

**Towards α -Functionalization of Aldehydes with Unactivated
Electrophiles
and
Catalytic Enantioselective Intramolecular [4+2] Annulation of Dienes
and Terminal Alkynes**

A Thesis Submitted by

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In partial fulfilment of the requirements for the degree of

Doctor of Philosophy

Declaration of Originality

I, Adekunle Francis Adeleke, declare that the research described in this manuscript was carried out under the supervision of Dr. Christopher J. Cordier, Imperial College London, and is my own unaided work unless otherwise stated and neither the whole nor any part has been submitted before for a degree in any other institution. All additional sources of information have been cited accordingly.

Adekunle Francis Adeleke

September 2023

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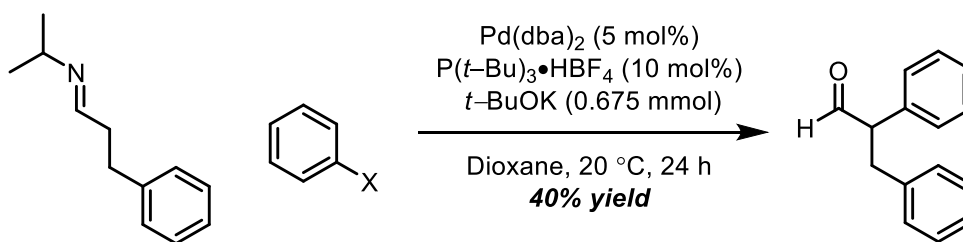
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Abstract

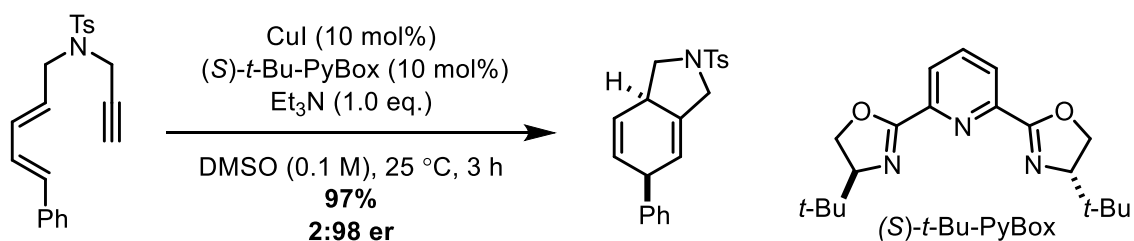
The union of organocatalysis with transition metal chemistry offers a myriad of novel methodologies for exploring chemical space. The versatility of enamine catalysis combined with Group 10 transition metal catalysis will therefore present unique opportunities for discovering hitherto unknown enantioselective transformations.

The work described herein presents investigations into syntheses of chiral secondary amine bases and reaction screening towards achieving α -functionalisation of aldehyde compounds. Our effort towards realizing α -alkylation of aldehydes was unsuccessful.

Subsequent exploration of α -arylation of aldehydes with pre-formed imine was moderately successful.



In part 2, enantioselective intramolecular copper catalyzed cycloaddition of diene and alkynes was achieved. A cheap Cu(I) source, copper iodide was used as the metal catalyst, and a readily synthetically accessible chiral PyBox was used as a chiral ligand. The reactions occur in excellent yields and high enantioselectivities. The reactions are robust; they tolerate the presence of water and air.



Acknowledgements

I would like to thank my supervisor, Dr. Christopher Cordier for the incredible opportunity to work in his group as his first student, and on this project. His constant enthusiasm, passion, and support has been a great source of inspiration, and a guiding light through of miry bog of the unknown. I would also like to thank Professor Alan Spivey for his support and encouragement for what has seemed like an eternity.

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I am also grateful to the academic and research staff at Imperial who have helped me along the way: Prof. Phil Parsons, Pete Haycock, Prof. Mark Crimmin to name a few.

Finally, I would like to thank my family, in particular my mum and my sister for their constant encouragement and support throughout my PhD and my life in general. This would have been impossible without you all.

“The main obligation is to amuse yourself.”

S.J. Perelman

Abbreviations

App	apparent
Aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
br	broad
BuLi	n-butyllithium
DMF	n,n-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
er	enantiomeric ratio
GC	gas chromatography
h	hour(s)
HPLC	high performance liquid chromatography
L	ligand
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
min	minutes(s)
min	minutes
mL	millilitre(s)
mmol	millimole(s)
mol	mole
mol%	mole percent
NMR	nuclear magnetic resonance
Nu	nucleophile
ppm	parts per million
r.t.	room temperature
SM	starting material
<i>t</i> or <i>tert</i>	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
Tol	toluene

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Part 1

Towards α -Functionalization of Aldehydes with Unactivated Electrophiles

Chapter One

General introduction

1. General introduction

1.1. Transition Metal Catalysis and Asymmetric Organocatalysis

Transition metal mediated processes are an integral part of modern synthetic organic chemistry. Transition metal mediated transformations are versatile, selective, and unique. Such transformations^{1–7} include carbon–carbon^{1,2,11–16,3–10} and carbon–heteroatom^{1,17,18} bond formation, allylic substitutions^{1,19}, *C–H* activation reactions^{1,20}, and olefin^{1,21} or alkyne metathesis^{1,22} reactions. These processes have proven to be a highly effective method for exploring chemical space.

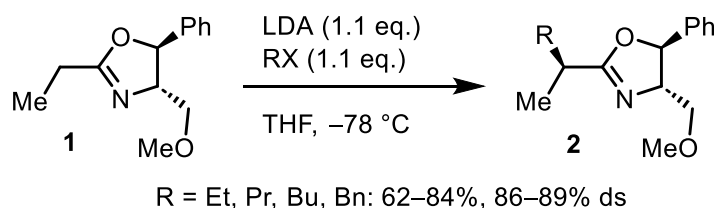
Asymmetric bond formations that combine the use of transition metals and chiral ligands facilitate challenging (or otherwise impossible) bond formation with chiral induction. In such reactions, the chiral ligand chelates to the metal centre and asymmetric induction is achieved during the reaction coordinate of the catalysed reaction. Numerous robust chiral ligands have been developed, with structures usually based upon the structural framework of the so-called ‘privileged ligands²³.’ Deviation from these frameworks has been met with limited success. Although the catalytic systems formed with these privileged ligands are known to mediate many different reactions, a systematic design based on these ligand frameworks is still a challenge.

Asymmetric organocatalysis is the use of sub-stoichiometric amounts of enantiomerically enriched organic compounds to catalyse stereoselective bond formation.^{24–28} Enamine activation catalysis is a major part of organocatalysis.^{24–28} Mechanistically enamine asymmetric catalysis involves the condensation of a secondary amine chiral catalyst and carbonyl compound to form an iminium ion, which tautomerizes to form an enamine. The enamine then reacts with an electrophile, with a stereochemical preference to form an

enantioenriched α -substituted carbonyl compound. The stereochemical information on the catalyst is transferred to the product in the catalytic cycle.

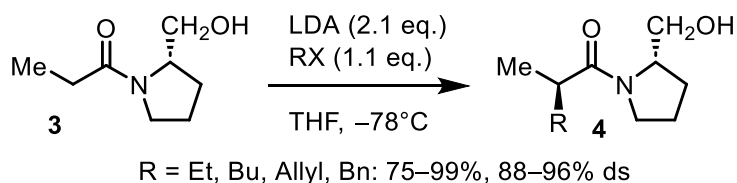
1.2. α -Alkylation of Masked Aldehydes

Several methods have been developed for the α -alkylation of aldehydes. The most prevalent examples involve the use of chiral auxiliaries. Meyers and co-workers reported the use of oxazoline **1** (Scheme 1) as a chiral auxiliaries for asymmetric alkylation of azaenolates.^{29–32}



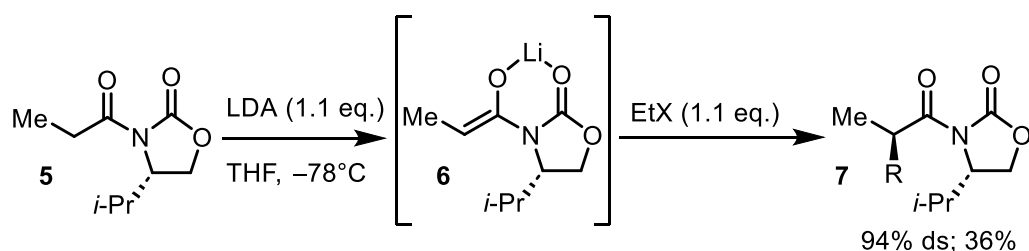
Scheme 1: Asymmetric enolate alkylation with Meyers' oxazolines.^{29–32}

The use of amides derived from proline has also been reported (Scheme 2) as substrates for asymmetric alkylation.^{33–35}



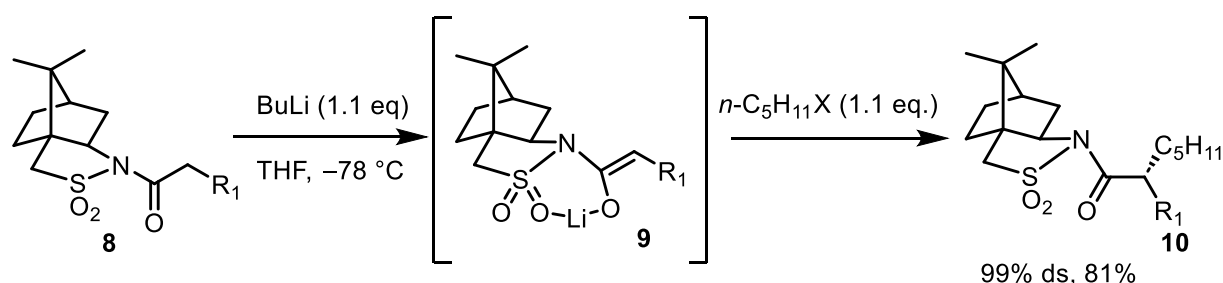
Scheme 2. Symmetric enolate alkylation with Evans' and Sonnet's proline amide.^{33–35}

Evans *et al.* developed the use of oxazolidinone imides as substrates for asymmetric alkylation.³⁶ These examples involve the use of unactivated primary electrophiles. The reaction (Scheme 3) proceeds with moderate yields and high diastereoselectivity particularly for less bulky (EtX) electrophile. The higher diastereoselectivity observed is due to an intraannular asymmetric induction that occurs due to the metal chelation; this in addition to the proximity of the stereochemical element (*i*-Pr) results in a stereoselective formation of the *Z*(*O*)-enolate **6** and *Si* face selectivity in the electrophilic attack. The low yields are observed primarily due to the low nucleophilicity of the enolate for an unactivated primary electrophile.²⁹



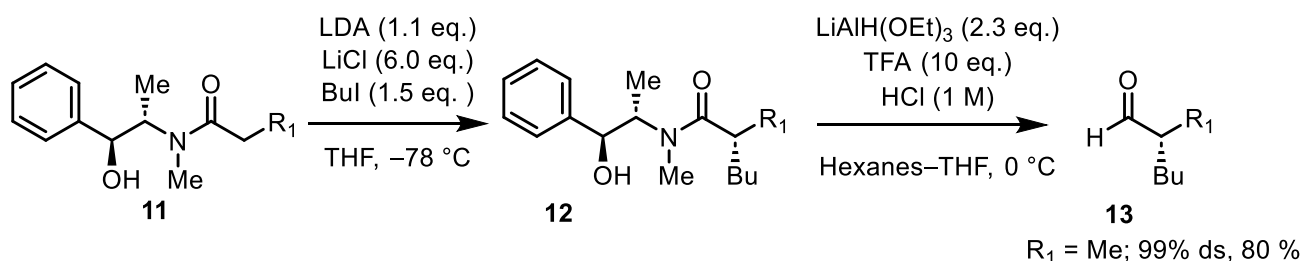
Scheme 3. Evans' asymmetric alkylation of oxazolidinone imide.³⁶

Oppolzer demonstrated that enolates **9** that are derived from N acyl sultams **8** of camphor undergo a highly selective alkylation with an unactivated electrophile (Scheme 4). Thus, an attack from the *Re* face of the chelated *Z(O)*-enolate on the *n*-pentyl halide results in compound **10**. Reduction with LAH resulted in an enantiomerically enriched alcohol.^{29,37}



Scheme 4. Oppolzer's asymmetric alkylation.^{29,37}

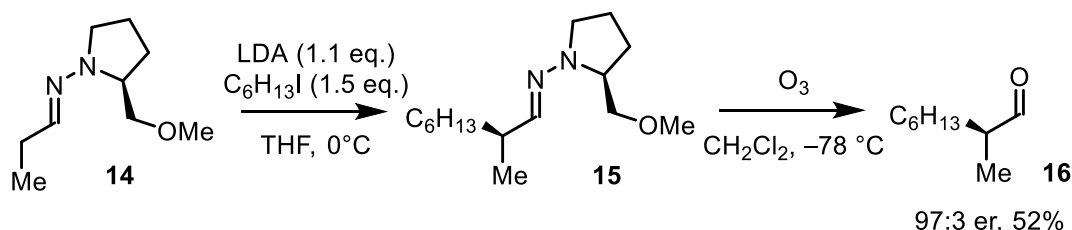
Myers and co-workers have used pseudoephedrine amides as chiral auxiliaries to synthesize α -alkylated aldehydes, ketones, carboxylic acids and alcohols. These reactions have been performed on an industrial scale. As before a *Z(O)*-enolate attacks the electrophile with *Si* face selectivity to produce the α -alkylated amide **12**. LiCl prevents alkoxide alkylation and accelerates the reaction.^{29,38–40}



Scheme 5. Myers' pseudoephedrine amide strategy for asymmetric enolate alkylation.^{29,38–40}

The methodology explored by the Enders group involved the α -alkylation of chiral *S*- or *R*-1-aminomethoxymethylpyrrolidine (SAMP or RAMP) hydrazones **14** (Scheme 6).^{29,41} The

hydrazone starting material must be pre-formed. The ‘*E*_{CC}, *Z*_{CN}’ enolate of hydrazone **14** undergoes a stereoselective α -alkylation of *via Re* face attack on the electrophile. The reaction occurs with high enantioselectivity and moderate yields with hexyl iodide. The use of hydrazone synthesized from a camphor-derived N-amino oxazolidinone was reported by Coltart *et al.*^{29,42} High enantioselectivity is also known in such cases (99:1 dr) with ethyl iodide.²⁹



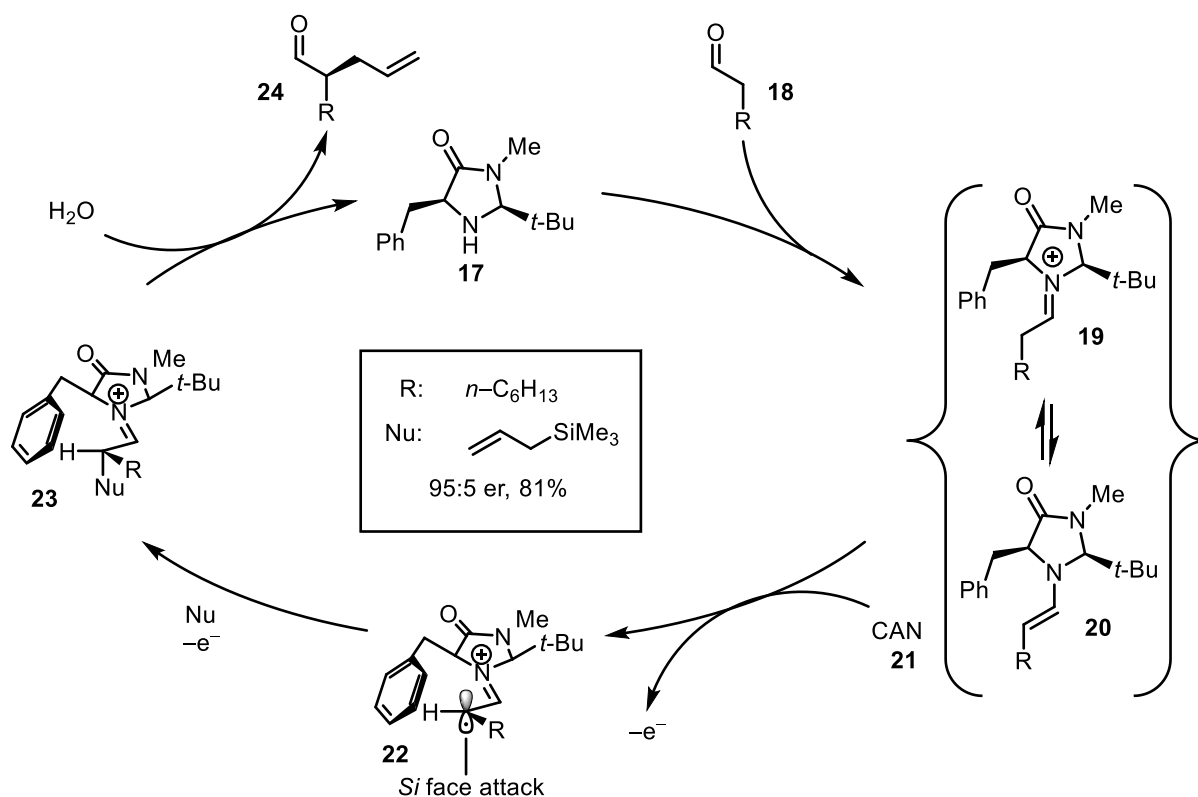
Scheme 6. Enders' asymmetric alkylation with SAMP hydrazone.^{29,41}

1.3. α -Alkylation of Free Aldehydes

In the methods described thus far, a prior synthesis of an auxiliary was necessary. The α -alkylated product was liberated in various oxidation states; therefore, an additional reaction to the desired (aldehyde) oxidation state is often required. The following methods involve the *in situ* activation of an aldehyde.

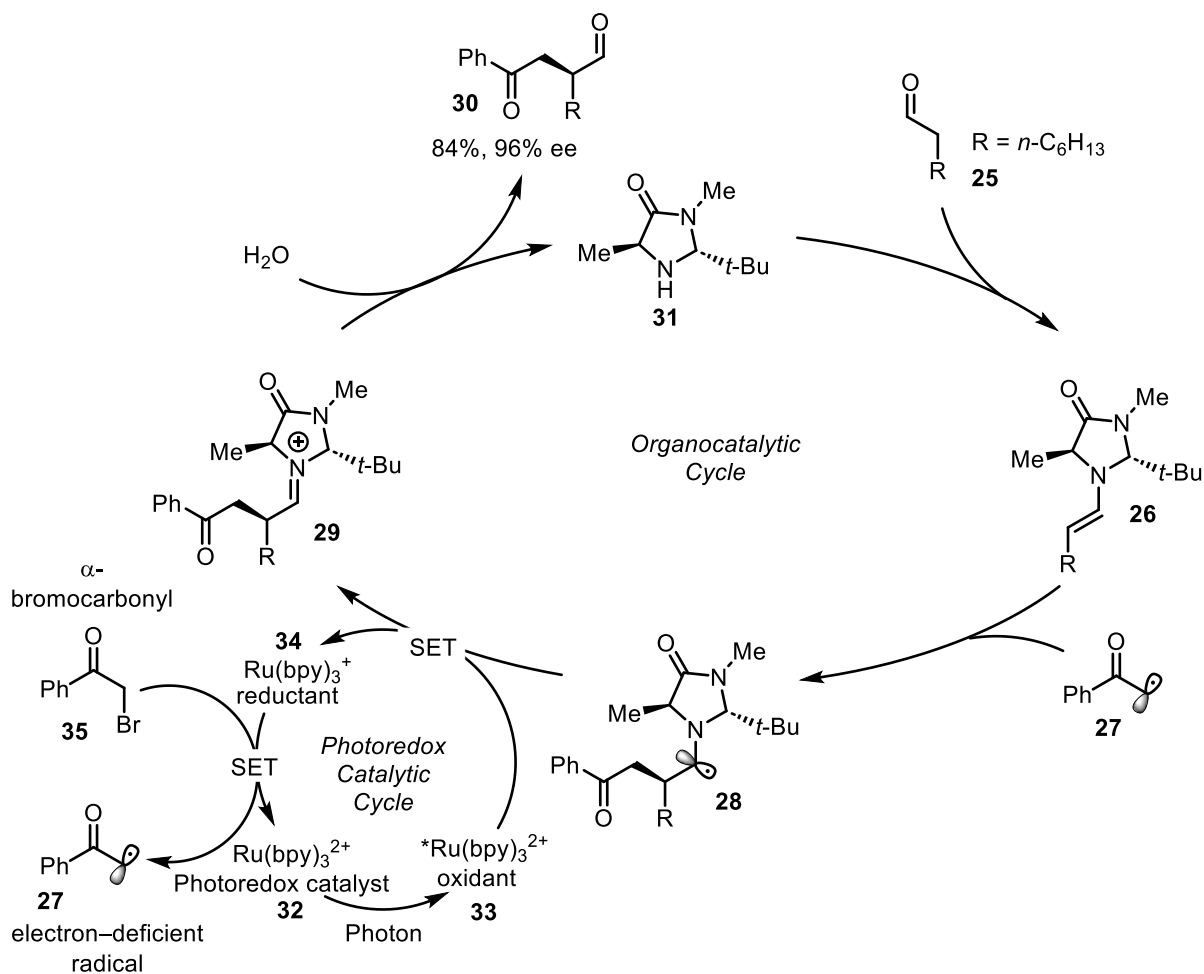
MacMillan *et al.* developed a SOMO-activation (Singly Occupied Molecular Orbital) catalysis of an α -alkylation of aldehydes.^{29,43} An example of this reaction type involved the oxidation of enamine **20** to radical cation **22** (Scheme 7) by cerium ammonium nitrate **21** (CAN). This *umpolung* activation of the enamine substrate is followed by a nucleophilic attack by an allylic nucleophile. A subsequent oxidation and hydrolysis furnishes the α -alkylated aldehyde **24**. When the reaction is performed with 20 mol% catalyst **17**, high enantioselectivity of α -

allylated aldehyde **24** is observed.^{29,43} MacMillan *et al.* have reported several analogous methods of SOMO activation of enamine.^{44–51}



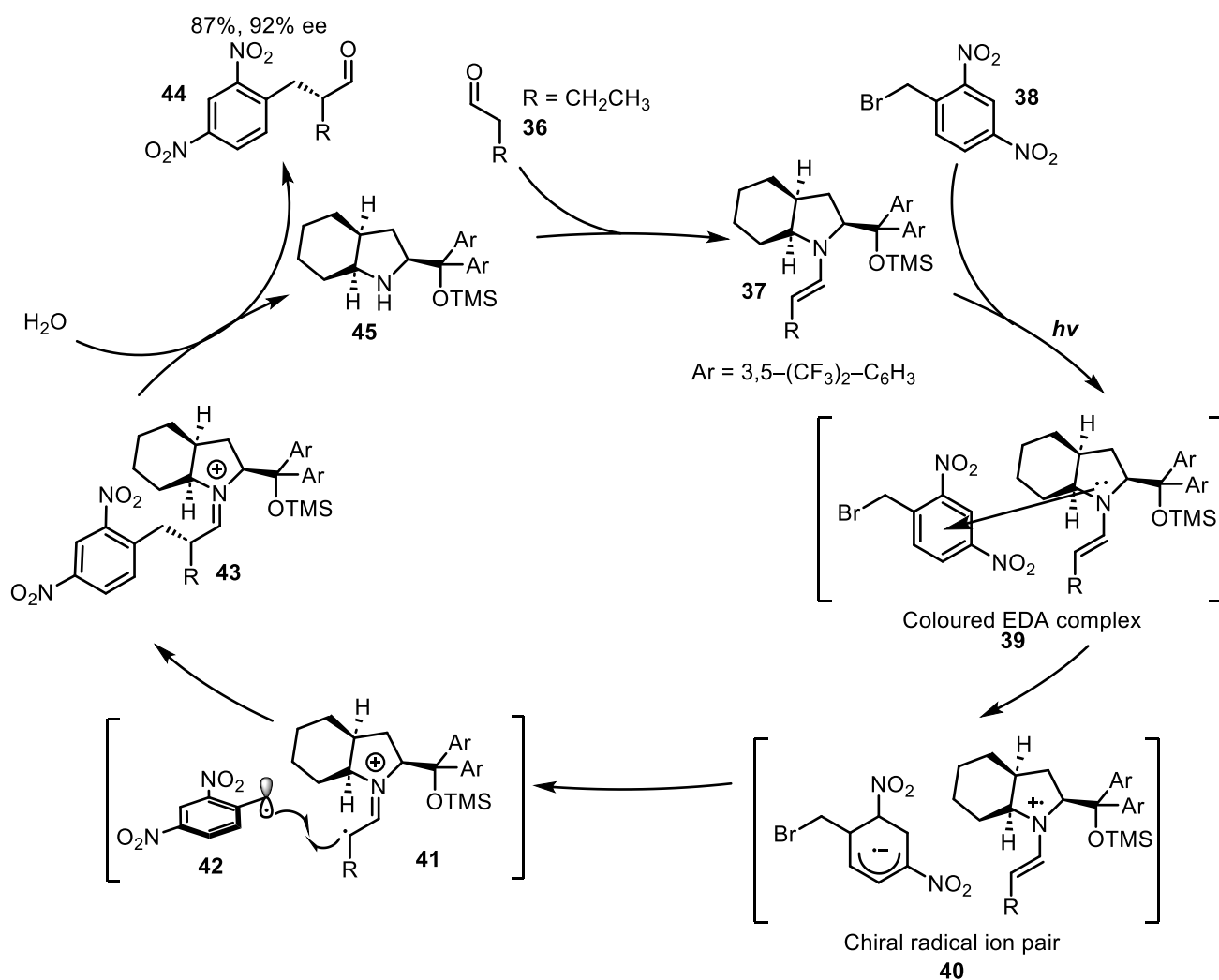
Scheme 7. SOMO activation organocatalysis^{29,43}

In 2008, MacMillan reported a process that combined photoredox catalysis with organocatalysis in the direct, asymmetric α -alkylation of an aldehyde.⁵² The reaction between a chiral enamine **26** (Scheme 8) and a reactive electron deficient radical **27** furnishes radical **28**. The acyl radical **27** was formed by the reduction of an α -bromocarbonyl **35** with reductant $\text{Ru}(\text{bpy})_3^+$ **34**. Radical **28** is oxidised to iminium ion **29** which produces α -alkylated aldehyde **30** after hydrolysis. The photoredox catalyst $\text{Ru}(\text{bpy})_3^{2+}$ **32** is activated by photon to form an excited oxidant $^*\text{Ru}(\text{bpy})_3^{2+}$ **33**. In a logical sequence, compound **33** oxidises a sacrificial amount of enamine **26** and is thus reduced to $\text{Ru}(\text{bpy})_3^+$ **34**. $\text{Ru}(\text{bpy})_3^+$ reduces the activated α -bromocarbonyl to acyl radical **27**. The acyl radical then reacts as previously described. An electron deficient radical is essential for the reaction to occur. High yield and high enantioselectivity are observed.⁵²



Scheme 8. Proposed mechanism for the union of photoredox catalysis with organocatalysis.⁵²

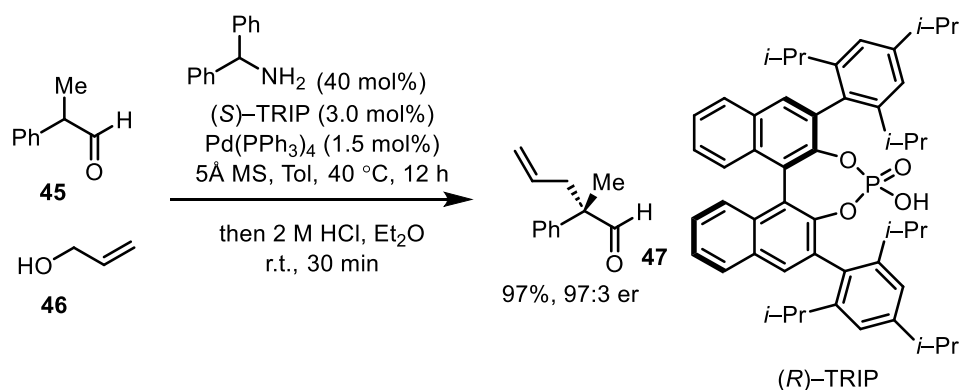
Melchiorre *et al.* demonstrated the α -alkylation of an aldehyde (Scheme 9) via the photochemical activation of an electron donor–acceptor (EDA) complex.⁵³ Chiral enamine **37** and an electron deficient benzyl bromide **38** react to form a coloured EDA complex **39** which undergoes a photo-induced electron transfer to form a chiral radical ion pair **40**. The loss of bromide leaving group competes with reverse electron transfer. Radical combination of **41** and **42** leads to iminium ion **43** which furnishes the desired α -alkylated aldehyde **44** after hydrolysis. This reaction shares the same limitation with MacMillan’s work in that electron deficient and activated substrates are required.⁵³



Scheme 9. Melchiorre's asymmetric α -alkylation of aldehydes.⁵³

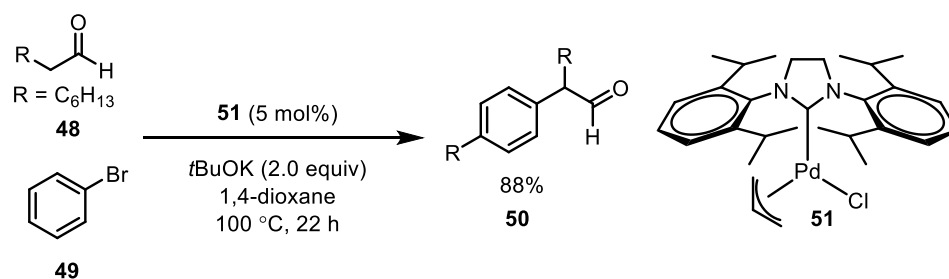
1.4. Palladium Catalysed Processes

Several palladium-catalysed processes have been reported. List *et al.* reported a palladium (0) catalysed asymmetric allylation of an α -disubstituted aldehyde **45** with allylating agent **46** to produce **47** with high enantioselectivity (Scheme 10).⁵⁴ There were no examples of α -monosubstituted aldehydes or unactivated alkylating agents.⁵⁴



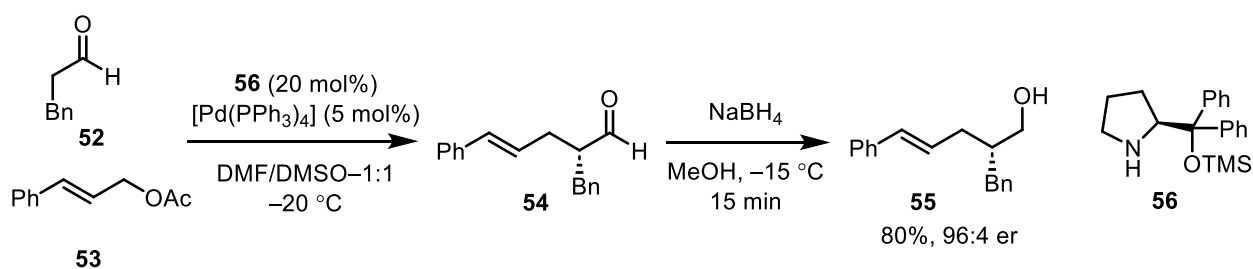
Scheme 10. List's asymmetric allylation of aldehydes.⁵⁴

Mazet *et al.* have described an α -arylation of aldehydes using an *N*-heterocyclic carbene complex with palladium, [(NHC)Pd].⁵⁵



Scheme 11. Mazet's α -arylation of aldehydes.⁵⁵

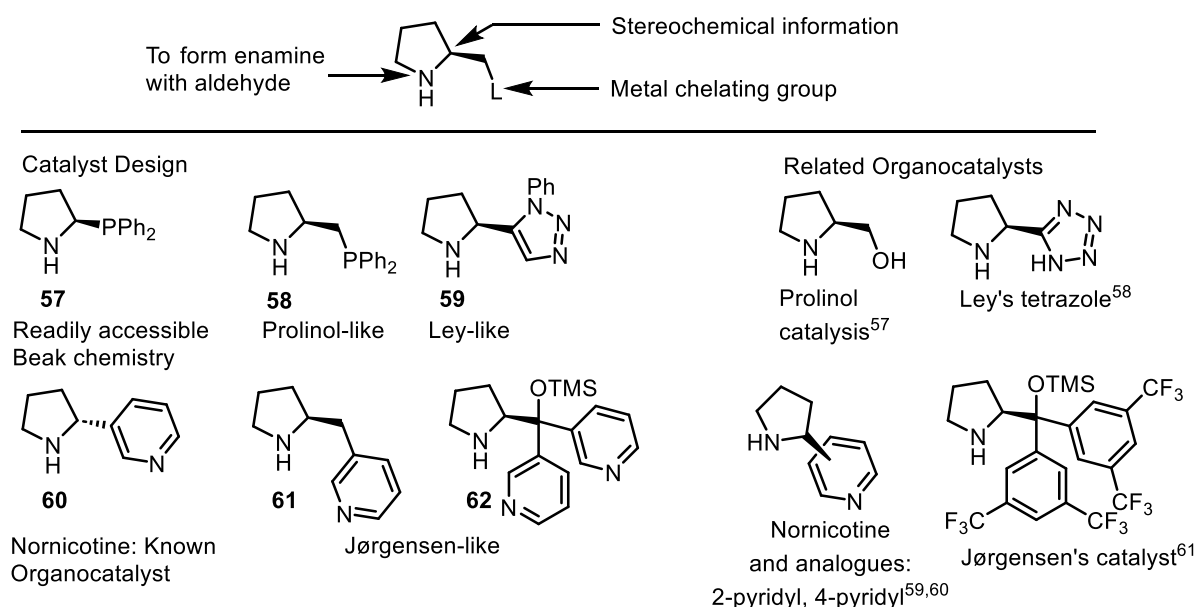
Finally, Córdova and co-workers have reported a methodology that combines organocatalysis with transition metal chemistry (Scheme 12).⁵⁶ Nucleophilic attack of the chiral enamine on Pd(II)- π -allyl moiety produces the desired compound after hydrolysis.



Scheme 12. Córdova α -allylation of aldehyde.⁵⁶

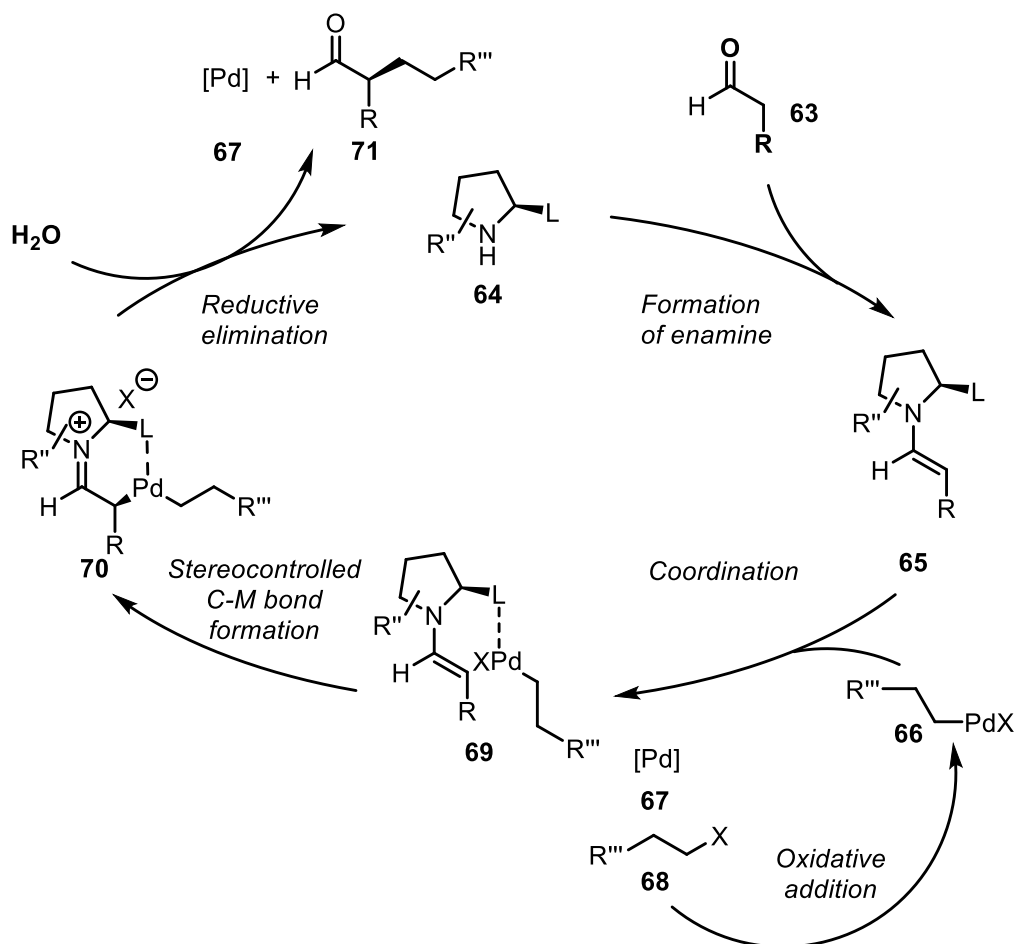
1.5. Initial Aims and Objectives

The aim of this project is to combine the tunability of organocatalysis with the diversity of transition metal mediated processes. The initial aim was the synthesis of chiral ligands based on privileged scaffolds. These ligand scaffold would be capable of both enamine catalysis and transition metal complexation.^{57–61} Proline-based chiral scaffolds are well represented in enamine organocatalysis (Scheme 13). Several ligands based on known organocatalyst would be synthesized.



