 7.09-7.01 (5H, m, Ar**H**), 6.95-6.89 (2H, m, Ar**H**), 6.85-6.81 (1H, m, Ar**H**), 6.79-6.74 (1H, m, Ar**H**), 6.70-6.65 (1H, m, Ar**H**), 3.60 (3H, s, OC**H**$_3$), 2.39 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (C), 144.9 (C), 135.8 (C), 135.1 (C), 133.6 (C), 132.7 (2 × CH), 132.3 (C), 130.6 (2 × CH), 130.3 (C), 129.6 (2 × CH), 129.3 (CH), 128.4 (CH), 127.9 (C), 127.8 (2 × CH), 127.7 (2 × CH), 127.3 (2 × CH), 126.9 (C), 126.6 (CH), 120.8 (CH), 120.0 (CH), 113.6 (CH), 113.1 (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: 502.1448.



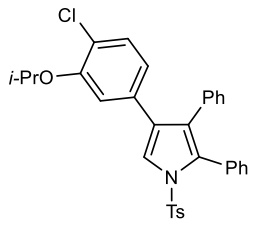
4-(3-Bromophenyl)-2,3-diphenyl-1-tosyl-1*H*-pyrrole (60ad). The title compound was prepared according to General Procedure A, using propargyl amide **1a** (117 mg, 0.30 mmol) and 3-bromophenylboronic acid (120.5 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (133 mg, 90%). R_f = 0.42 (35% EtOAc/petroleum ether); m.p. 177-178 °C (Et_2O); IR 3145, 3040, 2924, 1594, 1366, 1188, 1170, 1101, 1067, 788 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, s, Ar**H**), 7.41 (1H, t, *J* = 1.8 Hz, Ar**H**), 7.35-7.26 (3H, m, Ar**H**), 7.25-7.23 (1H, m, Ar**H**), 7.20-7.12 (4H, m, Ar**H**), 7.11-6.97 (7H, m, Ar**H**), 6.90-6.82 (2H, m, Ar**H**), 2.38 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 136.1 (C), 135.7 (C), 133.0 (C), 132.7 (2 × CH), 132.4 (C), 131.3 (CH), 130.5 (2 × CH), 130.1 (C), 129.79 (CH), 129.76 (CH), 129.6 (2 × CH), 128.5 (CH), 127.9 (2 × CH), 127.7 (2 × CH), 127.6 (C), 127.4 (2 × CH), 127.2 (CH), 126.7 (CH), 125.5 (C), 122.4 (C), 120.2 (CH), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{29}H_{22}BrNO_2SNa]^+$ $[M+Na]^+$: 550.0447, found: 550.0441.



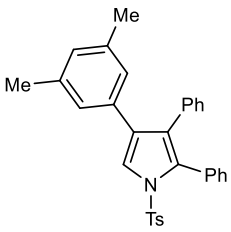
4-(2-Fluorophenyl)-2,3-diphenyl-1-tosyl-1*H*-pyrrole (60ae). The title compound was prepared according to General Procedure A, using propargyl amide **1a** (117 mg, 0.30 mmol) and 2-fluorophenylboronic acid (84.0 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (118 mg, 84%). R_f = 0.42 (40% EtOAc/petroleum ether); m.p. 171-173 °C (Et_2O); IR 3166, 3055, 2923, 1370, 1170, 1105, 1068, 780, 752, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, d, *J* = 1.8 Hz, Ar**H**), 7.48-7.40 (3H, m, Ar**H**), 7.37-7.25 (5H, m, Ar**H**), 7.23-7.04 (8H, m, Ar**H**), 7.01-6.90 (2H, m, Ar**H**), 2.51 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.15 (d, $J_{C\text{-}F}$ = 247.3 Hz, C), 144.9 (C), 135.7 (C), 133.6 (C), 132.8 (2 × CH), 131.8 (C), 131.7 (d, $J_{C\text{-}F}$ = 3.4 Hz, CH), 130.2 (C), 130.1 (2 × CH), 129.6 (2 × CH), 128.6 (d, $J_{C\text{-}F}$ = 8.1 Hz, CH), 128.4 (CH), 127.8 (2 × CH), 127.7 (2 × CH), 127.3 (2 × CH), 126.5 (CH), 123.8 (d, $J_{C\text{-}F}$ = 3.7 Hz, CH), 122.1 (d, $J_{C\text{-}F}$ = 5.4 Hz, CH), 121.6 (d, $J_{C\text{-}F}$ = 14.4 Hz, C), 120.1 (C), 115.8 (d, $J_{C\text{-}F}$ = 22.3 Hz, CH), 21.8 (CH_3) (one carbon signal merged with others); ^{19}F NMR (376 MHz, $CDCl_3$) δ –114.3 (s); HRMS (ESI) Exact mass calculated for $[C_{29}H_{22}FNO_2SNa]^+$ $[M+Na]^+$: 490.1247, found: 490.1236.