Scheme 13. Organocatalyst Design.^{57–61}

The proline-based organocatalyst would be derivatised with metal chelating groups. The metal chelating groups will bear an *N* or *P* Lewis basic functionality. This choice is consistent with known palladium ligands.¹ The anticipated chemistry of the dual catalytic system involves the activation of the aldehyde substrate by the formation of an enamine through condensation and tautomerization. This is followed by electronic interaction or coordination with the metal. A stereo-controlled *C–M* bond formation is anticipated after the coordination (Scheme 14).



Scheme 14. Anticipated reactivity in the dual catalyst system.

Enamine **65** (Scheme 14) is involved in several well-known catalytic cycles (Scheme 13). Transmetallation of alkali metal enolates with a transition metal followed by C–C cross-coupling to form α -arylated aldehydes has also been reported.³¹ Therefore a stereo-defined carbon–metal bond formation to produce **70** (Scheme 14) was anticipated. The intermediate **70** is the reaction platform upon which stereoselective C–C cross-coupling reactions will be effected to produce novel compounds.

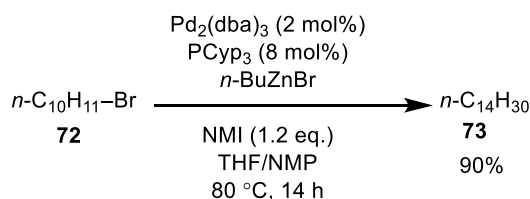
Several potential problems were also anticipated. A premature reaction between organocatalyst (e.g. **58**) and transition metal is possible. The catalysts in Scheme 13 can act as *N*, *P* bidentate ligands for a transition metal to form a stable 5-membered chelate ring. If this occurs, the aldehyde substrate will remain untouched by the organocatalyst and no α -functionalization

would be observed. It is possible to mitigate the chelate ring formation by catalytic structure such as **57**, whereby a less stable 4-membered chelate ring is formed. However, another challenge is that the enamine of organocatalyst **57** is now able to form a 6-membered chelate ring which might be stable. If this occurs, subsequent reactivity might be hindered.

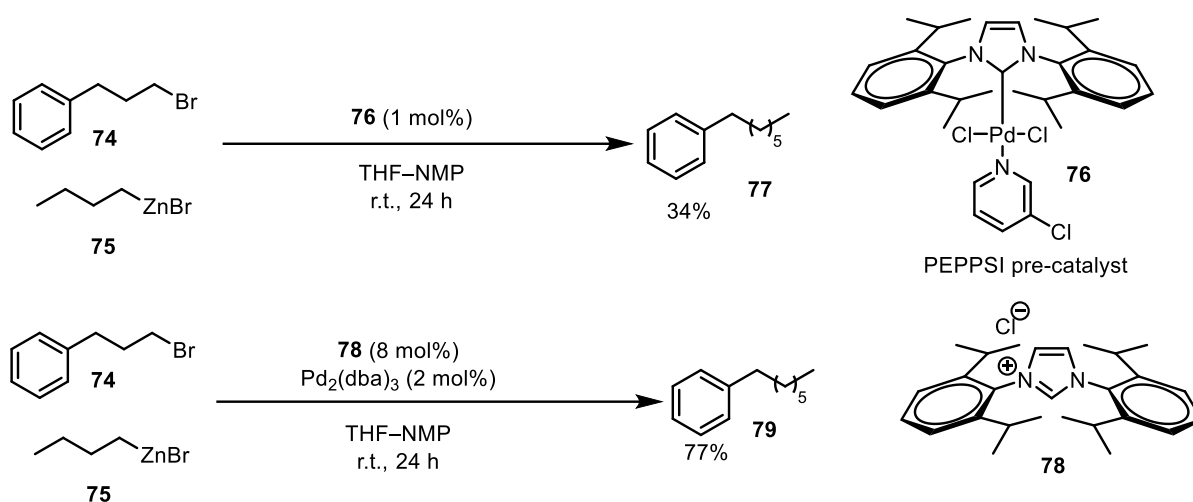
These considerations have been incorporated into the catalyst design. Except for compound **58** (Scheme 13), the intention is to avoid the formation of 5- or 6-membered chelate rings. Organocatalyst **58** was included for the sake of completeness since it is structurally related to prolinol organocatalysts. The design of organocatalysts **59** and **60** (*N, N* ligands) is such that the premature formation of a stable 6-membered chelate ring is unlikely. The design feature that ensures this unlikelihood is the substituents on the pyrrolidine which contain Csp^2 atoms so that it is not in the plane of the pyrrolidine, therefore **59** and **60** cannot act as *N, N* bidentate ligands for the transition metal. The formation of stable 7-membered chelate ring for organocatalysts **61** and **62** are thermodynamically unfavourable.

The choice of transition metals are *Pd* and *Ni* since primary alkyl-alkyl couplings with these metals are well preceded (Scheme 15).^{5,6,15,16} The major problems of Csp^3-Csp^3 transition metal-catalysed cross-coupling reactions lie with the alkyl electrophile. Slow rate of oxidative addition is the first problem; the second problem arises after a successful oxidative addition, when β -hydride elimination (before reductive elimination) is facile. Several catalyst systems have been developed to tackle these problems.^{5,6,15,16,62,63}

Pd-catalysed alkyl–alkyl coupling between unactivated primary halide or tosylates and primary alkyl zinc halide.¹²

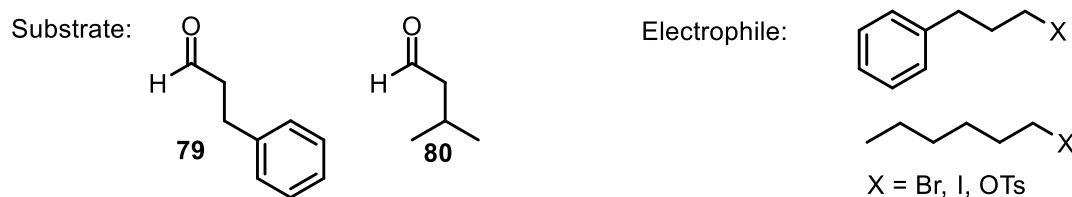


Pd/NHC-catalysed alkyl–alkyl coupling between unactivated primary bromide and primary alkyl zinc halide.^{62,63}



Scheme 15. Cross coupling of unactivated primary electrophiles and primary nucleophiles.^{5,6,15,16,62,63}

Electron-rich, strong σ electron donor, *N*-heterocyclic carbenes **76**, **78** would be used, combined with a stable Pd(0) source like $\text{Pd}_2(\text{dba})_3$. Aldehydes **79** and **80** (Scheme 16) would be used as substrates. Rapid analysis of the reaction mixture by gas chromatography (GC) would be used to monitor the reaction. Enantiomeric ratios will be determined by chiral high-performance liquid chromatography (chiral HPLC). The choice of electrophiles was set as *n*-hexyl halides and pseudohalides (Scheme 16) as unactivated primary electrophile.



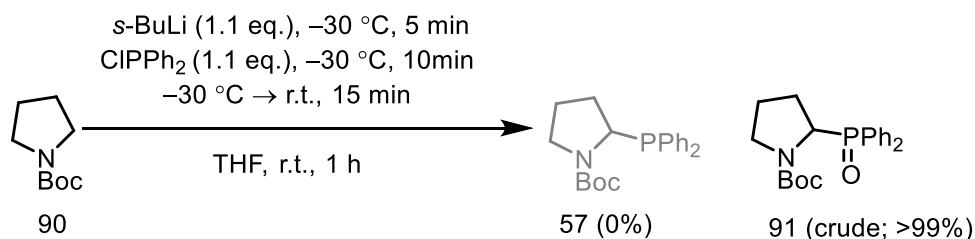
Scheme 16. Choice of substrate and electrophile.

Chapter Two

Synthesis of Chiral Ligands

2. Synthesis of Chiral Ligands

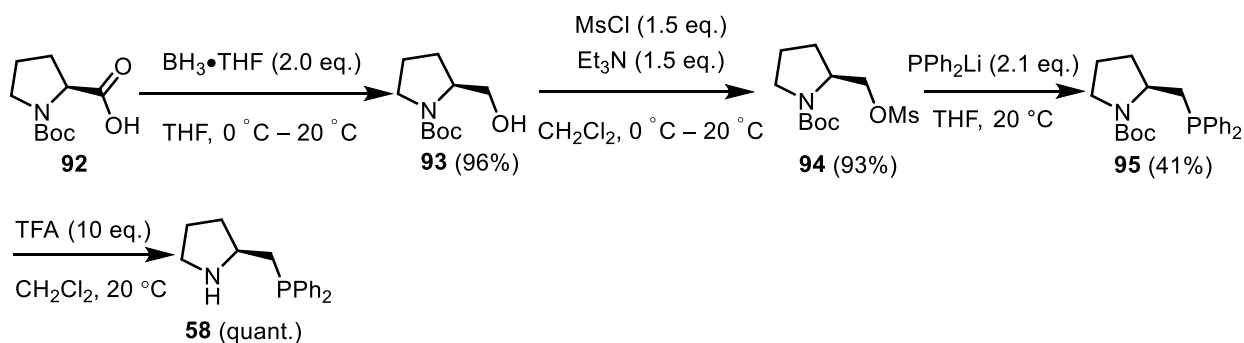
The initial strategy for the synthesis of compound **57** was to introduce the phosphine as an electrophile (Scheme 17). The nucleophile would be the lithiated Boc-pyrrolidine which is accessible through enantioselective lithiation with (–)-sparteine/*s*-BuLi; a methodology developed by Beak *et al.*^{64–66} An achiral strategy without (–)-sparteine was tested.



Scheme 17. Lithiation of Boc-pyrrolidine.^{64–66}

The crude product was analysed via ³¹P NMR. Phosphine oxide **91** was obtained in near quantitative yields. The desired product was not observed. Attempts to isolate **57** as a HBF salt were unsuccessful.

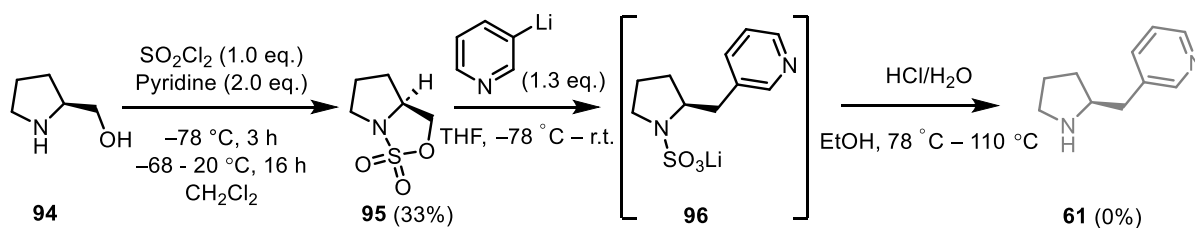
A chiral pool strategy was trialled for the synthesis of compound **58** (Scheme 18). Borane reduction of *N*-Boc proline produced alcohol compound **93**. Mesylation of the resulting prolinol followed by nucleophilic attack by Ph₂PLi produced **95** in moderate yield. Boc-deprotection with TFA produced the desired compound **58** in quantitative yield.^{67,68}



Scheme 18. Chiral pool strategy.^{67,68}

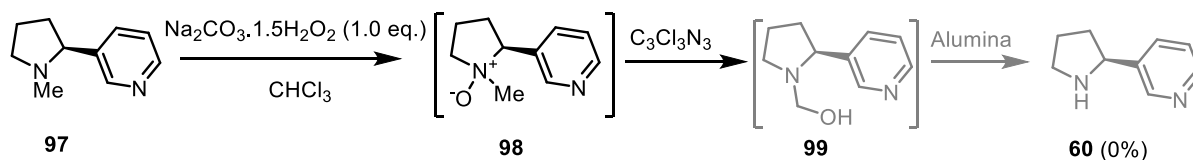
Attempts to synthesize compound **61** were unsuccessful. Sulfamidate **95** was obtained according to literature procedure. All attempts to generate **61** via the nucleophilic attack of 3–

lithiopyridine were unsuccessful. The product mixture was inseparable by flash column chromatography and preparative thin layer chromatography.^{69,70}



Scheme 19. Attempted Synthesis of compound 61.^{69,70}

Rosenau *et al.* reported the *N*-deoxygenative demethylation of Nicotine **97** in a column loaded with different solid reagents (Scheme 20).^{71–73}

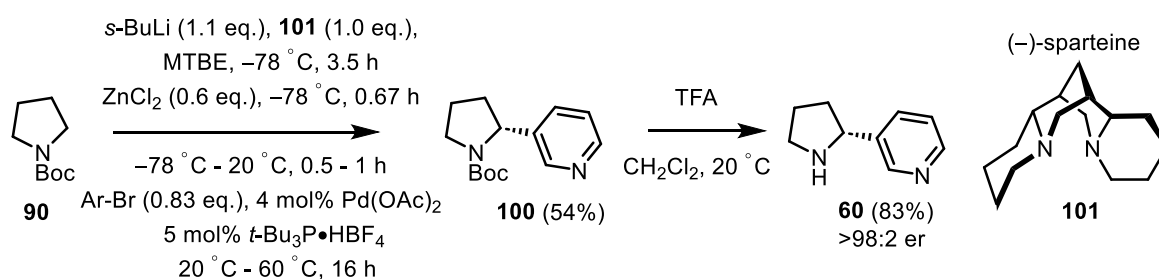


Scheme 20. Rosenau strategy for demethylation.^{71–73}

The Rosenau procedure was attempted with cyanuric chloride (Scheme 20). The column was packed as suggested in literature.^{71–73} It was eluted with chloroform. The reaction was performed with small sodium percarbonate granules. No product was isolated. The reaction was repeated but adapted to solution phase. Again, no product was isolated. TLC after *N*-oxidation at first seemed to show complete reaction but staining with KMnO_4 showed that no reaction had occurred. This reaction was also performed with small sodium percarbonate granules. Sodium percarbonate was pulverised behind a blast shield and the solution phase reaction was repeated. No oxidation was observed. Attempts to oxidise nicotine with sodium percarbonate at 50 °C also failed. Compound **98** was alternatively generated via oxidation of nicotine using 3-chloroperbenzoic acid to give an oil. Purification on a basic alumina column gave a pale pink solid (>50%). NMR was consistent with literature data of *N*-oxide enantiomers (splitting of peaks of the protons adjacent to nitrogen). A solution phase deoxygenative

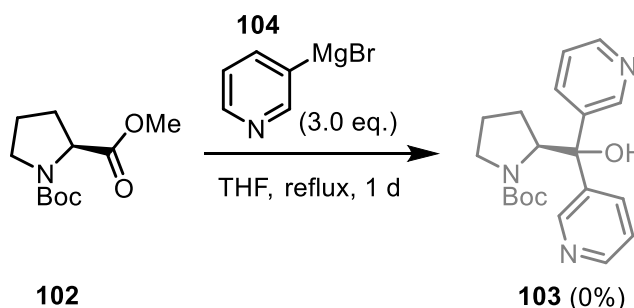
demethylation was attempted with this sample of the *N*-oxide. An unknown compound was observed by ^1H NMR.

Nornicotine **60** was synthesized according to methodology developed by Campos.^{68,74} Enantioselective lithiation of **90** by (–)-Sparteine/*s*-BuLi followed by transmetallation of the lithiated *N*-Boc pyrrolidine to zincated *N*-Boc pyrrolidine, then underwent Negishi coupling with 3-bromopyridine to form enantioenriched Nornicotine **60** (>98:2 er by chiral HPLC). A racemic sample of compound **60** (*rac*-**60**) was also prepared with the use of TMEDA instead of diamine **101**.



Scheme 21. Campos' procedure for synthesis of Nornicotine.^{68,74}

Compound **103** is a novel compound. A method by Ni *et al.* (with 3-bromobenzene) was adapted for the aborted synthesis of **62**.⁷⁵ No reaction was observed after 1 day under reflux. Complex NMR was observed after 2–3 days under reflux. The reaction was repeated with dry CeCl_3 as Lewis acid (Imamoto conditions⁷⁶). Desired product was not observed. Electron deficient Grignard reagent is the likely cause for this result.



Scheme 22. Failed Synthesis of compound **103**.

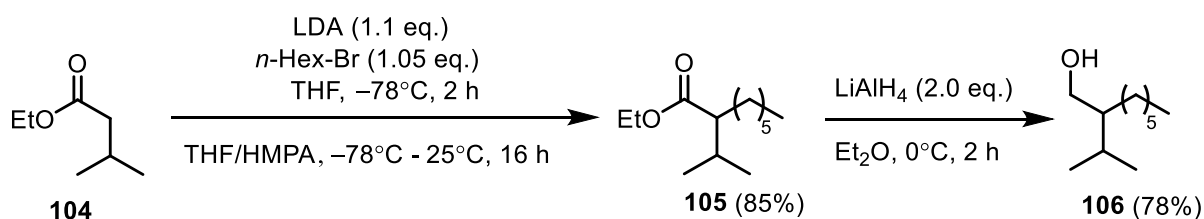
Two chiral ligands have been synthesized. Further synthesis was halted so that reaction screening could begin.

Chapter Three

Synthesis of authentic samples of α -alkylated product

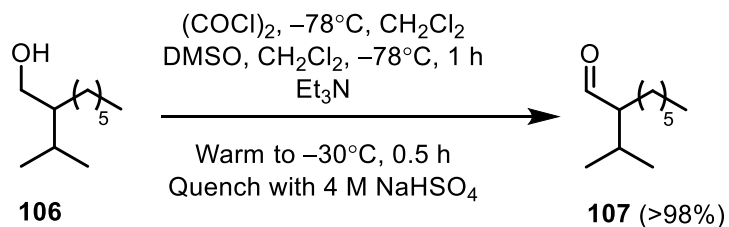
3. Synthesis of authentic samples of α -alkylated product

To monitor the α -alkylation of aldehydes **79** and **80** (Scheme 16) by Gas Chromatography, authentic samples of the α -hexyl aldehyde of **79** and **80** were synthesized. Deprotonation of the α -hydrogen on **104** followed by hexylbromide trapping of the resulting enolate produced **105**.



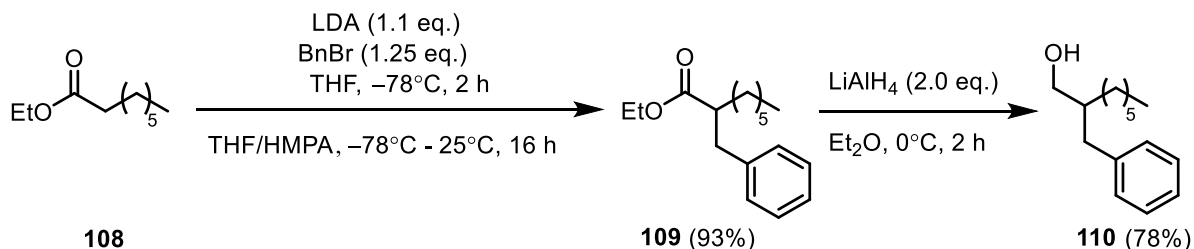
Scheme 23. Synthesis of alcohol 106.

Reduction of the ester **105**, followed by a Swern oxidation produced the desired aldehyde **107** excellent yield.



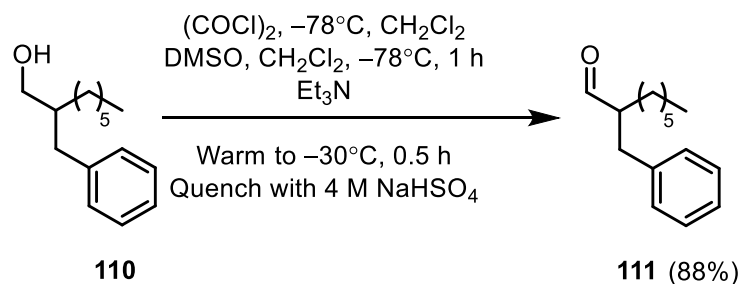
Scheme 24. Synthesis of authentic sample 107.

An authentic sample **80** was synthesized by the same procedure to produce alcohol **110**.



Scheme 25. Synthesis of alcohol 110.

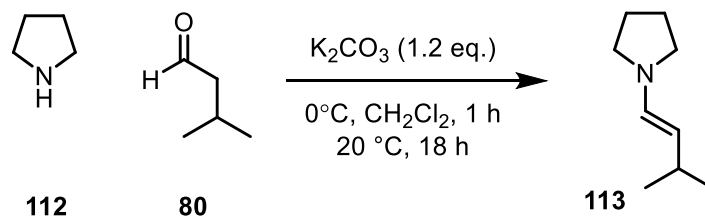
LAH reduction of the ester **110**, followed by a Swern oxidation produced the desired aldehyde **111**. Attempts to synthesize **109** by the alkylation of ethyl hydrocinnamate resulted in *C*- and *O*-alkylation products. Authentic samples of the products were used to calibrate the yields with Gas Chromatography.



Scheme 26. Synthesis of alcohol 111.

3.1. Preparation for Reaction Screening.

To prepare for reaction screening, enamine **113** of isovaleraldehyde **80** was synthesized (Scheme 27). The purpose for synthesizing a proline-based enamine was to preserve the synthesized chiral organocatalyst in the initial reaction screening. The chelating arm of the chiral ligand would obviously play a role in stereoinduction as well as a thermodynamic role in bond formation. The hypothesis was that reaction of enamine **113** with an electrophile would result in slightly poorer yields, which would then be improved by using more suitable catalyst.

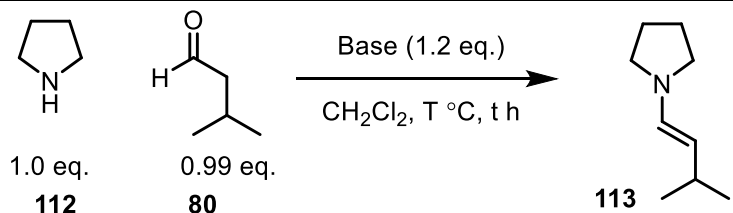


Scheme 27. Synthesis of Enamine 113.

Reaction screening was performed to measure the extent of *in situ* enamine formation under different reaction conditions (Table 1). The formation of enamine **113** proceeded with good to moderate yields. Lower yields were observed at elevated temperatures (Table 1, entries 7 and

8). Similar yields were obtained at 0 °C and room temperature (Table 1, entries 1 and 2). These results proved that enamine formation could be expected under various alkylation screening conditions.

Table 1. Test for Enamine Formation.

				
entry	Solvent	T (°C)	t (h)	Yield (%) ^b
1	CH ₂ Cl ₂	0	18	70
2	CH ₂ Cl ₂	20	18	73
3	THF	20	18	71
4	THF	60	18	75
5	Dioxane	80	24	81
6	Dioxane	80	48	74
7	Dioxane	100	24	32
8	Dioxane	100	48	46
9 ^c	Dioxane	80	24	67
10 ^d	Dioxane	80	24	78

^aCs₂CO₃ (1.20 mmol) is the base; Isovaleraldehyde (0.99 mmol); pyrrolidine (1.00 mmol). ^bYield of isolated product. ^cNa₂CO₃ is base. ^dNaHCO₃ is base.

Chapter Four

Reaction Screening for α -alkylation

4. Reaction Screening for α -alkylation

4.1. Pre-formed Enamine

Initial screenings were performed with enamine **113**. Alkylation reaction was attempted with hexylbromide at various temperatures and with various organic and inorganic bases. PEPPSI; a palladium (0) pre-catalysed was used (Table 2). Most reactions, in the literature involving PEPPSI as a pre-catalyst, are between an organometallic nucleophile and an organic halide.^{62,63,77} PEPPSI is activated by *X*-type Ligand substitution of chloride with the organometallic compound (e.g. an organozinc), the resulting reductive elimination provides the desired Pd(0) *in situ*. There are several reactions however that proceed in the presence of inorganic bases, including a room temperature amination with Cs₂CO₃ as base.^{78–80} No product formation was observed under any reaction condition.

Table 2. Reaction screening with PEPPSI pre-catalyst.

 0.12 mmol	 0.1 mmol	 107	 115
entry	Base	Temp. (°C)	107 (%) ^a
1 ^b	Cs ₂ CO ₃	20	<2
2 ^b	KOH	20	0
3 ^b	<i>t</i> -BuOK	20	0
4 ^b	Et ₃ N	20	0
5	Cs ₂ CO ₃	60	<2
6	KOH	60	0
7	<i>t</i> -BuOK	60	0
8	Et ₃ N	60	0

^aYield calculated via Gas Chromatography calibration with *n*-decane as internal standard, Reaction mixture was hydrolysed with NH₄Cl. ^bAdditional Reaction screening performed in THF/*i*-PrOH were unsuccessful.

Similar results were obtained after pre-activating PEPPSI with EtMgBr. Other pre-activation protocols in the presence of Ph₃P/KOAc did not alter the outcome of the reaction. Starting material **113** was recovered, but some consumption of **114** was observed.

4.2. Catalytic Pyrrolidine

The use of pre-formed enamine was abandoned for catalytic amounts of pyrrolidine (20 mol%) to screen the desired catalytic organocatalysis. The desired product was not observed under any reaction conditions evaluated. High depletion of *n*-hexyl bromide was observed at room temperature with all bases trialled (Table 3, entries 1–4). The reason for the low consumption at elevated temperature (Table 3, entries 6–7) is unknown. A repetition of the experiment in

Table 3 with *n*-hexyl iodide as the electrophile was also unsuccessful. No product was observed under any reaction conditions.

Table 3. Reaction screening with catalytic (20 mol%) pyrrolidine.

80	112	114		107
entry	Base	Temp. (°C)	107 (%) ^a	Consumption (%) ^b
1	Cs ₂ CO ₃	20	<2	60
2	KOH	20	0	81
3	<i>t</i> -BuOK	20	0	80
4	Et ₃ N	20	0	>99
5	Cs ₂ CO ₃	60	<2	71
6	KOH	60	0	3
7	<i>t</i> -BuOK	60	0	1
8	Et ₃ N	60	0	85

^aYield calculated via Gas Chromatography calibration with *n*-decane as internal standard. ^b*n*-hexylbromide consumption calculated via Gas Chromatography calibration with *n*-decane as internal standard.

Another screening was conducted with 40 mol% pyrrolidine for 48 h at 60 °C (Table 4). No product was observed. Higher consumption of hexyl bromide was observed with higher pyrrolidine catalyst loading and longer reaction times (Table 4, entries 2–3). Control reactions in the absence of PEPPSI **115** resulted in high consumption of **114** (Table 4, entries 5–6).

Table 4. Reaction screening with catalytic (40 mol%) pyrrolidine.

80	112	114	107

entry	Base	Yield (%) ^a	Consumption (%) ^b
1	Cs ₂ CO ₃	0	75
2	KOH	0	27
3	<i>t</i> -BuOK	0	46
4	Et ₃ N	0	89
5 ^c	Cs ₂ CO ₃	0	88
6 ^c	Cs ₂ CO ₃	0	94

^aYield calculated via Gas Chromatography calibration with *n*-decane as internal standard. ^b*n*-hexylbromide consumption calculated via Gas Chromatography calibration with *n*-decane as internal standard. ^cControl experiments; no PEPPSI^{IPr} was added.

The reaction was screened at even higher temperatures in dioxane with Cs₂CO₃ as base (Table 5). High depletions were observed at 80 °C and 100 °C, probably due to background reactions.

Table 5. Reaction Screening in dioxane at elevated temperatures.

80	112	114	107

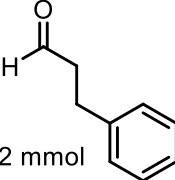
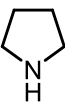
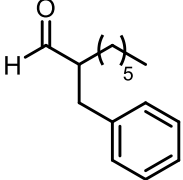
entry	Temp. (°C)	Time (h)	Yield (%) ^a	Consumption (%) ^b
1	80	24	0	86
2	80	48	0	95
3	100	24	0	>99
4	100	48	0	>99

^aYield calculated via Gas Chromatography calibration with *n*-decane as internal standard. ^b*n*-hexylbromide consumption calculated via Gas Chromatography calibration with *n*-decane as internal standard.

4.3. Reaction screening with hydrocinnamaldehyde

The reaction screening was continued but aldehyde **80** was replaced with aldehyde **79**. Product formation was not observed. Low consumption of bromide **114** was observed at room temperature (Table 6, entry 1) and at higher temperature in the absence of PEPPSI (Table 4, entry 3). High consumption was observed at 60 °C (Table 6, entry 2). In the absence of base, bromide **114** was recovered in near quantitative yield. Additional reactions with PEPPSI^{SIpr}; an analogue of **115** were unsuccessful. Reactions conducted in different solvents such as DMSO, DMF, Toluene, CH₂Cl₂, THF/DMSO were also unsuccessful.

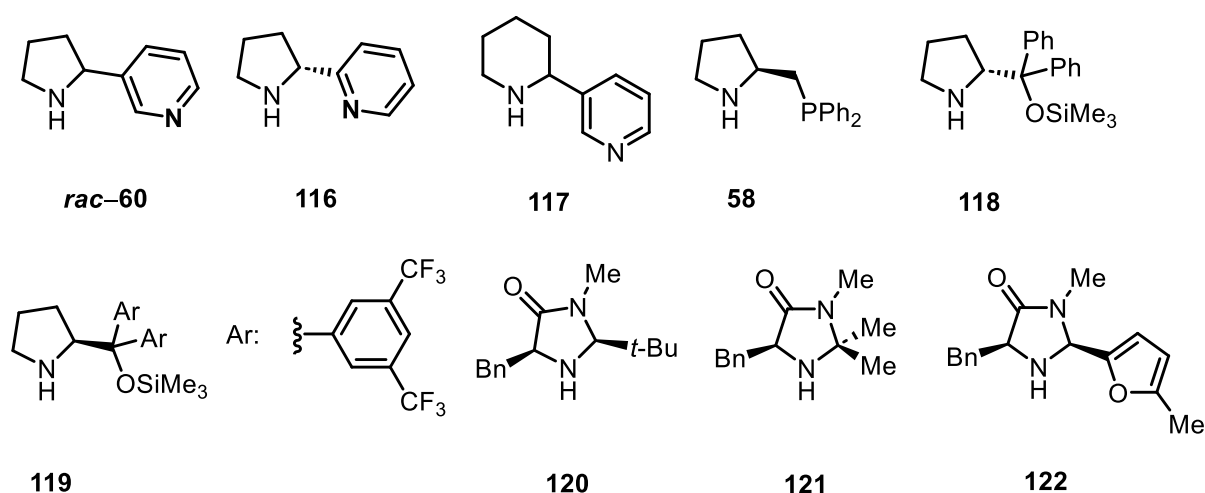
Table 6. Reaction screening with hydrocinnamaldehyde.

 79 0.12 mmol  112 20 mol% <i>n</i>-HexBr 114 0.1 mmol 115 (10 mol%) Base (0.12 mmol) THF (~0.5 ml), T (°C), 24 h  111				
entry	Base	Temp. (°C)	Yield (%) ^a	Consumption (%) ^b
1	Cs ₂ CO ₃	20	0	3
2	Cs ₂ CO ₃	60	0	78
3 ^c	Cs ₂ CO ₃	60	0	7
4	None	20	0	2
5	None	60	0	10
6 ^c	None	60	0	0
7 ^d	Cs ₂ CO ₃	20	0	4
8 ^d	Cs ₂ CO ₃	60	0	84

^aYield calculated via Gas Chromatography calibration with *n*-decane as internal standard. ^b*n*-hexylbromide consumption calculated via Gas Chromatography calibration with *n*-decane as internal standard. ^cControl experiments; no PEPPSI^{IPr} was added. ^dNornicotine **60** (20 mol%) instead of **112**.

4.4. Additional organocatalyst screening

Pyrrolidine was replaced with racemic nornicotine *rac*-**60** as secondary amine (Table 6, entries 7–8). No desired product was observed. Several other amine organocatalysts were also trialled (Scheme 28). 2-(2-Pyrrolidinyl)pyridine **116** and Anabasine **117** were also trialled. No product was observed. Trialling of *N*, *P*-ligand **58**, the Jørgensen–Hayashi organocatalyst **118**, the Jørgensen organocatalyst **119**, or the Macmillan Imidazolidinone organocatalysts **120–122** resulted in moderate consumption of hexyl bromide at 60 °C but no desired product was observed. Similar results were obtained when an excess (0.2 mmol) of bromide **114** was used. Slightly higher depletions of bromide were observed with increased *Pd* catalyst loading (20–50 mol%).

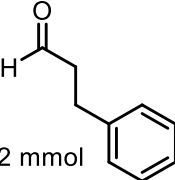
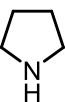
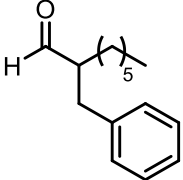


Scheme 28. Assorted amine organocatalysts.

4.5. Reaction screening with phosphine ligands

Electron-rich phosphines have been used alongside suitable *Pd* sources to initiate cross coupling reactions with primary unactivated electrophiles (Scheme 15).^{15,16} They facilitate oxidative addition to the poorly reactive, unactivated, electrophile. Also, these phosphines hinder unwanted β -hydride elimination by donating electrons to the *Pd* centre. Various *Pd* sources and phosphines were trialled (Table 7).

Table 7. Reaction screening with phosphine bases.

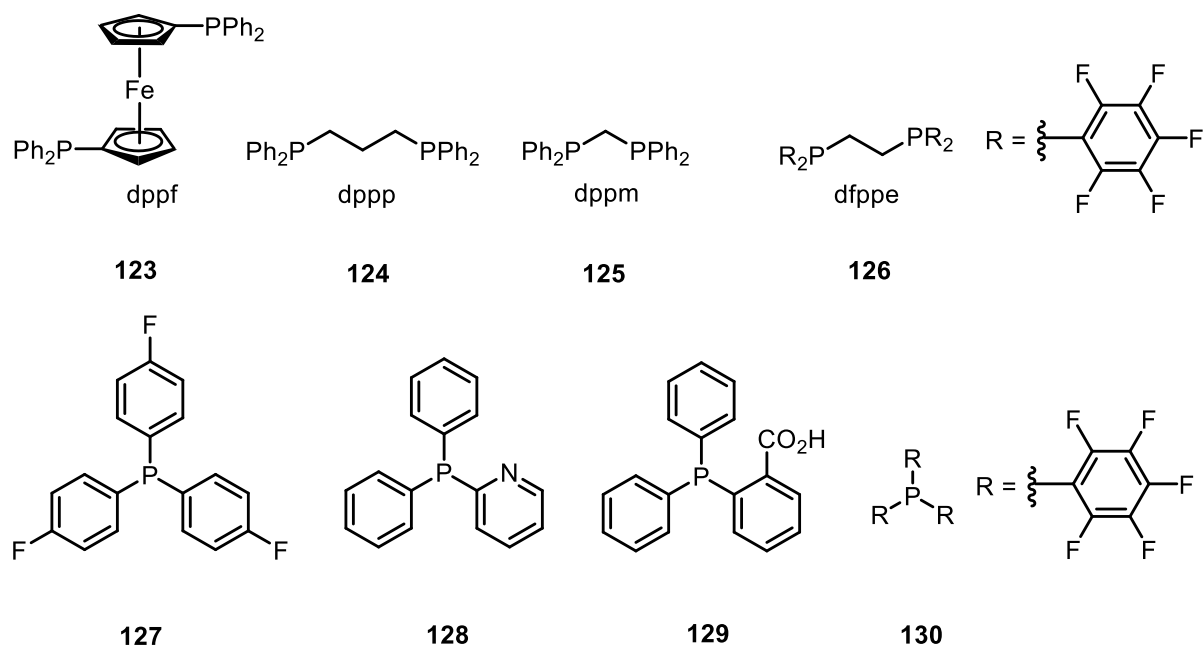
 79 0.12 mmol  112 20 mol% <i>n</i>-HexBr 114 0.1 mmol [Pd] (10 mol%) Phosphine (24 mol%) Cs₂CO₃ (0.12 mmol) THF (~0.5 ml), T (°C), 24 h  111					
entry	[Pd]	Phosphine	Temp. (°C)	Yield (%) ^a	Consumption (%) ^b
1	Pd(PPh ₃) ₄	(<i>t</i> -Bu) ₂ PMe•HBF ₄	20	0	6
2	Pd(PPh ₃) ₄	(<i>t</i> -Bu) ₂ PMe•HBF ₄	60	0	89
3 ^c	Pd(OAc) ₂	(<i>t</i> -Bu) ₂ PMe•HBF ₄	20	0	10
4 ^c	Pd(OAc) ₂	(<i>t</i> -Bu) ₂ PMe•HBF ₄	60	0	>99
5 ^c	Pd(OAc) ₂	PCy ₃ •HBF ₄	20	0	11
6 ^c	Pd(OAc) ₂	PCy ₃ •HBF ₄	60	0	>99
7 ^c	Pd(OAc) ₂	P(2-furyl) ₃	20	0	1
8 ^c	Pd(OAc) ₂	P(2-furyl) ₃	60	0	23
9 ^c	Pd(OAc) ₂	P(<i>t</i> -Bu) ₃ •HBF ₄	20	0	2
10 ^c	Pd(OAc) ₂	P(<i>t</i> -Bu) ₃ •HBF ₄	60	0	40
11 ^c	Pd(OAc) ₂	CyPPh ₂	20	0	13
12 ^c	Pd(OAc) ₂	CyPPh ₂	60	0	54
13 ^c	Pd(OAc) ₂	<i>t</i> -BuPPh ₂	20	0	16
14 ^c	Pd(OAc) ₂	<i>t</i> -BuPPh ₂	60	0	98
15 ^c	Pd(OAc) ₂	P(o-tolyl) ₃	20	0	1
16 ^c	Pd(OAc) ₂	P(o-tolyl) ₃	60	0	40

^aYield calculated via Gas Chromatography calibration with *n*-decane as internal standard. ^b*n*-hexylbromide consumption calculated via Gas Chromatography calibration with *n*-decane as internal standard. ^cAdditional experiments were conducted with Pd₂dba₃•CHCl₃ as *Pd* source.

No desired product was observed under any reaction conditions. The depletion of the hexyl bromide followed previously observed pattern. Consumption was low and room temperature and high at elevated temperatures. No discernible pattern in consumption of hexyl bromide was observed regarding the basicity, bite angle, and cone angle of the phosphine ligands.

4.6. Additional phosphine screening

Several other phosphine ligands were screened with $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ as *Pd* source (Scheme 29). Ferrocene-based **123**, diphosphines **124–126**, and triaryl phosphines **127–130**. Moderate depletions of hexyl bromide were observed.



Scheme 29. Additional phosphine screening.

4.7. Summary

All attempts to achieve α -alkylation were unsuccessful. The consumptions of hexyl bromide were attributed to unknown background reactions. Some possibilities include the alkylation of free secondary amine or the *Pd*-catalysed elimination of hexyl bromide to form 1-hexene. The enamine is less nucleophilic compared to an enolate, therefore nucleophilic attack on a hexyl- $\text{Pd}(\text{II})\text{-Br}$ is not as facile as anticipated. This might be the reason for the absence of desired

product under various reaction conditions. Future work should focus on *Ni* catalysis at ambient temperatures and photocatalysis. An enamine radical such as in scheme 7 can be generated and the coupling of this radical with *Ni* should be explored. A *Ni* catalyst compared to a *Pd* catalyst can more readily access several oxidation states (0, +1, +2, +3) which makes it more suitable for radical coupling (a one electron event).

Chapter Five

α -arylation of aldehydes

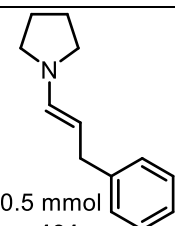
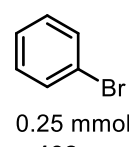
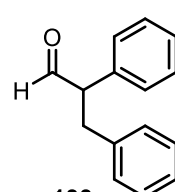
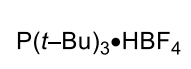
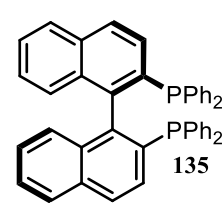
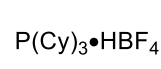
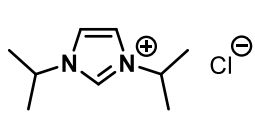
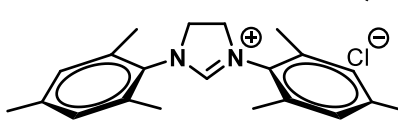
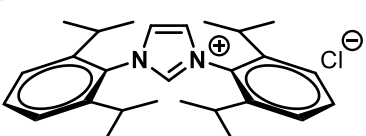
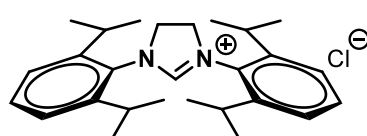
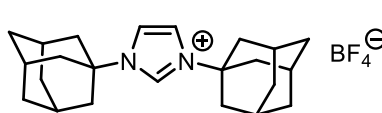
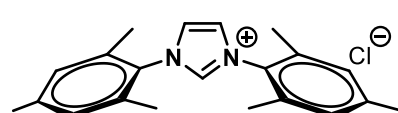
5. α -arylation of aldehydes

Several protocols have been reported for the α -arylation of aldehydes. These include the use of iodonium salts and imidazolidinone organocatalysts⁸¹, an intramolecular α -arylation via SOMO catalysis⁴⁵, *N*-Heterocyclic carbene-*Pd* catalysed α -arylation⁵⁵, *N*, *P*-ligand-*Pd* catalysed intramolecular α -arylation⁸², palladium catalysis with electron-rich phosphines⁸³, α -arylation involving ferrocene-based phosphines⁸⁴, asymmetric intermolecular α -arylation with chiral *N*, *P*-ligand-*Pd* system to form asymmetric quaternary centres⁸⁵. Various other ligand systems have also been reported.¹⁴

5.1. Arylation of enamine

The α -arylation of an enamine was explored, with the goal of achieving a dual catalytic asymmetric arylation. Electron-rich phosphines and *N*-Heterocyclic carbene ligands **134–142** (Table 8) are known to catalyse α -arylation of enolates. An enamine **131** was reacted with bromobenzene **132** under various reaction conditions (Table 8). No product was observed under the reaction conditions.

Table 8. Arylation reaction screening for enamine.

 0.5 mmol 131  0.25 mmol 132 Pd(OAc)₂ (5 mol%) Ligand (x mol%) Cs₂CO₃ (0.3 mmol) Dioxane, 90 °C, 24 h  133			
 134  135  136  137  138  139  140  141  142			
entry	Ligand	x mol%	Yield (%) ^a
1	134	10	0
2	135	5	0
3	136	10	0
4	137	5	0
5	138	5	0
6	139	5	0
7	140	5	0
8	141	5	0
9	142	5	0

^aYield was determined by NMR calibrated against 1,3,5-trimethoxybenzene internal standard.

5.2. Arylation of Imine

The results are unequivocal in stating that the reactivity of enamine towards functionalisation is negligible. Since enolates are known to react as described above, azaenolates formed in situ from a corresponding imine may also react. The initial exploration of this approach required the synthesis of imine **142**.

Table 9. Test of imine synthesis.

79	142	142
entry	Variation from 'standard' conditions	Result ^a
1	None	2:1 Product:SM
2	MgSO ₄ , dry CH ₂ Cl ₂ , r.t., 2 h, NMR after 1 d	>85% product and impurity
3	Dry CH ₂ Cl ₂ , 12 h	>85% product and SM
4	MgSO ₄ , dry CH ₂ Cl ₂ , r.t., 2 h,	>95% product, No SM

^aYield of isolated product.

Imine **142** was formed in excellent yields (Table 9, entry 4). A clean hydrolysis of **142** to aldehyde **79** was achieved after treatment with 1 M HCl for 1 h. Reaction screening was performed with **142** in dioxane at elevated temperatures.

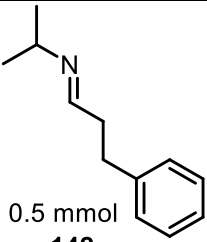
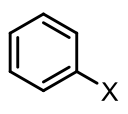
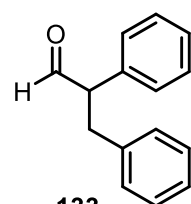
Table 10. Reaction screening with Cs₂CO₃.

<chem>CC(C)=NCCc1ccccc1</chem> (0.5 mmol, 142) + <chem>c1ccccc1Br</chem> (0.45 mmol, 132) $\xrightarrow[\text{Dioxane, 90 } ^\circ\text{C, 24 h}]{\text{[Pd] (5 mol\%), Ligand (x mol\%), Cs}_2\text{CO}_3 \text{ (1.35 mmol)}}$ <chem>O=C(Cc1ccccc1)Cc2ccccc2</chem> (133)				
entry	Ligand	[Pd]	x mol%	Yield (%) ^a
1	134	Pd(OAc) ₂	10	9
2	135	Pd(OAc) ₂	5	0
3	123	Pd(OAc) ₂	5	0
4	139	Pd(OAc) ₂	5	0
5	134	Pd(dba) ₂	10	11
6	135	Pd(dba) ₂	5	0
7	123	Pd(dba) ₂	5	0
8	139	Pd(dba) ₂	5	0

^aYield was determined by GC calibrated against decane internal standard.

Poor yields of desired product were observed with electron-rich phosphine ligand **134** (Table 10, entries 1 and 5). Pd(dba)₂, a Pd(0) source, resulted in essentially the same yield. Attempts with LDA (this was added to the imine separately) were unsuccessful. The use of a stronger base, *t*-BuOK, resulted in a more promising result (Table 11). The desired product was obtained in 23% yield (Table 11, entry 1). Ligand **139** produced similar yields. Reactions with aryl bromides resulted in higher yields than chloride and iodide. Additional experiments with a lower loading of *t*-BuOK (0.675 mmol) produced similar results. Additional experiments with K₃PO₄ produced similar results to those in Table 11, entries 1–4.

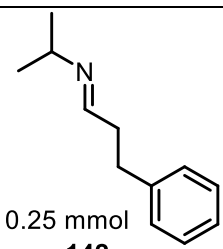
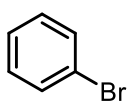
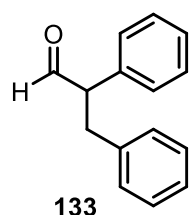
Table 11. Reaction screening with *t*-BuOK.

 0.5 mmol 142  0.45 mmol Pd(dba)₂ (5 mol%) Ligand (x mol%) <i>t</i>-BuOK (1.35 mmol) Dioxane, 100 °C, 24 h  133				
entry	Ligand	X	x mol%	Yield (%) ^a
1	134	Br	10	23
2	135	Br	5	6
3	123	Br	5	0
4	139	Br	5	21
5	134	Cl	10	16
6	135	Cl	5	0
7	123	Cl	5	0
8	139	Cl	5	5
9 ^b	134	I	10	12
10 ^b	135	I	5	3
11 ^b	123	I	5	0
12 ^b	139	I	5	8

^aYield was determined by GC calibrated against decane internal standard. ^b0.675 mmol *t*-BuOK was used. Additional experiment with 10 mol% **135** gave 16% yield.

When an excess of bromobenzene **132** was used, the product yield was increased (Table 12 *cf.* Table 11). Shorter reaction times (2–12 h) and lower temperature (20–60 °C) resulted in lower yields (16–18% *cf.* Table 12 entry 1). Attempts to reproduce Table 12, entry 1 with aldehyde **79** and catalytic amount (30 mol%) of amine **142** were unsuccessful. Additional reaction performed without amine **142** (just aldehyde **79**) resulted in <2% product.

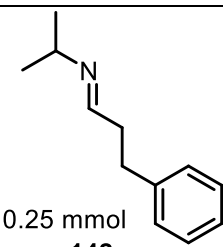
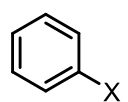
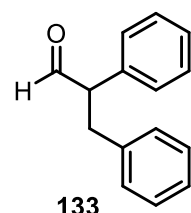
Table 12. Reaction screening with 2 eq. of bromobenzene.

 0.25 mmol 142  0.45 mmol 132 Pd(dba)₂ (5 mol%) Ligand (x mol%) <i>t</i>-BuOK (0.675 mmol) Dioxane, 100 °C, 24 h  133			
entry	Ligand	x mol%	Yield (%) ^a
1	134	10	36
2	135	5	10
3	123	5	5
4	139	5	42

^aYield was determined by GC calibrated against decane internal standard.

The promising result at room temperature was further investigated (Table 13). Poor yields were obtained with bromobenzene (Table 13, entry 1).

Table 13. Reaction screening at room temperature.

 0.25 mmol 142  0.23 mmol Pd(dba)₂ (5 mol%) Ligand (x mol%) <i>t</i>-BuOK (0.675 mmol) Dioxane, 20 °C, 24 h  133				
entry	Ligand	X	x mol%	Yield (%) ^a
1	134	Br	10	19
2	134	Cl	10	0
3	134	I	10	31
4 ^b	134	I	10	40
5 ^c	134	I	10	42

^aYield was determined by GC calibrated against decane internal standard. ^b0.675 mmol *t*-BuONa was used. ^c[Pd(π -cinnamyl)Cl]₂ (2.5 mol%) was used.

At room temperature, product yield has improved with iodobenzene (Table 13, entry 3). Similarly, moderate yield was obtained when base and *Pd* source was varied (Table 13, entry

4–5). Several attempts to exploit amine bases and Buchwald dialkylbiaryl phosphine ligands were unsuccessful.

5.3. Summary and outlook

Pre-formed imine **142** was successfully arylated at the α -position. The desired compound **133** was obtained in moderate yields. Future work should focus on further optimizations to improve product yield and more importantly to achieve comparable results without the use of pre-formed imine. The α -arylation reactions are a departure from the goal of α -alkylation, nevertheless achieving asymmetric intermolecular (non-quaternary) α -mono arylation of aldehyde would be a significant achievement.

Chapter Six

Experimental

6. Experimental

6.1. General methods

All reactions were carried out under dry nitrogen atmosphere and in oven-dried glassware unless stated otherwise. Flame- and oven-dried glassware were cooled under vacuum (ca. 1 mbar). For reactions performed under anhydrous conditions, Schlenk techniques were used. Anhydrous solvents THF, DMF, CH₂Cl₂, Et₂O, toluene and hexane were dried by alumina columns in a LC Technology Solutions Inc. SP-1 Solvent Purification System under N₂. Analytical grade solvents were used as received. Commercially available anhydrous MTBE (Aldrich; 99.8%) was degassed and stored under nitrogen atmosphere. Petroleum ether (b.p. 40–60 °C) was used.

Room temperature was taken as 20 °C, where no external heating or cooling was applied. Reactions at temperatures from –20 °C to ambient temperature were performed in an ice/water/NaCl(s) bath and –78 °C was achieved using an acetone/CO₂(s) bath. Prolonged periods of reaction cooling were accomplished by Huber cryocool apparatus.

Nuclear Magnetic Resonance (NMR) spectra were recorded on BRUKER AV (400 MHz) at 298 K. Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (chloroform at 7.26 and 77.00 ppm for ¹H and ¹³C NMR spectroscopy, respectively). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet; br., broad. Coupling constants were taken from the spectra directly and are uncorrected. Signals with the appearance of a given multiplicity are preceded with the term ‘app.’ to denote an apparent splitting pattern when chemically distinct nuclei display very similar coupling constants. ¹H and ¹³C NMR provided are taken directly using material for which the yield is quoted, without additional purification, and are representative of sample purity.

Purification of samples was achieved by flash column chromatography using Merck Flash Silica Gel 60 (230-400 mesh). Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualised initially by UV light (254 nm) or potassium permanganate or vanillin staining.

Chiral HPLC was performed on a HP Agilent 1260 infinity series system employing Daicel Chiralcel columns eluting with *i*-PrOH/hexane at 35 °C and monitored by a DAD (Diode Array Detector). Chiral GC was performed on an Agilent 7890 system (H₂ Flow Rate = 0.88 mL/min, Inlet Temperature = 250 °C) employing an Agilent CP-ChiraSil Dex CB column (25 m x 0.25 mm x 0.25 µm) and monitored by FID (Flame Ionisation Detector).

Reaction screenings were performed in 4 mL scintillation glass vials with a PTFE-lined cap, and all other reactions were performed in round-bottom flasks with rubber septa. Syringes were used to transfer air- and moisture-sensitive reagents.

6.2. General Procedures

General procedure A for enamine formation (113)

In an oven-dried vial or round-bottomed flask, was added a base (1.2 mmol). The reaction vessel was purged three times with nitrogen. Solvent (2 mL) and isovaleraldehyde (0.99 mmol) were added, followed by pyrrolidine (1.00 mmol) at the specified temperature. The reaction mixture was stirred at the specified temperature for the specified amount of time. The reaction mixture was filtered, and the solvent was removed *in vacuo*.

General procedure B for reaction screening with preformed enamine

PEPPSI (0.01 mmol, 10 mol%) and base (0.12 mmol) were added to an oven-dried vial. The vial was purged three times (liquid bases were added after purge cycle). Freshly prepared enamine (0.12 mmol) was added as stock solution in specified solvent. The mixture was stirred for 15 min and *n*-hexyl halide (0.1 mmol) was added as a neat liquid. The reaction mixture was stirred at the desired temperature for specified time. The mixture was filtered over Celite and washed with CH₂Cl₂. NMR and/or GC was recorded. Hydrochloric acid HCl (1 M) was added to the reaction mixture and stirred for 1 h. The organic phase was separated and concentrated at 200-250 mmHg.

General procedure C for reaction screening with catalytic pyrrolidine

PEPPSI (0.01 mmol, 10 mol%) and base (0.12 mmol) were added to an oven-dried vial. The vial was purged three times (liquid bases were added after purge cycle). Isovaleraldehyde, pyrrolidine (or pre-formed enamine) and *n*-hexyl halide were added. The reaction mixture was stirred for 3 min. Solvent was added and the reaction mixture was stirred at the specified

temperature for the specified time. The mixture was filtered over Celite and washed with CH_2Cl_2 . Decane (0.1 mmol) was added as the internal standard. GC was recorded.

General procedure D for imine formation (142)

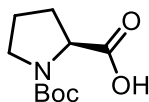
In an oven-dried vial or round-bottomed flask, was added a base (18.6 mmol). The reaction vessel was purged three times with nitrogen. Solvent (20 mL) and hydrocinnamaldehyde (9.30 mmol) were added, followed by isopropylamine (9.30 mmol) at specified temperature. The reaction mixture was stirred at the specified temperature for the specified amount of time. The reaction mixture was filtered, and the solvent was removed *in vacuo*.

General procedure E for reaction screening with preformed imine

Pd and base were added to an oven-dried vial. The vial was purged three times (liquid bases were added after purge cycle). Freshly prepared imine was added as stock solution in specified solvent. The mixture was stirred for 15 min and bromobenzene was added as a neat liquid. The reaction mixture was stirred at the desired temperature for specified time. The mixture was filtered over Celite and washed with CH_2Cl_2 . NMR and/or GC was recorded. Hydrochloric acid HCl (1 M) was added to the reaction mixture and stirred for 1 h. The organic phase was separated and concentrated at 200-250 mmHg.

6.3. Synthesis and Compound Characterization

1-*tert*-Butoxycarbonyl-2-pyrrolidinecarboxylic acid – 92

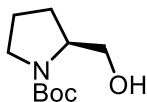


The synthesis was according to Bartoli *et al.* procedure.⁶⁷ An oven-dried 500 mL round-bottomed flask was charged with (*S*)-proline (15.0 g, 130 mmol), fitted with a stir bar, and purged with nitrogen. CH₂Cl₂ (250 mL) was added using a syringe and the stirred suspension was cooled to 0 °C using an ice–water bath (or a cryo-cool). Et₃N (23.6 mL, 169 mmol) was added using 2×20 mL syringes. A solution of di-*tert*-butyl dicarbonate (39.7 g, 182 mmol) in CH₂Cl₂ (10 mL) was added using a 20 mL syringe. The mixture was stirred at 0 °C for 2 h. Reaction was quenched with saturated aqueous citric acid (75 mL). The organic phase was separated, washed with saturated aqueous NaCl (2×75 mL) and water (150 mL), dried (Na₂SO₄) and concentrated. A crude white amorphous solid was isolated. The crude product was dissolved in hot ethyl acetate (minimal amount, *ca.* 7 mL) and hexane (500 mL) was added. After cooling to room temperature, the solution was cooled to 0 °C for 6 h and the product was isolated by filtration under reduced pressure, washing with hexane (*ca.* 30 mL). Compound **92** was isolated as colourless needles (20.5 g, 73%).

¹H NMR (400 MHz, CDCl₃): δ 11.16 (br. s, 1H), 4.39 – 4.21 (m, 1H), 3.63 – 3.31 (m, 2H), 2.34 – 1.82 (m, 4H), 1.48 (s, 4H), 1.42 (s, 5H).

*The data are consistent with those reported in literature.*⁶⁷

***tert*-Butyl 2-(hydroxymethyl)-1-pyrrolidinecarboxylate – 93**

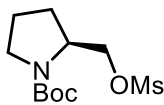


(*S*)-Boc-proline (5.00 g, 23.2 mmol) was dissolved in tetrahydrofuran (125 mL) in a round-bottomed flask under nitrogen atmosphere. $\text{BH}_3\cdot\text{SMe}_2$ (2 M in tetrahydrofuran, 12.8 mL, 25.5 mmol) was added dropwise via syringe over 1 h. Reaction was refluxed at 67 °C for 1 h, cooled to room temperature and concentrated. Residue was dissolved in CH_2Cl_2 (300 mL) and H_2O (200 mL). Organic layer was separated, washed with saturated aqueous NaHCO_3 , and brine, dried (Na_2SO_4) and concentrated. The target compound was isolated as a colourless oil (4.49 g, 96%).

^1H NMR (400 MHz, CDCl_3): δ 4.79 (br. s, 1H), 4.01 – 3.78 (m, 1H), 3.59 (m, 2H), 3.44 (m, 1H), 3.31 (m, 1H), 1.99 (m, 1H), 1.81 (m, 2H), 1.60 – 1.50 (m, 1H), 1.46 (s, 9H).

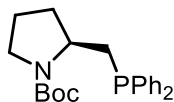
*The data are consistent with those reported in literature.*⁶⁷

Chemical structure of (S)-1-(tert-butoxycarbonyl)-2-methylpyrrolidine. The structure shows a pyrrolidine ring with a tert-butoxycarbonyl (Boc) group attached to the nitrogen atom and a methyl group attached to the 2-position. The stereochemistry at the 2-position is (S).



¹H NMR (400 MHz, CDCl₃): δ 4.37 – 3.92 (m, 3H), 3.47 – 3.26 (m, 2H), 3.00 (s, 3H), 2.12 – 1.76 (m, 4H), 1.46 (s, 9H).

***N*-Boc-2-diphenylphosphinomethyl pyrrolidine – 95**



The synthesis was according to Malkov *et al.* procedure.⁶⁸ *n*-BuLi (27.0 mL, 43.1 mmol) was added to a solution of Ph₂PH (7.50 mL, 43.1 mmol) in tetrahydrofuran (15 mL) at 0 °C under nitrogen atmosphere. A red-orange colour was observed. The mesylate (**94**; 5.80 g, 20.8 mmol) was dissolved in tetrahydrofuran (15 mL) and added dropwise. The reaction mixture was stirred at 0 °C for 1.5 h. The red mixture was poured over a short pad of Celite, and the pad was washed with dry tetrahydrofuran. The clear yellow filtrate was concentrated to leave a viscous yellow oil. The crude product was purified via flash column chromatography on silica gel column (Hexane/EtOAc, 9:1). The target compound was isolated as a colourless oil (3.11 g, 41%).

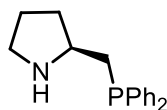
¹H NMR (400 MHz, CDCl₃): δ 7.69 – 7.32 (m, 10H), 4.10 – 3.78 (m, 1H), 3.52 – 3.20 (m, 2H), 3.04 – 2.58 (m, 1H), 2.19 – 1.86 (m, 4H), 1.81 (m, 1H), 1.44 (s, 9H);

¹³C NMR (101 MHz, CDCl₃): δ 154.34, 138.99, 133.04, 132.60, 128.76, 128.49, 76.73, 55.40, 55.19, 46.37, 31.20, 28.63, 23.34;

³¹P NMR (162 MHz, CDCl₃): δ -21.66 (s).

The data are consistent with those reported in literature.^{67,68}

2-diphenylphosphinomethyl pyrrolidine – 58



The synthesis was according to Malkov *et al.* procedure.⁶⁸ Trifluoroacetic acid (10.4 mL, 135 mmol) was added to a solution of phosphine (**95**: 2.50 g, 6.77 mmol) in CH₂Cl₂ (15 mL) in a round-bottomed flask at room temperature under nitrogen atmosphere. Reaction mixture was stirred at room temperature for 2 h. TLC showed reaction completion. Solvent and the bulk of TFA were removed *in vacuo*. The remainder of TFA was removed as an azeotrope with toluene. Saturated aqueous Na₂CO₃ was added to the residue. Aqueous phase was extracted with CH₂Cl₂ (5×50 mL). Combined organic phase was dried (Na₂SO₄) and concentrated. Target compound was isolated as a colourless oil (1.81 g, >98%).

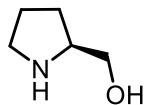
¹H NMR (400 MHz, CDCl₃): δ 7.56 – 7.19 (m, 10H), 3.14 – 2.99 (m, 2H), 2.89 – 2.76 (m, 1H), 2.38 (dd, *J* = 13.3, 6.7 Hz, 1H), 2.25 (dd, *J* = 13.3, 7.2 Hz, 2H), 2.02 – 1.91 (m, 1H), 1.89 – 1.64 (m, 2H), 1.51 – 1.38 (m, 1H);

¹³C NMR (101 MHz, CDCl₃): δ 138.73, 132.82, 128.55, 77.48, 76.85, 56.57, 46.30, 35.74, 33.03, 25.25;

³¹P NMR (162 MHz, CDCl₃): δ -20.70.

The data are consistent with those reported in literature.^{67,68}

(S)-pyrrolidin-2-ylmethanol – 94

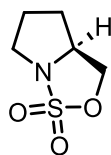


The synthesis was according to Abe *et al.* procedure.⁶⁹ A suspension of LiAlH₄ (5.0 g, 130 mmol) in tetrahydrofuran (100 mL) in a round-bottomed flask under nitrogen atmosphere was cooled to 0 °C. (S)-proline (10.0 g, 86.9 mmol) was added portion-wise and the reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction was quenched with KOH (20%, 15 mL) and filtered. The filtrate was kept, and the residue was refluxed in tetrahydrofuran (100 mL) for 1 h. The reaction mixture was filtered hot, and the combined filtrate was dried (Na₂SO₄) and concentrated. Prolinol was isolated as pale yellow oil (7.82 g, 89%).

¹H NMR (400 MHz, CDCl₃): δ 3.76 (s, 2H), 3.48 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.30 (dd, *J* = 10.9, 7.3 Hz, 1H), 3.19 – 3.09 (m, 1H), 2.88 – 2.74 (m, 2H), 1.84 – 1.50 (m, 3H), 1.32 (m, 1H).

*The data are consistent with those reported in literature.*⁶⁹

(S)-tetrahydro-3H-pyrrolo[1,2-c][1,2,3]oxathiazole 1,1-dioxide – 95

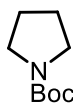


The synthesis was according to Alker *et al.* procedure.⁷⁰ Triethylamine (18.8 mL, 135 mmol) was added to a solution of (*S*)-prolinol (3.41 g, 33.7 mmol) in CH₂Cl₂ (200 mL) in a round-bottomed flask at –78 °C under nitrogen atmosphere. A solution of SO₂Cl₂ (4.1 mL, 50.6 mmol) in CH₂Cl₂ (300 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 3 h. The mixture was allowed to warm to room temperature overnight and then concentrated to 200 mL. The reaction mixture was washed with HCl (0.1 M, 100 mL), dried (Na₂SO₄) and concentrated. The crude product was purified via chromatography on silica gel column (Hexane/EtOAc, 6:4). The desired compound was isolated as an oil which solidified on standing at room temperature (1.82 g, 33%).

¹H NMR (400 MHz, CDCl₃): δ 4.55 (dd, *J* = 8.7, 6.9 Hz, 1H), 4.28 (m, 1H), 4.04 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.69 (dt, *J* = 11.1, 6.3 Hz, 1H), 3.27 (dt, *J* = 11.2, 7.1 Hz, 1H), 2.18 (m, 1H), 2.00 – 1.89 (m, 2H), 1.87 – 1.76 (m, 1H).

*The data are consistent with those reported in literature.*⁷⁰

***Tert*-butyl pyrrolidine-1-carboxylate – 90**

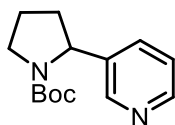


Triethylamine (21.6 mL, 155 mmol) was added to a solution of pyrrolidine (10.0 g, 141 mmol) in CH₂Cl₂ (100 mL) in a round-bottomed flask at 0 °C under nitrogen atmosphere. Boc₂O (30.8 g, 141 mmol) in CH₂Cl₂ (50 mL) was added via syringe. Reaction mixture was stirred at 0°C for 30 min and at room temperature overnight. Reaction was concentrated to 100 mL, washed with HCl (1 M, 100 mL), and brine (100 mL), dried (Na₂SO₄) and concentrated. The target compound was isolated as a colourless oil (18.9 g, 78%).

¹H NMR (400 MHz, CDCl₃): δ 3.32 – 3.16 (m, 4H), 1.77 (br. s, 4H), 1.43 – 1.37 (m, 9H).

*The data are consistent with those reported in literature.*⁸⁶

(±)-tert-butyl 2-(pyridin-3-yl)pyrrolidine-1-carboxylate – rac-100; Method 1.

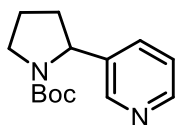


The procedure of O'Brien *et al.* was adapted.⁸⁷ ZnCl₂ (0.9524 g) was dried (140 °C, 0.8 mmHg, 4 h) and dissolved in Et₂O (7 mL). *s*-BuLi (1.86 mL, 2.60 mmol) was added dropwise to a solution of *N*-Boc-pyrrolidine (0.35 mL, 2.00 mmol) in tetrahydrofuran (7 mL) in a Schlenk tube under nitrogen atmosphere at –35 °C. The resulting yellow solution was stirred at –30 °C for 5 min. The freshly prepared ZnCl₂ solution (1 M, 1.2 mL, 1.2 mmol) was added dropwise to the reaction mixture. The mixture was stirred at –30 °C for 30 min, allowed to warm to room temperature, and stirred for a further 30 min. 3-bromopyridine (0.16 mL, 1.67 mmol) was added to the reaction mixture followed by Pd(OAc)₂ (22.5 mg, 0.10 mmol) and *t*-Bu₃P•HBF₄ (36.3 mg, 0.125 mmol) which were added in one portion. The reaction mixture was stirred at room temperature for 16 h. NH₄OH (28%, 1 mL) was added, and solution was stirred at room temperature for 1 h. The mixture was filtered over a short pad of Celite to remove the insoluble impurities and washed with Et₂O (100 mL). The filtrate was washed with H₂O (50 mL), brine (50 mL), and saturated aqueous NaHCO₃ (75 mL), dried (Na₂SO₄) and concentrated. The crude product was purified via chromatography on silica gel column (Hexane/EtOAc, 6:4). The target compound was isolated as an oil (0.18 g, 43%).

¹H NMR (400 MHz, CDCl₃): δ 8.45 – 8.36 (m, 2H), 7.43 (dt, *J* = 7.8, 1.4 Hz, 2H), 7.21 – 7.12 (m, 1H), 4.98 – 4.63 (m, 1H), 3.64 – 3.38 (m, 2H), 2.30 (br. s, 1H), 1.91 – 1.68 (m, 3H), 1.39 (s, 3H), 1.13 (s, 6H).

*The data are consistent with those reported in literature.*⁸⁷

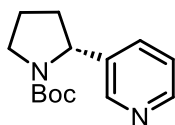
(±)-*tert*-butyl 2-(pyridin-3-yl)pyrrolidine-1-carboxylate – *rac*-100; Method 2.



The synthesis was according to Campos *et al.* procedure.⁸⁸ *s*-BuLi (1.60 mL, 2.20 mmol) was added dropwise to a solution of *N*-Boc-pyrrolidine (0.35 mL, 2.00 mmol) and TMEDA (0.30 mL, 2.00 mmol) in MTBE (3.2 mL) in a two-necked flask fitted with a condenser under nitrogen atmosphere at -78°C . Reaction mixture was stirred at -78°C for 3.5 h. Freshly prepared ZnCl_2 solution (1 M, 1.2 mL, 1.2 mmol) was added dropwise to the reaction mixture. The mixture was stirred at -78°C for 40 min, and at room temperature for 1 h. 3-bromopyridine (0.16 mL, 1.67 mmol) was added to the reaction mixture followed by $\text{Pd}(\text{OAc})_2$ (18.0 mg, 0.08 mmol) and *t*- $\text{Bu}_3\text{P}\cdot\text{HBF}_4$ (29.0 mg, 0.10 mmol) which were added in one portion. The reaction mixture was stirred at 60°C for 16 h. Mixture was cooled to room temperature, NH_4OH (28%, 0.35 mL) was added and solution was stirred at room temperature for 1 h. The mixture was filtered over a short pad of Celite to remove the insoluble impurities and washed with Et_2O (100 mL). The filtrate was washed with H_2O (50 mL), brine (50 mL), and saturated aqueous NaHCO_3 (50 mL), dried (Na_2SO_4) and concentrated. The crude product was purified via chromatography on silica gel column (Hexane/ EtOAc , 6:4). The target compound was isolated as an oil (0.06 g, 14%).

NMR data is consistent with those reported for rac-100 in Method 1.

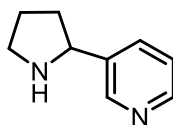
(R)-tert-butyl 2-(pyridin-3-yl)pyrrolidine-1-carboxylate – 100



The synthesis was according to Campos *et al.* procedure.⁸⁸ *s*-BuLi (8.0 mL, 11.0 mmol) was added dropwise to a solution of (–)-sparteine (2.3 mL, 10.0 mmol) and *N*-Boc-pyrrolidine (1.75 mL, 10.0 mmol) in MTBE (21 mL) in a two-necked flask fitted with a condenser under nitrogen atmosphere at –78 °C. Reaction mixture was stirred at –78 °C for 3.5 h. Freshly prepared ZnCl₂ solution (1 M, 6.0 mL, 6.00 mmol) was added dropwise to the reaction mixture. The mixture was stirred at –78 °C for 1 h, and at room temperature for 45 min. 3-bromopyridine (0.80 mL, 8.35 mmol) was added to the reaction mixture, then Pd(OAc)₂ (90.0 mg, 0.40 mmol) and *t*-Bu₃P•HBF₄ (145 mg, 0.50 mmol) were added in one portion. The reaction mixture was stirred at 60 °C for 16 h. Mixture was cooled to room temperature, NH₄OH (28%, 2.0 mL) was added and solution was stirred at room temperature for 1 h. The mixture was filtered over a short pad of Celite to remove the insoluble impurities and washed with Et₂O (200 mL). The filtrate was washed with H₂O (100 mL), brine (100 mL), and saturated aqueous NaHCO₃ (100 mL), dried (Na₂SO₄) and concentrated. The crude product was purified via chromatography on silica gel column (Hexane/EtOAc, 6:4). The target compound was isolated as an oil (1.13 g, 54%, >98:2 er).

NMR data is consistent with those reported for rac-100 in Method 1.

(±)-3-(pyrrolidin-2-yl)pyridine – *rac*-60

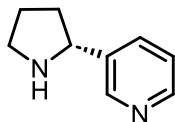


The synthesis was according to Campos *et al.* procedure.⁸⁸ Trifluoroacetic acid (5.28 mL, 69.0 mmol) was added dropwise to a solution of racemic Boc-nornicotine (*rac*-100; 785 mg, 3.16 mmol) in CH₂Cl₂ (50 mL) in a round-bottomed flask at room temperature under nitrogen atmosphere. Reaction mixture was stirred at room temperature for 2 h. TLC showed reaction completion. Solvent and the bulk of TFA were removed *in vacuo*. The remainder of TFA was removed as an azeotrope with toluene. Et₂O (50 mL) and NaOH (5M, 50 mL) were added to the residue and the two layers were separated. Aqueous phase was extracted with Et₂O (10×15 mL) and combined organic phase was dried (Na₂SO₄) and concentrated. The crude product was purified via chromatography on silica gel column (CH₂Cl₂/MeOH, 7:3). The target compound was isolated as an oil (353 mg, 75%).

¹H NMR (400 MHz, CDCl₃): 8.52 (d, *J* = 2.2 Hz, 1H), 8.40 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.65 (dt, *J* = 8.0, 2.1 Hz, 1H), 7.17 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.09 (t, *J* = 7.8 Hz, 1H), 3.17 – 3.07 (m, 1H), 3.03 – 2.92 (m, 1H), 2.37 (s, 1H), 2.21 – 2.09 (m, 1H), 1.93 – 1.74 (m, 2H), 1.65 – 1.52 (m, 1H).

*The data are consistent with those reported in literature.*⁸⁸

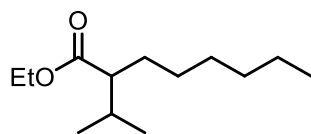
(R)-3-(pyrrolidin-2-yl)pyridine – 60



The synthesis was according to Campos *et al.* procedure.⁸⁸ Trifluoroacetic acid (5.27 mL, 69.0 mmol) was added dropwise to a solution of (R)-Boc-nornicotine (**100**; 854 mg, 3.44 mmol) in CH₂Cl₂ (50 mL) in a round-bottomed flask at room temperature under nitrogen atmosphere. Reaction mixture was stirred at room temperature for 3 h. TLC showed reaction completion. Solvent and the bulk of TFA were removed *in vacuo*. The remainder of TFA was removed as an azeotrope with toluene. Et₂O (50 mL) and NaOH (5M, 50 mL) were added to the residue and the two layers were separated. Aqueous phase was extracted with Et₂O (10×15 mL) and combined organic phase was dried (Na₂SO₄) and concentrated. The crude product was purified via chromatography on silica gel column (CH₂Cl₂/MeOH, 7:3). The target compound was isolated as an oil (425 mg, 83%, >98:2 er).

NMR data is consistent with those reported for rac-60.