4-(3,4-Dimethoxyphenyl)-2,3-diphenyl-1-tosyl-1*H*-pyrrole (60af). The title compound was prepared according to General Procedure A, using propargyl amide **1a** (117 mg, 0.30 mmol) and 3,4-dimethoxyphenylboronic acid (109.2 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (103 mg, 67%). R_f = 0.60 (35% EtOAc/petroleum ether); m.p. 152-154 °C (Et_2O); IR 3122, 3053, 2998, 2928, 2834, 1505, 1374, 1168, 1108, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, s, Ar**H**), 7.35-7.28 (3H, m, Ar**H**), 7.20-7.14 (4H, m, Ar**H**), 7.09-7.02 (5H, m, Ar**H**), 6.96-6.91 (2H, m, Ar**H**), 6.89-6.84 (1H, m, Ar**H**), 6.83-6.78 (1H, m, Ar**H**), 6.56 (1H, d, *J* = 2.0 Hz, Ar**H**), 3.88 (3H, s, OC**H**$_3$), 3.55 (3H, s, OC**H**$_3$), 2.40 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5 (C), 147.9 (C), 144.8 (C), 135.8 (C), 133.7 (C), 132.7 (2 × CH), 132.2 (C), 130.7 (2 × CH), 130.3 (C), 129.5 (2 × CH), 128.3 (CH), 127.9 (C), 127.8 (2 × CH), 127.6 (2 × CH), 127.3 (2 × CH), 126.7 (C), 126.5 (CH), 126.4 (C), 120.4 (CH), 119.2 (CH), 112.0 (CH), 111.1 (CH), 55.9 (CH_3), 55.5 (CH_3), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{31}H_{27}NO_4SNa]^+$ $[M+Na]^+$: 532.1553, found: 532.1545.

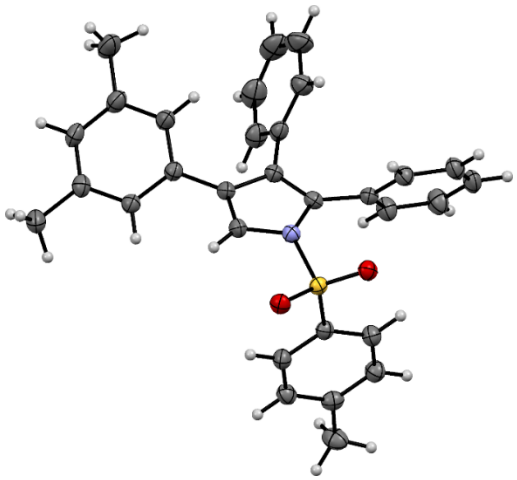


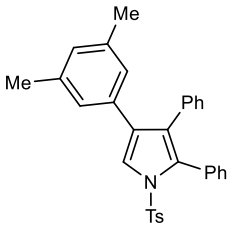
4-(4-Chloro-3-isopropoxyphenyl)-2,3-diphenyl-1-tosyl-1*H*-pyrrole (60ag). The title compound was prepared according to General Procedure A, using propargyl amide **1a** (117 mg, 0.30 mmol) and 3-chloro-4-isopropoxyphenylboronic acid (128.7 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a brown oil (117 mg, 72%). R_f = 0.42 (40% EtOAc/petroleum ether); IR 3060, 2978, 2929, 1490, 1369, 1170, 1102, 907, 728, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar**H**), 7.35-7.25 (4H, m, Ar**H**), 7.21-7.12 (4H, m, Ar**H**), 7.05 (5H, m, Ar**H**), 6.94-6.85 (3H, m, Ar**H**), 6.82-6.75 (1H, m, Ar**H**), 4.52 (1H, sept, *J* = 6.1 Hz, $(CH_3)_2$C**H**), 2.39 (3H, s, ArC**H**$_3$), 1.37 (6H, d, *J* = 6.1 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6 (C), 144.9 (C), 135.7 (C), 133.2 (C), 132.7 (2 × CH), 132.3 (C), 130.5 (2 × CH), 130.2 (CH), 129.6 (2 × CH), 128.4 (CH), 127.9 (2 × CH), 127.8 (CH), 127.67 (C), 127.65 (2 × CH), 127.34 (C), 127.30 (2 × CH), 126.6 (CH), 125.6 (C), 123.9 (C), 119.6 (CH), 115.6 (CH), 72.1 (CH), 22.2 (2 × CH_3), 21.8 (CH_3) (one carbon signal merged with others); HRMS (ESI) Exact mass calculated for $[C_{32}H_{28}ClNO_3SNa]^+$ $[M+Na]^+$: 564.1371, found: 564.1376.