Ethyl 2-isopropyloctanoate – 105

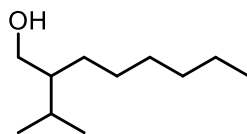


n-BuLi (1.6 M in hexanes, 10 mL, 16.0 mmol) was added dropwise to a solution of diisopropylamine (2.34 mL, 16.7 mmol) in tetrahydrofuran (12 mL) in a round-bottomed flask at $-78\text{ }^{\circ}\text{C}$ under nitrogen atmosphere. After 15 min of stirring, ethyl isovalerate (2 mL, 15.2 mmol) was added dropwise as a solution in tetrahydrofuran (10 mL) and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. *n*-hexyl bromide (2.25 mL, 16.0 mmol) was added dropwise as a solution in HMPA (3.4 mL). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h and allowed to warm to room temperature overnight. The reaction was quenched with NH_4Cl (50 mL), diluted with Et_2O (50 mL), and extracted with EtOAc (4×50 mL). Combined organic phase was washed with HCl (2 M, 100 mL), saturated aqueous NaHCO_3 , and brine, dried (Na_2SO_4) and concentrated. Target compound was obtained as a pale yellow oil (2.78 g, 85%).

^1H NMR (400 MHz, CDCl_3): δ 4.15 (q, $J = 7.1$ Hz, 2H), 2.12 – 2.05 (m, 1H), 1.90 – 1.78 (m, 1H), 1.65 – 1.41 (m, 2H), 1.38 – 1.16 (m, 11H), 0.98 – 0.84 (m, 9H).

*The data are consistent with those reported in literature.*⁸⁹

2-Isopropyloctan-1-ol – 106

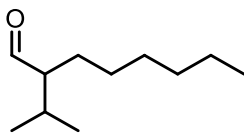


A suspension of LiAlH_4 (0.99 g, 26.0 mmol) in Et_2O (10 mL) in a round-bottomed flask under nitrogen atmosphere was cooled to 0 °C. The ester (2.78 g, 13.0 mmol) was added dropwise as a solution in Et_2O (15 mL). The reaction was stirred at 0 °C for 2 h and quenched with saturated aqueous NH_4Cl (20 mL). HCl (2 M, 100 mL) was added to dissolve the insoluble impurities. The mixture was extracted with EtOAc (3×75 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The desired compound was isolated as a colourless oil (1.75 g, 78%).

^1H NMR (400 MHz, CDCl_3): δ 3.65 – 3.55 (m, 2H), 1.87 – 1.77 (m, 1H), 1.59 – 1.50 (m, 2H), 1.39 – 1.19 (m, 10H), 0.95 – 0.84 (m, 8H).

*The data are consistent with similar spectra reported in literature.*⁹⁰

2-Isopropyloctanal – 107

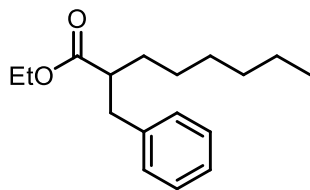


A solution of DMSO (1.35 mL, 19.0 mmol) in CH_2Cl_2 (20 mL) was added to a solution of $(\text{COCl})_2$ (1.61 mL, 19.0 mmol) in CH_2Cl_2 (20 mL) at $-78\text{ }^\circ\text{C}$ under nitrogen atmosphere. The resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 1 h. A solution of the alcohol (1.63 g, 9.47 mmol) in CH_2Cl_2 (40 mL) was added dropwise, and the reaction mixture was stirred for 1 h at $-78\text{ }^\circ\text{C}$. The reaction mixture was allowed to warm to $-30\text{ }^\circ\text{C}$ over 30 min and then quenched with NaHSO_4 (4 M, 60 mL). The mixture was extracted with CH_2Cl_2 ($3\times 75\text{ mL}$), washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified via chromatography on silica gel column (Hexane/EtOAc, 97:3). The desired compound was isolated as a colourless oil (1.59 g, 99%).

^1H NMR (400 MHz, CDCl_3): δ 9.62 (d, $J = 3.5\text{ Hz}$, 1H), 2.08 – 1.92 (m, 2H), 1.70 – 1.58 (m, 1H), 1.52 – 1.41 (m, 1H), 1.36 – 1.14 (m, 8H), 1.01 – 0.85 (m, 9H).

*The data are consistent with similar spectra reported in literature.*⁹¹

Ethyl 2-benzyl octanoate – 109

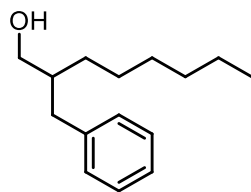


n-BuLi (1.6 M in hexanes, 10 mL, 16.0 mmol) was added dropwise to a solution of diisopropylamine (2.34 mL, 16.7 mmol) in tetrahydrofuran (10 mL) in a round-bottomed flask at -78°C under nitrogen atmosphere. After 15 min of stirring, ethyl octanoate (3 mL, 15.2 mmol) was added over 40 min as a solution in tetrahydrofuran (10 mL) and the reaction was stirred at -78°C for 1 h. HMPA (4 mL) was added to the reaction mixture, followed by benzyl bromide (2.26 mL, 19.0 mmol). The reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with NH_4Cl (50 mL), and extracted with EtOAc (4×50 mL). Combined organic phase was washed with HCl (2 M, 100 mL), saturated aqueous NaHCO_3 , and brine, dried (Na_2SO_4) and concentrated. Target compound was isolated as an oil (3.69 g, 93%).

^1H NMR (400 MHz, CDCl_3): δ 7.47 – 7.11 (m, 5H), 4.14 – 4.02 (q, $J = 7.2$ Hz, 2H), 2.95 (dd, $J = 13.5, 8.6$ Hz, 1H), 2.77 (dd, $J = 13.6, 6.5$ Hz, 1H), 2.72 – 2.60 (m, 1H), 1.67 (m, 1H), 1.51 (m, 1H), 1.38 – 1.22 (m, 8H), 1.17 (t, $J = 7.1$ Hz, 3H), 0.90 (t, $J = 6.8$ Hz, 3H).

*The data are consistent with similar spectra reported in literature.*⁹²

2-Benzyloctan-1-ol – 110

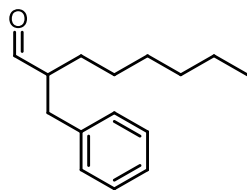


A suspension of LiAlH_4 (1.10 g, 29.0 mmol) in Et_2O (11 mL) in a round-bottomed flask under nitrogen atmosphere was cooled to 0 °C. The ester (3.80 g, 14.5 mmol) was added dropwise as a solution in Et_2O (15 mL). The reaction was stirred at 0 °C for 2 h and quenched with saturated aqueous NH_4Cl (20 mL). HCl (2 M, 100 mL) was added to dissolve the insoluble impurities. The mixture was extracted with EtOAc (3×100 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The desired compound was isolated as an oil (2.51 g, 78%).

^1H NMR (400 MHz, CDCl_3): δ 7.38 – 7.14 (m, 5H), 3.55 (d, J = 5.3 Hz, 2H), 2.66 (d, J = 7.2 Hz, 2H), 1.84 (m, 2H), 1.44 – 1.23 (m, 10H), 0.90 (t, J = 6.7 Hz, 3H).

*The data are consistent with those reported in literature.*⁹³

2-Benzyl-octanal – 111

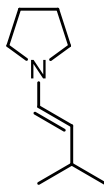


A solution of DMSO (63.9 μ l, 0.90 mmol) in CH_2Cl_2 (5 mL) was added to a solution of $(\text{COCl})_2$ (76.1 μ l, 0.90 mmol) in CH_2Cl_2 (3 mL) at -78°C under nitrogen atmosphere. The resulting solution was stirred at -78°C for 1 h. A solution of the alcohol (100 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the reaction mixture was stirred for 1 h at -78°C . The reaction mixture was allowed to warm to -30°C for 30 min and then quenched with NaHSO_4 (4 M, 6 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified via chromatography on silica gel column (Hexane/EtOAc, 9:1). The desired compound was isolated as a colourless oil (86.9 mg, 88%).

^1H NMR (400 MHz, CDCl_3): δ 9.69 (d, $J = 2.8$ Hz, 1H), 7.39 – 7.08 (m, 5H), 3.01 (dd, $J = 13.9, 7.4$ Hz, 1H), 2.75 (dd, $J = 14.0, 6.8$ Hz, 1H), 2.69 – 2.54 (m, 1H), 1.76 – 1.59 (m, 1H), 1.50 (m, 1H), 1.42 – 1.14 (m, 8H), 0.97 – 0.78 (m, 3H).

*The data are consistent with those reported in literature.*⁹⁴

(E)-1-(3-methylbut-1-en-1-yl)pyrrolidine – 113

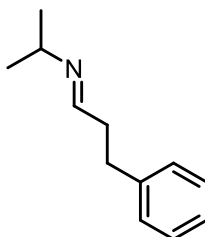


Prepared according to general procedure A using K_2CO_3 (1.55 g, 11.2 mmol), pyrrolidine (0.78 mL, 9.30 mmol), and isovaleraldehyde (0.99 mL, 9.20 mmol) in CH_2Cl_2 (50 mL) at 0 °C for 1 h and then at 20 °C for 18 h. The reaction mixture was filtered, and the solvent was removed *in vacuo*. **113** was isolated as a colourless oil (0.93 g, 73%).

^1H NMR (400 MHz, CDCl_3): δ 6.17 (d, J = 13.7 Hz, 1H), 4.14 (dd, J = 13.8, 7.0 Hz, 1H), 2.99 – 2.90 (m, 4H), 2.31 – 2.21 (m, 1H), 1.89 – 1.76 (m, 4H), 1.00 (d, J = 6.6 Hz, 6H).

Product was used without further purification. Crude NMR data conforms to structure.

(E)-N-Isopropyl-3-phenylpropan-1-imine – 142



Prepared according to general procedure D using MgSO_4 (2.24 g, 18.6 mmol), isopropylamine (0.80 mL, 9.30 mmol), and hydrocinnamaldehyde (1.23 mL, 9.30 mmol) in CH_2Cl_2 (20 mL) at 20 °C for 2 h. The reaction mixture was filtered, and the solvent was removed *in vacuo*. **142** was isolated as a colourless oil (1.54 g, 95%).

^1H NMR (400 MHz, CDCl_3) δ 7.72 (t, $J = 4.9$ Hz, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.20 (m, 3H), 3.29 (*app.* hept, $J = 6.4$ Hz, 1H), 2.87 (dd, $J = 9.0, 6.7$ Hz, 2H), 2.62 – 2.52 (m, 2H), 1.16 (d, $J = 6.2$ Hz, 7H).

Product was used without further purification. Crude NMR data conforms to structure.

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Part 2

Catalytic Enantioselective Intramolecular [4+2] Annulation of Dienes and Terminal Alkynes

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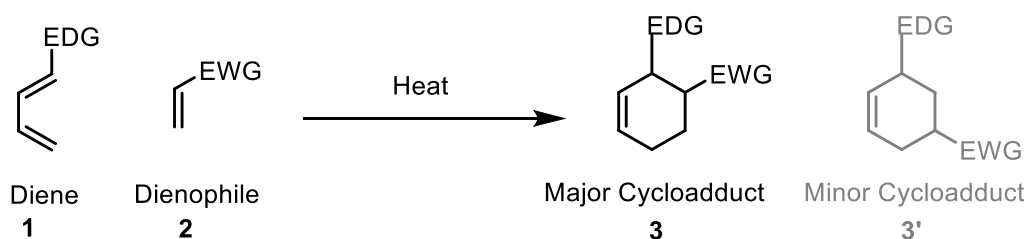
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Chapter One

General introduction

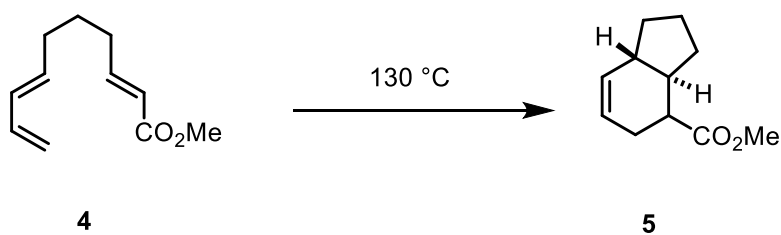
1. General introduction

Cycloaddition reactions are a landmark reaction in organic chemistry. They play a key role in the synthesis of versatile carbocyclic/heterocyclic compounds.¹ These reactions proceed with high atom- and step-economy. They are routinely deployed in the total synthesis of natural products.²⁻⁴ Cycloaddition reactions are a diverse, robust, and versatile tool for synthetic chemistry.¹⁻⁴ In cycloaddition reactions, two or more unsaturated molecules combine to form a cyclic adduct. The most well-known cycloaddition reaction is the Diels–Alder reaction. The diels–Alder reaction is a [4+2] cycloaddition reaction between a diene **1** and a dienophile **2**. The classic eponymous bimolecular Diels–Alder reaction was first reported in 1928 (Scheme 1).⁵ The classic reaction proceeds at elevated temperatures. There are numerous examples of metal catalysed cycloaddition reactions.



Scheme 1. Prototypical normal electron demand Diels–Alder reaction.

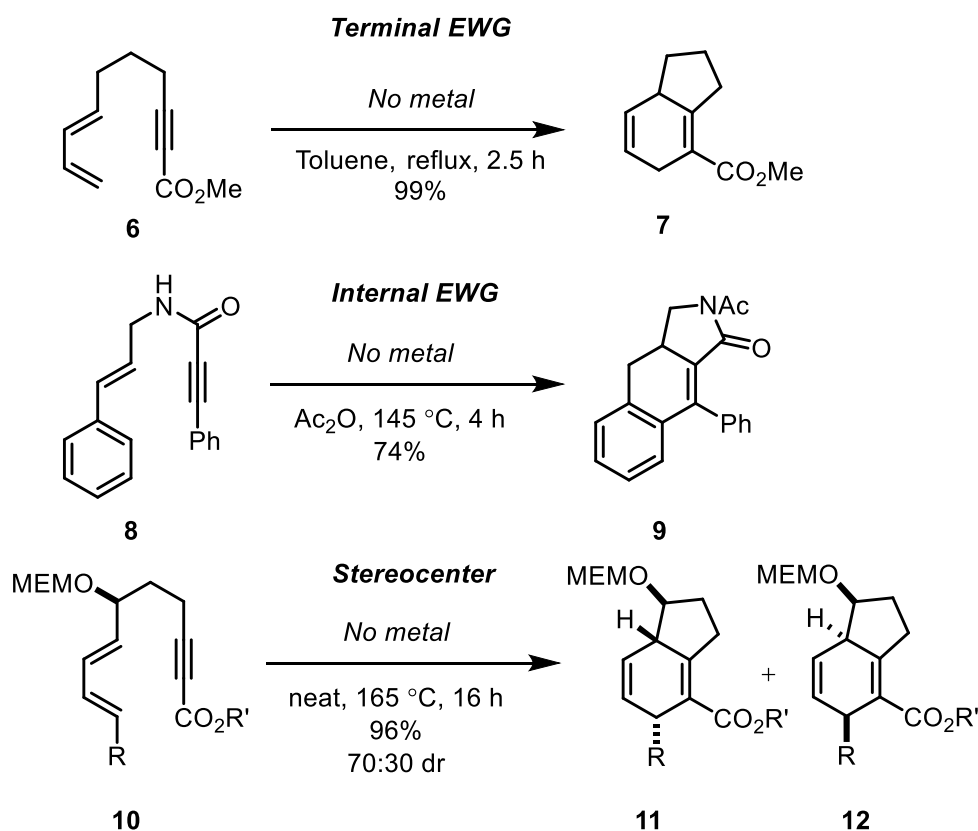
Intramolecular Diels–Alder reactions are of particular interest to organic chemists (Scheme 2) because they facilitate the rapid construction of complex bicyclic compounds **5**. These reactions are also known to proceed under thermal or catalytic conditions.³ It may also feature an alkyne as the dienophile to form a diene bicyclic adduct.



Scheme 2. Intramolecular Diels–Alder reaction.

1.1. Intramolecular [4+2] Annulations: uncatalyzed; activated systems

Intramolecular [4+2] cycloaddition reactions of uncatalyzed, activated systems feature a diene and an activated (possessing an electron-withdrawing group) alkyne in a single molecule which reacts to form a bicyclic compound.⁶⁻¹²

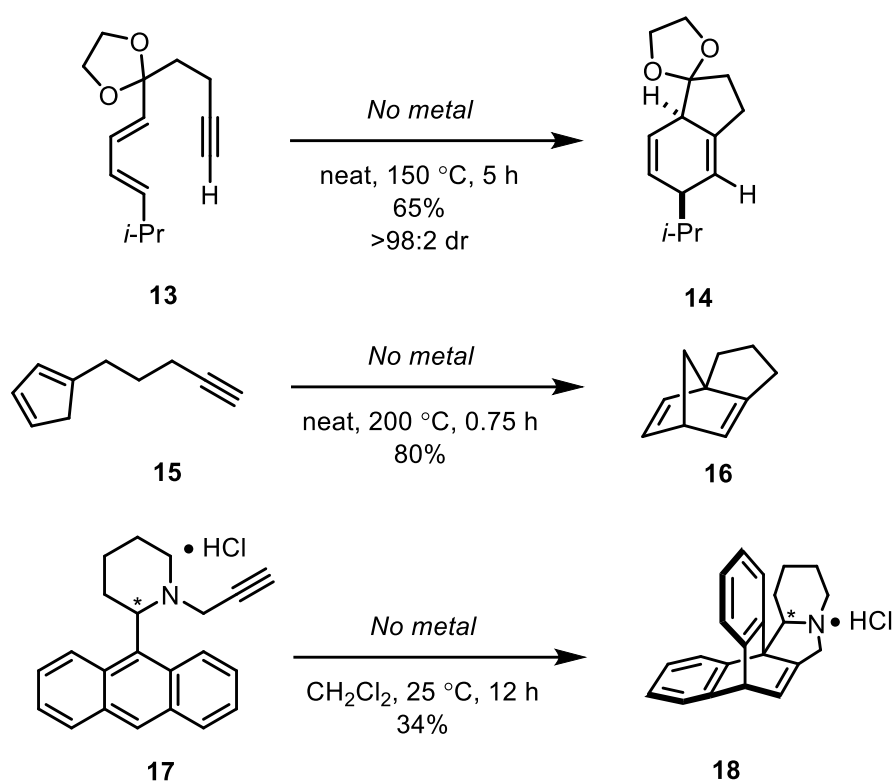


Scheme 3. Cycloaddition of uncatalyzed, activated systems.⁶⁻¹²

These reactions are slow and rarely proceed at ambient temperatures; elevated temperatures (Scheme 3) are typically required. The diene can be activated with an electron donating group. The alkyne moiety may also be activated by a terminal or internal electron withdrawing group. Diastereoselective examples are known (Scheme 3).⁶⁻¹²

1.2. Intramolecular [4+2] Annulations: uncatalyzed; unactivated systems

For terminal unactivated alkyne dienophile moieties, thermal intramolecular cycloaddition occurs at even higher temperature with longer reaction times (Scheme 4).^{7,13–15}

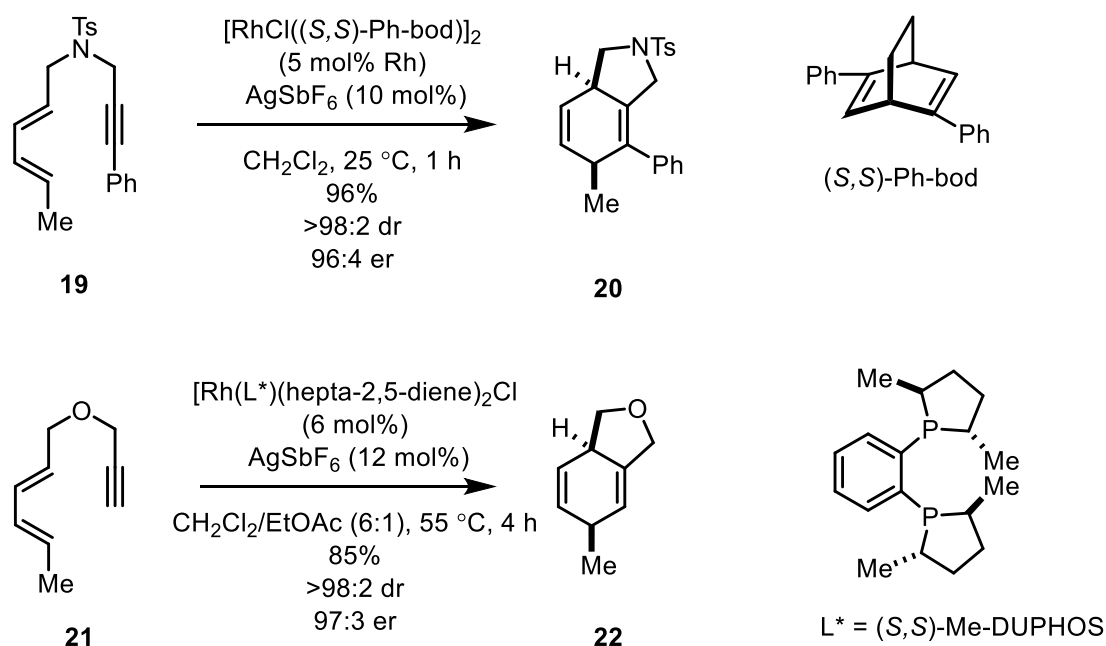


Scheme 4. Cycloaddition of uncatalyzed, unactivated systems.^{7,13–15}

Under very few circumstances, like the cycloaddition of **17** to **18**, geometry restrictions and the formation of a more stable aromatic system can mitigate the harsh conditions needed (Scheme 4). The use of transition metal catalysis has therefore been widely explored for these reactions. Harsh reaction conditions limit the applicability of these systems.^{7,13–15}

1.3. Intramolecular [4+2] Annulations: Rh(I)–Catalysed; unactivated systems

Group 9 metals like rhodium have been explored in the catalysis of intramolecular cycloaddition of dienes and alkynes (Scheme 5).^{16–19}

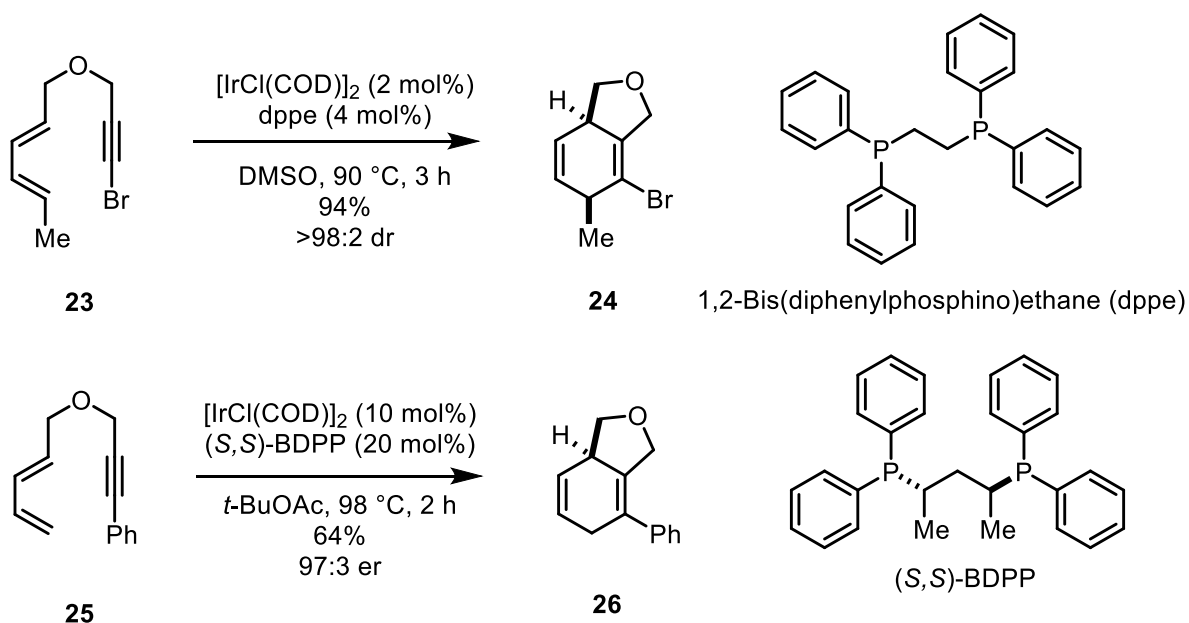


Scheme 5. Cycloaddition of Rh(I)–catalysed, unactivated systems.^{16–19}

Cationic Rh(I) catalyses the rapid cycloaddition of unactivated substrates. High product yields are typically observed in these systems. Examples with both internal and terminal alkynes are known (Scheme 5). High enantioselectivity is observed when chiral ligand is used. The drawback for this system is the high cost of Rh(I) catalyst. A typical precursor $[\text{RhCl}(\text{COD})]_2$ costs £350/mmol (Sigma Aldrich).^{16–19}

1.4. Intramolecular [4+2] Annulations: Ir(I)–Catalysed; unactivated systems

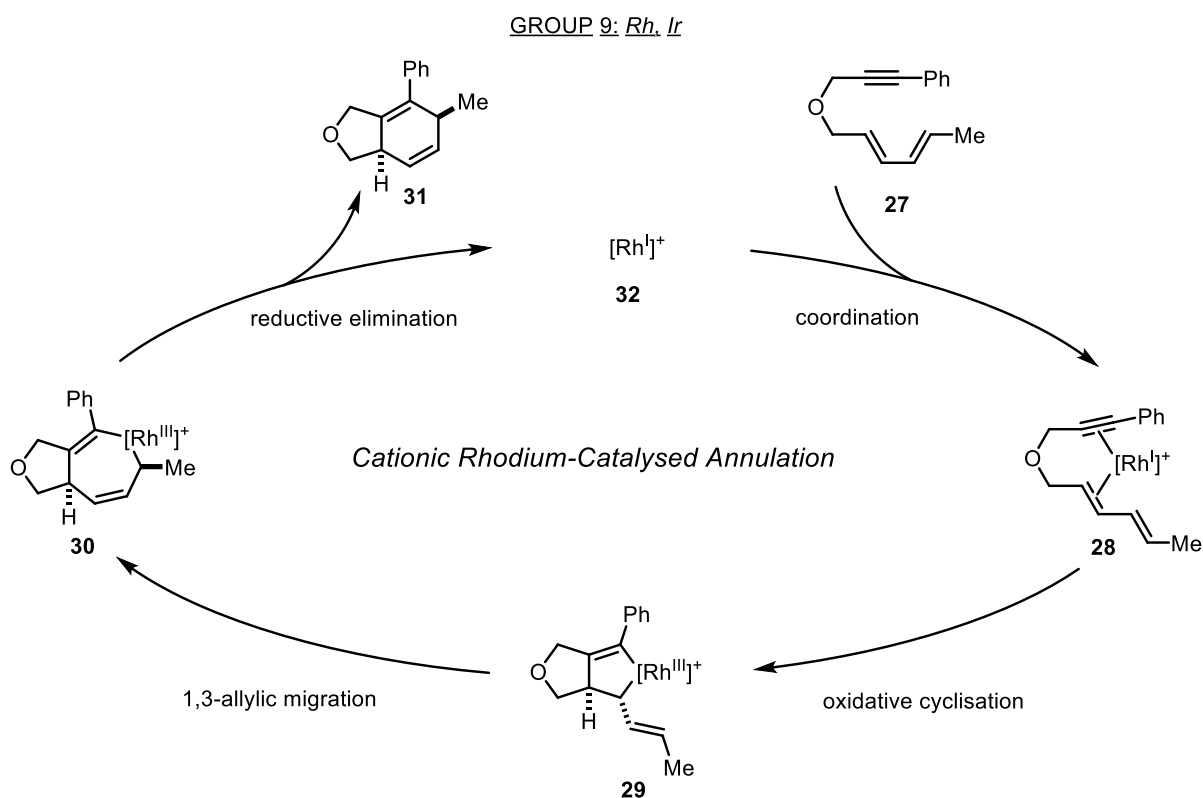
Iridium catalysed (group 9) intramolecular cycloaddition of dienes and alkynes (Scheme 6) has also been demonstrated.^{20,21}



Scheme 6. Cycloaddition of Ir(I)–catalysed, unactivated systems.^{20,21}

Ir(I) catalyses the intramolecular cycloaddition of dienes and internal alkynes. The reaction does not proceed with terminal alkynes. High temperatures and moderately fast reaction times have been observed. Highly enantioselective transformations were achieved using chiral diphosphines (Scheme 6). The typical iridium precursor $[\text{IrCl}(\text{COD})]_2$ is moderately expensive; £75/mmol (Sigma Aldrich).^{20,21}

The mechanism (Scheme 7) for group 9 catalysed cycloaddition typically involves the coordination of the active metal centre **32** to substrate **27** to form coordination complex **28**. Oxidative cyclization of **28** results in a cationic Rh(III) complex **29**. 1,3-allylic migration followed by reductive elimination produces bicyclic product **31**.^{20,21}

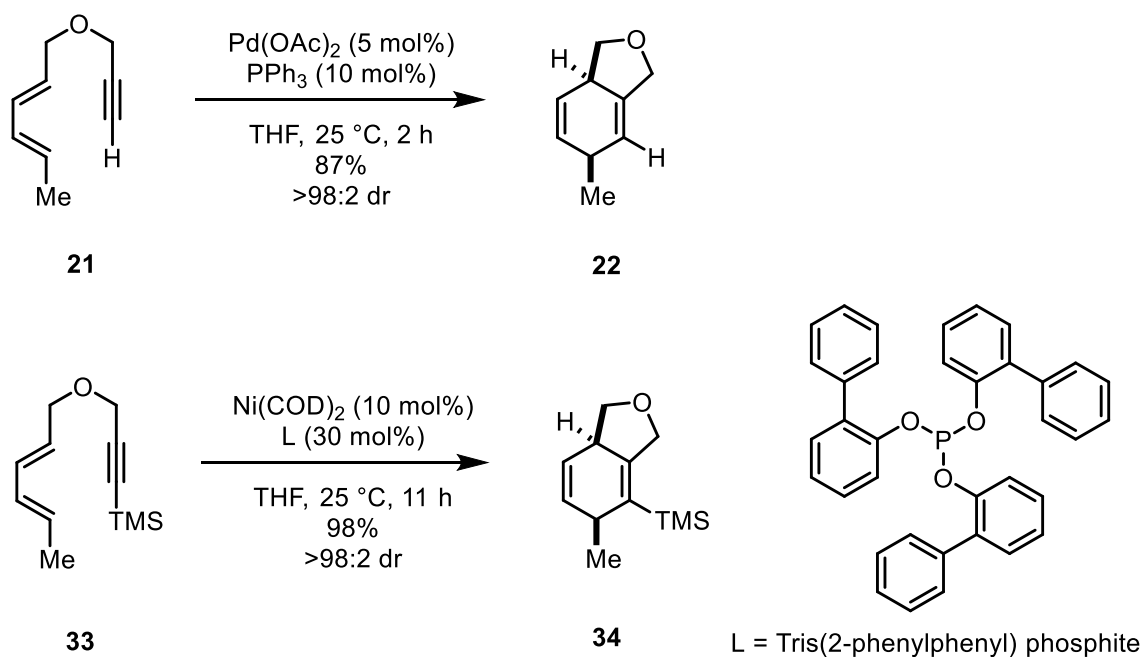


Scheme 7. Mechanistic outline for Group 9 catalysed cycloaddition.^{20,21}

The reason for iridium catalyst's inability to catalyse the cycloaddition of terminal alkyne moieties is unknown.^{20,21}

1.5. Intramolecular [4+2] Annulations: Pd(0)–, Ni(0)–Catalysed; unactivated systems

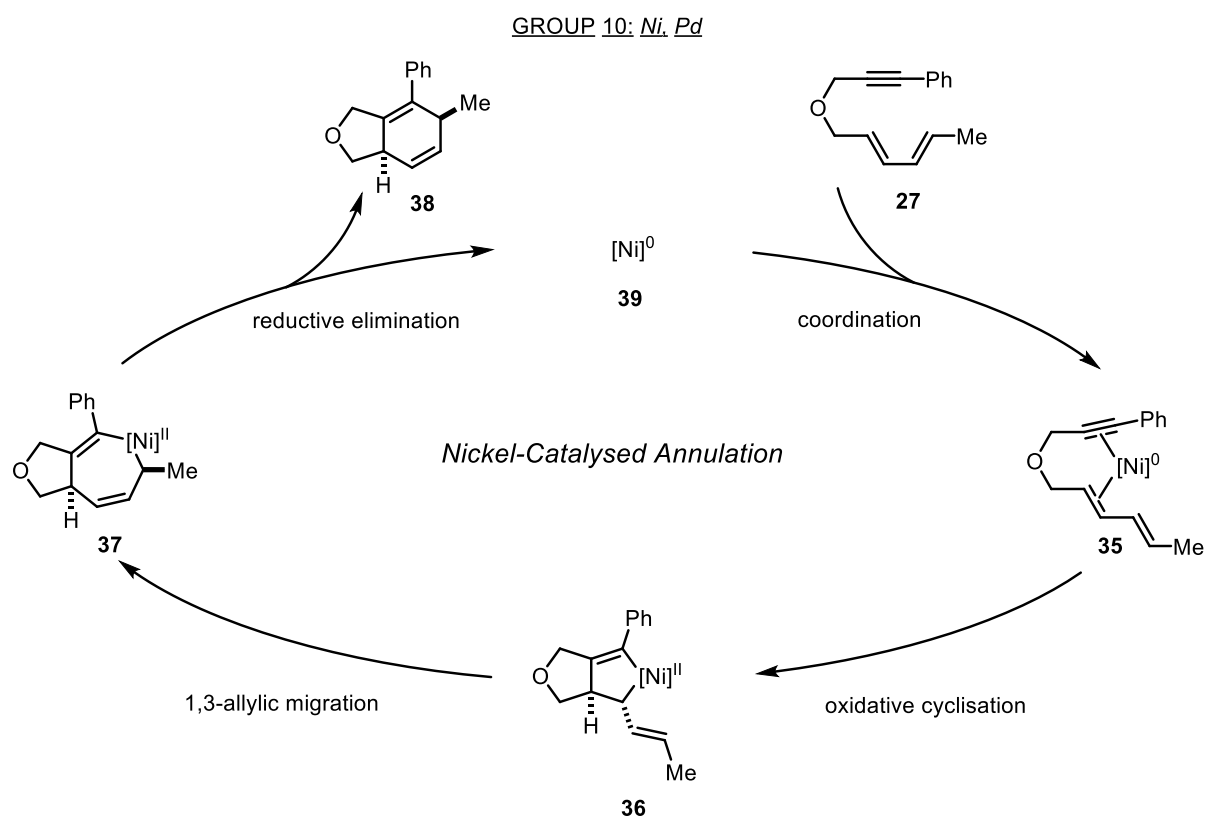
Group 10 metals, nickel, and palladium have been shown to catalyse intramolecular cycloaddition of dienes and alkynes (Scheme 8).^{22,23}



Scheme 8. Cycloaddition of Pd(0)–, Ni(0)–catalysed, unactivated systems.^{22,23}

For palladium, the substrate scope is quite limited. Examples involve only terminal alkynes. Conversely, only internal alkynes are known for nickel. The typical catalyst precursors are considerable cheaper than for group 9. $\text{Pd}(\text{OAc})_2$ is £15/mmol; $\text{Ni}(\text{COD})_2$ is £11/mmol.^{22,23}

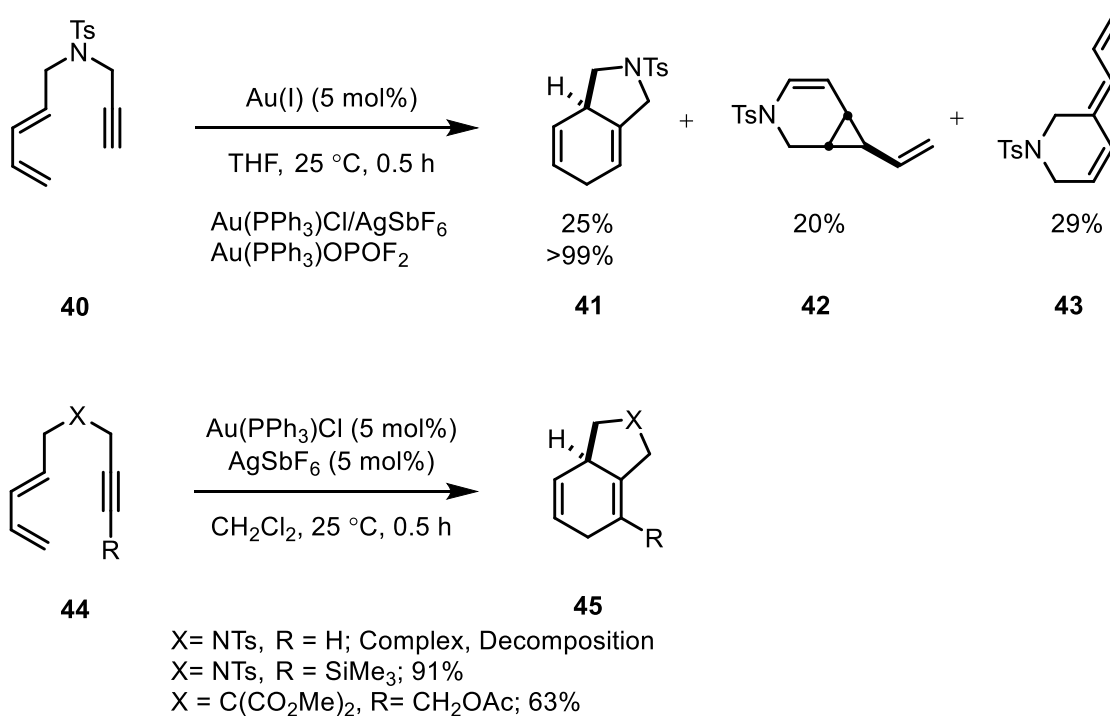
Pd(0)–, Ni(0)– catalysed reactions typically proceed via a similar mechanism to group 9. Coordination to the substrate, followed by oxidative cyclization, allylic migration, and reductive elimination produced the desired cycloadduct (Scheme 9).^{22,23}



Scheme 9. Mechanistic outline for Group 10 catalysed cycloaddition.^{22,23}

1.6. Intramolecular [4+2] Annulations: Au(I)–Catalysed; unactivated systems

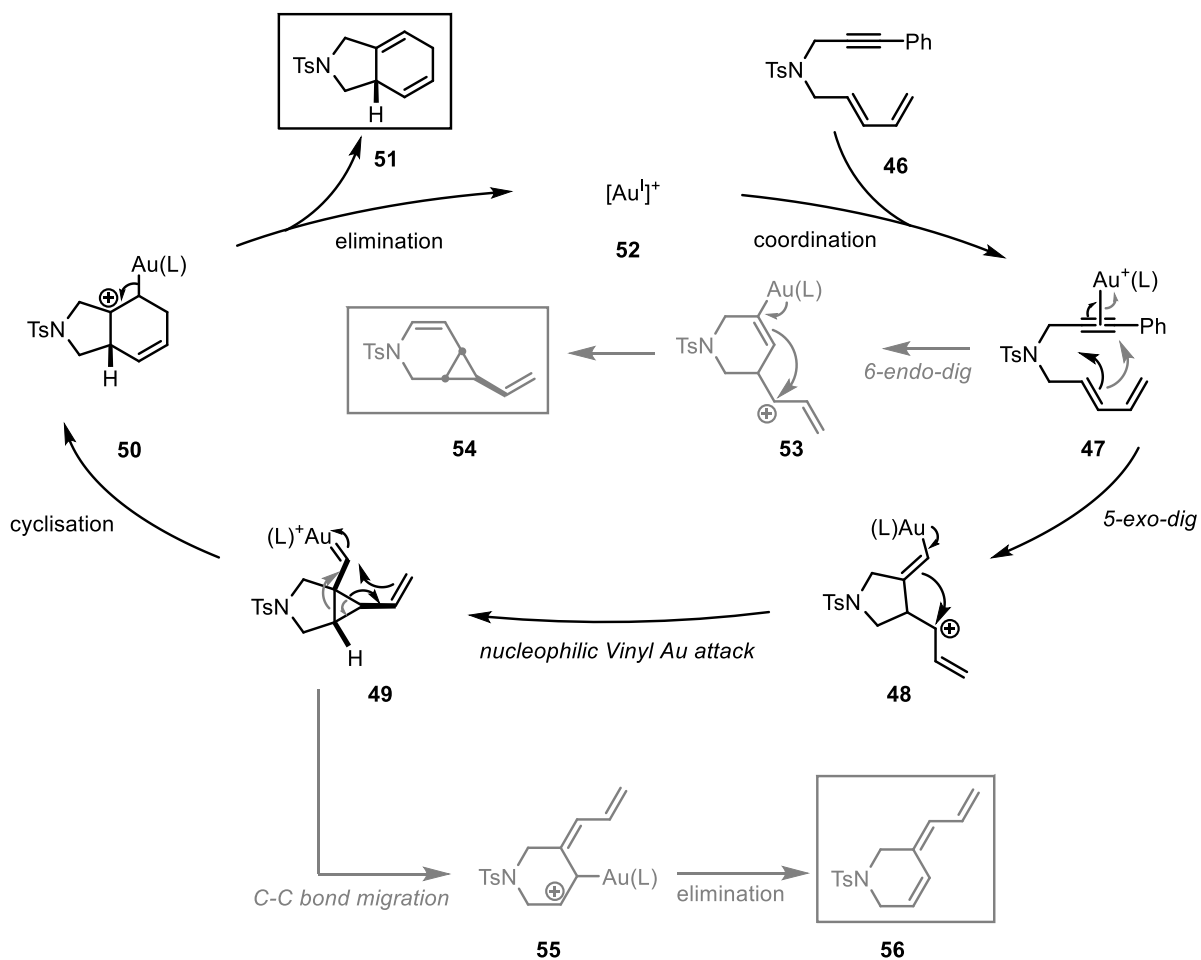
Cationic Au(I) (group 11) catalyses the intramolecular cycloaddition of diene and alkynes. The annulation reactions are typically fast at ambient temperatures. Examples with both internal and terminal alkynes are known. By-products are typically observed in these reactions (Scheme 10).^{24,25}



Scheme 10. Cycloaddition of Au(I)–catalysed, unactivated systems.^{24,25}

Gold catalysts are moderately expensive. AuCl(PPh₃) is £115/mmol (Sigma Aldrich).

A gold catalysed cycloaddition proceeds via a different mechanism (Scheme 11) compared to those previously described. Cationic Au(I) acts as a carbophilic Lewis acid and coordinates to alkyne to produce complex **47** which undergoes a 5-*exo*-dig cyclization to form **48**. A nucleophilic vinyl-*Au* attack forms bicyclic **49** which cyclizes to form adduct **50**. The desired product **51** is obtained after elimination.^{24,25}

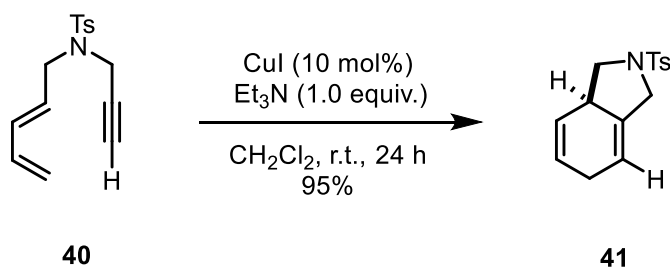


Scheme 11. Mechanistic outline for Group 10 catalysed cycloaddition.^{24,25}

As previously discussed, by-products are observed in these reactions. Alternatively, a 6-*endo*-dig cyclization can form **53**. Cyclization, followed by elimination produces **54**. A C-C bond migration followed by elimination can also occur from **49** to form **56** (Scheme 11).^{24,25}

1.7. Intramolecular [4+2] Annulations: Cu(I)–Catalysed; unactivated systems

Fürstner and co-workers have reported the intramolecular cycloaddition of diene and alkynes catalysed by Cu(I) (Scheme 12).²⁵

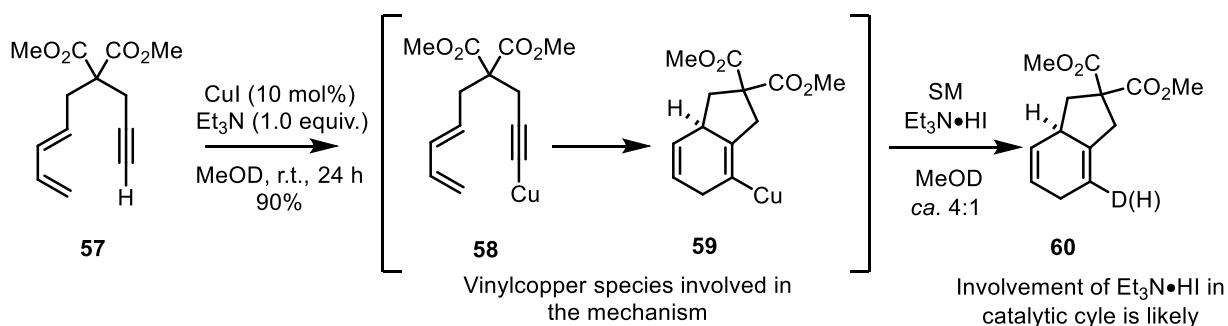


Scheme 12. Cycloaddition of Cu(I)–catalysed, unactivated systems.

The reactions proceed under mild reaction conditions to produce the desired cycloadduct in very high yield. Only terminal alkynes are known. The copper catalyst, CuI is cheap; £0.05/mmol (Sigma Aldrich). Examples using an enone instead of diene are known.²⁵

Nishibayashi *et al.* has also reported a sequential substitution reaction between propargylic acetates and (*E*)-2,4-pentadienylamine, followed by an intramolecular cycloaddition. The scope of the paper was very limited with only six examples.²⁶

Complexation of Cu(I) to alkyne **57** lowers the acidity of the alkyne proton which allows for deprotonation by Et₃N to form copper acetylide **58**. This intermediate cyclizes to form **59**. Protodecupration of **59** produces cycloadduct **80**. When the reaction was performed in rigorously dried MeOD, a 4:1 mixture of the deuterio- and proto-cycloadduct was observed. This proved the involvement of a copper acetylide in the mechanism, and that Et₃N•HI was involved in protonating **59** (Scheme 13).

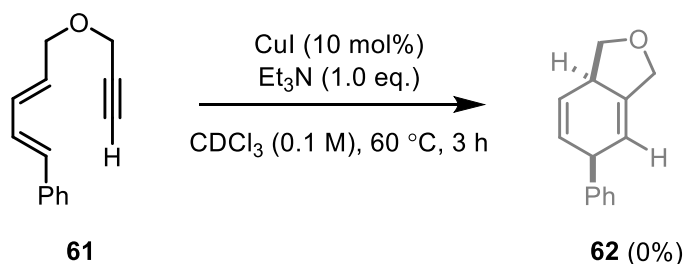


Scheme 13. Mechanistic outline for Group 11 catalysed cycloaddition.²⁵

When **57** was reacted a catalytic amount of mesitylcopper reagent, full conversion of starting material was observed. This proved proton transfer from terminal alkyne **57** to vinylcopper intermediate **59**. These results explain why no reaction was observed with internal alkynes.

1.8. Initial aims and objectives

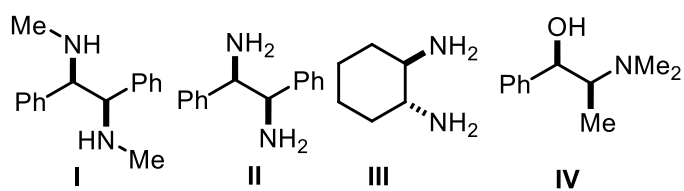
The aim of this project is to achieve an enantioselective intramolecular copper catalysed cycloaddition of diene and alkynes. The initial aim was the synthesis of different chiral ligands and starting materials. The obvious challenge to achieving an enantioselective metal–chiral ligand catalysed reaction is competing background metal catalysed reaction. As described in Scheme 13, the metal–catalysed reaction is facile at ambient temperatures. A careful choice of substrate is therefore important. Initial screening revealed that substrate **61** does not react under conditions shown after 3 h (Scheme 14). This scenario presents an opportunity for chiral ligand reaction rate acceleration. Substrates that are structurally related to **61** would be synthesized. The phenyl group chromophore will also be useful for Chiral HPLC analysis.



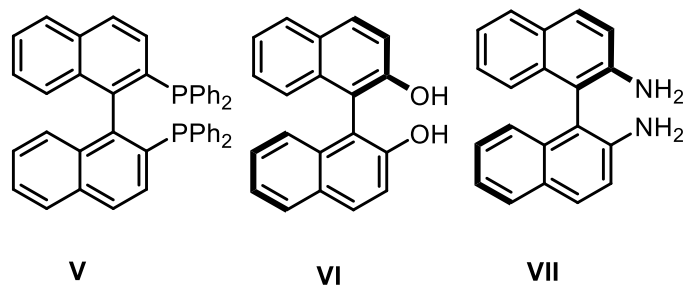
Scheme 14. Initial screening of substrate.

Chiral ligands known to catalyse enantioselective annulation would be synthesized. Chiral diamine, diphosphines, and other N,N–type ligands would be purchased or synthesized (Scheme 15).

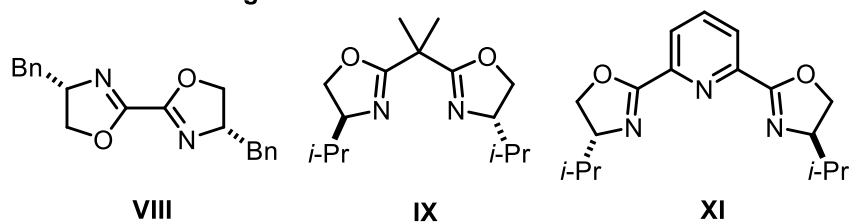
Chiral enantioenriched *O,N* and *N,N* ligands



Chiral enantioenriched binaphthyl ligands



Chiral bisoxazoline ligands



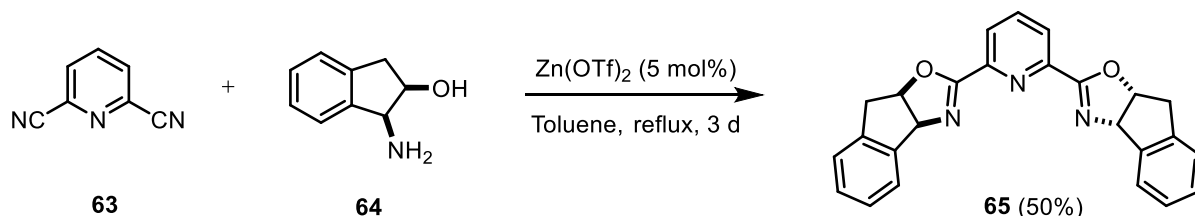
Scheme 15. Assorted chiral ligands.

Chapter Two

Synthesis of Chiral Ligands

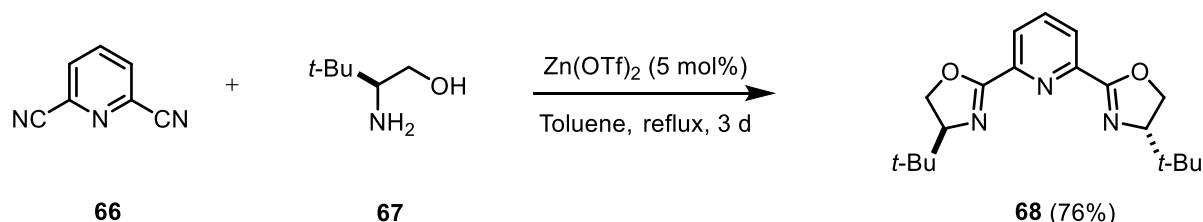
2. Synthesis of Chiral Ligands

The initial strategy for the synthesis of compound **65** was a Pinner-type reaction catalysed by a Lewis acid. “IndanylPybox” **65** was obtained in moderate yields.²⁷



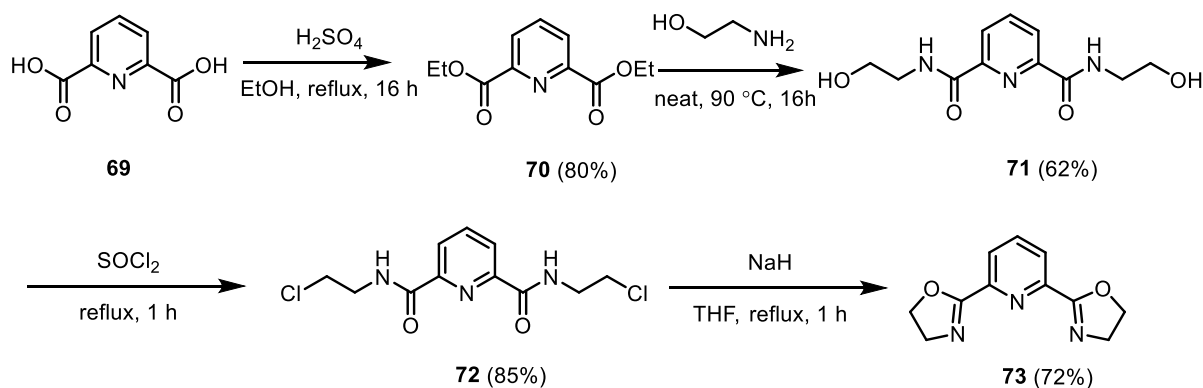
Scheme 16. Synthesis of Indanylpybox **65**.²⁷

In a similar process, *t*-BuPybox **68** was synthesized in good yields.²⁷



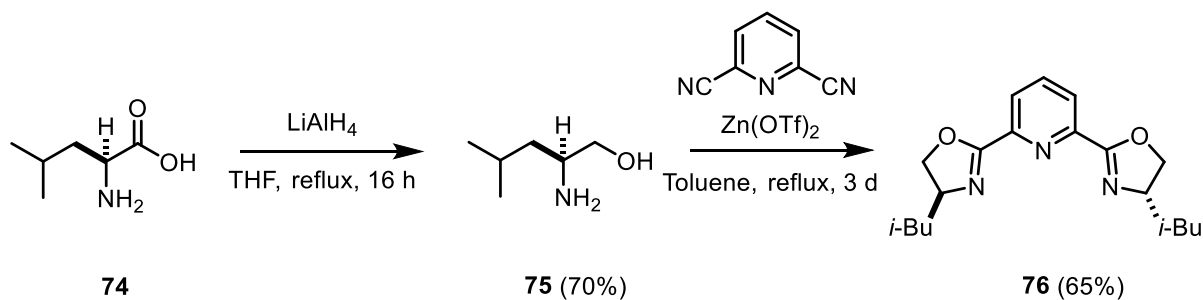
Scheme 17. Synthesis of *t*-BuPybox **68**.²⁷

Esterification of pyridine dicarboxylic acid **69** produced ester **70**. Nucleophilic substitution by an ethanolamine produced amide **71** in moderate yields, which reacts with thionyl chloride to form **72**. A base-mediated internal nucleophilic displacement cyclizes **72** to form pybox **73**. This achiral pybox ligand was used for reaction screening of non-asymmetric annulation.^{28–30} Attempts to synthesize **73** with the method described above were unsuccessful.



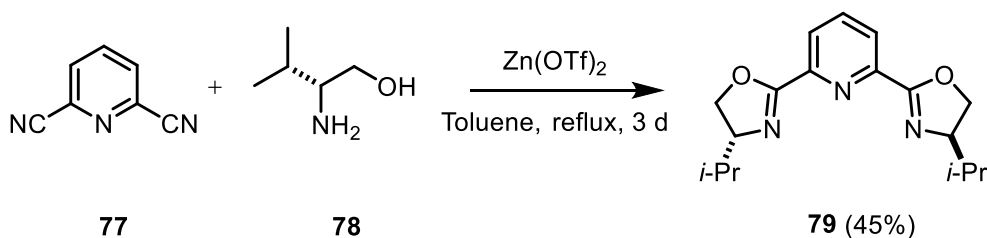
Scheme 18. Synthesis of Pybox **73**.^{28–30}

Lithium aluminium hydride reduction of leucine **74** followed by Pinner-type reaction of **75** produces *i*-BuPybox in moderate yields.²⁷



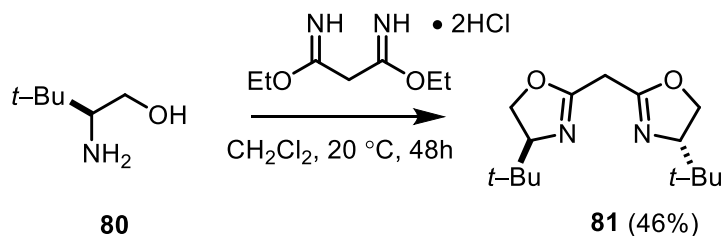
Scheme 19. Synthesis of *i*-BuPybox **76**.²⁷

i-Pybox **79** was synthesized in a similar fashion from aminoalcohol **78**.



Scheme 20. Synthesis of *i*-BuPybox **76**.²⁷

The condensation of *tert*-Leucinol with diethyl malonimidate produces *t*-BuBox ligand **81**.³¹



Scheme 21. Synthesis of *t*-BuBox **81**.³¹

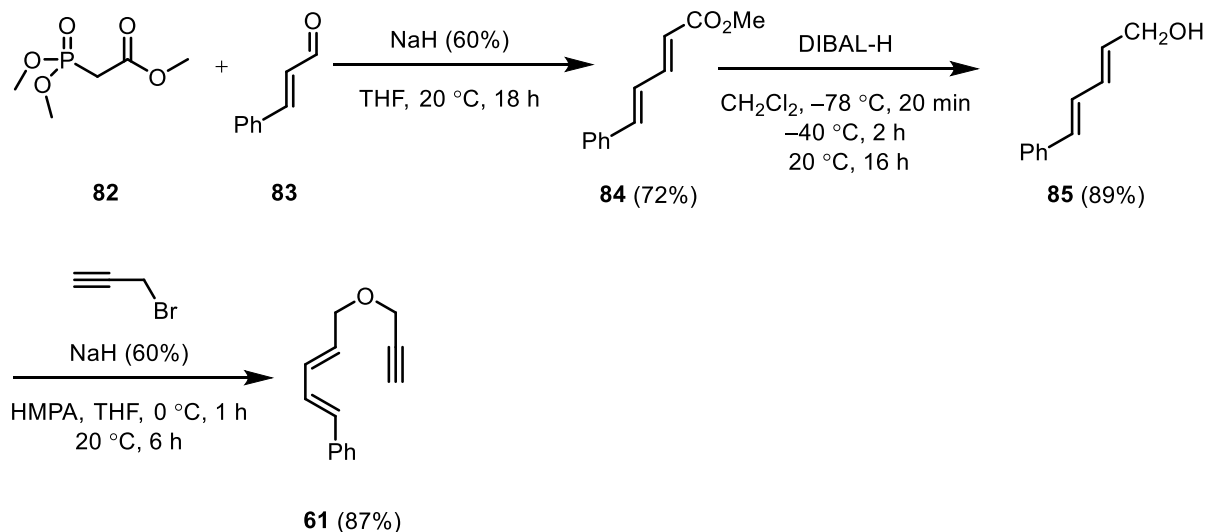
Several attempts to synthesize BenzylPyBox by the methodologies described in Schemes 16 and 18 were unsuccessful.

Chapter Three

Synthesis of Cycloaddition Substrate

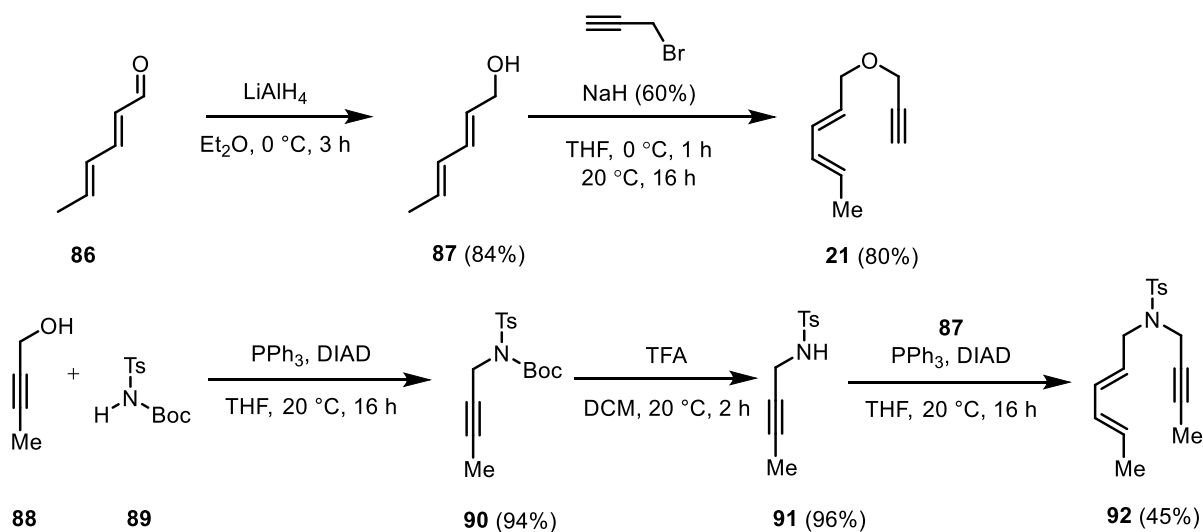
3. Synthesis of Cycloaddition Substrates

Horner–Wadsworth–Emmons reaction of phosphonate **82** and enone **83** produces diene ester **84**. The ester is reduced by DIBAL to form alcohol **85**. Nucleophilic displacement of propargyl bromide results in substrate **61** (Scheme 22).^{32,33}



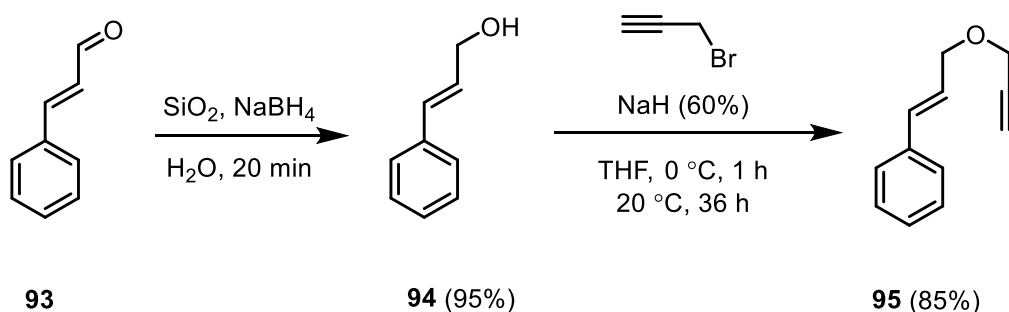
Scheme 22. Synthesis of substrate **61**.^{32,33}

Reduction of *trans,trans*-2,4-hexadienal **86** produced alcohol **87**. Displacement reaction of alcohol **87** and propargyl bromide produced substrate **21**. Mitsunobu reaction of alcohol **88** and amine **89** resulted in **90**, which after deprotection undergoes another Mitsunobu reaction with alcohol **87** to form substrate **92** (Scheme 23).³⁴



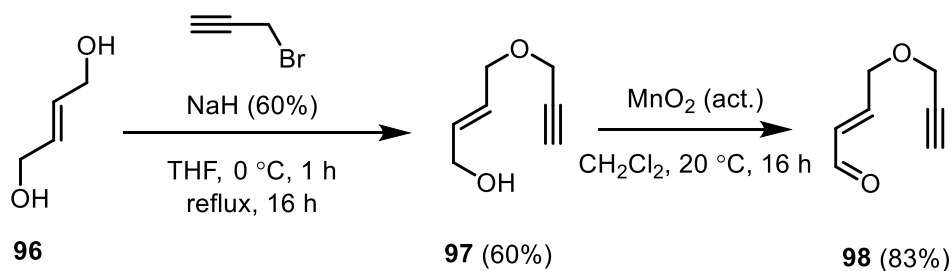
Scheme 23. Synthesis of substrates **21** and **92**.³⁴

Cinnamaldehyde **93** was reduced under solventless conditions with NaBH₄ and wet SiO₂. Cinnamyl alcohol **94** was produced in excellent yields. Propargyl displacement generated substrate **95** (Scheme 24).³⁵



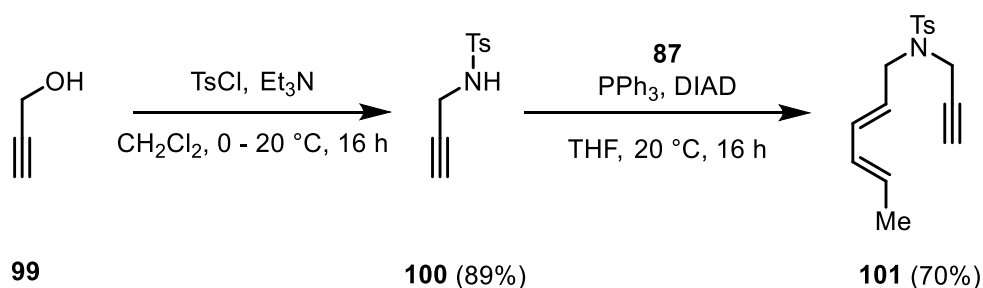
Scheme 24. Synthesis of substrate **95**.³⁵

Propargyl displacement by **96** followed by oxidation with activated MnO₂ formed substrate **98**.³⁶ Some inseparable impurities were isolated with desired product (Scheme 25).



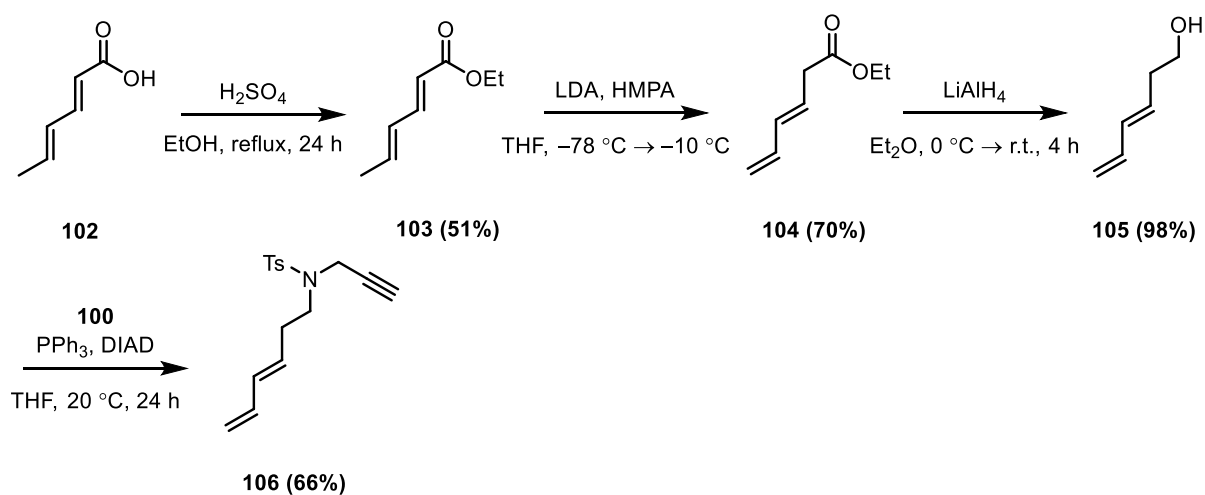
Scheme 25. Synthesis of Substrate **98**.³⁶

Propargyl alcohol **99** was tosylated to give **100** and reacted with alcohol **87** under Mitsunobu conditions to form substrate **101** (Scheme 26).³⁴



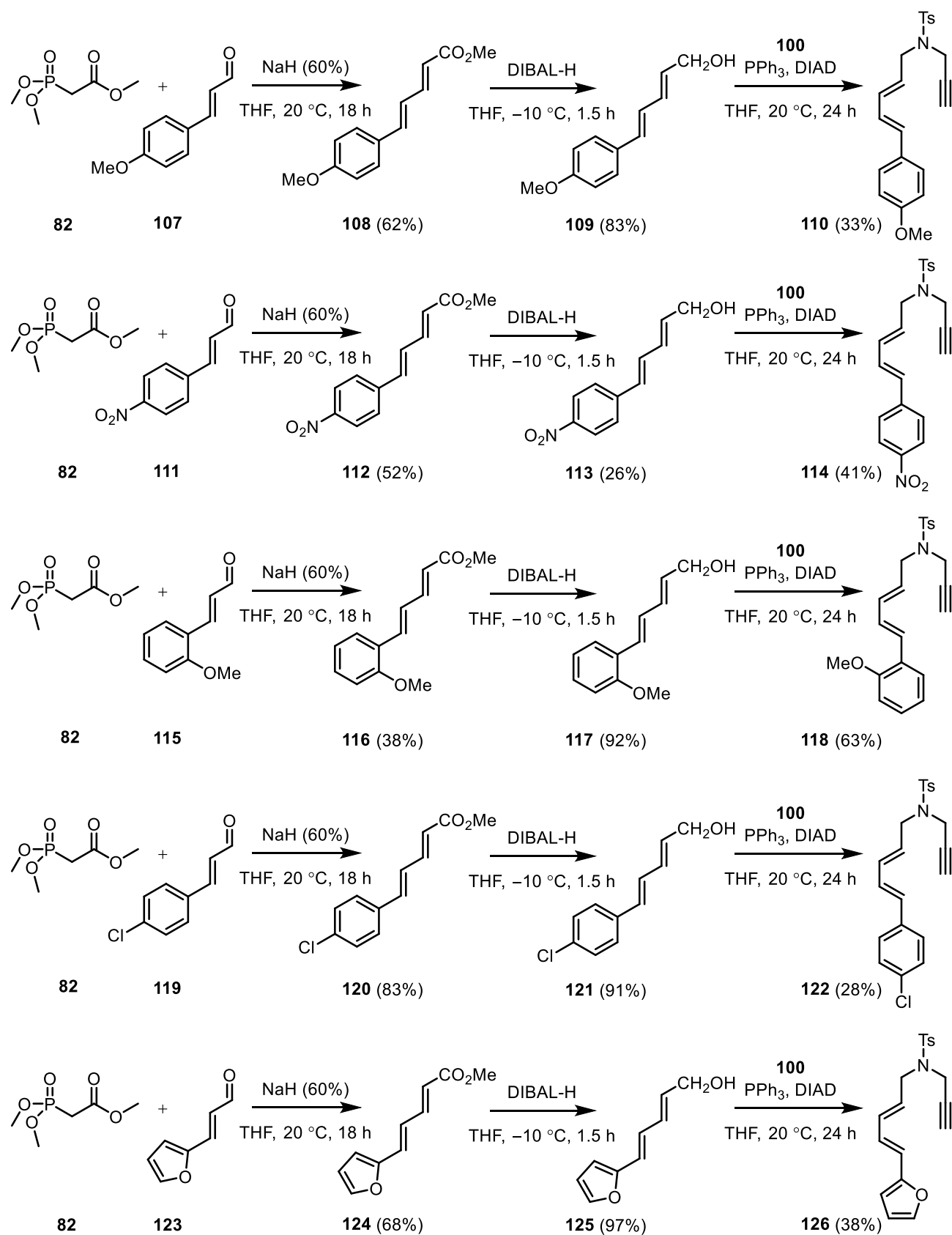
Scheme 26. Synthesis of Substrate **101**.³⁴

Carboxylic acid **102** was esterified in ethanol to form **103**. A base-mediated contra-thermodynamic rearrangement produced **104**, which was reduced to alcohol **105**. Subsequent Mitsunobu reaction with amine **100** generated substrate **106** (Scheme 27).³⁷



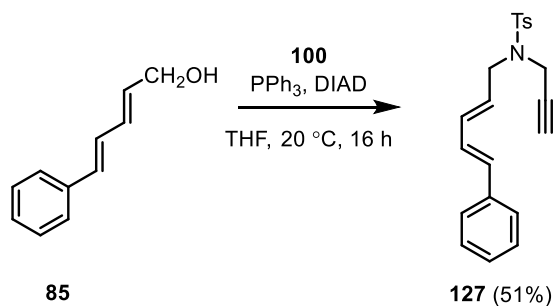
Scheme 27. Synthesis of substrate **106**.³⁷

Substrates **110**, **114**, **118**, **122**, **126** were synthesized by previously described methodologies.



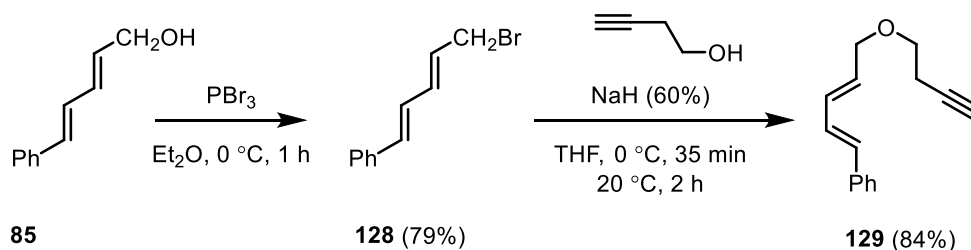
Scheme 28. Synthesis of substrate **110**, **114**, **118**, **122**, **126**.

Substrate **127** was synthesized via a Mitsunobu reaction from alcohol **85** (Scheme 29).



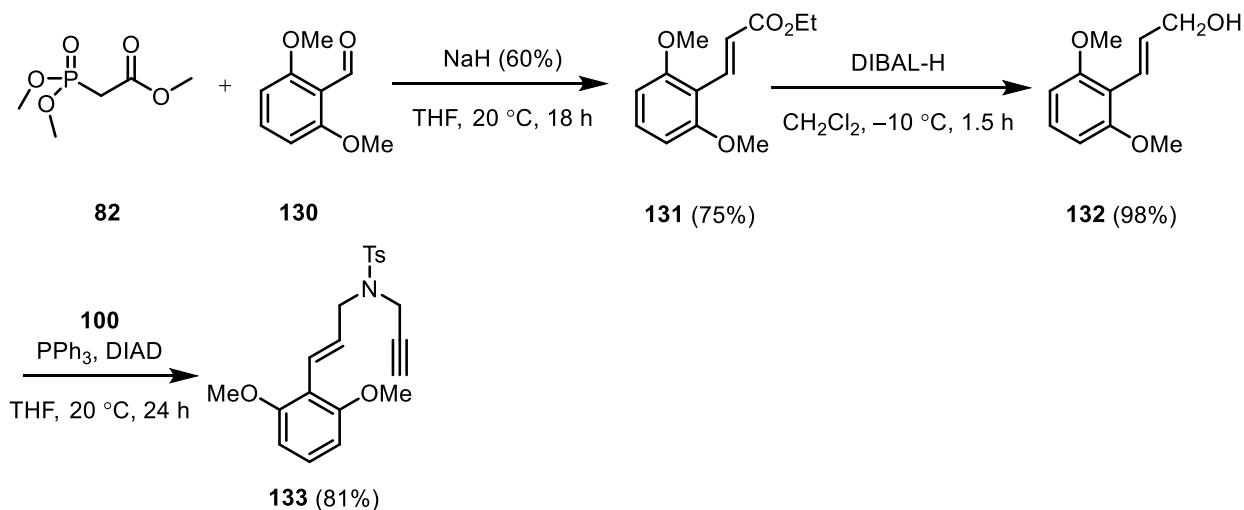
Scheme 29. Synthesis of Substrate 127.