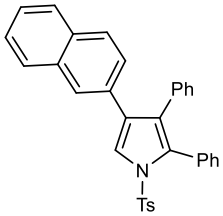
4-(3,5-Dimethylphenyl)-2,3-diphenyl-1-tosyl-1*H*-pyrrole (60ah). The title compound was prepared according to General Procedure A, using propargyl amide **1a** (117 mg, 0.30 mmol) and 3,5-dimethylphenylboronic acid (90.0 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (90.9 mg, 63%). R_f = 0.60 (40% EtOAc/petroleum ether); m.p. 148-150 °C (Et_2O); IR 3140, 3053, 2919, 1596, 1369, 1189, 1169, 1096, 769, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.64 (1H, s, Ar**H**), 7.32-7.28 (2H, m, Ar**H**), 7.28-7.24 (1H, m, Ar**H**), 7.20-7.11 (4H, m, Ar**H**), 7.07-7.00 (5H, m, Ar**H**), 6.92-6.84 (3H, m, Ar**H**), 6.79 (2H, s, Ar**H**), 2.38 (3H, s, C**H**$_3$), 2.20 (6H, s, 2 × C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 137.7 (2 × C), 135.9 (C), 133.6 (C), 132.8 (2 × CH), 132.1 (C), 130.6 (2 × CH), 130.4 (C), 129.6 (2 × CH), 128.5 (CH), 128.3 (CH), 128.0 (C), 127.7 (2 × CH), 127.6 (2 × CH), 127.3 (2 × CH), 127.2 (C), 126.43 (CH), 126.40 (2 × CH), 120.0 (CH), 21.8 (CH_3), 21.4 (2 × CH_3) (one carbon signal merged with others); HRMS (ESI) Exact mass calculated for $[C_{31}H_{27}NO_2SNa]^+$ $[M+Na]^+$: 500.1655, found: 500.1647.

Slow evaporation of a solution of **60ah** in $CDCl_3$ gave crystals that were suitable for X-ray crystallography:



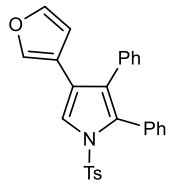


3ah
CCDC 1861043

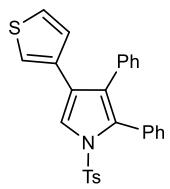


4-(Naphthalen-2-yl)-2,3-diphenyl-1-tosyl-1*H*-pyrrole (60ai). The title compound was prepared according to General Procedure A, using propargyl amide **1a** (117 mg, 0.30 mmol) and 2-naphthylboronic acid (103.0 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (104 mg, 70%). R_f = 0.42 (40% EtOAc/petroleum ether); m.p. 203-

205 °C (Et_2O); IR 3145, 3063, 2919, 1596, 1369, 1188, 1170, 1099, 1070, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.75 (2H, m, Ar**H**), 7.73-7.65 (3H, m, Ar**H**), 7.46-7.41 (2H, m, Ar**H**), 7.36-7.27 (3H, m, Ar**H**), 7.25-7.12 (5H, m, Ar**H**), 7.10-6.99 (5H, m, Ar**H**), 6.95-6.87 (2H, m, Ar**H**), 2.39 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 135.8 (C), 133.6 (C), 133.5(C), 132.8 (2 × CH), 132.4 (C), 131.4 (C), 130.6 (2 × CH), 130.3 (C), 129.6 (2 × CH), 128.4 (CH), 128.0 (CH), 127.91 (C), 127.85 (2 × CH), 127.8 (CH), 127.73 (2 × CH), 127.70 (CH), 127.3 (2 × CH), 127.1 (CH), 127.0 (CH), 126.6 (CH), 126.1 (CH), 125.8 (CH), 120.3 (CH), 21.8 (CH_3) (two carbon signal merged with others); HRMS (ESI) Exact mass calculated for $[C_{33}H_{25}NO_2SNa]^+$ $[M+Na]^+$: 522.1498, found: 522.1502.