Alcohol **85** was converted to bromide **128** with PBr_3 . Bromide displacement by 3-Butynol furnished substrate **129** (Scheme 30).³⁸



Scheme 30. Synthesis of substrate 128.³⁸

Finally, substrate **133** was synthesized by previously described protocols (Scheme 31).



Scheme 31. Synthesis of Substrate 132.

Several attempts to synthesize diyne equivalents of **61** and **127** were unsuccessful.

Chapter Four

Reaction Screening for [4+2] cycloaddition

4. Reaction screening for [4+2] cycloaddition

Initial screening was performed with substrate **61**. CuI was used as metal catalyst and an assortment of ligands were screened. The reaction was performed in deuterated chloroform at specified temperature for specified amount of time (Table 1).

Table 1. Reaction screening with substrate **61**.

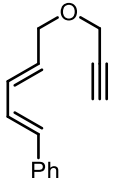
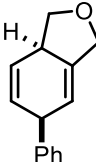
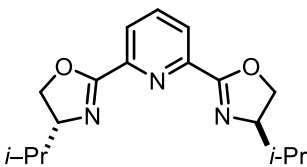
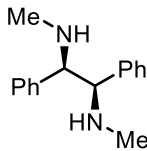
 134 (S) 79 (R) 135 (R,R) 136 (rac.) 137 (S,S)						
entry	Ligand	Temp. (°C)	Time (h)	Consumption (%) ^a	Yield (%) ^b	e.r. ^c
1	—	20	3	0	0	—
2	—	60	16	50	50	—
3	—	60	43	84	84	50:50
4	134	20	3	0	0	—
5	134	60	3	78	73	62:38
6	79	60	3	90	90	16:84
7	135	60	3	100	95	24:76
8 ^d	136	60	3	0	0	—
9	137	60	3	100	>98	56:44
10	79	20	24	50	46	10:90

^aConsumption of starting material. ^bNMR yields are calibrated with trimethoxybenzene or tetrachloroethane as internal standard. ^ce.r. is enantiomeric ratio obtained from chiral HPLC. ^d50% yield after 24 h.

In the absence of ligand, no reaction occurs at ambient temperature (Table 1, entry 1). At elevated temperatures, there is moderate to high yield and conversion after 16 h and 24 h (Table 1, entries 2 –3). With *i*-PrBox ligand **134**, moderate yields and enantioselectivity were observed, both the yield and enantioselectivity increased when *i*-PrPyBox **79** was used (Table 1, entries 5 and 6). With diamine ligand **135** (Table 1, entry 7) good yield but modest enantioselectivity was observed. These results are comparable to those of **desMethyl-135**. No product was detected with biphosphine ligand **136** after 3 h, but after 24 h, yield was 50%. Similar observations were made with 1,1'-Bi-2-naphthol **136-OH**. Excellent yields and low enantioselectivity was observed when DiPhPyBox **137** was used. Finally, the reaction was repeated at room temperature for 24 h with ligand **79**, moderate yield and significantly higher enantioselectivity was observed.

The effect of solvent on yield and enantioselectivity was evaluated (Table 2). Ligands **79** and **135** were screened (Table 2).

Table 2. Reaction screening of Substrate 61: Solvent effects.

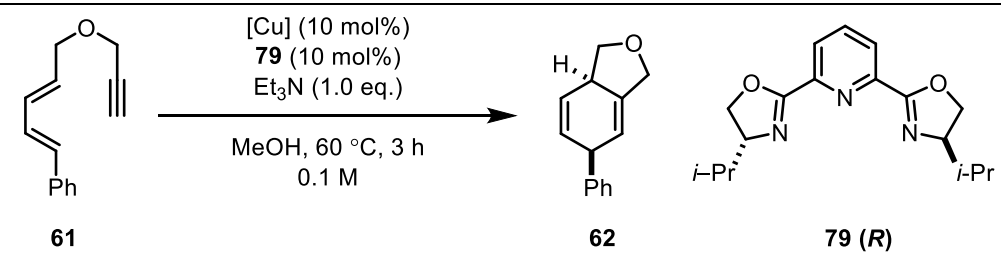
	CuI (10 mol%) L* (10 mol%) Et₃N (1.0 eq.) Solvent, 60 °C, 3 h 0.1 M			
61		62	79 (R)	135 (R,R)
entry	Ligand	Solvent	Yield (%) ^a	e.r. ^b
1	79	THF	33	22:78
2	135	THF	100	22:78
3	79	MeOH	100	6:94
4	135	MeOH	8	40:60
5	79	Dioxane	17	30:70
6	135	Dioxane	100	25:75
7	79	<i>i</i> -PrOH	100	12:88
8	135	<i>i</i> -PrOH	15	35:65
9	79	MeCN	100	13:87
10	135	MeCN	100	19:81
11	79	<i>t</i> -AmOH	52	17:83
12	135	<i>t</i> -AmOH	21	33:67
13	79	<i>t</i> -BuOH	75	13:87
14 ^c	79	DMSO	>98	4:96

^aNMR yields are calibrated with trimethoxybenzene or tetrachloroethane as internal standard. ^be.r. is enantiomeric ratio obtained from chiral HPLC. ^cAt 20 °C for 24 h, 62%; 4:96 er.

In THF, dioxane, the diamine ligand **135** produced higher yield than *i*-PrPyBox ligand **79**. But in protic solvents, the observation is reversed, and higher yields was observed with **79**. Overall, higher enantioselectivity was obtained with ligand **79**. The best solvent examined was DMSO (Table 2, entry 14), the cycloadduct was obtained in quantitative yield and excellent enantioselectivity. At room temperature for 24 h, moderate yield was observed.

Different Cu(I) and Cu(II) sources produced excellent yield and enantioselectivity in the reaction screening (Table 3). The results from the Cu(II) sources (Table 3, entries 1–4) can be explained by the formation L*Cu(II)–alkynyl complex³⁹ or in situ reduction of Cu(II). Comproportionation of Cu(II) and Cu(0) to Cu(I) in the presence of a terminal alkyne has been reported.⁴⁰ This presence of Cu(0) impurities in the Cu(II) sample might enable this mechanism.

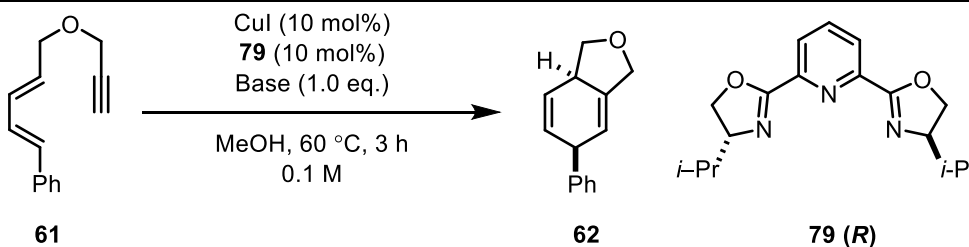
Table 3. Reaction screening of Substrate 61: Copper Sources.

			
entry	[Cu]	Yield (%) ^a	e.r. ^b
1	Cu(HCO ₂) ₂ •xH ₂ O	96	4:96
2	[Cu(OH)(Cl)(TMEDA)] ₂	95	6:94
3	(Phen)CuCl ₂	>98	27:73
4	CuTc	97	5:95
5	Cu(MeCN) ₄ BF ₄	96	5:95
6	Cu(OTf)•Tol	94	4:96
7	CuBr•DMS	95	5:95

^aNMR yields are calibrated with trimethoxybenzene or tetrachloroethane as internal standard. ^be.r. is enantiomeric ratio obtained from chiral HPLC.

No reaction occurred with amidine base DBN. Pyridine and Me₂NEt gave excellent yields but lower enantioselectivity compared to Et₃N (Table 4).

Table 4. Reaction Screening of Substrate 61: Base effect.

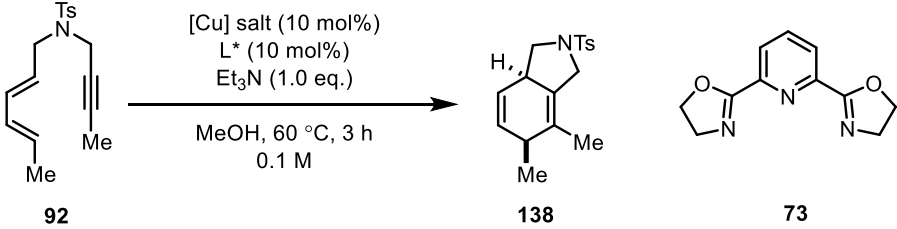
			
entry	Base	Yield (%) ^a	e.r. ^b
1	DBN	0	—
2	Pyridine	>98	11:89
3	Me ₂ NEt	>98	8:92

^aNMR yields are calibrated with trimethoxybenzene or tetrachloroethane as internal standard. ^be.r. is enantiomeric ratio obtained from chiral HPLC.

Additionally, reactions performed at higher concentration (0.2 M) reached completion after 1h. Enantioselectivity was unaffected.

As expected, cyclisation does not proceed with internal alkynes with either Cu(I) or Cu(II) due to its inability to form copper acetylides which is essential for cyclisation to occur (Table 5).

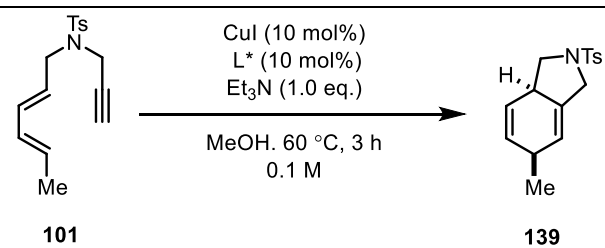
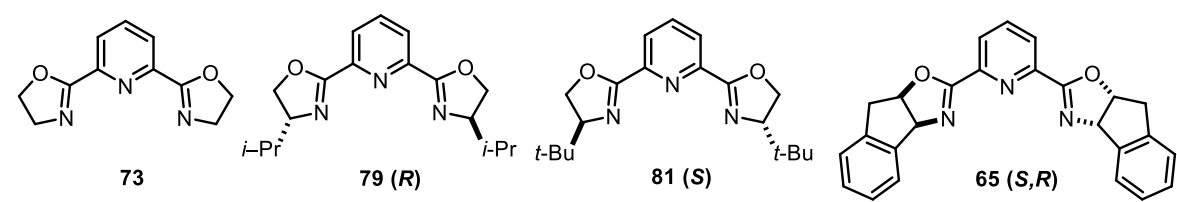
Table 5. Reaction screening of Substrate 92.

		
entry	[Cu]	Yield (%) ^b
1	CuI	0
2	CuI	0
3	Cu(HCO ₂) ₂ •xH ₂ O	0

^aNMR yields are calibrated with trimethoxybenzene or tetrachloroethane as internal standard. ^be.r. is enantiomeric ratio obtained from chiral HPLC.

Substrate **101** cyclises to **139** in excellent yields. Moderate enantioselectivity was observed for all ligands screened (Table 6). Ligand **81** with bulkier *tert*-butyl group gave slightly higher enantiomeric excess than **79**.

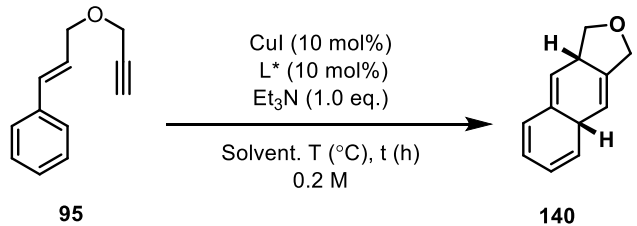
Table 6. Reaction screening of substrate 101.

			
			
entry	Ligand	Yield (%) ^a	e.r. ^b
1	73	98	50:50
2	79	80	36:64
3	81	78	72:28
4	65	98	45:55

^aNMR yields are calibrated with trimethoxybenzene or tetrachloroethane as internal standard. ^be.r. is enantiomeric ratio obtained from chiral HPLC.

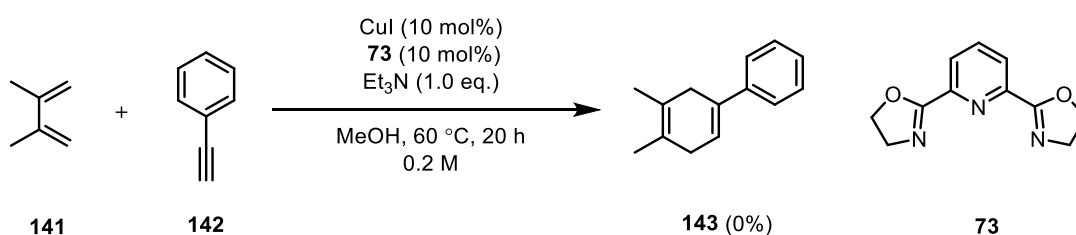
Dearomative cyclisation is a challenging reaction. The stability of the arene ring is a thermodynamic barrier to the cyclisation. The reaction usually proceeds under harsh conditions. Maestri *et. al.* has reported a cyclisation of the kind depicted below.⁴¹ These reactions were promoted by MeLi at $-78\text{ }^{\circ}\text{C}$.⁴¹ Under Cu(I) catalysed conditions, however, no reaction was observed (Table 7).

Table 7. Reaction screening for Substrate 95.

							
entry	[Cu]	Ligand	Solvent	Temp. ($^{\circ}\text{C}$)	Time (h)	yield (%) ^a	e.r. ^b
1	CuI	73	MeOH	20	24	0	—
2	CuI	73	MeOH	60	24	0	—

^aNMR yields are calibrated with trimethoxybenzene or tetrachloroethane as internal standard. ^be.r. is enantiomeric ratio obtained from chiral HPLC.

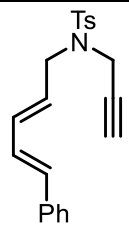
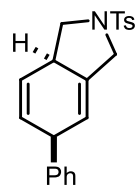
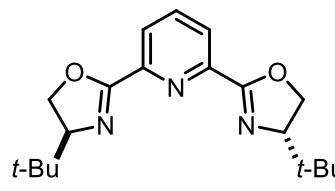
Attempts to achieve an intermolecular annulation to form product **143** were unsuccessful under the reaction conditions.



Scheme 32. Attempted Intermolecular Annulation.

With the optimum reaction conditions obtained, variations from the ‘standard’ condition were examined (Table 8).

Table 8. Variation from Standard conditions.

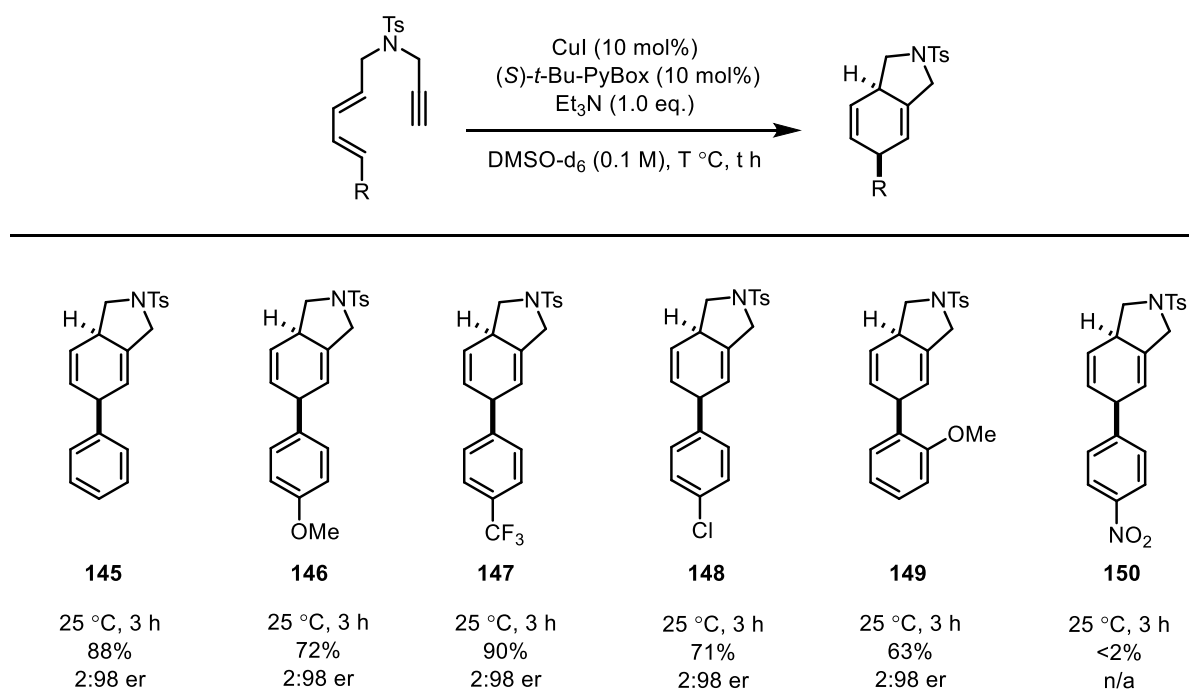
 127 CuI (10 mol%) (<i>S</i>)-<i>t</i>-Bu-PyBox (20 mol%) Et₃N (1.0 eq.) DMSO-<i>d</i>₆, 25 °C, 3 h 0.1M  144  81 (S)				
entry	variation from “standard” conditions ^a	Conv. (%) ^b	Yield (%) ^b	e.r. ^c
1	none	>98	97	2:98
2	no CuI	<2	<2	—
3	no Ligand	27	14	50:50
4	no Base	42	40	2:98
5	no CuI, no Ligand	<2	<2	—
6	5 mol% CuI/ 6 mol% ligand	>98	97	2:98
7	(<i>R</i>)- <i>t</i> -BuPyBox instead of (<i>S</i>)- <i>t</i> -BuPyBox	>98	97	98:2
8	(<i>R</i>)-(<i>i</i> -Pr)-PyBox instead of (<i>S</i>)-(<i>t</i> -Bu)-PyBox	>98	93	96:4
9	(<i>S,R</i>)-DiPh-PyBox instead of (<i>S</i>)-(<i>t</i> -Bu)-PyBox	80	80	90:10
10	(<i>R</i>)-BINAP instead of (<i>S</i>)-(<i>t</i> -Bu)-PyBox	<2	<2	—
11	(<i>R</i>)-(Cl)-(OMe)-BIPHEP of (<i>S</i>)-(<i>t</i> -Bu)-PyBox	<2	<2	—
12	MeOH instead of DMSO	95	52	2:98
13	CH ₂ Cl ₂ instead of DMSO	>98	64	2:98
14	DIPEA instead of Et ₃ N	>98	74	2:98
15	CuOTf•0.5PhMe	>98	83	2:98
16	Cu(HCO ₂) ₂ •xH ₂ O	88	88	4:96
17	DMSO/H ₂ O (10:1)	>98	>98	2:98
18	Open flask	>98	85	2:98

^aAll data are the average of two experiments performed using 0.1 mmol of substrate. [Cu] salts were used without further drying. [Cu] salt and ligand were pre-mixed at 60 °C for 1 h. ^bDetermined by analysis of crude reaction mixtures by ¹H NMR using anisole as an internal standard. ^ce.r. is enantiomeric ratio obtained from chiral HPLC.

As expected, no reaction occurs in the absence of CuI (Table 8, entry 2) after 3 h. There is some background reaction after 20 h. The reaction is slower in the absence of ligand. This proves

ligand reaction acceleration in the Cu–L catalysed cycle. There is some background reaction in the absence of base (Table 8, entry 4). The ligand might deprotonate the Cu–alkyne π -complex. High yield and enantioselectivity were observed at lower catalyst loading (Table 8, entry 6). (*R*)-PyBox ligand results in enantioenriched enantiomer of **141** (Table 8, entry 7). Other solvents reduce the reaction yield but not enantioselectivity. Other trialkylamine bases and Cu sources are similarly effective in the reaction. The reaction is robust and tolerates the presence of water (Table 8, entry 17). The reaction can be performed in an open flask.

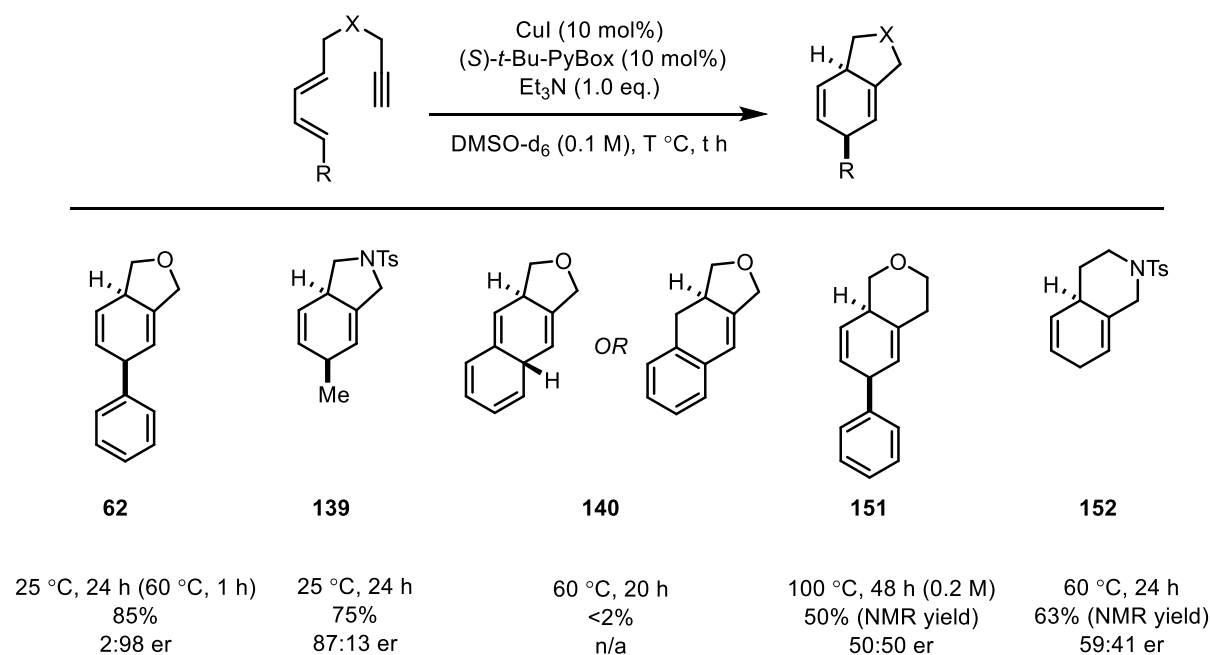
The synthesized substrates were reacted under the ‘standard’ conditions. The yields presented are calibrated NMR yields and are the average of two experiments (Scheme 33).



Scheme 33. Cycloaddition under 'standard' conditions.

Moderate to good yields were obtained for all the substrates apart from **150** where aromatised product (90%) was detected by NMR.

Homologated cycloadduct **151** was obtained in moderate yields (Scheme 34). Harsher conditions were required to enable the reaction. No enantioselectivity was observed, possibly due to the high temperature or due to the distal position of the chiral ligand from the stereoinducing C–C bond formation in the transition state of the homologated substrate. Similar results were obtained in homologated **152** (Scheme 34).

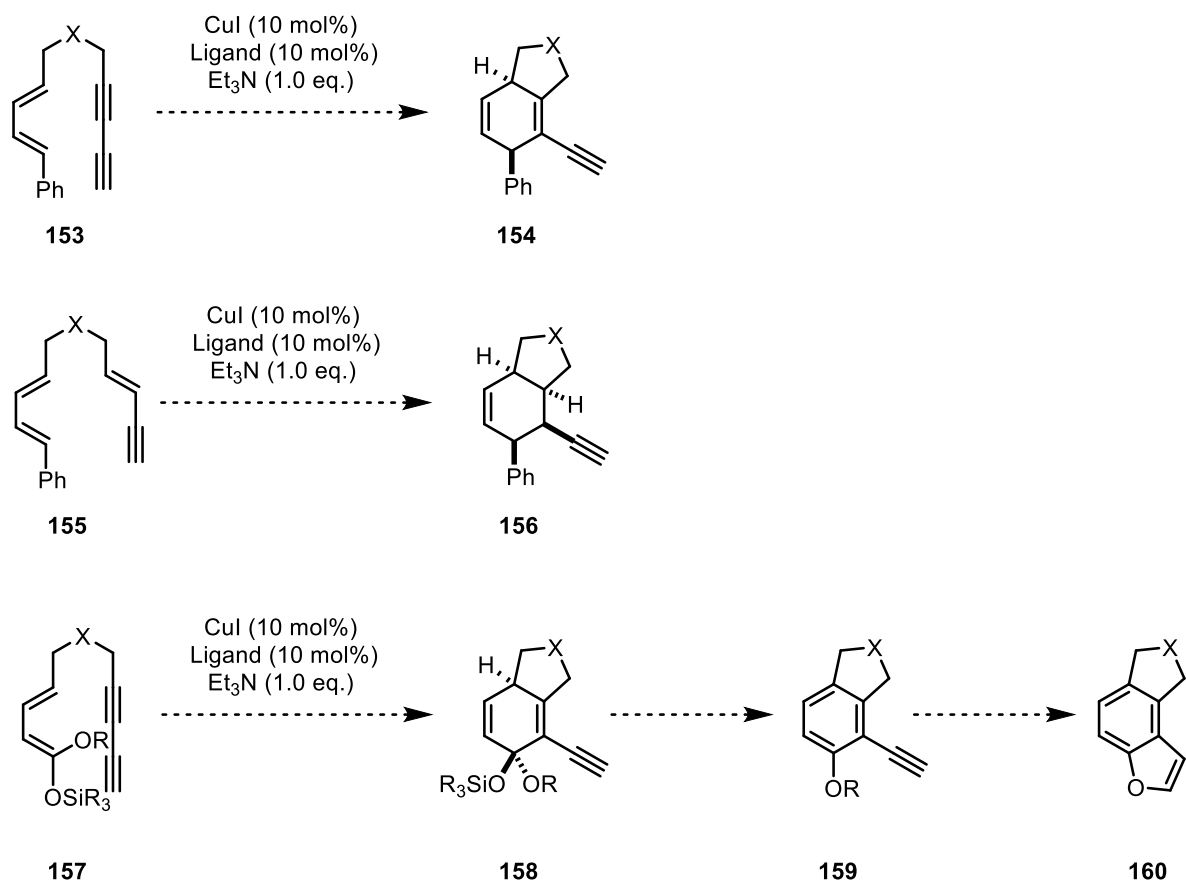


Scheme 34. Cycloaddition under 'standard' conditions.

4.1. Summary and outlook

Several chiral ligands were synthesized along with several substrates. Extensive reaction screenings were performed and optimum conditions for cycloaddition were achieved. Intramolecular [4+2] cycloaddition of diene and terminal alkynes was accomplished with several substrates. Future work should focus on expanding the substrate scope. Some examples are shown in Scheme 35. Diyne **153** and Enyne **155** could react to form **154** and **156** respectively. The alkyne moiety could then be further derivatized. Tricyclic compound **160** could also be synthesized from **157** as shown in the reaction sequence. Further work could be

done with substrates where the diene component has substituents. Such experiments would result in the syntheses of compounds with complex architecture which would facilitate the exploration of chemical space.



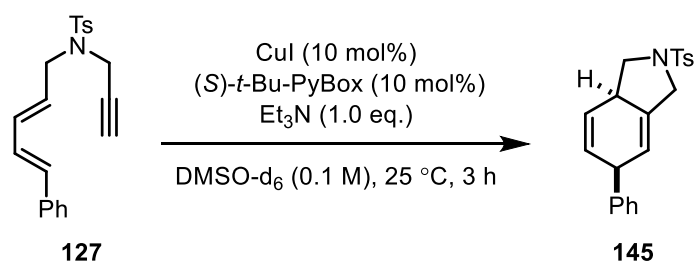
Scheme 35. Future work.

Chapter Five

Mechanistic Investigations

5. Mechanistic Investigations

The mechanism of the intramolecular cycloaddition reaction of reactant **127** to cycloadduct **145** was investigated. The effect of the amount of base used in the reaction was evaluated for the reaction. The decrease in concentration of the reactant was measured against time. The rate of reaction increases with the amount of base used in the reaction (Figure 1). This is expected because Et₃N plays a role in the rate-limiting step of the reaction.



Effect of Base Amount on Reaction Rate

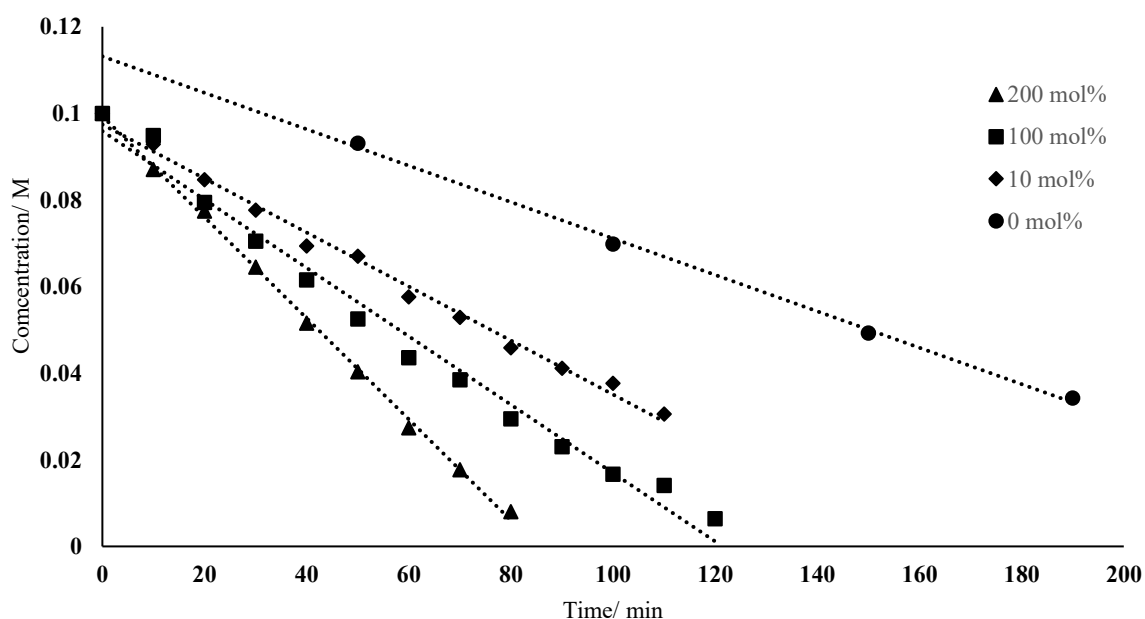


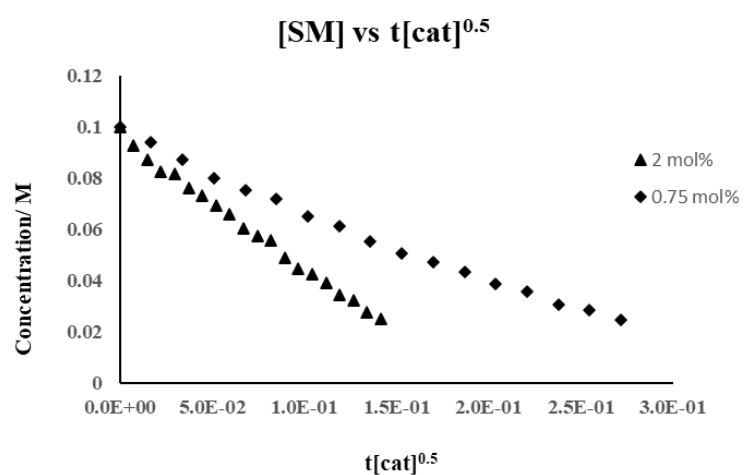
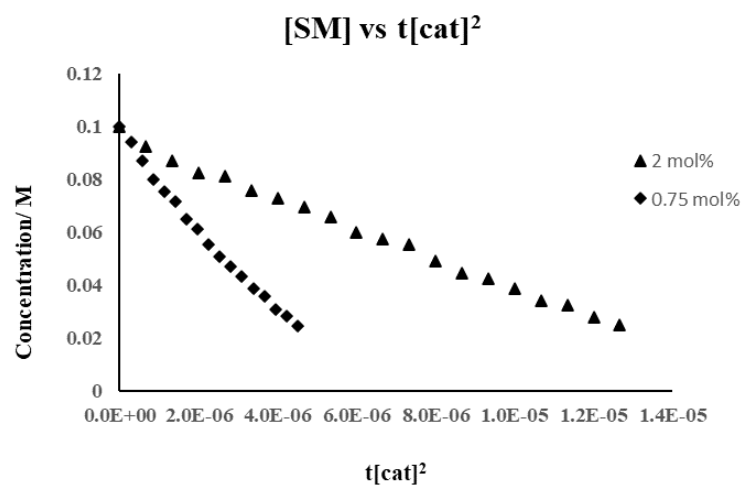
Figure 1. Effect of base amount on reaction rate.

The reaction profiles confirms that the cycloaddition reaction is pseudo-zero order with respect to the reactant.

The order in catalyst in the reaction of **127** to form **145** was also examined via the Burés methodology, which involves a variable time normalization analysis, $t[\text{cat}]_T^n$ to adjust entire reaction profiles constructed from concentration data.^{42,43} The normalization of the time scale at different catalyst loadings allows the direct comparison between different concentration profiles. This is possible because the total concentration of the catalyst is constant for the duration of the reaction, therefore the normalized time scale is a parameter that describes the reactant concentration during the reaction. The “n” exponent can be arbitrarily chosen and adjusted until a number is reached that causes the concentration profiles to overlay.^{42,43}

The concentration profiles of the reaction were recorded at different catalyst loadings, from 10 mol% to 0.75 mol%. This variation represents the course of the reaction cycle; A catalyst loading of 10 mol% indicates the start of the reaction cycle and a catalyst loading of 0.75 mol% indicates a later stage in the reaction cycle. Therefore, the order in catalyst can be measured at different stages of the reaction cycle.

In Figure 2, catalyst loading of 2 mol% and 0.75 mol% was investigated. When the exponent, n, is 2 or 0.5, there is no overlay between concentration profiles, however when the exponent of the normalized time scale $t[\text{cat}]_T^n$ is raised to 1, the concentration profiles overlay. Therefore, the order in catalyst between 2 mol% and 0.75 mol% is **1** (Figure 2).



CORRECT ORDER CAUSES LINES TO OVERLAY

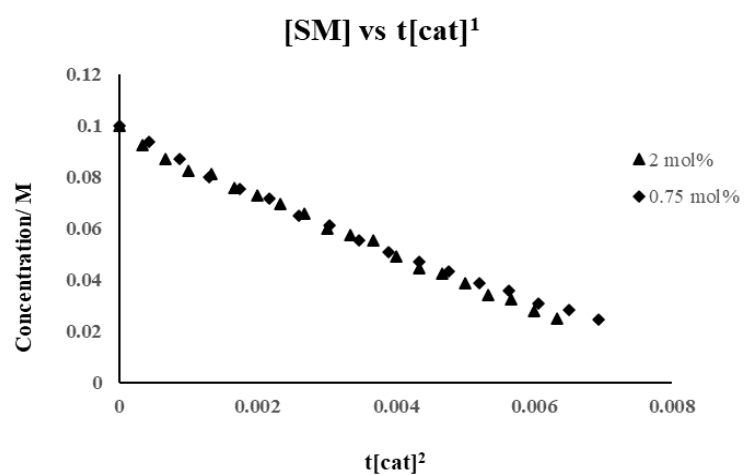
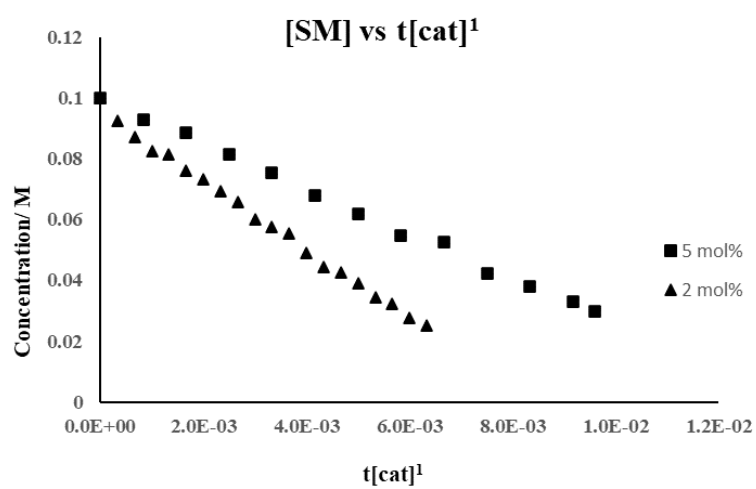
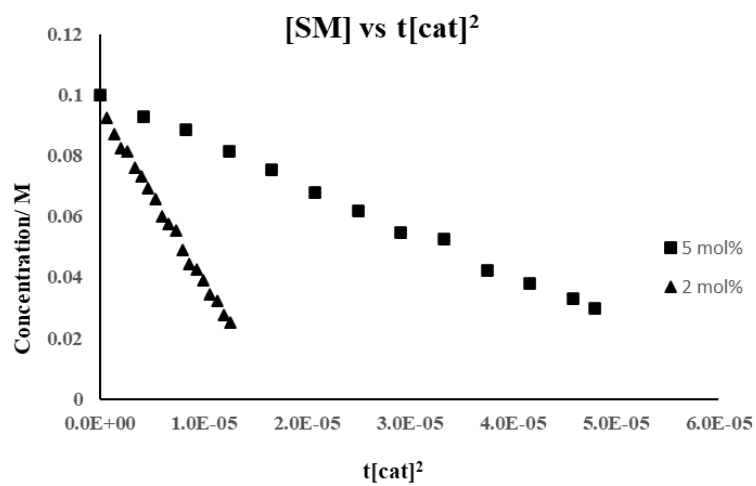


Figure 2. Correct order of 1 causes overlay.

Next, the concentration between 5 mol% and 2 mol% was investigated (Figure 3). When the exponent was raised to 2 or 1, there was no overlay between the concentration profiles, but there was overlay of the concentration profiles when the exponent, n , was set to 0.5. Therefore, the order in catalyst between 5 mol% and 2 mol% is **0.5** (Figure 3).



CORRECT ORDER CAUSES LINES TO OVERLAY

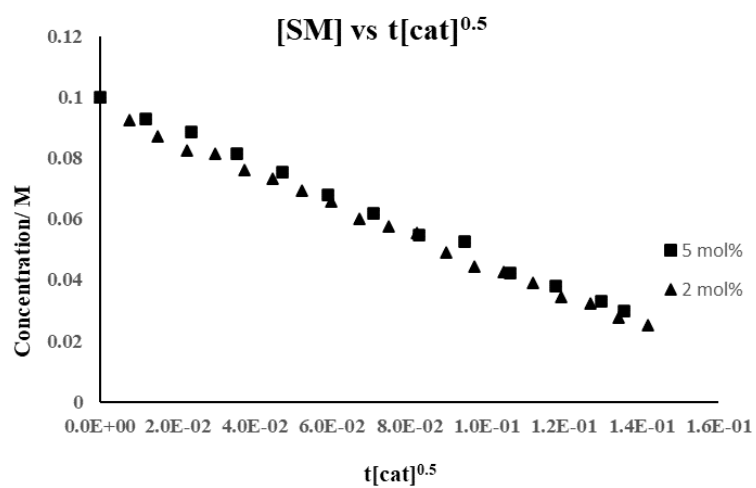
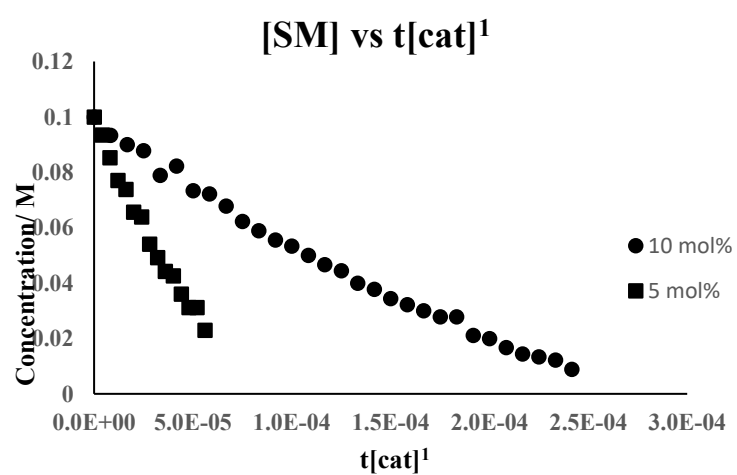
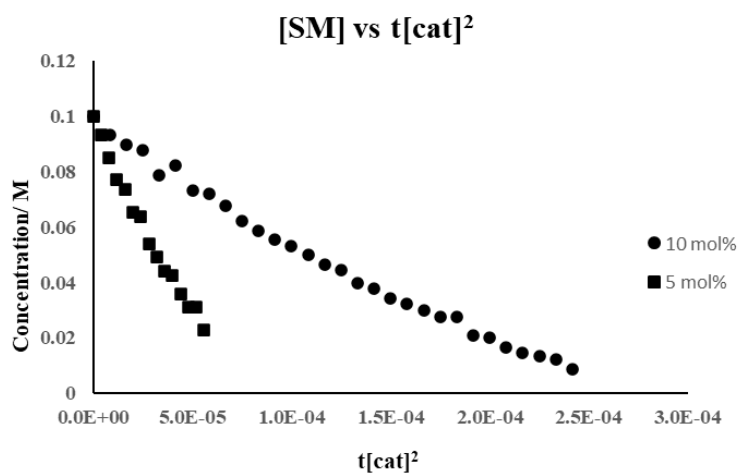


Figure 3. Correct order of 0.5 causes overlay.

Finally, the concentration between 10 mol% and 5 mol% was investigated (Figure 4). Similarly, when the exponent was raised to 2 or 1, no overlay between the concentration profiles was observed, however there was overlay of the concentration profiles when the exponent, n , was set to 0.5. Therefore, the order in catalyst between 10 mol% and 5 mol% is also **0.5** (Figure 4).



CORRECT ORDER CAUSES LINES TO OVERLAY

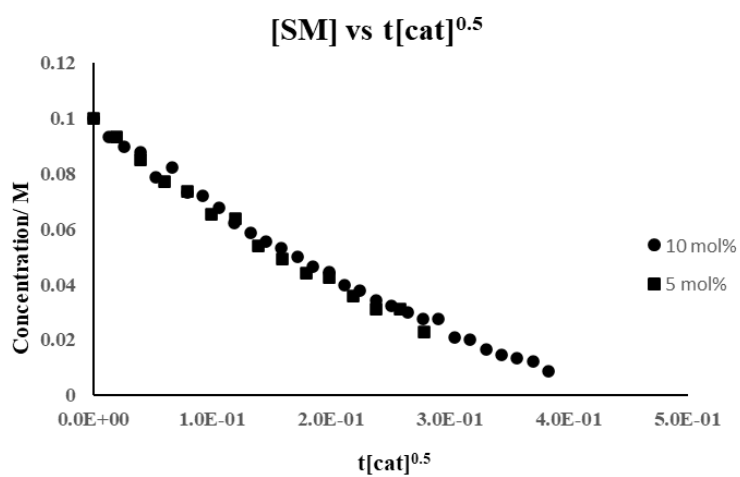


Figure 4. Correct order of 0.5 causes overlay.

From these analyses, we can deduce that the order in catalyst is dependent upon catalyst concentration, the order in catalyst changes from **1** to **0.5** during the reaction cycle. An order in catalyst of **1** indicates that the catalyst is present as the monomeric species, whereas an order in catalyst of **0.5** indicates that the catalyst is present as an inactive dimeric species. The active monomeric and off-cycle inactive dimeric species are in equilibrium. In conclusion, an inactive catalyst dimer is formed at the start of the reaction. This dimer is in equilibrium with monomeric species which catalyses the reaction.

A non-linear effect analysis was conducted for the reaction of reactant **61** to cycloadduct **62**. The enantiomeric excess of the product was recorded at different enantiomeric excess of the chiral pybox ligand. A negative non-linear effect was observed at room temperature (Figure 5), this means that a heterochiral complex of the chiral ligand (*RS*) is more reactive than the homochiral complex of the chiral ligand (*RR* or *SS*). This effect was absent at elevated temperatures (Figure 6). At room temperature (Figure 5), the partial linearity at low ligand ee, which deviated at high ligand ee can be interpreted as the presence of an active ML_4 system at low catalyst concentration.⁴⁴⁻⁴⁶

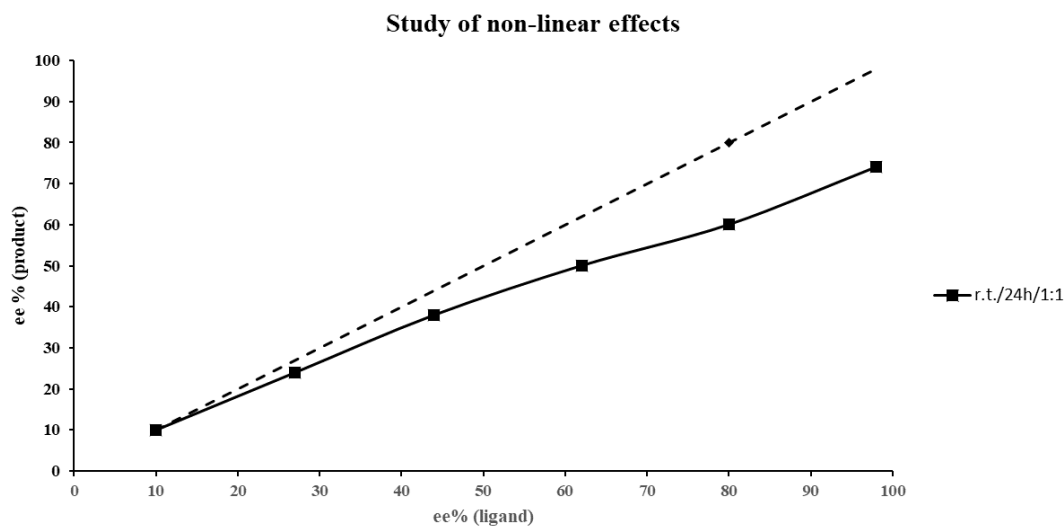
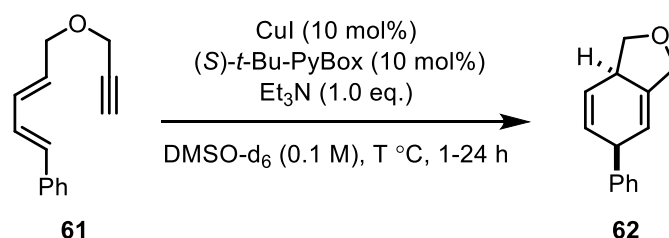


Figure 5. Non-Linear effect at room temperature.

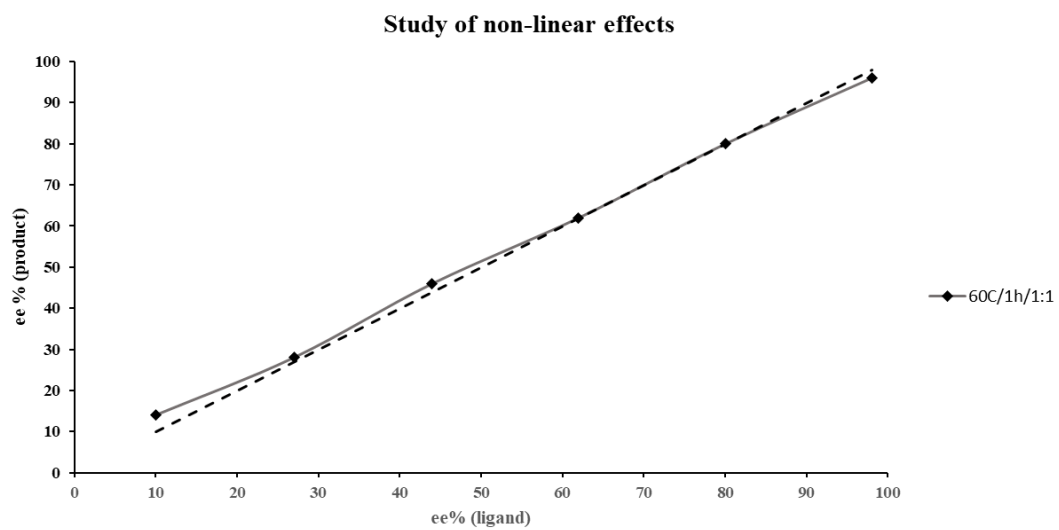
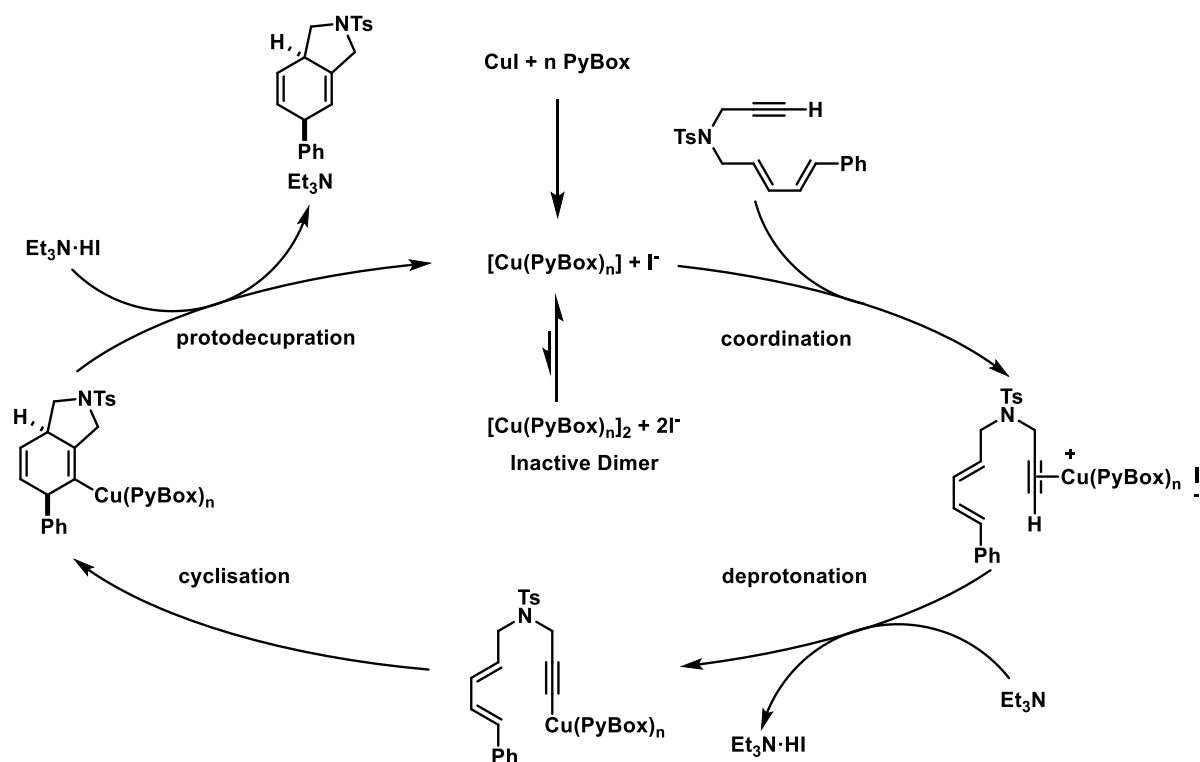


Figure 6. n-linear effect at 60°C.

5.1. Summary

The reaction proceeds via complexation to the alkyne by a Cu–L complex. This lowers the pKa and promotes abstraction of the proton. An inactive dimer is formed at the start of the reaction, but as the reaction progresses, equilibrium shifts towards the active form of the catalyst. Cyclisation followed by protodecupration produces the product (Scheme 36).



Scheme 36. Cu(PyBox)-Catalysed Annulation.

Chapter Six

Experimental

6. Experimental

6.1. General Methods

All reactions were carried out under dry nitrogen atmosphere and in oven-dried glassware unless stated otherwise. Flame- and oven-dried glassware was cooled under vacuum (ca. 1 mbar). For reactions performed under anhydrous conditions, Schlenk techniques were used. Anhydrous solvents were dried by alumina columns in a LC Technology Solutions Inc. SP-1 Solvent Purification System under N₂. Analytical grade solvents were used as received. Commercially available anhydrous MTBE (Aldrich; 99.8%) was degassed and stored under nitrogen atmosphere. Petroleum ether (b.p. 40–60 °C) was used.

Room temperature was taken as 20 °C, where no external heating or cooling was applied. Reactions at temperatures from –20 °C to ambient temperature were performed in an ice/water/NaCl(s) bath and –78 °C was achieved using an acetone/CO₂(s) bath. Prolonged periods of reaction cooling were accomplished by Huber cryocool apparatus.

Nuclear Magnetic Resonance (NMR) spectra were recorded on BRUKER AV (400 MHz) at 298 K. Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (chloroform at 7.26 and 77.00 ppm for ¹H and ¹³C NMR spectroscopy, respectively). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet; br., broad. Coupling constants were taken from the spectra directly and are uncorrected. Signals with the appearance of a given multiplicity are preceded with the term ‘app.’ to denote an apparent splitting pattern when chemically distinct nuclei display very similar coupling constants. ¹H and ¹³C NMR provided are taken directly using material for which the yield is quoted, without additional purification, and are representative of sample purity.

Purification of samples was achieved by flash column chromatography using Merck Flash Silica Gel 60 (230-400 mesh). Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualised initially by UV light (254 nm) or potassium permanganate or vanillin staining.

Chiral HPLC was performed on a HP Agilent 1260 infinity series system employing Daicel Chiralcel columns eluting with *i*-PrOH/hexane at 35 °C and monitored by a DAD (Diode Array Detector). Chiral GC was performed on an Agilent 7890 system (H₂ Flow Rate = 0.88 mL/min, Inlet Temperature = 250 °C) employing an Agilent CP-ChiraSil Dex CB column (25 m x 0.25 mm x 0.25 µm) and monitored by FID (Flame Ionisation Detector).

Reaction screenings were performed in 4 mL scintillation glass vials with a PTFE-lined cap, and all other reactions were performed in round-bottom flasks with rubber septa. Syringes were used to transfer air- and moisture-sensitive reagents.

6.2. General Procedures

General procedure A for Horner–Wadsworth–Emmons reaction

An oven-dried 500 mL two-necked round-bottomed flask was charged with NaH (67.2 mmol). The flask was evacuated (ca. 1 mbar) and back-filled with nitrogen three times. THF (400 mL) was added via cannula. The flask was cooled to 0 °C and phosphonate (57.6 mmol) was added dropwise at 0 °C. The reaction mixture was stirred vigorously for 2 h at 0 °C, and aldehyde (48.0 mmol) was added portion-wise. The reaction mixture was stirred at 0 °C for 10 minutes and allowed to warm to room temperature; the reaction mixture was subsequently stirred at room temperature for 16 h. The reaction was quenched with 10% HCl (200 mL), and 200 mL Et₂O was added. The organic phase was separated, and aqueous phase was extracted with Et₂O (50mL). The combined organic phases were washed with saturated NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to afford the appropriate ester.³²

General procedure B for DIBAL reduction

An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with ester (13.0 mmol) as a solution in CH₂Cl₂ (60 mL). The flask was cooled to –78 °C. DIBAL (1M in cyclohexane; 39.0 mmol) was added as a solution in CH₂Cl₂ (30 mL) over 40 minutes. The reaction mixture was warmed to –40 °C and stirred for 2 h. The reaction mixture was diluted with Et₂O (200 mL) and poured into flask containing Rochelle's salt (1 M; 70 mL). The reaction mixture was subsequently stirred at room temperature for 16 h. The organic phase was separated, and aqueous phase was extracted with Et₂O (50mL). The combined organic phases were washed with 10% HCl, saturated NaHCO₃, brine, dried (MgSO₄), filtered, and

concentrated *in vacuo*. The crude material was purified by flash column chromatography to afford the appropriate alcohol.³²

General procedure C for reaction with Propargyl bromide

An oven-dried 250 mL two-necked round-bottomed flask was charged with NaH (15.0 mmol). The flask was evacuated (ca. 1 mbar) and back-filled with nitrogen three times. THF (75 mL) was added via cannula. HMPA was added (13.8 mmol; if indicated). The flask was cooled to 0 °C. The alcohol (12.5 mmol) was a solution in THF (15 mL) and the reaction mixture was stirred at 0 °C for 1 h. Propargyl bromide (16.3 mmol) was added at 0 °C and the reaction mixture was allowed to warm to room temperature and then stirred for 6 h at room temperature. The reaction mixture was diluted with Et₂O/NH₄Cl. The organic phase was separated, and aqueous phase was extracted with Et₂O (50mL). The combined organic phases were washed with saturated NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to afford the appropriate compound.³²

General procedure D for Lithium Aluminium Hydride reduction

An oven-dried 250 mL two-necked round-bottomed flask was charged with LiAlH₄ (52.0 mmol) and the flask was evacuated (ca. 1 mbar) and back-filled with nitrogen three times. Et₂O (100 mL) was added to the flask, and the suspension was cooled to 0 °C. The aldehyde (52.0 mmol) in Et₂O was added dropwise over 20 minutes. The suspension was stirred at 0 °C for 3 h. The reaction was quenched with (NH₄)₂SO₄ (10%; 12 mL) and the organic phase was separated. The aqueous phase was extracted with Et₂O (50mL). The combined organic phases were washed with saturated NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to afford the appropriate compound.⁴⁷

General procedure E for Mitsunobu reaction

An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with amine (6.24 mmol) and PPh₃ (6.24 mmol). THF (70 mL) and alcohol (6.24 mmol) were added. DIAD (6.24 mmol) was added, and the reaction was stirred for 5–24 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to afford the appropriate compound.

General procedure F for deprotection with Trifluoroacetic acid

An oven-dried 50 mL two-necked round-bottomed flask under N₂ was charged with Boc-protected sample (5.63 mmol) dissolved in CH₂Cl₂ (20 mL). TFA (28.2 mmol) was added and the reaction mixture was stirred for 1 h. The reaction was quenched with saturated NaHCO₃. The organic phase was separated, and aqueous phase was extracted with CH₂Cl₂ (20 mL). The combined organic phases were washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was used without further purification.

General procedure G for tosylation

An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with amine (20.3 mmol in CH₂Cl₂ (50 mL). The reaction mixture was cooled to 0 °C, and Et₃N (50.2 mmol) was added. TsCl (20.3 mmol) was added portionwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with Et₂O (100 mL) and washed with 1 M HCl (3×50 mL), brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to afford the appropriate compound.

General procedure H for esterification

An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with carboxylic acid (86.2 mmol). EtOH (120 mL) was added. H₂SO₄ (5 drops) was added. The reaction mixture was refluxed for 16 h. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The residue was dissolved in CHCl₃ (100 mL) and saturated NaHCO₃ (100 mL) was added. The organic phase was separated, and aqueous phase was extracted with CHCl₃ (20 mL). The combined organic phases were washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was used without further purification.

General procedure I for PyBox ligand

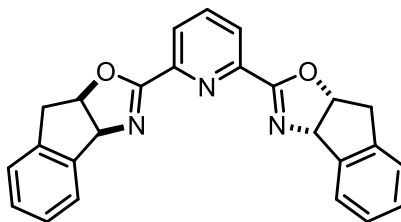
An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with pyridine-2,6-dicarbonitrile (6.00 mmol) and Zn(OTf)₂ (0.30 mmol). The flask was evacuated (ca. 1 mbar) and back-filled with nitrogen three times. Toluene (40 mL) was added. The solution was stirred for 10 minutes before the amino alcohol (12.0 mmol) was added. The reaction mixture was refluxed for 3 days. The reaction was allowed to cool to room temperature and then diluted with EtOAc (50 mL). The organic phase was separated, and aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with saturated NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was used without further purification.²⁷

General procedure J for reaction screening

CuI (0.01 mmol; dried under vacuum at 80 °C) was added to an oven-dried vial. The vial was evacuated (ca. 1 mbar) and back-filled with nitrogen three times. The ligand (0.01 mmol) in solvent (0.5 mL) was added from a stock standard solution. The reaction mixture was stirred for 30 minutes after which the substrate (0.1 mmol) and NMR internal standard in solvent (0.5 mL) were added from stock standard solutions. The reaction mixture was stirred for 10 minutes and then a base was added. The reaction mixture was stirred at the desired temperature for the specified time. The mixture was filtered over Celite and concentrated *in vacuo* and ¹H NMR spectra were recorded. For reactions in deuterated solvent, the reaction mixture was filtered over a plug of silica, washed with (0.2 mL) deuterated solvent and ¹H NMR spectra were recorded.

6.3. Synthesis and compound characterization.

2,6-bis((3aS,8aR)-3a,8a-dihydro-8H-indeno[1,2-d]oxazol-2-yl)pyridine – 65

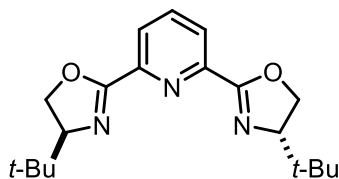


Prepared according to general procedure I using pyridine-2,6-dicarbonitrile (774 mg, 6.00 mmol), amino alcohol (1.79 g, 12.0 mmol), and $\text{Zn}(\text{OTf})_2$ (109 mg, 0.30 mmol). The aqueous phase was thoroughly washed with acetone, MeOH, CH_2Cl_2 , EtOAc. The combined organic phases were washed with saturated NaHCO_3 , and brine. The title compound **65** was isolated as a white solid (1.19 g, 50%).

^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, $J = 7.8$ Hz, 2H), 7.82 (t, $J = 7.9$ Hz, 1H), 7.61 – 7.55 (m, 2H), 7.37 – 7.25 (m, 2H), 7.28 (s, 4H), 5.82 (d, $J = 7.9$ Hz, 2H), 5.64 (dt, $J = 8.3, 4.4$ Hz, 2H), 3.52 (d, $J = 4.3$ Hz, 4H).

*The data are consistent with those reported in literature.*²⁷

2,6-bis((S)-4-(tert-butyl)-4,5-dihydrooxazol-2-yl)pyridine – 68

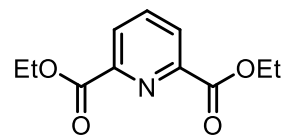


Prepared according to general procedure I using pyridine-2,6-dicarbonitrile (774mg, 6.00 mmol), amino alcohol (1.41 g, 12.0 mmol), and $\text{Zn}(\text{OTf})_2$ (218 mg, 0.60 mmol). The title compound **68** was isolated as a white solid (1.50 g, 76%).

^1H NMR (400 MHz, CDCl_3) δ 8.27 (d, $J = 7.7$ Hz, 2H), 7.88 (t, $J = 7.8$ Hz, 1H), 4.57 – 4.46 (m, 2H), 4.35 (t, $J = 8.7$ Hz, 2H), 4.14 (dd, $J = 10.3, 8.4$ Hz, 2H), 0.99 (s, 18H).

*The data are consistent with those reported in literature.*²⁷

diethyl pyridine-2,6-dicarboxylate – 70

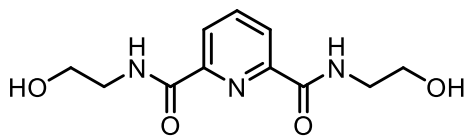


Prepared according to general procedure H using dicarboxylic acid (10 g, 59.8 mmol). The title compound **70** was isolated as a white solid (10.6 g, 80%).

¹H NMR (400 MHz, CDCl₃) δ 8.30 (d, J = 7.8 Hz, 2H), 8.02 (t, J = 7.8 Hz, 1H), 4.51 (q, J = 7.0 Hz, 4H), 1.47 (t, J = 7.1 Hz, 6H).

*The data are consistent with those reported in literature.*²⁸

N²,N⁶-bis(2-hydroxyethyl)pyridine-2,6-dicarboxamide – 71

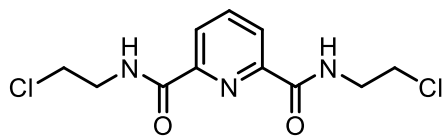


An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with **70** (2.41 g, 10.8 mmol). Ethanolamine (1.30 mL, 21.6 mmol) was added neat, and the reaction mixture was heated to 90 °C for 5 h. Precipitation occurred after 30 minutes. The reaction mixture was cooled to room temperature and the precipitated solid was washed with CHCl₃. The residue was collected and dried *in vacuo*. Title compound **71** was obtained as a white solid (2.55 g, 62%).²⁹

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.38 (t, *J* = 6.1 Hz, 2H), 8.23 – 8.12 (m, 3H), 4.86 (t, *J* = 5.4 Hz, 2H), 3.57 (q, *J* = 6.0 Hz, 4H), 3.44 (q, *J* = 6.2 Hz, 4H).

*The data are consistent with those reported in literature.*²⁹

N²,N⁶–bis(2-chloroethyl)pyridine-2,6-dicarboxamide – 72

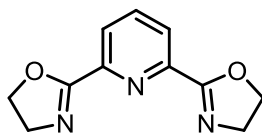


An oven-dried 100 mL two-necked round-bottomed flask under N₂ was charged with **71** (2.55 g, 10.1 mmol). SOCl₂ (37 mL, 500 mmol) was added dropwise, and the reaction mixture was refluxed for 1 h. After cooling to room temperature, excess SOCl₂ was removed. The residue was dissolved in CH₂Cl₂. The organic phase was washed with saturated NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. Title compound **72** was obtained as a white solid (2.60 g, 85%).

¹H NMR (400 MHz, CDCl₃) δ 8.40 (d, *J* = 7.8 Hz, 1H), 8.21 (t, *J* = 6.3 Hz, 2H), 8.13 – 8.04 (m, 1H), 3.90 (q, *J* = 5.7 Hz, 4H), 3.79 (t, *J* = 5.6 Hz, 4H).

*The data are consistent with those reported in literature.*³⁰

2,6-bis(4,5-dihydrooxazol-2-yl)pyridine – **73**

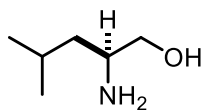


A flame dried Schlenk flask under N₂ was charged with NaH (60%, 0.43 g, 10.7 mmol). THF (7 mL) was added. **72** (1.0 g, 3.45 mmol) was added. Mixture was stirred at room temperature for 1 h. After 10 minutes, vigorous effervescence ensued which subsided after 5 minutes. The residue was filtered, washed with Et₂O, and CH₂Cl₂. The organic phase was washed with saturated NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. Title compound **73** was obtained as an off-white solid (536 mg, 72%).

¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, J = 7.8 Hz, 2H), 7.91 (t, J = 7.8 Hz, 1H), 4.57 (t, J = 9.7 Hz, 4H), 4.15 (t, J = 9.7 Hz, 4H).

*The data are consistent with those reported in literature.*³⁰

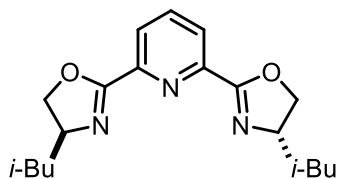
(S)-2-amino-4-methylpentan-1-ol – 75



Prepared according to general procedure D using *L*-Leucine (11.1 g, 8.50 mmol), LiAlH₄ (5.0 g, 131 mmol) in THF (100 mL). The reaction mixture was refluxed for 16 h. Title compound **75** was obtained as a colourless oil (6.87 g, 70%).

¹H NMR (400 MHz, CDCl₃) δ 3.57 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.25 (dd, *J* = 10.7, 7.9 Hz, 1H), 2.92 (qd, *J* = 7.4, 3.6 Hz, 1H), 2.70 – 2.55 (m, 3H), 1.69 (dp, *J* = 13.3, 6.7 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 2H), 0.91 (dd, *J* = 11.5, 6.6 Hz, 8H).

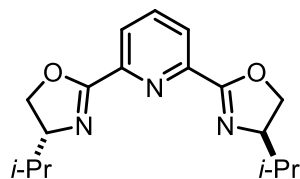
2,6-bis((S)-4-isobutyl-4,5-dihydrooxazol-2-yl)pyridine – 76



Prepared according to general procedure I using **75** (1.4 g, 12.0 mmol), pyridine-2,6-dicarbonitrile (774 mg, 6.00 mmol), and Zn(OTf)₂ (218 mg, 0.60mmol). The crude product mixture was purified by flash column chromatography (50% EtOAc in hexanes) to afford title compound **76** as a white solid (621 mg, 65%).

¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, J = 7.8 Hz, 2H), 7.88 (t, J = 7.9 Hz, 1H), 4.68 – 4.59 (m, 2H), 4.49 – 4.35 (m, 2H), 4.12 (t, J = 8.3 Hz, 2H), 1.87 (dp, J = 13.3, 6.7 Hz, 2H), 1.75 (dt, J = 13.6, 6.8 Hz, 2H), 1.42 (dt, J = 14.1, 7.2 Hz, 2H), 1.06 – 0.85 (m, 14H).

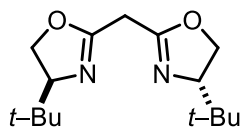
2,6-bis((R)-4-isopropyl-4,5-dihydrooxazol-2-yl)pyridine – 79



Prepared according to general procedure I using (*R*)-2-amino-3-methylbutan-1-ol (1.24 g, 12.0 mmol), pyridine-2,6-dicarbonitrile (774 mg, 6.00 mmol), and Zn(OTf)₂ (218 mg, 0.60 mmol). The crude product mixture was purified by flash column chromatography (50% EtOAc in hexanes) to afford title compound **79** as a white solid (1.24 g, 45%).

¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, *J* = 7.8 Hz, 2H), 7.88 (t, *J* = 7.9 Hz, 1H), 4.60 – 4.51 (m, 2H), 4.25 (t, *J* = 8.4 Hz, 2H), 4.17 (td, *J* = 9.1, 6.4 Hz, 2H), 2.27 (d, *J* = 13.1 Hz, 1H), 1.98 – 1.82 (m, *J* = 6.7 Hz, 2H), 1.38 – 1.27 (m, 1H), 1.28 (s, 1H), 1.08 (d, *J* = 6.8 Hz, 6H), 0.97 (d, *J* = 6.8 Hz, 6H).

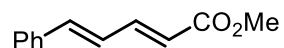
bis((S)-4-(tert-butyl)-4,5-dihydrooxazol-2-yl)methane – 81



An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with (S)-2-amino-3,3-dimethylbutan-1-ol (1.0 g, 8.53 mmol) as a solution in CH₂Cl₂ (40 mL). Diethyl malonimidate (0.99 g, 4.27 mmol) was added as a solid. A cloudy suspension was formed. The reaction mixture was stirred at room temperature for 3 d. The reaction mixture was diluted with CH₂Cl₂ and washed with water. The organic phase was separated, and aqueous phase was extracted with CH₂Cl₂. Combined organic phases were washed with saturated NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude product mixture was purified by flash column chromatography (50% EtOAc in hexanes) to afford title compound **81** as a white solid (630 mg, 46%).

¹H NMR (400 MHz, CDCl₃) δ 4.22 (dd, *J* = 10.2, 8.8 Hz, 2H), 4.15 – 4.07 (m, 2H), 3.95 – 3.85 (m, 2H), 3.36 (s, 1H), 1.37 – 1.25 (m, 1H), 0.91 (s, 18H).

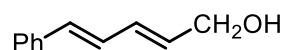
methyl (2*E*,4*E*)-5-phenylpenta-2,4-dienoate – 84



Prepared according to general procedure A using trimethyl phosphonoacetate (9.33 mL, 57.6 mmol), aldehyde (6.03 mL, 48.0 mmol), NaH (60%, 2.69 g, 67.2 mmol). The crude product mixture was purified by flash column chromatography (10:1 hexane, EtOAc) to afford title compound **84** as a white solid (6.50, 72%).

¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.44 (m, 3H), 7.44 – 7.34 (m, 2H), 7.38 – 7.27 (m, 1H), 6.98 – 6.84 (m, 2H), 6.03 (d, J = 15.4 Hz, 1H), 3.80 (s, 3H).

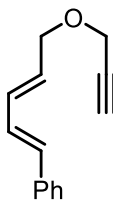
(2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol – 85



Prepared according to general procedure B using 84 (6.96 g, 37.0 mmol), DIBAL (1 M; 111 mL, 111 mmol). The crude product mixture was purified by flash column chromatography (7:3 hexane, EtOAc) to afford title compound **85** as a colourless oil (5.23 g, 89%).

¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.83 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.59 (d, *J* = 15.6 Hz, 1H), 6.46 (dd, *J* = 15.2, 10.5 Hz, 1H), 6.00 (dt, *J* = 15.2, 5.9 Hz, 1H), 4.29 (t, *J* = 5.7 Hz, 2H), 1.46 (t, *J* = 5.7 Hz, 1H).

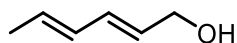
((1*E*,3*E*)-5-(prop-2-yn-1-yloxy)penta-1,3-dien-1-yl)benzene – 61



Prepared according to general procedure C using 85 (2.0 g, 12.5 mmol), propargyl bromide (80%; 1.82 mL, 16.3 mmol), NaH (60%, 0.60 g, 15.0 mmol), HMPA (2.40 mL) in THF (75 mL). The crude product mixture was purified by flash column chromatography (10:1 hexane, Et₂O) to afford title compound **61** as a colourless oil (2.16 g, 87%).

¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.22 (m, 1H), 6.82 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.60 (d, *J* = 15.7 Hz, 1H), 6.48 (dd, *J* = 15.3, 10.5 Hz, 1H), 5.90 (dt, *J* = 15.4, 6.3 Hz, 1H), 4.24 – 4.18 (m, 4H), 2.49 (t, *J* = 2.4 Hz, 1H).

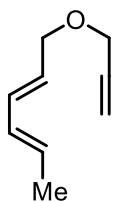
(2*E*,4*E*)-hexa-2,4-dien-1-ol – 87



Prepared according to general procedure D using (2*E*,4*E*)-hexa-2,4-dienal (5.74 mL, 52.0 mmol), LiAlH₄ (1.97 g, 52.0 mmol) in Et₂O (120 mL). The crude product mixture was purified by flash column chromatography (7:3 hexane, EtOAc) to afford title compound **87** as a colourless oil (4.28 g, 84%).

¹H NMR (400 MHz, CDCl₃) δ 6.23 (dd, *J* = 15.2, 10.5 Hz, 1H), 6.09 (ddd, *J* = 14.7, 10.5, 1.9 Hz, 1H), 5.73 (dt, *J* = 14.7, 6.7 Hz, 2H), 4.18 (t, *J* = 4.8 Hz, 2H), 3.66 (q, *J* = 5.2 Hz, 0H), 1.78 (dd, *J* = 6.8, 1.5 Hz, 3H).