4-(Furan-3-yl)-2,3-diphenyl-1-tosyl-1*H*-pyrrole (60ak). The title compound was prepared according to General Procedure C, using propargyl amide **1a** (117 mg, 0.30 mmol) and 3-furanylboronic acid (67.1 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (73.0 mg, 55%). R_f = 0.61 (35% EtOAc/petroleum ether); m.p. 202-203 °C (Et_2O); IR 3149, 2923, 1364, 1171, 1097, 1060, 760, 695, 666, 589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar**H**), 7.32 (1H, t, *J* = 1.7 Hz, Ar**H**), 7.30-7.26 (2H, m, Ar**H**), 7.25-7.21 (1H, m, ArH), 7.17-7.10 (7H, m, Ar**H**), 7.04-6.98 (4H, m, Ar**H**), 6.95 (1H, t, *J* = 1.2 Hz, Ar**H**), 6.35 (1H, dd, *J* = 1.9, 0.9 Hz, Ar**H**), 2.38 (3H, s, C**H**$_3$);^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 142.7 (CH), 139.3 (CH), 135.8 (C), 133.8 (C), 132.6 (C), 132.5 (2 × CH), 130.6 (2 × CH), 130.1 (C), 129.6 (2 × CH), 128.3 (CH), 128.04 (C), 128.00 (2 × CH), 127.6 (2 × CH), 127.3 (2 × CH), 127.1 (CH), 119.0 (CH), 118.6 (C), 118.3 (C), 109.9 (CH), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{21}NO_3SNa]^+$ $[M+Na]^+$: 462.1134, found: 462.1126.

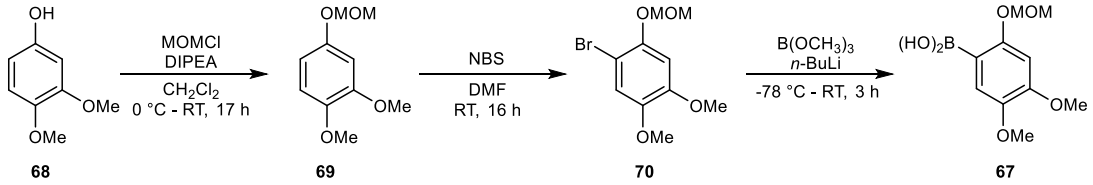


2,3-Diphenyl-4-(3-thienyl)-1-tosyl-1*H*-pyrrole (60al). The title compound was prepared according to General Procedure A, using propargyl amide **1a** (117 mg, 0.30 mmol) and 3-thienylboronic acid (76.8 mg, 0.60 mmol), and purified by column chromatography (5% to 15% EtOAc/petroleum ether) to give a white solid (123 mg, 90%). R_f = 0.42 (40% EtOAc/petroleum ether); m.p. 193-195 °C (Et_2O); IR 3134, 3062, 2924, 1366, 1189, 1168, 1088, 1074, 1030, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, s, Ar**H**), 7.42-7.28 (5H, m, Ar**H**), 7.25-7.19 (6H, m, Ar**H**), 7.12-7.04 (5H, m, Ar**H**), 6.91 (1H,

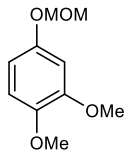
dd, J = 2.9, 1.4 Hz, Ar**H**), 2.47 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 135.8 (C), 134.0 (C), 133.8 (C), 132.6 (2 × CH), 132.4 (C), 130.6 (2 × CH), 130.1 (C), 129.6 (2 × CH), 128.3 (CH), 128.0 (C), 127.9 (2 × CH), 127.6 (2 × CH), 127.5 (CH), 127.2 (2 × CH), 126.9 (CH), 125.2 (CH), 122.2 (C), 121.2 (CH), 119.5 (CH), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{21}NO_2S_2Na]^+$ $[M+Na]^+$: 478.0906, found: 478.012.

3.3 Further Transformations

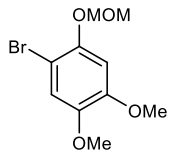
Preparation of Boronic Acid **67**



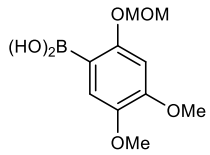
68 **69** **70** **67**



1,2-dimethoxy-4-(methoxymethoxy)benzene (69).[30] To stirred a solution of 3,4-dimethoxyphenol (1.0 g, 6.50 mmol) in CH_2Cl_2 (12 mL) was added dropwise MOMCl (0.75 mL, 9.75 mmol) under a nitrogen atmosphere at 0 °C. The resulting solution was warmed to room temperature and stirred for 17 h. The reaction was quenched with 1% aqueous HCl (20 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (100 mL) and brine (100 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 as a colourless oil (821 mg, 64%). The analytical data were consistent with those reported previously.[38]

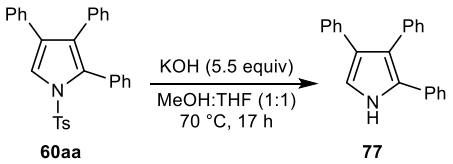


1-bromo-4,5-dimethoxy-2-(methoxymethoxy)benzene (70).[30] To a stirred solution of the protecting phenol **69** (500 mg, 2.50 mmol) in DMF (7.5 mL) was added dropwise NBS (493 mg, 2.77 mmol) in DMF (2.5 mL) under a nitrogen atmosphere in the dark at 0 °C. The resulting solution was 14 h in the dark. The reaction was quenched with water (20 mL) and extracted with Et_2O (3 × 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 as a reddish brown solid (577 mg, 83%). The analytical data were consistent with those reported previously.[38]



[4,5-dimethoxy-2-(methoxymethoxy)phenyl]boronic acid (67). [30] To stirred a solution of bromobenzene **70** (300 mg, 1.08 mmol) in THF (4 mL) was added dropwise *n*-BuLi (0.87 mL, 2.17 mmol) under a nitrogen atmosphere at -78 °C, the reaction mixture was stirred for 1 h. Trimethyl borate (0.19 ml, 1.62 mmol) was added, and the resulting solution was stirred for 1 h, followed by warming to room temperature and stirred for an additional 1 h. The reaction was quenched with saturated NH_4Cl (20 mL), acidified to pH = 3 with HCl, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (2 × 40 mL) and brine (40mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. to give the title compound as a brown solid (131 mg, 50%). The compound was unstable and used for the next reaction without further purification. The analytical data were consistent with those reported previously.[38]

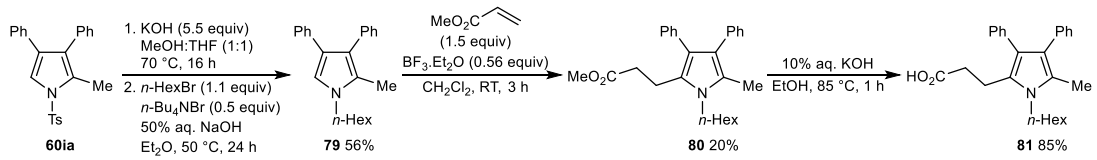
2,3,4-Triphenyl-1*H*-pyrrole (77)

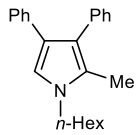


60aa **77**

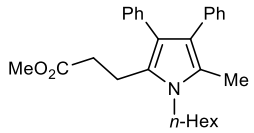
A mixture of pyrrole **60aa** (150 mg, 0.33 mmol) and KOH (103 mg, 1.84 mmol) in THF:MeOH (1:1, 15.6 mL) was stirred at 70 °C for 17 h. The mixture was cooled to room temperature and quenched with water (10 mL) followed by addition of 1 M aqueous HCl solution (1.8 mL). The resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo* to leave the title compound as a purple solid (100 mg, >99%) that required no further purification. R_f = 0.46 (20% EtOAc/petroleum ether); IR 3422, 3408, 2922, 2853, 1601, 1483, 1069, 766, 749, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, br s, N**H**), 7.33-7.21 (15H, m, Ar**H**), 7.05 (1H, d, *J* = 2.8 Hz, Ar**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7 (2 × C), 133.1 (C), 131.1 (2 × CH), 129.7 (C), 128.6 (2 × CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.3 (2 × CH), 126.7 (CH), 126.2 (CH), 126.0 (C), 125.7 (CH), 120.7 (C), 117 (CH); HRMS (ESI) Exact mass calculated for $[C_{22}H_{18}N]^+$ $[M+H]^+$: 296.1434, found 296.1433. The analytical data were consistent with those reported previously.[35]