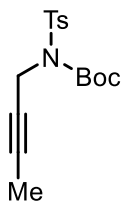
(2*E*,4*E*)-1-(prop-2-yn-1-yloxy)hexa-2,4-diene – 21



Prepared according to general procedure C using **87** (1.50 g, 15.3 mmol), propargyl bromide (80%; 1.77 mL, 19.9 mmol), NaH (60%, 0.74 g, 18.4 mmol), HMPA (2.92 mL) in THF (50 mL). The crude product mixture was purified by flash column chromatography (10:0.15 hexane, Et₂O) to afford title compound **21** as a pale yellow oil (1.67 g, 80%).

¹H NMR (400 MHz, CDCl₃) δ 6.27 (dd, *J* = 15.2, 10.3 Hz, 1H), 6.07 (tdd, *J* = 14.9, 10.5, 1.8 Hz, 1H), 5.76 (dq, *J* = 13.9, 6.7 Hz, 1H), 5.69 – 5.53 (m, 1H), 4.23 – 4.08 (m, 4H), 2.46 (dt, *J* = 4.5, 2.2 Hz, 1H), 1.79 (dd, *J* = 6.4, 1.5 Hz, 3H).

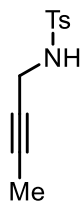
tert-butyl but-2-yn-1-yl(tosyl)carbamate – 90



Prepared according to general procedure E using but-2-yn-1-ol (0.45 mL, 6.00 mmol), *tert*-butyl tosylcarbamate (1.63 g, 6.00 mmol), PPh₃ (2.05 g, 7.80 mmol), and DIAD (1.54 mL, 7.8 mmol). The crude product mixture was purified by flash column chromatography (10:1, hexane, EtOAc) to afford title compound **90** as a white solid (1.82 g, 94%).

¹H NMR (400 MHz, CDCl₃) δ 7.97 – 7.91 (m, 2H), 7.33 (d, J = 8.2 Hz, 2H), 4.60 (q, J = 2.4 Hz, 2H), 2.47 (s, 3H), 1.86 (t, J = 2.4 Hz, 3H), 1.37 (s, 8H).

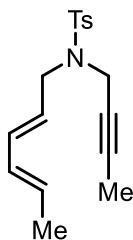
N-(but-2-yn-1-yl)-4-methylbenzenesulfonamide – 91



Prepared according to general procedure F using 90 (1.82 g, 5.63 mmol), Trifluoroacetic acid (2.16 mL, 28.2 mmol). Title compound **91** was obtained as a white solid (1.20 g, 95%).

¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.76 (m, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.62 (p, J = 5.4 Hz, 1H), 3.78 (dq, J = 5.2, 2.5 Hz, 2H), 2.45 (s, 3H), 1.62 (d, J = 4.9 Hz, 2H).

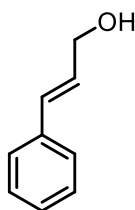
N-(but-2-yn-1-yl)-N-((2E,4E)-hexa-2,4-dien-1-yl)-4-methylbenzenesulfonamide – 92



Prepared according to general procedure E using **87** (220 mg, 2.24 mmol), **91** (500 mg, 2.24 mmol), PPh₃ (763 mg, 2.91 mmol), and DIAD (0.57 mL, 2.91 mmol). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **92** as an off-white solid (308 mg, 45%).

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.72 (m, 2H), 7.36 – 7.23 (m, 2H), 6.23 – 5.94 (m, 2H), 5.78 – 5.65 (m, 1H), 5.43 (dt, J = 14.4, 6.9 Hz, 1H), 4.02 (q, J = 2.4 Hz, 2H), 3.81 (d, J = 6.9 Hz, 2H), 2.44 (s, 3H), 1.77 (d, J = 6.1 Hz, 2H), 1.57 (dt, J = 6.9, 2.4 Hz, 3H).

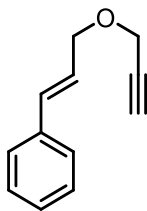
(E)-3-phenylprop-2-en-1-ol – 94



Into a beaker (100 mL) was added silica (Silica Gel 60; 230-400 mesh). Water was added (HPLC grade, 11.4 mL). The mixture was stirred at room temperature for 5 minutes. Cinnamaldehyde was added and mixture was stirred for 5 minutes. NaBH₄ (1.43g, 37.8 mmol) was added and mixture was stirred for 1.5 h. The reaction progress was followed by TLC. Mixture was washed with CH₂Cl₂. The combined organic phases were washed with saturated, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude product mixture was purified by flash column chromatography (7:3 hexane, EtOAc) to afford title compound **94** as a colourless oil (3.63 g, 95%).

¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, J = 7.3 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 6.70 – 6.61 (m, 1H), 6.40 (dt, J = 16.0, 5.8 Hz, 1H), 4.35 (dd, J = 5.6, 1.6 Hz, 2H).

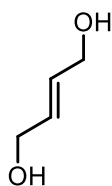
(*E*)-(3-(prop-2-yn-1-yloxy)prop-1-en-1-yl)benzene – 95



Prepared according to general procedure C using **94** (0.84 g, 6.25 mmol), propargyl bromide (80%; 0.91 mL, 8.15 mmol), NaH (60%, 0.30g 7.50 mmol), HMPA (1.2 mL) in THF (45 mL). The crude product mixture was purified by flash column chromatography (10:0.5 hexane, EtOAc) to afford title compound **95** as a colourless oil (0.92 g, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.24 (m, 5H), 6.73 – 6.63 (m, 1H), 6.31 (dt, *J* = 16.0, 6.1 Hz, 1H), 4.33 – 4.21 (m, 4H), 2.49 (t, *J* = 2.4 Hz, 1H).

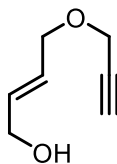
(E)-but-2-ene-1,4-diol - 96



Prepared according to general procedure D using but-2-yne-1,4-diol (10 g, 116 mmol), LiAlH_4 (5.28 g, 139 mmol) in THF (400 mL). The reaction mixture was refluxed for 2 h. The mixture was cooled to 0 °C and was treated with NaOH (3 M) until effervescence stopped. The mixture was adjusted to pH 8 with HCl (3 M). Et_2O and silica was added to the mixture and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (50:50 EtOAc in hexanes to 100% EtOAc). The title compound **96** was obtained as a colourless oil (7.99 g, 80%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.98 – 5.89 (m, 1H), 5.93 – 5.77 (m, 1H), 5.43 (d, $J = 16.4$ Hz, 1H), 4.27 – 4.04 (m, 4H), 1.38 – 1.22 (m, 1H).

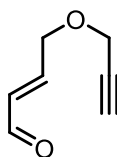
(E)-4-(prop-2-yn-1-yloxy)but-2-en-1-ol – 97



Prepared according to general procedure C using but-2-yne-1,4-diol (1.5 g, 17.4 mmol), propargyl bromide (80%; 0.65 mL), NaH (60%, 0.23 g, 5.80 mmol) in THF (15 mL). The crude product mixture was purified by flash column chromatography (6:4 hexane, EtOAc) to afford title compound **97** as a colourless oil (435 mg, 60%).

¹H NMR (400 MHz, CDCl₃) δ 5.96 (dt, J = 15.6, 5.2 Hz, 1H), 5.84 (dt, J = 15.7, 5.9 Hz, 1H), 4.23 – 4.15 (m, 4H), 4.11 (d, J = 5.8 Hz, 2H), 2.47 (t, J = 2.4 Hz, 1H).

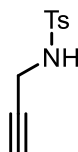
(E)-4-(prop-2-yn-1-yloxy)but-2-enal – 98



An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with activated MnO₄ (3.76 g, 43.2 mmol). CH₂Cl₂ was added. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered over Celite[®] with CH₂Cl₂. The mixture was concentrated *in vacuo*. The crude product mixture was purified by flash column chromatography (100% hexane – 20% EtOAc in hexane) to afford title compound **98** as a colourless oil (341 mg, 83%). Some inseparable impurity was present in the sample.

¹H NMR (400 MHz, CDCl₃) δ 9.62 (d, J = 7.9 Hz, 1H), 6.86 (dt, J = 15.7, 4.0 Hz, 1H), 6.39 (ddt, J = 15.8, 7.9, 2.0 Hz, 1H), 4.39 (dd, J = 4.3, 2.0 Hz, 2H), 4.27 (d, J = 2.4 Hz, 2H), 2.51 (t, J = 2.3 Hz, 1H).

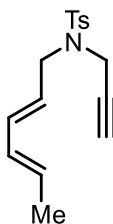
4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide – 100



Prepared according to general procedure G using propargyl amine (1.3 mL, 20.3 mmol), Et₃N (7 mL, 50.2 mmol), and TsCl (3.8g, 20.0 mmol). Title compound **100** was obtained as a white solid (3.71 g, 89%).

¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.76 (m, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.70 (t, J = 6.0 Hz, 1H), 3.86 (dd, J = 5.9, 2.5 Hz, 2H), 2.46 (s, 3H), 2.13 (t, J = 2.5 Hz, 1H).

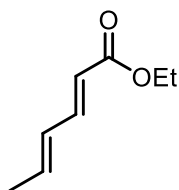
N-((2*E*,4*E*)-hexa-2,4-dien-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide – 101



Prepared according to general procedure E using **87** (0.61 g, 6.24 mmol), **100** (1.31 g, 6.24 mmol), PPh₃ (1.64 g, 6.24 mmol), and DIAD (1.23 mL, 6.24 mmol). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **101** as an off-white solid (1.23g, 70%).

¹H NMR (400 MHz, CDCl₃) δ 7.75 (dd, *J* = 8.3, 3.8 Hz, 2H), 7.32 (dd, *J* = 8.4, 2.4 Hz, 2H), 6.20 (dd, *J* = 15.1, 10.4 Hz, 1H), 6.10 – 5.97 (m, 1H), 5.73 (dq, *J* = 13.6, 6.7 Hz, 1H), 5.62 – 5.37 (m, 1H), 4.19 – 4.03 (m, 2H), 3.88 (dd, *J* = 22.8, 7.0 Hz, 1H), 2.45 (s, 2H), 2.43 (d, *J* = 8.0 Hz, 0H), 2.09 – 1.99 (m, 1H), 1.76 (td, *J* = 7.3, 1.7 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 1H).

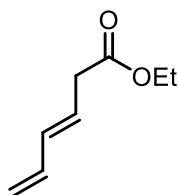
ethyl (2*E*,4*E*)-hexa-2,4-dienoate – 103



Prepared according to general procedure H using carboxylic acid (10 g, 89.2 mmol). The title compound **103** was isolated as a colourless oil (6.3 g, 50%).

¹H NMR (400 MHz, CDCl₃) δ 7.28 (dd, *J* = 15.3, 10.0 Hz, 1H), 6.28 – 6.09 (m, 2H), 5.80 (d, *J* = 15.5 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.88 (d, *J* = 5.8 Hz, 3H), 1.32 (t, *J* = 7.3 Hz, 3H).

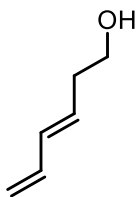
ethyl (*E*)-hexa-3,5-dienoate – 104



An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with diisopropylamine (5.40 mL, 38.5 mmol) in THF (26 mL) and cooled to –78 °C. *n*-BuLi (2.5 M, 15.4 mL, 38.5 mmol) was added dropwise. Flask was removed from dry ice bath and allowed to stir for 30 min. The mixture was cooled to –78 °C and HMPA (8.5 mL) was added. Precipitation was observed. The reaction mixture was stirred for 20 minutes at –78 °C. 103 (3g, 21.4 mmol) in THF (14 mL) was added. A dark red solution was formed. The reaction mixture was stirred at –78 °C for 20 minutes. The reaction mixture was quenched by pouring into flask containing water (43 mL), AcOH (7.7 mL). The organic phase was separated, and aqueous phase was extracted with hexanes (20mL). The combined organic phases were washed with saturated NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The title compound **104** was isolated as a colourless oil (2.1 g, 70%).

¹H NMR (400 MHz, CDCl₃) δ 6.37 (dt, *J* = 17.1, 10.3 Hz, 1H), 6.23 – 6.12 (m, 1H), 5.82 (dt, *J* = 14.8, 7.2 Hz, 1H), 5.20 (dd, *J* = 16.9, 1.6 Hz, 1H), 5.09 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.14 (dd, *J* = 7.1, 1.4 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

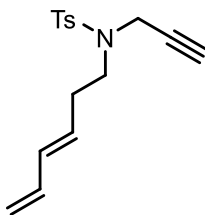
(E)-hexa-3,5-dien-1-ol – 105



Prepared according to general procedure D using **104** (2.02 g, 11.3 mmol), LiAlH₄ (0.58 g, 15.4 mmol) in Et₂O (40 mL). After completion, mixture was cooled to 0 °C, diluted with Et₂O and quenched with Rochelle's salt solution (100 mL). Mixture was stirred for 16 h. Title compound **105** was obtained as a colourless oil (1.08 g, 98%).

¹H NMR (400 MHz, CDCl₃) δ 6.35 (dt, J = 17.0, 10.3 Hz, 1H), 6.19 (dd, J = 15.2, 10.5 Hz, 1H), 5.71 (dt, J = 14.8, 7.2 Hz, 1H), 5.17 (dd, J = 17.1, 1.7 Hz, 1H), 5.05 (dd, J = 10.2, 1.7 Hz, 1H), 3.71 (q, J = 6.1 Hz, 2H), 2.39 (q, J = 6.8 Hz, 2H), 1.54 (t, J = 5.7 Hz, 1H).

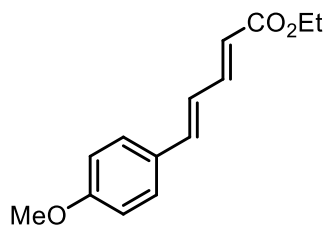
(*E*)-N-(hexa-3,5-dien-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide – 106



Prepared according to general procedure E using **105** (200 mg, 2.04 mmol), **100** (437 mg, 2.04 mmol), PPh₃ (695 mg, 2.65 mmol), and DIAD (0.52 mL, 2.65 mmol). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **106** as a colourless oil (391 mg, 66%).

¹H NMR (400 MHz, CDCl₃) δ 7.78 – 7.69 (m, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.31 (dt, *J* = 16.9, 10.2 Hz, 1H), 6.13 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.64 (dt, *J* = 14.7, 7.1 Hz, 1H), 5.15 (dd, *J* = 16.9, 1.6 Hz, 1H), 5.04 (dd, *J* = 9.8, 1.6 Hz, 1H), 4.16 (d, *J* = 2.6 Hz, 2H), 3.34 – 3.22 (m, 2H), 2.47 – 2.36 (m, 5H), 2.06 (t, *J* = 2.5 Hz, 1H).

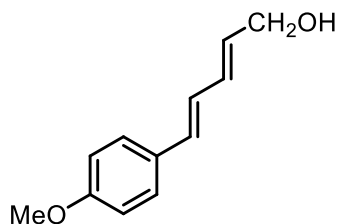
methyl (2*E*,4*E*)-5-(4-methoxyphenyl)penta-2,4-dienoate – 108



Prepared according to general procedure A using triethyl phosphonoacetate (7.34 mL, 37.0 mmol), aldehyde (5.00 g, 30.8 mmol), NaH (60%, 1.72 g, 43.1 mmol). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **108** as a white solid (4.43 g, 62%).

¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, *J* = 8.7 Hz, 2H), 6.95 – 6.84 (m, 3H), 6.78 (dd, *J* = 15.6, 10.8 Hz, 1H), 5.96 (d, *J* = 15.2 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

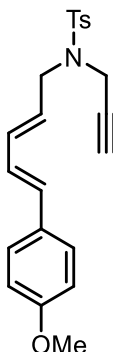
(2*E*,4*E*)-5-(4-methoxyphenyl)penta-2,4-dien-1-ol – 109



Prepared according to general procedure B using **108** (2.00 g, 8.62 mmol), DIBAL (1 M; 26 mL, 25.9 mmol). The crude product mixture was purified by flash column chromatography (6:4 hexane, EtOAc) to afford title compound xx as a colourless oil (1.36 g, 83%).

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.32 (m, 2H), 6.93 – 6.84 (m, 2H), 6.69 (dd, J = 15.6, 10.4 Hz, 1H), 6.54 (d, J = 15.7 Hz, 1H), 6.42 (dd, J = 15.2, 10.4 Hz, 1H), 5.94 (dt, J = 15.1, 5.9 Hz, 1H), 4.26 (t, J = 5.7 Hz, 2H), 3.84 (s, 3H).

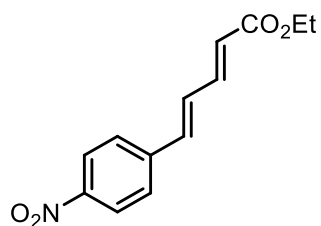
N-((2E,4E)-5-(4-methoxyphenyl)penta-2,4-dien-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide – 110



Prepared according to general procedure E using **109** (1.20 g, 6.31 mmol), **100** (1.32 g, 6.31 mmol), PPh₃ (1.66 g, 6.31 mmol), and DIAD (1.24 mL, 6.31 mmol). The crude product mixture was purified by flash column chromatography (8:2 hexane, EtOAc) to afford title compound **110** as a brown oil (0.60 g, 33%).

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.71 (m, 2H), 7.39 – 7.27 (m, 3H), 7.31 – 7.13 (m, 2H), 6.93 – 6.78 (m, 3H), 6.13 – 5.93 (m, 1H), 4.24 – 4.02 (m, 3H), 3.93 (d, J = 6.9 Hz, 1H), 3.83 (s, 4H), 3.92 – 3.74 (m, 1H), 2.62 (ddt, J = 16.6, 9.7, 2.8 Hz, 1H), 2.50 – 2.35 (m, 4H).

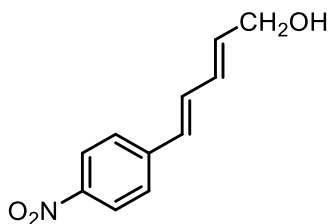
methyl (2*E*,4*E*)-5-(4-nitrophenyl)penta-2,4-dienoate – 112



Prepared according to general procedure A using triethyl phosphonoacetate (2.70 mL, 13.6 mmol), aldehyde (2.00 g, 11.3 mmol), NaH (60%, 0.63 g, 15.8 mmol). The crude product mixture was purified by recrystallization (EtOH/hexane) to afford title compound **112** as a yellow solid (1.46 g, 52%).

¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.47 (dd, *J* = 15.3, 10.3 Hz, 1H), 7.09 – 6.91 (m, 2H), 6.13 (d, *J* = 15.2 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H).

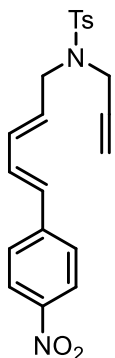
(2*E*,4*E*)-5-(4-nitrophenyl)penta-2,4-dien-1-ol – 113



Prepared according to general procedure B using **112** (1.20 g, 4.85 mmol), DIBAL (1 M; 14.6 mmol). The crude product mixture was purified by flash column chromatography (5:5 hexane, EtOAc) to afford title compound **113** as a colourless oil (402 mg, 41%).

¹H NMR (400 MHz, CDCl₃) δ 8.24 – 8.16 (m, 2H), 7.57 – 7.50 (m, 2H), 6.97 (dd, *J* = 15.7, 10.6 Hz, 1H), 6.90 – 6.83 (m, 0H), 6.62 (d, *J* = 15.7 Hz, 1H), 6.50 (dd, *J* = 15.3, 10.5 Hz, 1H), 6.15 (t, *J* = 5.5 Hz, 1H), 6.15 – 6.00 (m, 1H), 4.34 (d, *J* = 5.4 Hz, 2H).

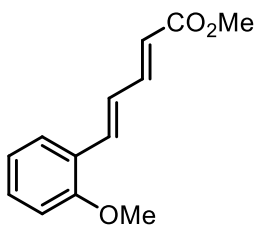
4-methyl-N-((2*E*,4*E*)-5-(4-nitrophenyl)penta-2,4-dien-1-yl)-N-(prop-2-yn-1-yl)benzenesulfonamide – 114



Prepared according to general procedure E using **113** (100 mg, 0.49 mmol), **100** (103 mg, 0.49 mmol), PPh₃ (129 mg, 0.49 mmol), and DIAD (97 μ L, 0.49 mmol). The crude product mixture was purified by flash column chromatography (5:5 hexane, EtOAc) to afford title compound **114** as a white solid (80 mg, 41%).

¹H NMR (400 MHz, CDCl₃) δ 8.23 – 8.16 (m, 2H), 7.82 – 7.74 (m, 2H), 7.56 – 7.49 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.91 (dd, *J* = 15.7, 10.5 Hz, 1H), 6.61 (d, *J* = 15.7 Hz, 1H), 6.45 (dd, *J* = 15.2, 10.6 Hz, 1H), 5.93 – 5.81 (m, 1H), 4.14 (d, *J* = 2.5 Hz, 2H), 3.97 (d, *J* = 6.7 Hz, 2H), 2.46 (s, 3H), 2.10 – 2.04 (m, 1H).

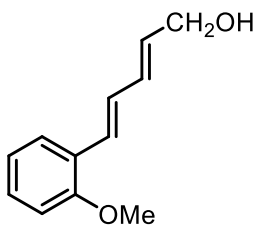
methyl (2E,4E)-5-(2-methoxyphenyl)penta-2,4-dienoate – 116



An oven-dried 250 mL two-necked round-bottomed flask under N₂ was charged with aldehyde (1.95 g, 12.0 mmol), (Carbethoxymethylene)triphenylphosphorane (5.00 g, 14.4 mmol). CHCl₃ was added (150 mL) The reaction mixture was refluxed for 7 h. The mixture was cooled to room temperature and stirred for 16 h. The crude product mixture was concentrated *in vacuo* and purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **116** as a colourless oil (1.06 g, 38%).

¹H NMR (400 MHz, CDCl₃) δ 8.20 (dd, J = 15.9, 11.4 Hz, 1H), 7.68 (dd, J = 7.9, 1.7 Hz, 1H), 7.34 – 7.21 (m, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.81 (t, J = 11.3 Hz, 1H), 5.73 (d, J = 11.2 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H).

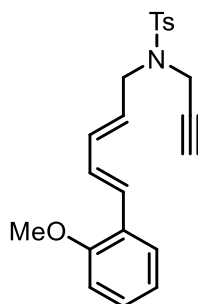
(2E,4E)-5-(2-methoxyphenyl)penta-2,4-dien-1-ol – 117



Prepared according to general procedure B using 116 (1.50 g, 6.46 mmol), DIBAL (1 M; 20 mL, 19.4 mmol). The crude product mixture was purified by flash column chromatography (6:4 hexane, EtOAc) to afford title compound **117** as a colourless oil (1.12 g, 92%).

Product was used directly in the next step.

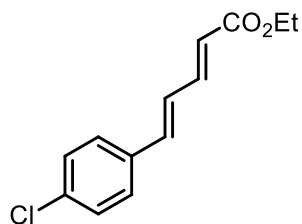
N-((2*E*,4*E*)-5-(2-methoxyphenyl)penta-2,4-dien-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide – 118



Prepared according to general procedure E using **117** (800 mg, 4.21 mmol), **100** (851 mg, 4.21 mmol), PPh₃ (1.10 g, 4.21 mmol), and DIAD (0.83 mL, 4.21 mmol). The crude product mixture was purified by flash column chromatography (8:2 hexane, EtOAc) to afford title compound **118** as a white solid (1.06 g, 63%).

¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 1.8 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.29 (s, 1H), 7.33 – 7.18 (m, 2H), 7.06 – 6.82 (m, 4H), 6.44 (dd, J = 15.1, 10.2 Hz, 1H), 5.67 (dt, J = 14.6, 6.9 Hz, 1H), 4.14 (d, J = 2.5 Hz, 2H), 3.94 (d, J = 7.4 Hz, 2H), 3.88 (s, 3H), 3.89 – 3.74 (m, 1H), 2.46 (s, 3H), 2.45 – 2.37 (m, 1H).

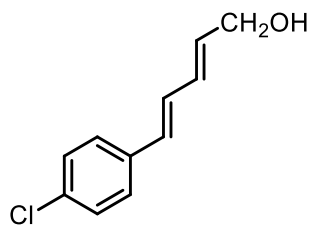
methyl (2*E*,4*E*)-5-(4-chlorophenyl)penta-2,4-dienoate – 120



Prepared according to general procedure A using triethyl phosphonoacetate (1.43 mL, 7.20 mmol), aldehyde (1.00 g, 6.00 mmol), NaH (60%, 0.34 g, 8.40 mmol). The crude product mixture was purified by flash column chromatography (10:0.5 hexane, EtOAc) to afford title compound **120** as a white solid (1.18 g, 83%).

¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.38 (m, 3H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.90 – 6.80 (m, 2H), 6.03 (d, *J* = 15.2 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

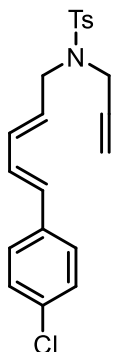
(2*E*,4*E*)-5-(4-chlorophenyl)penta-2,4-dien-1-ol – 121



Prepared according to general procedure B using *120* (1.00 g, 4.22 mmol), DIBAL (1 M; 12.7 mL, 12.7 mmol). Title compound **121** was isolated as a colourless oil (0.74 g, 91%).

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.27 (m, 4H), 6.79 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.44 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.01 (dt, *J* = 15.3, 5.8 Hz, 1H), 4.29 (td, *J* = 5.9, 1.5 Hz, 2H), 1.43 (t, *J* = 5.9 Hz, 1H).

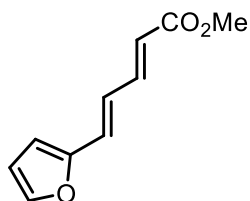
N-((2E,4E)-5-(4-chlorophenyl)penta-2,4-dien-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide – 122



Prepared according to general procedure E using **121** (500 mg, 2.57 mmol), **100** (538 mg, 2.57 mmol), PPh₃ (674 mg, 2.57 mmol), and DIAD (0.51 mL, 2.57 mmol). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **122** as a white solid (278 mg, 28%).

¹H NMR (400 MHz, CDCl₃) δ 7.78 (s, 1H), 7.76 (s, 1H), 7.36 – 7.29 (m, 6H), 6.73 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.40 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.72 (dt, *J* = 14.5, 7.0 Hz, 1H), 4.13 (d, *J* = 2.5 Hz, 2H), 3.94 (d, *J* = 6.9 Hz, 2H), 2.46 (s, 3H), 2.49 – 2.37 (m, 1H).

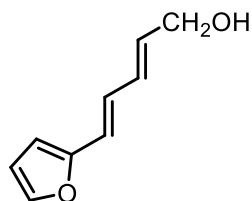
methyl (2*E*,4*E*)-5-(furan-2-yl)penta-2,4-dienoate – 124



Prepared according to general procedure A using triethyl phosphonoacetate (6.82 mL, 34.4 mmol), aldehyde (3.50g, 28.7 mmol), NaH (60%, 1.60 g, 40.1 mmol). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **124** as a red solid (3.74 g, 68%).

¹H NMR (400 MHz, CDCl₃) δ 7.48 – 7.34 (m, 2H), 6.80 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.68 (d, *J* = 15.5 Hz, 1H), 6.46 (s, 2H), 5.99 (d, *J* = 15.3 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

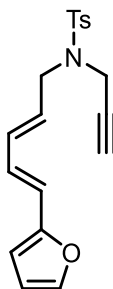
(2E,4E)-5-(furan-2-yl)penta-2,4-dien-1-ol – 125



Prepared according to general procedure B using **124** (1.18 g, 6.14 mmol), DIBAL (1 M; 18.4 mmol). The crude product mixture was purified by flash column chromatography (8:2 hexane, EtOAc) to afford title compound **125** as pale yellow solid (0.89 g, 97%). Compound was isolated with inseparable impurities.

¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 1.8 Hz, 1H), 6.72 (dd, J = 15.5, 10.9 Hz, 1H), 6.43 – 6.32 (m, 3H), 6.29 (d, J = 3.3 Hz, 1H), 5.97 (dt, J = 15.4, 5.9 Hz, 1H), 4.25 (d, J = 5.8 Hz, 2H).

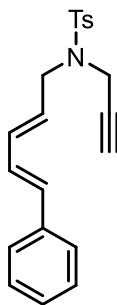
N-((2*E*,4*E*)-5-(furan-2-yl)penta-2,4-dien-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide – 126



Prepared according to general procedure E using **125** (0.50, 3.33 mmol), 100 (0.70 g, 3.33 mmol), PPh₃ (0.87 g, 3.33 mmol), and DIAD (0.66 mL, 3.33 mmol). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **126** as a white solid (0.43g, 38%).

Included for completeness. Sadly, NMR of relevant fraction B (product) was lost.

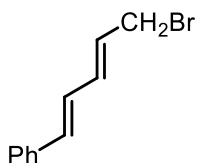
4-methyl-N-((2E,4E)-5-phenylpenta-2,4-dien-1-yl)-N-(prop-2-yn-1-yl)benzenesulfonamide – 127



Prepared according to general procedure E using **85** (500 mg, 3.12 mmol), **100** (653 mg, 3.12 mmol), PPh₃ (818 mg, 3.12 mmol), and DIAD (0.61 mL, 3.12 mmol). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **127** as a pale yellow solid (0.56 g, 51 %).

¹H NMR (400 MHz, CDCl₃) δ 7.86 – 7.75 (m, 2H), 7.45 – 7.22 (m, 8H), 6.77 (dd, J = 15.6, 10.4 Hz, 1H), 6.57 (d, J = 15.7 Hz, 1H), 6.42 (dd, J = 15.1, 10.7 Hz, 1H), 5.80 – 5.60 (m, 1H), 4.14 (d, J = 2.5 Hz, 2H), 3.95 (d, J = 6.9 Hz, 2H), 2.46 (s, 3H), 2.42 (d, J = 14.8 Hz, 1H).

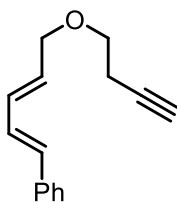
((1E,3E)-5-bromopenta-1,3-dien-1-yl)benzene – 128



An oven-dried 100 mL two-necked round-bottomed flask under N₂ was charged with PBr₃ (0.49 mL, 5.24 mmol), Et₂O (15 mL). The flask was cooled to 0 °C. Alcohol 85 (700 mg, 4.37 mmol) in Et₂O (7 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into ice-cold mixture of water/Et₂O. The organic phase was separated, and aqueous phase was extracted with Et₂O (20mL). The combined organic phases were washed with NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. Title compound **128** was isolated as a white solid (772 mg, 79%).

Product was used directly in the next step.

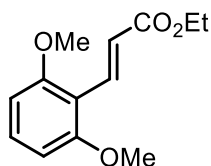
((1*E*,3*E*)-5-(but-3-yn-1-yloxy)penta-1,3-dien-1-yl)benzene – 129



Prepared according to general procedure C using 3-Butyn-1-ol (0.29 mL, 3.81), bromide 128 (772 mg, 3.46 mmol), NaH (60%, 208 mg, 5.19 mmol) in THF (30 mL). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **129** was obtained as a colourless oil (0.62 g, 84%).

¹H NMR (400 MHz, CDCl₃) δ 7.42 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.38 – 7.21 (m, 3H), 6.81 (dd, *J* = 15.6, 10.6 Hz, 1H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.51 – 6.40 (m, 1H), 5.91 (dt, *J* = 15.2, 6.1 Hz, 1H), 4.15 (dd, *J* = 6.2, 1.4 Hz, 2H), 3.62 (t, *J* = 7.0 Hz, 2H), 2.53 (td, *J* = 6.9, 2.6 Hz, 2H), 2.03 (t, *J* = 2.7 Hz, 1H).

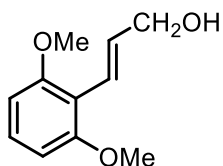
ethyl (E)-3-(2,6-dimethoxyphenyl)acrylate – 131



Prepared according to general procedure A using triethyl phosphonoacetate (9.40 mL, 54.2 mmol), aldehyde (4.50g, 27.1 mmol), NaH (60%, 2.17g, 54.2 mmol). The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **131** as a white solid (4.78 g, 75%).

¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, J = 16.2 Hz, 1H), 7.07 (d, J = 2.9 Hz, 1H), 6.94 (dd, J = 8.9, 3.0 Hz, 1H), 6.88 (d, J = 9.2 Hz, 1H), 6.52 (d, J = 16.1 Hz, 1H), 4.29 (q, J = 7.0 Hz, 2H), 3.87 (s, 2H), 3.82 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H).

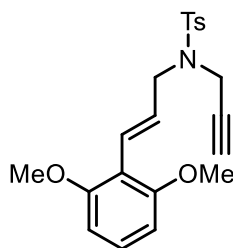
(*E*)-3-(2,6-dimethoxyphenyl)prop-2-en-1-ol – 132



Prepared according to general procedure B using 131 (2.50g, 10.6 mmol), DIBAL (1 M; 32 mL, 32.0 mmol). The crude product mixture was purified by flash column chromatography (6:4 hexane, EtOAc) to afford title compound **132** as a colourless oil (2.02 g, 98%).

¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, *J* = 2.7 Hz, 1H), 6.93 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.87 – 6.77 (m, 2H), 6.40 (dt, *J* = 16.1, 5.9 Hz, 1H), 4.35 (td, *J* = 5.9, 1.6 Hz, 2H), 3.82 (d, *J* = 8.5 Hz, 6H), 1.61 (td, *J* = 6.2, 2.2 Hz, 1H).

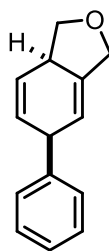
**(*E*)-N-(3-(2,6-dimethoxyphenyl)allyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide –
133**



Prepared according to general procedure E using **132** (600mg, 3.09 mmol), **100** (647 mg, 3.09 mmol), PPh₃ (811 mg, 3.09 mmol), and DIAD (0.61 mL, 3.09 mmol). The crude product mixture was purified by flash column chromatography (8:2 hexane, EtOAc) to afford title compound **133** as a colourless oil (0.96g, 81%).

¹H NMR (400 MHz, CDCl₃) δ 7.82 – 7.75 (m, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 6.95 – 6.91 (m, 1H), 6.91 – 6.85 (m, 1H), 6.81 (d, *J* = 2.3 Hz, 2H), 6.10 (dt, *J* = 15.8, 7.0 Hz, 1H), 4.16 (d, *J* = 2.5 Hz, 2H), 4.02 (dd, *J* = 7.2, 1.4 Hz, 2H), 3.80 (d, *J* = 1.3 Hz, 6H), 2.46 (s, 3H), 2.06 (t, *J* = 2.4 Hz, 1H).

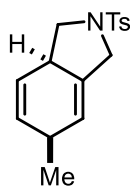
(3aR,6S)-6-phenyl-1,3,3a,6-tetrahydroisobenzofuran – 62



Prepared according to general procedure J using **61** (20.0 mg, 0.1 mmol), CuI (1.91 mg, 0.01 mmol), Et₃N (14 μ L, 0.1 mmol), ligand **68** (3.29 mg, 0.01 mmol) in DMSO (1 mL) at 25 °C for 24 h. The crude product mixture was purified by flash column chromatography (10:1 petroleum ether, Et₂O) to afford title compound **62** was obtained as a colourless oil (17 mg, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.36 (t, *J* = 7.4 Hz, 2H), 7.31 – 7.18 (m, 3H), 5.87 (dtd, *J* = 12.0, 9.8, 2.2 Hz, 2H), 5.57 (q, *J* = 2.0 Hz, 1H), 4.49 (ddt, *J* = 11.8, 3.5, 1.8 Hz, 1H), 4.38 – 4.27 (m, 2H), 4.04 (dp, *J* = 10.2, 2.5 Hz, 1H), 3.40 (dd, *J* = 11.1, 7.5 Hz, 1H), 3.21 (tdd, *J* = 11.0, 8.6, 2.5 Hz, 1H).

(3aR,6S)-6-methyl-2-tosyl-2,3,3a,6-tetrahydro-1H-isoindole – 139



Prepared according to general procedure J using 101 (29.0 mg, 0.1 mmol), CuI (1.91 mg, 0.01 mmol), Et₃N (14 μ L, 0.1 mmol), ligand 68 (3.29 mg, 0.01 mmol) in DMSO (1 mL) at 25 °C for 24 h. The crude product mixture was purified by flash column chromatography (9:1 hexane, EtOAc) to afford title compound **139** was obtained as a pale yellow oil (15 mg, 75%).

¹H NMR (400 MHz, CDCl₃) δ 7.76 (dd, J = 19.0, 8.3 Hz, 2H), 7.34 (dd, J = 8.0, 5.6 Hz, 2H), 5.64 (s, 2H), 5.40 (s, 1H), 4.03 (d, J = 2.1 Hz, 1H), 3.86 (t, J = 8.4 Hz, 1H), 3.75 (dd, J = 13.1, 2.0 Hz, 1H), 3.01 – 2.88 (m, 1H), 2.84 – 2.71 (m, 1H), 2.68 (dd, J = 11.2, 8.8 Hz, 1H), 2.45 (s, 3H), 1.07 (d, J = 7.4 Hz, 3H).

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“If at first you don't succeed, try, try again. Then quit. There's no point in being a fool about it.”

W. C. Fields