Synthesis of *N*-alkyl Diphenyl Pyrrolyl Propionic Acid



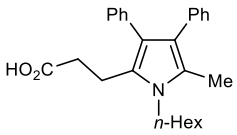


1-Hexyl-2-methyl-3,4-diphenyl-1*H*-pyrrole (79). A mixture of pyrrole **60ia** (332 mg, 0.83 mmol) and KOH (256 mg, 4.57 mmol) in THF:MeOH (1:1, 33 mL) was stirred at 70 °C for 16 h. The mixture was cooled to room temperature and quenched with water (20 mL), followed by addition of 1 M aqueous HCl solution (4.6 mL). The resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The crude material (168 mg) was dissolved in Et_2O (4.2 mL), and *n*-Bu_4NBr (134 mg, 0.42 mmol), 1-hexyl bromide (151 mg, 0.90 mmol), and 50% aqueous NaOH solution (2.1 mL) was added. The mixture was stirred at 50 °C for 24 h, cooled to room temperature, and diluted with water (20 mL). The mixture was extracted with Et_2O (3 × 20 mL), and 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 on neutral alumina (0 to 1% EtOAc/*n*-pentane) to give the title compound as a colorless oil (148 mg, 56%). R_f = 0.62 (20% EtOAc/petroleum ether); IR 2927, 2856, 1601, 1537, 1390, 1204, 1181, 764, 738, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (2H, m, Ar**H**), 7.25-7.10 (8H, m, Ar**H**), 6.80 (1H, s, Ar**H**), 3.90-3.86 (2H, m, NC**H**$_2$), 2.26 (3H, s, ArC**H**$_3$), 1.87-1.79 (2H, m, $NCH_2C\mathbf{H}_2$), 1.47-1.33 (6H, m, $(C\mathbf{H}_2)_3CH_3$), 0.97-0.92 (3H, m, $CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (C), 136.2 (C), 130.7 (2 × CH), 128.11 (2 x CH), 128.08 (2 × CH), 128.06 (2 × CH), 126.6 (C), 125.6 (CH), 125.1 (CH), 122.8 (C), 120.4 (C), 118.2 (CH), 47.2 (CH_2), 31.6 (CH_2), 31.4 (CH_2), 26.7 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 10.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{27}NNa]^+$ $[M+Na]^+$: 318.2216, found 318.2209. This compound has been described previously but no characterisation data were reported.[36]



Methyl 3-(1-hexyl-5-methyl-3,4-diphenyl-1*H*-pyrrol-2-yl)propanoate (80). A solution of pyrrole **79** (230 mg, 0.72 mmol) in CH_2Cl_2 (3 mL) was added methyl acrylate (98 µL, 1.09 mmol) and $BF_3.Et_2O$ (50 µL, 0.40 mmol). The mixture was stirred at room temperature for 3 h and diluted water (10 mL). The resulting mixture was extracted with diethyl ether (3 x 10 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 on neutral alumina (0 to 2.5% EtOAc/*n*-pentane) to give the title compound as a pale yellow oil (64 mg, 20%). R_f = 0.52 (20% EtOAc/petroleum ether); IR 2927, 1734 (C=O), 1602, 1437, 1365, 1273, 1156, 910, 767, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.11 (6H, m, Ar**H**), 7.09-7.04 (4H, m, Ar**H**), 3.89-3.85 (2H, m, NC**H**$_2$), 3.64 (3H, s, OC**H**$_3$), 3.04-2.99 (2H, m, C**H**$_2$$CH_2CO_2Me$), 2.51-2.46 (2H, m, CH_2C**H**$_2$$CO_2Me$), 2.31 (3H, s, ArC**H**$_3$), 1.80-1.72 (2H, m, NCH_2C**H**$_2$), 1.46-1.35 (6H, m, (C**H**$_2$)$_3CH_3$), 0.96-0.92 (3H, m, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C), 136.5 (C), 136.4 (C), 130.5 (2 x CH), 130.4 (2 x CH), 128.0 (2 x CH), 127.8 (2 x CH), 126.6 (C), 125.5 (CH), 125.1 (CH), 124.8 (C), 121.2 (C), 121.0 (C), 51.8 (CH_3), 44.3 (CH_2), 35.3 (CH_2), 31.7 (CH_2), 31.6 (CH_2), 26.9 (CH_2), 22.7 (CH_2), 20.4 (CH_2), 14.1 (CH_3), 11.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{33}NO_2Na]^+$ $[M+Na]^+$: 426.2404, found 426.2399.



3-(1-Hexyl-5-methyl-3,4-diphenyl-1*H*-pyrrol-2-yl)propanoic acid (81). A mixture of pyrrole **80** (64 mg, 0.72 mmol) in EtOH (1.30 mL) was added 10% aqueous KOH (800 µL, 1.43 mmol). The mixture was refluxed for 1 h. After cooling the solution was poured into 5% aqueous NaCl (10 ml). The resulting mixture was acidified to pH = 4 using H_3PO_4 and extracted Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. to give the title compound as a brown oil (52.9 mg, 85%). R_f = 0.30 (30% EtOAc/petroleum ether); IR 2926, 1705 (C=O), 1602, 1415, 1366, 1280, 910, 766, 699, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.03 (10H, m, Ar**H**), 3.88-3.84 (2H, m, NC**H**$_2$), 3.04-3.00 (2H, m, C**H**$_2$$CH_2CO_2H$), 2.54-2.50 (2H, m, CH_2C**H**$_2$$CO_2H$), 2.30 (3H, s, ArC**H**$_3$), 1.79-1.72 (2H, m, NCH_2C**H**$_2$), 1.46-1.33 (6H, m, (C**H**$_2$)$_3CH_3$), 0.95-0.91 (3H, m, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7 (C), 136.5 (C), 136.3 (C), 130.5 (2 x CH), 130.4 (2 x CH), 128.1 (2 x CH), 127.8 (2 x CH), 126.2 (C), 125.6 (CH), 125.1 (CH), 124.9 (C), 121.4 (C), 121.0 (C), 44.3 (CH_2), 35.2 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 26.9 (CH_2), 22.7 (CH_2), 20.2 (CH_2), 14.1 (CH_3), 11.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{31}NO_2Na]^+$ $[M+Na]^+$: 412.2247, found 412.2244.

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Appendix

Herein is included the relevant publication discussed in the research & discussion section.

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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**.

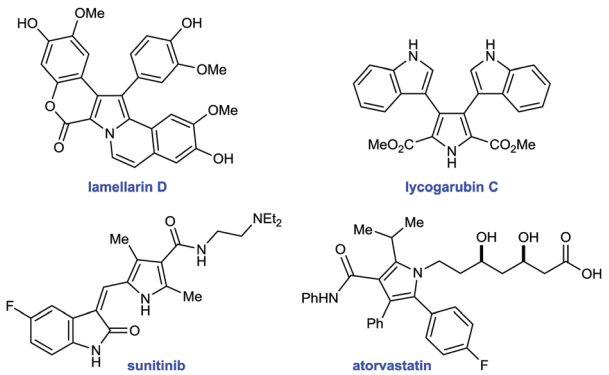
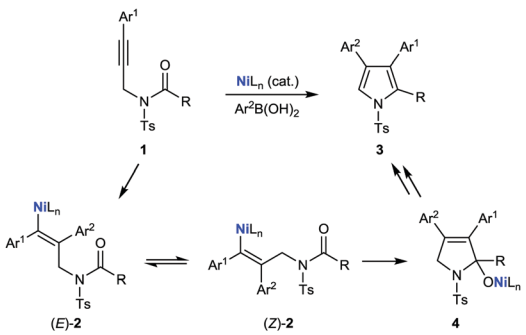


Fig. 1 Representative pyrrole-containing natural products and drugs.



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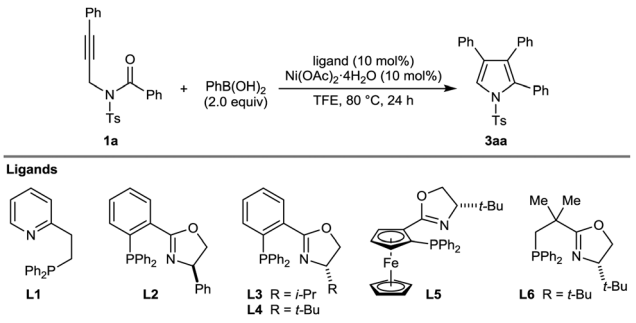
† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data for **3ah**. CCDC 1861043. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc06649c

‡ These authors contributed equally.

Table 1 Evaluation of reaction conditions[a]

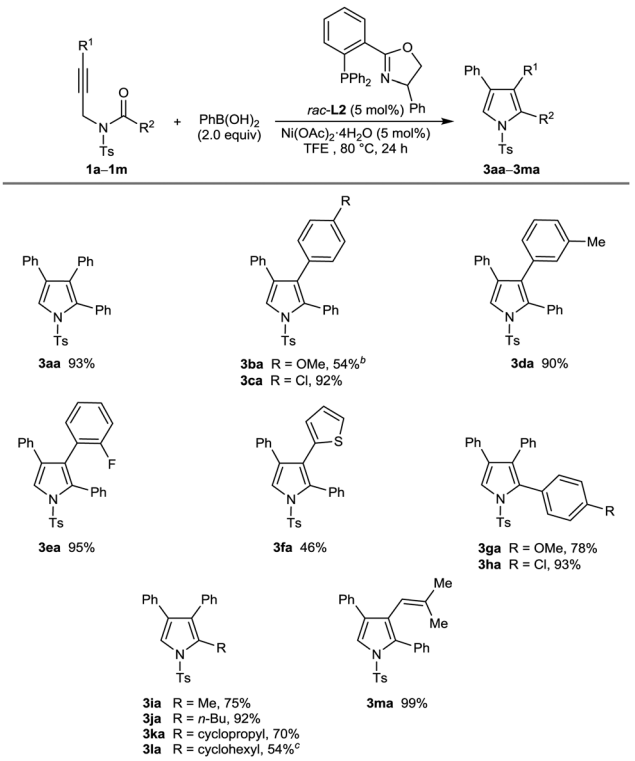


Entry	Ligand	Yield of **1a**[b] [%]	Yield of **3aa**[b] [%]
1	—	>95	<5
2	**L1**	33	27
3	**L2**	—	90
4	**L3**	18	52
5	**L4**	13	70
6	**L5**	10	63
7	**L6**	11	52

[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.

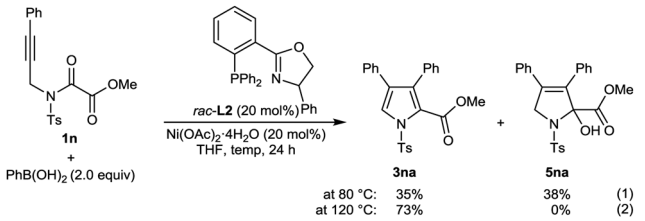
were added (entries 2–7). The achiral ligand **L1** gave **3aa** in 27% yield as determined by ^{1}H NMR analysis, but significant quantities of **1a** remained (entry 2). Chiral phosphinooxazolines **L2–L6** were then examined (entries 3–7) and of these, (*R*)-Ph-PHOX (**L2**) gave **3aa** in 90% NMR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

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.

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.

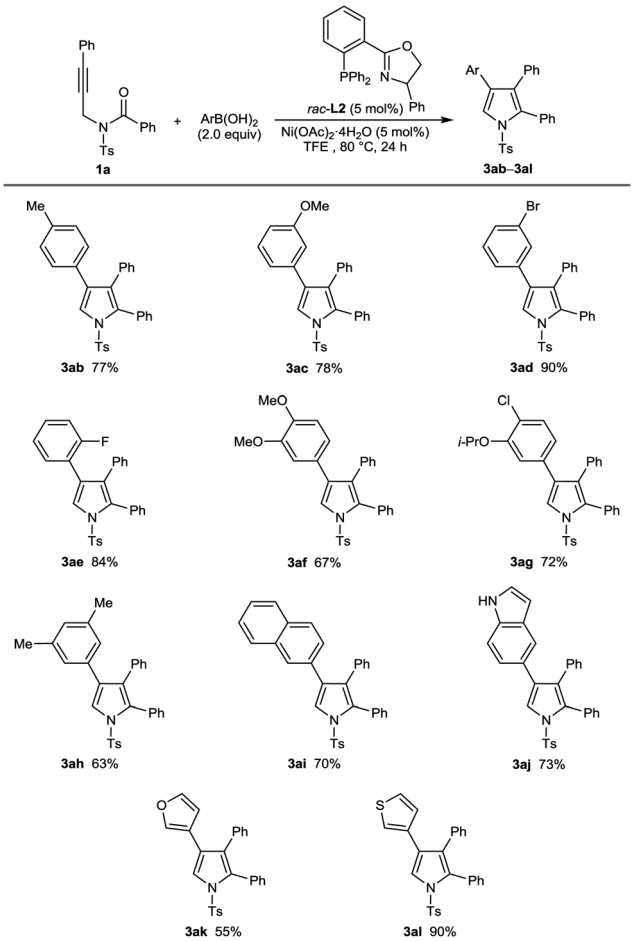


The cyclization of carbomethoxy-containing substrate **1n** failed under the standard conditions, and led only to decomposition by cleavage of the methyl oxalyl group. However, changing the solvent to THF and increasing the catalyst loading to 20 mol% successfully gave pyrrole **3na** in 35% yield, along 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

Table 3 Scope of boronic acids[a]

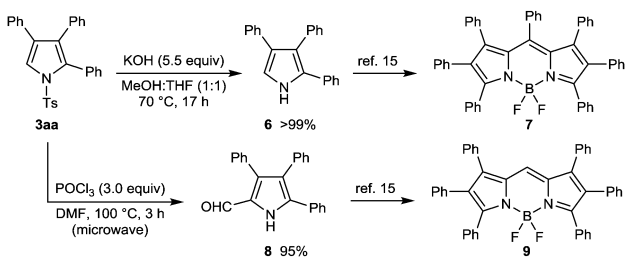


[a] Reactions were conducted with 0.30 mmol of **1a** in TFE (3 mL). Yields are of isolated products.

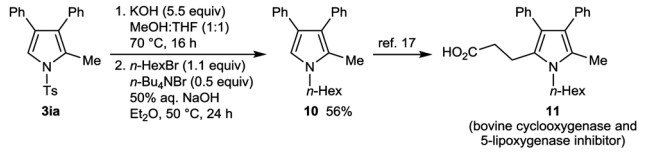
in a microwave reactor resulted in formylation with concomitant removal of the tosyl group to give pyrrole **8**, which has been used in the synthesis of BODIPY derivative **9**.[16]

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.

